



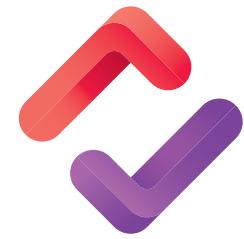
Select Health

Select Health Medical Policies

Genetic Testing Policies

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Genetic Testing Policies

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MEDICAL POLICY

GENE EXPRESSION PROFILING FOR MONITORING ACUTE REJECTION IN CARDIAC TRANSPLANT PATIENTS (ALLOMAP)

Policy # 357

Implementation Date: 7/1/07

Review Dates: 6/19/08, 6/11/09, 8/16/11, 8/16/12, 8/15/13, 8/20/15, 8/25/16, 8/17/17, 7/20/18, 6/13/19, 2/21/23, 2/15/24

Revision Dates: 11/10/08, 8/16/10, 8/28/14, 6/17/15, 7/17/15, 8/2/19, 7/1/23, 12/6/23, 1/20/25

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Cardiac transplantation is considered the definitive therapy for end-stage heart disease. Continuing advancements in organ procurement, surgical techniques, and immunosuppressive drugs have reduced mortality rates in the early post-transplant period. A common complication to arise post-transplantation is rejection of the donor heart. This may result in significant morbidity and mortality. The incidence of rejection peaks about one month after transplant and then rapidly declines. Biopsy evidence of rejection usually is present before other signs and symptoms of myocardial compromise, and cardiac rejection is often asymptomatic. Endomyocardial biopsy has been the standard of care for rejection monitoring and drug titration management. However, this is an invasive and imperfect measure of rejection that has risks for significant adverse events.

Less invasive indicators of early rejection (e.g., echocardiography) have been studied, but all have limited sensitivity and specificity compared to endomyocardial biopsy. One test, gene expression profiling of peripheral blood lymphocytes, attempts to quantify the relative levels of messenger RNA (mRNA) for large numbers of genes in specific cells or tissues. The goal is to measure differences in the level of translation (expression) of different genes and utilize patterns of differential gene expression in order to identify early changes in the immune system that correlate with rejection of the transplanted organ.

AlloMap is the only commercially available gene expression profile test currently available for heart transplant patients. The test identifies 11 genes that distinguish transplant rejection from quiescence (i.e., ISHLT grade 0). These genes are *ITGA4* (associated with T-cell infiltration at the site of inflammation); *PDCD1* (limits potential autoreactivity); *PF4* and *G6b* (associated with rejection and expressed by platelets); *MIR*, *WDR40A* (erythrocytes), and *SEMA7A* (granulocytes; expressed by immature lymphocytes and elevated in rejection); *IL1R2*, *ITGAM*, and *FLT3* (expressed in monocytes; level of expression correlates with increasing steroid doses); and *RHOU* (involved in modulation of cytoskeletal organization; undetermined role in rejection). The assay also measures expression levels of an additional nine "housekeeping" genes that serve as reference standards.

Reverse transcription polymerase chain reaction (RT- PCR) is used to measure the relative expression of these 20 genes in peripheral blood mononuclear cells. A proprietary algorithm is applied to the results to generate a score ranging from 0–40 and the corresponding 95% confidence interval. The value of the score is then used to predict the likelihood of rejection. The exact cut-point for low-risk of rejection varies depending on the time since the initial transplant.

Genetic Testing Policies, Continued

Gene Expression Profiling for Monitoring Acute Rejection in Cardiac Transplant Patients (ALLOMAP), continued

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers genetic expression profiling for monitoring acute rejection in cardiac transplant patients using the AlloMap when ordered by an Intermountain Health Transplant Provider or Intermountain Health Cardiovascular Provider; or when the following criteria are met:

Criteria for coverage:

Criteria for coverage include meeting the criteria for the IMAGE trial, and after a physical and echocardiogram have been performed.

IMAGE Trial Guidelines:

1. Heart transplant recipients who are \geq 55 days post-transplant
2. Age $>$ 15 years
3. Stable outpatient being seen for routine monitoring of rejection. Stability is defined as absence of prior or current evidence of either severe cardiac allograft vasculopathy (CAV) or antibody-mediated rejection (AMR) with associated hemodynamic compromise
 - Severe CAV is defined as either
 - 50% left main stenosis;
 - \geq 50% stenosis in \geq 2 primary vessels (proximal 1/3 or middle 1/3 of the LAD or LCx, RCA to takeoff of PDA in right-dominant coronary circulations) or
 - Isolated branch stenosis of $>$ 50% in all 3 systems (diagonal branches, obtuse marginal branches, distal 1/3 of LAD or LCx, PDA, PLB, and RCA to takeoff of PDA in non-dominant systems)
 - AMR with associated hemodynamic compromise is defined as AMR (defined according to local criteria) with either:
 - A left ventricular ejection fraction (LVEF) \leq 30% or at least 25% lower than the baseline value,
 - A cardiac index $<$ 2 l/min/m², or
 - The use of inotropic agents to support circulation
4. Left ventricular ejection fraction \geq 45% by Echocardiography, Multiple Gated Acquisition (MUGA) scan, or ventriculography at study entry (baseline/enrollment study).
5. Testing being performed as part of an established post-transplant surveillance protocol*

Exclusion Criteria:

1. Any clinical signs of declining graft function:
 - Symptoms of congestive heart failure (CHF)
 - Signs of decompensated heart failure, including the development of a new S3 gallop
 - Elevated right heart pressures with diminished cardiac index $<$ 2.2 L/min/m² that is new compared to a previous measurement within 6 months
 - Decrease in LVEF as measured by echocardiography: \geq 25% compared to prior measurement within 6 months.

Genetic Testing Policies, Continued

Gene Expression Profiling for Monitoring Acute Rejection in Cardiac Transplant Patients (ALLOMAP), continued

2. Rejection therapy for biopsy-proven ISHLT Grade 3A or higher during the preceding 2 months
3. Major changes in immunosuppression therapy within previous 30 days (e.g., discontinuation of calcineurin inhibitors, switch from mycophenolate mofetil to sirolimus or vice versa)
4. Patient receiving hematopoietic growth factors (e.g., Neupogen, Epogen) currently or during the previous 30 days
5. Patients receiving \geq 20 mg/day of prednisone-equivalent corticosteroids
6. Patient enrolled in a trial requiring routine surveillance endomyocardial biopsies
7. Patient received transfusion within preceding 4 weeks
8. Patients with end-stage renal disease requiring some form of renal replacement therapy (hemodialysis or peritoneal dialysis)
9. Pregnancy
10. Age < 15 years

*Current Intermountain protocol based upon the study for which AlloMap gained approval, lists the following biopsy frequency post-transplant.

1. 1st year post-transplant:
 - a. Monthly until month 7
 - b. Every 6 weeks (until month 10)
 - c. Then at 1st year annual
2. 2nd year post-transplant: every 3 months
3. 3rd year post-transplant: every 4 months
4. 4th year post-transplant: every 6 months
5. 5th year: Once

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

Three studies have been published that attempt to use gene expression profiling of blood samples to detect rejection in cardiac transplant patients. Schoels et al. in 2004 collected 58 blood samples from 44 patients. The blood samples included 32 with < ISHLT grade 2 rejection and 26 with \geq ISHLT grade 2 rejections. The authors used rt-PCR to amplify 39 candidate genes selected for analysis based on their suspected association with transplant rejection. Discriminate analysis identified 5 gene products that discriminated between grade \geq 2 rejection and grade < 2 rejection. The optimal cutoff led to a sensitivity of 82% and specificity of 84%; no cross-validation was reported.

Horowitz et al. biopsied 409 endomyocardial samples from 189 transplant patients, of which 81% showed no evidence of allograft rejection (ISHLT grades 0, 1A, or 1B) and 6% showed clinically significant rejection (\geq grade 3A). Of these, blood samples from 7 patients with \geq grade 3A rejection (rejection) and 7

Genetic Testing Policies, Continued

Gene Expression Profiling for Monitoring Acute Rejection in Cardiac Transplant Patients (ALLOMAP), continued

patients with grade 0 or 1A rejection (controls). Using an Affymetrix microarray with 22,215 transcripts, the investigators initially identified 91 candidate gene products that differentiated between rejection and controls. Of these, 40 transcripts representing 30 unique gene products maximally differentiated between rejection and non-rejection. Validation of the 91 candidate gene markers involved 7 additional rejection patients who underwent augmented immunosuppressive resulting in resolution of rejection to ≤ grade 2. The change in these gene markers before and after therapy was consistent with a response to immunosuppressive therapy.

Deng et al. reported on the results of the CARGO study, which formed the basis of the AlloMap test. This study involved several phases that identified and validated candidate genes that discriminate between rejection and quiescence. The gene discovery phase used a custom microarray of 7,370 gene sequences to identify 97 candidate genes in 285 samples, 98 cardiac transplant patients. The investigators used rt-PCR in 145 samples (36 rejections; 109 quiescent samples) to further refine that number to 68 genes that distinguished between rejection and quiescent samples (ISHLT grade ≥ 3A vs. grade 0). A discriminant function equation yielded a group of 11 genes (5 from the gene discovery phase and 6 from the literature) that best distinguished between rejection and quiescence.

The primary validation involved 63 samples (63 patients not included in the first phases of the study). The secondary validation included these 63 samples (31 grade ≥ 3A; 32 grade 0) and an additional 184 samples, 30 of which were also used in the gene discovery phase. Using a prospectively defined score ≥ 20 as the rejection threshold, the test had a sensitivity of 84% (95% CI 66%–94%) and a specificity of 38% (95% CI 22%–56%). The secondary validation study yielded similar results (sensitivity 76%, specificity 41%). The authors also noted that time since transplant was highly correlated with AlloMap scores and suggested a cutoff of 28 at ≥ 6 months and 30 for ≥ 1-year post-transplant.

The authors also conducted a prevalence population study to determine the predictive value of test results in a population that more closely represented the distribution of patients likely to be encountered in clinical practice (the initial study phases over-sampled for rejection). This validation sample included samples from 166 patients ≥ 1-year post-transplant. These included 160 (56.9%) grade 0 samples, 68 (24.1%) grade 1A, 23 (8.1%) grade 1B, 21 (7.4%) grade 2, and 9 (3.2%) grade ≥ 3A, a distribution representative of the entire CARGO database. At a threshold of 30, the positive predictive value was 6.8% while the negative predictive value was 99.6%.

Evans et al. assessed economic implications of using the AlloMap test for monitoring cardiac transplant patients relative to endomyocardial biopsy. Their analysis examined the outpatient costs of biopsy and did not include costs for hospitalization and right heart catheterization. They estimated average reimbursement for biopsy to range from \$3,581 and \$4,140. Their analysis further assumed a roughly 60% reduction in the number of routine biopsies performed during the first-year post-transplant, replaced by AlloMap testing; 20% of AlloMap tests would be followed by a biopsy. In years 2–5 post-transplant, the number of routine biopsies per year is reduced by 80% with approximately 20% follow-up biopsies. The price of AlloMap testing was estimated at \$2950. Using these parameters, Evans et al. assumed a per patient savings between \$4,193 and \$6,511 over 5 years. They estimated an annual savings to U.S. health insurers of approximately \$12 million.

The last study by Yamani et al. evaluated the validity of AlloMap test results in patients with transplant vasculopathy. The authors found that patients with vasculopathy had higher AlloMap scores than control patients. The authors conclude that prospective studies are needed to determine the predictive capacity of the AlloMap test in identifying patients at risk for transplant vasculopathy without concomitant transplant rejection.

The primary weakness in this literature is a lack of prospective research to examine the predictive utility of the AlloMap test in clinical populations. The primary study of this test (Deng et al.) used multiple overlapping patient samples and suggests the test has poor positive predictive value in clinical populations. The negative predictive value is high (99.6%), though, it should be noted that if the test had classified all the samples in this study as negative, the negative predictive value would be 96.8%. In other words, because of the low prevalence of biopsy-proven rejection, a negative AlloMap test contributes only a small amount of negative predictive value to the evaluation.

A 2006 evaluation by the California Technology Assessment forum further noted that none of the 11 genes used for the AlloMap test match the genes identified by Horowitz et al. or Schoels et al., which raises concerns about the ability to generalize this particular gene set to other cardiac transplant

Genetic Testing Policies, Continued

Gene Expression Profiling for Monitoring Acute Rejection in Cardiac Transplant Patients (ALLOMAP), continued

populations. Moreover, the time-dependent cutoffs proposed by the authors also require additional validation. Finally, the Yamani et al. study highlights the complexities of interpreting AlloMap findings in light of multiple clinical factors, the effect of which on AlloMap scores have not been adequately reported in the literature. At a minimum, a validation study in an independent population would increase confidence in the predictive utility of AlloMap test results. More informative, would be a prospective randomized controlled trial in which the utility of AlloMap and cardiac biopsy could be examined.

Due to the FDA approval of the AlloMap test a re-review of the literature was undertaken in October 2008. This review identified an ongoing prospective, randomized clinical trial (also multicenter, non-blinded), the Invasive Monitoring Attenuation Through Gene Expression (IMAGE) trial: "... designed to test the hypothesis that a primarily non-invasive rejection surveillance strategy utilizing GEP testing is not inferior to an invasive EMB-based strategy with respect to cardiac allograft dysfunction, rejection with hemodynamic compromise (HDC) and all-cause mortality."

All previous studies are retrospective, case-control studies. In this regard: "... the limitations of a case-control study design restricts the clinical and causal conclusions one can make." Mehra also states that: "... we call for validation [of AlloMap] within the context of randomized intervention trials that seek to study conventional surveillance vs. gene expression profiling-based patient management in the early time-period after transplantation. Additionally, Deng et al. state that: "... additional clinical experience is needed to establish the role of molecular testing for clinical event prediction and immunosuppression management."

Also, there have been additional publications reflecting the continued questions and concerns about the value and use of endomyocardial biopsies. Hamour et al. for example, suggests that the "frequency of such biopsies should be reevaluated in light of their low yield with current immunosuppression." These conclusions are supported by multiple other studies. The recent trend away from protocol-based EMBs, independent of the introduction of the AlloMap test, reflects the recognition that the benefits of the procedure have moved toward parity with its risks, especially after the first year.

A technology assessment performed in July 2010 identified a new article by Pham et al. presenting their data from the IMAGE trial. This was a prospective, randomized non-blinded study utilizing AlloMap in patients with a recent cardiac transplantation to assess rejection post-transplant (> 6 months). This study compares outcomes between the standard of care approach, endomyocardial biopsy and gene expression testing. Primary outcomes were defined as: 1) rejection with hemodynamic compromise; 2) graft dysfunction due to other causes; 3) death; or 4) retransplantation.

Statistical analysis required a 95% confidence interval to satisfy a non-inferiority position for gene-expression testing. Key aspects of the study showed primary outcomes were fewer in the genetic expression group, 14.5% vs. 15.3%, biopsy frequency was 0.5 vs. 3.0 per patient year in favor of the gene expression group and death from any cause was more frequent in the gene expression group, 6.3% vs. 5.5%. The authors concluded that gene expression testing decreases the complications and frequency of endomyocardial biopsy without jeopardizing risk of rejection or all-cause mortality. Their assumptions were tempered by numerous design concerns of the protocol and results of the study.

The study was biased; physicians could determine which patients could be enrolled. Only 20% of the initial candidates eventually became randomized. This raises the concern that the patient selection favored patients with less risk of rejection. This would favor the gene expression arm of the study due to AlloMap's high negative predictive value. The study also included patients with inherent low risk. The criteria for "low risk" were not fully described in the study, thus, making it difficult for physicians to determine how this test would be utilized in clinical situations.

Patients with antibody mediated rejection were excluded from the study, yet an estimated 15%-40% of transplant recipients will experience a form of antibody mediated rejection. How this influenced the outcome of the study is unclear.

The study only included patients 6 months post-transplant. The literature demonstrates the dramatic increase risk of cellular rejection in the first 6 months and the dramatic decrease in rejection after 24 months post-transplant. Endomyocardial biopsy which may detect rejection prior to physical or echocardiographic changes of rejection would still be required early post-transplant. Discouraging, is the result that of all the patients in the gene expression group who underwent an endomyocardial biopsy, most had a biopsy done due to physical findings of echo findings (28/34) and not due to the genetic

Genetic Testing Policies, Continued

Gene Expression Profiling for Monitoring Acute Rejection in Cardiac Transplant Patients (ALLOMAP), continued

expression score. The use of AlloMap during the first 6 months would not help determine early rejection if used alone in the clinical assessment.

Rejection rates varied among the groups. Eighty-one discrete rejection episodes occurred. Fifty-nine percent of the rejections in the gene expression group were detected by overt heart failure on clinical exam or by echo. Only 18% of rejection episodes were detected by gene expression alone. This compared with the rate of 47% in the endomyocardial biopsy group who were asymptomatic. This observation illustrates not necessarily the non-inferior status for gene expression testing but raises the concern that studies are needed to address the current protocol for monitoring post-transplant patients. Treating only those with clinical or echocardiographic findings of worsening cardiac function should be treated. This raises the issue of overly aggressive treatment of rejection since those in the gene expression group undoubtedly had silent rejection but were not treated and yet did well without an increase in rejection.

In an editorial by Jarcho, he states: "This observation suggests that, even if rejection is not identified until graft dysfunction is present, the clinical outcomes may not be substantially worse than when rejection is detected early. Perhaps it is time to perform a randomized trial that compares a strategy for continuing endomyocardial biopsies indefinitely with that of discontinuing routine endomyocardial biopsies at some specified interval."

Finally, the wide confidence interval allows for extreme statistical variability. The trials reduced power was reflected in a relatively wide confidence interval that does not exclude the possibility of a 33% decrease in primary event rates or a 68% increase among patients in the gene-profiling group. This troubling analysis raises serious questions about the reliability of AlloMap despite its 99.2% negative predictive value seen in the CARGO trial. The poor sensitivity of AlloMap is reflected in that 54% of patients who tested above the 34-value (positive test) had no evidence of rejection.

Several positive aspects of the IMAGE trial were the improved quality of life perceived by the patients enrolled in the gene expression group and the associated decrease in complications and costs due to the reduction in endomyocardial biopsies associated with the use of gene expression testing.

A review article by Lipshultz et al, published in 2014 covers the use of AlloMap in acute rejection monitoring. It stated that current practice entails use of the test in patients 15 years of age or older. This is also the age of use referred to in the International Society of Heart and Lung Transplantation (ISHLT) Guidelines from 2010 (Rogers et al., 2010) for use of Allomap. AlloMap scores in patients less than age 15 years remain to be validated.

A review of the literature in mid-2016 found one publication presenting the results of the CARGO II study on gene expression profiling (GEP) in cardiac rejection surveillance (Crespo-Leiro et al., 2016) to further clinically validate GEP. The results based on 938 biopsies continue to show high negative predictive value and low positive predictive value (due to the rarity of rejection) confirming previous studies.

Billing/Coding Information

Covered: For the conditions outlined above

CPT CODES

0018M	Transplantation medicine (allograft rejection, renal), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score
0055U	Cardiology (heart transplant), cell-free DNA, PCR assay of 96 DNA target sequences (94 single nucleotide polymorphism targets and two control targets), plasma
0087U	Cardiology (heart transplant), mRNA gene expression profiling by microarray of 1283 genes, transplant biopsy tissue, allograft rejection and injury algorithm reported as a probability score
0118U	Transplantation medicine, quantification of donor-derived cell-free DNA using whole genome next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA in the total cell-free DNA
81479	Unlisted molecular pathology procedure

Genetic Testing Policies, Continued

Gene Expression Profiling for Monitoring Acute Rejection in Cardiac Transplant Patients (ALLOMAP), continued

- 81560** Transplantation medicine, measurement of donor and third party-induced CD154+T-cytotoxic memory cells
- 81595** Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subtraction of peripheral blood, algorithm reported as a rejection risk score

HCPCS CODES

No specific codes identified

Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
12/6/23	For Commercial Plan Policy, removed previous Exclusion#1: "Patients < 7 calendar months or > 5 years after heart transplantation."
1/20/25	For Commercial Plan Policy, added the following language to coverage criteria as an option for qualifying for this testing: "Select Health covers genetic expression profiling for monitoring acute rejection in cardiac transplant patients using the AlloMap when ordered by an Intermountain Health Transplant Provider or Intermountain Health Cardiovascular Provider ; or when the following criteria are met ..."

Key References

1. AlloMap Molecular Expression Testing. 510(k) Substantial Equivalence Determination Decision Summary Assay And Instrument Combination Template.
2. Avello, N, Molina, BD, Llorente, E, et al. (2007). N-terminal pro-brain natriuretic peptide as a potential non-invasive marker of cardiac transplantation rejection. Ann Clin Biochem 44 Pt 2: 182-8.
3. Bernstein, D, Williams, GE, Eisen, H, et al. (2007). Gene expression profiling distinguishes a molecular signature for grade 1B mild acute cellular rejection in cardiac allograft recipients. J Heart Lung Transplant 26.12: 1270-80.
4. CareDx Inc. AlloMap Heart. Available: <https://caredx.com/products-and-services/transplant-services/heart/allomap/>. Date Accessed: February 15, 2024.
5. Crespo-Leiro, M. G., J. Stypmann, U. Schulz, A. Zuckermann, P. Mohacsi, C. Bara, H. Ross, J. Parameshwar, M. Zakliczynski, R. Fiocchi, D. Hoefer, M. Colvin, M. C. Deng, P. Leprince, B. Elashoff, J. P. Yee and J. Vanhaecke (2016). "Clinical usefulness of gene-expression profile to rule out acute rejection after heart transplantation: CARGO II." Eur Heart J.
6. Deng MC, Eisen HJ, Mehra MR, et al. (2006). Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. Am J Transplant 6.1: 150-60.
7. Deng MC. (2017). The AlloMap™ genomic biomarker story: 10 years after. Clin Transplant. 31(3).
8. Dixon V, Macauley C, Burch M, Sebire NJ. (2007). Unsuspected rejection episodes on routine surveillance endomyocardial biopsy post-heart transplant in paediatric patients. Pediatr Transplant 11.3: 286-90.
9. Eisen, H.J. Heart transplantation in adults: Diagnosis of allograft rejection. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Available: <https://www.uptodate.com/contents/heart-transplantation-in-adults-diagnosis-of-allograft-rejection> - Date Accessed: February 15, 2024.
10. Evans RW, Williams GE, Baron HM, et al. (2005). The economic implications of noninvasive molecular testing for cardiac allograft rejection." Am J Transplant 5.6: 1553-8.
11. Hamour, IM, Burke, MM, Bell, AD, et al. (2008). Limited utility of endomyocardial biopsy in the first year after heart transplantation. Transplantation 85.7: 969-74.
12. Horwitz PA, Tsai EJ, Putt ME, et al. (2004). Detection of cardiac allograft rejection and response to immunosuppressive therapy with peripheral blood gene expression. Circulation 110, 25: 3815-21.
13. Intermountain Heart Institute. Heart Transplant. Intermountain Health. Available: <https://intermountainhealthcare.org/services/heart-care/heart-institute/our-medical-services-and-specialties/heart-failure-transplant-artificial-heart-programs/heart-transplant/> - Date Accessed: February 15, 2024,
14. Jarcho, JA. (2010). Fear of rejection—monitoring the heart-transplant recipient. N Engl J Med 362.20: 1932-3.
15. Kamath M, Shekhtman G, Grogan T, et al. (2022). Variability in Donor-Derived Cell-Free DNA Scores to Predict Mortality in Heart Transplant Recipients - A Proof-of-Concept Study. Front Immunol 13:825108.
16. Kobashigawa, J., Patel, J., Babak, A., Kittleson, M., Chang, D., Czer, L. ... Esmailian, F. (2015). Randomized Pilot Trial of Gene Expression Profiling Versus Heart Biopsy in the First Year After Heart Transplant Early Invasive Monitoring Attenuation Through Gene Expression Trial. Circ Heart Fail, 8:557–564. doi: 10.1161/CIRCHEARTFAILURE.114.001658

Genetic Testing Policies, Continued

Gene Expression Profiling for Monitoring Acute Rejection in Cardiac Transplant Patients (ALLOMAP), continued

17. Kobashigawa J., et al., Results of a Randomized Trial of Allomap vs Heart Biopsy in the 1st Year after Heart Transplant: Early Invasive Monitoring Attenuation through Gene Expression Trial. *The Journal of Heart and Lung Transplantation*, 2013. 32(4, Supplement): p. S203.
18. Levi DS, DeConde AS, Fishbein MC, et al. (2004). "The yield of surveillance endomyocardial biopsies as a screen for cellular rejection in pediatric heart transplant patients. *Pediatr Transplant* 8.1: 22-8.
19. Lipshultz, S. E., et al. (2014). "Issues in solid-organ transplantation in children: translational research from bench to bedside." *Clinics (Sao Paulo)* 69 Suppl 1: 55-72.
20. Marboe CC, Billingham M, Eisen H, et al. (2005). Nodular endocardial infiltrates (Quilty lesions) cause significant variability in diagnosis of ISHLT Grade 2 and 3A rejection in cardiac allograft recipients." *J Heart Lung Transplant* 24.7 Suppl: S219-26.
21. Mehra MR, Kobashigawa JA, Deng MC, et al. (2007). Transcriptional signals of T-cell and corticosteroid-sensitive genes are associated with future acute cellular rejection in cardiac allografts. *J Heart Lung Transplant* 26.12: 1255-63.
22. Mehra, MR, Kobashigawa, JA, Deng, MC, et al. (2008). Clinical implications and longitudinal alteration of peripheral blood transcriptional signals indicative of future cardiac allograft rejection. *J Heart Lung Transplant* 27.3: 297-301.
23. Morgan, A, Shulzhenko, N, Perez-Diez, A, et al. (2006). Molecular profiling improves diagnoses of rejection and infection in transplanted organs. *Circ Res* 98.12: e74-83.
24. Moayedi Y, Forutan F, Miller RJH, et al. (2019). Risk evaluation using gene expression screening to monitor for acute cellular rejection in heart transplant recipients. *J Heart Lung Transplant* 38(1):51-58.
25. Pham, MX, Teuteberg, JJ, Kfoury, AG, et al. (2010). Gene-expression profiling for rejection surveillance after cardiac transplantation. *N Engl J Med* 362.20: 1890-900.
26. Schoels M, Dengler TJ, Richter R, Meuer SC, Giese T. (2004). Detection of cardiac allograft rejection by real-time PCR analysis of circulating mononuclear cells. *Clin Transplant* 18.5: 513-7.
27. Starling RC, Pham M, Valentine H, et al. (2006). Molecular testing in the management of cardiac transplant recipients: initial clinical experience. *J Heart Lung Transplant* 25.12: 1389-95.
28. Velleca A, et al. (2023). "The International Society of Heart and Lung Transplantation (ISHLT) Guidelines for the care of heart transplant recipients." *J Heart Lung Transplant* 42(5): e1-e141.
29. Wagner K, Oliver MC, Boyle GJ, et al. (200). Endomyocardial biopsy in pediatric heart transplant recipients: a useful exercise? (Analysis of 1,169 biopsies). *Pediatr Transplant* 4.3: 186-92.
30. Yamani MH, Taylor DO, Haire C, Smedira N, Starling RC. (2007). "Post-transplant ischemic injury is associated with up-regulated AlloMap gene expression. *Clin Transplant* 21.4: 523-5.
31. Yamani MH, Taylor DO, Rodriguez ER, et al. (2007). Transplant vasculopathy is associated with increased AlloMap gene expression score. *J Heart Lung Transplant* 26.4: 403-6.

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENE EXPRESSION PROFILING: CUTANEOUS MALIGNANCIES

Policy # 667

Implementation Date: 7/1/23

Review Dates: 7/11/24, 8/6/24

Revision Dates: 9/1/23, 7/22/24, 9/3/24

Related Medical Policies:

[#680: Gene Expression Profiling: Uveal Melanomas](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Cutaneous malignancies (skin cancers) are more common than all other cancers combined, and, collectively, their incidence is rising faster than that of any other cancer.

Cutaneous melanoma (CM) is a malignant tumor formed from pigment-producing cells called melanocytes. This type of skin cancer has highest mortality rate and has demonstrated a rising incidence over the last several decades. Data provided by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program estimate that there were 97,610 new melanoma cases in the United States in 2023, a nearly three-fold increase in the rate of new cases per 100,000 people per year since 1975. It is now the fifth most common newly diagnosed cancer in the United States, representing 5% of all new cancer cases.

Cutaneous squamous cell carcinoma (CSCC), also known as squamous cell carcinoma (SCC), is a type of skin cancer that starts in the epidermis, or outer layer of the skin. It is the second most common form of skin cancer, after basal cell carcinoma. While the prognosis of cutaneous squamous cell carcinoma (SCC) is generally favorable, an estimated 6% of the greater than 1,000,000 cases diagnosed annually develop regional or distant metastasis, with approximately 2% dying from this disease.

Gene expression profile (GEP) tests aim to provide more accurate prognostication based on an individual patient's own tumor tissue. Several GEP-based tests are currently available and are used in some situations for the clinical management and prognostication of CM and SCC in the absence of high-quality prospective clinical trials. In addition to identifying targets for treatment, gene expression profiling (GEP) also allows for the identification of groups of genes that when expressed together as a "signature" can serve as a biomarker for the prognosis of certain cancers, including predicting recurrence or metastatic risk.

GEP brings us closer to understanding tumors on an individual basis, and to tailoring treatment and surveillance to a specific tumor rather than using generalizations. As such, there are innumerable efforts in this arena to better understand and optimize the use of GEP in clinical decision making. It is important to recognize that currently, neither the American Academy of Dermatology (AAD) nor the National Comprehensive Cancer Network (NCCN) endorse GEP testing. Randomized clinical trials that study patient outcomes based on the results of GEP tests are not yet available, and it remains unclear how these tests should best be interpreted and utilized in clinical practice.

Genetic Testing Policies, Continued

Gene Expression Profiling: Cutaneous Malignancies, continued

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when recommended by a genetic counselor, medical geneticist, or other provider with recognized expertise in this area; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers DecisionDx-Melanoma for either of the following indications (3 or 4):

3. Patients with T1a-HR*, T1b, T2a or T2b melanoma**/** to guide sentinel lymph node biopsy (SLNB) decisions; **OR**
4. Patients with clinical or pathological Stage I or II melanoma to inform subsequent follow-up imaging, screening frequency, referrals and/or additional management protocols.

Select Health does not cover the myPath Melanoma test or non-invasive gene expression tests (e.g., DermTech Pigmented Lesion Assay) in the evaluation of cutaneous melanomas, as there is a lack of evidence available in peer-reviewed literature which would support either sufficient sensitivity or specificity that would be necessary in defining a valid clinical role. This meets the plan's definition of experimental/investigational.

Select Health does not cover the DecisionDx-SCC in the evaluation of squamous cell carcinoma, as there is a lack of evidence available in peer-reviewed literature which would support either sufficient sensitivity or specificity that would be necessary in defining a valid clinical role. This meets the plan's definition of experimental/investigational.

*HR (High Risk) - includes melanomas with an elevated mitotic rate, young patient age, regression, a transected base (where the true depth of the melanoma is not known), limited sampling of a larger lesion.

****Table 1 – UpToDate, AJCC 8th edition melanoma TNM definitions**

Primary tumor (T)	Thickness	Ulceration status
TX: Primary tumor thickness cannot be assessed (eg, diagnosis by curettage)	Not applicable	Not applicable
T0: No evidence of primary tumor (eg, unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma <i>in situ</i>)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration

Genetic Testing Policies, Continued

Gene Expression Profiling: Cutaneous Malignancies, continued

	0.8 to 1 mm	With or without ulceration
T2	>1 to 2 mm	Unknown or unspecified
T2a	>1 to 2 mm	Without ulceration
T2b	>1 to 2 mm	With ulceration
T3	>2 to 4 mm	Unknown or unspecified
T3a	>2 to 4 mm	Without ulceration
T3b	>2 to 4 mm	With ulceration
T4	>4 mm	Unknown or unspecified
T4a	>4 mm	Without ulceration
T4b	>4 mm	With ulceration

***Table 2 – UpToDate, AJCC 8th edition melanoma TNM prognostic stage groups

When T is...	And N is...	And M is...	Then the clinical stage group is...
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [http://www.cms.gov/medicare-coverage-database/manuals/](#)

Genetic Testing Policies, Continued

Gene Expression Profiling: Cutaneous Malignancies, continued

SELECT HEALTH COMMUNITY CARE (MEDICAID)

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Billing/Coding Information

CPT CODES

0314U Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 35 genes (32 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (i.e., benign, intermediate, malignant)

81479 Unlisted molecular pathology procedure

81529 Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis; Decision Dx

81599 Unlisted multianalyte assay with algorithmic analysis

84999 Unlisted chemistry procedure

Not covered for the indications listed above

0315U Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (i.e., Class 1, Class 2A, Class 2B)

0089U Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)

0090U Oncology (cutaneous melanoma) mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a categorical result (i.e., benign, indeterminate, or malignant)

Key References

1. Arnot, S.P., Han, G., Fortino, J., Han, D., Fowler, G., and Vetto, J.T. Utility of a 31-gene expression profile for predicting outcomes in patients with primary cutaneous melanoma referred for sentinel node biopsy. *Am J Surg.* 2021;221(6):1195-1199. doi: 10.1016/j.amjsurg.2021.03.028
2. Borman, S., Wilkinson, J., Meldi-Sholl, L. et al. Analytical validity of DecisionDx-SCC, a gene expression profile test to identify risk of metastasis in cutaneous squamous cell carcinoma (SCC) patients. *Diagn Pathol* 17, 32 (2022). <https://doi.org/10.1186/s13000-022-01211-w>
3. Dillon L.D., McPhee, M., Davidson, R.S., et al. Expanded evidence that the 31-gene expression profile test provides clinical utility for melanoma management in a multicenter study. *Curr Med Res Opin.* 2022;38(8):1267-1274. doi:10.1080/03007995.2022.2033560
4. Dubin, D.P., Dinehart, S.M., & Farberg, A.S. Level of Evidence Review for a Gene Expression Profile Test for Cutaneous Melanoma. *Am J Clin Dermatol.* 2019;20(6):763-770. doi:10.1007/s40257-019-00464-4\
5. Eggermont, A.M.M., Bellomo, D., Arias-Mejias, S.M., et al. Identification of stage I/IIA melanoma patients at high risk for disease relapse using a clinicopathologic and gene expression model. *Eur J Cancer.* 2020;140:11-18. doi: 10.1016/j.ejca.2020.08.029
6. Gastman, B.R., Zager, J.S., Messina, J.L., et al. Performance of a 31-gene expression profile test in cutaneous melanomas of the head and neck. *Head Neck.* 2019;41(4):871-879. doi:10.1002/hed.25473
7. Gastman, B.R., Gerami, P., Kurley, S.J., Cook, R.W., Leachman, S., & Vetto, J.T. Identification of patients at risk of metastasis using a prognostic 31-gene expression profile in subpopulations of melanoma patients with favorable outcomes by standard criteria. *J Am Acad Dermatol.* 2019;80(1):149-157.e4. doi: 10.1016/j.jaad.2018.07.028
8. Greenhaw, B.N., Covington, K.R., Kurley, S.J., et al. Molecular risk prediction in cutaneous melanoma: A meta-analysis of the 31-gene expression profile prognostic test in 1,479 patients. *J Am Acad Dermatol.* 2020;83(3):745-753. doi: 10.1016/j.jaad.2020.03.053

Genetic Testing Policies, Continued

Gene Expression Profiling: Cutaneous Malignancies, continued

9. Grossman, D., Kim, C. C., Hartman, R. I., Berry, E., Nelson, K. C., Okwundu, N., Curiel-Lewandrowski, C., Leachman, S. A., & Swetter, S. M. (2019). Prognostic gene expression profiling in melanoma: necessary steps to incorporate into clinical practice. *Melanoma management*, 6(4), MMT32. <https://doi.org/10.2217/mmt-2019-0016>
10. Grossman, D., Okwundu, N., Bartlett, E.K., et al. Prognostic Gene Expression Profiling in Cutaneous Melanoma: Identifying the Knowledge Gaps and Assessing the Clinical Benefit. *JAMA Dermatol.* 2020;156(9):1004-1011. doi:10.1001/jamadermatol.2020.1729
11. Hieken, T.J., Sadurní, M.B., Quattrochi, E., et al. Using the Merlin assay for reducing sentinel lymph node biopsy complications in melanoma: a retrospective cohort study. *Int J Dermatol.* 2022;61(7):848-854. doi:10.1111/ijd.16056
12. Hsueh, E.C., DeBloom, J.R., Lee, J.H., et al. Long-Term Outcomes in a Multicenter, Prospective Cohort Evaluating the Prognostic 31-Gene Expression Profile for Cutaneous Melanoma. *JCO Precis Oncol.* 2021;5:PO.20.00119. Published 2021 Apr 6. doi:10.1200/PO.20.00119
13. Hyams, D.M., Covington, K.R., Johnson, C.E., Plasseraud, K.M., & Cook, R.W. Integrating the melanoma 31-gene expression profile test with surgical oncology practice within national guideline and staging recommendations. *Future Oncol.* 2021;17(5):517-527. doi:10.2217/fon-2020-0827
14. Jarell, A., Skenderis, B., Dillon, L.D., et al. The 31-gene expression profile stratifies recurrence and metastasis risk in patients with cutaneous melanoma. *Future Oncol.* 2021;17(36):5023-5031. doi:10.2217/fon-2021-0996
15. Keller, J., Schwartz, T.L., Lizalek, J.M., et al. Prospective validation of the prognostic 31-gene expression profiling test in primary cutaneous melanoma. *Cancer Med.* 2019;8(5):2205-2212. doi:10.1002/cam4.2128
16. Marchetti, M.A., Coit, D.G., Dusza, S.W., et al. Performance of Gene Expression Profile Tests for Prognosis in Patients With Localized Cutaneous Melanoma: A Systematic Review and Meta-analysis. *JAMA Dermatol.* 2020;156(9):953-962. doi:10.1001/jamadermatol.2020.1731
17. Martin, B.J., Covington, K.R., Quick, A.P., & Cook, R.W. Risk Stratification of Patients with Stage I Cutaneous Melanoma Using 31-Gene Expression Profiling. *J Clin Aesthet Dermatol.* 2021;14(9): E61-E63.
18. Sun, J., Karasaki, K. M., & Farma, J. M. (2024). The Use of Gene Expression Profiling and Biomarkers in Melanoma Diagnosis and Predicting Recurrence: Implications for Surveillance and Treatment. *Cancers*, 16(3), 583. <https://doi.org/10.3390/cancers16030583>
19. Vetto, J.T., Hsueh, E.C., Gastman, B.R., et al. Guidance of sentinel lymph node biopsy decisions in patients with T1-T2 melanoma using gene expression profiling. *Future Oncol.* 2019;15(11):1207-1217. doi:10.2217/fon-2018-0912
20. Whitman, E.D., Koshenkov, V.P., Gastman, B.R., et al. Integrating 31-Gene Expression Profiling With Clinicopathologic Features to Optimize Cutaneous Melanoma Sentinel Lymph Node Metastasis Prediction. *JCO Precis Oncol.* 2021;5:PO.21.00162. Published 2021 Sep 13. doi:10.1200/PO.21.00162
21. Yousaf, A., Tjen-Fooh, F.J., Rentoia-Pacheco, B., et al. Validation of CP-GEP (Merlin Assay) for predicting sentinel lymph node metastasis in primary cutaneous melanoma patients: A U.S. cohort study. *Int J Dermatol.* 2021;60(7):851-856. doi:10.1111/ijd.15594

Revision History

Revision Date	Summary of Changes
9/1/23	For Commercial Plan Policy, added the DermTech Pigmented Lesion Assay to list of excluded tests.
7/22/24	For Commercial Plan Policy, added coverage criteria for the Decision DX-Melanoma test.
9/3/24	Modified title of policy to include broader term of "Cutaneous Malignancies" whereas previously was just "Cutaneous Melanomas" – and added the DecisionDx-SCC in the evaluation of squamous cell carcinoma as an excluded test.

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Genetic Testing Policies, Continued

Gene Expression Profiling: Cutaneous Malignancies, continued

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MEDICAL POLICY

GENE EXPRESSION PROFILING: UVEAL MELANOMAS

Policy # 680

Implementation Date: 3/8/24

Review Dates:

Revision Dates:

Related Medical Policies:

[#667: Gene Expression Profiling: Cutaneous Melanomas](#)

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Uveal melanoma is a rare malignancy that arises from melanocytes within the uveal tract of the eye, which includes the iris, ciliary body, and choroid. Uveal melanoma comprises approximately 85 percent of all ocular melanomas, with the remainder arising mostly from the conjunctiva (5 percent) or other sites (10 percent).

The molecular pathogenesis of uveal melanoma is distinct from that of cutaneous melanoma and other melanoma subtypes, including conjunctival melanoma. Uveal melanomas usually harbor specific initiating mutations in GNAQ, GNA11, or other members of the G protein alpha subunit signaling pathway, as well as secondary driver mutations with prognostic significance in genes such as BAP1, SF3B1, and EIF1AX.

Patients with metastatic uveal melanoma should have their tumors assessed using next generation sequencing (NGS) or gene expression profiling. While molecular alterations that are targetable for treatment are limited in uveal melanoma, some alterations may offer insights into prognosis as well as clinical trial options.

COMMERCIAL PLAN POLICY/CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request

1. Select Health covers genetic testing when recommended by a genetic counselor, medical geneticist, or other provider with recognized expertise in this area; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health considers gene expression profiling for patients with a diagnosis of primary, localized uveal melanoma to be medically necessary; one test per diagnosis.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

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Genetic Testing Policies, Continued

Gene Expression Profiling: Uveal Melanomas, continued

please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Billing/Coding Information

CPT CODES

Covered when the above criteria are met

- 81552** Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RTPCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis

Key References

1. Carvajal, R. D., & Harbour, J. W. Metastatic uveal melanoma. *UpToDate*. Last updated: Nov 03, 2023.

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENE EXPRESSION TESTING FOR INDETERMINATE THYROID NODULE BIOPSY

Policy # 538

Implementation Date: 8/13/13

Review Dates: 10/15/15, 10/20/16, 12/19/18, 10/15/20, 11/18/21, 9/12/22, 3/14/23, 6/12/24

Revision Dates: 10/13/14, 1/30/17, 1/25/18, 2/28/18, 8/7/18, 1/29/21, 10/24/22, 7/1/23, 7/15/24

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Description

A thyroid nodule is an abnormal structure that is anatomically distinct from the surrounding thyroid parenchyma. Thyroid nodules can be visible or palpable when they are big enough or superficially located; however, most nodules are found incidentally on an imaging study performed for a different purpose. Nodules may be single or multiple and may occur with or without symptoms of thyroid hormone excess or deficiency. Most thyroid nodules are benign, but they may be malignant in 5% to 15% of cases. The primary objective of the evaluation of a thyroid nodule is to determine whether the nodule is benign or malignant; the secondary objective is to determine whether the nodule is associated with thyroid dysfunction.

The prevalence of thyroid nodules varies depending on the population studied and is estimated at 2% to 6% with palpation, 19% to 35% with ultrasonography and 8% to 65% at autopsy. Nodules are found up to six times more often in women, based on clinical examination, with smaller differences when imaging is used. The rates of malignancy in nodules are higher in men.

Ruling out malignancy in thyroid nodules historically depended on thyroid resection and histopathological evaluation until fine needle aspiration (FNA). Thyroid FNA biopsy identified most thyroid nodules as benign, obviating the need for surgery in over half of the patients. However, 15%–30% of thyroid FNAs yields an indeterminate cytological interpretation that leads to surgical biopsy, even though most of these biopsied nodules prove to be benign. These indeterminate nodules harbor an approximate 24% risk of malignancy; too high to ignore but driving surgery where most nodules are benign. FNA is the preferred technique for obtaining thyroid follicular cells from thyroid nodules in the office setting. Cytopathologic examination of these cells provides the best information available, short of surgical excision, to assess whether a nodule is benign or malignant.

Several genetic testing panels, also known as molecular markers, have been developed to improve diagnosis of thyroid FNA. These include the Afirma Gene Sequencing Classifier (GSC) test (Veracyte, Inc., South San Francisco, CA) and the ThyroSeq Gene Classifier (GC) test (Sonic Healthcare, USA), which tests have been developed and can be run on the FNA sample to predict which cytologically indeterminate thyroid nodules are benign and to potentially avoid surgery on these nodules. These tests assess PAX8-PPAR γ translocation, PPAR γ -CREB $_1$ L $_2$ fusions, RAS mutations, LGALS $_3$ expression, BRAF mutations, RET-PTC rearrangements, PCSK $_2$ CCDN $_2$ and PLAB expression and TFF $_3$ expression among other abnormalities have all been associated with thyroid cancer with varying degrees of evidence; in recent years the positive predictive value (PPV) and specificity for these tests has increased substantially.

The Afirma Thyroid FNA Analysis combines specialized cytopathology (if requested) and the novel Afirma GSC Physicians submit to Veracyte thyroid nodule FNA samples collected in a single patient visit. Alternatively, an FNA sample is submitted for GSC alone only after a local cytopathologist has made a diagnosis of a Bethesda 3 or 4 nodule. Then, a thyroid cytopathology specialist at Thyroid Cytopathology



Genetic Testing Policies, Continued

Gene Expression Testing for Indeterminate Thyroid Nodule Biopsy, continued

Partners (TCP), an independent partner of Veracyte, performs cytopathology assessment of a thyroid nodule FNA sample under the microscope. If the cytopathology diagnosis is benign or malignant, the analysis is complete. Only when TCP's cytopathology diagnosis is indeterminate (a recent study showed TCP's indeterminate rate to be 16%) is the proprietary Afirma GSC performed. ThyroSeq GC is also based on next-generation sequencing of DNA and RNA. However, it is expanded to analyze 112 genes, providing information on > 12,000 mutation hotspots and > 120 gene fusion types. The test detects 4 classes of genetic alterations: mutations (SNVs, indels); gene fusions; gene expression alterations; and copy number variations (CNVs). The test utilizes a proprietary genomic classifier (GC) based on the algorithmic analysis of all detected genetic alterations to report the test result as positive or negative.

ThyraMIR and ThyGenX were developed in-house by Interpace Diagnostics, Inc. and are performed in a laboratory regulated by and certified under the Clinical Laboratory Improvement Amendments. ThyraMIR is a PCR-based micro-RNA (miRNA) expression classifier which evaluates the expression of 10 miRNA genes. ThyGenX performs targeted next-generation sequencing (NGS) analysis to identify over 100 genetic alterations within 5 thyroid cancer-relevant genes. The test combination has been designed to both rule out malignancy as well as confirm it if present.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers genetic testing for indeterminate thyroid nodule biopsy using the Afirma GSC test, ThyroSeq GC, or ThyGeNEXT/ThyraMIR, when criteria are met:

- A. One fine needle aspiration (FNA) of the thyroid nodule interpreted as meeting one of the Bethesda guidelines (either III or IV) listed below*

*Bethesda Guidelines:

- I. Nondiagnostic
- II. Benign – This includes macrofollicular or adenomatoid/hyperplastic nodules, colloid adenomas, nodular goiter, and Hashimoto's thyroiditis
- III. Follicular lesion or atypia of undetermined significance (FLUS or AUS) – This includes lesions with atypical cells, or mixed macro- and microfollicular nodules
- IV. Follicular neoplasm – This includes microfollicular nodules, including Hürthle cell lesions
- V. Suspicious for malignancy
- VI. Malignant

Select Health does NOT cover genetic testing using Afirma XA as current evidence is inadequate to reach conclusions on the clinical and statistical validity of these tests; this test meets the plan's definition of experimental/investigational.

Select Health does NOT cover other genetic testing for indeterminate thyroid biopsies/fine needle aspirates as current evidence is inadequate to reach conclusions on the clinical and statistical validity of these tests; these tests meet the plan's definition of experimental/investigational.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage,

Genetic Testing Policies, Continued

Gene Expression Testing for Indeterminate Thyroid Nodule Biopsy, continued

please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

Thyroid cancer is most found on routine physical examination as a palpable thyroid nodule. A fine-needle aspiration (FNA) biopsy is usually performed to rule out malignancy. In some cases, the nodules are not clearly benign or malignant based on FNA results alone. Those patients with cytologically indeterminate nodules are often referred for diagnostic surgery, though, most of these nodules turn out to be benign. The 2013 guidelines from the National Comprehensive Cancer Network (NCCN) state that: "Molecular diagnostics ... using molecular classifiers may be useful in the evaluation of FNA samples that are indeterminate." Several tests have been developed to reduce the incidence of nondiagnostic biopsy results to better guide surgical decision making. The bulk of the literature focuses on the Veracyte, Afirma test. The literature on the other genetic tests used in the evaluation of indeterminate thyroid biopsies is inadequate to draw conclusions regarding the clinical validity and clinical utility of these tests.

Afirma: No approval by the FDA is required for the Afirma analysis, as it was developed in-house by Veracyte, Inc. All tests are performed by Veracyte in their laboratory which is certified under the Clinical Laboratory Improvement Amendments.

A single study has examined the analytical validity of the Afirma analysis. Chudova and colleagues (2010) reported on the development process and performance validation of the GEC. Microarray data was generated from 178 thyroid tissue specimens representing the 8 most common types of benign and malignant lesions. Messenger RNA transcripts were used to develop a molecular classifier. After testing of the final test set, the sensitivity was determined to be 100%, and the specificity at 73.3%, to yield a negative predictive value (NPV) of 96%.

Clinical validity of the GEC was evaluated by Alexander et al. (2012) in a multicenter study of independently and prospectively collected thyroid FNA specimens. Of 3,789 samples, 265 were classified as indeterminate, had an adequate specimen for analysis, and had results of a histopathological examination, and were included in the analysis. 142 genes were used in the main GEC, which would classify the FNA samples as benign or suspicious. Of the 265 indeterminate specimens, 85 were classified as malignant after evaluation of thyroid tissue. Of these 85 specimens, 78 were correctly classified as suspicious by the Afirma® analysis for a sensitivity of 92%. There were therefore 7 incorrectly classified malignancies. Of the 180 nonmalignant samples, 93 were correctly classified as benign by the GEC for a specificity of 52%. For the entire set of test samples, the positive predictive value (PPV) and NPV was reported at 47% and 93%, respectively.

A single study by Duick et al., in 2012 has documented the impact of the Afirma FNA analysis on the management of patients with indeterminate thyroid nodules. In a retrospective, multicenter study, the researchers evaluated data from endocrinology practices that ordered the Afirma analysis for which the result was benign for at least three patients. A total of 51 endocrinologists from 21 centers reported data on a total of 368 patients. Physicians reported on their management decisions for each patient. According to the survey, surgery was performed in 28 patients with a benign GEC result; the reasons most often given for surgery was nodule size, a nodule causing symptoms of pressure, and a rapidly growing nodule. Hemithyroidectomy was performed in 19 and total thyroidectomy was recommended in 8. The percentage of patients who were operated on (7.4%) represented a significant decrease from the previously reported rate of diagnostic surgery (74%).

ThyraMIR and ThyGenX: The tests were developed in-house by Interpace Diagnostics, Inc. and are performed in a laboratory regulated by and certified under the Clinical Laboratory Improvement Amendments. No approval by the FDA is required.

Genetic Testing Policies, Continued

Gene Expression Testing for Indeterminate Thyroid Nodule Biopsy, continued

In terms of analytic validity, the methodologies used in these tests are reliable, well-known, and reproducible. ThyraMIR is a PCR-based micro-RNA (miRNA) expression classifier which evaluates the expression of 10 miRNA genes. ThyGenX performs targeted next-generation sequencing (NGS) analysis to identify over 100 genetic alterations within 5 thyroid cancer-relevant genes. The test combination has been designed to both rule out malignancy as well as confirm it, if present.

Clinical validity has been studied prospectively using a high number of samples in multiple settings. In a recent study by Labourier et al. in 2015, 638 FNA and surgical specimens were tested for 17 validated gene alterations. The molecular results were compared to surgical histopathology to determine the diagnostic accuracy. miRNA testing correctly identified 64% of malignant cases and 98% of benign cases. Negative predictive value was reported at 94%. The authors reported that the rate of avoidable diagnostic surgeries was reduced by 69%. In another study by Beaudenon et al., 2014, in a prospective, multicenter, double-blind study, 769 FNAs were evaluated. Based on the high rate of cancer detection when present, the authors concluded that the use of molecular testing decreases the rate of two-stage thyroidectomy surgeries.

Clinical utility specific to this testing has not been established and relies on the general acceptance of molecular genomic testing in avoiding unnecessary surgeries and reducing the need for two-stage surgeries.

ThyroSeq: The ThryoSeq test was developed by researchers at the University of Pittsburgh Medical Center. The available evidence for this test is not as decisive as that for the other commercially available tests, but the methodology used is established, and known to be reproducible. There is adequate validation that ThryoSeq can accurately identify point mutations in the genes and fusions in an FNA sample, facilitating treatment decisions in patients with indeterminate thyroid FNA biopsies. The latest version (ThryoSeq GC) offers detection of more than 1,000 cancer "hotspots" (single nucleotide polymorphisms, or SNPs) on 14 thyroid cancer-related genes and 42 fusion genes known to occur in thyroid cancer. In a validation study of 143 consecutive FNA samples with indeterminate diagnosis of follicular neoplasm or suspicious for follicular neoplasm, the test resulted in 104 benign nodules and 39 malignant nodules, which correlated with surgical pathology results for a 90% sensitivity, 83% positive predictive value, and negative predictive value of 96%.

Billing/Coding Information

CPT CODES

0018U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy
0026U	Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or "Negative, low probability of malignancy")
0204U	Oncology (thyroid), mRNA, gene expression analysis of 593 genes (including BRAF, RAS, RET, PAX8, and NTRK) for sequence variants and rearrangements, utilizing fine needle aspirate, reported as detected or not detected
0245U	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next-generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage
0287U	Oncology (thyroid), DNA and mRNA, next-generation sequencing analysis of 112 genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high)
0362U	Oncology (papillary thyroid cancer), gene-expression profiling via targeted hybrid capture-enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, formalin-fixed paraffin embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB,

Genetic Testing Policies, Continued

Gene Expression Testing for Indeterminate Thyroid Nodule Biopsy, continued

	PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
81479	Unlisted molecular pathology procedure
81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)

HCPCS CODES

No specific codes identified

Key References

1. Agretti, P, Ferrarini, E, Rago, T, et al. (2012). MicroRNA expression profile helps to distinguish benign nodules from papillary thyroid carcinomas starting from cells of fine-needle aspiration. *Eur J Endocrinol* 167.3: 393-400.
2. Ali, SZM, Fish, SAM, Lanman, RM, et al. (2013). Use of the Afirma(R) Gene Expression Classifier for Preoperative Identification of Benign Thyroid Nodules with Indeterminate Fine Needle Aspiration Cytopathology. *PLoS Curr* 5.
3. Alexander, EK, Kennedy, GC, Baloch, ZW, et al. (2012). Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *N Engl J Med* 367.8: 705-15.
4. American Thyroid Association Guidelines Taskforce on Thyroid, N, Differentiated Thyroid, C, Cooper, DS, et al. (2009). Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 19.11: 1167-214.
5. Aschebrook-Kilfoy, B, Schechter, RB, Shih, YC, et al. (2013). The Clinical and Economic Burden of a Sustained Increase in Thyroid Cancer Incidence. *Cancer Epidemiol Biomarkers Prev*.
6. Cerutti, JM. (2011). Employing genetic markers to improve diagnosis of thyroid tumor fine needle biopsy. *Curr Genomics* 12.8: 589-96.
7. Chen et al. The Role of the ThyroSeq v3 Molecular Test in the Surgical Management of Thyroid Nodules in the Canadian Public Health Care Setting Thyroid. Sep 2020.1280-1287.
8. Davies, L. and G. Randolph (2014). "Evidence-based evaluation of the thyroid nodule." *Otolaryngol Clin North Am* 47(4): 461-474.
9. Duick, DS, Klopper, J, Diggans, JC, et al. (2012). The Impact of Benign Gene Expression Classifier Test Results on the Endocrinologist-Patient Decision to Operate on Patients with Thyroid Nodules with Indeterminate FNA Cytopathology. *Thyroid*.
10. Endo et al. Use of Molecular Diagnostic Tests in Thyroid Nodules with Hurthle Cell-Dominant Cytology. *Thyroid* 2020, Vol 00. doi: 10.1089/thy.2020.0021
11. Ganly, I., et al., Integrated Genomic Analysis of Hurthle Cell Cancer Reveals Oncogenic Drivers, Recurrent Mitochondrial Mutations, and Unique Chromosomal Landscapes. *Cancer Cell*, 2018. 34(2): p. 256-270.e5.
12. Gharib, H, Papini, E, Paschke, R, et al. (2010). American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. *Endocr Pract* 16.3: 468-75.
13. Gopal, R.K., et al., Widespread Chromosomal Losses and Mitochondrial DNA Alterations as Genetic Drivers in Hurthle Cell Carcinoma. *Cancer Cell*, 2018. 34(2): p. 242-255.e5.
14. Gilfillan, CP. (2010). Review of the genetics of thyroid tumours: diagnostic and prognostic implications. *ANZ J Surg* 80.1-2: 33-40.
15. Hao et al. Identification of Hürthle cell cancers: solving a clinical challenge with genomic sequencing and a trio of machine learning algorithms *BMC Systems Biology* 2019, 13(Suppl 2):27 <https://doi.org/10.1186/s12918-019-0693-z>
16. Hegedus, L. (2004). Clinical practice. The thyroid nodule. *N Engl J Med* 351.17: 1764-71.
17. Hila Benjamin, MSc; Temima Schnitzer-Perlmutter, MSc; Alexander Shtabensky, MD, PhD; Christopher J. VandenBussche, MD; Syed Z. Ali, MD; Zdenek Kolar, MD, PhD; Fabio Pagni, MD; Rosetta Genomics Group; Dganit Bar, PhD; and Eti Meiri, PhD Analytical Validity of a MicroRNA-Based Assay for Diagnosing Indeterminate Thyroid FNA Smears From Routinely Prepared Cytology Slides. *Cancer Cytopathol* 2016; 124:711-21.
18. Hodak, SP, Rosenthal, DS, erican Thyroid Association Clinical Affairs, C. (2013). Information for clinicians: commercially available molecular diagnosis testing in the evaluation of thyroid nodule fine-needle aspiration specimens. *Thyroid* 23.2: 131-4.
19. Jameson, JL. (2012). Minimizing unnecessary surgery for thyroid nodules. *N Engl J Med* 367.8: 765-7.
20. Jeffrey F. Krane, MD, et al. Afirma Xpression Atlas for Thyroid Nodules and Thyroid Cancer Metastases: Insights to Inform Clinical Decision-Making from a Fine-Needle Aspiration Sample. *Cancer Cytopathology* July 2020.
21. Kloos, RT, Reynolds, JD, Walsh, PS, et al. (2013). Does addition of BRAF V600E mutation testing modify sensitivity or specificity of the Afirma Gene Expression Classifier in cytologically indeterminate thyroid nodules? *J Clin Endocrinol Metab* 98.4: E761-8.
22. Labourier, E., Shifrin, A., Busseniers, A.E., et al (2015). Molecular testing for miRNA, mRNA and DNA on fine needle aspiration improves the preoperative diagnosis of thyroid nodules with indeterminate cytology. *Journal of Clinical Endocrinology and Metabolism* [E-Pub] doi: 10.1210/jc.2015-1158.
23. Livhits MJ, Zhu CY, Kuo EJ, Nguyen DT, Kim J, Tseng CH, Leung AM, ... Levin M, ML. Beckett Effectiveness of Molecular Testing Techniques for Diagnosis of Indeterminate Thyroid Nodules: A Randomized Clinical Trial. *JAMA Oncol*. 2021 Jan 1;7(1):70-77. doi: 10.1001/jamaoncol.2020.5935. PMID: 33300952
24. Lee, K. H., et al. (2014). "Atypia of undetermined significance in thyroid fine-needle aspiration cytology: prediction of malignancy by US and comparison of methods for further management." *Ann Surg Oncol* 21(7): 2326-2331.
25. Lee, L., et al. (2014). "Cost-effectiveness of molecular testing for thyroid nodules with atypia of undetermined significance cytology." *J Clin Endocrinol Metab* 99(8): 2674-2682.

Genetic Testing Policies, Continued

Gene Expression Testing for Indeterminate Thyroid Nodule Biopsy, continued

26. Li, H, Robinson, KA, Anton, B, et al. (2011). Cost-effectiveness of a novel molecular test for cytologically indeterminate thyroid nodules. *J Clin Endocrinol Metab* 96.11: E1719-26.
27. Liebertpub.com. (2018). 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer | Thyroid. [online] Available at: <https://www.liebertpub.com/doi/full/10.1089/thy.2015.0020> [Accessed 21 May 2018].
28. Lithwick-Yanai G, et al. *J Clin Pathol* 2016;0:1–8. doi:10.1136/jclinpath-2016-204089
29. Livhitis MJ, Zhu CY, Kuo EJ, Nguyen DT, Kim J, Tseng CH, Leung AM, Rao J, Levin M, Douek ML, Beckett KR, Cheung DS, Gofnung YA, Smoake-Praw S, Yeh MW. Effectiveness of Molecular Testing Techniques for Diagnosis of Indeterminate Thyroid Nodules: A Randomized Clinical Trial. *JAMA Oncol.* 2021 Jan 1;7(1):70-77. doi: 10.1001/jamaonc.2020.5935. PMID: 33300952; PMCID: PMC7729582.
30. Mekel, M, Nucera, C, Hodin, RA, et al. (2010). Surgical implications of B-RafV600E mutation in fine-needle aspiration of thyroid nodules. *Am J Surg* 200.1: 136-43.
31. Nasr, C. (2011) Thyroid nodule. August 30, 2011. Elsevier. Available: <https://www.clinicalkey.com/#!/ContentPlayerCtrl/doPlayContent/21-s2.0-1014753/> {"scope":"all","query":"Thyroid Nodules"}. Date Accessed: July 11, 2013.
32. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in OncologyTM. Thyroid Carcinoma. v.1.2017. [cited 05/21/2018]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
33. Network, NCC. (2013) Thyroid Carcinoma. Available: NCCN.org. Date Accessed: July 26, 2013.
34. Nikiforov, Y.E., Carty, S.E., Chlosea, S.I. et al (2014) Highly accurate diagnosis of cancer in thyroid nodules with follicular neoplasm/suspicious for a follicular neoplasm cytology by ThyroSeq v.2 next-generation sequencing assay. *Cancer* 120, 3627-34.
35. Nikiforova, M.N., Wald, A.I., Roy, S. et al (2013) Targeted next-generation sequencing panel (ThyroSeq) for detection of mutations in thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* 98, E1852-60.
36. Nikiforova, et al. Analytical performance of the ThyroSeq v3 genomic classifier for cancer diagnosis in thyroid nodules. *Cancer*. 2018;124(8):1682.
37. Nishino M, Mateo R, Kilim H, Feldman A, Elliott A, Shen C, Hasselgren PO, Wang H, Hartzband P, Hennessey JV. Repeat Fine Needle Aspiration Cytology Refines the Selection of Thyroid Nodules for Afirma Gene Expression Classifier Testing. *Thyroid*. 2021 Aug;31(8):1253-1263. doi: 10.1089/thy.2020.0969. Epub 2021 Jun 22. PMID: 33813868; PMCID: PMC8377518.
38. Patel et al. Performance of a Genomic Sequencing Classifier for the Preoperative Diagnosis of Cytologically Indeterminate Thyroid Nodules *JAMA Surgery* March 2018.
39. Sarah Pearlstein,¹ Arash H. Lahouti,² Elana Opher,² Yuri E. Nikiforov,³ and Daniel B. Kurloff^{4,5} Thyroseq V3 Molecular Profiling for Tailoring the Surgical Management of Hürthle Cell Neoplasms *Case Reports in Endocrinology* 16 Jul 2018.
40. Steward DL, Carty SE, Sippel RS, et al. Performance of a Multigene Genomic Classifier in Thyroid Nodules with Indeterminate Cytology: A Prospective Blinded Multicenter Study. *JAMA Oncol.* 2019;5(2):204–212. doi:10.1001/jamaonc.2018.4616
41. Walsh, PS, Wilde, JI, Tom, EY, et al. (2012). Analytical performance verification of a molecular diagnostic for cytology-indeterminate thyroid nodules. *J Clin Endocrinol Metab* 97.12: E2297-306.
42. Ward, LS, Kloos, RT. (2013). Molecular markers in the diagnosis of thyroid nodules. *Arq Bras Endocrinol Metabol* 57.2: 89-97.
43. Veracyte. (2013) Afirma Thyroid FNA Analysis. Veracyte. Available: <http://www.veracyte.com/afirma/Overview/>. Date Accessed: July 11, 2013.

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Genetic Testing Policies, Continued

Gene Expression Testing for Indeterminate Thyroid Nodule Biopsy, continued



MEDICAL POLICY

GENE EXPRESSION TESTING FOR INDETERMINATE THYROID NODULE BIOPSY

Policy # 538

Implementation Date: 8/13/13

Review Dates: 10/15/15, 10/20/16, 12/19/18, 10/15/20, 11/18/21, 9/12/22, 3/14/23, 6/12/24

Revision Dates: 10/13/14, 1/30/17, 1/25/18, 2/28/18, 8/7/18, 1/29/21, 10/24/22, 7/1/23, 7/15/24

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

A thyroid nodule is an abnormal structure that is anatomically distinct from the surrounding thyroid parenchyma. Thyroid nodules can be visible or palpable when they are big enough or superficially located; however, most nodules are found incidentally on an imaging study performed for a different purpose. Nodules may be single or multiple and may occur with or without symptoms of thyroid hormone excess or deficiency. Most thyroid nodules are benign, but they may be malignant in 5% to 15% of cases. The primary objective of the evaluation of a thyroid nodule is to determine whether the nodule is benign or malignant; the secondary objective is to determine whether the nodule is associated with thyroid dysfunction.

The prevalence of thyroid nodules varies depending on the population studied and is estimated at 2% to 6% with palpation, 19% to 35% with ultrasonography and 8% to 65% at autopsy. Nodules are found up to six times more often in women, based on clinical examination, with smaller differences when imaging is used. The rates of malignancy in nodules are higher in men.

Ruling out malignancy in thyroid nodules historically depended on thyroid resection and histopathological evaluation until fine needle aspiration (FNA). Thyroid FNA biopsy identified most thyroid nodules as benign, obviating the need for surgery in over half of the patients. However, 15%–30% of thyroid FNAs yields an indeterminate cytological interpretation that leads to surgical biopsy, even though most of these biopsied nodules prove to be benign. These indeterminate nodules harbor an approximate 24% risk of malignancy; too high to ignore but driving surgery where most nodules are benign. FNA is the preferred technique for obtaining thyroid follicular cells from thyroid nodules in the office setting. Cytopathologic examination of these cells provides the best information available, short of surgical excision, to assess whether a nodule is benign or malignant.

Several genetic testing panels, also known as molecular markers, have been developed to improve diagnosis of thyroid FNA. These include the Afirma Gene Sequencing Classifier (GSC) test (Veracyte, Inc., South San Francisco, CA) and the ThyroSeq Gene Classifier (GC) test (Sonic Healthcare, USA), which tests have been developed and can be run on the FNA sample to predict which cytologically indeterminate thyroid nodules are benign and to potentially avoid surgery on these nodules. These tests assess PAX8-PPAR γ translocation, PPARY-CREB $_3$ L $_2$ fusions, RAS mutations, LGALS $_3$ expression, BRAF mutations, RET-PTC rearrangements, PCSK $_2$ CCDN $_2$ and PLAB expression and TFF $_3$ expression among other abnormalities have all been associated with thyroid cancer with varying degrees of evidence; in recent years the positive predictive value (PPV) and specificity for these tests has increased substantially.

The Afirma Thyroid FNA Analysis combines specialized cytopathology (if requested) and the novel Afirma GSC Physicians submit to Veracyte thyroid nodule FNA samples collected in a single patient visit. Alternatively, an FNA sample is submitted for GSC alone only after a local cytopathologist has made a diagnosis of a Bethesda 3 or 4 nodule. Then, a thyroid cytopathology specialist at Thyroid Cytopathology

Genetic Testing Policies, Continued



MEDICAL POLICY

GENE THERAPY, TESTING, AND COUNSELING

Policy # 123

Implementation Date: 7/98

Review Dates: 1/4/00, 2/27/01, 8/27/02, 1/03, 10/23/03, 11/18/04, 12/15/05, 12/20/07, 12/18/08, 11/29/12, 10/24/13, 10/23/14, 10/15/15, 10/20/16, 4/23/18, 6/20/19, 6/2/20, 5/31/21, 5/19/22, 1/31/23, 6/13/23, 8/20/24

Revision Dates: 3/8/04, 9/14/06, 6/25/07, 12/17/09, 10/21/10, 10/12/11, 6/7/17, 6/5/18, 12/5/18, 6/26/23, 8/18/23, 10/6/23, 11/27/23, 1/10/24, 5/24/24, 9/4/24, 12/12/24

Disclaimer:

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Gene Therapy

Gene therapy or gene-based therapies are any treatments which modifies a person's gene(s) to treat or cure disease. This includes technology such as plasmid DNA, viral vectors, bacterial vectors, human gene editing technology, and patient-derived cellular gene therapy products.

Genetic Testing

Genetic testing is the analysis, for clinical purposes, of human genetic material (i.e., DNA, RNA, and chromosomes), proteins, and metabolites to detect abnormalities related to an inheritable disorder or trait. There are seven categories of germline genetic testing: diagnostic, predictive/pre-symptomatic, carrier testing, pharmacogenetics, prenatal testing, newborn screening, preimplantation testing. Testing may also be done on somatic tissue to determine disease prognosis or treatment.

Genetic Counseling

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources and research.
- Counseling to promote informed choices and adaptation to the risk or condition.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.



Genetic Testing Policies, Continued

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing.

and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

I. **Select Health covers gene therapy (gene-based therapy) when the P&T committee AND the Chief Medical Officer (CMO) determine that the proposed gene therapy will affect clinical outcome.**

II. **Select Health covers genetic testing as follows when any of the following are met (A or B or C or D):**

A. **Genetic Testing for Inherited Disease:** Genetic testing to establish a diagnosis or susceptibility for an inherited condition may be **medically necessary** when all the following criteria are met:

1. Member exhibits clinical features or signs/symptoms of an inherited condition or is at significant risk of an inherited condition based on family history; and
2. Diagnostic results from physical examination, pedigree analysis, and conventional testing are inconclusive and a definitive diagnosis is uncertain; and
3. The clinical record must document:
 - i. How test results will guide decisions regarding disease treatment, prevention, or management, such as averting treatment for other possible diagnosis; and
 - ii. That the test being performed is the most appropriate according to currently accepted literature or guidelines.

OR

B. **Genetic Testing Not Related to Inherited Conditions:** Genetic testing for indications *other than* determining risk or establishing a diagnosis for a genetically inherited disease (e.g., genetic expression analysis in breast cancer) may be considered **medically necessary** when all the following criteria are met:

1. An association of the marker with the natural history of the disease has been established; and
2. The clinical records must document:
 - i. How test results will guide decisions regarding disease treatment or management; and
 - ii. That the test being performed is the most appropriate according to currently accepted literature or guidelines.

OR

C. **Familial Variant Testing:** Single gene or single variant testing is considered **medically necessary** when there is a known pathogenetic or likely pathogenic variant in a close (first, second, or third-degree) relative and test results will directly impact the individual's medical management.

1. **Select Health does not cover testing for Variants of Uncertain Significance (VUS).** This meets the plan's definition of experimental/investigational.

OR

Genetic Testing Policies, Continued

Gene Therapy, Testing, and Counseling continued

- i. Both parents are known carriers of an autosomal recessive disease; OR
- ii. At least one parent is a known carrier of an autosomal dominant, sex-linked, or mitochondrial condition; OR
- iii. At least one parent is a carrier of a balanced structural chromosome rearrangement.

Select Health will only cover preimplantation genetic testing for aneuploidy (PGT-A) when performed in concert with either preimplantation genetic testing for mutation (PGT-M) or preimplantation genetic testing for chromosome structural rearrangements (PGT-SR). Select Health does NOT cover PGT-A alone, due to a lack of sufficient evidence supporting efficacy of this testing; this meets the plan's definition of experimental/investigational.

Select Health considers duplicative genetic testing (a test with the same genetic content as a previous test) to be not medically necessary, unless sufficient clinical rationale to support the need for repeat testing is documented in the clinical notes.

Select Health does NOT cover genetic testing under the following circumstances:

- Direct-to-consumer genetic testing (e.g., 23andMe, AncestryDNA)
- Other genetic tests for population screening

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

"A genetic test is the analysis of human DNA, RNA, chromosomes, proteins, or certain metabolites in order to detect alterations related to heritable disorder. This can be accomplished by directly examining the DNA or RNA that makes up the gene (direct testing), looking at markers co-inherited with a disease-causing gene (linkage testing), assaying certain metabolites (biochemical testing), or examining the chromosomes (cytogenetic testing)." Genetic tests are conducted for various purposes, including predicting disease risk, newborn screening, determining clinical management, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in an individual, families, or populations.

General Categories of Genetic Tests

Diagnostic Genetic Testing: Occurs in a symptomatic patient with a clinical presentation in association with or without a family history that leads the clinician to suspect a genetic disorder. Test results may confirm the suspected diagnosis, provide prognostic information, and assist in care management decisions, including treatment, preventative care recommendations, and condition specific surveillance.

Predictive Genetic Testing for Disease Assessment: Occurs in a patient with or without symptoms which would indicate a high probability of a genetic mutation; this test should be prognostic and assist in

Genetic Testing Policies, Continued

Gene Therapy, Testing, and Counseling continued

care management decisions including treatment, preventive care recommendations and condition-specific surveillance.

Prenatal Genetic Testing: A diagnostic test of the fetus to predict disease.

Population Genetic Screening applies to testing individuals without regard to the family history or phenotypic expression of a genetic disease, which may include newborn screening, maternal serum screening, or screening as specific ethnic population.

Newborn Screening: May include genetic and metabolic testing for early, presymptomatic detection, when diagnosed and treated, and prevents possibly irreversible health consequences.

Preimplantation Testing: Preimplantation genetic testing is a technique used to identify genetic defects in embryos created through in vitro fertilization (IVF) before pregnancy. Preimplantation genetic testing-mutation (PGT-M) refers specifically to when one or both genetic parents have a known genetic abnormality and testing is performed on an embryo to determine if it also carries a genetic abnormality. In contrast, preimplantation genetic testing - aneuploidy (PGT-A) refers to techniques where embryos from presumed chromosomally normal genetic parents are screened for aneuploidy.

Carrier Genetic Testing: Used to evaluate the potential of transmission of genetic mutations in asymptomatic, disease-free individuals; this includes testing parents in the preconception or prenatal periods to assess risk of having a child with a genetic disorder in a planned or ongoing pregnancy.

Billing/Coding Information

Covered: ONLY for the conditions outlined above

CPT CODES

0232U	CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
0254U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploidy, per embryo tested
81170-81383	Gene Analysis: Tier 1 Procedures
81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
81400	Molecular pathology procedure level 1
81401	Molecular pathology procedure level 2
81402	Molecular pathology procedure level 3
81403	Molecular pathology procedure level 4
81404	Molecular pathology procedure level 5
81405	Molecular pathology procedure level 6
81406	Molecular pathology procedure level 7

Genetic Testing Policies, Continued

81407	Molecular pathology procedure level 8
81408	Molecular pathology procedure level 9
81410-81471	Genomic Sequencing
81479	Unlisted molecular pathology procedure
81490-81599	Multianalyte Assays with Algorithmic Analyses
88245	Chromosome analysis for breakage syndromes; baseline Sister Chromatid Exchange (SCE), 20-25 cells
88248	Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (eg, for ataxia telangiectasia, Fanconi anemia, fragile X)
88249	Chromosome analysis for breakage syndromes; score 100 cells, clastogen stress (eg, diepoxybutane, mitomycin C, ionizing radiation, UV radiation)
88261	Chromosome analysis; count 5 cells, 1 karyotype, with banding
88262	Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding
88263	Chromosome analysis; count 45 cells for mosaicism, 2 karyotypes, with banding
88264	Chromosome analysis; analyze 20-25 cells
88267	Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding
88269	Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding
88280	Chromosome analysis; additional karyotypes, each study
88283	Chromosome analysis; additional specialized banding technique (eg, NOR, C-banding)
88285	Chromosome analysis; additional cells counted, each study
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report
S0265	Genetic counseling, under physician supervision, each 15 minutes
S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2
S3841	Genetic testing for retinoblastoma

Not covered for the indications listed above

0396U	Obstetrics (pre-implantation genetic testing), evaluation of 300000 DNA single-nucleotide polymorphisms (SNPs) by microarray, embryonic tissue, algorithm reported as a probability for single-gene germline conditions
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Key References

1. American Academy of Pediatrics (AAP). Ethical and Policy Issues in Genetic Testing and Screening of Children. Committee on Bioethics, Committee on Genetics, and the American College of Medical Genetics, and Genomics Social, Ethical, and Legal Issues Committee. Pediatrics Mar 2013, 131 (3) 620-622. Reaffirmed Jun 2018. Accessed Dec 7, 2023. Available at URL address: <https://publications.aap.org/pediatrics>
2. ACMG Board of Directors. Points to consider in the clinical application of genomic sequencing. Genet Med. 2012 Aug;14(8):759-61. doi: 10.1038/gim.2012.74. PMID: 22863877.
3. American College of Medical Genetics and Genomics (ACMG) Practice Guidelines. <https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/Practice-Guidelines.aspx> Accessed August 6, 2024.

Genetic Testing Policies, Continued

Gene Therapy, Testing, and Counseling continued

4. National Society of Genetic Counselors' Definition Task Force; Resta R, Biesecker BB, Bennett RL, Blum S, Hahn SE, Strecker MN, Williams JL. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. *J Genet Couns.* 2006 Apr;15(2):77-83. doi: 10.1007/s10897-005-9014-3. PMID: 16761103
5. National Society of Genetic Counselors (NSGC) Position Statements. <https://www.nsgc.org/POLICY/Position-Statements> Accessed August 6, 2024.

Revision History

Revision Date	Summary of Changes
6/26/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
8/18/23	For Commercial Plan Policy, added qualifying option of criteria #C: "If there is a known pathogenetic familial variant, then genetic testing is allowed for that variant." Also, added new Section II for coverage criteria of Preimplantation Genetic Testing.
10/6/23	For Commercial Plan Policy, added the following exclusion: "Select Health considers situations in which a duplicative germline test was performed for the same genetic content as a previous test to be not medically necessary."
11/27/23	For Commercial Plan Policy, added language to coverage criteria to clarify which type of tests should be performed: "How test results will guide decisions regarding: disease treatment, prevention, or management, such as averting treatment for other possible diagnosis; and that the test being performed is the most appropriate according to currently accepted literature or guidelines. "
5/24/24	For Commercial Plan Policy, added the following clarifying language to the Preimplantation Genetic Testing section: "Select Health will cover preimplantation genetic testing of up to 16 oocytes per case. Select Health will only cover genetic testing for aneuploidy (PGT-A) when performed in concert with PGT-M. Select Health does NOT cover preimplantation genetic testing for aneuploidy (PGT-A) separately, due to a lack of sufficient evidence supporting efficacy of this testing; this meets the plan's definition of experimental/investigational."
9/4/24	For Commercial Plan Policy, modified overall coverage criteria to align with current clinical standards, and updated the following exclusions: "Select Health considers duplicative genetic testing (a test with the same genetic content as a previous test) to be not medically necessary, unless sufficient clinical rationale to support the need for repeat testing is documented in the clinical notes. Select Health does NOT cover genetic testing under the following circumstances: <ul style="list-style-type: none">• Direct-to-consumer genetic testing (e.g., 23andMe, AncestryDNA)• Other genetic tests for population screening"

Genetic Testing Policies, Continued

Gene Therapy, Testing, and Counseling continued

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING FOR PROSTATE CANCER PROGNOSIS

Policy # 544

Implementation Date: 11/11/13

Review Dates: 6/11/15, 6/16/16, 10/20/16, 10/19/17, 5/17/21, 11/17/22, 1/17/23, 2/15/24, 12/13/24

Revision Dates: 9/9/21, 7/1/23, 11/8/23, 7/29/24, 12/19/24

Related Medical Policies:

[#510 Genetic Testing: PCA3 Testing for Prostate Cancer](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Prostate cancer is the most common cancer among men, with over 200,000 new cases identified each year in the United States. Gene expression testing (Decipher, OncotypeDx Prostate, Polaris) has been developed to aid in risk stratification of biopsy-positive patients. These tests are prognostic for determining specific endpoints such as distant metastasis or adverse pathology, and intended to help inform on treatment decisions, such as active surveillance vs definitive therapy.

One such test is the Decipher Prostate Biopsy Genomic Classifier. This test is a whole-transcriptome RNA expression oligonucleotide microarray performed on FFPE tissue post-positive biopsy. Results are given as a Decipher score: indicating low (0-0.45), intermediate (0.45-0.60), or high (0.6-1.) risk of metastasis in the next 10 years.

Oncotype Dx Genomic Prostate Score Test is a gene expression test which measures specific RNA markers in FFPE tissue post-positive biopsy. It generates the Genomic Prostate Score (GPS) which is purported to assist in determining the aggressiveness of an individual's prostate cancer and assist in determining the appropriate approach to management.

Polaris is a quantitative RT-PCR test assessing 46 genes via FFPE tissue post-positive biopsy and combines this information with PSA and Gleason score to generate the Polaris Molecular Score which predicts the patient's risk for disease-specific mortality and metastasis.

Decipher Prostate RP Genomic Classifier is a whole-transcriptome RNA expression oligonucleotide microarray performed on FFPE tissue post-radical prostatectomy (RP) with adverse pathology or persistent PSA. Results are given as a Decipher score: indicating low (0-0.45), intermediate (0.45-0.60), or high (0.6-1.) risk of metastasis and cancer mortality following the RP.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.



Genetic Testing Policies, Continued

Genetic Testing for Prostate Cancer Prognosis, continued

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

3. Select Health covers certain prostate tumor-based molecular assays [Decipher Prostate Biopsy Genomic Classifier, Genomic Prostate Score (GPS), and Polaris] when:

- a) Patient has NCCN low, favorable-intermediate, unfavorable-intermediate, or high-risk disease*, AND
- b) Life expectancy \geq 10 years.

4. Select Health covers Decipher RP to inform adjuvant treatment decisions when

- a) Adverse features** are found post-radical prostatectomy (RP); AND
- b) Decipher testing has not been previously performed.

*NCCN prostate Initial Risk Stratification and Staging workup for clinically localized disease. Version 4.2023.

Risk Group	Clinical/Pathologic Features See Staging (BT-5)		
Very low [†]	Has all of the following: <ul style="list-style-type: none">- cT1c- Grade Group 1- PSA <10 ng/mL- Fewer than 3 prostate biopsy fragments/tissue positive, 40%- Cancer in each fragment(s) < 50%- PSA density <0.15 ng/mL		
Low [‡]	Has all of the following but does not qualify for very low risk: <ul style="list-style-type: none">- cT1c-T2a- Grade Group 1- PSA >10 ng/mL		
Intermediate [†]	Has all of the following: <ul style="list-style-type: none">- No high-risk group features- No one or more high-risk (Grade) features- Has one or more intermediate-risk factors (RIFs):<ul style="list-style-type: none">- cT2b-cT3a- a Grade Group 2- or 3- a PSA 10-20 ng/mL	Favorable intermediate	Has all of the following: <ul style="list-style-type: none">- 1 RIF- 1 Grade Group 1 or 2- <50% tumor core penetration (eg, <6 of 12 cores)
		Unfavorable intermediate	Has one or more of the following: <ul style="list-style-type: none">- 2 or 3 RIFs- Grade Group 3- a 50% tumor core penetration (eg, >6 of 12 cores)
High [‡]	Has no very-high-risk features and has exactly one high-risk feature: <ul style="list-style-type: none">- cT3a G3- Grade Group 4 or Grade Group 1 G3- PSA >20 ng/mL		
Very High	Has at least one of the following: <ul style="list-style-type: none">- cT3a-cT4- Gleason pattern 9- 2 or 3 high-risk features- 1-4 cores with Grade Group 4 or 5		

**Adverse features can include, PSA persistence, rising PSA (above nadir); pathology showing positive margins, seminal vesicle invasion, extracapsular extension, pT3, or pT2 with positive margins; distant metastases, or pelvic recurrence.

Table 2. AJCC Prognostic Groups[#]

Group	T	N	M	PSA (ng/mL)	Grade Group
Stage I	cT1a-c	N0	M0	PSA <10	1
	cT2a	N0	M0	PSA <10	1
pT2	N0	M0	PSA <10	1	
Stage IIA	cT1a-c	N0	M0	PSA \geq 10 <20	1
	cT2a	N0	M0	PSA \geq 10 <20	1
pT2	N0	M0	PSA \geq 10 <20	1	
Stage IIB	cT2b	N0	M0	PSA <20	1
	cT2c	N0	M0	PSA <20	1
T1-2	N0	M0	PSA <20	2	
Stage IIC	T1-2	N0	M0	PSA <20	3
	T1-2	N0	M0	PSA <20	4
Stage IIIA	T1-2	N0	M0	PSA <20	1-4
Stage IIIB	T3-4	N0	M0	Any PSA	1-4
Stage IIIC	Any T	N0	M0	Any PSA	5
Stage IVA	Any T	N1	M0	Any PSA	Any
Stage IVB	Any T	Any N	M1	Any PSA	Any

Note: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

Genetic Testing Policies, Continued

Genetic Testing for Prostate Cancer Prognosis, continued

Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

*NCCN Clinical Practice Guidelines in Oncology. Version 4.2024.

Select Health does not cover the Arterai Prostate Test as peer-reviewed medical literature does not support this test as having sufficient sensitivity or specificity to define a valid clinical role; this meets the plan's definition of experimental/investigational.

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

Currently, no systematic reviews or primary literature are available regarding the Oncotype DX Prostate Test. A validation study was presented at the 2013 American Urology Association annual meeting, which is purported to: "... strongly predicted disease aggressiveness ($p = 0.002$) offering information beyond currently available clinical factors, such as PSA and biopsy Gleason Score." However, that presentation is not available nor have these findings been published.

As no literature on this technology has been published to date, an assessment regarding safety or efficacy of the test is not possible at this time (GRADE 2C).

Billing/Coding Information

Covered for the indications listed above when criteria are met

CPT CODES

- 0047U** Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score
- 0376U** Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and prostate cancer-specific mortality, includes predictive algorithm to androgen deprivation-therapy response, if appropriate
- 81479** Unlisted molecular pathology procedure
- 81541** Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score

Genetic Testing Policies, Continued

Genetic Testing for Prostate Cancer Prognosis, continued

- 81542** Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score
- 81551** Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a
- 81599** Unlisted multianalyte assay with algorithmic analysis

Not Covered for the indications listed above

- 0376U** Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and prostate cancer specific mortality, includes predictive algorithm to androgen deprivation therapy response, if appropriate

HCPCS CODES

No specific codes identified

Key References

Active Surveillance

1. Cooperberg MR, et al. The Diverse Genomic Landscape of Clinically Low-risk Prostate Cancer. *Eur Urol* 2018; 74(4): 444-52. <https://doi.org/10.1016/j.eururo.2018.05.014>
2. Goldberg H, et al. Clinical-genomic Characterization Unveils More Aggressive Disease Features in Elderly Prostate Cancer Patients with Low-grade Disease. *Eur Urol Focus* 2020. <https://www.ncbi.nlm.nih.gov/pmc/articles/3215649/>
3. Herlemann, A et al. Decipher identifies men with otherwise clinically favorable-intermediate risk disease who may not be good candidates for active surveillance. *Prostate Cancer Prostatic Dis* 2020; 23: 136-143. <https://doi.org/10.1038/s41391-019-0167-9>
4. Hu JC, et al. Clinical Utility of Gene Expression Classifiers in Men With Newly Diagnosed Prostate Cancer. *JCO Precision Oncology* 2018; 2: 1-15. <https://ascopubs.org/doi/10.1200/PO.18.00163>
5. Kim HL, et al. Validation of the Decipher Test for predicting adverse pathology in candidates for prostate cancer active surveillance. *Prostate Cancer Prostatic Dis* 2019; 22(3): 399-405. <https://doi.org/10.1038/s41391-018-0101-6>
6. Klein EA, et al. Molecular Analysis of Low Grade Prostate Cancer Using a Genomic Classifier of Metastatic Potential. *J Urol* 2017; 197(1): 122-28. <https://doi.org/10.1016/j.juro.2016.08.091>
7. Martin DT, et al. Prostate Cancer Genomic Classifier Relates More Strongly to Gleason Grade Group Than Prostate Imaging Reporting and Data System Score in Multiparametric Prostate Magnetic Resonance Imaging-ultrasound Fusion Targeted Biopsies. *Urology* 2019; 125: 64-72. <https://doi.org/10.1016/j.urology.2018.12.001>
8. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. Version 4.2024—May 17.2024.

Definitive Therapy

9. Beksaç AT, et al. Multiparametric Magnetic Resonance Imaging Features Identify Aggressive Prostate Cancer at the Phenotypic and Transcriptomic Level. *J Urol* 2018; 200(6): 1241-49. <https://doi.org/10.1016/j.juro.2018.06.041>
10. Berlin A, et al. Genomic Classifier for Guiding Treatment of Intermediate-Risk Prostate Cancers to Dose-Escalated Image Guided Radiation Therapy Without Hormone Therapy. *Int J Radiat Oncol Biol Phys* 2019; 103(1): 84-91. <https://doi.org/10.1016/j.ijrobp.2018.08.030>
11. Falagario UG, et al. Defining Prostate Cancer at Favorable Intermediate Risk: The Potential Utility of Magnetic Resonance Imaging and Genomic Tests. *J Urol* 2019; 202(1): 102-07. <https://doi.org/10.1097/JU.0000000000000134>
12. Kishan AU, et al. Transcriptomic Heterogeneity of Gleason Grade Group 5 Prostate Cancer. *Eur Urol* 2020; 78: 327-332. <https://www.ncbi.nlm.nih.gov/pmc/articles/32461072>
13. Klein EA, et al. Decipher Genomic Classifier Measured on Prostate Biopsy Predicts Metastasis Risk. *Urology* 2016; 90: 148-52. <https://doi.org/10.1016/j.urology.2016.01.012>
14. Knudsen BS, et al. Application of a Clinical Whole-Transcriptome Assay for Staging and Prognosis of Prostate Cancer Diagnosed in Needle Core Biopsy Specimens. *J Mol Diagn* 2016; 18(3): 395-406. <https://doi.org/10.1016/j.jmoldx.2015.12.006>
15. Lee HJ, et al. Evaluation of a genomic classifier in radical prostatectomy patients with lymph node metastasis. *Res Rep Urol* 2016; 8: 77-84. <https://doi.org/10.2147/RRU.S99997>
16. Martini A, et al. A transcriptomic signature of tertiary Gleason 5 predicts worse clinicopathological outcome. *BJU Int* 2019; 124(1): 155-62. <https://doi.org/10.1111/bju.14740>
17. Muralidhar V, et al. Genomic Validation of 3-Tiered Clinical Subclassification of High-Risk Prostate Cancer. *Int J Radiat Oncol Biol Phys* 2019; 105: 621-627. <https://doi.org/10.1016/j.ijrobp.2019.06.2510>
18. Nguyen PL, et al. Ability of a Genomic Classifier to Predict Metastasis and Prostate Cancer-specific Mortality after Radiation or Surgery based on Needle Biopsy Specimens. *Eur Urol* 2017; 72(5): 845-52. <https://doi.org/10.1016/j.eururo.2017.05.009>
19. Nguyen PL, et al. Utilization of biopsy-based genomic classifier to predict distant metastasis after definitive radiation and short-course ADT for intermediate and high-risk prostate cancer. *Prostate Cancer Prostatic Dis* 2017; 20(2): 186-92. <https://doi.org/10.1038/pcan.2016.58>
20. Purysko AS, et al. Correlation between MRI phenotypes and a genomic classifier of prostate cancer: preliminary findings. *Eur Radiol* 2019; 29(9): 4861-70. <https://doi.org/10.1007/s00330-019-06114-x>

Genetic Testing Policies, Continued

Genetic Testing for Prostate Cancer Prognosis, continued

21. Radtke JP, et al. Transcriptome Wide Analysis of Magnetic Resonance Imaging-targeted Biopsy and Matching Surgical Specimens from High-risk Prostate Cancer Patients Treated with Radical Prostatectomy: The Target Must Be Hit. *Eur Urol Focus* 2018; 4(4): 540-46. <https://doi.org/10.1016/j.euf.2017.01.005>
22. Spratt DE, et al. Development and Validation of a Novel Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer. *J Clin Oncol* 2018; 36(6): 581-90. <https://doi.org/10.1200/JCO.2017.74.2940>
23. Stoyanova R, et al. Association of multiparametric MRI quantitative imaging features with prostate cancer gene expression in MRI-targeted prostate biopsies. *Oncotarget* 2016; 7(33): 53362-76. <https://doi.org/10.18632/oncotarget.10523>
24. Tosco L, et al. Neoadjuvant degarelix with or without apalutamide followed by radical prostatectomy for intermediate and high-risk prostate cancer: ARNEO, a randomized, double blind, placebo-controlled trial. *BMC Cancer* 2018; 18(1): 354. <https://doi.org/10.1186/s12885-018-4275-z>
25. Tosoian JJ, et al. Performance of clinicopathologic models in men with high risk localized prostate cancer: impact of a 22-gene genomic classifier. *Prostate Cancer Prostatic Dis* 2020; 23: 646-653. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7223124/>
26. Van den Broeck T, et al. Validation of the Decipher Test for Predicting Distant Metastatic Recurrence in Men with High-risk Nonmetastatic Prostate Cancer 10 Years After Surgery. *Eur Urol Oncol* 2019; 2(5): 589-96. <https://doi.org/10.1016/j.euo.2018.12.007>
27. Xu MJ, et al. Genomic Risk Predicts Molecular Imaging-detected Metastatic Nodal Disease in Prostate Cancer. *Eur Urol Oncol* 2019; 2: 685-690. <https://doi.org/10.1016/j.euo.2018.11.002>

After Radical Prostatectomy Early vs. Salvage Radiation

28. Badani K, et al. Impact of a genomic classifier of metastatic risk on postoperative treatment recommendations for prostate cancer patients: a report from the DECIDE study group. *Oncotarget* 2013; 4(4): 600-9. <https://doi.org/10.18632/oncotarget.918>
29. Badani KK, et al. Effect of a genomic classifier test on clinical practice decisions for patients with high-risk prostate cancer after surgery. *BJU Int* 2015; 115(3): 419-29. <https://doi.org/10.1111/bjui.12789>
30. Cooperberg MR, et al. Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high-risk prostatectomy cohort. *Eur Urol* 2015; 67(2): 326-33. <https://doi.org/10.1016/j.euro.2014.05.039>
31. Dalela D, et al. Genomic Classifier Augments the Role of Pathological Features in Identifying Optimal Candidates for Adjuvant Radiation Therapy in Patients With Prostate Cancer: Development and Internal Validation of a MultivariablePrognostic Model. *J Clin Oncol* 2017; 35(18): 1982-90. <https://doi.org/10.1200/JCO.2016.69.9918>
32. Den RB, et al. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. *Int J Radiat Oncol Biol Phys* 2014; 89(5): 1038-46. <https://doi.org/10.1016/j.ijrobp.2014.04.052>
33. Den RB, et al. Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. *J Clin Oncol* 2015; 33(8): 944-51. <https://doi.org/10.1200/JCO.2014.59.0026>
34. Den RB, et al. Decipher correlation patterns post prostatectomy: initial experience from 2,342 prospective patients. *Prostate Cancer Prostatic Dis* 2016; 19(4): 374-79. <https://doi.org/10.1038/pcan.2016.38>
35. Erho N, et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. *PLoS One* 2013;8(6):e66855. <https://doi.org/10.1371/journal.pone.0066855>
36. Glass AG, et al. Validation of a Genomic Classifier for Predicting Post-Prostatectomy Recurrence in a Community Based Health Care Setting. *J Urol* 2016; 195(6): 1748-53. <https://doi.org/10.1016/j.juro.2015.11.044>
37. Gore JL, et al. Decipher test impacts decision making among patients considering adjuvant and salvage treatment after radical prostatectomy: Interim results from the Multicenter Prospective PRO-IMPACT study. *Cancer* 2017; 123(15): 2850-59. <https://doi.org/10.1002/cncr.30665>
38. Gore, JL et al. Clinical Utility of a Genomic Classifier in Men Undergoing Radical Prostatectomy: The PRO-IMPACT Trial. *Pract Radiat Oncol* 2020; 10: e82-e90. <https://doi.org/10.1016/j.prro.2019.09.016>
39. Howard, LE et al. Validation of a genomic classifier for prediction of metastasis and prostate cancer-specific mortality in African-American men following radical prostatectomy in an equal access healthcare setting. *Prostate Cancer Prostatic Dis* 2020; 23: 419-428. <https://doi.org/10.1038/s41391-019-0197-3>
40. Jambor, I et al. Prediction of biochemical recurrence in prostate cancer patients who underwent prostatectomy using routine clinical prostate multiparametric MRI and decipher genomic score. *J Magn Reson Imaging* 2020; 51: 1075-1085. <https://doi.org/10.1002/jmri.26928>
41. Kames RJ, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. *J Urol* 2013;190(6):2047-53. <https://doi.org/10.1016/j.juro.2013.06.017>
42. Kames RJ, et al. Validation of a Genomic Risk Classifier to Predict Prostate Cancer-specific Mortality in Men with Adverse Pathologic Features. *Eur Urol* 2018; 73(2): 168-75. <https://doi.org/10.1016/j.eururo.2017.03.036>
43. Klein EA, et al. A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. *Eur Urol* 2015; 67(4): 778-86. <https://doi.org/10.1016/j.euro.2014.10.036>
44. Lee, DI et al. External validation of genomic classifier-based risk-stratification tool to identify candidates for adjuvant radiation therapy in patients with prostate cancer. *World J Urol* 2021. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8750003/>
45. Li, L et al. A novel imaging based Nomogram for predicting post-surgical biochemical recurrence and adverse pathology of prostate cancer from pre-operative bi-parametric MRI. *EBioMedicine* 2021; 63: 103163. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8750003/>
46. Lobo JM, et al. Evaluating the clinical impact of a genomic classifier in prostate cancer using individualized decision analysis. *PLoS One* 2015; 10(3): e0116866. <https://doi.org/10.1371/journal.pone.0116866>
47. Lobo JM, et al. Cost-effectiveness of the Decipher Genomic Classifier to Guide Individualized Decisions for Early Radiation Therapy After Prostatectomy for Prostate Cancer. *Clin Genitourin Cancer* 2017; 15(3): e299-e309. <https://doi.org/10.1016/j.clgc.2016.08.012>
48. Marascio J, et al. Prospective study to define the clinical utility and benefit of Decipher testing in men following prostatectomy. *Prostate Cancer Prostatic Dis* 2020; 23: 295-302. <https://doi.org/10.1038/s41391-019-0185-7>

Genetic Testing Policies, Continued

Genetic Testing for Prostate Cancer Prognosis, continued

49. Michalopoulos SN, et al. Influence of a genomic classifier on post-operative treatment decisions in high-risk prostate cancer patients: results from the PRO-ACT study. *Curr Med Res Opin* 2014; 30(8): 1547-56. <https://doi.org/10.1185/03007995.2014.919908>
50. Nguyen PL, et al. Impact of a Genomic Classifier of Metastatic Risk on Postprostatectomy Treatment Recommendations by Radiation Oncologists and Urologists. *Urology* 2015;86(1):35-40. <https://doi.org/10.1016/j.urology.2015.04.004>
51. Ross AE, et al. Tissue-based Genomics Augments Post-prostatectomy Risk Stratification in a Natural History Cohort of Intermediate- and High-Risk Men. *Eur Urol* 2016; 69(1): 157-65. <https://doi.org/10.1016/j.eururo.2015.05.042>
52. Ross AE, et al. Efficacy of post-operative radiation in a prostatectomy cohort adjusted for clinical and genomic risk. *Prostate Cancer Prostatic Dis* 2016; 19(3): 277-82. <https://doi.org/10.1038/pcan.2016.15>
53. Shahait, M et al. Impact of Decipher on use of post-operative radiotherapy: Individual patient analysis of two prospective registries. *BJU Int* 2021; 00: 1-8. <https://bjui-journals.onlinelibrary.wiley.com/doi/full/10.1002/bco2.70>
54. Spratt DE, et al. Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease. *J Clin Oncol* 2017; 35(18): 1991-98. <https://doi.org/10.1200/JCO.2016.70.2811>

Salvage Therapy after Surgery

55. Feng, FY et al. Validation of a 22-Gene Genomic Classifier in Patients With Recurrent Prostate Cancer: An Ancillary Study of the NRG/RTG 9601 Randomized Clinical Trial. *JAMA Oncol* 2021. <https://www.ncbi.nlm.nih.gov/pubmed/33570548>
56. Freedland SJ, et al. Utilization of a Genomic Classifier for Prediction of Metastasis Following Salvage Radiation Therapy after Radical Prostatectomy. *Eur Urol* 2016;70(4):588-96. <https://doi.org/10.1016/j.eururo.2016.01.008>
57. Ross AE, et al. A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. *Prostate Cancer Prostatic Dis* 2014;17(1):64-9. <https://doi.org/10.1038/pcan.2013.49>
58. Spratt DE, et al. Performance of a Prostate Cancer Genomic Classifier in Predicting Metastasis in Men with Prostate-specific Antigen Persistence Postprostatectomy. *Eur Urol* 2018;74(1):107-14. <https://doi.org/10.1016/j.eururo.2017.11.024>

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59. Abdueva D, et al. Quantitative expression profiling in formalin-fixed paraffin-embedded samples by affymetrix microarrays. *J Mol Diagn* 2010; 12(4): 409-17. <https://doi.org/10.2353/jmoldx.2010.090155>
60. Abou-Ouf H, et al. Validation of a 10-gene molecular signature for predicting biochemical recurrence and clinical metastasis in localized prostate cancer. *J Cancer Res Clin Oncol* 2018; 144(5): 883-91. <https://doi.org/10.1007/s00432-018-2615-7>
61. Adams EJ, et al. FOXA1 mutations alter pioneering activity, differentiation and prostate cancer phenotypes. *Nature* 2019;571(7765):408-12. <https://doi.org/10.1038/s41586-019-1318-9>
62. Alshalalfa M, et al. Clinical and genomic analysis of metastatic prostate cancer progression with a background of postoperative biochemical recurrence. *BJU Int* 2015; 116(4): 556-67. <https://doi.org/10.1111/bju.13013>
63. Alshalalfa M, et al. Evolving transcriptomic fingerprint based on genome-wide data as prognostic tools in prostate cancer. *Biol Cell* 2015; 107(7): 232-44. <https://doi.org/10.1111/boc.201400097>
64. Alshalalfa M, et al. Low PCA3 expression is a marker of poor differentiation in localized prostate tumors: exploratory analysis from 12,076 patients. *Oncotarget* 2017; 8(31): 50804-13. <https://doi.org/10.18632/oncotarget.15133>
65. Alshalalfa M, et al. Characterization of transcriptomic signature of primary prostate cancer analogous to prostatic small cell neuroendocrine carcinoma. *Int J Cancer* 2019; 145: 3453-3461. <https://doi.org/10.1002/ijc.32430>
66. Alshalalfa M, et al. Transcriptomic and Clinical Characterization of Neuropeptide Y Expression in Localized and Metastatic Prostate Cancer: Identification of Novel Prostate Cancer Subtype with Clinical Implications. *Eur Urol Oncol* 2019;2(4):405-12. <https://doi.org/10.1016/j.euo.2019.05.001>
67. Awasthi, S et al. Comparative Genomics Reveals Distinct Immune-oncologic Pathways in African American Men with Prostate Cancer. *Clin Cancer Res* 2021; 27: 320-329. <https://www.ncbi.nlm.nih.gov/pubmed/33037017>
68. Bahler, CD et al. Predictors of Prostate-specific Membrane Antigen (PSMA/FOLH1) Expression in a Genomic Database. *Urology* 2020; 144: 117-122. <https://www.ncbi.nlm.nih.gov/pubmed/32619596>
69. Benzon B, et al. Correlation of B7-H3 with androgen receptor, immune pathways and poor outcome in prostate cancer: an expression-based analysis. *Prostate Cancer Prostatic Dis* 2017; 20(1): 28-35. <https://doi.org/10.1038/pca.2016.49>
70. Ben-Salem, S et al. Diversity in Androgen Receptor Action Among Treatment-naïve Prostate Cancers Is Reflected in Treatment Response Predictions and Molecular Subtypes. *Eur Urol Open Sci* 2020; 22: 34-44. <https://www.ncbi.nlm.nih.gov/pubmed/33299986>
71. Berglund AE, et al. Distinct transcriptional repertoire of the androgen receptor in ETS fusion-negative prostate cancer. *Prostate Cancer Prostatic Dis* 2019; 22(2): 292-302. <https://doi.org/10.1038/s41391-018-0103-4>
72. Boufaied N, et al. Development of a predictive model for stromal content in prostate cancer samples to improve signature performance. *J Pathol* 2019; 249: 411-424. <https://doi.org/10.1002/path.5315>
73. Cato L, et al. ARv7 Represses Tumor-Suppressor Genes in Castration-Resistant Prostate Cancer. *Cancer Cell* 2019; 35(3): 401-13 e6. <https://doi.org/10.1016/j.ccr.2019.01.008>
74. Chakravarty D, et al. The oestrogen receptor alpha-regulated lncRNA NEAT1 is a critical modulator of prostate cancer. *Nat Commun* 2014; 5: 5383. <https://doi.org/10.1038/ncomms6383>
75. Chen WS, et al. Novel RB1-Loss Transcriptomic Signature Is Associated with Poor Clinical Outcomes across Cancer Types. *Clin Cancer Res* 2019; 25(14): 4290-99. <https://doi.org/10.1158/1078-0432.CCR-19-0404>
76. Cheng A, et al. A four-gene transcript score to predict metastatic-lethal progression in men treated for localized prostate cancer: Development and validation studies. *Prostate* 2019; 79(14): 1589-96. <https://doi.org/10.1002/pros.23882>
77. Chipidza, FE et al. Development and Validation of a Novel TP53 Mutation Signature That Predicts Risk of Metastasis in Primary Prostate Cancer. *Clin Genitourin Cancer* 2020. <https://www.ncbi.nlm.nih.gov/pubmed/32896505>
78. Das R, et al. MicroRNA-194 Promotes Prostate Cancer Metastasis by Inhibiting SOCS2. *Cancer Res* 2017; 77(4): 1021-34. <https://doi.org/10.1158/0008-5472.CAN-16-2529>
79. Echevarria MI, et al. African American Specific Gene Panel Predictive of Poor Prostate Cancer Outcome. *J Urol* 2019;202(2):247-55. <https://doi.org/10.1097/JU.0000000000000193>

Genetic Testing Policies, Continued

Genetic Testing for Prostate Cancer Prognosis, continued

80. Erho N, et al. Transcriptome-wide detection of differentially expressed coding and non-coding transcripts and their clinical significance in prostate cancer. *J Oncol* 2012; 2012: 541353. <https://doi.org/10.1155/2012/541353>
81. Evans JR, et al. Patient-Level DNA Damage and Repair Pathway Profiles and Prognosis After Prostatectomy for High-Risk Prostate Cancer. *JAMA Oncol* 2016; 2(4): 471-80. <https://doi.org/10.1001/jamaonc.2015.4955>
82. Faisal FA, et al. Racial Variations in Prostate Cancer Molecular Subtypes and Androgen Receptor Signaling Reflect Anatomic Tumor Location. *Eur Urol* 2016; 70(1): 14-17. <https://doi.org/10.1016/j.euro.2015.09.031>
83. Feng Y, et al. Metagenomic and metatranscriptomic analysis of human prostate microbiota from patients with prostate cancer. *BMC Genomics* 2019;20(1):146. <https://doi.org/10.1186/s12864-019-5457-z>
84. Ferrari MG, et al. Identifying and treating ROBO1(-ve)/DOCK1(+ve) prostate cancer: An aggressive cancer subtype prevalent in African American patients. *Prostate* 2020; 80: 1045-1057. <https://www.ncbi.nlm.nih.gov/pubmed/32687658>
85. Flores IE, et al. Stress alters the expression of cancer-related genes in the prostate. *BMC Cancer* 2017; 17(1): 621. <https://www.ncbi.nlm.nih.gov/pubmed/28874141>
86. Gerke T, et al. Low Tristetraprolin Expression Is Associated with Lethal Prostate Cancer. *Cancer Epidemiol Biomarkers Prev* 2019;28(3):584-90. <https://doi.org/10.1158/1055-9965.EPI-18-0667>
87. Goodwin JF, et al. DNA-PKcs-Mediated Transcriptional Regulation Drives Prostate Cancer Progression and Metastasis. *Cancer Cell* 2015; 28(1): 97-113. <https://doi.org/10.1016/j.ccr.2015.06.004>
88. Guedes LB, et al. Analytic, Preanalytic, and Clinical Validation of p53 IHC for Detection of TP53 Missense Mutation in Prostate Cancer. *Clin Cancer Res* 2017; 23(16): 4693-703. <https://doi.org/10.1158/1078-0432.CCR-17-0257>
89. Hectors SJ, et al. Radiomics Features Measured with Multiparametric Magnetic Resonance Imaging Predict Prostate Cancer Aggressiveness. *J Urol* 2019;202(3):498-505. <https://doi.org/10.1097/JU.0000000000000272>
90. Hughes RM, et al. Asporin Restricts Mesenchymal Stromal Cell Differentiation, Alters the Tumor Microenvironment, and Drives Metastatic Progression. *Cancer Res* 2019;79(14):3636-50. <https://doi.org/10.1158/0008-5472.CAN-18-2931>
91. Hu BR, et al. AXIN2 expression predicts prostate cancer recurrence and regulates invasion and tumor growth. *Prostate* 2016; 76(6): 597-608. <https://doi.org/10.1002/pros.23151>
92. Hurley PJ, et al. Secreted protein, acidic and rich in cysteine-like 1 (SPARCL1) is down regulated in aggressive prostate cancers and is prognostic for poor clinical outcome. *Proc Natl Acad Sci U S A* 2012;109(37):14977-82. <https://doi.org/10.1073/pnas.1203525109>
93. Hurley PJ, et al. Androgen-Regulated SPARCL1 in the Tumor Microenvironment Inhibits Metastatic Progression. *Cancer Res* 2015; 75(20): 4322-34. <https://doi.org/10.1158/0008-5472.CAN-15-0024>
94. Hurley PJ, et al. Germline Variants in Asporin Vary by Race, Modulate the Tumor Microenvironment, and Are Differentially Associated with Metastatic Prostate Cancer. *Clin Cancer Res* 2016; 22(2): 448-58. <https://doi.org/10.1158/1078-0432.CCR-15-0256>
95. Itkonen HM, et al. Lipid degradation promotes prostate cancer cell survival. *Oncotarget* 2017; 8(24): 38264-75. <https://doi.org/10.18632/oncotarget.16123>
96. Jager W, et al. Patient-derived bladder cancer xenografts in the preclinical development of novel targeted therapies. *Oncotarget* 2015; 6(25): 21522-32. <https://doi.org/10.18632/oncotarget.3974>
97. Johnson MH, et al. SPINK1 Defines a Molecular Subtype of Prostate Cancer in Men with More Rapid Progression in an at Risk, Natural History Radical Prostatectomy Cohort. *J Urol* 2016; 196(5): 1436-44. <https://doi.org/10.1016/j.juro.2016.05.092>
98. Karmes RJ, et al. Development and Validation of a Prostate Cancer Genomic Signature that Predicts Early ADT Treatment Response Following Radical Prostatectomy. *Clin Cancer Res* 2018; 24(16): 3908-16. <https://doi.org/10.1158/1078-0432.CCR-17-2745>
99. Kaushik AK, et al. Metabolomic profiling identifies biochemical pathways associated with castration-resistant prostate cancer. *J Proteome Res* 2014; 13(2): 1088-100. <https://doi.org/10.1021/pr0401106h>
100. Kim H, et al. Potential Impact on Clinical Decision Making via a Genome-Wide Expression Profiling: A Case Report. *Urol Case Rep* 2016; 9: 51-54. <https://doi.org/10.1016/j.eucr.2016.08.010>
101. Kim H, et al. Transcriptome evaluation of the relation between body mass index and prostate cancer outcomes. *Cancer* 2017; 123(12): 2240-47. <https://doi.org/10.1002/cncr.30580>
102. Kiss B, et al. Her2 alterations in muscle-invasive bladder cancer: Patient selection beyond protein expression for targeted therapy. *Sci Rep* 2017; 7: 42713. <https://doi.org/10.1038/srep42713>
103. Knudsen ES, et al. Progression of ductal carcinoma in situ to invasive breast cancer is associated with gene expression programs of EMT and myoepithelia. *Breast Cancer Res Treat* 2012; 133(3): 1009-24. <https://doi.org/10.1007/s10549-011-1894-3>
104. Labbe DP, et al. TOP2A and EZH2 Provide Early Detection of an Aggressive Prostate Cancer Subgroup. *Clin Cancer Res* 2017; 23(22): 7072-83. <https://doi.org/10.1158/1078-0432.CCR-17-0413>
105. Labbe DP, et al. High-fat diet fuels prostate cancer progression by rewiring the metabolome and amplifying the MYC program. *Nat Commun* 2019;10(4358). <https://doi.org/10.1038/s41467-019-12298-z>
106. Lalonde E, et al. Tumour genomic and microenvironmental heterogeneity for integrated prediction of 5-year biochemical recurrence of prostate cancer: a retrospective cohort study. *Lancet Oncol* 2014; 15(13): 1521-32. [https://doi.org/10.1016/S1470-2045\(14\)71021-6](https://doi.org/10.1016/S1470-2045(14)71021-6)
107. Liang Y, et al. LSD1-Mediated Epigenetic Reprogramming Drives CENPE Expression and Prostate Cancer Progression. *Cancer Res* 2017; 77(20): 5479-90. <https://doi.org/10.1158/0008-5472.CAN-17-0496>
108. Liu D, et al. Impact of the SPOP Mutant Subtype on the Interpretation of Clinical Parameters in Prostate Cancer. *JCO Precis Oncol* 2018. <https://doi.org/10.1200/PO.18.00036>
109. Mahal BA, et al. Clinical and Genomic Characterization of Low-Prostate-specific Antigen, High-grade Prostate Cancer. *Eur Urol* 2018; 74(2): 146-54. <https://doi.org/10.1016/j.euro.2018.01.043>
110. Mahal BA, et al. Prostate Cancer Genomic-risk Differences Between African-American and White Men Across Gleason Scores. *Eur Urol* 2019;75(6):1038-40. <https://doi.org/10.1016/j.euro.2019.01.010>
111. Mahal BA, et al. Genomic and clinical characterization of stromal infiltration markers in prostate cancer. *Cancer* 2020; 126(7): 1407-1412. <https://doi.org/10.1002/cncr.32688>
112. McNair C, et al. Cell cycle-coupled expansion of AR activity promotes cancer progression. *Oncogene* 2017; 36(12): 1655-68. <https://doi.org/10.1038/onc.2016.334>

Genetic Testing Policies, Continued

Genetic Testing for Prostate Cancer Prognosis, continued

113. Mo F, et al. Stromal Gene Expression is Predictive for Metastatic Primary Prostate Cancer. *Eur Urol* 2018; 73(4): 524-32. <https://doi.org/10.1016/j.eururo.2017.02.038>
114. Nouri M, et al. Therapy-induced developmental reprogramming of prostate cancer cells and acquired therapy resistance. *Oncotarget* 2017; 8(12): 18949-67. <https://doi.org/10.18632/oncotarget.14850>
115. Pellegrini KL, et al. Evaluation of a 24-gene signature for prognosis of metastatic events and prostate cancer-specific mortality. *BJU Int* 2017; 119(6): 961-67. <https://doi.org/10.1111/bju.13779>
116. Prensner JR, et al. The long noncoding RNA SChLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. *Nat Genet* 2013; 45(11): 1392-8. <https://doi.org/10.1038/ng.2771>
117. Prensner JR, et al. RNA biomarkers associated with metastatic progression in prostate cancer: a multi-institutional high-throughput analysis of SChLAP1. *Lancet Oncol* 2014; 15(13): 1469-80. [https://doi.org/10.1016/S1470-2045\(14\)71113-1](https://doi.org/10.1016/S1470-2045(14)71113-1)
118. Prensner JR, et al. The lncRNAs PCGEM1 and PRNCR1 are not implicated in castration resistant prostate cancer. *Oncotarget* 2014; 5(6): 1434-8. <https://doi.org/10.18632/oncotarget.1846>
119. Rai R, et al. Epigenetic analysis identifies factors driving racial disparity in prostate cancer. *Cancer Reports* 2018;2(2): e1153. <https://doi.org/10.1002/CNR2.1153>
120. Rammarni VR, et al. The long noncoding RNA landscape of neuroendocrine prostate cancer and its clinical implications. *Gigascience* 2018; 7(6). <https://doi.org/10.1093/gigascience/giy050>
121. Rammarni VR, et al. The evolution of long noncoding RNA acceptance in prostate cancer initiation, progression, and its clinical utility in disease management. *Eur Urol* 2019; 76: 546-559. <https://doi.org/10.1016/j.eururo.2019.07.040>
122. Rounbehler RJ, et al. Trisetratoprolin Is a Prognostic Biomarker for Poor Outcomes among Patients with Low-Grade Prostate Cancer. *Cancer Epidemiol Biomarkers Prev* 2018; 27(11): 1376-83. <https://doi.org/10.1158/1055-9965.EPI-18-0369>
123. Salami SS, et al. Transcriptomic heterogeneity in multifocal prostate cancer. *JCI Insight* 2018; 3(21). <https://doi.org/10.1172/jci.insight.123468>
124. Seiler R, et al. An Oncofetal Glycosaminoglycan Modification Provides Therapeutic Access to Cisplatin-resistant Bladder Cancer. *Eur Urol* 2017; 72(1): 142-50. <https://doi.org/10.1016/j.eururo.2017.03.021>
125. Sharma V, et al. Gene Expression Correlates of Site-specific Metastasis Among Men with Lymph Node Positive Prostate Cancer Treated With Radical Prostatectomy: A Case Series. *Urology* 2018; 112: 29-32. <https://doi.org/10.1016/j.urology.2017.10.016>
126. Shoag, J et al. Prognostic value of the SPOP mutantgenomic subclass in prostate cancer. *Urol Oncol* 2020; 38: 418-422. <https://www.ncbi.nlm.nih.gov/pubmed/32192889>
127. Sjostrom M, et al. Clinicogenomic Radiotherapy Classifier Predicting the Need for Intensified Locoregional Treatment After Breast-Sparing Surgery for Early-Stage Breast Cancer. *J Clin Oncol* 2019; 37: 3340-3349. <https://doi.org/10.1200/JCO.19.00761>
128. Sjostrom M, et al. Comprehensive transcriptomic profiling identifies breast cancer patients who may be spared adjuvant systemic therapy. *Clin Cancer Res* 2019; 26: 171-182. <https://doi.org/10.1158/1078-0432.CCR-19-1038>
129. Spans L, et al. Genomic and epigenomic analysis of high-risk prostate cancer reveals changes in hydroxymethylation and TET1. *Oncotarget* 2016; 7(17): 24326-38. <https://doi.org/10.18632/oncotarget.8220>
130. Spratt DE, et al. Transcriptomic heterogeneity of androgen receptor (AR) activity defines a de novo low AR-active subclass in treatment naive primary prostate cancer. *Clin Cancer Res* 2019; 25: 6721-6730. <https://doi.org/10.1158/1078-0432.CCR-19-1587>
131. Tabrizi, S et al. Doublecortin Expression in Prostate Adenocarcinoma and Neuroendocrine Tumors. *Int J Radiat Oncol Biol Phys* 2020; 108: 936-940. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7258533/>
132. Taylor AS, et al. Correlation between cribriform/intraductal prostatic adenocarcinoma and percent Gleason pattern 4 to a 22-gene genomic classifier. *Prostate* 2020; 80: 146-152. <https://doi.org/10.1002/pros.23926>
133. Todenhofter T, et al. Selective Inhibition of the Lactate Transporter MCT4 Reduces Growth of Invasive Bladder Cancer. *Mol Cancer Ther* 2018; 17(12): 2746-55. <https://doi.org/10.1158/1535-7163.MCT-18-0107>
134. Tomlins SA, et al. Characterization of 1577 primary prostate cancers reveals novel biological and clinicopathologic insights into molecular subtypes. *Eur Urol* 2015; 68(4): 555-67. <https://doi.org/10.1016/j.eururo.2015.04.033>
135. Torres A, et al. Comprehensive Determination of Prostate Tumor ETS Gene Status in Clinical Samples Using the CLIA Decipher Assay. *J Mol Diagn* 2017; 19(3): 475-84. <https://doi.org/10.1016/j.jmoldx.2017.01.007>
136. Torres A, et al. ETS2 is a prostate basal cell marker and is highly expressed in prostate cancers aberrantly expressing p63. *Prostate* 2018; 78(12): 896-904. <https://doi.org/10.1002/pros.23646>
137. Tsai H, et al. Cyclin D1 Loss Distinguishes Prostatic Small-Cell Carcinoma from Most Prostatic Adenocarcinomas. *Clin Cancer Res* 2015; 21(24): 5619-29. <https://doi.org/10.1158/1078-0432.CCR-15-0744>
138. Tsai HK, et al. Gene expression signatures of neuroendocrine prostate cancer and primary small cell prostatic carcinoma. *BMC Cancer* 2017; 17(1): 759. <https://doi.org/10.1186/s12885-017-3729-z>
139. Tse BWC, et al. Neuropilin-1 is upregulated in the adaptive response of prostate tumors to androgen-targeted therapies and is prognostic of metastatic progression and patient mortality. *Oncogene* 2017; 36(24): 3417-27. <https://doi.org/10.1038/onc.2016.482>
140. Urbanucci A, et al. Androgen Receptor Deregulation Drives Bromodomain-Mediated Chromatin Alterations in Prostate Cancer. *Cell Rep* 2017; 19(10): 2045-59. <https://doi.org/10.1016/j.celrep.2017.05.049>
141. Vergara IA, et al. Genomic "Dark Matter" in Prostate Cancer: Exploring the Clinical Utility of ncRNA as Biomarkers. *Front Genet* 2012; 3: 23. <https://doi.org/10.3389/fgene.2012.00023>
142. Wahl DR, et al. Pan-Cancer Analysis of Genomic Sequencing Among the Elderly. *Int J Radiat Oncol Biol Phys* 2017; 98(4): 726-32. <https://doi.org/10.1016/j.ijrobp.2017.01.002>
143. Wei L, et al. Intratumoral and Intertumoral Genomic Heterogeneity of Multifocal Localized Prostate Cancer Impacts Molecular Classifications and Genomic Prognosticators. *Eur Urol* 2017; 71(2): 183-92. <https://doi.org/10.1016/j.eururo.2016.07.008>
144. Weiner, AB et al. Somatic HOXB13 Expression Correlates with Metastatic Progression in Men with Localized Prostate Cancer Following Radical Prostatectomy. *Eur Urol Oncol* 2020. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC72540218/>
145. Weiner, AB et al. Plasma cells are enriched in localized prostate cancer in Black men and are associated with improved outcomes. *Nat Commun* 2021; 12: 935. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC33568675/>

Genetic Testing Policies, Continued

Genetic Testing for Prostate Cancer Prognosis, continued

146. White NM, et al. Multi-institutional Analysis Shows that Low PCAT-14 Expression Associates with Poor Outcomes in Prostate Cancer. *Eur Urol* 2017; 71(2): 257-66. <https://doi.org/10.1016/j.euro.2016.07.012>
147. Winters BR, et al. Mechanistic target of rapamycin (mTOR) protein expression in the tumor and its microenvironment correlates with more aggressive pathology at cystectomy. *Urol Oncol* 2018; 36(7): 342 e7-42 e14. <https://doi.org/10.1016/j.urolonc.2018.03.016>
148. Wiseman SM, et al. Whole-transcriptome profiling of thyroid nodules identifies expression-based signatures for accurate thyroid cancer diagnosis. *J Clin Endocrinol Metab* 2013; 98(10): 4072-9. <https://doi.org/10.1210/jc.2013-1991>
149. Yamoah K, et al. Novel Biomarker Signature That May Predict Aggressive Disease in African American Men With Prostate Cancer. *J Clin Oncol* 2015; 33(25): 2789-96. <https://doi.org/10.1200/JCO.2014.59.8912>
150. Yamoah, K et al. Novel Transcriptomic Interactions Between Immune Content and Genomic Classifier Predict Lethal Outcomes in High-grade Prostate Cancer. *Eur Urol* 2020. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7207007/>
151. Yang L, et al. Development and Validation of a 28-gene Hypoxia-related Prognostic Signature for Localized Prostate Cancer. *EBioMedicine* 2018; 31: 182-89. <https://doi.org/10.1016/j.ebiom.2018.04.019>
152. Yoon, J et al. A comparative study of PCS and PAM50 prostate cancer classification schemes. *Prostate Cancer Prostatic Dis* 2021. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8170770/>
153. You S, et al. Integrated Classification of Prostate Cancer Reveals a Novel Luminal Subtype with Poor Outcome. *Cancer Res* 2016; 76(17): 4948-58. <https://doi.org/10.1158/0008-5472.CAN-16-0902>
154. Zhao SG, et al. High-throughput transcriptomic analysis nominates proteasomal genes as age-specific biomarkers and therapeutic targets in prostate cancer. *Prostate Cancer Prostatic Dis* 2015; 18(3): 229-36. <https://doi.org/10.1038/pca.2015.22>
155. Zhao SG, et al. Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis. *Lancet Oncol* 2016; 17(11): 1612-20. [https://doi.org/10.1016/S1470-2045\(16\)30491-0](https://doi.org/10.1016/S1470-2045(16)30491-0)
156. Zhao SG, et al. The Landscape of Prognostic Outlier Genes in High-Risk Prostate Cancer. *Clin Cancer Res* 2016; 22(7): 1777-86. <https://doi.org/10.1158/1078-0432.CCR-15-1250>
157. Zhao SG, et al. Associations of Luminal and Basal Subtyping of Prostate Cancer With Prognosis and Response to Androgen Deprivation Therapy. *JAMA Oncol* 2017; 3(12): 1663-72. <https://doi.org/10.1001/jamaoncol.2017.0751>
158. Zhao SG, et al. Clinical and Genomic Implications of Luminal and Basal Subtypes Across Carcinomas. *Clin Cancer Res* 2019; 25(8): 2450-57. <https://doi.org/10.1158/1078-0432.CCR-18-3121>
159. Zhao SG, et al. The Immune Landscape of Prostate Cancer and Nomination of PD-L2 as a Potential Therapeutic Target. *J Natl Cancer Inst* 2019; 111(3): 301-10. <https://doi.org/10.1093/jnci/djy141>

Reviews

160. Alam S, et al. Prostate cancer genomics: comparing results from three molecular assays. *Can J Urol* 2019;26(3):9758-62. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6700000/>
161. Alford AV, et al. The Use of Biomarkers in Prostate Cancer Screening and Treatment. *Rev Urol* 2017;19(4):221-34. <https://doi.org/10.3909/riu0772>
162. Al Hussein Al Awamli B, et al. Genomics and risk stratification in high-risk prostate cancer. *Nat Rev Urol* 2019;16(11):641-42. <https://doi.org/10.1038/s41585-019-0227-x>
163. Al-Salama ZT. Apalutamide: A Review in Non-Metastatic Castration-Resistant Prostate Cancer. *Drugs* 2019;79(14):1591-98. <https://doi.org/10.1007/s40265-019-01194-x>
164. Banerjee et al. A review on the role of tissue-based molecular biomarkers for active surveillance. *World J Urol* 2021. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8170770/>
165. Bostrom PJ, et al. Genomic Predictors of Outcome in Prostate Cancer. *Eur Urol* 2015;68(6):1033-44. <https://doi.org/10.1016/j.euro.2015.04.008>
166. Bronnimann, S et al. An overview of current and emerging diagnostic, staging and prognostic markers for prostate cancer. *Expert Rev Mol Diagn* 2020; 20: 841-850. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7207007/>
167. Carneiro A, et al. Are localized prostate cancer biomarkers useful in the clinical practice? *Tumour Biol* 2018;40(9):1010428318799255. <https://doi.org/10.1177/1010428318799255>
168. Clinton TN, et al. Tissue-based biomarkers in prostate cancer. *Expert Rev Precis Med Drug Dev* 2017;2(5):249-60. <https://doi.org/10.1080/23808993.2017.1372687>
169. Colicchia M, et al. Genomic tests to guide prostate cancer management following diagnosis. *Expert Rev Mol Diagn* 2017;17(4):367-77. <https://doi.org/10.1080/14737159.2017.1302332>
170. Cozar JM, et al. The role of miRNAs as biomarkers in prostate cancer. *Mutat Res* 2019;781:165-74. <https://doi.org/10.1016/j.mrrev.2019.05.005>
171. Creed JH, et al. Commercial Gene Expression Tests for Prostate Cancer Prognosis Provide Paradoxical Estimates of Race-Specific Risk. *Cancer Epidemiol Biomarkers Prev* 2019. <https://doi.org/10.1158/1055-9965.EPI-19-0407>
172. Cucchiara V, et al. Genomic Markers in Prostate Cancer Decision Making. *Eur Urol* 2018;73(4):572-82. <https://doi.org/10.1016/j.euro.2017.10.036>
173. da Costa JB, et al. Molecular tumor heterogeneity in muscle invasive bladder cancer: Biomarkers, subtypes, and implications for therapy. *Urol Oncol* 2018. <https://doi.org/10.1016/j.urolonc.2018.11.015>
174. Dalela D, et al. Contemporary Role of the Decipher(R) Test in Prostate Cancer Management: Current Practice and Future Perspectives. *Rev Urol* 2016;18(1):1-9. <https://doi.org/10.3909/riu0706>
175. Dall'Era M, Evans C. Genomic and Biological Markers to Select Treatment for Patients with Prostate Cancer: Choose Wisely, My Friend. *J Urol* 2017;197(1):8-9. <https://doi.org/10.1016/j.juro.2016.10.048>
176. Davis JW. Novel commercially available genomic tests for prostate cancer: a roadmap to understanding their clinical impact. *BJU Int* 2014;114(3):320-2. <https://doi.org/10.1111/bju.12695>
177. Davis J. Use of genomic markers to risk stratify men with prostate cancer. *Trends in Urology & Men's Health* 2015;6(3):36-39. <https://doi.org/10.1002/tre.461>
178. De Marzo AM, et al. Premalignancy in Prostate Cancer: Rethinking What we Know. *Cancer Prev Res* 2016;9(8):648-56. <https://doi.org/10.1158/1940-6207.CAPR-15-0431>
179. Duffy MJ. Biomarkers for prostate cancer: prostate-specific antigen and beyond. *Clin Chem Lab Med* 2020;58(3):326-39.

Genetic Testing Policies, Continued

Genetic Testing for Prostate Cancer Prognosis, continued

- <https://www.ncbi.nlm.nih.gov/pubmed/31714881>
180. Eggener SE, et al. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline. *J Clin Oncol* 2019; JCO1902768. <https://doi.org/10.1200/JCO.19.02768>
181. Falzarano SM, et al. Novel biomarkers and genomic tests in prostate cancer: a critical analysis. *Minerva Urol Nefrol* 2015;67(3):211-31. <https://www.ncbi.nlm.nih.gov/pubmed/26054411>
182. Fine ND, et al. Genomic Classifiers for Treatment Selection in Newly Diagnosed Prostate Cancer. *BJU Int* 2019. <https://doi.org/10.1111/bju.14799>
183. Gadzinski AJ, Cooperberg MR. Prostate Cancer Markers. *Cancer Treat Res* 2018; 175:55-86. https://doi.org/10.1007/978-3-319-93339-9_3
184. Gaudreau PO, et al. The Present and Future of Biomarkers in Prostate Cancer: Proteomics, Genomics, and Immunology Advancements. *Biomark Cancer* 2016;8(Suppl 2):15-33. <https://doi.org/10.4137/BIC.S31802>
185. Goldenberg SL, et al. A new era: artificial intelligence and machine learning in prostate cancer. *Nat Rev Urol* 2019;16(7):391-403. <https://doi.org/10.1038/s41585-019-0193-3>
186. Jairath, NK et al. A Systematic Review of the Evidence for the Decipher Genomic Classifier in Prostate Cancer. *Eur Urol* 2021; 79: 374-383. <https://www.ncbi.nlm.nih.gov/pubmed/33293078>
187. Jalanko, T et al. Genomic Subtyping in Bladder Cancer. *Curr Urol Rep* 2020; 21: 9. <https://www.ncbi.nlm.nih.gov/pubmed/32166460>
188. Kim SP, et al. Physician attitudes about genetic testing for localized prostate cancer: A national survey of radiation oncologists and urologists. *Urol Oncol* 2018;36(11):501 e15-01 e21. <https://doi.org/10.1016/j.urolonc.2018.07.002>
189. Kohaar I, et al. A Rich Array of Prostate Cancer Molecular Biomarkers: Opportunities and Challenges. *Int J Mol Sci* 2019;20(8). <https://doi.org/10.3390/ijms20081813>
190. Komberg Z, et al. Genomic biomarkers in prostate cancer. *Transl Androl Urol* 2018;7(3):459-71. <https://dx.doi.org/10.21037%2Ftau.2018.06.02>
191. Kretschmer A, Tiki D. Biomarkers in prostate cancer - Current clinical utility and future perspectives. *Crit Rev Oncol Hematol* 2017; 120:180-93. <https://doi.org/10.1016/j.critrevonc.2017.11.007>
192. Kretschmer A, et al. [Molecular biomarkers and prognostic factors for prostate cancer]. *Urologe A* 2017;56(7):933-44. <https://doi.org/10.1007/s00120-017-0418-0>
193. Kristiansen G. Markers of clinical utility in the differential diagnosis and prognosis of prostate cancer. *Mod Pathol* 2018;31(S1): S143-55. <https://doi.org/10.1038/modpathol.2017.168>
194. Lamy PJ, et al. Prognostic Biomarkers Used for Localised Prostate Cancer Management: A Systematic Review. *Eur Urol Focus* 2018;4(6):790-803. <https://doi.org/10.1016/j.euf.2017.02.017>
195. Loeb S, Ross AE. Genomic testing for localized prostate cancer: where do we go from here? *Curr Opin Urol* 2017;27(5):495-99. <https://doi.org/10.1097/MOU.0000000000000419>
196. Loeb S, Toscoian JJ. Biomarkers in active surveillance. *Transl Androl Urol* 2018;7(1):155-59. <https://dx.doi.org/10.21037%2Ftau.2017.12.26>
197. Martin NE. New developments in prostate cancer biomarkers. *Curr Opin Oncol* 2016;28(3):248-52. <https://doi.org/10.1097/CCO.0000000000000279>
198. Marrone M, et al. A 22 Gene-expression Assay, Decipher (R) (GenomeDx Biosciences) to Predict Five-year Risk of Metastatic Prostate Cancer in Men Treated with Radical Prostatectomy. *PLoS Curr* 2015;7. <https://doi.org/10.1371/currents.eogt.761b81608129ed61b0b48d42c04f92a4>
199. McCormick BZ, et al. Biochemical recurrence after radical prostatectomy: Current status of its use as a treatment endpoint and early management strategies. *Indian J Urol* 2019;35(1):6-17. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6334583/>
200. McKay RR, et al. Recent Advances in the Management of High-Risk Localized Prostate Cancer: Local Therapy, Systemic Therapy, and Biomarkers to Guide Treatment Decisions. *Am Soc Clin Oncol Educ Book* 2020; 40:1-12. <https://pubmed.ncbi.nlm.nih.gov/32412803/>
201. Morlacco A, Karnes RJ. Early salvage radiation therapy post-prostatectomy: key considerations. *Future Oncol* 2016;12(22):2579-87. <https://doi.org/10.2217/fon-2016-0208>
202. Moschini M, et al. Incorporation of tissue-based genomic biomarkers into localized prostate cancer clinics. *BMC Med* 2016; 14:67. <https://doi.org/10.1186/s12916-016-0613-7>
203. Na R, et al. Clinically available RNA profiling tests of prostate tumors: utility and comparison. *Asian J Androl* 2016;18(4):575-9. <https://doi.org/10.4103/1008-682X.175096>
204. Necchi, A et al. Converging Roads to Early Bladder Cancer. *Eur Urol* 2020; 78: 127-130. <https://www.ncbi.nlm.nih.gov/pubmed/32197887>
205. Nguyen HG, Welty CJ, Cooperberg MR. Diagnostic associations of gene expression signatures in prostate cancer tissue. *Curr Opin Urol* 2015;25(1):65-70. <https://doi.org/10.1097/MOU.0000000000000131>
206. Norris, JM et al. Genetic landscape of prostate cancer conspicuity on multiparametric MRI: a protocol for a systematic review and bioinformatic analysis. *BMJ Open* 2020; 10: e034611. <https://www.ncbi.nlm.nih.gov/pubmed/31992607>
207. Nowroozi, A et al. Adjuvant vs. salvage Radiation Therapy after Radical Prostatectomy: Role of Decipher(R) in the Era of Personalized Medicine. *Urol J* 2021. <https://www.ncbi.nlm.nih.gov/pubmed/33423246>
208. Olleik G, et al. Evaluation of New Tests and Interventions for Prostate Cancer Management: A Systematic Review. *J Natl Compr Canc Netw* 2018;16(11):1340-51. <https://doi.org/10.6004/jnccn.2018.7055>
209. Pisansky TM. Salvage Radiotherapy for Postoperative Biochemical Failure of Prostate Cancer: The Path Toward Personalized Medicine. *Eur Urol* 2016;70(4):597-98. <https://doi.org/10.1016/j.euro.2016.01.033>
210. Reichard CA, Klein EA. Clinical and molecular rationale to retain the cancer descriptor for Gleason score 6 disease. *Nat Rev Urol* 2017;14(1):59-64. <https://doi.org/10.1038/nrurol.2016.240>
211. Reiter RE. Risk stratification of prostate cancer 2016. *Scand J Clin Lab Invest Suppl* 2016;245: S54-9. <https://doi.org/10.1080/00365513.2016.1208453>
212. Ross AE, D'Amico AV, Freedland SJ. Which, when and why? Rational use of tissue-based molecular testing in localized prostate cancer. *Prostate Cancer Prostatic Dis* 2016;19(1):1-6. <https://doi.org/10.1038/pcan.2015.31>
213. Ross AE, et al. Utility of Risk Models in Decision Making After Radical Prostatectomy: Lessons from a Natural History Cohort of Intermediate- and High-Risk Men. *Eur Urol* 2016;69(3):496-504. <https://doi.org/10.1016/j.eururo.2015.04.016>

Genetic Testing Policies, Continued

Genetic Testing for Prostate Cancer Prognosis, continued

214. Schulster M. Bladder Cancer Academy 2019 Selected Summaries. *Rev Urol* 2019;21(1):23-28. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6585182/>
215. Sharma P, Zargar-Shoshtari K, Pow-Sang JM. Biomarkers for prostate cancer: present challenges and future opportunities. *Future Sci OA* 2016;2(1): FSO72. <https://doi.org/10.4155/fso.15.72>
216. Spahn M, et al. What is the Need for Prostatic Biomarkers in Prostate Cancer Management? *Curr Urol Rep* 2015;16(10):70. <https://doi.org/10.1007/s11934-015-0545-3>
217. Spratt DE. Performance and Utility of Prognostic Genomic Biomarkers After Prostatectomy: Decipher-ing the Data. *J Clin Oncol* 2017;35(25):2977-78. <https://doi.org/10.1200/JCO.2017.73.6470>
218. Spratt DE, et al. A Systematic Review and Framework for the Use of Hormone Therapy with Salvage Radiation Therapy for Recurrent Prostate Cancer. *Eur Urol* 2018;73(2):156-65. <https://doi.org/10.1016/j.euro.2017.06.027>
219. Stoyanova R, et al. Prostate cancer radiomics and the promise of radiogenomics. *Transl Cancer Res* 2016;5(4):432-47. <https://www.ncbi.nlm.nih.gov/pubmed/29188191>
220. Teo MY, et al. Drug development for noncastrate prostate cancer in a changed therapeutic landscape. *Nat Rev Clin Oncol* 2018;15(3):150. <https://doi.org/10.1038/nrclinonc.2017.160>
221. Tilki D, Evans CP. The Decipher Genomic Classifier Independently Improves Prognostication for Patients After Prostatectomy. *Eur Urol* 2018;73(2):176-77. <https://doi.org/10.1016/j.euro.2017.04.020>
222. Vandekerckhove, G et al. Plasma ctDNA is a tumor tissue surrogate and enables clinical-genomic stratification of metastatic bladder cancer. *Nat Commun* 2021; 12: 184. <https://www.ncbi.nlm.nih.gov/pubmed/33420073>
223. Vince RA, Jr., et al. Tissue-based genomics: which test and when. *Curr Opin Urol* 2019;29(6):598-604. <https://doi.org/10.1097/MOU.0000000000000673>
224. Zhuang L, Johnson MT. How Precisely Can Prostate Cancer Be Managed? *Int Neurourol J* 2016;20(Suppl 2): S120-30. <https://doi.org/10.5213/inj.1632724.362>
225. Zumsteg ZS, Spratt DE. Precision Medicine for Localized Prostate Cancer: Time to Move Beyond NCCN Risk Stratification? *Int J Radiat Oncol Biol Phys* 2019;103(1):92-94. <https://doi.org/10.1016/j.ijrobp.2018.09.040>

Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
11/8/23	For Commercial Plan Policy, added coverage criteria for the Decipher PR Test.
7/29/24	For Commercial Plan Policy, consolidated coverage criteria for individual tests in criteria #3 (Decipher Prostate Biopsy Genomic Classifier, OncotypeDx Prostate, and ProLaris) into one uniform set of criteria to align with updated NCCN guidelines. Also, added exclusion of the Arterai Prostate test.
12/19/24	For Commercial Plan Policy, modified requirements in criterion #1 in first section: "Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history. Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing."; and changed name of the OncotypeDX Prostate test to the Genomic Prostate Score (GPS) test in criteria #3, to reflect current branding.

Disclaimer

This document is for informational purposes only and should not be relied on in the diagnosis and care of individual patients. Medical and Coding/Reimbursement policies do not constitute medical advice, plan preauthorization, certification, an explanation of benefits, or a contract. Members should consult with appropriate healthcare providers to obtain needed medical advice, care, and treatment. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the member's individual benefit plan that is in effect at the time services are rendered.

Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: 5-FLUOROURACIL TESTING IN CANCER PATIENTS

Policy # 594

Implementation Date: 1/13/17

Review Dates: 12/21/17, 12/13/18, 4/5/23, 5/10/24

Revision Dates: 7/1/23

Related Medical Policies:

[#123 Gene Therapy, Testing, and Counseling](#)
[#590 Pharmacogenomic Testing for Drug Metabolism](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Cancer is the second leading cause of death in the United States behind heart disease. Fluoropyrimidine drugs, such as 5-fluorouracil (5-FU) and capecitabine (oral FU), are a mainstay in the treatment of numerous solid tumors, including colorectal cancers, breast, stomach, and pancreatic cancers. These drugs work to interfere with the synthetic pathway for thymidine, a critical component in DNA synthesis required for cell division. This interference in turn stops cancer cell proliferation. The levels of this drug may fluctuate in different patients due to genetic propensities of these individual patients. Theoretically, identifying individual doses may improve outcomes for patients as it may result in optimal levels of the medicines available in the patient's system to treat their condition. 5-FU is used alone or as part of combination therapies.

5-FU degradation occurs in all tissues, including tumor tissues, but is highest in the liver. In humans, 70%–90% of an administered dose of 5-FU is degraded by dihydropyrimidine dehydrogenase (DPD). Severe and even lethal toxicity reactions occur in 10–40% of patients treated with fluoropyrimidine. Toxicity due to reduced enzyme activity may result in hand-foot syndrome, fever, mucositis, stomatitis, severe diarrhea, nausea, vomiting, rectal bleeding, and neurologic abnormalities such as cerebellar ataxia (uncoordinated muscle movement) and changes in cognitive ability. Variants in the *DPYD* gene that result in reduced, or absent, DPD enzyme activity can cause this toxicity. Testing for genetic variants in *DPYD* is beneficial for reducing the risk of toxicity as there are Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for prescribing and dosing fluoropyrimidines based on an individual's *DPYD* genotype.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.



Genetic Testing Policies, Continued

Genetic Testing: 5-Fluorouracil Testing in Cancer Patients, continued

Select Health considers testing for genetic variants in *DPYD* either by gene sequencing or targeted genotyping as medically necessary for individuals considering or currently on therapy with any 5-FU containing drug including, but not limited to:

- 5-fluorouracil (Fluorouracil, Adrucil)
- Capecitabine (Xeloda)
- Fluorouracil topical formulations (Carac, Efudex, Fluropex)

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the **Select Health Commercial policy applies**. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the **Select Health Commercial criteria will apply**. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

Fluoropyrimidine drugs are frequently used for treating solid tumors. Toxicity from fluoropyrimidines have been reported in 10-40% of patients. Genetic variants in the *DPYD* gene can increase the chance of this toxicity. There are CPIC guidelines for prescribing and dosing fluoropyrimidines based on an individual's *DPYD* genotype.

There is mounting evidence about the utility and cost-effectiveness of *DPYD* genetic testing. A study by Lunenburg et al. in 2016 prospectively genotyped *DPYD* in 275 patients prior to their first fluoropyrimidine treatment and found 5% had variants that required 25–50% dose reductions. None of these patients developed toxicity. A larger, prospective, multi-center study was conducted by Deenen et al. in 2016 on 2,038 patients and variants were found in 1% of patients who were dose adjusted. In this group the risk of grade III toxicity was significantly reduced to 28% compared to 73% in historical controls ($p < 0.001$) and the drug induced rate was reduced from 10% to 0.

The group also evaluated the cost-effectiveness and found that the overall cost for screening was less than for usual care. Another cost simulation study by Cortesoso et al. in 2016 also argue that testing of 1000 patients at their center will be cost-effective in preventing neutropenia given their costs for genotyping and treatment of neutropenia given the published rates of neutropenia.

The Lunenburg reviewed concluded that there is “convincing evidence to implement prospective *DYPYD* genotyping with an upfront dose adjustment in DPD deficient patients. Immediate benefit in patient care can be expected through decreasing toxicity, while maintaining efficacy.”

Although none of the studies they cite were randomized, they point out that such studies have been attempted but have been halted due to deaths in the standard care arm, suggesting that randomized control studies will not be forthcoming (and serving as further argument for the utility of this testing).

Billing/Coding Information

CPT CODES

81232 *DPYD* (dihydropyrimidine dehydrogenase) (eg, 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, common variant(s) (eg, *2A, *4, *5, *6)

Genetic Testing Policies, Continued

Genetic Testing: 5-Fluorouracil Testing in Cancer Patients, continued

81346 TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)

81479 Unlisted molecular pathology procedure

HCPCS CODES

G0452 Molecular pathology procedure; physician interpretation and report

S3722 Dose optimization by area under the curve (AUC) analysis, for infusional 5-fluorouracil

Key References

1. Bocci G, Barbara C, Vannozzi F, et al. "A pharmacokinetic-based test to prevent severe 5-fluorouracil toxicity." *Clin Pharmacol Ther* 80.4 (2006): 384-95.
2. Boisdran-Celle M, Remaud G, Traore S, et al. "5-Fluorouracil-related severe toxicity: a comparison of different methods for the pretherapeutic detection of dihydropyrimidine dehydrogenase deficiency." *Cancer Lett* 249.2 (2007): 271-82.
3. Amstutz, U., et al. (2018). "Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 Update." *Clin Pharmacol Ther* 103(2):210-216.
4. Ciccolini J, Mercier C, Evrard A, et al. "A rapid and inexpensive method for anticipating severe toxicity to fluorouracil and fluorouracil-based chemotherapy." *Ther Drug Monit* 28.5 (2006): 678-85.
5. Cortejoso, L., X. Garcia-Gonzalez, M. I. Garcia, P. Garcia-Alfonso, M. Sanjurjo and L. A. Lopez-Fernandez (2016). "Cost-effectiveness of screening for DPYD polymorphisms to prevent neutropenia in cancer patients treated with fluoropyrimidines." *Pharmacogenomics* 17(9): 979-984.
6. Deenen, M. J., D. Meulendijks, A. Cats, M. K. Sechterberger, J. L. Severens, H. Boot, P. H. Smits, H. Rosing, C. M. Mandigers, M. Soesan, J. H. Beijnen and J. H. Schellens (2016). "Upfront Genotyping of DPYD*2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis." *J Clin Oncol* 34(3): 227-234.
7. Di Paolo A, Lencioni M, Amatori F, et al. "5-Fluorouracil Pharmacogenetics Predicts Disease-free Survival in Patients Administered Adjuvant Chemotherapy for Colorectal Cancer." *Clin Cancer Res* 14.9 (2008): 2749-55.
8. Diasio RB, Johnson MR. "The role of pharmacogenetics and pharmacogenomics in cancer chemotherapy with 5-fluorouracil." *Pharmacology* 61.3 (2000): 199-203.
9. Ezzeldin HH, Diasio RB. "Predicting fluorouracil toxicity: can we finally do it?" *J Clin Oncol* 26.13 (2008): 2080-2.
10. Gamelin, E, Delva, R, Jacob, J, et al. (2008). Individual fluorouracil dose adjustment based on pharmacokinetic follow-up compared with conventional dosage: results of a multicenter randomized trial of patients with metastatic colorectal cancer. *J Clin Oncol* 26.13: 2099-105.
11. Lunenburg, C. A., L. M. Henricks, H. J. Guchelaar, J. J. Swen, M. J. Deenen, J. H. Schellens and H. Gelderblom (2016). "Prospective DPYD genotyping to reduce the risk of fluoropyrimidine-induced severe toxicity: Ready for prime time." *Eur J Cancer* 54: 40-48.
12. Lunenburg, C. A., M. C. van Staveren, H. Gelderblom, H. J. Guchelaar and J. J. Swen (2016). "Evaluation of clinical implementation of prospective DPYD genotyping in 5-fluorouracil- or capecitabine-treated patients." *Pharmacogenomics* 17(7): 721-729.
13. Marsh S, McLeod HL. "Cancer pharmacogenetics." *Br J Cancer* 90.1 (2004): 8-11.
14. Nordgard SH, Alnaes GI, Hihm B, et al. "Pathway based analysis of SNPs with relevance to 5-FU therapy: relation to intratumoral mRNA expression and survival." *Int J Cancer* 123.3 (2008): 577-85.
15. Offer, S. M., et al. (2014). "Comparative functional analysis of DPYD variants of potential clinical relevance to dihydropyrimidine dehydrogenase activity." *Cancer Res* 74(9): 2545-2554.
16. Roche Laboratories I. "Patient information-Xeloda." (2008).
17. Saif, MW, Choma, A, Salamone, SJ, et al. (2009). Pharmacokinetically guided dose adjustment of 5-fluorouracil: a rational approach to improving therapeutic outcomes. *J Natl Cancer Inst* 101.22: 1543-52.
18. Schwab M, Zanger UM, Marx C, et al. "Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: a prospective clinical trial by the German 5-FU Toxicity Study Group." *J Clin Oncol* 26.13 (2008): 2131-8.
19. Technology Evaluation Center. (2010) Special Report: Laboratory Testing to Allow Area Under the Curve (AUC)-Targeted 5-Fluorouracil Dosing for Patients Administered Chemotherapy for Cancer. June.
20. U.S. Food and Drug Administration. Label Information Xeloda (capecitabine). 2015. www.fda.gov.

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Genetic Testing Policies, Continued

Genetic Testing: 5-Fluorouracil Testing in Cancer Patients, continued

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Genetic Testing Policies, Continued

Genetic Testing: 5-Fluorouracil Testing in Cancer Patients, continued



MEDICAL POLICY

GENETIC TESTING: 5-FLUOROURACIL TESTING IN CANCER PATIENTS

Policy # 594

Implementation Date: 1/13/17

Review Dates: 12/21/17, 12/13/18, 4/5/23, 5/10/24

Revision Dates: 7/1/23

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)
[#590 Pharmacogenomic Testing for Drug Metabolism](#)

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Description

Cancer is the second leading cause of death in the United States behind heart disease. Fluoropyrimidine drugs, such as 5-fluorouracil (5-FU) and capecitabine (oral FU), are a mainstay in the treatment of numerous solid tumors, including colorectal cancers, breast, stomach, and pancreatic cancers. These drugs work to interfere with the synthetic pathway for thymidine, a critical component in DNA synthesis required for cell division. This interference in turn stops cancer cell proliferation. The levels of this drug may fluctuate in different patients due to genetic propensities of these individual patients. Theoretically, identifying individual doses may improve outcomes for patients as it may result in optimal levels of the medicines available in the patient's system to treat their condition. 5-FU is used alone or as part of combination therapies.

5-FU degradation occurs in all tissues, including tumor tissues, but is highest in the liver. In humans, 70%–90% of an administered dose of 5-FU is degraded by dihydropyrimidine dehydrogenase (DPD). Severe and even lethal toxicity reactions occur in 10–40% of patients treated with fluoropyrimidine. Toxicity due to reduced enzyme activity may result in hand-foot syndrome, fever, mucositis, stomatitis, severe diarrhea, nausea, vomiting, rectal bleeding, and neurologic abnormalities such as cerebellar ataxia (uncoordinated muscle movement) and changes in cognitive ability. Variants in the *DYPD* gene that result in reduced, or absent, DPD enzyme activity can cause this toxicity. Testing for genetic variants in *DYPD* is beneficial for reducing the risk of toxicity as there are Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for prescribing and dosing fluoropyrimidines based on an individual's *DYPD* genotype.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Genetic Testing Policies, Continued

Genetic Testing: 5-Fluorouracil Testing in Cancer Patients, continued



MEDICAL POLICY

GENETIC TESTING: 5-FLUOROURACIL TESTING IN CANCER PATIENTS

Policy # 594

Implementation Date: 1/13/17

Review Dates: 12/21/17, 12/13/18, 4/5/23, 5/10/24

Revision Dates: 7/1/23

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Genetic Testing Policies, Continued

Genetic Testing: 5-Fluorouracil Testing in Cancer Patients, continued



MEDICAL POLICY

GENETIC TESTING: 5-FLUOROURACIL TESTING IN CANCER PATIENTS

Policy # 594

Implementation Date: 1/13/17

Review Dates: 12/21/17, 12/13/18, 4/5/23, 5/10/24

Revision Dates: 7/1/23

Related Medical Policies:

[#123 Gene Therapy, Testing, and Counseling](#)

[#590 Pharmacogenomic Testing for Drug Metabolism](#)

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COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: AGE-RELATED MACULAR DEGENERATION

Policy # 530

Implementation Date: 6/27/13

Review Dates: 4/17/14, 5/7/15, 4/14/16, 4/27/17, 7/18/18, 4/14/19, 3/7/23, 5/10/24

Revision Dates: 7/1/23

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Age-related macular degeneration (AMD) is a progressive eye disorder most often found in individuals over age 50. Age, family history, and gender are the most common variables contributing to its development. It is a major cause of blindness and visual impairment in older adults (age > 50 years). There are two types of AMD: wet and dry. Central geographic atrophy, the "dry" form of advanced AMD, results from atrophy of the retinal pigment epithelial layer below the retina, which causes vision loss through loss of photoreceptors (rods and cones) in the central part of the eye. No medical or surgical treatment is available for this condition. Neovascular or exudative AMD, the "wet" form of advanced AMD, causes vision loss due to abnormal growth of fragile and leaky blood vessels in the macula. Several intraocular therapies have been approved in recent years to treat this condition. These therapies may slow the vision loss through their reduction in new blood vessel production and associated macular edema.

Several genetic tests have been developed to assess for the potential development of "wet" AMD, or the probability of it progressing. These tests differ in the number of genetic markers as well as the methods used for calculation of risk. However, the American Academy of Ophthalmology currently does not recommend genetic testing for AMD.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover genetic testing for age-related macular degeneration. It is considered experimental/investigational due to the lack of demonstrated clinical utility.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit

Genetic Testing Policies, Continued

Genetic Testing: Age-Related Macular Degeneration, continued

their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

Laboratory-developed genetic testing evaluates the risk of patients with early or intermediate age-related macular degeneration (AMD). These tests are done by either a blood sample or swabbing the inside of the cheek. It combines a patient's disease stage with genetic predisposition, age, and smoking history to provide the probability of converting to AMD. Studies demonstrating the value of predictive testing for AMD are limited. Published studies have not identified the clinical validity or clinical utility of genetic testing in predicting the speed of advancement of AMD in those already at increased risk based on age or early evidence of AMD. This concept has been validated in a study by Hagstrom et al. in 2013. This study analyzed 834 patients; each patient was genotyped for the four genetic variants that are associated with AMD. After one year of treatment, researchers compared genotypic frequencies to therapeutic response. The study determined the genetic tests didn't serve a significant purpose helping with treatment.

Ivana et al. also reviewed genetic testing for AMD. This study found that at the present time there does not appear to be significant ethical, legal, and social implications of genetic testing for AMD, but should only be considered for early-stage disease and not for young pre-symptomatic individuals. However, it was possible to assess the risk of advanced AMD without necessarily doing the genetic test and continue to explore how the results of testing will be applied to the management of patients with AMD.

In addition to the lack of definitive published evidence, statements from specialty societies regarding the use of genetic testing for AMD do not support this testing. All saying similar statements, for example, the American Academy of Ophthalmology (AAO) has reiterated its position that eye physicians and surgeons should avoid genetic testing for age-related macular degeneration (AMD). They request testing avoidance until specific trials have shown a benefit of its use. Recommending genotyping of such patients should only be for research studies because this genetic testing has not been shown to improve clinical outcome.

Billing/Coding Information

CPT CODES

0205U	Ophthalmology (age-related macular degeneration), analysis of 3 gene variants (2 CFH gene, 1 ARMS2 gene), using PCR and MALDI-TOF, buccal swab, reported as positive or negative for neovascular age-related macular-degeneration risk associated with zinc supplements
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81479	Unlisted molecular pathology procedure

HCPCS CODES

No specific codes identified

Key References

1. AAO Task Force on Genetic Testing. (2014). Recommendations for Genetic Testing of Inherited Eye Diseases – 2014. <https://www.aoa.org/education/clinical-statement/recommendations-genetic-testing-of-inherited-eye-diseases>
2. Assel MJ, Li F, Wang Y, Allen AS, Baggerly KA, Vickers AJ. Ophthalmology. 2018 Mar;125(3):391-397. doi: 10.1016/j.ophtha.2017.09.008. Epub; 2017, Oct 9.
3. DeAngelis MM, Silveira AC, Carr EA, Kim IK. Genetics of age-related macular degeneration: current concepts, future directions. *Semin Ophthalmol*. 2011, May 26; (3):77-93.
4. Stone, E. M. (2015). "Genetic testing for age-related macular degeneration: not indicated now." *JAMA Ophthalmol*, 133(5): 598-600.
5. Warwick A, Lotery A. Genetics and genetic testing for age-related macular degeneration. *Eye (Lond)*. 2018 May; 32(5): 849–857.

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Genetic Testing Policies, Continued

Genetic Testing: Age-Related Macular Degeneration, continued

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: APOLIPOPROTEIN (APOE) TESTING

Policy # 339

Implementation Date: 4/19/07

Review Dates: 4/24/08, 4/26/09, 5/19/11, 6/21/12, 5/7/15, 4/14/16, 4/27/17, 6/21/18, 4/12/19, 2/14/23, 2/15/24

Revision Dates: 2/18/10, 5/29/13, 7/1/23

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)

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Description

Dementia is a disorder that is characterized by impairment of memory and at least one other cognitive domain (aphasia, apraxia, agnosia, executive function). The term dementia does not imply a specific cause or pathologic process. Indeed, symptoms of dementia may arise from a number of etiologies. This policy addresses genetic testing for Alzheimer's and frontotemporal dementias.

Alzheimer's disease (AD) is the most common form of dementia in the elderly, accounting for 60% to 80% of cases, and it is estimated to affect more than 4.2–5.8 million Americans. Because of increased life expectancy, the number of people living with AD is expected to triple.

Four major types of familial AD have been identified. Types 1, 3, and 4 are classified as early-onset AD because their signs and symptoms appear before age 65. Of early onset cases, 61% have a family history of AD (i.e., early onset familial Alzheimer's disease [EOFAD]) and less than 2% of all AD cases can be attributed to EOFAD. The diagnosis of EOFAD is made in families with multiple cases of AD in which the mean age of onset is before age 60–65 years. Type 2 AD is classified as late-onset AD because its signs and symptoms appear after age 65. Other than age of onset, these 2 forms of AD present very similarly.

Frontotemporal dementia (FTD) is a heterogeneous term for spectrum of diagnoses that includes disorders such as Pick's disease, progressive non-fluent aphasia, semantic dementia, FTD with Parkinsonism-17, FTD/motor-neuron disease, and progressive supranuclear palsy. FTD is characterized by focal atrophy of the frontal and temporal lobes in the absence of Alzheimer pathology. Onset usually occurs between the ages of 35–75 years, and only rarely after age 75; the mean age of onset is the sixth decade. The exact prevalence is unknown, though some estimates place FTD at 10% of dementia cases. Clinically, the disorder presents in a variety of ways, but 2 signs are typically associated with FTD: 1) gradual and progressive behavioral change, and 2) gradual and progressive language dysfunction. The most common presenting symptom is word-finding difficulty. However, decreased fluency or hesitancy in producing speech, difficulty with language comprehension, and motor speech difficulties (e.g., dysarthria) are also common.

Coronary heart disease risk assessment is another clinical circumstance in which ApoE is being used. ApoE plays a key role in lipoprotein metabolism and cardiovascular disease, which remove excess cholesterol from the blood and transports cholesterol to the liver for processing. ApoE genetic testing has been proposed for use in predicting risk of cardiovascular disease (e.g., heart attack, stroke) hyperlipoproteinemia type III, and therapy response. Testing for ApoE may sometimes be ordered to help guide lipid treatment. In cases of high cholesterol and triglyceride levels, statins are usually considered the treatment of choice to decrease the risk of developing CVD; however, there is a wide variability in the

POLICY #339: GENETIC TESTING: APOLIPOPROTEIN (APOE) TESTING



Genetic Testing Policies, Continued

Genetic Testing: Apolipoprotein (APOE)Testing, continued

response to these lipid-lowering drugs that is in part influenced by the Apo E genotype. Some evidence suggests though appropriately responsive to a low-fat diet, people with ApoE e4 may be less likely than those with ApoE e2 to respond to statins by decreasing their levels of LDL-C and may require adjustments to their treatment plans. At present, the clinical utility of this type of information is yet to be totally understood. Dietary adjustment and statin drugs are the preferred agents for lipid-lowering therapy. ApoE testing may also be ordered occasionally to help diagnose type III hyperlipoproteinemia in a person with symptoms that suggest the disorder and to evaluate the potential for the condition in other family members.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover genetic testing for Alzheimer's disease or any type of dementia. This meets the plan's definition of experimental/investigational.

Select Health does NOT cover Apolipoprotein E (apoE) testing for assessing increased risk of cardiovascular disease. This meets the plan's definition of experimental/investigational.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

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Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

Alzheimer's disease. The early-onset forms of AD (types 1, 3, and 4) are inherited in an autosomal dominant pattern (i.e., 1 copy of the altered gene in each cell is sufficient to cause the disorder). In most cases, an affected person inherits the altered gene from one affected parent. Researchers have identified three missense gene mutations that cause these forms of AD: the APP gene on chromosome 21 (21q21), the PSEN1 gene on chromosome 14 (14q24.3), and the PSEN2 gene on chromosome 1 (1q31-q42). Penetrance for these genes is around 100%.

The APP gene codes for the amyloid precursor protein and the PSEN1 and PSEN2 genes code for the presenilin-1 and presenilin-2 proteins, respectively. These proteins are part of a process in which amyloid precursor protein is cut into smaller segments (peptides). One of these peptides, soluble amyloid precursor protein (sAPP), has growth-promoting properties and may play a role in the formation of nerve cells in both embryonic and adult brain tissue.

More than 140 PSEN1 mutations have been identified in patients with type 3 AD and approximately 11 PSEN2 mutations have been shown to cause type 4 AD. At least 22 APP mutations have been described in patients with type 1 AD. Mutations to these genes appear to negatively affect the processing of amyloid precursor protein, which leads to increased production of amyloid beta peptide, which can build up in the brain and form the amyloid plaques characteristic of AD. Amyloid plaques may lead to the death of nerve cells and the progressive signs and symptoms of this disorder.

PSEN1 mutations account for 30%–70% of cases of early-onset familial AD. PSEN2 mutations account for less than 5% of early-onset familial AD cases. APP mutations are responsible for about 2%–15% of all early-onset familial AD cases. Kindreds with autosomal dominant EOFAD with no identifiable mutations in

Genetic Testing Policies, Continued

Genetic Testing: Apolipoprotein (APOE)Testing, continued

the PSEN1, PSEN2, or APP genes have been described; thus, it is likely that other causative genes will be identified. Penetrance of PSEN1 is 100% by age 65. Penetrance of PSEN2 is 95%.

The genetic causes of late-onset (type 2) familial AD are less clear. This disorder is likely related to mutations in one or more risk factor genes in combination with lifestyle and environmental factors. Mutations to the APOE gene on chromosome 19 (19q13.2) are associated with increased risk for late-onset familial AD. The APOE gene codes for apolipoprotein E and packages and transports cholesterol (and other fats) through the bloodstream, and then delivers them to the appropriate locations in the body for processing and use. Apolipoprotein E is a major component of very low-density lipoproteins (VLDLs), which remove excess cholesterol from the blood to the liver for processing.

There are 3 common APOE alleles ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$) and 6 possible genotypes. Evidence for a genetic risk factor in late onset AD is strongest for the $\epsilon 4$ allele of APOE. The APOE $\epsilon 4$ allele is associated with an increased number of amyloid plaques in the brain tissue of people with AD. There appears to be a dose-response effect of $\epsilon 4$: each additional copy is associated with an increased risk of AD and earlier age of onset; 68 years in $\epsilon 4$ homozygotes, 77 years for heterozygotes, and about 85 years for no $\epsilon 4$ allele. However, while the APOE $\epsilon 4$ allele conveys an increased risk of developing AD, not all people with AD disease have the $\epsilon 4$ allele, nor will all people with the $\epsilon 4$ allele develop the disease. APOE mutations appear to predispose to the psychiatric complications associated with AD and $\epsilon 4$ may also affect the risk for development of vascular dementia.

A 2003 Hayes Directory on gene mutations portending risk for AD concluded that genetic testing for APP and Presenilin mutations has utility in suspected cases of early onset AD but that testing is of limited additional clinical value in young (under age 50) symptomatic patients with a confirmed autosomal dominant family history of AD. The review also gave a 'B' rating for use of this testing to predict risk for AD in asymptomatic patients younger than 50 with a confirmed history of early-onset AD. The basis for the 'B' rating lies in the benefits conferred by a positive test result; namely, that such information affords patients the luxury of making health and family decisions in the context of almost certain disease risk. No literature has been published which suggests that genetic testing for early onset AD has any impact on clinical management of the disease.

The genetic causes of late-onset (type 2) familial AD are less clear. This disorder is likely related to mutations in one or more risk factor genes in combination with lifestyle and environmental factors. Mutations to the APOE gene on chromosome 19 (19q13.2) are associated with increased risk for late-onset familial AD. There are 3 common APOE alleles ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$) and 6 possible genotypes. Evidence for a genetic risk factor in late onset AD is strongest for the $\epsilon 4$ allele of APOE. The APOE $\epsilon 4$ allele is associated with an increased number of amyloid plaques in the brain tissue of people with AD. There appears to be a dose-response effect of $\epsilon 4$: each additional copy is associated with an increased risk of AD and earlier age of onset; 68 years in $\epsilon 4$ homozygotes, 77 years for heterozygotes, and about 85 years for no $\epsilon 4$ allele. However, while the APOE $\epsilon 4$ allele conveys an increased risk of developing AD, not all people with AD disease have the $\epsilon 4$ allele, nor will all people with the $\epsilon 4$ allele develop the disease.

The literature offers minimal support for genetic testing for APOE alleles either to diagnose AD or identify persons at risk for developing the disease. While the literature suggests a potential use of APOE genotyping to predict the rate of cognitive decline or treatment response AD patients, the research is not consistent in this area. A positive APOE test may also provide confirmatory evidence of an AD diagnosis, but there is little evidence to suggest that such information would have any impact on subsequent treatment decisions. Given the high prevalence of $\epsilon 4$ alleles in the population, APOE genotyping in asymptomatic individuals, is unlikely to further clarify an individual's risk for AD over other information such as family history or cognitive test results. Consequently, APOE genetic testing is more appropriately used in a research context as opposed to a clinical tool for diagnosing AD.

The American College of Medical Genetics practice guideline for genetic testing in Alzheimer's disease (Goldman et al) recommends against testing for APOE alleles. If a genetic cause for EOAD is found, its clinical utility is debatable since there are no medical treatments for EOAD. However, it may be beneficial for asymptomatic individuals in the same family to be tested (for planning purposes) and on a societal level identifying individuals with these known mutations may allow participation in research studies or trials to try and discover more about causes/treatments for AD. A case for testing in families with autosomal AD and possible parameters/guidelines are in the ACMG guideline (Goldman et al).

Genetic Testing Policies, Continued

Genetic Testing: Apolipoprotein (APOE)Testing, continued

Frontotemporal Dementia. While 40%–50% of FTD patients have some family history of dementia or neurodegenerative disease, only 5%–10% of FTD patients have a family history suggestive of an autosomal dominant pattern of inheritance, i.e. a clear pattern of FTD-type diagnoses being passed from parent to child, with virtually every patient having an affected parent and each child of an affected person having a 50% chance to inherit the disorder. The age of onset can often be younger with familial and inherited forms of FTD (30s and 40s) and the disease may progress more rapidly.

Mutations of the microtubule-associated protein tau (MAPT) gene on chromosome 17 (17q21-22) are responsible for about 10% of familial FTD cases but up to 50% of autosomal dominant FTD. MAPT codes for the tau protein. Thirty to 40 different MAPT mutations causing FTD have been identified most of which are located between exons 9 and 13. Mutations form mutant tau proteins in cells or change the proportion of the forms of tau normally expressed in the brain. These changes promote tau aggregation into filaments and harm the ability of tau to bind to microtubules.

MAPT mutations are associated with one inherited form of FTD called Frontotemporal Dementia with Parkinsonism-17 (FTDP-17). MAPT mutations account for approximately 70% of autosomal dominant FTDP-17 and 33% of cases with a positive family history.

In some families with frontotemporal dementia showing with an inheritance pattern suggestive of linkage to chromosome 17q21.1, neither mutations in the MAPT gene nor tau pathology at neuropathologic examination has been found. Moreover, heterogeneity in clinical presentation is observed even within families with the same MAPT mutation. These findings suggest that additional gene mutations and other risk factors likely play a role in development of FTD and its phenotypic expression. Indeed, recent studies point to mutations of the progranulin gene as playing some role in the development of sporadic ubiquitin-associated FTD.

The primary literature on genetic testing for FTD is still in the early stages with articles focused primarily on describing genetic mutations. Although there are no systematic reviews on genetic testing and FTD, several literature reviews have been published, which summarize the extant research on the genetics of FTD and the clinical utility of testing. These reviews suggest several conclusions about the state of genetic testing for FTD:

- FTD is a complex disorder with a heterogeneous presentation and poorly understood neuropathology. Knowledge about the genetics of this disorder is rapidly emerging.
- Persons with a family history of dementia or neurodegenerative disorders are at higher risk for developing FTD than the general population. Individuals with a clear history of FTD are at extremely high risk.
- Tau pathology occurs in a percentage FTD cases and is particularly common in persons with an autosomal dominant pattern of FTD.
- MAPT mutations linked to tau pathology are associated with FTD, particularly among persons with a family history of autosomal dominant FTD. Goldman et al. estimates the risk of having a tau mutation to be 80% in persons with more than three family members with a history of fulminate FTD.
- The penetrance of the many MAPT mutations is variable, though penetrance of some may be 100%.
- Many additional genes and other risk factors likely play a role in the development of FTD and its phenotypic expression.
- For a particularly rare form of FTD, FTDP-17, genetic testing for certain MAPT mutations may be informative.
- The clinical utility of genetic testing for FTD in most patients with dementia has not been established.

A literature review performed in February 2010 identified a study by Mihaescu et al. recognized that genotyping is not considered useful for screening, presymptomatic testing, or diagnosing Alzheimer's disease. They concluded their study by stating "Most research on genome-based applications in AD is still in the first phase of the translational research framework, which means that massive research is still needed before their implementation can be considered."

Genetic Testing Policies, Continued

Genetic Testing: Apolipoprotein (APOE)Testing, continued

Apolipoprotein E (apoE) testing for risk of coronary heart disease. Multiple studies and reviews have evaluated the relationship between apo E genotypes (particularly the apo E4 allele) and both LDL-cholesterol and the incidence of CHD. However, these reports may have been both underpowered to detect the true relationship and also subject to publication bias. The largest meta-analysis of the impact of the presence of the apo E allele on LDL-cholesterol levels and CHD risk came to the conclusions that there was an approximately linear relationship of apoE genotypes (when ordered E2/E2, E2/E3, E3/E3, E3/E4, and E4/E4) with LDL-cholesterol. There was a weakly inverse relationship of these genotypes with HDL-cholesterol level and a non-linear relationship with triglycerides, with the E3/E3 genotype having the lowest triglyceride levels. The lack of predictability in use of ApoE as a screening test for clinically defined atherosclerotic disease was also verified in systematic review published in 2002. The study suggests that apoE genotype may be related with lipid levels and CAD but is probably not useful in providing additional clinically relevant information beyond established risk factors. Apo E is considered not an effective predictor of CAD, when compared to other established procedures.

Similarly, the role of apolipoprotein E (APOE) phenotypes in cerebrovascular disease and ischemic stroke is unsettled. This apolipoprotein is a ligand for hepatic chylomicron and VLDL remnant receptors, leading to clearance of these lipoproteins from the circulation, and for LDL receptors. The APOE e4 allele has been reported to be a stroke risk factor in some but not other studies.

Billing/Coding Information

CPT CODES

81401 Molecular pathology procedure, Level 2

HCPCS CODES

S3852 DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

0355U APOL1 (apolipoprotein L1) (eg, chronic kidney disease), risk variants (G1, G2)

Key References

1. Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Berry-Kravis E, Bennett DA. The apolipoprotein E epsilon4 allele and incident Alzheimer's disease in persons with mild cognitive impairment. *Neurocase* 11.1 (2005): 3-7.
2. Babic T, Mahovic Lakusic D, Sertic J, Petrovecki M, Stavlenic-Rukavina A. ApoE genotyping and response to galanthamine in Alzheimer's disease—a real life retrospective study. *Coll Antropol* 28.1 (2004): 199-204.
3. Basun H, Corder EH, Guo Z, Lannfelt L, Corder LS, Manton KG, Winblad B, Viitanen M. Apolipoprotein E polymorphism and stroke in a population aged 75 years or more. *Stroke*. 1996;27(8):1310.
4. Bennet AM, DiAngelantonio E, Ye Z, Wensley F, Dahlin A, Ahlbom A, Keavney B, Collins R, Wiman B, de Faire U, Danesh J. Association of apolipoprotein E genotypes with lipid levels and coronary risk. *JAMA*. 2007;298(11):1300.
5. Bird TD. Alzheimer Disease Overview. 2005. GeneClinics. Available: <http://geneclinics.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=SYm8NGkWWp5MZ&gry=&fcn=y&fw=qqcl&filename=/profiles/alzheimer/index.html>. Date Accessed: January 30, 2007.
6. Bird TD. Early-Onset Familial Alzheimer Disease. 2005. GeneClinics. Available: <http://geneclinics.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=UsiYldmu9bVP8&gry=&fcn=y&fw=jbhN&filename=/profiles/alzheimer-early/index.html>. Date Accessed: December 19, 2006.
7. Bizzarro A, Marra C, Acciari A, et al. Apolipoprotein E epsilon4 allele differentiates the clinical response to donepezil in Alzheimer's disease. *Dement Geriatr Cogn Disord* 20.4 (2005): 254-61.
8. Berkely HeartLab Apolipoprotein E (apoE) Genotype for Cardiovascular Disease Management <http://www.bhllc.com/clinicians/clinical-references/reference-manual/chapter19>
9. Bunce D, Fratiglioni L, Small BJ, Winblad B, Backman L. APOE and cognitive decline in preclinical Alzheimer disease and non-demented aging. *Neurology* 63.5 (2004): 816-21.
10. Casas JP, Hingorani AD, Bautista LE, Sharma P. Meta-analysis of genetic studies in ischemic stroke: thirty-two genes involving approximately 18,000 cases and 58,000 controls. *Arch Neurol*. 2004;61(11):1652.
11. Caselli RJ, Reiman EM, Osborne D, et al. Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE e4 allele. *Neurology* 62.11 (2004): 1990-5.
12. Cervilla J, Prince M, Joels S, Lovestone S, Mann A. Premorbid cognitive testing predicts the onset of dementia and Alzheimer's disease better than and independently of APOE genotype. *J Neurol Neurosurg Psychiatry* 75.8 (2004): 1100-6.
13. Devanand DP, Pelton GH, Zamora D, et al. Predictive utility of apolipoprotein E genotype for Alzheimer disease in outpatients with mild cognitive impairment. *Arch Neurol* 62.6 (2005): 975-980.
14. Frikke-Schmidt R, Tybjaerg-Hansen A, Steffensen R, Jensen G, Nordestgaard BG. Apolipoprotein E genotype: epsilon32 women are protected while epsilon43 and epsilon44 men are susceptible to ischemic heart disease: the Copenhagen City Heart Study. *J Am Coll Cardiol*. 2000;35(5):1192.

Genetic Testing Policies, Continued

Genetic Testing: Apolipoprotein (APOE)Testing, continued

15. Frikke-Schmidt R, Nordestgaard BG, Thudium D, Moes Gronholdt ML, Tybjaerg-Hansen A APOE genotype predicts AD and other dementia but not ischemic cerebrovascular disease. *Neurology*. 2001;56(2):194.
16. Genetics Home Reference. Alzheimer disease. 2006. National Library of Medicine. Available: <http://ghr.nlm.nih.gov/condition=alzheimerdisease>. Date Accessed: December 19, 2006.
17. Genetics Home Reference. APOE. 2006. National Library of Medicine. Available: <http://ghr.nlm.nih.gov/gene=apoe>. Date Accessed: December 19, 2006.
18. Genetics Home Reference. APP. 2006. National Library of Medicine. Available: <http://ghr.nlm.nih.gov/gene=app>. Date Accessed: December 19, 2006.
19. Genetics Home Reference. PSEN1. 2006. National Library of Medicine. Available: <http://ghr.nlm.nih.gov/gene=pSEN1>. Date Accessed: December 19, 2006.
20. Genetics Home Reference. PSEN2. 2006. National Library of Medicine. Available: <http://ghr.nlm.nih.gov/gene=pSEN2>. Date Accessed: December 19, 2006.
21. Goldman, J. S., S. E. Hahn, J. W. Catania, S. LaRusse-Eckert, M. B. Butson, M. Rumbaugh, M. N. Strecker, J. S. Roberts, W. Burke, R. Mayeux, T. Bird, G. American College of Medical and C. the National Society of Genetic (2011). "Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors." *Genet Med.* 13(6): 597-605.
22. Goldman, J. S., S. E. Hahn, J. W. Catania, S. LaRusse-Eckert, M. B. Butson, M. Rumbaugh, M. N. Strecker, J. S. Roberts, W. Burke, R. Mayeux, T. Bird, G. American College of Medical and C. the National Society of Genetic (2011). "Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors." *Genet Med.* 13(6): 597-605.
23. Gorevic PD. Genetic factors in the amyloid diseases. 2006. UpToDate. Available: <http://www.utdol.com/utd/content/topic.do?topicKey=othrheum/13759>. Date Accessed: December 19, 2006.
24. Hayden KM, Zandi PP, Lyketsos CG, et al. Apolipoprotein E genotype and mortality: findings from the Cache County Study. *J Am Geriatr Soc* 53.6 (2005): 935-42.
25. Hayes Directory. Genetic Testing for Susceptibility to Alzheimer's Disease. Lansdale, PA: Winifred S. Hayes, Inc., 2003.
26. Hsiung GY, Sadovnick AD, Feldman H. Apolipoprotein E epsilon4 genotype as a risk factor for cognitive decline and dementia: data from the Canadian Study of Health and Aging. *Cmaj* 171.8 (2004): 863-7.
27. Huang W, Qiu C, von Strauss E, Winblad B, Fratiglioni L. APOE genotype, family history of dementia, and Alzheimer disease risk: a 6-year follow-up study. *Arch Neurol* 61.12 (2004): 1930-4.
28. June E, Eichner, 1 S. Terence Dunn, 2 Ghazala Perveen, 1 David M. Thompson, 1 Kenneth E. Stewart, 1 and Berit Apolipoprotein E Polymorphism and Cardiovascular Disease: A Huge Review. *Am J Epidemiol* 2002; 155:487-95.
29. Khachaturian AS, Corcoran CD, Mayer LS, Zandi PP, Breitner JC. "Apolipoprotein E epsilon4 count affects age at onset of Alzheimer disease, but not lifetime susceptibility: The Cache County Study." *Arch Gen Psychiatry* 61.5 (2004): 518-24.
30. Klages JD, Fisk JD, Rockwood K. "APOE genotype, memory test performance, and the risk of Alzheimer's disease in the Canadian Study of Health and Aging." *Dement Geriatr Cogn Disord* 15.1 (2003): 1-5.
31. Kleiman T, Zdanys K, Black B, et al. "Apolipoprotein E epsilon4 allele is unrelated to cognitive or functional decline in Alzheimer's disease: retrospective and prospective analysis." *Dement Geriatr Cogn Disord* 22.1 (2006): 73-82.
32. Knopman DS, DeKosky ST, Cummings JL, et al. "Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology." *Neurology* 56.9 (2001): 1143-53.
33. Kuljis RO. Alzheimer Disease. 2005. EMedicine Website. Available: <http://www.emedicine.com/neuro/topic13.htm>. Date Accessed: August 18, 2006.
34. Lab Tests Online. PSEN1. 2005. American Association for Clinical Chemistry. Available: <http://www.labtestsonline.org/understanding/analytes/pSEN1/glance.html>. Date Accessed: December 19, 2006.
35. Lab Test Online ApoE Genotyping ApoE cardiac risk; ApoE 2 mutations; APOE4 genotype <http://labtestsonline.org/understanding/analytes/apoe/tab/test>
36. Lavados M, Farias G, Rothhammer F, et al. ApoE alleles and tau markers in patients with different levels of cognitive impairment. *Arch Med Res* 36.5 (2005): 474-9.
37. Lee DY, Youn JC, Choo IH, et al. Combination of clinical and neuropsychologic information as a better predictor of the progression to Alzheimer disease in questionable dementia individuals. *Am J Geriatr Psychiatry* 14.2 (2006): 130-138.
38. Marra C, Bizzarro A, Daniele A, et al. Apolipoprotein E epsilon4 allele differently affects the patterns of neuropsychological presentation in early- and late-onset Alzheimer's disease patients. *Dement Geriatr Cogn Disord* 18.2 (2004): 125-31.
39. McCarron MO, Delong D, Alberts MJ APOE genotype as a risk factor for ischemic cerebrovascular disease: a meta-analysis. *Neurology*. 1999;53(6):1308.
40. Mihaescu R, Detmar SB, Cornel MC, et al. (2010) Translational Research in Genomics of Alzheimer's Disease: A Review of Current Practice and Future Perspectives. *J Alzheimers Dis*. Feb 24.
41. Murrell JR, Price B, Lane KA, et al. Association of apolipoprotein E genotype and Alzheimer disease in African Americans. *Arch Neurol* 63.3 (2006): 431-4.
42. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 56.9 (2001): 1133-42.
43. Post SG, Whitehouse PJ, Binstock RH, et al. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA* 277.10 (1997): 832-6.
44. Press D, Alexander M. Treatment of Dementia. 2006. UpToDate Online. Available: <http://www.utdol.com/utd/content/topic.do?topicKey=nuroegen/2315&type=A&selectedTitle=4~38>. Date Accessed: August 18, 2006.
45. Rigaud A-S, Traykov L, Latour F, Couderc Rm, Moulin F, Forette Fo. Presence or absence of at least one epsilon 4 allele and gender are not predictive for the response to donepezil treatment in Alzheimer's disease. *Pharmacogenetics* 12.5 (Print) (2002): 415-420.
46. Schneider JA, Bienias JL, Wilson RS, Berry-Kravis E, Evans DA, Bennett DA. The apolipoprotein E epsilon4 allele increases the odds of chronic cerebral infarction [corrected]detected at autopsy in older persons. *Stroke*. 2005;36(5):954.

Genetic Testing Policies, Continued

Genetic Testing: Apolipoprotein (APOE)Testing, continued

47. Shadlen M-F, Larson EB. Dementia syndromes. 2006. UpToDate Online. Available: <http://www.utdol.com/utd/content/topic.do?topicKey=nuroegen/5175&type=A&selectedTitle=2~38>. Date Accessed: August 11, 2006.
48. Shadlen M-F, Larson EB. Risk factors for dementia. 2006. UpToDate. Available: <http://www.utdol.com/utd/content/topic.do?topicKey=nuroegen/5651&type=A&selectedTitle=2~13>. Date Accessed: December 19, 2006.
49. Statement on use of apolipoprotein E testing for Alzheimer disease. American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer disease. JAMA 274.20 (1995): 1627-9.
50. Sturgeon JD, Folsom AR, Bray MS, Boerwinkle E, Ballantyne CM, Atherosclerosis Risk in Communities Study Investigators Apolipoprotein E genotype and incident ischemic stroke: the Atherosclerosis Risk in Communities Study. Stroke. 2005;36(11):2484.
51. Tervo S, Kivipelto M, Hanninen T, et al. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. Dement Geriatr Cogn Disord 17.3 (2004): 196-203.
52. Tschanz JT, Welsh-Bohmer KA, Lyketsos CG, et al. Conversion to dementia from mild cognitive disorder: the Cache County Study. Neurology 67.2 (Electronic) (2006): 229-234.
53. Walden CC, Hegele RA. Apolipoprotein E in hyperlipidemia. Ann Intern Med. 1994;120(12):1026 Wilson PW, Myers RH, Larson MG, Ordovas JM, Wolf PA, Schaefer EJ. Apolipoprotein E alleles, dyslipidemia, and coronary heart disease. The Framingham Offspring Study. JAMA. 1994;272(21):1666.
54. Yip AG, McKee AC, Green RC, et al. APOE, vascular pathology, and the AD brain. Neurology 65.2 (2005): 259-65.
55. Zhu L, Fratiglioni L, Guo Z, Basun H, Corder EH, Winblad B, Viitanen M. Incidence of dementia in relation to stroke and the apolipoprotein E epsilon4 allele in the very old. Findings from a population-based longitudinal study. Stroke. 2000;31(1):53.

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: BREAST, OVARIAN, PANCREATIC, AND PROSTATE CANCER

Policy # 664

Implementation Date: 7/1/23

Review Dates: 8/16/24

Revision Dates: 11/8/23, 4/19/24, 9/4/24, 12/20/24

Related Medical Policies:

[#438 Genetic Testing: PTEN Mutation Analysis](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Nearly 2 million individuals are diagnosed with cancer each year in the United States. Breast and prostate cancer are the most common, respectively accounting for 16% and 15% of all cancer diagnoses. Ovarian and pancreatic cancers are less common but associated with significant mortality. While most cancer is sporadic, 5-10% of individuals have hereditary cancer, meaning there is an underlying genetic variant that predisposes the individual to developing cancer. Several genes are known to increase the risk of developing breast, ovarian, pancreatic, and/or prostate cancer, with many of these genes increasing the risk for multiple of these types of cancers. This includes, but is not limited to, *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, *STK11*, and *TP53*.

Personal and family history factors which suggest an individual may have a genetic cancer predisposition include early-onset cancer, multiple family members over several generations with cancer diagnoses, or a history of certain types of cancers. For individuals who have suggestive personal or family histories, genetic testing for cancer susceptibility genes (i.e., germline testing) may be useful for determining whether there is an underlying genetic cause. Identifying a genetic variant causing a hereditary cancer susceptibility can help guide an individual's cancer-related screening and management, to improve health outcomes. Diagnosing a genetic cancer susceptibility can also help identify at-risk family members who may also benefit from genetic testing.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Genetic Testing Policies, Continued

Genetic Testing: Breast, Ovarian, Pancreatic, and Prostate Cancer, continued

3. Select Health covers panel testing for breast, ovarian, prostate, and pancreatic cancer susceptibility genes, which must include at minimum the following genes: *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, *STK11*, and *TP53*, when one of the following criteria are met (A–G):
 - A. Personal history of breast cancer diagnosed \leq 50 years; **OR**
 - B. Personal history of breast cancer at any age and one of the following (1–8):
 1. To aid in systemic treatment decisions using PARP inhibitors^a for breast cancer in the metastatic setting, or
 2. To aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer; or
 3. Triple-negative breast cancer; or
 4. Multiple primary breast cancers (synchronous or metachronous); or
 5. Lobular breast cancer with personal or family history of diffuse gastric cancer; or
 6. Male breast cancer; or
 7. Ashkenazi Jewish ancestry; or
 8. ≥ 1 close blood relative^b with any of the following (i–vii):
 - i. Breast cancer at age \leq 50; or
 - ii. Male breast cancer; or
 - iii. Ovarian cancer; or
 - iv. Pancreatic cancer; or
 - v. Prostate cancer at any age with metastatic^c, or high- or very-high-risk group*; or
 9. ≥ 3 total diagnoses of breast and/or prostate cancer (any grade) on the same side of the family, including the patient with breast cancer; **OR**
 - C. Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age; **OR**
 - D. Personal history of exocrine pancreatic cancer; **OR**
 - E. Personal history of prostate cancer and any of the following (1–4):
 1. Metastatic or high- or very-high risk group per NCCN.
 2. ≥ 1 close blood relative^b with one of the following (i–v):
 - i. Breast cancer at age \leq 50 years; or
 - ii. Triple-negative breast cancer at any age; or
 - iii. Male breast cancer at any age; or
 - iv. Ovarian cancer at any age; or
 - v. Pancreatic cancer at any age; or
 - vi. Metastatic, high- or very-high risk group prostate cancer.
 3. ≥ 3 close blood relatives^b with prostate cancer (any grade) and/or breast cancer at any age on the same side of the family, including the patient with prostate cancer;
 4. Ashkenazi Jewish ancestry; **OR**
 - F. An affected individual (not meeting testing criteria listed above) or unaffected individual with any of the following:
 1. a first- or second-degree blood relative meeting any of criteria A–C (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making^d); or
 2. a first-degree blood relative meeting any of criteria D–E; or
 3. a personal or family history of a known pathogenic or likely pathogenic variant in a breast, ovarian, pancreatic, and/or prostate cancer susceptibility gene who have a family history suggesting a different syndrome in addition to the known variant; **OR**

Genetic Testing Policies, Continued

Genetic Testing: Breast, Ovarian, Pancreatic, and Prostate Cancer, continued

- G. An affected or unaffected individual, who otherwise does not meet the criteria above, but has a probability > 5% of a BRCA1/2 pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk); must be performed by the ordering physician.

Note: If a multigene cancer panel is performed, the appropriate panel code should be used.

a- The two FDA approved PARP inhibitors - olaparib and talazoparib are included as a category 1, preferred options for those with germline BRCA1/2 mutations. The NCCN Panel recommends assessing for germline BRCA1/2 mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA indicated in HER2-negative disease, the NCCN Panel supports use in any breast cancer subtype associated with germline BRCA1/2 mutations.

b- Close blood relatives include first-, second-, and third-degree relatives on the same side of the family.

c- Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence only. Prostate cancer-specific mortality should be a surrogate for metastatic disease for family history purposes.

d- This may be extended to an affected third-degree relative if related through two male relatives (e.g., paternal grandfather's mother or sister). If the affected first-degree relative underwent genetic testing and is negative for detectable P/LP variants and there is no other family history of cancer, there is a low probability that any finding will have documented clinical utility.

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Billing/Coding Information

CPT Codes

0037U Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden [FoundationOne CDx]

0102U Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated [17 genes (sequencing and deletion/duplication)]

0103U Hereditary ovarian cancer (eg, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated [24 genes (sequencing and deletion/duplication); EPCAM (deletion/duplication only)]

Genetic Testing Policies, Continued

Genetic Testing: Breast, Ovarian, Pancreatic, and Prostate Cancer, continued

- 0131U** Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure) (Use 0131U in conjunction with 81162, 81432, 0102U)
- 0129U** Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
- 0132U** Hereditary ovarian cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure) (Use 0132U in conjunction with 81162, 81432, 0103U)
- 0134U** Hereditary pan cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure)
- 0135U** Hereditary gynecological cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure)
- 0137U** PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0138U** BRCA1(BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0172U** Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score
- 0235U** PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
- 81162** BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
- 81163** BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
- 81164** BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
- 81165** BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
- 81166** BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
- 81167** BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)

Genetic Testing Policies, Continued

Genetic Testing: Breast, Ovarian, Pancreatic, and Prostate Cancer, continued

- 81212** BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
- 81215** BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
- 81216** BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
- 81217** BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
- 81307** PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
- 81308** PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
- 81321** PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
- 81322** PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
- 81323** PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
- 81351** TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
- 81352** TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
- 81353** TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant
- 81404** Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
- 81405** Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
- 81406** Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
- 81432** Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
- 81433** Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
- 81449** Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF,

Genetic Testing Policies, Continued

Genetic Testing: Breast, Ovarian, Pancreatic, and Prostate Cancer, continued

CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis

- 81445** Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
- 81455** Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
- 81456** Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
- 81450** Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
- 81451** Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

81479 Unlisted molecular pathology procedure

88271 - 88275 Molecular cytogenetics

Key References

1. Centers for Disease Control and Prevention (CDC). Genetic Testing for Hereditary Breast and Ovarian Cancer.
2. NCCN Guidelines. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3.2024 – February 12, 2024.

Revision History

Revision Date	Summary of Changes
11/8/23	For Commercial Plan Policy, modified overall coverage criteria regarding required panel of genes to be tested (changed <i>should</i> to <i>must</i>): “Select Health covers panel testing for high-penetrance breast cancer susceptibility genes, which must include the following genes (BRCA1/2, CDH1, PALB2, PTEN, and TP53)”
4/19/24	For Commercial Plan Policy, added the STK11 gene as part of the required genes to qualify for panel testing: “Select Health covers panel testing for high-penetrance breast cancer susceptibility genes, which must include the following genes (BRCA1/2, CDH1, PALB2, PTEN, STK11, and

Genetic Testing Policies, Continued

Genetic Testing: Breast, Ovarian, Pancreatic, and Prostate Cancer, continued

	TP53" and modified criterion #E3: "3. > 3 close blood relatives with prostate cancer (any grade) and/or breast cancer at any age on the same side of the family including the patient with prostate cancer; ..."
9/4/24	Modified title of policy to include addition of "Ovarian, Pancreatic, and Prostate Cancer," and for Commercial Plan Policy, incorporated coverage criteria for evaluation of genetic testing for these cancers, and modified overall coverage criteria to align with current clinical standards; and added the following note: "If a multigene cancer panel is performed, the appropriate panel code should be used."
12/20/24	For Commercial Plan Policy, modified requirements in criterion #1 in first section: "Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history. Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing."

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: CARDIOMYOPATHY

Policy # 665

Implementation Date: 7/1/23

Review Dates: 8/16/24

Revision Dates: 12/6/23, 9/3/24

Related Medical Policies:
[#123: Gene Therapy, Testing, and Counseling](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Cardiomyopathy is a disease where the heart muscle has become abnormally thickened, enlarged, or rigid, making it difficult to pump blood. Over time, cardiomyopathy weakens the heart so that it is less effective in pumping blood throughout the body and maintaining a normal rhythm. This can result in heart failure, arrhythmia, or other complications.

There are several types of cardiomyopathy, including:

- Arrhythmogenic cardiomyopathy: heart muscle is replaced by scar tissue and fat, disrupting the electrical signals of the heart, causing arrhythmias
- Dilated cardiomyopathy: the muscle of the heart (typically the left ventricle) stretches and becomes thinner, causing enlargement of the heart chamber, which decreases the ability of the heart to pump blood effectively; for details on subtypes of dilated cardiomyopathy, see footnote c
- Hypertrophic cardiomyopathy: the walls of the heart chamber become thickened, reducing the amount of blood that can enter the chamber and be pumped out with each heartbeat
- Restrictive cardiomyopathy: the walls of the ventricles in the heart become rigid, making it so they don't relax and fill with blood like they would normally, resulting in enlargement of the atria
- Peripartum cardiomyopathy: a form of dilated cardiomyopathy that occurs in the last month of pregnancy or in the postpartum period
- Cardiac amyloidosis: deposits of amyloid protein build up on the heart muscle, decreasing the ability of the heart to pump blood effectively

Cardiomyopathy can be acquired or inherited. There are many underlying causes for acquired cardiomyopathy including coronary artery disease, congenital heart disease, inflammatory conditions, infection, toxins, thyroid disease, aortic stenosis, radiation, chronic hypertension, and "athlete's heart." For individuals who do not have an identifiable acquired cause for their cardiomyopathy, genetic testing may be useful for determining whether there is an underlying genetic cause. Establishing a genetic cause for cardiomyopathy in an individual can help guide medical management recommendations and identify at risk family members who would also benefit from genetic testing for the known family variant.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers genetic testing for cardiomyopathy when either I or II are met:

Genetic Testing Policies, Continued

Genetic Testing: Cardiomyopathy, continued

I. Select Health considers genetic testing for cardiomyopathy as medically necessary, if recommended by Intermountain Heart Institute;

OR

II. For all other clinicians, Select Health considers genetic testing for cardiomyopathy as medically necessary, when the following criteria are met:

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested; and
3. Select Health considers genetic testing for the following panel tests for cardiomyopathy as medically necessary, when the following criteria are met:

i. Non-genetic causes of cardiomyopathy have been ruled out, such as prior myocardial infarction from coronary artery disease, valvular and congenital heart disease, toxins (most commonly anthracyclines or other chemotherapeutic agents, various drugs with idiosyncratic reactions), thyroid disease, inflammatory or infectious conditions, severe long-standing hypertension, radiation, aortic stenosis, and extreme physiologic hypertrophy (aka "athlete's heart").

AND

- ii. Meets one of the following criteria (A–F):

A. Arrhythmogenic cardiomyopathy

1. The member meets the task force criteria for at least possible arrhythmogenic cardiomyopathy (defined by Corrado, et al. table 1^a and supplementary figure 1^b)

OR

B. Dilated cardiomyopathy (DCM)

1. The member has a diagnosis of DCM^c from a cardiologist or documented left ventricular enlargement and systolic dysfunction (e.g., ejection fraction <50%) based on echocardiogram, cardiac MRI and/or left ventricular angiogram

OR

C. Hypertrophic cardiomyopathy (HCM)

1. The member has a diagnosis of HCM from a cardiologist or documented to have unexplained left ventricular hypertrophy with myocardial wall thickness of 15mm or greater (in adults) or a z-score greater than or equal to 2 (in children) based on echocardiogram or cardiac MRI

OR

D. Restrictive cardiomyopathy (RCM)

1. The member has a diagnosis of RCM from a cardiologist or based on echocardiogram showing diastolic dysfunction of a non-dilated ventricle.

OR

E. Peripartum cardiomyopathy

Genetic Testing Policies, Continued

Genetic Testing: Cardiomyopathy, continued

1. The member has a diagnosis of peripartum cardiomyopathy from a cardiologist in the last month of pregnancy or within 3 months following delivery by left ventricular enlargement and systolic dysfunction (e.g., ejection fraction < 45%).

OR

F. Cardiac amyloidosis

1. The member has a diagnosis of cardiac amyloidosis based on pyrophosphate (PYP) scan or biopsy.

Select Health considers genetic testing for ischemic cardiomyopathy to be not medically necessary as the underlying factors that cause this condition are non-genetic.

For genetic testing of a known familial variant in a cardiomyopathy gene, please reference Select Health Medical Policy #123.

a - Table 1 from Corrado, et al.

Table 1
European Task Force criteria for diagnosis of Arrhythmogenic Cardiomyopathy.

Category	RV Phenotype	LV Phenotype
I. Morpho-functional ventricular abnormalities	Major <ul style="list-style-type: none">Regional RV akinesia, dyskinesis, or aneurysmAll 3 of the following:<ul style="list-style-type: none">global RV dilation (increase of RV EDV according to the imaging test specific nongenograms for age, sex and BSA^a)EFglobal RV systolic dysfunction (reduction of RV EF according to the imaging test specific nongenograms for age and sex)^b Minor <ul style="list-style-type: none">Regional RV akinesia, dyskinesis or aneurysm of the free wall	Minor <ul style="list-style-type: none">Global LV systolic dysfunction, with or without LV dilatation (increase of LV EDV according to the imaging test specific nongenograms for age, sex, and BSA^a)
II. Structural alterations	Major <ul style="list-style-type: none">Thickened myocardium of the septum in ≥1 sample, with or without fatty tissue, at histology Minor <ul style="list-style-type: none">Unipolar RV LGE (conditioned to 2 orthogonal planes) in ≥1 RV regional branching (septal or lateral)	Major <ul style="list-style-type: none">"Ring-like" LV LGE (subepicardial or epicardio-septal stripe pattern) of ≥2 segments (conditioned to 2 orthogonal views). Minor <ul style="list-style-type: none">LV LGE (subepicardial or epicardio-septal pattern) of 1 or 2 (all 3 type segment(s)) (in 2 orthogonal views) of the free wall, septum, or both (excluding parasy, basal or septal junctional LGE^c)
III. Repolarization abnormalities	Major <ul style="list-style-type: none">Negative T waves in right precordial leads (V₁, V₂, and V₃) or beyond in individuals ≥14 year-old (in the absence of complete RBBB and not preceded by ST-segment elevation)Minor<ul style="list-style-type: none">Negative T waves in leads V₁ and V₂ in males ≥14 year-old (in the absence of RBBB and not preceded by ST-segment elevation)Negative T waves beyond V₃ in the presence of complete RBBBNegative T waves beyond V₃ in individuals <14 year-old	Minor <ul style="list-style-type: none">Negative T waves in left precordial leads (V₄-V₆) (in the absence of complete LBBB)
IV. Depolarization and conduction abnormalities	Minor <ul style="list-style-type: none">Sixteen wave (unipolar) low-amplitude stokes-like QRS complex in most of the T waves in the right precordial leads (V₁ to V₃)Terminal activation duration of QRS >55 ms measured from the onset of the P-wave to the end of the QRS, including V₁, in V₁, V₂, or V₃ (in the absence of complete RBBB)	Major <ul style="list-style-type: none">Low QRS voltages (<0.5 mV peak-to-peak) in all leads (leads in the absence of other causes (e.g. cardiac myopathies, obesity, emphysema, or precordial effusion))
V. Arrhythmias	Major <ul style="list-style-type: none">Frequent ventricular extrasystoles (>80 per 24 h), non-sustained or sustained ventricular tachycardia of LBBB morphology with non-inferior axis Minor <ul style="list-style-type: none">Frequent ventricular extrasystoles (>80 per 24 h), non-sustained or sustained ventricular tachycardia of LBBB morphology with inferior axis (L'WVOT pattern^d)History of cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia of unknown morphology	Minor <ul style="list-style-type: none">Frequent (>50) per 24 h or exercise-induced ventricular extrasystoles with a RBBB morphology or multiple RBBB morphologies (excluding the "fascicular pattern")Non-sustained or sustained ventricular tachycardia with a RBBB morphology (excluding the "fascicular pattern")History of another arrest due to ventricular fibrillation or sustained ventricular tachycardia of unknown morphology
VI. Family history/genetics	Major <ul style="list-style-type: none">Identification of a pathogenic ACM-gene variant in the patient under evaluationACM confirmed in a first-degree relative who meets diagnostic criteriaACM confirmed pathologically at autopsy or surgery in a first-degree relative Minor <ul style="list-style-type: none">Identification of a likely pathogenic ACM-gene variant in the patient under evaluationHistory of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets diagnostic criteriaPremature sudden death (<55 years of age) due to suspected ACM in a first-degree relativeACM confirmed pathologically or by diagnostic criteria in second-degree relative	

Note best practice is to use a reference range derived using the diagnostic approach and the same segmentation method as for patients. ACM = arrhythmogenic cardiomyopathy; BSA = body surface area; EDV = end diastolic volume; EF = ejection fraction; ITF = International Task Force; LBBB = left bundle-branch block; LGE = late gadolinium enhancement; LV = left ventricle; RBBB = right bundle-branch block; RV = right ventricle; RVOT = right ventricular outflow tract.

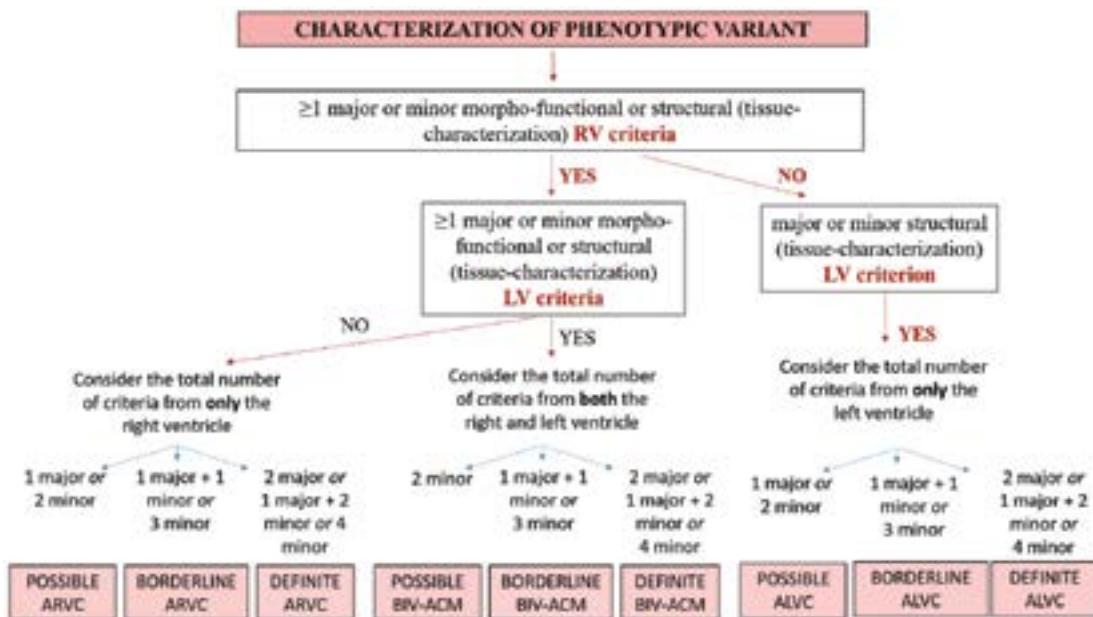
^a Cut-off values of EDV and EF of the European TF criteria for respectively RV dilation and systolic dysfunction are reported in Table 2.

^b Septal junctional LGE at the RV insertion points.

Genetic Testing Policies, Continued

Genetic Testing: Cardiomyopathy, continued

b – Supplementary Figure 1 from Corrado, et al.



c - DCM is the presence of left ventricular dilation and either global or regional systolic dysfunction. This dysfunction is unexplained solely by an abnormal loading condition (such as hypertension, valve disease, or a congenital heart defect) or coronary artery disease. Dysfunction and dilation in the right ventricle may be present as well. Non-dilated left ventricular cardiomyopathy (NDLVC) is the presence of non-ischemic left ventricular scarring or fatty replacement. This can be further delineated into NDLVC with or without systolic function, regional or global. Global and regional wall motion abnormalities and isolated global left ventricular hypokinesis without scarring may be present. This category includes conditions such as arrhythmogenic left ventricular cardiomyopathy (ALVC), left dominant arrhythmogenic right ventricular cardiomyopathy (ARVC), or arrhythmogenic DCM. Often these conditions do not fulfill diagnostic criteria for ARVC.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Billing/Coding Information

CPT CODES

Genetic Testing Policies, Continued

Genetic Testing: Cardiomyopathy, continued

- 0237U** Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
- 81410** Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
- 81411** Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1
- 81413** Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCH5A
- 81414** Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1
- 81439** Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, DSG2, MYBPC3, MYH7, PKP2, TTN)
- 81479** Unlisted molecular pathology procedure
- 81493** Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score

Key References

- Corrado, D., et al. Evolving Diagnostic Criteria for Arrhythmogenic Cardiomyopathy. *Journal of the American Heart Association.* September 2021; 10(18). Available at: <https://doi.org/10.1161/JAHA.121.021987>
- Corrado, D., et al. Proposed diagnostic criteria for arrhythmogenic cardiomyopathy: European Task Force consensus report. *International Journal of Cardiology.* 2024 Jan 15:395:131447. Available from: doi: 10.1016/j.ijcard.2023.131447
- Hershberger, R. E., et al. Genetic Evaluation of Cardiomyopathy—A Heart Failure Society of America Practice Guideline. *Journal of Cardiac Failure.* March 2018. Available at: <https://doi.org/10.1016/j.cardfail.2018.03.004>
- Hershberger, R. E., et al. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genetics in Medicine.* 2018 Sep;20(9):899-909. Available at: doi: 10.1038/s41436-018-0039-z
- Landstrom, A. P., et al. Genetic Testing for Heritable Cardiovascular Diseases in Pediatric Patients: A Scientific Statement from the American Heart Association. *Circulation: Genomic and Precision Medicine.* October 2021; 14(5). Available at: <https://doi.org/10.1161/HCG.0000000000000086>
- Maron, B. J., et al. Diagnosis and Evaluation of Hypertrophic Cardiomyopathy: JACC State-of-the-Art Review. *Journal of the American College of Cardiology.* 2022;79(4):372-389. Available from: <https://doi.org/10.1016/j.jacc.2021.12.002>
- Muchtar, E., Blauwet, L. A., Gertz, M. A. Restrictive Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. *Circulation Research.* 2017 Sep 15;121(7):819-837. Available from: doi: 10.1161/CIRCRESAHA.117.310982
- Musunuru, K., et al. Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement from the American Heart Association. *Circulation: Genomic and Precision Medicine.* August 2020; 13(4). Available at: <https://doi.org/10.1161/HCG.0000000000000067>
- Ommen, S. R., et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2020 Dec 22;142(25): e558-e631. Available from: <https://doi.org/10.1161/CIR.0000000000000937>
- Sliwa, K., et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working

Genetic Testing Policies, Continued

Genetic Testing: Cardiomyopathy, continued

- Group on peripartum cardiomyopathy. European Journal of Heart Failure. June 2010; 12: 767–778. Available at: <https://doi.org/10.1093/eurjh/hfq120>
11. Srivastava, S., et al. Ventricular non-compaction review. Heart Failure Reviews. 2022; 27:1063-1076. Available at: <https://doi.org/10.1007/s10741-021-10128-3>
 12. Towbin, J.A., et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy: Executive summary. Heart Rhythm Society. November 2019; 16(11). Available at: <https://doi.org/10.1016/j.hrthm.2019.09.019>
 13. Wilde, A. A. M., et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. Europace. 2022 Aug; 24(8): 1307–1367. Available at: doi: 10.1093/europace/euac030

Revision History

Revision Date	Summary of Changes
12/6/23	For Commercial Plan Policy, modified criteria to include option of recommendation by Intermountain Heart Institute as a qualifying factor.
9/3/24	For Commercial Plan Policy, updated overall criteria to align with current clinical standards, including inputting reference tables to help with evaluation; and added the following exclusion: "Select Health considers genetic testing for ischemic cardiomyopathy to be not medically necessary as the underlying factors that cause this condition are non-genetic."

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MEDICAL POLICY

GENETIC TESTING: CELIAC DISEASE

Policy # 286

Implementation Date: 11/15/05

Review Dates: 10/19/06, 12/20/07, 12/18/08, 10/20/09, 10/21/10, 10/13/11, 10/24/13, 10/23/14, 10/15/15, 10/20/16, 10/19/17, 10/12/18, 10/20/19, 2/7/23, 2/15/24

Revision Dates: 11/29/12, 7/1/23, 7/23/24

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Celiac disease also known as celiac sprue or gluten-sensitive enteropathy is an immune-mediated disorder of the small intestine characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia, which occur upon exposure to gluten (a protein contained in wheat, rye, barley, and a multitude of prepared foods) and which demonstrate improvement with withdrawal of gluten from the diet. People with celiac disease have an abnormal immune system reaction against gluten, the consequences of which cause damage to the lining of the small intestine. Celiac disease occurs in people of any age and affects both genders.

The generally accepted diagnostic criteria are that there should be an abnormal small intestinal mucosa while individuals continue to take a gluten-containing diet. There should then be unequivocal improvement in villous architecture on a repeat small intestinal biopsy procedure after some months on a gluten-free diet with symptomatic improvement. A repeat biopsy should usually be taken four to six months after induction of treatment and if there has been no improvement in the small intestinal mucosal morphology, the original diagnosis should be questioned. Most clinicians do not undertake formal gluten challenge to show the resultant deterioration of the small intestinal villous architecture. However, gluten challenge should be performed if there is any doubt concerning the correct diagnosis.

When the diagnosis of celiac disease is uncertain because of indeterminate results, testing for certain genetic markers (HLA haplotypes) can stratify individuals to high or low risk for celiac disease. Even though celiac disease is a complex genetic disorder, HLA status appears to be the strongest genetic determinant of risk for celiac autoimmunity. There is a propensity for individuals with celiac disease to carry specific HLA class II alleles, which has been estimated to account for up to 40% of the genetic load. In affected individuals, 95% have either DQ2 (HLA-DQA1*05-DQB1*02) or DQ8 (HLA-DQA1*03-DQB1*0302), in comparison with the general population in which 39.5% have either DQ2 or DQ8. However, only 3% of individuals in the general population carrying DQ2 will develop evidence of celiac autoimmunity, suggesting that HLA typing could be used to identify increased genetic risk, but not for defining celiac disease, as is possible with many monogenic disorders. DQ2 homozygous individuals have an even higher risk for expressing transglutaminase autoantibodies and celiac disease, and among patients with type 1 diabetes almost one third of patients homozygous for DQ2 express transglutaminase autoantibodies. One half of these individuals have high levels of transglutaminase autoantibodies and celiac disease on intestinal biopsy examination. In a recent European report, only 0.5% of celiac patients lacked both DQ2 and DQ8. Greater than 97% of celiac disease individuals have the DQ2 and/or DQ8 marker, compared to about 40% of the general population. Therefore, an individual negative for DQ2 or DQ8 is extremely unlikely to have celiac disease (high negative predictive value).

Genetic Testing Policies, Continued

Genetic Testing: Celiac Disease (Celiagene), continued

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. SelectHealth covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

SelectHealth covers genetic testing for celiac disease in patients with symptoms suggestive of celiac disease who have failed to achieve an appropriate diagnosis through other standard testing.* This testing meets the plan guidelines for genetic testing as it has demonstrated statistical validity and clinical utility in appropriately selected individuals undergoing this testing.

*Standard testing for celiac disease includes IgA endomysial, IgA transglutaminine, and small bowel biopsy.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

The population estimate of a 0.5%–1.0% prevalence of celiac disease among persons of Northern European descent has been fairly well established by several large epidemiological studies. The association between celiac disease and other medical conditions and problems has also been well studied. Type 1 diabetes, autoimmune thyroiditis, Down syndrome, Turner syndrome, William's syndrome, Selective IgA deficiency, and having an affected first degree relative all portend risk for celiac disease that is much higher than the population risk.

Likewise, a large body of literature exists (most with fairly small sample sizes) to support the association between celiac disease and histocompatibility complex class II antigens (primarily DQ2 and DQ8). Some literature suggests an association between homozygosity for DQ2 alleles and early onset celiac disease, though the relationship between particular HLA genotypes and the clinical presentation of the disorder is generally not well studied. Likewise, the prevalence of HLA genotypes in the aforementioned high-risk groups is only beginning to be investigated. In Sumnik et al., for example, the DQ2 molecule was more common in diabetic children with celiac disease (80%) than in diabetic children without the disorder (49%). The DQ2 molecule conferred a four-fold risk of celiac disease among diabetic children. In contrast, Doolan et al. found no significant difference for HLA genotypes (DQ2 and DR4) among Australian patients (age range 10–37 years) with diabetes mellitus Type 1 with or without celiac disease.

Many studies have reported generally high sensitivity and negative predictive values, but poor specificity and positive predictive values of HLA genotyping for celiac disease, though percentages do vary widely. Zubillaga found DQ2 or DQ8 alleles in 98% of celiac patients while Agardh et al. found DQ2 in 65% of

Genetic Testing Policies, Continued

Genetic Testing: Celiac Disease (Celiagene), continued

celiac patients and 36% of those without celiac disease. Pena-Quintana reported that the sensitivity, specificity, and the positive and negative predictive values of HLA typing were 92.4%, 78.4%, 68.1%, and 95.4%, respectively.

The American College of Gastroenterology's clinical guidelines on diagnosis and management of celiac disease (CD) (Rubio-Tapia et al., 2013) include the use of HLA DQ2 and DQ8 genotyping in the clinical algorithm when other modalities are not able to reach a diagnosis. They also state that intestinal permeability tests, D-xylose, and small-bowel follow-through are not recommended for CD diagnosis (strong recommendation, moderate level of evidence) and that stool studies or salivary tests are neither validated nor recommended for use in the diagnosis of CD (strong recommendation, weak level of evidence).

Billing/Coding Information

Covered: For the conditions outlined above

CPT CODES

- | | |
|--------------|---|
| 81376 | HLA Class II typing, low resolution (e.g., antigen equivalents); one locus (e.g., HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each |
| 81377 | HLA Class II typing, low resolution (e.g., antigen equivalents); one antigen equivalent, each |
| 81382 | HLA Class II typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each |
| 81383 | HLA Class II typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, HLA-DQB1*06:02P), each |

HCPCS CODES

- | | |
|--------------|--|
| G0452 | Molecular pathology procedure; physician interpretation and report |
|--------------|--|

Key References

1. Agardh, D., et al., Prediction of silent celiac disease at diagnosis of childhood type 1 diabetes by tissue transglutaminase autoantibodies and HLA. *Pediatr Diabetes*/01. 2(2): p. 58-65.
2. American Gastroenterological Association medical position statement: Celiac Sprue. *Gastroenterology*/01. 120(6): p. 1522-5.
3. Bao, F., et al., One third of HLA DQ2 homozygous patients with type 1 diabetes express celiac disease-associated transglutaminase autoantibodies. *J Autoimmun*/99. 13(1): p. 143-8.
4. Brown, N. K., et al. A Clinician's Guide to Celiac Disease HLA Genetics. *Am J Gastroenterol*. 2019 Oct;114(10):1587-1592.
5. Ciclitira, P.J., King, A.L., and Fraser, J.S. AGA technical review on Celiac Sprue. *American Gastroenterological Association. Gastroenterology*/01. 120(6): p. 1526-40.
6. Collin, P., et al., Celiac disease and HLA DQ in patients with IgA nephropathy. *Am J Gastroenterol*/02. 97(10): p. 2572-6.
7. Csizmadia, C.G., et al., Accuracy and cost-effectiveness of a new strategy to screen for celiac disease in children with Down syndrome. *J Pediatr*/00. 137(6): p. 756-61.
8. Dolinssek, J., et al., The prevalence of celiac disease among family members of celiac disease patients. *Wien Klin Wochenschr*/04. 116 Suppl 2: pp. 8-12.
9. Doolan, A., et al., Use of HLA typing in diagnosing celiac disease in patients with type 1 diabetes. *Diabetes Care*/05. 28(4): pp. 806-809.
10. Fasano, A., et al., Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med*/03. 163(3): p. 286-92.
11. Greco, L., et al., The first large population based twin study of coeliac disease. *Gut*/02. 50(5): p. 624-8.
12. Grodzinsky, E., Screening for coeliac disease in apparently healthy blood donors. *Acta Paediatr Suppl*/96. 412: p. 36-8.
13. Hill, I.D., et al., Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*/05. 40(1): p. 1-19.
14. Johnston, S.D., et al., Preliminary results from follow-up of a large-scale population survey of antibodies to gliadin, reticulin and endomysium. *Acta Paediatr Suppl*/96. 412: p. 61-4.
15. Johnson, T.C., et al., Relationship of HLA-DQ8 and severity of celiac disease: comparison of New York and Parisian cohorts. *Clin Gastroenterol Hepatol*/04. 2(10): p. 888-94.
16. Karell, K., et al., HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease. *Hum Immunol*/03. 64(4): p. 469-77.
17. Kaukinen, K., et al., HLA-DQ typing in the diagnosis of celiac disease. *Am J Gastroenterol*/02. 97(3): p. 695-9.

Genetic Testing Policies, Continued

Genetic Testing: Celiac Disease (Celiagene), continued

18. Kelly, C., Patient information: Celiac disease. UpToDate/03. <http://www.utdol.com/>.
19. Kelly, C., Diagnosis of celiac disease. UpToDate/05. <http://www.utdol.com>.
20. Kimball Genetics, Celiac Disease DNA Test. 2004.
21. Lenhardt, A., et al., Role of human-tissue transglutaminase IgG and anti-gliadin IgG antibodies in the diagnosis of coeliac disease in patients with selective immunoglobulin A deficiency. *Dig Liver Dis/04.* 36(11): p. 730-4.
22. Liu, E., Rewers, M., and Eisenbarth, G.S., Genetic testing: who should do the testing and what is the role of genetic testing in the setting of celiac disease? *Gastroenterology/05.* 128(4 Suppl 1): p. S33-7.
23. Maki, M., et al., Prevalence of Celiac disease among children in Finland. *N Engl J Med/03.* 348(25): p. 2517-24.
24. National Institutes of Health Consensus Development Conference Statement on Celiac Disease, 6/28-30/04. *Gastroenterology/05.* 128(4 Suppl 1): p. S1-9.
25. Neuhausen, S.L., et al., HLA DQA1-DQB1 genotypes in Bedouin families with celiac disease. *Hum Immunol/02.* 63(6): p. 502-507.
26. Not, T., et al., Celiac disease risk in the USA: high prevalence of antiendomysium antibodies in healthy blood donors. *Scand J Gastroenterol/98.* 33(5): p. 494-8.
27. Pena-Quintana, L., et al., Assessment of the DQ heterodimer test in the diagnosis of celiac disease in the Canary Islands (Spain). *J Pediatr Gastroenterol Nutr/03.* 37(5): p. 604-8.
28. Polvi, A., et al., HLA-DQ2-negative celiac disease in Finland and Spain. *Hum Immunol/98.* 59(3): p. 169-75.
29. Rutherford, R.M., et al., Prevalence of coeliac disease in patients with sarcoidosis. *Eur J Gastroenterol Hepatol/04.* 16(9): p. 911-5.
30. Sumnik, Z., et al., HLA-DQA1*05-DQB1*0201 positivity predisposes to coeliac disease in Czech diabetic children. *Acta Paediatr/00.* 89(12): p. 1426-30.
31. Rubio-Tapia, A., et al. (2013). "ACG clinical guidelines: diagnosis and management of celiac disease." *Am J Gastroenterol* 108(5): 656-676; quiz 677.
32. Taylor, A. K. et al. Celiac Disease. National Library of Medicine. Last Updated: January 31, 2019.
33. Vidales, M.C., et al., Allele and haplotype frequencies for HLA class II (DQA1 and DQB1) loci in patients with celiac disease from Spain. *Hum Immunol/04.* 65(4): p. 352-8.
34. Zubillaga, P., et al., HLA-DQA1 and HLA-DQB1 genetic markers and clinical presentation in celiac disease. *J Pediatr Gastroenterol Nutr/02.* 34(5): p. 548-54.

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Genetic Testing Policies, Continued

Genetic Testing: Celiac Disease (Celiagene), continued



MEDICAL POLICY

GENETIC TESTING: CELIAC DISEASE

Policy # 286

Implementation Date: 11/15/05

Review Dates: 10/19/06, 12/20/07, 12/18/08, 10/20/09, 10/21/10, 10/13/11, 10/24/13, 10/23/14, 10/15/15, 10/20/16, 10/19/17, 10/12/18, 10/20/19, 2/7/23, 2/15/24

Revision Dates: 11/29/12, 7/1/23, 7/23/24

Related Medical Policies:

[#123 Gene Therapy, Testing, and Counseling](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Celiac disease also known as celiac sprue or gluten-sensitive enteropathy is an immune-mediated disorder of the small intestine characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia, which occur upon exposure to gluten (a protein contained in wheat, rye, barley, and a multitude of prepared foods) and which demonstrate improvement with withdrawal of gluten from the diet. People with celiac disease have an abnormal immune system reaction against gluten, the consequences of which cause damage to the lining of the small intestine. Celiac disease occurs in people of any age and affects both genders.

The generally accepted diagnostic criteria are that there should be an abnormal small intestinal mucosa while individuals continue to take a gluten-containing diet. There should then be unequivocal improvement in villous architecture on a repeat small intestinal biopsy procedure after some months on a gluten-free diet with symptomatic improvement. A repeat biopsy should usually be taken four to six months after induction of treatment and if there has been no improvement in the small intestinal mucosal morphology, the original diagnosis should be questioned. Most clinicians do not undertake formal gluten challenge to show the resultant deterioration of the small intestinal villous architecture. However, gluten challenge should be performed if there is any doubt concerning the correct diagnosis.

When the diagnosis of celiac disease is uncertain because of indeterminate results, testing for certain genetic markers (HLA haplotypes) can stratify individuals to high or low risk for celiac disease. Even though celiac disease is a complex genetic disorder, HLA status appears to be the strongest genetic determinant of risk for celiac autoimmunity. There is a propensity for individuals with celiac disease to carry specific HLA class II alleles, which has been estimated to account for up to 40% of the genetic load. In affected individuals, 95% have either DQ2 (HLA-DQA1*05-DQB1*02) or DQ8 (HLA-DQA1*03-DQB1*0302), in comparison with the general population in which 39.5% have either DQ2 or DQ8. However, only 3% of individuals in the general population carrying DQ2 will develop evidence of celiac autoimmunity, suggesting that HLA typing could be used to identify increased genetic risk, but not for defining celiac disease, as is possible with many monogenic disorders. DQ2 homozygous individuals have an even higher risk for expressing transglutaminase autoantibodies and celiac disease, and among patients with type 1 diabetes almost one third of patients homozygous for DQ2 express transglutaminase autoantibodies. One half of these individuals have high levels of transglutaminase autoantibodies and celiac disease on intestinal biopsy examination. In a recent European report, only 0.5% of celiac patients lacked both DQ2 and DQ8. Greater than 97% of celiac disease individuals have the DQ2 and/or DQ8 marker, compared to about 40% of the general population. Therefore, an individual negative for DQ2 or DQ8 is extremely unlikely to have celiac disease (high negative predictive value).

Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: CELL-FREE FETAL DNA TESTING

Policy # 679

Implementation Date: 3/25/24

Review Dates:

Revision Dates: 7/22/24

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Cell-free fetal DNA (cffDNA) testing [also called noninvasive prenatal testing (NIPT) or noninvasive prenatal screening (NIPS)] is a screen for fetal aneuploidies. This testing evaluates short segments of cell-free fetal DNA in the maternal plasma during pregnancy. The clinical utility of cffDNA has been established for detecting fetal trisomy 13, 18, and 21, at \geq 8–10 weeks gestation with a viable singleton or twin pregnancy. This testing can identify fetuses at increased risk for aneuploidy but cannot definitively diagnose, confirm, or exclude. Screening tests that show increased risk should be confirmed by diagnostic testing prior to any intervention.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers cell-free fetal DNA testing for common aneuploidy (chromosomes 13, 18, 21, X, Y) once per singleton or twin pregnancy.

Select Health does not cover this testing solely for the purposes of fetal sex determination; this is considered NOT medically necessary.

Select Health does NOT cover cell-free fetal DNA testing for the evaluation of the following:

- Microdeletions/microduplications
- Expanded aneuploidies (chromosomes other than 13, 18, 21, X, Y)
- Twin zygosity
- Whole genome or whole exome screening
- Single gene disorders
- Non-viable pregnancies
- Fetal trophoblast cells (such as Luna Prenatal Test)
- Higher order multiple gestation (\geq 3 fetuses)

Use of this testing for these indications meets the plan's definition of experimental/investigational.

Genetic Testing Policies, Continued

Genetic Testing: Cell-free Fetal DNA Testing, continued

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Billing/Coding Information

Covered for the indications listed above when criteria are met

CPT CODES

- | | |
|--------------|---|
| 81420 | Fetal chromosomal aneuploidy (eg, trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21 |
| 81507 | Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy |
| 0327U | Fetal aneuploidy (trisomy 13, 18, and 21), DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy, includes sex reporting, if performed |
| 81479 | Unlisted molecular pathology procedure |

Not covered for the indications listed above

- | | |
|--------------|---|
| 81422 | Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, digeorge syndrome, cri-du-chat syndrome), circulating cell-free fetal dna in maternal blood |
|--------------|---|

Key References

1. American College of Obstetricians and Gynecologists (ACOG). Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. *Obstet Gynecol.* 2020;136(4):e48-e69. Epub 2020/08/18. PMID: 32804883
2. Gregg AR, Skotko BG, Benkendorf JL, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. *Genet Med.* 2016;18(10):1056-65. Epub 2016/07/29. PMID: 27467454
3. Palomaki GE, Chiu RWK, Pertile MD, et al. International Society for Prenatal Diagnosis Position Statement: cell free (cf)DNA screening for Down syndrome in multiple pregnancies. *Prenat Diagn.* 2021;41(10):1222-32. Epub 2020/10/06. PMID: 33016373
4. Rose NC, Barrie ES, Malinowski J, et al. Systematic evidence-based review: The application of noninvasive prenatal screening using cell-free DNA in general-risk pregnancies. *Genet Med.* 2022;24(7):1379-91. Epub 2022/05/25. PMID: 35608568

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Genetic Testing Policies, Continued

Genetic Testing: Cell-free Fetal DNA Testing, continued

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: CELL-FREE TUMOR DNA/LIQUID BIOPSY

Policy # 581

Implementation Date: 7/8/16

Review Dates: 6/15/17, 9/18/18, 8/8/19, 10/21/20, 5/19/22, 1/17/23, 2/29/24

Revision Dates: 8/21/17, 8/16/19, 9/23/20, 1/29/21, 5/9/22, 7/1/23, 7/24/24, 8/26/24

Related Medical Policies:

[#570 Genetic Testing: Genetic Mutation Analysis Utilizing Solid Tumor Tissue](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Detecting and monitoring cancer recurrence can sometimes be problematic. Additionally, for individuals who have a relapse while on therapy determining optimal approaches to therapy modification can also be problematic as tumor samples may not be accessible via biopsy, or the patient may not be able to well-tolerate an invasive procedure. New methods to identify and characterize the molecular characteristics of persistent or recurrent tumors are being developed which are intended to eliminate invasive biopsies but retain similar sensitivities and specificities. One such technology is the "liquid biopsy." This technology uses next-generation sequencing to characterize tumors based on the capture and analysis of circulating tumor DNA (ctDNA). This technology involves a blood test that provides detailed information on the genomic make up of any tumor present with the ability to identify the percentage of each mutation found in an individual's blood. The concentration of tumor DNA in the blood stream has been speculated to also indicate how advanced the cancer may be and if current therapies are impacting.

Laboratories pursuing this technology include Foundation Medicine, Guardant Health, and Tempus, with many more in various stages of development.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.
Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.
 - A. **Select Health covers either the Guardant360CDx liquid biopsy assay or FoundationOne LiquidCDx if one of the following is present:**

1. Tissue-based CGP (comprehensive genomic profiling) is infeasible* specifically in non-solids.



Genetic Testing Policies, Continued

Genetic Testing: Cell-free Tumor DNA/Liquid Biopsy, continued

OR

2. Tissue-based CGP is infeasible* and an FDA-approved indication or NCCN recommendation requires information about the presence or absence of a tumor genetic biomarker

OR

3. Member is considering participating in a clinical trial** intended to assess the effectiveness of targeted therapies based on tumor genetic biomarker, and tissue-based CGP is infeasible*.

OR

4. Liquid biopsy is allowable independently or concurrently with tissue-based CGP for advanced or metastatic breast cancer.

*Infeasible: i.e., quantity not sufficient for tissue-based CGP or invasive biopsy is medically contraindicated

**Clinical trial must meet one (i–iii) of the following clinical conditions:

- i. Any advanced stage III or IV solid tumors, or
- ii. All lymphomas, or
- iii. Multiple myeloma

Select Health does not cover the Guardant Health Shield blood test in the evaluation of colorectal cancer. This test is considered not medically necessary as the clinical utility has not been determined due to a lack of evidence available in peer-reviewed literature supporting either sufficient sensitivity or specificity.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

For individuals who have cancer who receive molecular characterization of tumor using cell-free tumor DNA (ctDNA), the evidence includes case series and systematic reviews of these case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Ultrasensitive methods to detect mutations from ctDNA have been developed, but there is limited evidence on the analytic validity of these methods. There is a need for further optimization and standardization of testing methods. Clinical validity consists of case series that report correlations between mutations detected in ctDNA with mutations detected in tumor tissue. Results have shown variable results for clinical sensitivity. Although some reports have suggested that clinical sensitivity may

Genetic Testing Policies, Continued

Genetic Testing: Cell-free Tumor DNA/Liquid Biopsy, continued

be high, this finding has not been consistent. Published studies have consistently reported high clinical specificity; however, most study population have consisted of small and heterogeneous, and it is not known to what degree mutations detected by ctDNA are representative of the primary tumor. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether mutation analysis by ctDNA can replace mutation analysis in tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding Information

CPT CODES

Covered for the Indications Listed Above

- | | |
|--------------|---|
| 0091U | Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result |
| 0179U | Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s) |
| 0239U | Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations |
| 0242U | Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements |
| 0285U | Oncology, response to radiation, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported as a radiation toxicity score |
| 0317U | Oncology (lung cancer), four-probe FISH (3q29, 3p22.1, 10q22.3, 10cen) assay, whole blood, predictive algorithm generated evaluation reported as decreased or increased risk for lung cancer |
| 0333U | Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in highrisk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein desgammacarboxy-prothrombin (DCP), algorithm reported as normal or abnormal result |
| 0338U | Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker-expressing cells, peripheral blood |
| 0485U | Oncology (solid tumor), cell-free DNA and RNA by next-generation sequencing, interpretative report for germline mutations, clonal hematopoiesis of indeterminate potential, and tumor-derived single-nucleotide variants, small insertions/deletions, copy number alterations, fusions, microsatellite instability, and tumor mutational burden |
| 81445 | Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed |
| 81449 | Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, |

Genetic Testing Policies, Continued

Genetic Testing: Cell-free Tumor DNA/Liquid Biopsy, continued

	PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
81451	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, 3 RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81456	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81479	Unlisted molecular pathology procedure

Not Covered for the Indications Listed Above

0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0356U	Oncology (oropharyngeal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence

HCPCS CODES

No specific codes identified

Key References

1. NCCN Clinical Practice Guidelines in Oncology. NSCLC. Version 2.2024 February 9, 2024.
2. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 1.2024. January 25, 2024.
3. Iams WT, Benson AB 3rd. et al. (2024). Concurrent Tissue and Circulating Tumor DNA Molecular Profiling to Detect Guideline-Based Targeted Mutations in a Multicancer Cohort. *JAMA Netw Open*. 7(1): e2351700. PMID: 38252441.
4. Krebs, M. G., et al. (2022). Practical Considerations for the Use of Circulating Tumor DNA in the Treatment of Patients With Cancer. *JAMA Oncology*, 8 (12), 1830-1839. PMID 36264554.
5. Patelli G, Sartore-Bianchi A. et al. (2021). Liquid Biopsy for Prognosis and Treatment in Metastatic Colorectal Cancer: Circulating Tumor Cells vs Circulating Tumor DNA. *Target Oncol*. 16(3):309-324. Erratum in: *Target Oncol*. PMID: 33738696.
6. Zhou, J., Huang, A., et al. (2016). Liquid Biopsy and its Potential for Management of Hepatocellular Carcinoma. *J Gastrointest Cancer*. 47(2): 157-67; PMID:26969471.

Genetic Testing Policies, Continued

Genetic Testing: Cell-free Tumor DNA/Liquid Biopsy, continued

Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
7/24/24	For Commercial Plan Policy, added criteria #4: "Liquid biopsy is allowable independently or concurrently with tissue-based CGP for advanced or metastatic breast cancer." as an additional qualifying factor.
8/26/24	For Commercial Plan Policy, added an exclusion for the Guardant Health Shield blood test.

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GENETIC TESTING: CHARCOT-MARIE-TOOTH SYNDROME (HEREDITARY MOTOR SENSORY NEUROPATHY)

Policy # 134

Implementation Date: 3/6/10

Review Dates: 7/18/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 9/13/18, 8/7/19, 1/24/23, 2/15/24

Revision Dates: 7/1/23

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Charcot-Marie-Tooth is a spectrum of disorders and is one of the most common inherited neurological disorders, affecting approximately 1 in 2,500 people in the US. It is a polyneuropathic process that can be demyelinating or axonal and affects patients typically in the first or early second decade, but infants may be symptomatic. The neuropathy of CMT affects both motor and sensory nerves.

Heredity motor sensory neuropathy (Charcot-Marie-Tooth disease) has been classified as types 1–7 and consists of at least 30 different disorders. The major division comprises type 1 and type 2, which together are the most common hereditary peripheral neuropathies, with an estimated prevalence of 40 per 100,000. Common features include both motor and sensory nerve manifestations with distal leg weakness, foot deformities (pes cavus, hammer toes), and sensory deficits.

Early symptoms may include frequent sprained ankles caused by distal muscle weakness or difficulty running and keeping up with peers. The only obvious physical findings may be loss of reflexes, pes cavus foot deformity, and hammer toes. Calf muscle atrophy often occurs, causing the classic "stork leg" deformity. Walking is clumsy because of both muscle weakness and sensory loss. Sensory loss is gradual and mainly involves proprioception and vibration. Later changes include atrophy of the intrinsic hand and foot muscles. Palpable enlargement of the peripheral nerves may occur secondary to nerve hypertrophy. In addition, kyphosis or scoliosis often develops.

Treatment is symptomatic. Affected individuals are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Quality of life has been measured and compared among various groups of individuals with Charcot-Marie-Tooth. Special shoes, including those with good ankle support, may be needed. Affected individuals often require ankle/foot orthoses (AFOs) to correct foot drop and aid walking. Orthopedic surgery may be required to correct severe pes cavus deformity. Some individuals require forearm crutches or canes for gait stability, but fewer than 5% of individuals need wheelchairs. Exercise is encouraged within the individual's capability and many individuals remain physically active. The cause of any pain should be identified as accurately as possible.

HMSN type 1, also known as Charcot-Marie-Tooth type 1 (CMT1) disease, is a demyelinating disorder of peripheral nerves. It has been subdivided based on genetic markers into types 1A, 1B, and 1C, (with type 1A being most common), although the clinical manifestations are similar. Affected patients typically present in the first or early second decade, but infants may be symptomatic. Type 1 disease is caused by mutations in genes that are expressed in Schwann cells, the myelinating cells of the peripheral nervous

Genetic Testing Policies, Continued

Genetic Testing: Charcot Marie-Tooth Syndrome (Hereditary Motor Sensory Neuropathy, continued)

system. The types that typically exhibit autosomal dominance have been subdivided into types 1A, 1B, and 1C. However, autosomal recessive and X-linked forms also occur.

CMT hereditary neuropathy needs to be distinguished from acquired non-genetic causes of peripheral neuropathy and other genetic neuropathies. The CMT phenotype consists of motor and sensory neuropathy without an established acquired cause. Individuals with CMT who experience blindness, seizures, dementia, and intellectual disability are not part of the CMT hereditary neuropathy syndrome and should be suggestive of some other diagnosis. The probability of any given group possessing a mutation for CMT is not established. Furthermore, among those with identifiable mutations, the penetrance and expressivity of mutations is also unknown.

Currently, there are no established, effective treatments to either slow or reverse the natural disease process for the various CMT variants, though, multiple treatment regimens are being explored.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does not cover genetic testing for Charcot-Marie-Tooth Syndrome, including inheritable motor/sensory neuropathy. This testing has not been established as medically necessary in the management of patients with peripheral neuropathy.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

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Summary of Medical Information

Extensive literature has been published on Charcot-Marie-Tooth; this evidence demonstrates the reliability of this testing (statistical validity). From this evidence, it is clear that genetic mutation is responsible, at least in part, for a wide variety of otherwise undiagnosed motor-sensory peripheral neuropathies.

GeneReviews lists 4 major types of CMT with about 30 subtypes. This will likely expand as further research on this group of disorders becomes better understood. However, it is not yet clear from the evidence what the accuracy of available genetic tests is, the penetrance or expressivity of mutations, or the necessity/importance of performing genetic testing vs. clinical testing.

The American Academy of Neurology's guideline from 2009 on genetic testing for neuropathy and subsequently reaffirmed in 2013 (England et al.), noted: "Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies (Level A)". Despite this recommendation, there is insufficient evidence to support performing testing in this situation, as it does not alter patient management in a substantive manner nor presents significant clinical utility. The guideline goes on to state, genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (Level C). Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features, and should focus on the most common abnormalities which are CMT1A duplication/HNPP deletion, Cx32 (GJB1), and MFN2 mutation screening.

Genetic Testing Policies, Continued

Genetic Testing: Charcot Marie-Tooth Syndrome (Hereditary Motor Sensory Neuropathy, continued)

There is insufficient evidence to determine the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy who do not exhibit a hereditary neuropathy phenotype (Level U).

Currently, there remains a lack of information demonstrating the clinical utility of this testing.

Billing/Coding Information

CPT CODES

81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81403	Molecular pathology procedure, Level 4
81404	Molecular pathology procedure, Level 5
81405	Molecular pathology procedure, Level 5
81406	Molecular pathology procedure, Level 7
81448	Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraparesis), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report
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Key References

1. Bird TD. Charcot-Marie-Tooth Hereditary Neuropathy Overview. 1998 Sep 28 [Updated 2023 Feb 23]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1358/>
2. Bassam, B. A. (2014). "Charcot-Marie-Tooth disease variants-classification, clinical, and genetic features and rational diagnostic evaluation." *J Clin Neuromuscul Dis* 15(3): 117-128.
3. DiVincenzo, C., C. D. Elzinga, A. C. Medeiros, I. Karbassi, J. R. Jones, M. C. Evans, C. D. Braastad, C. M. Bishop, M. Jaremko, Z. Wang, K. Liaquat, C. A. Hoffman, M. D. York, S. D. Batish, J. R. Lupski and J. J. Higgins (2014). "The allelic spectrum of Charcot-Marie-Tooth disease in over 17,000 individuals with neuropathy." *Mol Genet Genomic Med* 2(6): 522-529.
4. England, J. D. (2014). "The shifting landscape of genetic testing for Charcot-Marie-Tooth disease." *Muscle Nerve* 49(4): 467-468.
5. Ostem, R., et al. (2013). "Diagnostic laboratory testing for Charcot Marie Tooth disease (CMT): the spectrum of gene defects in Norwegian patients with CMT and its implications for future genetic test strategies." *BMC Med Genet* 14: 94.
6. Pipis M, Rossor AM, Laura M, Reilly MM. Next-generation sequencing in Charcot-Marie-Tooth disease: opportunities and challenges. *Nat Rev Neurol*. 2019;15(11):644-656. doi:10.1038/s41582-019-0254-5
7. Rossor, A. M., et al. (2013). "Clinical implications of genetic advances in Charcot-Marie-Tooth disease." *Nat Rev Neurol* 9(10): 562-571.
8. Siskind CE, Panchal S, Smith CO, et al. A review of genetic counseling for Charcot Marie Tooth disease (CMT). *J Genet Couns*. 2013;22(4): 422-436.

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Genetic Testing Policies, Continued

Genetic Testing: Charcot Marie-Tooth Syndrome (Hereditary Motor Sensory Neuropathy, continued)

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: CHROMOSOMAL MICROARRAY ANALYSIS (CMA)

Policy # 297

Implementation Date: 2/15/06

Review Dates: 5/17/07, 4/24/08, 2/18/10, 5/19/11, 6/21/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 6/16/18, 4/17/19, 2/14/23, 2/15/24, 2/17/25

Revision Dates: 4/23/09, 5/26/16, 8/7/18, 7/1/23, 5/24/24

Related Medical Policies:

[#123 Gene Therapy, Testing and Counseling](#)

[#514 Whole Genomic Sequencing \(WGS\)/Whole Exome Sequencing \(WES\)](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (CHIP) plans. Refer to the "Policy" section for more information.

Description

Developmental disabilities are a family of chronic disorders of early onset, affecting between 5%–10% of children. Global developmental delay (DD), a heterogeneous subset of developmental disabilities, is defined as significant delay in 2 or more developmental areas and is associated with deficits in adaptation and learning skills. Those deficits are evident in comparison with the skills-attainment of chronological peers. "Significant" delay is defined as performance 2 standard deviations or more below the mean on age-appropriate, standardized norm referenced testing. The term global developmental delay is usually reserved for younger children (i.e., typically less than 5 years of age), whereas the term intellectual disability (ID) is usually applied to older children when IQ testing is more valid and reliable.

Chromosomal microarray (CMA) has been recommended as a first-tier genetic test for individuals with DD/ID, ASD, and/or multiple congenital anomalies (MCA) since 2010. One of the main advantages of CMA is its use as a discovery tool, as it requires no prior knowledge of the chromosome imbalance that is involved.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers chromosomal microarray (CMA) as outlined below.

Criteria for coverage:



Genetic Testing Policies, Continued

Genetic Testing: Comparative Genomic Hybridization (CGH)/Chromosomal Microarray (CMA), continued

A. Diagnostic Testing for Symptomatic Individuals:

- 1) Testing performed on living child or adult; and
- 2) Diagnosis cannot be made on clinical evaluation alone; and
- 3) Common aneuploidy (trisomy 13, 18, 21, or sex chromosome) is not a suspected diagnosis; and
- 4) At least one of the following presentations:
 - i. Isolated developmental delay (DD)/intellectual disability (ID)
 - ii. DD>ID associated with other findings that are not consistent with an easily recognizable syndrome
 - iii. Autism spectrum disorder
 - iv. Multiple congenital anomalies^a not specific to a well-delineated genetic syndrome.

B. Diagnostic Testing on products of conception for Intrauterine Fetal Demise or Stillbirth:

- 1) Common aneuploidy (trisomy 13, 18, 21, or sex chromosome) is not a suspected diagnosis; and
- 2) At least one of the following:
 - i. Multiple congenital anomalies^a not specific to a well-delineated genetic syndrome
 - ii. Fetal demise or stillbirth occurred at 20 weeks of gestation or later
 - iii. Recurrent pregnancy loss (beginning at second pregnancy loss).

C. Select Health covers use of chromosomal microarray analysis (CMA) in pregnancy, when the following criteria are met.

- 1) Any one of the following:
 - i. Patients with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnostic testing
 - ii. Patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing

^aMultiple congenital anomalies defined as 1) two or more major anomalies affecting different organ systems or 2) one major and two or more minor anomalies affecting different organ systems. [Major structural abnormalities are generally serious enough as to require medical treatment on their own (such as surgery) and are not minor developmental variations that may or may not suggest an underlying disorder.]

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Genetic Testing Policies, Continued

Genetic Testing: Comparative Genomic Hybridization (CGH)/Chromosomal Microarray (CMA), continued

Billing/Coding Information

Covered: For the indications outlined above

CPT CODES

- 0156U** Copy number (eg, intellectual disability, dysmorphology), sequence analysis [SMASH from New York Genomic Center]
- 0209U** Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities [CNGenome from Revvity]
- 0318U** Pediatrics (congenital epigenetic disorders), whole genome methylation analysis by microarray for 50 or more genes, blood [EpiSign Complete, Greenwood Genetic Center]
- 81228** Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
- 81229** Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
- 81349** Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
- 81479** Unlisted molecular pathology procedure

HCPCS CODES

- G0452** Molecular pathology procedure; physician interpretation and report
- S3870** Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability

Key References

1. ACOG Committee Opinion No. 446: array comparative genomic hybridization in prenatal diagnosis. Obstet Gynecol. 2009 Nov;114(5):1161-1163. doi: 10.1097/AOG.0b013e3181c33cad. PMID: 20168129. (reaffirmed 2021)
2. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstet Gynecol. 2018 Nov;132(5): e197-e207. doi: 10.1097/AOG.0000000000002899. PMID: 30157093
3. Committee on Genetics and the Society for Maternal-Fetal Medicine. Committee Opinion No.682: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. Obstet Gynecol. 2016 Dec;128(6): e262-e268. doi: 10.1097/AOG.0000000000001817. PMID: 27875474.(reaffirmed 2023)
4. Miller DT, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010 May 14;86(5):749-64. doi: 10.1016/j.ajhg.2010.04.006. PMID: 20466091.

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Genetic Testing Policies, Continued

Genetic Testing: Comparative Genomic Hybridization (CGH)/Chromosomal Microarray (CMA), continued

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Genetic Testing Policies, Continued

Genetic Testing: Comparative Genomic Hybridization (CGH)/Chromosomal Microarray (CMA), continued



MEDICAL POLICY

GENETIC TESTING: CHROMOSOMAL MICROARRAY ANALYSIS (CMA)

Policy # 297

Implementation Date: 2/15/06

Review Dates: 5/17/07, 4/24/08, 2/18/10, 5/19/11, 6/21/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 6/16/18, 4/17/19, 2/14/23, 2/15/24, 2/17/25

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[#123 Gene Therapy, Testing, and Counseling](#)

[#514 Whole Genomic Sequencing \(WGS\)/Whole Exome Sequencing \(WES\)](#)

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Description

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COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.
Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers chromosomal microarray (CMA) as outlined below.

Criteria for coverage:



MEDICAL POLICY

GENETIC TESTING: CYSTIC FIBROSIS (CF)

Policy # 289

Implementation Date: 12/15/05

Review Dates: 2/21/08, 2/26/09, 2/18/10, 2/17/11, 2/16/12, 4/25/13, 2/11/16, 2/16/17, 2/15/18, 2/18/19, 2/7/23, 2/15/24

Revision Dates: 2/15/07, 2/20/14, 2/11/15, 2/25/19, 7/1/23, 8/7/23

Related Medical Policies:

[#123 Gene Therapy, Testing, and Counseling](#)

Disclaimer:

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Cystic fibrosis (CF) is a multisystem genetic disease in which defective chloride transport across membranes causes dehydrated secretions. This leads to tenacious mucus in the lungs, to mucous plugs in the pancreas, and to the characteristically high sweat chloride levels. Intelligence and cognitive function are typically normal. More than 25,000 Americans have CF, with approximately 850 individuals newly diagnosed each year. Cystic fibrosis is inherited as an autosomal recessive disorder; the responsible gene, the CF transmembrane conductance regulator (CFTR), was mapped to chromosome 7 and identified in 1989.

Cystic fibrosis has a highly variable presentation and course. Median age at diagnosis is 6–8 months; nearly 2/3 of individuals are diagnosed before 1 year of age. Some individuals have severe pulmonary and/or gastrointestinal disease while others have relatively mild disease with presentation during adolescence and young adulthood. There is a range of outcomes, from early death from pulmonary complications to mild atypical disease in second and third decades, but rarely a normal length of life. Even though median survival has increased from 18 years in 1976 to 30.1 years in 1995, there has been little life-span extension between 1990 and 1995. Survival has improved thus far, through aggressive management of pulmonary, pancreatic, and intestinal complications.

Even though there have been advances in treatment, there is no cure for CF. Severity of lung disease is the key to the quality and length of life. Ninety percent of persons who have CF die from pulmonary complications. Pulmonary function tests, especially forced expiratory volume (FEV1), are predictive of mortality: when the FEV1 is 30%, mortality is 50% in 2 years. Poor prognosis is related to respiratory complications before 1 year of age, malnutrition, and denial of the condition. Better prognosis is indicated from mild symptoms at diagnosis, pancreatic sufficiency, and atypical presentation. A survey in 1995 reported that 35% of young adults with CF worked full-time, and almost 90% had completed at least a high school education.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and



Genetic Testing Policies, Continued

Genetic Testing: Cystic Fibrosis (CF), continued

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

1. Select Health covers genetic testing of cystic fibrosis for members in any of the following groups:

- a) Couples seeking prenatal care; or
- b) Couples who are planning a pregnancy; or
- c) Persons with a family history of cystic fibrosis; or
- d) Persons with a first-degree relative identified as a cystic fibrosis carrier; or
- e) Reproductive partners of persons with cystic fibrosis.

2. Diagnostic Testing for Symptomatic Individuals:

- a) Individuals with an intermediate range-equivocal sweat chloride test (30-59mmol/L), or
- b) Individuals with a negative sweat chloride test when symptoms of CF are present, or
- c) Infants with meconium ileus or other symptoms indicative of CF and are too young to produce adequate volumes of sweat for sweat chloride test, or
- d) Infants with an elevated IRT value on newborn screening, or
- e) Males with oligospermia/azoospermia/congenital absence of vas deferens (CAVD), OR
- f) Mutation Identification to Guide Pharmacologic Therapy Selection (individuals who meet diagnostic criteria for CF and are eligible for FDA-approved CFTR mutation-specific therapies), OR

3. Prenatal Testing:

- a) Either biological parent has a diagnosis of CF, or
- b) Family history of CF in a first degree relative, or
- c) Both parents are carriers of CF mutations included in the panel, or
- d) Echogenic bowel has been identified on ultrasound in a fetus.

4. CFTR Intron 8 Poly T Analysis:

Diagnostic Testing:

- a) CFTR mutation analysis performed and R117H mutation detected, or
- b) Diagnosis of male infertility (e.g., congenital absence of vas deferens [CAVD], obstructive azoospermia), or
- c) Diagnosis of non-classic CF.

Select Health does not cover genetic carrier testing for cystic fibrosis for all other indications as the effectiveness of testing for other indications other than the ones listed above have not been established. Use of this testing in these circumstances is considered experimental/investigational.

Select Health considers a core panel of 40 mutations recommended by the American College of Medical Genetics (ACMG) medically necessary for cystic fibrosis genetic testing. Preadmission will be required for full sequencing review. The standard CF transmembrane regulator (CFTR) mutation panel is as follows (Available at: <http://www.acmg.net>):

ΔF508	ΔI507	G542X	G551D	W1282X	N1303K
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Genetic Testing Policies, Continued

Genetic Testing: Cystic Fibrosis (CF), continued

R553X	621+1G→T	R117H	1717-1G→A	A455E	R560T
R1162X	G85E	R334W	R347P	711+1G→T	1898+1G→A
2184delA	1078delT	3849+10kbC→T	2789+5G→A	3659delC	I148T
3120+1G→A					

Select Health considers screening for cystic fibrosis mutations that extend beyond the standard mutation panel recommended by the ACMG to be experimental/investigational.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp> or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

Cystic fibrosis is one of the most common genetic diseases in Caucasians, with an incidence of about one in 3,300. The disease also has a fairly high incidence among Hispanics: 1 in 9,500. Cystic fibrosis is a rare disorder in native African and native Asians, estimated to occur in less than 1 in 50,000, but higher incidences are observed in American populations of these ethnic groups (1 in 15,300 and 1 in 32,100, respectively), suggesting Caucasian admixture. Recent surveys of some Native American populations also indicate high incidences: 1 in 3,970 in the Pueblo people, and 1 in 1,580 among the Zuni.

Since the identification of the gene and the major mutation responsible for CF, more than 600 mutations and DNA sequence variations have been identified in the CFTR gene. The Delta F508 mutation is represented in almost all populations, although its relative frequency varies among different geographic locations. The highest frequency is observed in Caucasian populations, where it accounts for approximately 70% of the CF alleles. Delta F508 mutation accounts for large portions of the alleles in other racial/ethnic groups: 48% in African Americans, 46% in Hispanics, and 30% in Asian Americans and Ashkenazi Jews. Some 15–20 other "common" mutations account for 2%–15% of CF alleles, depending on the ethnic composition of the patient group studied. Most of the remaining mutations are rare. The proportion of detectable mutations is an important indicator of the utility of a population-screening program. Combining detection of the Delta F508 with other mutations common to specific ethnic groups, it appears that there are several examples of populations for which 90% to 95% sensitivity can now be achieved with the current technology: the Ashkenazi Jews, Celtic Bretons, French Canadians from Quebec, and some Native Americans. In Caucasians in the United States, it is feasible to approach 90%

Genetic Testing Policies, Continued

Genetic Testing: Cystic Fibrosis (CF), continued

sensitivity at the current time. Because the remaining mutations are rare, expanding the panel of screened mutations is expected to achieve only marginal gains in the sensitivity. The detection rate in African Americans is about 75%. Despite the relatively high incidence in Hispanics, the detectable alleles account for only 57% of the CF mutations in this group. The promise appears to be weak in Asian Americans at 30% sensitivity.

Studies have shown that interest in CF genetic screening is limited in the general population and that agreement to participate in genetic education and testing procedures occurs primarily among pregnant women and persons with positive family histories. Uptake of prenatal genetic testing for CF varies widely, with acceptance ranging from about 50% to a high of 78% in one HMO population. Participation has been affected by factors relating to convenience, education, cost, views regarding abortion, concerns about the low sensitivity of the test, and the manner of presentation of the testing opportunity. Concerns about confidentiality and insurability and simply "not wanting to know," are often mentioned as reasons to forgo testing.

Guidelines published by the American College of Medical Genetics (ACMG) in 2001 and affirmed by the American College of Obstetrics and Gynecology (ACOG) in their policy statement published in 2001 recommend that genetic testing be offered to individuals with a family history of CF and partners of those with CF. As a group, individuals with a family history have relatively high frequencies of mutations in the CFTR gene. Members of this group have increased awareness of their risk of being carriers, as well as increased familiarity with the disease and its impact on the family. Testing may assist in making informed reproductive choices and decisions regarding family health. To date, over 900 mutations in the CF gene have been identified. As it is impractical to test for every known mutation, the ACMG Accreditation of Genetic Services Committee has compiled a standard screening panel of 25 CF mutations, which represents the standard panel that ACMG recommends for screening in the U.S. population. This 25-mutation panel incorporates all CF-causing mutations with an allele frequency of greater than or equal to 0.1 % in the general U.S. population, including mutation subsets shown to be sufficiently predominant in certain ethnic groups, such as Ashkenazi Jews and African Americans. This standard panel of mutations is intended to provide the greatest pan-ethnic detectability that can practically be performed.

The ACOG's update on carrier screening for CF (2011) added the recommendations stating that a patient previously screened should not be re-screened and the results should be documented and complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening.

The NIH, ACOG, and the ACMG also recommend that CF genetic testing be offered prenatally and to couples planning a pregnancy. Data indicates that a significant level of interest in CF testing exists in this group. This is a vulnerable population and because of the inherent time constraints, it is particularly important that they receive adequate and balanced information. This information includes, but is not limited to, the implications of genetic testing, its limitations and strengths, and the risks of ensuing potential therapies and interventions, sensitivity of the test, a description of the range of severity of the disease. Care should be given to ensure decisions of couples considering testing or subsequent reproductive options are completely voluntary and made without coercion from care providers. The NIH Consensus Statement on Genetic Testing for CF and the ACMG has not recommended CF testing for the general population. Given the low incidence and prevalence of CF and the demonstrable lack of interest in the general population, there is little justification for testing. Genetic testing for CF should begin with education concerning CF. It should be clear that the patient has received the material and has had an opportunity for questions to be answered before testing is undertaken—all persons undergoing genetic testing should give written informed consent for the test.

As with any genetic testing, provision of accurate genetic counseling, particularly when the results are provided to the patient or when the intervention strategies are discussed, is essential. The implications of genetic testing, its limitations and strengths, and the risks of ensuing potential therapies and interventions mandate that individuals knowledgeable in genetics provide these services. The counseling skills required must combine respect for a patient's right to make an autonomous decision with an appropriate level of support to facilitate the decision-making process. Any strategy attempting to provide these services to the public carries with it a responsibility to enhance the educational process for physicians and other healthcare providers.

Genetic Testing Policies, Continued

Genetic Testing: Cystic Fibrosis (CF), continued

Billing/Coding Information

Covered: For the conditions outlined above

CPT CODES

- 81220** CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines)
- 81221** ; known familial variants
- 81222** ; duplication/deletion variants
- 81223** ; full gene sequence
- 81224** ; intron 8 poly-T analysis

HCPCS CODES

No specific codes identified

Key References

1. American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG). Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and Laboratory Provider Guidelines. ACOG/ACMG Position Statement. Washington, DC: ACOG; 2001.
2. American College of Obstetrics and Gynecology. Policy statement on prenatal Cystic Fibrosis Testing, 12/12/01.
3. American College of Obstetricians and Gynecologists (ACOG). Update on carrier screening for cystic fibrosis. ACOG Committee Opinion No. 325. Washington, DC: ACOG; December 2005
4. American College of Obstetricians and Gynecologists. Update on carrier screening for cystic fibrosis. Committee Opinion No. 486. Obstet Gynecol, 2011;117(4):1028-1031.
5. Cystic Fibrosis Diagnosed After 2 Months of Age Leads to Worse Outcomes and Requires More Therapy. Pediatrics. <http://pediatrics.aappublications.org/cgi/content/full/119/1/19>. 2/14/07.
6. Genetic Testing for Cystic Fibrosis. NIH Consensus Statement Available on-line at <http://text.nlm.nih.gov/> or at NIH Consensus Program Information Center, P.O. Box 2577, Kensington, MD 20891, Telephone: 1-888-NIH-CONSENSUS (888-644-2667) Fax: (301) 816-2494.
7. Guidelines for Population-Based Cystic Fibrosis Carrier Screening. Adapted from the American College of Medical Genetics; Genetics in Medicine/01, Vol. 3 No. 2:149-154; on-line at http://www.acmg.net/Pages/ACMG_Activities/PoliciesStatements.htm. American College of Medical Genetics, 9650 Rockville Pike, Bethesda, MD 20814-3998, Phone: 301-530-7127, Fax: 301-571-1895
8. Watson, M. S., et al. (2004). "Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel." *Genet Med*, 6(5): 387-391.

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MEDICAL POLICY

GENETIC TESTING: DONOR-DERIVED CELL-FREE DNA FOR MONITORING OF REJECTION IN HEART AND KIDNEY TRANSPLANTATION

Policy # 671

Implementation Date: 7/1/23

Review Dates: 8/20/24

Revision Dates: 1/22/24

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Heart Transplant

Donor-derived cell-free deoxyribonucleic acid (dd-cfDNA) is released from damaged donor heart cells and can be quantified relative to the amount of background circulating recipient cell-free DNA. An increase in the percentage of dd-cfDNA in the blood indicates injury to the transplanted (i.e., donor) heart that may be caused by acute cellular rejection (ACR) or antibody-mediated rejection (AMR), as well as other forms of injury, such as cardiac allograft vasculopathy.

The accuracy of dd-cfDNA for the detection of ACR and AMR was reported in a large prospective study of 171 patients who had undergone transplantation at least seven days prior. The study assessed the ability of dd-cfDNA to detect grade 2 ACR or grade 1 AMR. The study reported the following:

- For the detection of ACR in patients who were at least 14 days post-transplantation, the sensitivity and specificity of dd-cfDNA were 83 and 82 percent, respectively, for the cutoff value of 0.25 percent dd-cfDNA .
- For the detection of AMR in similar patients, the sensitivity and specificity of dd-cfDNA were 88 and 82 percent, respectively, for the cutoff value of 0.25 percent dd-cfDNA . For either AMR or ACR and at the 0.25 percent cutoff, the sensitivity and specificity were 88 and 82 percent, respectively.
- Given the limitations of endomyocardial biopsy to detect ACR and AMR, the study also evaluated dd-cfDNA as the reference standard to assess the accuracy of endomyocardial biopsy. When dd-cfDNA \geq 0.25 percent was used as the reference standard, the study found that endomyocardial biopsy had a sensitivity of 20 percent and specificity of 99 percent.

After obtaining serologic tests for rejection, confirmatory biopsies are performed based on the test results as follows:

- Simultaneous gene expression and cell free DNA test results: If a GEP test and dd-cfDNA are obtained simultaneously, the result of each test must be considered. If the dd-cfDNA result is positive, a biopsy is obtained regardless of the GEP result. If the dd-cfDNA result is negative and the GEP result is positive, the approach to performance of a biopsy is individualized and may be

Genetic Testing Policies, Continued

Genetic Testing: Donor-Derived Cell-Free DNA for Monitoring Rejection of Heart and Kidney Transplantation, continued

influenced by such factors as the severity and frequency of past episodes of rejection. If both tests are negative, we do not perform a biopsy. This approach is based on the diagnostic characteristics of these tests.

- Isolated gene expression profiling: If an isolated GEP test is negative, an endomyocardial biopsy is not performed. If an isolated GEP test is positive, a biopsy is typically obtained. In patients who have two negative biopsies following elevated GEP test results, further biopsies are not obtained based on GEP results and cease GEP testing. This approach is motivated by the high negative predictive value and low positive predictive value of GEP testing.
- Isolated donor-derived cell-free DNA: In the presence of an isolated positive dd-cfDNA, a endomyocardial biopsy is obtained, while a negative dd-cfDNA result does not require a follow-up biopsy. This approach is motived by the high diagnostic accuracy of the dd-cfDNA test.

Kidney Transplant

The use of routine monitoring of donor-derived cell-free DNA (dd-cfDNA) after kidney transplant may allow clinicians to identify subclinical allograft injury and intervene prior to development of clinically evident graft injury. To evaluate this, data from 1092 kidney transplant recipients monitored for dd-cfDNA over a three-year period was analyzed to assess the association of dd-cfDNA with histologic evidence of allograft rejection. Elevation of dd-cfDNA (0.5% or more) was significantly correlated with clinical and subclinical allograft rejection. dd-cfDNA values of 0.5% or more were associated with a nearly three-fold increase in risk development of de novo donor-specific antibodies (hazard ratio 2.71) and were determined to be elevated a median of 91 days (interquartile range of 30-125 days) ahead of donor specific antibody identification.

Persistently elevated dd-cfDNA (more than one result above the 0.5% threshold) predicted over a 25% decline in the estimated glomerular filtration rate over three years (hazard ratio 1.97). Therefore, routine monitoring of dd-cfDNA allowed early identification of clinically important graft injury. Biomarker monitoring complemented histology and traditional laboratory surveillance strategies as a prognostic marker and risk-stratification tool post-transplant. Thus, persistently low dd-cfDNA levels may accurately identify allograft quiescence or absence of injury, paving the way for personalization of immunosuppression trials.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Donor-derived cell-free DNA (dd-cfDNA) for monitoring of rejection in heart or kidney transplantation is covered if ordered by an Intermountain Health Transplant Provider, or when the following criteria are met:

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested; and

Genetic Testing Policies, Continued

Genetic Testing: Donor-Derived Cell-Free DNA for Monitoring Rejection of Heart and Kidney Transplantation, continued

3. To assess the probability of allograft rejection in kidney and cardiac transplant recipients with clinical suspicion of rejection and to inform clinical decision-making about the necessity of cardiac or renal biopsy. Frequency of genetic testing to be determined by the transplant provider.

I. Frequency of Testing Recommendations for Heart

A. Year 1:

Starting day 30 post-transplantation; and then, once every 2 weeks x 2; and then, once every 3 weeks x 3; and then, monthly up to 6 months post-transplantation; and then, every 6 weeks till the end of the first-year post-transplantation.

B. Year 2:

Every 3 months.

C. Year 3:

Every 6 months.

D. Year 4:

Once yearly.

E. Year 5 and Beyond:

As needed.

II. Frequency of Testing Recommendations for Kidney

A. These are the recommended frequencies for post-kidney transplant: 2,4,7,10, and 13 months post-transplant.

B. After the 13th month, determinations will be made on a case-by-case basis, or if more frequent testing will be allowed, based on further concern of renal rejection.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Billing/Coding Information

Covered for the indications outlined above when criteria are met

CPT CODES

81479 Unlisted molecular pathology procedure

Genetic Testing Policies, Continued

Genetic Testing: Donor-Derived Cell-Free DNA for Monitoring Rejection of Heart and Kidney Transplantation, continued

Not covered: the following codes are considered experimental/investigational

- 0540U** Transplantation medicine, quantification of donor-derived cell-free DNA using next-generation sequencing analysis of plasma, reported as percentage of donor-derived cell-free DNA to determine probability of rejection

Key References

1. Bu, L., Gupta, G., Pai, A., Anand, S., Stites, E., Moinuddin, I., ... Alhamad, T. Clinical outcomes from the Assessing Donor-derived cell-free DNA Monitoring Insights of Kidney Allografts with Longitudinal surveillance (ADMIRAL) study. *Kidney Int.* 2022;101(4):793. Epub 2021 Dec 22.
2. Eisen, H. J. Heart transplantation in adults: Diagnosis of allograft rejection. UpToDate. Last updated: Jan. 10, 2023. Retrieved from: <https://www.uptodate.com/contents/heart-transplantation-in-adults-diagnosis-of-allograft-rejection>
3. Halloran, P. F., Reeve, J., Madill-Thomsen, K.S., Demko, Z., Prewett, A., Billings, P., & The Trifecta Investigators. The Trifecta Study: Comparing Plasma Levels of Donor-derived Cell-Free DNA with the Molecular Phenotype of Kidney Transplant Biopsies. *JASN*. 2022; 33: 387–400. doi: <https://doi.org/10.1681/ASN.2021091191>
4. Kim, P. J., et al. A novel donor-derived cell-free DNA assay for the detection of acute rejection in heart transplantation. *J Heart Lung Transplant*. 2022; 41: 919–927.
5. Kobashigawa J, Hall S, Shah P, Fine B, Halloran P, Jackson AM, Khush KK, Margulies KB, Sani MM, Patel JK, Patel N, Peyster E. The Evolving Use of Biomarkers in Heart Transplantation: Consensus of an Expert Panel. *American Journal of Transplantation*. 27 Feb 2023. <https://doi.org/10.1016/j.ajt.2023.02.025>
6. Martuszewski, A., et al. Donor-Derived Cell-Free DNA in Kidney Transplantation as a Potential Rejection Biomarker: A Systematic Literature Review. *J. Clin. Med.* 2021; 10: 193.
7. Qazi, Y., Patel, A., Fajardo, M., McCormick, S., Fehringer, G., Ahmed, E., ... Gauthier, P. Incorporation of Donor-derived Cell-free DNA Into Clinical Practice for Renal Allograft Management. *Transplantation Proceedings*. 2021; 000: 1–7.
8. Sidgel, T. K., Archila, F. A., Constantin, T., Prins, S. A., Liberto, J., Damm, I., ... Sarwal, M. M. Optimizing Detection of Kidney Transplant Injury by Assessment of Donor-Derived Cell-Free DNA via Massively Multiplex PCR. *J. Clin. Med.* 2019, 8, 19; doi:10.3390/jcm8010019

Revision History

Revision Date	Summary of Changes
1/22/24	For Commercial Plan Policy, revised to provide coverage of this testing with criteria.

Disclaimer

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: EPILEPSY

Policy # 602

Implementation Date: 5/19/17

Review Dates: 7/18/18, 4/12/19, 8/7/19, 4/5/23, 5/10/24

Revision Dates: 7/1/23, 7/21/23

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Epilepsy is a disorder characterized by recurrent, unprovoked seizures. It is a heterogeneous condition that encompasses many different types of seizures and that varies in age of onset and severity. Some individuals experience seizures without any additional clinical symptoms, while others have comorbidities including autism spectrum disorder, developmental delays or regression, intellectual disability, encephalopathy, birth defects, or characteristic facial features. The causes for epilepsy vary and can include trauma, stroke, infection, structural brain abnormalities, autoimmune conditions, and genetic factors. It is estimated that 30% of epilepsies have an underlying genetic cause.

Workup of patients with epilepsy can include EEG, imaging, and laboratory testing for metabolic, autoimmune, toxic, and infectious causes of epilepsy. When these evaluations do not identify a cause, the patient is considered to have unexplained epilepsy. Genetic testing is recommended by the National Society of Genetic Counselors and endorsed by the American Epilepsy Society for individuals with unexplained epilepsy. Identifying an underlying genetic cause for epilepsy can impact treatment, providing guidance on anti-seizure medication, diet, and surgical decisions. It can also provide insight into the natural history of the condition and anticipatory guidance for healthcare providers and families. Further, it can inform recurrence risk. Commercial genetic testing for epilepsy genes is available from numerous companies. Because of the large number of epilepsy-associated genes, testing is often done by multi-gene panel testing, whole exome sequencing, or whole genome sequencing.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

A. Select Health covers genetic testing for epilepsy by genome sequencing, exome sequencing, or multi-gene panel, when all the following criteria are met:

1. The patient has epilepsy of unexplained etiology with onset at any age; and
2. Alternate etiologies have been considered and ruled out when possible (e.g., head

Genetic Testing Policies, Continued

Genetic Testing: Epilepsy, continued

- trauma, toxic exposures, stroke, infections, autoimmune conditions, metabolic conditions, tumors, prenatal injury), and
3. Clinical presentation does not fit a well-described syndrome for which more targeted testing is available.

B. Exclusions

- Genetic testing for epilepsy is considered not medically necessary in individuals who do not meet the above criteria.
- Comprehensive genetic testing for epilepsy is not medically necessary for individuals with a known familial variant unless targeted genetic testing has been performed and is negative.
- Genetic testing is considered experimental/investigational for screening for genetic epilepsy in asymptomatic individuals.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were identified. The available commercial genetic tests for epilepsy are offered as laboratory-developed tests. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); (2) clinical validity (the diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

Genetic epilepsies can be divided into the rare epileptic syndromes that may be caused by a single-gene mutation and the common epilepsy syndromes that are thought to have a multifactorial genetic basis.

Rare Epilepsy Syndromes Associated with Single-Gene Mutations:

There are numerous rare syndromes that have seizures as their primary symptom, some of these include Dravet syndrome, early infantile epileptic encephalopathy, generalized epilepsy with febrile seizures plus (GEFS+), epilepsy and intellectual disability limited to females (EFMR), and Nocturnal frontal lobe epilepsy. These generally present in infancy or early childhood. Many of them are thought to be caused by single-gene mutations. The published literature on these syndromes generally consists of small cohorts of patients treated in tertiary care centers, with descriptions of genetic mutations that are detected in affected individuals.

Genetic Testing Policies, Continued

Genetic Testing: Epilepsy, continued

These syndromes can be evaluated by single-gene analysis, which is generally performed by direct sequencing. Direct sequencing is the gold standard for identifying specific mutations. This testing method has an analytic validity of greater than 99%. They can also be evaluated by genetic panel testing, which is generally done by next-generation sequencing. This method has a lower analytic validity compared to direct sequencing, but is still considered to be very accurate, in the range of 95% to 99%.

The literature on the clinical validity of these rare syndromes is limited, and for most syndromes, the clinical sensitivity and specificity is not defined. Dravet syndrome (Hirose and Mulley et al) is probably the most well-studied, and some evidence on the clinical validity of SCN1A mutations is available. The clinical sensitivity has been reported to be in the 70% to 80% range. In 1 series of 64 patients, 51 (79%) were found to have SCN1A mutations. The false-positive rate and the frequency of variants of uncertain significance, is not well characterized.

For the other syndromes, the associations of the genetic mutations with the syndromes have been reported in case reports or very small numbers of patients. Therefore, it is not possible to determine the clinical validity of the putative causative genetic mutations.

One potential area of clinical utility for genetic testing may be in making a definitive diagnosis and avoiding further testing. For most of these syndromes, the diagnosis is made by clinical criteria, and it is not known how often genetic testing leads to a definitive diagnosis when the diagnosis cannot be made by clinical criteria.

Another potential area of clinical utility may be in directing pharmacologic treatment. For Dravet syndrome, the seizures are often refractory to common medications. Some experts (Mulley and Ottman et al.) have suggested that diagnosis of Dravet syndrome may therefore prompt more aggressive treatment, and/or avoidance of certain medications that are known to be less effective, such as carbamazepine. However, there are no studies that examine the frequency with which genetic testing leads to changes in medication management, and there are no studies that report on whether the efficacy of treatment directed by genetic testing is superior to efficacy of treatment without genetic testing.

Therefore, there are numerous rare epileptic syndromes which may be caused by single-gene mutations, but the evidence on genetic testing for these syndromes is insufficient to form conclusions on the clinical validity and clinical utility of genetic testing. The syndrome with the greatest amount of evidence is Dravet syndrome. The clinical sensitivity of testing patients with clinically defined Dravet syndrome is relatively high in small cohorts of patients. There may be clinical utility in avoiding further testing and directing treatment, but there is only a small amount of evidence to suggest this and no evidence demonstrating that outcomes are improved.

Common Epilepsies

The common epilepsy syndromes, also known as idiopathic epilepsy, generally present in childhood, adolescence, or early adulthood. They may be generalized or focal in nature, and may be convulsant (grand mal) or absence type. They are generally thought to have a multifactorial genetic component.

The common epilepsies are generally evaluated by genetic panel testing. The larger, commercially available panels that include many mutations are generally performed by next-generation sequencing. This method has a lower analytic validity compared to direct sequencing, but is still considered to be very accurate, in the range of 95% to 99%. Less commonly, deletion/duplication analysis may be performed; this method is also considered to have an analytic validity of greater than 95%.

The literature on clinical validity includes many studies that report the association of various genetic variants with the common epilepsies. There are a large number of case-control studies that compare the frequency of genetic variants in patients with epilepsy to the frequency in patients without epilepsy. There is a smaller number of genome-wide association studies (GWAS) that evaluate the presence of single-nucleotide polymorphisms (SNPs) associated with epilepsy across the entire genome. No studies were identified that reported the clinical sensitivity and specificity of genetic mutations in various clinically defined groups of patients with epilepsy. In addition to these studies on the association of genetic variants with the diagnosis of epilepsy, there are numerous other studies that evaluate the association of genetic variants with pharmacogenomics of anti-epileptic medications.

Genetic Testing Policies, Continued

Genetic Testing: Epilepsy, continued

Diagnosis of Epilepsy

The Epilepsy Genetic Association Database (epiGAD) (Tan et al.) published an overview of genetic association studies in 2010. This review identified 165 case-control studies published between 1985 and 2008. There were 133 studies that examined the association of 77 different genetic variants with the diagnosis of epilepsy. Approximately half of these studies (65/133) focused on patients with genetic generalized epilepsy. Most of these studies had relatively small sample sizes, with a median of 104 cases (range, 8–1361) and 126 controls (range, 22–1390). There were less than 200 case patients in 80% of the studies. The majority of the studies did not show a statistically significant association. Using a cutoff of $p < 0.01$ as the threshold for significance, there were 35 studies (21.2%) that reported a statistically significant association. According to standard definitions for genetic association, all of the associations were in the weak-to-moderate range, with no associations reported that were considered strong.

The EPICURE Consortium published one of the larger GWAS of genetic generalized epilepsy in 2012 (12). This study included 3,020 patients with genetic generalized epilepsy (GGE) and 3,954 control patients, all of European ancestry. A 2-stage approach was used, with a discovery phase and a replication phase, to evaluate a total of 4.56 million single-nucleotide polymorphisms (SNPs). In the discovery phase, 40 candidate SNPs were identified that exceeded the significance for the screening threshold (1×10^{-5}), although none of these reached the threshold defined as statistically significant for genome-wide association (1×10^{-8}). After stage 2 analysis, there were 4 SNPs identified that had suggestive associations with GGE on genes *SCN1A*, *CHRM3*, *ZEB2*, and *NLE2F1*.

A second GWAS (Guo et al.), with a relatively large sample size of Chinese patients, was also published in 2012. Using a similar 2-stage methodology, this study evaluated 1,087 patients with epilepsy and 3,444 matched controls. Two variants were determined to have the strongest association with epilepsy. One of these was on the *CAMSAP1L1* gene and the second was on the *GRIK2* gene. There were several other loci on genes that were suggestive of an association on genes that coded for neurotransmitters or other neuron function.

In contrast to the 2 studies, a GWAS published from the UK (Kasperaviciute et al.) failed to show any robust associations of SNPs with partial epilepsy. This study included 3,445 patients with partial epilepsies and 6,935 controls of European ancestry. Using a threshold of an odds ratio greater than 1.3, the authors reported that no SNPs were identified that had a statistically significant association at that level.

In 2012, Heinzen et al. used whole exome sequencing to evaluate the association of genetic variants with genetic generalized epilepsy in 118 individuals with the disorder and 242 control patients of European origin. No variants were found that reached the statistical threshold for a statistical association. From this initial data, the researchers selected 3,897 candidate genetic variants. These variants were tested in a replication sample of 878 individuals with GGE and 1,830 controls. None of the tested variants showed a statistically significant association.

In addition to the individual studies, there are a number of meta-analyses that evaluate the association of particular genetic variants with different types of epilepsy. Most of these have not shown a significant association. For example, Cordoba et al. evaluated the association of *SLC6A4* gene variants with temporal lobe epilepsy in a total of 991 case patients and 1,202 controls and failed to demonstrate a significant association on combined analysis. Nurmohamed et al. performed a meta-analysis of 9 case-control studies that evaluated the association of the *ABC1* gene polymorphisms with epilepsy. There was a total of 2,454 patients with epilepsy and 1,542 control patients. No significant associations were found. One meta-analysis that did report a significant association was published by Kauffman et al. in 2008. This study evaluated the association of variants in the *IL1B* gene with temporal lobe epilepsy and febrile seizures, using data from 13 studies of 1,866 patients with epilepsy and 1,930 controls. Combined analysis showed a significant relationship between one SNP (511T) and temporal lobe epilepsy, with a strength of association that was considered modest (odds ratio [OR]=1.48; 95% confidence interval [CI], 1.1 to 2.0; $p=0.01$).

Genetic Testing Policies, Continued

Genetic Testing: Epilepsy, continued

The evidence on genetic testing for the common epilepsies is characterized by a large number of studies that evaluate associations of many different genetic variants with the various categories of epilepsy. The evidence on clinical validity is not consistent in showing an association of any specific genetic mutation with any specific type of epilepsy. Where associations have been reported, they are not of strong magnitude, and in most cases, have not been replicated independently or through the available meta-analyses. Because of the lack of established clinical validity, the clinical utility of genetic testing for the common epilepsies is also lacking.

In conclusion, genetic testing for epilepsy covers a wide range of clinical syndromes and possible genetic defects. For rare epilepsy syndromes, which may be caused by single-gene mutations, there is only a small body of research, which is insufficient to determine the clinical validity and clinical utility of genetic testing. There may be a potential role in differentiating these syndromes from the common epilepsies and from each other, and in improving the efficiency of the diagnostic work-up. There also may be a potential role for genetic testing in identifying syndromes that are resistant to particular medications, and thereby directing treatment. However, now the evidence is limited and the specific way in which genetic testing leads to improved outcomes is ill-defined.

For the common epilepsies, which are thought to have a complex, multifactorial basis, the role of specific genetic mutations remains uncertain. Despite a large body of literature of associations between genetic variants and common epilepsies, the clinical validity of genetic testing is poorly understood. Published literature is characterized by weak and inconsistent associations, which have not been replicated independently or by meta-analyses. This literature does not permit conclusions on the clinical validity of genetic testing. Because of the lack of conclusions on clinical validity, conclusions on clinical utility are also lacking.

Billing/Coding Information

CPT CODES

0232U	CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, UnverrichtLundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
81401	Molecular pathology procedure level 2
81403	Molecular pathology procedure level 4
81404	Molecular pathology procedure level 5
81405	Molecular pathology procedure level 6
81406	Molecular pathology procedure level 7
81407	Molecular pathology procedure level 8
81419	Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, GT.80 32 Codes Number Description PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2
81479	Unlisted molecular pathology procedure

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report
81188	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81189	; full gene sequence

Genetic Testing Policies, Continued

Genetic Testing: Epilepsy, continued

81190

; known familial variant(s)

Key References

1. Berg AT, Berkovic SF, Brodie MJ et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010; 51(4):676-85.
2. Cavalleri GL, McCormack M, Alhusaini S et al. Pharmacogenomics and epilepsy: the road ahead. *Pharmacogenomics* 2011; 12(10):1429-47.
3. Cordoba M, Consalvo D, Moron DG et al. SLC6A4 gene variants and temporal lobe epilepsy susceptibility: a meta-analysis. *Mol Biol Rep* 2012; 39(12):10615-9.
4. Epicure Consortium, Consortium EM, Steffens M et al. Genome-wide association analysis of genetic generalized epilepsies implicates susceptibility loci at 1q43, 2p16.1, 2q22.3 and 17q21.32. *Hum Mol Genet* 2012; 21(24):5359-72.
5. Guo Y, Baum LW, Sham PC et al. Two-stage genome-wide association study identifies variants in CAMSAP1L1 as susceptibility loci for epilepsy in Chinese. *Hum Mol Genet* 2012; 21(5):1184-9.
6. Haerian BS, Roslan H, Raymond AA et al. ABCB1 C3435T polymorphism and the risk of resistance to antiepileptic drugs in epilepsy: a systematic review and meta-analysis. *Seizure* 2010; 19(6):339-46.
7. Heinzen EL, Depondt C, Cavalleri GL et al. Exome sequencing followed by large-scale genotyping fails to identify single rare variants of large effect in idiopathic generalized epilepsy. *Am J Hum Genet* 2012; 91(2):293-302.
8. Helbig I, Lowenstein DH. Genetics of the epilepsies: where are we and where are we going? *Curr Opin Neurol* 2013; 26(2):179-85.
9. Hirose S, Scheffer IE, Marini C et al. SCN1A testing for epilepsy: application in clinical practice. *Epilepsia* 2013; 54(5):946-52.
10. Jang SY, Kim MK, Lee KR et al. Gene-to-gene interaction between sodium channel-related genes in determining the risk of antiepileptic drug resistance. *J Korean Med Sci* 2009; 24(1):62-8.
11. Kasperaviciute D, Catarino CB, Heinzen EL et al. Common genetic variation and susceptibility to partial epilepsies: a genome-wide association study. *Brain* 2010; 133(Pt 7):2136-47.
12. Kauffman MA, Moron DG, Consalvo D et al. Association study between interleukin 1 beta gene and epileptic disorders: a HuGe review and meta-analysis. *Genet Med* 2008; 10(2):83-8.
13. Kwan P, Poon WS, Ng HK et al. Multidrug resistance in epilepsy and polymorphisms in the voltage-gated sodium channel genes SCN1A, SCN2A, and SCN3A: correlation among phenotype, genotype, and mRNA expression. *Pharmacogenet Genomics* 2008; 18(11):989-98.
14. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; 342(5):314-9.
15. Mervick A, O'Brien M, Delanty N. Complex single gene disorders and epilepsy. *Epilepsia* 2012; 53 Suppl 4:S1-91.
16. Mulley JC, Nelson P, Guerrero S et al. A new molecular mechanism for severe myoclonic epilepsy of infancy: exonic deletions in SCN1A. *Neurology* 2006; 67(6):1094-5.
17. Nurmohamed L, Garcia-Bourmisen F, Buono RJ et al. Predisposition to epilepsy—does the ABCB1 gene play a role? *Epilepsia* 2010; 51(9):1882-5.
18. Ottman R, Hirose S, Jain S et al. Genetic testing in the epilepsies—report of the ILAE Genetics Commission. *Epilepsia* 2010; 51(4):655-70.
19. Petrovski S, Kwan P. Unraveling the genetics of common epilepsies: approaches, platforms, and caveats. *Epilepsy Behav* 2013; 26(3):229-33.
20. Patient-Centered Laboratory Utilization Guidance Services (PLUGS). *Epilepsy Genetic Testing Policy*. February 2023.
21. Smith, L., et al. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. *J Genet Couns*. 2023; 32:266–280.
22. Tan NC, Berkovic SF. The Epilepsy Genetic Association Database (epiGAD): analysis of 165 genetic association studies, 1996-2008. *Epilepsia* 2010; 51(4):686-9.
23. Williams CA, Battaglia A. Molecular biology of epilepsy genes. *Exp Neurol* 2013; 244:51-8.

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Genetic Testing Policies, Continued

Genetic Testing: Epilepsy, continued

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: BARRETT'S ESOPHAGUS

Policy # 678

Implementation Date: 2/19/24

Review Dates:

Revision Dates: 11/11/24

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

The EsoGuard test and the EsoCheck device (Lucid Diagnostics, Inc., New York, NY) have been proposed as a screening kit for the detection of Barrett's Esophagus (BE). The EsoCheck is a specimen collection device in the form of a vitamin-sized, encapsulated balloon. The device is swallowed and surface textures on the balloon collect a gentle brushing of the esophageal mucosa. The balloon is collapsed to protect the collected specimen and drawn back out through the upper esophagus and mouth. The specimen is submitted to a laboratory for EsoGuard testing. The EsoGuard uses next generation sequencing bisulfate converted DNA to detect the presence of Vimentin and CyclinA1 methylation signatures at 31 sites within those genes to identify the presence of BE. The EsoCheck device has received a 510(k) clearance from the FDA while the EsoGuard was granted a breakthrough device designation. Use of the EsoGuard test for detection of BE is not considered in accordance with generally accepted standards of medical practice.

For individuals with Barrett's esophagus who receive multi-analyte assays with algorithmic analyses (MAAs) TissueCypher Barrett's Esophagus Assay, the evidence includes four case control studies and one prospective cohort study. In a Hayes, Inc. Molecular Test Assessment regarding TissueCypher Barrett's Esophagus Assay (Castle Biosciences Inc.), literature search through October 2023, the overall body of evidence was rated very low quality and insufficient to evaluate the use of this assay. While the limited evidence may suggest that TissueCypher Barrett's Esophagus Assay may identify some patients at high-risk for progression who would be candidates for eradication therapy, the evidence also suggests this test may not reliably identify patients at low risk of progression who would be candidates for reduced surveillance. This questions whether clinical decisions based on this assay result would lead to patient benefit or harm. There were no studies found evaluating whether this testing impacted clinical outcomes. Based on current evidence uncertainty exists due to study limitations that include questions related to test accuracy and the lack of evidence directly evaluating clinical outcomes with testing. Randomized controlled trials (RCTs) are needed to validate the clinical utility of the TissueCypher Barrett's Esophagus Assay in its use to improve patient outcomes in guiding management. The evidence is insufficient to determine if this technology results in an improvement in net health outcome.

For Individuals with eosinophilic esophagitis who receive multi-analyte assays with algorithmic analyses (MAAs) Esophageal String Test (EST), the evidence includes two prospective case studies. While these studies may be promising, no randomized controlled trials (RCTs) were found, and it remains unclear whether this test could be used to guide management in individual patients. RCTs are needed to validate the clinical utility of the EST in its use to improve patient outcomes in guiding management. The evidence is insufficient to determine if this technology results in an improvement in net health outcome.

Genetic Testing Policies, Continued

Genetic Testing: Barrett's Esophagus, continued

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover genetic testing to screen for the likelihood of Barrett's esophagus, esophageal cancer, or esophagogastric junction cancer (e.g., methylation analysis, EsoGuard). The effectiveness of this testing has not been established; therefore, this meets the plan's definition of experimental/investigational.

Select Health does NOT cover multi-analyte assays with biomarker analysis (e.g., **TissueCypher, Esophageal String Test**) for the management of Barrett's Esophagus and other esophageal disorders such as eosinophilic esophagitis as the effectiveness of this testing has not been established. Therefore, this meets the plan's definition of experimental/investigational.

SELECT HEALTH MEDICARE

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SELECT HEALTH COMMUNITY CARE (MEDICAID)

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Billing/Coding Information

Not covered: Experimental/Investigational for the indications listed above

CPT CODES

- 0095U** Inflammation (eosinophilic esophagitis), ELISA analysis of eotaxin-3 (CCL26 [C-C motif chemokine ligand 26]) and major basic protein (PRG2 [proteoglycan 2, pro eosinophil major basic protein]), specimen obtained by swallowed nylon string, algorithm reported as predictive probability index for active eosinophilic esophagitis
- 0108U** Gastroenterology (Barrett's esophagus), whole slide–digital imaging, including morphometric analysis, computer-hyphenassisted quantitative immunolabeling of 9 protein biomarkers (p16, AMACR, p53, CD68, COX-hyphen2, CD45RO, HIF1a, HER-hyphen2, K20) and morphology, formalin-hyphenfixed paraffin-hyphenembedded tissue, algorithm reported as risk of progression to high-hyphengrade dysplasia or cancer
- 0114U** Gastroenterology (Barrett's esophagus), VIM and CCNA1 methylation analysis, esophageal cells, algorithm reported as likelihood for Barrett's esophagus EsoGuard™, Lucid Diagnostics, Lucid Diagnostics

Key References

1. Anthem. Clinical UM Guideline. Testing for Oral and Esophageal Cancer. Last Review Date: 05/11/2023.
2. Biomarker Testing for Barrett's Esophagus and Other Esophageal Disorders. Wellmark Blue Cross and Blue Shield. Last Review Date: October 2023.
3. Poppers, D. M., et al. Novel Screening and DNA Testing for the Detection of Esophageal Precancerous Disease. *Gastroenterology & Hepatology*. Volume 18, Issue 5. May 2022.

Genetic Testing Policies, Continued

Genetic Testing: Barrett's Esophagus, continued

Revision History

Revision Date	Summary of Changes
11/11/24	Modified title of policy from "Genetic Testing: EsoGuard" to "Genetic Testing: Barrett's Esophagus" to incorporate consideration of other tests related to Barrett's Esophagus. And for Commercial Plan Policy, added language excluding coverage of the TissueCypher and Esophageal String tests: " Select Health does NOT cover multi-analyte assays with biomarker analysis (e.g., TissueCypher, Esophageal String Test) for the management of Barrett's Esophagus and other esophageal disorders such as eosinophilic esophagitis as the effectiveness of this testing has not been established. Therefore, this meets the plan's definition of experimental/investigational."

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: EXPANDED CARRIER SCREENING

Policy # 452

Implementation Date: 8/9/10

Review Dates: 9/15/11, 7/18/13, 8/28/14, 5/7/15, 4/14/16, 4/27/17, 2/18/19, 8/16/23, 8/16/24

Revision Dates: 12/5/11, 6/1/17, 1/26/18, 8/17/23, 5/14/24, 9/4/24

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Genetic diseases inherited through Mendelian genetics impose a significant public health burden on society, with single-gene disorders accounting for at least 10% of pediatric admissions and 20% of infant mortality. Over 6,000 genetic disorders are inherited through Mendelian genetics, each of which affect less than 200,000 Americans, but combine to afflict 25–30 million people worldwide. Because of this heterogeneity, diagnosis and treatment are difficult for most individuals with a genetic disease.

Couples who test positive as carriers have several options to conceive a child without a lethal disease, such as a pre-implantation genetic diagnosis (PGD) or donor gametes with in vitro fertilization. With forewarning of a positive test result, couples might choose to adopt, to conceive naturally and engage in watchful waiting, have an amniocentesis-based genetic test performed for the suspected disease, or decide not to conceive. Finally, those carrier couples who choose to conceive without any intervention at all, will at minimum, benefit from knowing the diagnosis of an affected child; for some diseases ameliorative options are available, involving special drugs or rigorous diets from birth.

New technologies such as next-generation sequencing have made it possible to screen for mutations in many genes more efficiently than testing mutations in a single gene or a small number of population-specific mutations in several genes. Commercial laboratories offer these expanded carrier screening panels. There is no standardization to the makeup of these genetic panels, the composition of the panels varies among labs, and different commercial products for the same condition may test a different set of genes. Although ECS panels may include conditions that are routinely assessed in carrier testing, they also include many conditions that are not routinely evaluated.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers expanded carrier screening, only once per lifetime.*

Genetic Testing Policies, Continued

Genetic Testing: Expanded Carrier Screening, continued

*Select Health will cover CPT 81443 (at least 15 genes [see code description below]) once per lifetime; and if appropriate, will also cover CPT 81412 (Ashkenazi panel, see code description below) once per lifetime.

Select Health covers the five genes (**CFTR, SMN1, HBB, HBA1, and HBA2**) recommended by the American College of Obstetricians and Gynecologists (ACOG) for carrier testing, when ordered individually.

Select Health does not cover the **UNITY Carrier Screen** as it does not align with the minimum gene panel recommendations for expanded carrier screening, per the American College of Medical Genetics and Genomics (ACMG) and Select Health guidelines; and could lead to duplication of appropriate testing.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

There is consensus on core conditions that should be offered universally. Some of these conditions are included in one or both of societal guidelines, the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG), including cystic fibrosis, fragile X, and spinal muscular atrophy. Recently, these groups co-published a statement (Edwards et al., 2015), which demonstrates an approach for how healthcare providers and laboratories that wish to or that are currently offering expanded carrier screening to their patients. It was not put forward as a replacement to existing guidelines and does not advance the use of large carrier screening panels (beyond those conditions already recommended).

In a recent literature search it was found that the American College of Obstetrics and Gynecologists (ACOG, 2017) now recommends information and counseling about carrier screening should be provided to every pregnant woman, ideally before pregnancy. If the individual or reproductive partner choose to be tested, it should only happen once in a lifetime, and if either are found to be a carrier for a genetic condition, then counseling about potential reproductive outcomes should be offered. The cost to the patient and the healthcare system should be considered when an individual requests a test for a specific condition because the use of expanded carrier screening testing may be cheaper.

Billing/Coding Information

CPT CODES

81412 Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1

Genetic Testing Policies, Continued

Genetic Testing: Expanded Carrier Screening, continued

- 81443** Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
- 81479** Unlisted molecular pathology procedure

Not covered for the indications listed above

- 0449U** Carrier screening for severe inherited conditions (eg, cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia), regardless of race or self-identified ancestry, genomic sequence analysis panel, must include analysis of 5 genes (CFTR, SMN1, HBB, HBA1, HBA2)

HCPCS CODES

No specific codes identified

Key References

1. American College of Obstetrics and Gynecology. (2017) ACOG committee opinion No. 691: Carrier screening for genetic conditions. *Obstet Gynecol* 129: e41-55.
2. Franasiak, J. M., et al. (2016). "Expanded carrier screening in an infertile population: how often is clinical decision making affected?" *Genet Med*.
3. Gregg, A.R, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021 Oct;23(10):1793-1806.

Revision History

Revision Date	Summary of Changes
8/17/23	Reactivated policy; and for Commercial Plan Policy, reimplemented the following guideline: "Select Health covers expanded carrier screening, only once per lifetime."
5/14/24	For Commercial Plan Policy, clarified the following coverage criteria and exclusion: " Select Health covers expanded carrier screening, only once per lifetime. * *Select Health will cover CPT 81443 (at least 15 genes [see code description below]) once per lifetime; and if appropriate, will also cover CPT 81412 (Ashkenazi panel, see code description below) once per lifetime. Select Health covers the individual five genes (CFTR, SMN1, HBB, HBA1, HBA2) recommended by the American College of Obstetricians and Gynecologists (ACOG) for carrier testing. Select Health does not cover the UNITY Carrier Screen as it does not align with the minimum gene panel recommendations for expanded carrier screening, per the American College of Medical Genetics and Genomics (ACMG) and Select Health guidelines; and could lead to duplication of appropriate testing."
9/4/24	For Commercial Plan Policy, reworded the following guideline for clarification: "Select Health covers the five genes (CFTR, SMN1, HBB, HBA1, and HBA2) recommended by the American College of Obstetricians and Gynecologists

Genetic Testing Policies, Continued

Genetic Testing: Expanded Carrier Screening, continued

(ACOG) for carrier testing, <i>when ordered individually.</i>
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GENETIC TESTING: GENE EXPRESSION PROFILING IN THE MANAGEMENT OF BREAST CANCER

Policy # 281

Implementation Date: 8/30/05

Review Dates: 8/17/06, 8/21/08, 8/13/09, 8/19/10, 6/21/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 5/25/18, 4/17/19, 9/29/20, 9/15/22, 2/7/23, 2/15/24

Revision Dates: 9/17/07, 5/3/11, 8/22/14, 11/13/14, 1/1/15, 9/8/15, 5/25/18, 9/17/18, 7/1/23, 7/29/24

Related Medical Policies:

[#664 Genetic Testing: Breast, Ovarian, Pancreatic, and Prostate Cancer](#)

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Excluding cancers of the skin, breast cancer is the most common cancer among women, accounting for nearly 1 in 4 cancers diagnosed in US women. Although initial treatment decisions (e.g., mastectomy versus breast conserving therapy, preoperative chemotherapy) may be made based on the size and appearance of the primary tumor, and the presence of palpable axillary nodes (i.e., the clinical stage), the surgical findings are used to determine the pathologic disease stage, which dictates the prognosis and need for adjuvant systemic therapy. Physical examination is unreliable. Up to one-third of women with non-palpable axillary lymph nodes will be found to harbor metastases, while one-third of those with palpable nodes will be pathologically free of nodal involvement.

Treatment for early-stage breast cancer continues to evolve rapidly. Surgical resection is required in all patients with invasive breast cancer. Oncologic outcomes are similar with mastectomy and breast-conserving therapy (lumpectomy plus breast radiation therapy) in appropriately selected patients. Adjuvant systemic therapy (chemotherapy) can be recommended for those individuals at high risk for distant recurrence.

Gene expression profiling attempts to identify markers that will predict the likelihood of recurrence in women with early-stage breast cancer. The results of these tests may be used to determine whether adjuvant chemotherapy would be a benefit. Currently, there are multiple commercially available gene expression profile assays.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

Select Health covers the following gene expression tests for patients with *invasive breast cancer* in *limited circumstances*. (Only one gene expression test will be covered per new breast cancer diagnosis.)

A. Coverage criteria for Oncotype DX, Prosigna, MammaPrint, EndoPredict:

1. Patient is newly diagnosed with Stage I or II breast cancer with a primary tumor that is over 5 mm, node-negative, estrogen receptor positive (ER+) and/or progesterone receptor positive (PR+), and human epidermal receptor negative (HER2-).

OR

2. Patient is newly diagnosed with ER + and/or PR+ and HER2- breast cancer involving axillary-node micrometastasis (pN1mi) no greater than 2.0 mm or 1–3 lymph nodes and no distant metastasis.

AND

3. Patient is a candidate for adjuvant chemotherapy (i.e., chemotherapy is not disallowed due to other factors, such as advanced age or comorbidities) and willing to consider adjuvant chemotherapy.

B. Coverage criteria for Breast Cancer Index to assess necessity of adjuvant chemotherapy or adjuvant endocrine therapy in females or males with recently diagnosed breast tumors (when all the following criteria are met):

1. Patient is newly diagnosed with Stage I or II breast cancer with a primary tumor that is over 5mm, node-negative, hormone receptor positive, and human epidermal receptor negative (HER2-).

OR

2. Patient is newly diagnosed with hormone receptor positive and HER2- breast cancer involving axillary-node micrometastasis (pN1mi) no greater than 2.0 mm or 1–3 lymph nodes and no distant metastasis.

AND

3. Patient is a candidate for adjuvant therapy (i.e., adjuvant therapy is not disallowed due to other factors, such as advanced age or comorbidities) and willing to consider adjuvant therapy.

Select Health does NOT cover gene expression testing to assist in decision-making regarding continuation of endocrine therapy after 5 years.

Select Health does NOT cover use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with non-invasive ductal carcinoma *in situ* (i.e., Oncotype DX DCIS) to inform treatment planning following excisional surgery; this is considered experimental/investigational.

Select Health does NOT cover the use of other gene expression assays (e.g., Mammostrat Breast Cancer Test, the Breast Cancer Index 5-Year Test, the BreastOncPx, NexCourse Breast IHC4, TheraPrint, BluePrint, or TargetPrint for any indication, as they are considered experimental/investigational.

Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

13 Clinical risk assessment according to modified Adjuvant!Online

Table 5 13: Classification of patients according to clinical risk assessment by the modified version of Adjuvant!Online

ER status	HER2 status	Grade	Nodal status	Tumor Size	Clinical Risk in MINDACT
ER positive	HER2 negative	well differentiated	N-	≤ 3 cm	C-low
				3.1-5 cm	C-high
		moderately differentiated	1-3 positive nodes	≤ 2 cm	C-low
				2.1-5 cm	C-high
			N-	≤ 2 cm	C-low
		poorly differentiated or undifferentiated	1-3 positive nodes	2.1-5 cm	C-high
				Any size	C-high
			N-	≤ 1 cm	C-low
	HER2 positive	well differentiated OR moderately differentiated	N-	1.1-5 cm	C-high
				1-3 positive nodes	Any size
				≤ 2 cm	C-low
		poorly differentiated or undifferentiated	N-	2.1-5 cm	C-high
				1-3 positive nodes	Any size
			N-	≤ 1 cm	C-low
ER negative	HER2 negative	well differentiated	N-	1.1-5 cm	C-high
				1-3 positive nodes	Any size
		moderately differentiated OR poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
	HER2 positive	well differentiated OR moderately differentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	Any	Any size	C-high

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Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

SELECT HEALTH COMMUNITY CARE (MEDICAID)

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Summary of Medical Information

Since OncoType Dx first became available, other gene expression profile tests touting to perform similar functions have come to market. Several of these tests have been reviewed multiple times and the information below is intended to provide of summary of multiple previous reviews and technology assessments.

Oncotype DX Breast Cancer Assay

The initial indications for the 21-gene expression profile (Oncotype DX) were newly diagnosed invasive breast cancer patients with stage I or II disease that is node-negative and estrogen-receptor (ER)-positive, who would be treated with tamoxifen. Primary validation studies enrolled node-negative patients; this indication is reviewed first. More recently, Genomic Health has expanded their indication to include all stage II disease (tumor < 2 cm with spread to axillary lymph nodes or 2–5 cm without lymph node involvement); this indication for lymph node-positive disease will be reviewed separate from lymph node-negative disease.

Results from the Oncotype DX 21-gene expression profile are combined into a recurrence score (RS). Based on a study of analytic validity, tissue sampling, rather than technical performance of the assay is likely to be the greatest source of variability in results. The 21-gene expression profile was validated in studies using archived tumor samples from subsets of patients enrolled in already completed randomized controlled trials (RCTs) of early breast cancer treatment. Patients enrolled in the trial arms from which specimens were obtained had primary, unilateral breast cancer with no history of prior cancer and were treated with tamoxifen; tumors were ER-positive, most were human epidermal growth factor receptor 2 (HER2)-negative, and in the case of at least 1 trial, multifocal tumors were excluded.

Lymph Node-Negative Patients

Studies delineating the association between the 21-gene RS and recurrence risk are shown in Table 1. Results indicate strong, independent associations between the RS and distant disease recurrence or death from breast cancer. In secondary reclassification analyses of the Paik et al. data, patient risk levels were individually classified by conventional risk classifiers, then re-classified by Oncotype DX. Oncotype DX adds additional risk information to the conventional clinical classification of individual high-risk patients and identifies a subset of patients who would otherwise be recommended for chemotherapy but who are actually at lower risk of recurrence (average 7–9% risk at 10 years; upper 95% confidence interval [CI] limits: 11–15%). The analysis does not indicate significant erroneous reclassification, given known outcomes. Thus, a woman who prefers to avoid the toxicity and inconvenience of chemotherapy and whose Oncotype DX RS value shows that she is at very low risk of recurrence might reasonably decline chemotherapy. The lower the RS value, the greater the confidence the woman can have that chemotherapy will not provide net benefit; outcomes are improved by avoiding chemotherapy toxicity.

Table 1. Summary of Oncotype DX RS and recurrence risk studies

Study	Total N	Study Objective	Results			
			RS risk	% of patients	K-M distant recurrence at 10 yr, % (95% CI)	
Paik et al. 2004a (7) TAM arm of NSABP B-14 RCT	668	Predict recurrence	Low (<18)	51	6.8	(4.0–9.6)
			Intermed (18–30)	22	14.3	(8.3–20.3)
			High (>31)	27	30.5	(23.6–37.4)
			All	100	15	(12.5–17.9)

Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

Paik et al. 2004b (8) Additional analysis of Paik et al 2004a data	668	Reclassification study; determine incremental risk compared to conventional classifier	Risk classification by NCCN ¹	Risk reclassification by Oncotype DX	N	% DRF at 10 yr (95% CI ²)	
			Low (8%)	Low	38	100 (NR)	
			High (92%)	Intermed	12	80 (59–100)	
			High (92%)	High	3	56 (13–100)	
Bryant 2005 (9) Additional analysis of Paik et al. 2004a data	668	N % recurrence at reclassification	Risk 10-yr classification By Adjuvant! Online ¹	Low	301	93 (89–96)	
				Intermed	137	86 (80–92)	
				High	178	70 (62–77)	
Habel et al. 2006 (10) Case control	255 ER+ TAM+; 361 ER+ TAM-	Predict mortality	RS risk	Risk (95%CI ²) by Oncotype DX			
				Low (53%)	Low	214	5.6 (2.5–9)
			Int-High (47%)	Int-High	140	2.9 (7–19)	
				Low	120	8.9 (4–14)	
				Int-High	194	30.7 (24–38)	

Abbreviations: DRF, distant recurrence-free; ER, estrogen receptor; N, total number of patients; NR, not reported; RS, Oncotype DX recurrence score; K-M, Kaplan Meier; NSABP, National Surgical Adjuvant Breast and Bowel Project; RCT, randomized controlled trial; TAM, tamoxifen; NCCN, National Comprehensive Cancer Network (2004); Int/Intermed, Intermediate.

¹Percentages are percent of total N.

²Estimated from graphs. Note that different outcomes were reported between Paik et al. 2004b and Bryant 2005 and could not be converted to similar outcomes with confidence intervals

An additional study, in which samples from a RCT of ER-positive, node-negative breast cancer patients treated with tamoxifen versus tamoxifen plus chemotherapy were tested by Oncotype DX, provides supportive evidence. RS high-risk patients derived clear benefit from chemotherapy, whereas the average benefit for other patients was statistically not significant, although the confidence intervals were wide and included the possibility of a small benefit.

Lymph Node-Positive Patients

Albain et al. evaluated samples from the Southwest Oncology Group Trial 8814, in which randomized node-positive, ER-positive patients treated with tamoxifen for 5 years were compared to those treated with cyclophosphamide, doxorubicin, fluorouracil (CAF) chemotherapy, followed by tamoxifen (CAF-T) for 5 years. Samples were available for determination of RS for 41% (n=148) and 39% (n=219) of the trial arms, respectively.

In this study, 10-year disease-free survival (DFS) and overall survival (OS) outcomes in the tamoxifen study arm differed by RS risk category ($p=0.017$ and 0.003 , respectively), indicating that the RS is prognostic. When the 2 treatment arms were compared within RS risk categories, only patients in the high RS category significantly benefited from the addition of CAF to tamoxifen (for DFS, 42% [tamoxifen] vs. 55% [CAF-T], $p=0.033$; for OS, 51% [tamoxifen] vs. 68% [CAF-T], $p=0.027$), suggesting that RS is also predictive of response to chemotherapy.

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A multivariable analysis of RS interaction with DFS, adjusted for number of positive nodes, was significant for the first 5 years of follow-up at $p=0.029$ and remained significant after adjusting for age, race, tumor size, progesterone receptor status, grade, p53, and HER2. However, the interaction was not significant ($p=0.15$) after adjusting for ER level (ER gene expression is a component of the 21-gene profile). Interaction results were similar for OS.

Dowsett et al. included a separate evaluation of node-positive patients in their examination of the ATAC trial samples. Of 306 node-positive patients, 243 had 1–3 involved nodes, and 63 patients, 4 or more; these were not evaluated separately. Rates of distant recurrence at 9 years were 17% (95% CI: 12–24%), 28% (20–39%), and 49% (35–64%), respectively. It is not clear that the risk of distant recurrence in low-risk RS patients would be sufficiently low to forgo the choice of chemotherapy. The authors note that their study "... did not directly evaluate the value of RS in predicting the benefit of chemotherapy."

Goldstein et al. evaluated samples from the Eastern Cooperative Oncology Group E2197 trial, which included patients with 0–3 positive lymph nodes and operable tumors greater than 1 cm in size. Patients were randomly assigned to doxorubicin plus cyclophosphamide or docetaxel plus 5 years of endocrine therapy; outcomes were not significantly different for the study arms. A case-control study of samples from this trial found that low-risk RS patients with 0–1 positive node had a recurrence risk of 3.3% (95% CI: 2.2–5%), and low-risk patients with 2–3 positive nodes had a recurrence risk of 7.9% (4.3–14.1%). RS was also a significant predictive of risk regardless of nodal status.

A previous study by Chang et al. reported that in women with locally advanced breast cancer treated with neoadjuvant docetaxel ($n=97$), a complete response was more likely in those with a high RS ($p=0.008$). Gianni et al. studied 93 patients with locally advanced breast cancer who received neoadjuvant taxane chemotherapy, then post-surgery CMF treatment and tamoxifen (if ER-positive). The authors reported that pathological complete response was more likely in patients with high RS results than with low RS results ($p < 0.01$).

One study surveyed oncologists ordering the 21-gene profile for lymph node-positive patients to determine the effect of the assay results on treatment recommendations and reported that approximately half changed their recommendations after receiving RS results, with 33% recommending endocrine therapy alone instead of endocrine plus chemotherapy. However, only medical oncologists who were already using the assay (16% response rate) were surveyed, thus biasing the results. Finally, no outcomes were reported, providing no firm evidence of clinical utility.

Additional studies are necessary before it is possible to confidently withhold currently recommended chemotherapy from lymph node-positive invasive breast cancer patients with low/intermediate RS results. The RxPONDER (Rx for Positive Node, Endocrine Responsive Breast Cancer) trial, led by the Southwest Oncology Group, will enroll 4,000 women with RS < 25 who have early-stage, hormone receptor-positive, HER2-negative breast cancer involving 1 to 3 lymph nodes. Patients will be randomized to receive either chemotherapy with endocrine therapy or endocrine therapy alone. The primary trial outcomes are expected to be completed in December 2016 (available online at: <http://clinicaltrials.gov/ct2/show/NCT01272037>).

Patients with DCIS

Ductal carcinoma in situ (DCIS) is breast cancer located in the lining of the milk ducts that has not yet invaded nearby tissues. It may progress to invasive cancer if untreated. The frequency of DCIS diagnosis in the U.S. has increased in tandem with the widespread use of screening mammography, accounting for about 20% of all newly diagnosed invasive plus noninvasive breast tumors. Recommended treatment is lumpectomy (mastectomy is also an option) with or without radiation treatment; post-surgical tamoxifen treatment is recommended for ER-positive DCIS, especially if excision alone is used. Because the overall rate of ipsilateral tumor recurrence (DCIS or invasive carcinoma) is about 25% at 10 years, it is believed many women are over treated with radiation therapy. Thus, accurate prediction of recurrence risk may identify those women who may safely avoid radiation.

The Oncotype DX DCIS test uses information from 12 of the 21 genes assayed in the standard Oncotype DX test for early breast cancer. According to the Oncotype website, analyses from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 study and the Habel et al. case-control study (10) were used to select genes that predict the risk of recurrence independent of tamoxifen treatment and ER status. Scaling and category cut-points were based on an analysis of DCIS Score results from a separate cohort of patients with DCIS; this study has not yet been published and is available only as a meeting

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abstract. In a retrospective analysis of data and samples from patients in the prospective Eastern Cooperative Oncology Group E5194 study, the Oncotype DX Score for DCIS was compared with the 10-year recurrence risk in a subset of DCIS patients treated only with surgery and some with tamoxifen (n=327). DCIS Score was significantly associated with recurrence outcomes (HR: 2.34 per 50 units; 95% CI: 1.15, 4.59; p=0.02) whether or not patients were treated with tamoxifen. The standard Oncotype DX Score for early breast cancer was not associated with DCIS recurrence outcomes. This study is available as a meeting abstract but has not yet been published. These studies address the development of the Oncotype DX DCIS Score and the clinical validity (association of the test result with recurrence outcomes). Whether women are better categorized as to their recurrence risk by the Oncotype DX DCIS Score compared with standard clinical indicators of risk has not yet been addressed. Full evaluation awaits publication of studies.

MammaPrint

In the most recent review completed in April 2014, two systematic reviews and thirteen primary literature articles met inclusion criteria for this report. MammaPrint was reviewed May 2011, which concluded, "Of note, to date, no studies have been performed which assess the comparative effectiveness of MammaPrint to any other gene expression profile test such as Oncotype DX to assess whether a seventy gene signature or a twenty-one gene signature or any other gene signature has greater sensitivity or specificity especially given the fact they do not all assess similar genes. Since mid-2011, there have been a number of studies which have compared MammaPrint to other gene expression tests.

One of the two systematic reviews published by Paik et al. speaks to the fact that Oncotype Dx is the only breast cancer prognostic that has reached level IB evidence and that tests such as MammaPrint and MapQuantDx are further behind in their publication of clinically relevant data. However, the group acknowledges that other gene expression tests such as MammaPrint are expected to provide similar information to already marketed adjuvant chemotherapy prognostic tests. Notably, the recently published recommendation by NICE does not advise using MammaPrint in general practice, as there are still unanswered questions regarding its clinical utility and cost-effectiveness.

The primary literature, dating back to the last review, is generally favorable regarding the MammaPrint test. For example, in a prospective comparative trial with MammaPrint and Adjuvant! Online, MammaPrint was able to decrease the number of patients considered to be at high risk, and therefore, in need of adjuvant chemotherapy. Similarly, Drukker et al. showed that fewer patients would continue adjuvant chemotherapy with the use of MammaPrint in a 427-patient prospective study. Though some evidence demonstrates potential clinical utility, no published guidelines, systematic reviews, or society statements illustrate how the test should be used and interpreted within the clinical setting.

Since the last review, new evidence demonstrates Mammaprint offers the potential for use in clinical practice for prognostic stratification and treatment selection for patients with breast cancer, particularly if they are hormone receptor-positive. However, questions remain as to how the test will be employed in the clinical setting.

TargetPrint

TargetPrint is a microarray-based gene expression test that offers a quantitative assessment of ER, PR, and HER2 overexpression in breast cancer. TargetPrint is offered in conjunction with MammaPrint gene expression profiling to provide the physician an even more complete basis for treatment decisions. The manufacturer states that, as compared to Immunohistochemistry (IHC), TargetPrint provides additional information. Whereas IHC provides a semi-quantitative positive or negative result, the gene expression result produced by TargetPrint, provides data on the absolute level of ER, PR, and HER2 gene expression. Published information on the TargetPrint is limited to studies examining its correlation with measurements of ER, PR, and HER2 receptors (Gunven et al, 2011; Gevensleben et al, 2010; Roepman et al, 2009). There is a lack of evidence from published prospective clinical studies that demonstrates that quantification of ER, PR, and HER2 gene expression by TargetPrint alters management such that clinical outcomes are improved.

BluePrint

BluePrint is an 80-gene expression assay that classifies breast cancer into basal type, luminal type, or HER2-type. The test is marketed as an additional stratifier into a molecular subtype after risk assessment with MammaPrint®. Krijgsman et al. (2012) noted that classification of breast cancer into molecular subtypes may be important for the proper selection of therapy, as tumors with seemingly similar

Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

histopathological features can have strikingly different clinical outcomes. Herein, these researchers reported the development of a molecular subtyping profile (BluePrint), which enables rationalization in patient selection for either chemotherapy or endocrine therapy prescription. An 80-Gene Molecular Subtyping Profile (BluePrint) was developed using 200 breast cancer patient specimens and confirmed on 4 independent validation cohorts ($n = 784$). Additionally, the profile was tested as a predictor of chemotherapy response in 133 breast cancer patients, treated with T/FAC neoadjuvant chemotherapy. BluePrint classification of a patient cohort treated with neoadjuvant chemotherapy ($n = 133$) showed improved distribution of pathological Complete Response (pCR), among molecular subgroups compared with local pathology: 56% of the patients had a pCR in the Basal-type subgroup, 3% in the MammaPrint low-risk, luminal-type subgroup, 11% in the MammaPrint high-risk, luminal-type subgroup, and 50% in the HER2-type subgroup. The group of genes identifying luminal-type breast cancer is highly enriched for genes having an Estrogen Receptor binding site proximal to the promoter-region, suggesting that these genes are direct targets of the Estrogen Receptor. Implementation of this profile may improve the clinical management of breast cancer patients, by enabling the selection of patients who are most likely to benefit from either chemotherapy or from endocrine therapy, but current studies are inadequate to prove the clinical utility of this testing in clinical practice. Furthermore, there is no information regarding BluePrint/molecular subtyping from NCCN's clinical practice guideline on "Breast cancer" (Version 2.2013).

The aim of this study was to analyze the correlation between the pathologic complete response (pCR) rate after neoadjuvant chemotherapy and long-term outcome (distant metastases-free survival [DMFS]) in patients with early-stage breast cancer using BluePrint and MammaPrint molecular subtyping versus clinical subtyping using immunohistochemistry/fluorescence in situ hybridization (IHC/FISH) for the determination of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 (HER2). Data were analyzed from 437 patients in four neoadjuvant chemotherapy trials. BluePrint and MammaPrint outcomes were determined from 44K Agilent arrays, the I-SPY 1 data portal, or Affymetrix U133A arrays. The pCR rate differed substantially among BluePrint molecular subgroups: 6% in Luminal A-type, 10% in Luminal B-type, 47% in HER2-type, and 37% in Basal-type patients. In the Luminal A-type group ($n = 90$; including seven HER2-positive patients and eight triple-negative patients by IHC/FISH), the 5-year DMFS rate was 93%. The pCR rate provided no prognostic information, suggesting these patients may not benefit from chemotherapy. Forty-three of 107 (40%) HER2-positive patients were classified as Luminal-type by BluePrint and may have lower response rates to targeted therapy. Molecular subtyping identified 90 of 435 (21%) patients as Luminal A-type (BluePrint Luminal-type/MammaPrint Low Risk) with excellent survival. The pCR rate provided no prognostic information. Molecular subtyping can improve the stratification of patients in the neoadjuvant setting: Luminal A-type (MammaPrint Low Risk) patients have a good prognosis with excellent survival and do not seem to benefit from chemotherapy. We observed marked benefit in response and DMFS to neoadjuvant treatment in patients subtyped as HER2-type and Basal-type. BluePrint with MammaPrint molecular subtyping helps to improve prognostic estimation and the choice of therapy versus IHC/FISH.

Marked differences are observed between BluePrint and MammaPrint (microarray-based) breast cancer subtypes and centrally re-assessed pathological surrogates (based on ER, PR, HER2 & Ki67). The greatest discordance is seen in the substratification of Luminal patients, and in the HR+/HER2+ patients. The observed subtype discrepancies may have an important impact on treatment decision-making. Concordances are in line with recent observation that the four main breast cancer subtypes have common etiology and similar therapeutic opportunities [TCGA, 2012].

TheraPrint

TheraPrint is a microarray-based gene assay of 55 biomarkers and variant analysis results for 4 genes that have been identified as potential markers for predicting prognosis and therapeutic response to a variety of therapies. It is still in experimental stages and is used in conjunction with MammaPrint. TheraPrint for breast cancer patients provides an individualized genomic fingerprint of the patient's tumor and correlates gene expression and variant analysis results with a likely response or resistance to a variety of hormonal, chemical, and biological therapies. These include important therapies using SERMs, aromatase inhibitors, anti-androgen, alkylating agents, anti-metabolites, anthracyclines, mitotic inhibitors, platinum-based chemotherapy, topoisomerase inhibitors, angiogenesis inhibitors, HER2/EGFR and HER2/PI3K pathway inhibitors, and others.

Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

Breast Cancer Index SM

The Breast Cancer Index is a simultaneous assessment of HOXB13:IL17BR (H/I) Index and the MGISM (Molecular Grade Index). The 2008 TEC Assessment (3) reviewed available studies for the original component assays. There was insufficient evidence to determine whether the H/I Ratio is better than conventional risk assessment tools in predicting recurrence. Ten-year recurrence rates of patients classified as low risk in available studies were 17–25%, likely too high for most patients and physicians to consider forgoing chemotherapy. The Molecular Grade Index is intended to measure tumor grade using the expression of 5 cell-cycle genes and to provide prognostic information in ER-positive patients regardless of nodal status.

Ma et al. evaluated MGI along with H/I in 93 patients with lymph node-negative tumors who received adjuvant hormone therapy and found that each index modified the other's predictive performance. High MGI was associated with significantly worse outcome only in patients with high H/I and vice versa. When the H/I Ratio and MGI were categorically combined into a single predictor, the estimates of 10-year distant metastasis-free survival were 98% (95% CI: 96–100%), 87% (77–99%), and 60% (47–78%) for the low, intermediate, and high-risk groups, respectively.

Jerevall et al. combined the H/I Ratio and MGI into a continuous risk model using 314 ER-positive, node-negative postmenopausal patients from the tamoxifen-only arm of an RCT. The continuous model was also categorized, resulting in proportions of low-, intermediate-, and high-risk patients similar to those reported in the Ma et al. study. This continuous predictor was tested in patients from the no adjuvant treatment arm (n=274) of the same clinical trial, with estimates of rates of distant metastasis at 10 years in the low-, intermediate-, and high-risk groups of 8.3% (95% CI: 4.7–14.4), 22.9% (14.5–35.2), and 28.5% (17.9–43.6), respectively. The estimates of breast cancer-specific death were 5.1% (95% CI: 1.3–8.7), 19.8% (10.0–28.6), and 28.8% (15.3–40.2). An independent population of otherwise similar but tamoxifen-treated patients was not tested.

Jankowitz et al. evaluated tumor samples from 265 ER-positive, lymph node (LN)-negative, tamoxifen-treated patients from a single academic institution's cancer research registry. BCI categorized 55%, 21%, and 24% of patients as low-, intermediate- and high-risk, respectively, for distant recurrence. The 10-year rates of distant recurrence were 6.6% (95% CI: 2.3–10.9%), 12.1% (95% CI: 2.7–21.5%), and 31.9% (95% CI: 19.9–43.9) and of breast cancer-specific mortality were 3.8%, 3.6%, and 22.1% in low-, intermediate-, and high-risk groups, respectively. In a multivariate analysis, BCI was a significant predictor of distant recurrence and breast cancer-specific mortality. In a time-dependent (10-year) ROC curve analysis of recurrence risk, the addition of BCI to Adjuvant! Online risk prediction increased maximum predictive accuracy in all patients from 66% to 76% and in tamoxifen-only treated patients from 65% to 81%.

Mammostrat Breast Cancer Test

Mammostrat is an immunohistochemistry (IHC) test intended to evaluate risk of breast cancer recurrence in postmenopausal, node-negative, ER-positive invasive breast cancer patients who will receive endocrine therapy and are considering adjuvant chemotherapy. The test employs 5 monoclonal antibodies to detect gene expression of proteins biologically independent of each other and not involved in cell proliferation, hormone receptor status, or growth/differentiation, thus potentially allowing integration with clinically routine biomarkers. A proprietary diagnostic algorithm is used to calculate a risk score and to classify patients into high-, moderate-, or low-risk categories.

One published study described the development of the assay but provides no information on technical performance (analytic validity). In a validation study in an independent cohort, a multivariable model predicted 50%, 70%, and 87% 5-year DFS for patients classified as high, moderate, and low prognostic risk, respectively, by the test results ($p=0.0008$). An additional study of the same trial samples used for Oncotype DX validation (NSABP B-14 and B-20 trials) found that among patients with early, node-negative breast cancer treated only with tamoxifen, those stratified by Mammostrat into low-, moderate-, and high-risk groups had recurrence-free survival estimates of 85%, 85%, and 73%, respectively. Both low- and high-risk groups benefited significantly from chemotherapy treatment, but high-risk patients benefited to a greater degree. The moderate-risk group was not well-separated from the low-risk group and thus, moderate-risk results do not appear to provide clinically useful information. A test for an interaction between chemotherapy and the risk group stratification was not significant ($p=0.13$).

Genetic Testing Policies, Continued

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Bartlett et al. used Mammostrat on 1,540 of 1,812 patient samples from a consecutive cohort for which minimum 9-year outcomes were available. The tested samples were from tamoxifen-treated patients; 568 of these were from node-negative patients treated only with tamoxifen and whose tumors were ER-positive. In the latter group, the distant recurrence rates at 10 years for low-, moderate-, and high-risk patients were 7.6% (95% CI: 4.6–10.5%), 16.3% (10.0–22.6%), and 20.9% (12.3–29.5%), respectively. In multivariable analysis, Mammostrat was not a significant predictor of recurrence-free survival in node-negative, ER-positive patients treated only with tamoxifen. However, when all patients (24% node-positive, 20% tumors > 2.0 cm, 18% ER-negative, and 46% treated with chemotherapy) with complete Mammostrat data (n=1,300) were included in a multivariable analysis, Mammostrat scores were independent predictors of recurrence-free survival ($p=0.0007$). In exploratory analyses of various subpopulations (e.g., node-negative vs. node-positive, ER-negative), Mammostrat appeared to perform similarly in terms of identifying risk groups. However, numbers of subsets were small.

BreastOncPx

The BreastOncPx test is a reverse transcriptase-polymerase chain reaction (RT-PCR) test performed on formalin-fixed, paraffin embedded tissue that measures the gene expression of 14 genes associated with key functions such as cell-cycle control, apoptosis, and DNA recombination and repair. The results are combined into a metastasis score, which is reported to be associated with the risk of distant metastases in patients who are node-negative and estrogen-receptor positive.

Tutt et al. published information on the development and validation of the test; no information on analytic validity was provided. In order to develop a gene signature that was completely prognostic for distant recurrence and not confounded by treatment prediction, samples from untreated patients with early breast cancer were used. The training set (n=142) was derived from a cohort diagnosed with lymph node-negative stage T1 and T2 breast cancer from 1975 to 1986; ER-positive samples from patients who had had no systemic treatment were selected for analysis. Fourteen genes were eventually selected as most prognostic of time-to-distant metastasis and were given equal weighting in a summary metastasis score (MS). Using a single cutoff, patients are separated into high- and low-risk groups.

The 14-gene signature was validated on ER-positive samples (n=279) from a separate cohort of patients diagnosed with lymph node-negative primary breast cancer between 1975 and 2001. The estimated rates of distant metastasis-free survival were 72% (95% CI: 64–78%) for high-risk patients and 96% (95% CI: 90–99%) for low-risk patients at 10 years' follow-up. Overall, 10-year survival for high- and low-risk patients was 68% (95% CI: 61% to 75%) and 91% (95% CI: 84 to 95%), respectively. After adjusting for age, tumor size, and tumor grade in a Cox multivariate analysis, the HRs for distant metastasis-free survival for the high- versus low-risk group were 4.02 (95% CI: 1.91–8.44) and 1.97 (95% CI: 1.28 to 3.04) for distant metastasis-free survival and overall survival, respectively. However, this difference in risk between groups was not maintained when the analysis was restricted to patients with tumors larger than 2 cm (p value for interaction 0.012).

ROC analysis of the continuous MS for distant metastasis and for death at 10 years, compared to Adjuvant! resulted in slightly higher area under the curves (AUCs) for the MS in each case: 0.715 vs. 0.661 for distant metastases, and 0.693 vs. 0.655 for death. MS was not added to Adjuvant! and compared to Adjuvant! alone.

NexCourse Breast IHC4

NexCourse Breast IHC4 evaluates the protein expression of ER/PR, HER2, and Ki-67 to provide a combined recurrence risk score. The assay technology uses quantitative image analysis to measure immunofluorescent signals, with results that can be combined in an algorithm to generate the recurrence risk score. The use of quantitative immunofluorescence is said to increase sensitivity, be more reproducible, and allow specific measurement of tumor cells.

Cuzick et al. evaluated 1,125 ER-positive patients from the Arimidex, Tamoxifen, and Alone or in Combination (ATAC) trial, who did not receive adjuvant chemotherapy, already had the Oncotype DX Recurrence Score (RS) computed, and had adequate tissue for the IHC4 measurements. Of these, 793 were node-negative and 59 were HER2-positive (but were not treated with trastuzumab). A prognostic model that combined the 4 immunohistochemical markers was created (IHC4). In a model combining either IHC4 or Oncotype DX RS with classical prognostic variables, the IHC4 score was found to be similar to the Oncotype DX RS, and little additional prognostic value was seen in the combined use of both scores. In a direct comparison, the IHC4 score was modestly correlated with the Oncotype DX RS

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($r=0.72$); the correlation was similar for node-negative patients ($r=0.68$). As an example, for a 1–2 cm, node-negative poorly differentiated tumor treated with anastrozole, 9-year distant recurrence at the 25th versus 75th percentiles for IHC4 and Oncotype DX were 7.6% versus 13.9% and 9.2% versus 13.4%, respectively. The IHC4 score was validated in a separate cohort of 786 ER-positive women, about half of whom received no endocrine treatment. The IHC4 score was significant for recurrence outcomes (HR: 4.1; 95% CI: 2.5–6.8).

Barton et al. assessed the clinical utility of IHC4 plus clinicopathologic factors (IHC4 + C) by comparison with Adjuvant! Online and the Nottingham Prognostic Index (NPI). The study prospectively gathered clinicopathologic data for consecutively treated postmenopausal patients ($n=101$ evaluable) with hormone receptor-positive, HER2-negative, LN-negative or -positive with 1–2 nodes, resected early breast cancer. Of 59 patients classified as intermediate-risk group by the NPI, IHC4 reclassified 24 to low risk and 13 to high risk. IHC4 reclassified 13 of 32 Adjuvant! high-risk patients to intermediate risk, and 3 of 32 to low risk. In addition, 15 of 26 Adjuvant! intermediate-risk patients were reclassified to low-risk. No Adjuvant! low-risk patients were reclassified as high-risk.

Prosigna

The Prosigna ROR score is an algorithmic calculation that combines gene expression results and clinicopathological parameters/metrics that are specific to each individual patient. In some respects, the

Prosigna ROR represents an individual patient prediction tool, fortified with the PAM50 gene assay.

The NanoString nCounter Analysis System is one of several next-generation genomic tools that is being applied to clinical applications. The nCounter System is a standalone platform that was FDA 510(k) cleared for use with Prosigna in September 2013. In contrast to first-generation genomic tools such as DNA microarrays and quantitative PCR, the nCounter platform was designed to be an enzyme-free nucleic acid detection system that is easy to use and applicable to clinically-relevant biological samples such as FFPE tissue samples. The NanoString technology directly measures and counts single molecules of nucleic acids and therefore, similar to Next-Generation Sequencing technologies, is a digital technology. The digital data sets apart these next-generation technologies from their first-generation counterparts. The digital data is much more accurate and precise and is simpler to interpret than analog data that must be calibrated to facilitate data interpretation.

The NanoString nCounter system, consisting of a Prep Station and a Digital Analyzer, can be installed locally, hence FFPE samples do not need to be shipped to a centralized lab for analysis. The local pathology laboratory maintains ownership of the diagnostic work-up and remains the service provider. The advantages of this decentralized business model are a more rapid turn-around time and interface with the local care team. NanoString oversees the production and distribution of the consumable Prosigna Kits, consisting of the 50 gene-based CodeSet and 8 controls, other consumables require for the assay, and an associated RNA isolation kit.

In a recent review that was completed in September of 2015, two systematic reviews and 9 primary studies were identified which met inclusion criteria for this report. The literature primarily illustrates the analytical validity and clinical validity of the Prosigna PAM50 gene panel. Meaningful conclusions from the literature include the following:

- PAM50 was prognostic for disease-free survival and overall survival but immunohistochemistry was not.
- PAM50 was predictive of tamoxifen benefit but not statistically significantly.
- More patients were identified as high-risk and fewer as intermediate-risk with PAM50 than with Oncotype DX.
- PAM50 gene test has shown in one study to be clinically relevant for predicting distant recurrence.
- PAM50 results changed treatment recommendations in 20% of patients.

Though many studies have been published regarding the analytical validity and clinical validity of the Prosigna assay, little information regarding the clinical utility of the test has been published. Current evidence is insufficient to draw conclusions regarding the clinical relevance of the Prosigna test.

Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

Billing/Coding Information

Covered: For the conditions outlined above

CPT CODES

- 0008M** Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (FFPE) tissue, prognostic algorithm reported as a risk score
- 0045U** Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by realtime RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
- 0153U** Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement
Insight TNBCtype™, Insight Molecular Labs
- 0262U** Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch), formalin-fixed paraffin-embedded (FFPE), algorithm reported as gene pathway activity score
- 0295U** Oncology (breast ductal carcinoma in situ), protein expression profiling by immunohistochemistry of 7 proteins (COX2, FOXA1, HER2, Ki-67, p16, PR, SIAH2), with 4 clinicopathologic factors (size, age, margin status, palpability), utilizing formalin-fixed paraffin- embedded (FFPE) tissue, algorithm reported as a recurrence risk score
- 0297U** Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification
- 0298U** Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification
- 81479** Unlisted molecular pathology procedure
- 81518** Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
- 81519** Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score.
- 81520** Oncology (breast), mRNA, gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score
- 81521** Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis
- 81522** Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score
- 81523** Oncology, mRNA, next-generation sequencing gene expression profiling

Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

81599 Unlisted multianalyte assay with algorithmic analysis

HCPCS CODES

Covered: For the conditions outlined above

S3854 Gene expression profiling panel for use in the management of breast cancer treatment

Key References

1. Abdullah-Sayani, A., Bueno-de-Mesquita, J.M., & van de Vijver, M. J. (2006). Technology insight tuning into the genetic orchestra using microarrays-limitations of DNA microarrays in clinical practice. *Nat Clin Pract Oncol*, 20, 3(9): p. 501-16.
2. Ademuyiwa FO, Miller A, O'Connor T et al. The effects of oncotype DX recurrence scores on chemotherapy utilization in a multi-institutional breast cancer cohort. *Breast Cancer Res Treat* 2011; 126(3):797-802.
3. Albain KS, Barlow WE, Shak S et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol* 2010; 11(1):55-65.
4. Albain, KS, Paik, S, van't Veer, L. (2009). Prediction of adjuvant chemotherapy benefit in endocrine responsive, early breast cancer using multigene assays. *Breast* 18 Suppl 3: S141-5.
5. Allred DC, Carlson RW, Berry DA et al. NCCN Task Force Report: Estrogen Receptor and Progesterone Receptor Testing in Breast Cancer by Immunohistochemistry. *J Natl Compr Canc Netw* 2009; 7 Suppl 6:S1-S21; quiz S22-3.
6. Badve SS, Baehner FL, Gray RP et al. Estrogen- and progesterone-receptor status in ECOG 2197: comparison of immunohistochemistry by local and central laboratories and quantitative reverse transcription polymerase chain reaction by central laboratory. *J Clin Oncol* 2008; 26(15):2473-81.
7. Baehner FL, Achacoso N, Maddala T et al. Human epidermal growth factor receptor 2 assessment in a case-control study: comparison of fluorescence *in situ* hybridization and quantitative reverse transcription polymerase chain reaction performed by central laboratories. *J Clin Oncol* 2010; 28(28):4300-6.
8. Baehner FL, Butler SM, Yoshizawa CN et al. The development of the DCIS score: Scaling and normalization in the Marin General Hospital cohort. *J Clin Oncol* 2012; 30(Suppl 27): Abstr 190.
9. Bartlett JM, Starczynski J. Quantitative reverse transcriptase polymerase chain reaction and the Oncotype DX test for assessment of human epidermal growth factor receptor 2 status: time to reflect again? *J Clin Oncol* 2011; 29(32):4219-21.
10. Bartlett JM, Thomas J, Ross DT et al. Mammostrat as a tool to stratify breast cancer patients at risk of recurrence during endocrine therapy. *Breast Cancer Res* 2010; 12(4): R47.
11. Barton S, Zabaglo L, A'Hern R et al. Assessment of the contribution of the IHC4+C score to decision making in clinical practice in early breast cancer. *Br J Cancer* 2012; 106(11):1760-5.
12. Bighin C, Del Mastri L, Canavese G et al. Use in current clinical practice of 70-gene signature in early breast cancer. *Int J Cancer* 2010; 127(11):2736-7.
13. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Gene expression profiling for managing breast cancer treatment. *Technol Eval Cent Asses Program* 2005; 20(Tab 3).
14. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Gene expression profiling of breast cancer to select women for adjuvant chemotherapy. *Technol Eval Cent Asses Program* 2008; 22(Tab 13).
15. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Gene Expression Profiling in Women with Lymph-Node-Positive Breast Cancer to Select Adjuvant Chemotherapy Treatment. *Technol Eval Cent Asses Program* 2010; 25(Tab 1).
16. Blue Cross Blue Shield TEC. (2005). Gene expression profiling for managing breast cancer treatment. *Technol Eval Cent Asses Program Exec Summ* 20,3: 1-5.
17. BlueCross BlueShield Association. Gene Expression Profiling in Women with Lymph Node-Negative Breast Cancer to Select Adjuvant Chemotherapy. 2014 October 2014 [cited 2015 June 16]; Available from: http://www.bcbs.com/blueresources/tec/vols/29/29_3.pdf.
18. Bryant J. Toward a more rational selection of tailored adjuvant therapy data from the National Surgical Adjuvant Breast and Bowel Project. 2005 St. Gallen Breast Cancer Symposium. [Complete slide presentation via Genomic Health] 2005.
19. Bueno-de-Mesquita JM, Linn SC, Keijzer R et al. Validation of 70-gene prognosis signature in node-negative breast cancer. *Breast Cancer Res Treat* 2009; 117(3):483-95.
20. Buyse M, Loi S, van't Veer L et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *J Natl Cancer Inst* 2006; 98(17):1183-92.
21. Buyse, M., et al. (2006). Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *J Natl Cancer Inst.* 98(17): p. 1183-92.
22. Caan, B.J., et al., Intrinsic subtypes from the PAM50 gene expression assay in a population-based breast cancer survivor cohort: prognostication of short- and long-term outcomes. *Cancer Epidemiol Biomarkers Prev*, 2014. 23(5): p. 725-34.
23. Carlson, RW, Allred, DC, Anderson, BO, et al. (2011) NCCN Clinical Practice Guidelines in Oncology: Breast Cancer: National Comprehensive Cancer Network (NCCN).
24. Cary, L.A. Prognostic molecular profiles of breast cancer. 2013 March 20, 2013 [cited 2013 July 25]; Available from: http://www.uptodate.com/contents/prognostic-molecular-profiles-of-breast-cancer?detectedLanguage=en&source=search_result&search=mammarray&selectedTitle=1~2&provider=noProvider
25. Chang JC, Makris A, Gutierrez MC et al. Gene expression patterns in formalin-fixed, paraffin-embedded core biopsies predict docetaxel chemosensitivity in breast cancer patients. *Breast Cancer Res Treat* 2008; 108(2):233-40.
26. Cheang MC, Voduc KD, Tu D et al. Responsiveness of Intrinsic Subtypes to Adjuvant Anthracycline Substitution in the NCIC.CTG MA.5 Randomized Trial. *Clin Cancer Res* 2012; 18(8):2402-12.
27. Chia, S.K., et al., A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. *Clin Cancer Res*, 2012. 18(16): p. 4465-72.
28. Coates, A.S., et al., Tailoring therapies-improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol*, 2015. 26(8): p. 1533-46.

Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

29. Cronin M, Sangli C, Liu ML et al. Analytical validation of the Oncotype DX genomic diagnostic test for recurrence prognosis and therapeutic response prediction in node-negative, estrogen receptor-positive breast cancer. *Clin Chem* 2007; 53(6):1084-91.
30. Cuadros, M, Llanos, A. (2010). [Validation and clinical application of MammaPrint((R)) in patients with breast cancer.]. *Med Clin (Barc)*.
31. Cusumano, P.G., et al., European inter-institutional impact study of MammaPrint. *Breast*, 2014.
32. Cuzick J, Dowsett M, Pineda S et al. Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. *J Clin Oncol* 2011; 29(32):4273-8.
33. Dabbs DJ, Klein ME, Mohsin SK et al. High false-negative rate of HER2 quantitative reverse transcription polymerase chain reaction of the Oncotype DX test: an independent quality assurance study. *J Clin Oncol* 2011; 29(32):4279-85.
34. Dowsett M, Cuzick J, Wale C et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol* 2010; 28(11):1829-34.
35. Dowsett M, Houghton J, Iden C et al. Benefit from adjuvant tamoxifen therapy in primary breast cancer patients according oestrogen receptor, progesterone receptor, EGF receptor and HER2 status. *Ann Oncol* 2006; 17(5):818-26.
36. Dowsett M. on Behalf of the ATAC Trialists Group. Analysis of time to recurrence in the ATAC (arimidex, tamoxifen, alone or in combination) trial according to estrogen receptor and progesterone receptor status. Twenty-sixth Annual San Antonio Breast Cancer Symposium 2003.
37. Dowsett, M., et al., Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. *J Clin Oncol*, 2013. 31(22): p. 2783-90.
38. Drukker, C.A., et al., A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. *Int J Cancer*, 2013. 133(4): p. 929-36.
39. Espinosa E, Vara JA, Redondo A et al. Breast cancer prognosis determined by gene expression profiling: a quantitative reverse transcriptase polymerase chain reaction study. *J Clin Oncol* 2005; 23(29):7278-85.
40. Esserman LJ, Berry DA, Cheang MC et al. Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: results from the I-SPY 1 TRIAL (CALGB 150007/150012/ACRIN 6657). *Breast Cancer Res Treat* 2012; 132(3):1049-62.
41. Esteva, et.al. (2005). Prognostic role of a multigene reverse transcriptase-PCR assay in patients with node-negative breast cancer not receiving adjuvant systemic therapy. *Clin Cancer Res*. 5/1;11(9):3315-9.
42. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. (2009). Recommendations from the EGAPP Working Group: can tumor gene expression profiling improve outcomes in patients with breast cancer? *Genet Med* 11: 66-73.
43. Fan C, Oh DS, Wessels L et al. Concordance among gene-expression-based predictors for breast cancer. *N Engl J Med* 2006; 355(6):560-9.
44. Food and Drug Administration (FDA). (2007) 510(k) Substantial equivalence determination decision summary. U.S. Department of Health & Human Services. Available: http://www.accessdata.fda.gov/cdrh_docs/reviews/K062694.pdf. Date Accessed: February 17, 2011.
45. Food and Drug Administration. ProsignaTM Breast Cancer Prognostic Gene Signature Assay. 2013 September 6, 2013 [cited 2015 July 9]; Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf13/K130010.pdf.
46. Gennari A, Sormani MP, Pronzato P et al. HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: a pooled analysis of randomized trials. *J Natl Cancer Inst* 2008; 100(1):14-20.
47. Gevensleben, H, Gohring, UJ, Buttner, R, et al. (2010). Comparison of MammaPrint and TargetPrint results with clinical parameters in German patients with early stage breast cancer. *Int J Mol Med* 26:6: 837-43.
48. Gianni L, Zambetti M, Clark K et al. Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer. *J Clin Oncol* 2005; 23(29):7265-77.
49. Glas AM, Floore A, Delahaye LJ et al. Converting a breast cancer microarray signature into a high-throughput diagnostic test. *BMC Genomics* 2006; 7:278.
50. Glinsky, G.V., T. Higashiyama, and A.B. Glinskii. (2004). Classification of human breast cancer using gene expression profiling as a component of the survival predictor algorithm. *Clin Cancer Res*. 10(7): p. 2272-83.
51. Gnant, M., et al., Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. *Ann Oncol*, 2014. 25(2): p. 339-45.
52. Goetz MP, Suman VJ, Ingle JN et al. A two-gene expression ratio of homeobox 13 and interleukin-17B receptor for prediction of recurrence and survival in women receiving adjuvant tamoxifen. *Clin Cancer Res* 2006; 12(7 Pt 1):2080-7.
53. Goldhirsch A, Ingle JN, Gelber RD et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. *Ann Oncol* 2009; 20(8):1319-29.
54. Goldstein LJ, Gray R, Badve S et al. Prognostic utility of the 21-gene assay in hormone receptor-positive operable breast cancer compared with classical clinicopathologic features. *J Clin Oncol* 2008; 26(25):4063-71.
55. Grant, K.A., et al., MammaPrint Pre-screen Algorithm (MPA) reduces chemotherapy in patients with early-stage breast cancer. *S Afr Med J*, 2013. 103(8): p. 522-6.
56. Gunven P, Randén M, Elmberger G, et al. Gene expression profiling guiding diagnosis and therapy of rare mammary-like anogenital gland carcinomas. *Med Oncol*. 2012;29(1):127-132.
57. Habel LA, Shak S, Jacobs MK et al. A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. *Breast Cancer Res* 2006; 8(3): R25.
58. Habel, et.al. Gene expression and breast cancer mortality in Northern California Kaiser Permanente Patients: A large population based case control study. Presented at: 41st Annual Meeting of the American Society of Clinical Oncology. 5/13-17/05, Orlando, FL. Abstract #603.
59. Harris L, Fritsche H, Mennel R et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 2007; 25(33):5287-312.
60. Hartmann, S., et al., The 70-Gene Signature as Prognostic Factor for Elderly Women with Hormone Receptor-Positive, HER2-Negative Breast Cancer. *Breast Care (Basel)*, 2012. 7(1): p. 19-24.

Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

61. Hassett MJ, Silver SM, Hughes ME et al. Adoption of gene expression profile testing and association with use of chemotherapy among women with breast cancer. *J Clin Oncol* 2012; 30(18):2218-26.
62. Hayes, D.F. (2007). Adjuvant systemic therapy for early breast cancer: Rationale, assessing the need for and benefit from therapy, and treatment guidelines. 2007. Available: <http://www.utdol.com/utd/content/topic.do?topicKey=breastcn/11453&type=A&selectedTitle=4~6>.
63. Hayes, D.F. (2007). An overview of breast cancer and treatment for early stage disease. [cited 2007 June 11]; Available from: <http://www.utdol.com/utd/content/topic.do?topicKey=breastcn/10067>.
64. Hayes, DF. (2010) An overview of breast cancer and treatment for early stage disease. 18.3. September 24, 2010. UpToDate. Available: <http://www.utdol.com/utd/content/topic.do?topicKey=breastcn/10067>. Date Accessed: February 17, 2011.
65. Henry LR, Stojadinovic A, Swain SM et al. The influence of a gene expression profile on breast cancer decisions. *J Surg Oncol* 2009; 99(6):319-23.
66. Hornerberger, et.al. (2005). Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer. *Am J Manag Care*. May;11(5):313-24.
67. Ishitobi, M, Goranova, TE, Komoike, Y, et al. (2010). Clinical utility of the 70-gene MammaPrint profile in a Japanese population. *Jpn J Clin Oncol* 40:6: 508-12.
68. Jankowitz RC, Cooper K, Erlander MG et al. Prognostic utility of the breast cancer index and comparison to Adjuvant! Online in a clinical case series of early breast cancer. *Breast Cancer Res* 2011; 13(5): R98.
69. Jansen MP, Siewerts AM, Look MP et al. HOXB13-to-IL17BR expression ratio is related with tumor aggressiveness and response to tamoxifen of recurrent breast cancer: a retrospective study. *J Clin Oncol* 2007; 25(6):662-8.
70. Jereval PL, Brommesson S, Strand C et al. Exploring the two-gene ratio in breast cancer--independent roles for HOXB13 and IL17BR in prediction of clinical outcome. *Breast Cancer Res Treat* 2008; 107(2):225-34.
71. Jereval PL, Ma XJ, Li H et al. Prognostic utility of HOXB13: IL17BR and molecular grade index in early-stage breast cancer patients from the Stockholm trial. *Br J Cancer* 2011.
72. Joh JE, Esposito NN, Kiluk JV et al. The effect of Oncotype DX recurrence score on treatment recommendations for patients with estrogen receptor-positive early stage breast cancer and correlation with estimation of recurrence risk by breast cancer specialists. *Oncologist* 2011; 16(11):1520-6.
73. Jonsdottir, K., et al., Prognostic value of gene signatures and proliferation in lymph-node-negative breast cancer. *PLoS One*, 2014. 9(3): p. e90642.
74. Kelly CM, Bernard PS, Krishnamurthy S et al. Agreement in Risk Prediction Between the 21-Gene Recurrence Score Assay (Oncotype DX(R)) and the PAM50 Breast Cancer Intrinsic Classifier in Early-Stage Estrogen Receptor-Positive Breast Cancer. *Oncologist* 2012; 17(4):492-8.
75. Kelly CM, Krishnamurthy S, Bianchini G et al. Utility of oncotype DX risk estimates in clinically intermediate risk hormone receptor-positive, HER2-normal, grade II, lymph node-negative breast cancers. *Cancer* 2010; 116(22):5161-7.
76. Klang SH, Hammerman A, Liebermann N et al. Economic implications of 21-gene breast cancer risk assay from the perspective of an Israeli-managed health-care organization. *Value Health* 2010; 13(4):381-7.
77. Knauer, M, Mook, S, Rutgers, EJ, et al. (2010). The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. *Breast Cancer Res Treat* 120:3: 655-61.
78. Krijgsman O, Roepman P, Zwart W, et al. A diagnostic gene profile for molecular subtyping of breast cancer associated with treatment response. *Breast Cancer Res Treat*. 2012;133(1):37-47.
79. Kunz G. Use of a genomic test (MammaPrint) in daily clinical practice to assist in risk stratification of young breast cancer patients. *Arch Gynecol Obstet* 2011; 283(3):597-602.
80. Linn SC, Drukker CA, Retel VP et al. When to add chemotherapy to endocrine therapy and endocrine sensitivity. 8th European Breast Cancer Conference 2012: Abstract 207.
81. Lo SS, Mumby PB, Norton J et al. Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. *J Clin Oncol* 2010; 28(10):1671-6.
82. Lyman GH, Cosler L, Hormerger J. A 21-gene RT-PCR assay in lymph node negative (LN-) estrogen receptor positive (ER+) early-stage breast cancer (ESBC): an age-specific economic analysis. Presented at: 27th Annual San Antonio Breast Cancer Symposium. 12/8-11/04. San Antonio, TX. Abstract #2081.
83. Lyman GH, Cosler L, Hormerger J. Gene Expression profiles of paraffin-embedded core biopsy tissue predict response to chemotherapy in patients with locally advanced breast cancer. Presented at: 40th Annual Meeting of the American Society of Clinical Oncology. 6/5-8/04 New Orleans, LA. Abstract #501.
84. Ma XJ, Hilsenbeck SG, Wang W et al. The HOXB13:IL17BR expression index is a prognostic factor in early-stage breast cancer. *J Clin Oncol* 2006; 24(28):4611-9.
85. Ma XJ, Salunga R, Dahiya S et al. A five-gene molecular grade index and HOXB13:IL17BR are complementary prognostic factors in early stage breast cancer. *Clin Cancer Res* 2008; 14(9):2601-8.
86. Ma, P. Overview of gene expression profiling, proteomics, and microRNA profiling in clinical oncology. 2015 March 18, 2015 [cited 2015 July 10]; Available from: http://www.uptodate.com/contents/overview-of-gene-expression-profiling-proteomics-and-microrna-profiling-in-clinical-oncology?source=search_result&search=gene+expression+profiling&selectedTitle=1-150#H17.
87. Mamounas EP, Tang G, Fisher B et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. *J Clin Oncol* 2010; 28(10):1677-83.
88. Marchionni, L, Wilson, RF, Wolff, AC, et al. (2008). Systematic review: gene expression profiling assays in early-stage breast cancer. *Ann Intern Med* 148:5: 358-69.
89. Martin, M., et al., Prospective study of the impact of the Prosigna assay on adjuvant clinical decision-making in unselected patients with estrogen receptor positive, human epidermal growth factor receptor negative, node negative early-stage breast cancer. *Curr Med Res Opin*, 2015. 31(6): p. 1129-37.
90. Mayo Clinic Staff. (2011) Breast Cancer Definition. February 11, 2011. Mayo Foundation for Medical Education and Research (MFMR). Available: <http://www.mayoclinic.com/health/breast-cancer/ds00328>. Date Accessed: February 12, 2011.
91. Mina L, Soule SE, Badve S et al. Predicting response to primary chemotherapy: gene expression profiling of paraffin-embedded core biopsy tissue. *Breast Cancer Res Treat* 2007; 103(2):197-208.
92. Mook S, Schmidt MK, Viale G et al. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1-3 positive lymph nodes in an independent validation study. *Breast Cancer Res Treat* 2009; 116(2):295-302.

Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

93. Mook S, Schmidt MK, Weigelt B et al. The 70-gene prognosis signature predicts early metastasis in breast cancer patients between 55 and 70 years of age. *Ann Oncol* 2010; 21(4):717-22.
94. Mook, S., Bonnefoi, H., Pruneri, G. et al. (2009). Daily clinical practice of fresh tumour tissue freezing and gene expression profiling: logistics pilot study preceding the MINDACT trial. *Eur J Cancer* 45.7: 1201-8.
95. Mook, S., Knauer, M., Bueno-de-Mesquita, JM, et al. (2010). Metastatic potential of T1 breast cancer can be predicted by the 70-gene MammaPrint signature. *Ann Surg Oncol* 17.5: 1406-13.
96. Naderi, A., et al. (2007). A gene-expression signature to predict survival in breast cancer across independent data sets. *Oncogene*. 26(10): p. 1507-16.
97. National Cancer Institute (NCI). (2010) SEER Stat Fact Sheets: Breast. November 2009. U.S. National Institutes of Health. Available: <http://seer.cancer.gov/statfacts/html/breast.html>. Date Accessed: February 17, 2011.
98. National Cancer Institute (NCI). SEER Stat Fact Sheets: Breast. 2010 November 2009 [cited 2011 February 17]; Available from: <http://seer.cancer.gov/statfacts/html/breast.html>
99. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Breast Cancer. V.3.2012.2012; http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 2012.
100. National Comprehensive Cancer Network. (2007) NCCN Clinical Practice Guidelines in Oncology™ Breast Cancer. Available: http://nccn.org/professionals/physician_gls/PDF/breast.pdf. Date Accessed: June 11, 2007.
101. National Comprehensive Cancer Network. Breast Cancer. 2014 2014 [cited 2014 April 22].
102. National Comprehensive Cancer Network. Breast Cancer. 2015 2015 [cited 2015 August 10].
103. National Institute for Health and Care Excellence. Gene expression profiling and expanded immunohistochemistry test for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat. 2013 September 13, 2013 [cited 2014 March 4]; Available from: <http://www.nice.org.uk/nicemedia/live/14279/65265/65265.pdf>.
104. NCCN Guidelines. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version .2024 – February 12, 2024.
105. Nguyen, B., et al., Comparison of molecular subtyping with BluePrint, MammaPrint, and TargetPrint to local clinical subtyping in breast cancer patients. *Ann Surg Oncol*, 2012, 19(10): p. 3257-63.
106. Nielsen, T., et al., Analytical validation of the PAM50-based Prosigna Breast Cancer Prognostic Gene Signature Assay and nCounter Analysis System using formalin-fixed paraffin-embedded breast tumor specimens. *BMC Cancer*, 2014, 14: p. 177.
107. Nielsen, T.O., et al., A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. *Clin Cancer Res*, 2010, 16(21): p. 5222-32.
108. NICE. The Prosigna gene expression profiling assay for assessing long-term risk of breast cancer recurrence. 25 March 2015 [cited 2015 June 16]; Available from: <http://www.nice.org.uk/advice/mib2/resources/the-prosigna-gene-expression-profiling-assay-for-assessing-long-term-risk-of-breast-cancer-recurrence-63499050167749>.
109. NICE. Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. 19 December 2018. Available from <https://www.nice.org.uk/guidance/dg34>
110. Nielsen TO, Parker JS, Leung S et al. A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. *Clin Cancer Res* 2010; 16(21):5222-32.
111. Nuyten, D.S., et al. (2006). Predicting a local recurrence after breast-conserving therapy by gene expression profiling. *Breast Cancer Res*, 8(5): p. R62.
112. Oncotype DX. Oncotype DX® Test for DCIS Overview. 2013 [cited 2013 August 23]; Available from: <http://www.oncotypedx.com/en-US/Breast/PatientsCaregiversDCIS/OncotypeDX/Overview>
113. Oratz R, Kim B, Chao C et al. Physician Survey of the Effect of the 21-Gene Recurrence Score Assay Results on Treatment Recommendations for Patients With Lymph Node–Positive, Estrogen Receptor–Positive Breast Cancer. *Journal of Oncology Practice* 2011; 7(2):94-9.
114. Paik S, Shak S, Tang G et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004; 351(27):2817-26.
115. Paik S, Shak S, Tang G et al. Risk classification of breast cancer patients by the Recurrence Score assay: comparison to guidelines based on patient age, tumor size, and tumor grade. [Meeting Abstract]. *Breast Cancer Res Treat* 2004; 88(suppl 1): A104.
116. Paik S, Shak S, Tang G, et al. (2004). A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer. *NEJM*. 351(27):2817-26.
117. Paik S, Shak S, Tang G, et al. Expression of the 21 genes in the Recurrence Score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20. Presented at: 27th Annual San Antonio Breast Cancer Symposium. 12/8-11/04. San Antonio, TX. Abstract #24.
118. Paik S, Shak S, Tang G, et al. Risk classification of breast cancer patients by the Recurrence Score assay: comparison to guidelines based on patient age, tumor size, and tumor grade. Presented at: 27th Annual San Antonio Breast Cancer Symposium. 12/8-11/04. San Antonio, TX. Abstract #104.
119. Paik S, Tang G, Shak S et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006; 24(23):3726-34.
120. Paik, et.al. Expression of the 21 genes in the Recurrence Score assay and tamoxifen clinical benefit in the NSABP study B-14 of node-negative, estrogen receptor positive breast cancer. Presented at: 41st Annual Meeting of the American Society of Clinical Oncology. 5/13-17/05, Orlando, FL. Abstract #510.
121. Paik, S., Is gene array testing to be considered routine now? *Breast*, 2011. 20 Suppl 3: p. S87-91.
122. Parker JS, Mullins M, Cheang MC et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. *J Clin Oncol* 2009; 27(8):1160-7.
123. Prat A, Parker JS, Fan C et al. Concordance among gene expression-based predictors for ER-positive breast cancer treated with adjuvant tamoxifen. *Ann Oncol* 2012, 23(11): p. 2866-73.
124. Prat, A., et al., Concordance among gene expression-based predictors for ER-positive breast cancer treated with adjuvant tamoxifen. *Ann Oncol*, 2012. 23(11): p. 2866-73.
125. Prat, A., et al., Prediction of Response to Neoadjuvant Chemotherapy Using Core Needle Biopsy Samples with the Prosigna Assay. *Clin Cancer Res*, 2015.

Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

126. Prosigna. Use PAM50 to generate an individualized Prosigna Score* for every patient. 2015 [cited 2015 June 29]; Available from: <http://prosigna.com/overview/>.
127. Reid JF, Lusa L, De Cecco L et al. Limits of predictive models using microarray data for breast cancer clinical treatment outcome. *J Natl Cancer Inst* 2005; 97(12):927-30.
128. Retel, VP, Joore, MA, Knauer, M, et al. (2010). Cost-effectiveness of the 70-gene signature versus St. Gallen guidelines and Adjuvant Online for early breast cancer. *Eur J Cancer* 46.8: 1382-91.
129. Ring BZ, Seitz RS, Beck R et al. Novel prognostic immunohistochemical biomarker panel for estrogen receptor-positive breast cancer. *J Clin Oncol* 2006; 24(19):3039-47.
130. Roepman P, Horlings HM, Krijgsman O, et al. Microarray-based determination of estrogen receptor, progesterone receptor, and HER2 receptor status in breast cancer. *Clin Cancer Res*. 2009;15(22):7003-7011.
131. Ross DT, Kim CY, Tang G et al. Chemosensitivity and stratification by a five monoclonal antibody immunohistochemistry test in the NSABP B14 and B20 trials. *Clin Cancer Res* 2008; 14(20):6602-9.
132. Rutgers E, Piccart-Gebhart MJ, Bogaerts J et al. The EORTC 10041/BIG 03-04 MINDACT trial is feasible: results of the pilot phase. *Eur J Cancer* 2011; 47(18):2742-9.
133. Saghatchian, M., et al., Additional prognostic value of the 70-gene signature (MammaPrint((R))) among breast cancer patients with 4-9 positive lymph nodes. *Breast*, 2013.
134. Society, A.C. Breast Cancer Overview. 2013. [cited 2013 July]; Available from: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003037-pdf.pdf>
135. Solin L, Gray R, Baehner F et al. A Quantitative Multigene RT-PCR Assay For Predicting Recurrence Risk After Surgical Excision Alone Without Irradiation For Ductal Carcinoma in Situ (DCIS): A Prospective Validation Study of the DCIS Score From ECOG E5194. Presented at: 34th Annual San Antonio Breast Cancer Symposium; December 6-10, 2011; San Antonio, TX. 2011: Abstract S4-6.
136. Sotiriou, C, Piccart, MJ. (2007). Taking gene-expression profiling to the clinic: when will molecular signatures become relevant to patient care? *Nat Rev Cancer* 7.7: 545-53.
137. Sparano JA, Solin LJ. Defining the clinical utility of gene expression assays in breast cancer: the intersection of science and art in clinical decision making. *J Clin Oncol* 2010; 28(10):1625-7.
138. Sun, Y., et al. (2007). Improved breast cancer prognosis through the combination of clinical and genetic markers. *Bioinformatics*. 23(1); p. 30-7.
139. Tang G, Shak S, Paik S et al. Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: results from NSABP B-14 and NSABP B-20. *Breast Cancer Res Treat* 2011; 127(1):133-42.
140. Toi M, Iwata H, Yamanaka T et al. Clinical significance of the 21-gene signature (Oncotype DX) in hormone receptor-positive early stage primary breast cancer in the Japanese population. *Cancer* 2010; 116(13):3112-8.
141. Tornisi, R., et al., Potential impact of the 70-gene signature in the choice of adjuvant systemic treatment for ER positive, HER2 negative tumors: A single institution experience. *Breast*, 2013. 22(4): p. 419-24.
142. Tutt A, Wang A, Rowland C et al. Risk estimation of distant metastasis in node-negative, estrogen receptor-positive breast cancer patients using an RT-PCR based prognostic expression signature. *BMC Cancer* 2008; 8:339.
143. Tzeng JP, Mayer D, Richman AR et al. Women's experiences with genomic testing for breast cancer recurrence risk. *Cancer* 2010; 116(8):1992-2000.
144. van de Vijver, M.J., et al., (2002). A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med*. 347(25); p. 1999-2009.
145. van't Veer LJ, Dai H, van de Vijver MJ et al. Gene expression profiling predicts clinical outcome of breast cancer. *Nature* 2002; 415(6871):530-6.
146. Weigelt, B., et al. (2005). Molecular portraits and 70-gene prognosis signature are preserved throughout the metastatic process of breast cancer. *Cancer Res*. 65(20): p. 9155-8.
147. Welsh AW, Moeder CB, Kumar S et al. Standardization of estrogen receptor measurement in breast cancer suggests false-negative results are a function of threshold intensity rather than percentage of positive cells. *J Clin Oncol* 2011; 29(22):2978-84.
148. Wittner BS, Sgroi DC, Ryan PD et al. Analysis of the MammaPrint breast cancer assay in a predominantly postmenopausal cohort. *Clin Cancer Res* 2008; 14(10):2988-93.
149. Wolff AC, Hammond ME, Schwartz JN et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol* 2007; 25(1):118-45.
150. Yang, M., S. Rajan, and A.M. Issa, Cost effectiveness of gene expression profiling for early stage breast cancer: a decision-analytic model. *Cancer*, 2012. 118(20): p. 5163-70.
151. Zujewski JA, Kamin L. Trial assessing individualized options for treatment for breast cancer: the TAILORx trial. *Future Oncol* 2008; 4(5):603-10.

Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards. Also, revised to incorporate coverage criteria for EndoPredict and standard Breast Cancer Index tests (both tests were previously not covered), and added exclusion for Breast Cancer Index 5-Year Test.
7/29/24	For Commercial Plan Policy, consolidated coverage criteria for Oncotype DX, Prosigna, MammaPrint, and EndoPredict tests into one

Genetic Testing Policies, Continued

Genetic Testing: Gene Expression Profiling in the Management of Breast Cancer, continued

	uniform set of coverage criteria that aligns with updated NCCN Guidelines. Also, updated coverage criteria for Breast Cancer Index test to align with updated NCCN Guidelines.
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MEDICAL POLICY

GENETIC TESTING: GENETIC MUTATION ANALYSIS UTILIZING SOLID TUMOR TISSUE

Policy # 570

Implementation Date: 7/28/15

Review Dates: 10/20/16, 7/21/17, 9/18/18, 8/8/19, 10/21/20, 5/19/22, 1/17/23, 2/15/24

Revision Dates: 7/21/17, 10/26/18, 11/29/18, 8/23/19, 10/18/19, 9/23/20, 1/29/21, 7/1/23, 8/17/23, 7/12/24, 9/4/24, 2/19/25

Related Medical Policies:

[#581 Genetic Testing: Cell-Free Tumor DNA/Liquid Biopsy](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Cancer is a complex genetic disease influenced by both inherited variants in germline DNA and somatic alterations acquired during formation of the tumor. Prior to tumor genome sequencing, many genes that play a role in cancer were discovered through studies of the germline. Linkage studies in families with inherited, typically childhood cancers, identified rare germline mutations in genes related to DNA damage repair, RAS signaling, or PIK3 signaling. In contrast to childhood cancers, adult tumors have largely been considered 'sporadic'; however, mounting evidence points to a potentially substantial influence from the germline.

Somatic genetic testing for the purpose of cancer management guidance is a rapidly evolving field of molecular medicine. Genetic testing of a solid or hematologic tumor can provide important information regarding the prognosis, risk for recurrence, or help predict tumor response to chemotherapeutic agents. In addition, genetic testing of tissue (e.g., blood) or stool, for evidence of a tumor is becoming an important tool in the early detection of cancer. While this is an area of rapid and ongoing research, clinical validity and utility is proven for only a subset of companion diagnostic genetic tests at this time.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Genetic Testing Policies, Continued

Genetic Testing: Genetic Mutation Analysis Utilizing Solid Tumor Tissue, continued

Select Health covers multi-marker tumor panels using next-generation sequencing in the diagnosis and treatment of cancer as a method to guide the selection of therapeutic agents for malignant tumors in *limited circumstances*.

Members must meet one of the following (A, B, C, D, or E) of the following to be eligible for next-generation sequencing:

- A. Member is considering participating in a clinical trial* intended to assess the effectiveness of targeted therapies based on tumor marker; **OR**
- B. Non-small cell lung cancer (NSCLC) regardless of stage; **OR**
- C. For any stage III or IV solid organ tumor, and the panel must include BRAF, TMB, MSI, and NTRK; (NTRK using RNA is mandatory in secretory carcinoma of breast and salivary glands; congenital fibrosarcoma; cellular mesoblastic nephroma; thyroid cancer, particularly in children (frequency 2 to 28 percent, depending on the series); glioma (particularly select pediatric high-grade gliomas); specific sarcomas, such as inflammatory myofibroblastic tumor; Spitzoid neoplasms; and suggested in all other tumors with > 1% risk of harboring NTRK fusion); **OR**
- D. Comprehensive next-generation sequencing for endometrial cancers, including endometrioid, clear cell, serous and carcinosarcoma subtypes, will be covered if either of the following criteria have been met:
 1. Intact mismatch repair (MMR) protein expression with abnormal p53 immunohistochemical staining pattern; or
 2. High/high-intermediate risk as determined by GOG 99 criteria with or without abnormal p53 immunohistochemical staining pattern; **OR**
- E. A genomic biomarker-linked therapy has been approved by the FDA for their cancer clinical scenario, or there are established genomic biomarker-based treatment contraindications or exclusions.

Specifically related to homologous recombination deficiency (HRD), possibly present in breast, ovarian, pancreatic, and prostate cancer, the following tests must be performed to identify HRD: including BRCA1/2, genomic patterns of loss of heterozygosity (gLOH)^a, number of telomeric imbalances (TAI)^b, and large-scale transitions (LST)^c

^a which are regions of intermediate size (>15 MB and < whole chromosome)

^b which are the number of regions with allelic imbalance which extend to the sub-telomere but not cross the centromere

^c which are chromosome breaks (translocations, inversions, or deletions)

*Clinical trial must meet one (i–iii) of the following clinical conditions:

- i. Any advanced stage III or IV solid tumors*, or
- ii. All lymphomas, or
- iii. Multiple myeloma

Note: Testing will be allowed once for a specific tumor diagnosis.

Genetic Testing Policies, Continued

Genetic Testing: Genetic Mutation Analysis Utilizing Solid Tumor Tissue, continued

Separate RNA testing will be allowed once, either if DNA testing has been performed previously or is being performed concurrently.

PD-L1 can be billed separately from genetic testing.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the [manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

Molecular profiling for malignant tumors catalogues specific biomarker information and generates potential treatment options. The personalized tumor molecular profiling services or tests addressed in this document are similar in that they all take an individual's tumor tissue and, from it, produce a molecular profile of the tumor and a list of potential therapies. However, their individual testing methods vary from matching over-expressed genes with drugs to more complex systems biology approaches.

Foundation CDx uses next generation sequencing: "... to interrogate the entire coding sequence of 236 cancer-related genes (3,769 exons) plus 47 introns from 19 genes frequently altered or rearranged in cancer." Foundation CDx helps match the genomic alterations present in a tumor with specific targeted therapies or clinical trials. Recent small studies (Drilon, 2013; Lipson, 2012; Vignot, 2013) have investigated next-generation sequencing in individuals with lung cancer. Others have used next-generation sequencing in those with breast cancer (Ross, 2013a); colorectal cancer (Lipson, 2012), ovarian cancer (Ross, 2013b), and prostate cancer (Beltran, 2013). Limitations of these studies include small sample sizes.

The most widely used of the tumor molecular profiles has been the Target Now Molecular Profiling Service (Caris Life Sciences). According to the Caris Life Sciences website, their tumor profiling service is now being promoted as the Molecular Intelligence Service. The published literature addressing these services is limited. Von Hoff and colleagues (2010) evaluated 86 individuals with refractory metastatic cancer. Progression-free survival (PFS) using a treatment regimen selected by Target Now molecular profiling of a malignant tumor was compared with the PFS of the most recent treatment regimen on which the individual experienced progression. A molecular target was detected in 84 of 86 (98%) participants. A total of 66 (78.6%) individuals were treated according to the molecular profile results with 18 of the 66 (27%) having a PFS ratio (defined as PFS on molecular profile-selected therapy or PFS on prior therapy) of greater than or equal to 1.3 (95% confidence interval [CI], 17% to 38%; P=0.007).

An editorial (Doroshow, 2010) accompanying the study reported that the trial had several significant limitations, including uncertainty surrounding the achievement of time to progression (the study's primary endpoint), and a lack of a randomized design. Additional limitations include a small number of participants and lack of duplication of study results by an independent dataset. GeneKey and OncoInsights have even less validation. To date, there are no studies in the published literature specifically addressing these tests.

In a related study examining intratumor heterogeneity, Gerlinger and colleagues (2012) obtained multiple spatially separated biopsy samples from primary renal carcinomas and associated metastatic sites of 4 individuals. Intratumor heterogeneity was characterized using immunohistochemical analysis, profiling of messenger ribonucleic acid (mRNA) expression, and mutation functional analysis. An unexpected finding

Genetic Testing Policies, Continued

Genetic Testing: Genetic Mutation Analysis Utilizing Solid Tumor Tissue, continued

of this study revealed intratumor heterogeneity at the RNA-expression level, with gene expression signatures of good and poor prognosis detected in different regions of the same tumor. The authors concluded that genomics analyses from single tumor biopsy specimens may underestimate the mutational burden of heterogeneous tumors. It was also noted that this may explain difficulties encountered in the validation of oncology biomarkers owing to sampling bias, contribute to Darwinian selection of preexisting drug-resistant clones, and predict therapeutic resistance.

Molecular profiling has also been investigated for gastric cancer. Lei and colleagues (2013) sought to identify subtypes of gastric adenocarcinomas with particular biological properties and responses to chemotherapy and targeted agents. Gene expression patterns among 248 gastric tumors were compared. Three major subtypes of gastric adenocarcinoma were identified: proliferative, metabolic, and mesenchymal. Tumors of the proliferative subtype had high levels of genomic instability, TP53 mutations, and DNA hypomethylation. Cancer cells of the metabolic subtype were more sensitive to 5-fluorouracil than the other subtypes. Also, in two independent groups of subjects, those with tumors of the metabolic subtype appeared to have greater benefits with 5-fluorouracil treatment. Tumors of the mesenchymal subtype contain cells with features of cancer stem cells, and cell lines of this subtype were particularly sensitive to phosphatidylinositol 3-kinase-AKT-mTOR inhibitors *in vitro*. The authors concluded that if study results are confirmed and extended in future studies, the classification of gastric adenocarcinomas reported here could guide development of therapies tailored to the molecular subtypes.

In 2012, Tsimberidou and colleagues developed a personalized medicine program at a single facility in the context of early clinical trials. Their goal was to observe whether molecular analysis of advanced cancer and use of targeted therapy to counteract the effects of specific aberrations would be associated with improved clinical outcomes. Participants with advanced or metastatic cancer refractory to standard therapy underwent molecular profiling. A total of 175 subjects were treated with matched therapy, and the overall response rate was 27%. Of the 116 subjects treated with non-matched therapy, the response rate was 5%. The median time-to-failure was 5.2 months for those on matched therapy versus 2.2 months on non-matched therapy. At a median of 15 months follow-up, median survival was 13.4 months versus 9.0 months in favor of matched therapy.

Jameson and colleagues in 2012 performed a small pilot study investigating multi-omic molecular profiling (MMP) for the selection of breast cancer treatment. MMP treatment recommendations were selected in 25 cases and original treatment plans were revised accordingly. Partial responses were reported in 5/25 (25%), stable disease in 8/25 (32%) and 9/25 had no disease progression at 4 months. This study was limited by its small size and non-randomization. A large randomized prospective trial is needed for further evaluation. Primarily marketed to researchers, Life Technologies Inc. offers several variations of their Ion Torrent Next Generation Sequencing Ion AmpliSeq panels, according to the company website. The Ion AmpliSeq Comprehensive Cancer Panel analyzes more than 400 cancer-related genes and tumor suppressor genes. The Ion AmpliSeq Cancer Hotspot Panel v2 analyzes the "hotspot" regions of 50 cancer-related and tumor suppressor genes.

The nonrandomized study by Haslem et al. in 2016 adds some support to NGS from both the clinical utility and cost-effectiveness standpoint. In their retrospective matched cohort study of 72 patients (36 tested and 36 matched controls), the precision medicine treated cohort had longer progression-free survival than did the control group (22.0 vs 12-week, $p = .002$) and had similar weekly costs (\$4,665 vs \$5000). The study is small, but the findings warrant validation in a larger prospective study. Some studies are finding a high rate of clinical actionability, at least in terms of tumors found to have mutations for which there is a therapy. Hirshfield and coworkers in 2016 found that 96% (88/92) patients with rare refractory tumors had at least one mutation that triggered a guided therapy in 35% of cases, but this study did not report on the effect of this therapy.

Other studies (also small) have been less supportive. Blumenthal et al. in 2016 reported use in 43 patients with glioblastoma. In 13 of these an actionable target was found but none responded to the therapy. Grenader et al. in 2016 studied 30 patients with advanced tumors using tumor sequencing. Ten of the patients received treatments based on genomic profiling. Of these only 3 benefited. Median progression-free survival in this small cohort was actually worse in the profile-guided group (12 weeks) compared to the control group (48 weeks).

In summary, there is a growing body of evidence, which, though insufficient to support the general use of molecular profiling to guide treatment decisions for all malignant tumors, provides a basis for allowing

Genetic Testing Policies, Continued

Genetic Testing: Genetic Mutation Analysis Utilizing Solid Tumor Tissue, continued

limited coverage of this testing in support of advancing current clinical knowledge and potentially improving patient outcomes.

Billing/Coding Information

CPT CODES

Covered for the indications listed above if criteria are met

0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)
0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin embedded tumor tissue
0334U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0379U	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by next-generation sequencing, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutational burden
0478U	Oncology (non-small cell lung cancer), DNA and RNA, digital PCR analysis of 9 genes (EGFR, KRAS, BRAF, ALK, ROS1, RET, NTRK 1/2/3, ERBB2, and MET) in formalin-fixed paraffin-embedded (FFPE) tissue, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and reported as actionable detected variants for therapy selection
0499U	Oncology (colorectal and lung), DNA from formalin-fixed paraffin embedded (FFPE) tissue, nextgeneration sequencing of 8 genes (NRAS, EGFR, CTNNB1, PIK3CA, APC, BRAF, KRAS, and TP53), mutation detection
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81449	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (EG, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

Genetic Testing Policies, Continued

Genetic Testing: Genetic Mutation Analysis Utilizing Solid Tumor Tissue, continued

81456	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (EG, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81479	Unlisted molecular pathology procedure

Not covered for the indications listed above

0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden
0538U	Oncology (solid tumor), nextgeneration targeted sequencing analysis, formalin-fixed paraffinembedded (FFPE) tumor tissue, DNA analysis of 600 genes, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and copy number alterations, microsatellite instability, tumor mutation burden, reported as actionable variant
0539U	Oncology (solid tumor), cellfree circulating tumor DNA (ctDNA), 152 genes, nextgeneration sequencing, interrogation for singlenucleotide variants, insertions/deletions, gene rearrangements, copy number alterations, and microsatellite instability, using whole-blood samples, mutations with clinical actionability reported as actionable variant
0543U	Oncology (solid tumor), nextgeneration sequencing of DNA from formalin-fixed paraffin-embedded (FFPE) tissue of 517 genes, interrogation for singlenucleotide variants, multinucleotide variants, insertions and deletions from DNA, fusions in 24 genes and splice variants in 1 gene from RNA, and tumor mutation burden

HCPCS CODES

No specific codes identified

Key References

1. Beltran H, Yelensky R, Frampton GM. Targeted next-generation sequencing of advanced prostate cancer identifies potential therapeutic targets and disease heterogeneity. *Eur Urol.* 2013; 63(5):920-926.
2. Blumenthal, D. T., A. Dvir, A. Lossos, T. Tzuk-Shina, T. Lior, D. Limon, S. Yust-Katz, A. Lokiec, Z. Ram, J. S. Ross, S. M. Ali, R. Yair, L. Soussan-Gutman and F. Bokstein (2016). "Clinical utility and treatment outcome of comprehensive genomic profiling in high grade glioma patients." *J Neurooncol.* 130(1): 211-219.
3. Chakravarty D, Johnson A, Sklar J, Lindeman NI, Moore K, Ganesan S, Lovly CM, Perlmutter J, Gray SW, Hwang J, Lieu C, André F, Azad N, Borad M, Tafe L, Messersmith H, Robson M, Meric-Bernstam F. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. *J Clin Oncol.* 2022 Apr 10;40(11):1231-1258. Erratum in: *J Clin Oncol.* 2022 Jun 20;40(18):2068. PMID: 35175857.
4. Doroshow JH. Selecting systemic cancer therapy one patient at a time: is there a role for molecular profiling of individual patients with advanced solid tumors? *J Clin Oncol.* 2010; 28(33):4869-4871.
5. Drilon A, Wang L, Hasanovic A. Response to Cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov.* 2013; 3(6):630-635.
6. Garber K. Ready or not: personal tumor profiling tests take off. *J Natl Cancer Inst.* 2011; 103(2):84-86.
7. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med.* 2012; 366(10):883-892.
8. Grenader, T., R. Tauber and L. Shavit (2016). "Next-generation sequencing in patients with advanced cancer: are we ready for widespread clinical use? A single institute's experience." *Anticancer Drugs* 27(9): 899-907.
9. Haslem, D. S., S. B. Van Norman, G. Fulde, A. J. Knighton, T. Belnap, A. M. Butler, S. Rhagunath, D. Newman, H. Gilbert, B. P. Tudor, K. Lin, G. R. Stone, D. L. Loughmiller, P. J. Mishra, R. Srivastava, J. M. Ford and L. D. Nadauld (2016). "A Retrospective Analysis of Precision Medicine Outcomes in Patients With Advanced Cancer Reveals Improved Progression-Free Survival Without Increased Health Care Costs." *J Oncol Pract.*
10. Hirshfield, K. M., D. Tolkunov, H. Zhong, S. M. Ali, M. N. Stein, S. Murphy, H. Vig, A. Vazquez, J. Glod, R. A. Moss, V. Belyi, C. S. Chan, S. Chen, L. Goodell, D. Foran, R. Yelensky, N. A. Palma, J. X. Sun, V. A. Miller, P. J. Stephens, J. S. Ross, H. Kaufman, E. Poplin, J. Mehnert, A. R. Tan, J. R. Bertino, J. Aisner, R. S. DiPaola, L. Rodriguez-Rodriguez and S. Ganesan (2016). "Clinical Actionability of Comprehensive Genomic Profiling for Management of Rare or Refractory Cancers." *Oncologist.*

Genetic Testing Policies, Continued

Genetic Testing: Genetic Mutation Analysis Utilizing Solid Tumor Tissue, continued

11. Jameson GS, Petricoin EF, Sachdev J, et al. A pilot study utilizing multi-omic molecular profiling to find potential targets and select individualized treatments for patients with previously treated metastatic breast cancer. *Breast Cancer Res Treat.* 2014; 147(3):579-588.
12. Lei Z, Tan IB, Das K, et al. Identification of molecular subtypes of gastric cancer With different responses to PI3-kinase inhibitors and 5-fluorouracil. *Gastroenterology.* 2013; 145(3):554-565.
13. Lipson D, Capelletti M, Yelensky R. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. *Nat Med.* 2012; 18(3):382-384.
14. Marchio, C, Scaltriti, M., Ladanyi, M., Lafrate, A.J., Bibeau, A.F., Dietel, M. ... Reis-Filho, J.S. ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research. *Annals of Oncology.* 30: 1417–1427, 2019 doi:10.1093/annonc/mdz204
15. Mosele F, Remon J, Mateo J, Westphalen CB, Barlesi F, Lolkema MP, Normanno N, Scarpa A, Robson M, Meric-Bernstam F, Wagle N, Stenzinger A, Bonastre J, Bayle A, Michiels S, Bièche I, Rouleau E, Jezdic S, Douillard JY, Reis-Filho JS, Dienstmann R, André F. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. *Ann Oncol.* 2020 Nov;31(11):1491-1505. PMID: 32853681.
16. NCCN Clinical Practice Guidelines in Oncology. NSCLC (Version 2.2024), Uterine Neoplasms (Version 1.2024). Accessed February 15, 2024.
17. Ross JS, Ali SM, Wang K. Comprehensive genomic profiling of epithelial ovarian cancer by next generation sequencing-based diagnostic assay reveals new routes to targeted therapies. *Gynecol Oncol.* 2013a; 130(3):554-559.
18. Ross JS, Wang K, Sheehan CE. Relapsed classic E-cadherin (CDH1)-mutated invasive lobular breast cancer shows a high frequency of HER2 (ERBB2) gene mutations. *Clin Cancer Res.* 2013b; 19(10):2668-2676.
19. Stenzinger A, Cuffel B, Paracha N, Vail E, Garcia-Foncillas J, Goodman C, Lassen U, Vassal G, Sullivan SD. Supporting Biomarker-Driven Therapies in Oncology: A Genomic Testing Cost Calculator. *Oncologist.* 2023 May 8;28(5):e242-e253. PMID: 36961477.
20. Tsimerman AM, Iskander NG, Hong DS, et al. Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. *Clin Cancer Res.* 2012;18(22):6373-6383.
21. Vignot S, Frampton GM, Soria JC. Next-generation sequencing reveals high concordance of recurrent somatic alterations between primary tumor and metastases from patients with non-small-cell lung cancer. *J Clin Oncol.* 2013; 31(17):2167-2172.
22. Von Hoff DD, Stephenson JJ Jr., Rosen P, et al. Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. *J Clin Oncol.* 2010; 28(33):4877-4883.

Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
8/17/23	For Commercial Plan Policy, included BRAF and NTRK as genes required to be in panel for criteria #C, and added criteria #E: "E. A genomic biomarker-linked therapy has been approved by the FDA for their cancer clinical scenario, or there are established genomic biomarker-based treatment contraindications or exclusions. Specifically related to homologous recombination deficiency (HRD), possibly present in breast, ovarian, pancreatic, and prostate cancer, the following tests must be performed to identify HRD: including BRCA1/2, genomic patterns of loss of heterozygosity (gLOH), number of telomeric imbalances (TAI), and large-scale transitions (LST); which are regions of intermediate size (>15 MB and < whole chromosome); which are the number of regions with allelic imbalance which extend to the sub-telomere but not cross the centromere; which are chromosome breaks (translocations, inversions, or deletions)."
7/12/24	For Commercial Plan Policy, added the following clarifying language to criteria #C: "For any stage III or IV solid organ tumor, and the panel must include BRAF, TMB, MSI, and NTRK; (NTRK using RNA is mandatory in secretory carcinoma of breast and salivary glands; congenital fibrosarcoma; cellular mesoblastic nephroma;

Genetic Testing Policies, Continued

Genetic Testing: Genetic Mutation Analysis Utilizing Solid Tumor Tissue, continued

	<i>thyroid cancer, particularly in children (frequency 2 to 28 percent, depending on the series); glioma (particularly select pediatric high-grade gliomas); specific sarcomas, such as inflammatory myofibroblastic tumor; Spitzoid neoplasms; and suggested in all other tumors with > 1% risk of harboring NTRK fusion).</i> "
9/4/24	For Commercial Plan Policy, added the following limitation: " <u>Note:</u> Testing will be allowed once for a specific tumor diagnosis."
2/19/25	For Commercial Plan Policy, added the following clarifying notes below sections of criteria: "Separate RNA testing will be allowed once, either if DNA testing has been performed previously or is being performed concurrently; PD-L1 can be billed separately from genetic testing."

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: HEARING LOSS

Policy # 666

Implementation Date: 7/1/23

Review Dates: 8/20/24

Revision Dates: 9/4/24

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Prelinguinal hearing loss affects about 1 out of every 500 individuals. Approximately 20% of cases are attributed to environmental causes, including viral (cytomegalovirus) or bacterial (meningitis) infection, trauma, prenatal exposure to certain drugs, and other environmental factors. The remaining 80% of cases are thought to be genetic, either as part of a recognized genetic syndrome, or as isolated, non-syndromic hearing loss (NSHL).

70–80% of genetic hearing loss is non-syndromic, with no related systemic findings. Some syndromic forms of hearing loss and deafness may masquerade as non-syndromic in infancy and early childhood, before additional symptoms emerge. For example, goiter does not develop until puberty or adulthood in Pendred syndrome; retinitis pigmentosa emerges in adolescence in Usher syndrome; and males with Deafness-Dystonia-Optic Neuronopathy (Mohr-Tranebjærg) Syndrome begin having progressive neurological symptoms in their teens.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers panel genetic testing for non-syndromic hearing loss, mild or greater (Decibel level > 25), after testing for secondary conditions has been excluded (e.g., environmental/infectious causes).

The following genes can be tested: *CDH23*, *CLRN1*, *GJB2*, *GPR98*, *MTRNR1*, *MYO7A*, *MYO15A*, *PCDH15*, *OTOF*, *SLC26A4*, *TMC1*, *TMPRSS3*, *USH1C*, *USH1G*, *USH2A*, and *WFS1* [this list is not meant to be all-inclusive].

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage,

Genetic Testing Policies, Continued

Genetic Testing: Hearing Loss, continued

please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Billing/Coding Information

CPT CODES

- 81252** GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
- 81253** GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants
- 81254** GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6- D13S1854)])
- 81400** Molecular pathology procedure, Level 1(eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
- 81401** Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
- 81403** Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
- 81404** Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
- 81405** Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
- 81406** Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
- 81407** Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
- 81408** Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
- 81430** Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1

Genetic Testing Policies, Continued

Genetic Testing: Hearing Loss, continued

81431 Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes

81479 Unlisted molecular pathology procedure

Key References

1. Li MM, et al; ACMG Professional Practice and Guidelines Committee. Clinical evaluation and etiologic diagnosis of hearing loss: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2022 Jul;24(7):1392-1406. PMID: 35802133.
2. Belcher, R, Virgin, R, Duis, J., & Wootten, C. Genetic and Non-genetic Workup for Pediatric Congenital Hearing Loss. *frontiers in Pediatrics.* 22 March 2021. <https://doi.org/10.3389/fped.2021.536730>
3. Shearer AE, Hildebrand MS, Schaefer AM, et al. Genetic Hearing Loss Overview. 1999 Feb 14 [Updated 2023 Sep 28]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1434/>
4. Liming, B.J., et al. International Pediatric Otolaryngology Group (IPOG) consensus recommendations: Hearing loss in the pediatric patient. *International Journal of Pediatric Otorhinolaryngology.* 5 Sep 2016, 90:251-258. doi: 10.1016/j.ijporl.2016.09.016 PMID: 27729144

Revision History

Revision Date	Summary of Changes
9/4/24	For Commercial Plan Policy, clarified that for this testing, only panel testing is covered with criteria.

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Genetic Testing Policies, Continued

Genetic Testing: Hearing Loss, continued

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

Policy # 240

Implementation Date: 3/1/04

Review Dates: 1/13/05, 12/15/05, 2/16/06, 2/15/07, 2/21/08, 2/26/09, 2/18/10, 2/17/11, 2/16/12, 4/25/13, 2/20/14, 3/19/15, 2/11/16, 2/16/17, 2/15/18, 2/18/19, 1/31/23, 2/15/24

Revision Dates: 7/1/23

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Hereditary hemorrhagic telangiectasia (HHT) results from the presence of multiple arteriovenous malformations (AVMs) that lack intervening capillaries and result in direct connections between arteries and veins. Small arteriovenous malformations are called telangiectasias. Telangiectasias present on the nose, lips, and tongue typically vary in size from pinpoint to that of a small pea. Because of their thin walls, narrow tortuous paths, and closeness to the surface of the skin or to a mucous membrane, these vessels can rupture and bleed after only slight trauma. Since the contractile elements in the vessel wall are lacking, the bleeding may not stop spontaneously.

The term AVM usually refers to the "large" telangiectasias, greater than 0.5 inch in diameter and sometimes up to 3–6 inches in diameter. Large AVMs frequently cause symptoms and complications when they occur in the brain, lung, or gastrointestinal tract. Complications of large AVMs may be catastrophic and may occur without warning. Common complications include hemorrhage of the nose, mouth, tongue, gastrointestinal tract, lungs, fingers, toes, and occasionally the eyes, liver, and other organs.

Hereditary hemorrhagic telangiectasia presents with unexpected or difficult to control bleeding problems. It can present as iron deficiency anemia. It may not manifest clinical signs to alert patients and their physicians to its presence until age 40 or 50. The most common manifestations are epistaxis (nosebleeds) and telangiectasias. Epistaxis is usually the earliest symptom with an average age of onset of about 12 years of age. As many as 95% of affected individuals eventually experience recurrent epistaxis, with 1/3 having onset by age 10 years and 80%–90% by age 21 years. Bleeding can occur from other sites of telangiectasias also. About one-quarter of all individuals with HHT have gastrointestinal bleeding.

Cerebral AVMs may manifest as a hemorrhage, however, often the presenting symptom may be transient ischemic attacks (TIAs), embolic stroke, and cerebral abscess. Migraine headache, polycythemia, hypoxemia with cyanosis, and clubbing of the nails are other frequent complications of pulmonary AVMs. The presenting signs of pulmonary AVMs are usually exercise intolerance and cyanosis.

Hereditary hemorrhagic telangiectasia is inherited in an autosomal dominant manner. Most individuals have an affected parent. Each child of a proband and the sibs of most probands have a 50% risk of inheriting the mutation.

Indications for HHT genetic testing are: 1) to confirm the diagnosis in symptomatic individuals; and 2) to identify a familial mutation in clinically affected individuals, enabling diagnostic testing of at-risk relatives covered by the health plan. HHT is caused by mutations in 3 genes (ACVRL1, ENG, and SMAD4);

Genetic Testing Policies, Continued

Genetic Testing: Hereditary Hemorrhagic Telangiectasia (HHT), continued

however, mutations in other genes (RASA1 and BMP9) can cause findings with significant clinical overlap.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers genetic testing for hereditary hemorrhagic telangiectasia (HHT), as available evidence strongly supports its clinical utility, and such testing is the accepted standard of care in the at-risk population.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

No systematic reviews were identified related to HHT. Several recent traditional reviews were identified and obtained. Search of the medical literature database revealed 1,563 "hits" on HHT. Seven clinical trials (5 on epistaxis treatment [total n = 122] and 2 relating to AVMs in the liver [total n = 105]) were identified from this group. Only 1 of these was a randomized controlled trial (RCT). There is a distinct absence of diagnostic studies (e.g., observational trials) on this topic.

Analysis of the available literature identifies significant costs related to the treatment of unrecognized HHT. Given its incidence and prevalence in the U.S., identification of patients with HHT prior to development of significant medical complications and elimination from consideration those patients without the genetically inheritable traits is a cost-effective strategy and in the patient's interest.

Billing/Coding Information

Covered: For the conditions outlined above

CPT CODES

- | | |
|--------------|--|
| 81405 | Molecular pathology procedure, Level 6 |
| 81406 | Molecular pathology procedure, Level 7 |
| 81479 | Unlisted molecular pathology procedure |

Genetic Testing Policies, Continued

Genetic Testing: Hereditary Hemorrhagic Telangiectasia (HHT), continued

HCPCS CODES

No specific codes identified

Key References

1. ARUP Technical Bulletin, 1/2004: Hereditary Hemorrhagic Telangiectasia.
2. Begbie ME, Wallace GM, Shovlin CL. Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome): a view from the 21st century. Postgrad Med J. 2003 Jan; 79(927): 18-24. Review. PMID: 12566546
3. de Gussem, E. M., et al. (2014). "Outcomes of pregnancy in women with hereditary hemorrhagic telangiectasia." Obstet Gynecol 123(3): 514-520.
4. Dupuis-Girod, S., et al. (2010). "Hereditary hemorrhagic telangiectasia: from molecular biology to patient care." J Thromb Haemost 8(7): 1447-1456.
5. Dupuis-Girod, S., et al. (2014). "ELLIPSE Study: A Phase 1 study evaluating the tolerance of bevacizumab nasal spray in the treatment of epistaxis in hereditary hemorrhagic telangiectasia." MAbs 6(3).
6. Fuchizaki U, Miyamori H, Kitagawa S, Kaneko S, Kobayashi K. Hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber disease). Lancet. 2003 Nov 1; 362(9394): 1490-4. No abstract available. PMID: 14602446
7. Guttmacher AE & J McDonald. Hereditary Hemorrhagic Telangiectasia. GeneClinics.org.
8. McDonald, J., et al. (2011). "Hereditary hemorrhagic telangiectasia: an overview of diagnosis, management, and pathogenesis." Genet Med 13(7): 607-616.
9. Mei-Zahav M. [Osler-Weber-Rendu—a life-threatening disease in adults and children] Harefuah. 2003 Dec; 142(12): 852-6, 876. Hebrew. PMID: 14702755
10. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H, On behalf of the Scientific Advisory Board of the HHT Foundation International. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet. 2000 Mar 6;91(1):66-7. PMID: 10751092
11. Susan O. Lewin, M.D., Medical Geneticist, HHT Clinic, University of Utah (letter dated: 1-9-04).

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: HERITABLE THORACIC AND ABDOMINAL ANEURYSM AND DISSECTION (TAAD) RELATED DISORDERS

Policy # 453

Implementation Date: 8/9/10

Review Dates: 9/15/11, 11/29/12, 12/19/13, 12/18/14, 12/10/15, 12/15/16, 12/21/17, 12/20/18, 3/7/23, 5/14/24

Revision Dates: 4/6/15, 7/1/23, 11/27/23, 12/6/23, 9/9/24

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Aortic aneurysms, dissections, and rupture have ranked as high as the 15th major cause of death in the United States, accounting for nearly 15,000 deaths annually. Family studies demonstrate that up to 19% of persons with TAAD without a known genetic syndrome have a first-degree relative with TAAD.

Heritable thoracic and abdominal aneurysm and dissection (TAAD) related disorders are an overlapping group of conditions that result in dilation of the aorta, and, depending on the condition, other vessels with an elevated risk of dissection and rupture. Included in this growing group of conditions are the better-known syndromic forms of aortopathy, including Marfan and Loeys-Dietz syndromes, but the various types of non-syndromic heritable TAAD are also included.

There is significant overlap in clinical features of heritable TAAD-related disorders such that clinical evaluation and family history is often insufficient to diagnose a specific TAAD disorder. Determining which TAAD-associated gene harbors a mutation has direct implications on treatment and surveillance. Given the inability to clinically discern which specific gene mutation may be present, the use of gene panels allows for an accurate and rapid determination of the most appropriate clinical approach to patients.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers panel genetic testing for thoracic and abdominal inherited aortopathy disorders (TAAD) when either I or II are met:

I. Select Health considers panel genetic testing for TAAD as medically necessary, if recommended by Intermountain Heart Institute. (Genes include, but are not limited to: *FBN1*, *LOX*, *COL3A1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *ACTA2*, *MYH11*, *MYLK*, and *PRKG1*);

OR

II. For all other clinicians, Select Health considers panel genetic testing for TAAD as medically necessary, when the following criteria are met:

Genetic Testing Policies, Continued

Genetic Testing: Heritable TAAD-Related Disorders, continued

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

AND when the following criteria are met:

3. Select Health covers panel genetic testing for TAAD in limited circumstances when specific criteria are met. (Genes include, but are not limited to: *FBN1, LOX, COL3A1, TGFBR1, TGFBR2, SMAD3, TGFB2, ACTA2, MYH11, MYLK, and PRKG1.*)

- a) The patient has had an evaluation for a vascular abnormality either by ultrasound or CT scan, or by cardiology/vascular consult; AND (b or c)
- b) The patient is under age 60 and displays 1 major* clinical feature OR a strong clinical suspicion of a TAAD disorder as evidenced by 3 or more minor clinical features**; OR
- c) The patient is \geq age 60 and displays 1 major clinical feature* AND
 - i. 3 or more minor clinical features**; OR
 - ii. a first- or second-degree relative with a major* clinical feature

Select Health does not cover this testing if the only concern is hypermobile Ehlers Danlos Syndrome and the member does not meet the above criteria as this test lacks clinical utility. There must also be concern for other types of connective tissue disorders with cardiovascular involvement, which first must be excluded.

*Major clinical features, include aortic aneurysm, dilation, or dissection; unexplained arterial rupture; unexplained intestinal rupture; unexplained uterine rupture; ectopia lentis.

**Minor clinical features, include pectus carinatum/excavatum; scoliosis; clubfoot; chronic joint subluxations/dislocations; congenital dislocation of the hips; hypermobility (Beighton score ≥ 4); wrist and thumb sign; mitral valve prolapse; arteriovenous carotid cavernous sinus fistula; acrogeria (aged appearance to extremities, particularly hands); characteristic facial appearance (thin lips and philtrum, small chin, thin nose, large eyes); thin, translucent skin (especially noticeable on chest/abdomen); early-onset varicose veins; easy bruising (spontaneous or with minimal trauma); bifid uvula; gingival recession; pneumothorax/pneumohemothorax; tendon/muscle rupture.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Genetic Testing Policies, Continued

Genetic Testing: Heritable TAAD-Related Disorders, continued

Summary of Medical Information

Genetic alterations that lead to abnormalities in connective tissue metabolism predispose to thoracic aortic aneurysm. Genetically-mediated TAA accounts for about 5 percent of TAA. About 20 percent of patients with a TAA/aortic dissection have a family history of aneurysmal disease that is independent of any known genetic connective tissue syndrome. Genetic syndromes such as Marfan syndrome, Ehlers Danlos (ED) syndrome, Turner syndrome, and Loeys-Dietz syndrome, have more aggressive rates of aortic expansion and are more likely than sporadic TAA to require intervention.

Familial TAA refers to patients who have thoracic aortic disease associated with a family history of aneurysmal disease who do not meet strict criteria for known connective tissue syndrome. Familial TAA/dissection is increasingly being recognized and can include patients with a dilated aorta and a family history of dissection, rupture, or sudden unexplained death. The ascending thoracic aorta is involved in about 80 percent and the descending aorta is affected in the remaining 20 percent. Patients with familial TAA generally present at an earlier age (56.8 years) compared with patients with sporadic TAA (57 versus 64 years in one study), and also have faster rates of aortic expansion.

Studies of the family trees of patients with isolated TAA or dissection have found that at least 21 percent of probands have at least one family member with a known arterial aneurysm. The rate of inheritance may be higher, since many family members may not be aware that an aneurysm is present. About 80 percent of familial TAA appears to be inherited in an autosomal-dominant manner, but other genetic patterns are also expressed. The reduced penetrance and variable expression of these genetic conditions make obtaining a definitive clinical diagnosis difficult. Mutations in the transforming growth factor beta receptor 2 gene (*TGFRB2*) may be responsible for about 5 percent of familial cases. Other mutations include *ACTA2* and *MYH11*. *ACTA2* is the most common cause of familial TAA, accounting for up to 14 percent of genetic mutations associated with familial syndromes.

The location of the TAA in the proband closely mirrors aneurysm location in family members, supporting the notion that the etiology of aneurysmal disease is differentiated proximal and distal to the ligamentum arteriosum. Disease proximal to the ligament is predominantly nonatherosclerotic in nature, whereas disease distal to it, is strongly associated with atherosclerosis.

Marfan syndrome — Marfan syndrome, which is associated with mutations in the *FBN1* gene, is usually localized to the aortic root, but may extend to the ascending aorta and is associated with an accelerated expansion compared with degenerative aneurysms and a high risk of aortic complications at a relatively young age. Aortic root dilatation, aortic regurgitation, and aortic dissection are the main causes of morbidity and mortality. Marfan syndrome is discussed in detail elsewhere.

As recommended in the 2010 ACC/AHA/AATS guidelines for thoracic aortic disease, patients with MFS should have echocardiography performed at the time of diagnosis and six months later to determine the aortic root and ascending aortic diameters and their rate of enlargement.

In adults, if the aortic diameter is documented as stable over time, then annual imaging is recommended if the aortic dimension is less than 45 mm. If the aortic diameter is ≥ 45 mm or shows significant growth over time, then more frequent imaging is suggested (e.g., twice yearly) and surgery may be indicated. More frequent imaging is also recommended if the aortic diameter shows rapid change (≥ 0.5 cm/year) or if there are concerns regarding heart or valve function.

For children with MFS, annual imaging is recommended if the aortic dimension is documented as stable over time and not markedly enlarged. There are no validated age-specific absolute aortic diameters that can be used to determine when more frequent imaging should be performed or when prophylactic aortic surgery is indicated. It is recommended that aortic measurements be compared to the body surface area. Sonographic measurement of aortic diameter should be performed annually, as long as the increase in aortic size remains proportional to the increase in body surface area. Twice-yearly measurements are recommended if aortic size (expressed as a percentage increase) diverges from the height when expressed in the same fashion.

Individuals under 20 years of age with systemic findings suggestive of MFS, but without cardiovascular involvement, should also have annual echocardiograms due to the potential risk of development of aortic disease. Adults with repeatedly normal and stable aortic measurements, without a definitive genetic predisposition for aortic enlargement, but with a sense of predisposition based upon family history or borderline aortic measurements can be seen at two- to three-year intervals

Genetic Testing Policies, Continued

Genetic Testing: Heritable TAAD-Related Disorders, continued

Loeys-Dietz syndrome — Loeys-Dietz syndrome is an autosomal dominant condition due to mutations in the transforming growth factor beta receptor genes (TGFBR1, TGFBR2). Patients with Loeys-Dietz syndrome have many clinical features in common with patients with Marfan syndrome and are also at high risk for aortic dilation, rupture, or dissection at a young age.

As recommended in the 2010 ACC/AHA/AATS guidelines, complete aortic imaging should be performed at the time of diagnosis, and 6 months after in patients with Loeys-Dietz syndrome or a confirmed genetic mutation associated with aortic aneurysms and aortic dissections (eg, TGFBR1, TGFBR2, SMAD3, TGFB2, FBN1, ACTA2, or MYH11), to determine if aortic enlargement is occurring.

If the aortic dimension is stable and no other specific problem in another vascular segment has been identified, patients with Loeys-Dietz syndrome (potentially caused by mutations in TGFBR1, TGFBR2, SMAD3, TGFB2, or TGFB3) should have serial MRI from the cerebrovascular circulation to the pelvis (with a maximal interval between studies of two years) since they commonly develop aneurysms that are amenable to prophylactic surgical management. Prophylactic repair of the aorta is indicated in these patients at an ascending aortic measurement of 4.2cm by TEE.

Ehlers-Danlos syndrome — The Ehlers-Danlos syndrome is a group of conditions due to defects in type III procollagen that cause hyperelasticity and fragility of the skin and hypermobility of the joints (see Ehlers Danlos Society Diagnostic Criteria). Most types of Ehlers-Danlos are not associated with aortic dilation, although mild mitral valve prolapse is often present. However, in the vascular type (previously Type IV) Ehlers-Danlos syndrome, vascular and connective tissue integrity is markedly impaired and spontaneous rupture of large and medium-sized arteries can occur.

Aneurysm-osteoarthritis syndrome — Aneurysm osteoarthritis syndrome, caused by pathogenic variants of SMAD3 (mothers against decapentaplegic homolog 3), is a recently described autosomal dominant syndrome characterized by aneurysms and arterial tortuosity in combination with early-onset osteoarthritis. Aneurysms are most frequently localized to the aortic root, but can be found throughout the arterial tree, including the iliac, visceral, and intracranial arteries. In one review of 38 patients, 71 percent had aortic root dilation.

Billing/Coding Information

Covered: For the conditions outlined above

CPT CODES

- | | |
|-------|---|
| 81405 | Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) |
| 81410 | Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK |
| 81411 | Aortic dysfunction or dilation (eg, Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1 |
| 81479 | Unlisted molecular pathology procedure |

HCPCS CODES

- | | |
|-------|--|
| G0452 | Molecular pathology procedure; physician interpretation and report |
|-------|--|

Key References

1. Byers, P.H. Vascular Ehlers-Danlos Syndrome. 1999 Sep 2 [Updated 2019 Feb 21]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1494/>
2. Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS). The Ehlers Danlos Society. Available at: <https://www.ehlers-danlos.com/wp-content/uploads/2017/05/hEDS-Dx-Criteria-checklist-1.pdf>
3. Dietz, H. FBN1-Related Marfan Syndrome. 2001 Apr 18 [Updated 2022 Feb 17]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1335/>

Genetic Testing Policies, Continued

Genetic Testing: Heritable TAAD-Related Disorders, continued

4. Hakim, A. Hypermobility Ehlers-Danlos Syndrome. 2004 Oct 22 [Updated 2024 Feb 22]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1279/>
5. Isselbacher, E. M., Preventza, O., Black, J. H., et al. 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;146: e334–e482. <https://www.ahajournals.org/doi/10.1161/CIR.000000000001106#d4001557e1>
6. Loeys, B. L. & Dietz, H. C. Loeys-Dietz Syndrome. 2008 Feb 28 [Updated 2018 Mar 1]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1133/>
7. Milewicz, D. M. & Cecchi, A. C. Heritable Thoracic Aortic Disease Overview. 2003 Feb 13 [Updated 2023 May 4]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1120/>
8. Tinkle, B. T., Lacro, R. V., & Burke, L. W. Health Supervision for Children and Adolescents with Marfan Syndrome. *Pediatrics*. 2023; 151(4): e2023061450

Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
11/27/23	For Commercial Plan Policy, modified formatting and verbiage of overall criteria, and added the following exclusion: "Select Health does not cover this testing, if the only concern is hypermobile Ehlers Danlos Syndrome and the member does not meet the above criteria, this test lacks clinical utility. There must also be concern for other types of connective tissue disorders with cardiovascular involvement, which first must be excluded."
12/6/23	For Commercial Plan Policy, modified criteria to include option of recommendation by Intermountain Heart Institute as a qualifying factor.
9/9/24	For Commercial Plan policy, added new criterion #3a: "The patient has had an evaluation for a vascular abnormality either by ultrasound or CT scan, or by cardiology/vascular consult ..."; and updated list of Major and Minor Clinical Features.

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Genetic Testing Policies, Continued

Genetic Testing: Heritable TAAD-Related Disorders, continued



MEDICAL POLICY

GENETIC TESTING: HERITABLE THORACIC AND ABDOMINAL ANEURYSM AND DISSECTION (TAAD) RELATED DISORDERS

Policy # 453

Implementation Date: 8/9/10

Review Dates: 9/15/11, 11/29/12, 12/19/13, 12/18/14, 12/10/15, 12/15/16, 12/21/17, 12/20/18, 3/7/23, 5/14/24

Revision Dates: 4/6/15, 7/1/23, 11/27/23, 12/6/23, 9/9/24

Related Medical Policies:

[#123 Gene Therapy, Testing, and Counseling](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Aortic aneurysms, dissections, and rupture have ranked as high as the 15th major cause of death in the United States, accounting for nearly 15,000 deaths annually. Family studies demonstrate that up to 19% of persons with TAAD without a known genetic syndrome have a first-degree relative with TAAD.

Heritable thoracic and abdominal aneurysm and dissection (TAAD) related disorders are an overlapping group of conditions that result in dilation of the aorta, and, depending on the condition, other vessels with an elevated risk of dissection and rupture. Included in this growing group of conditions are the better-known syndromic forms of aortopathy, including Marfan and Loeys-Dietz syndromes, but the various types of non-syndromic heritable TAAD are also included.

There is significant overlap in clinical features of heritable TAAD-related disorders such that clinical evaluation and family history is often insufficient to diagnose a specific TAAD disorder. Determining which TAAD-associated gene harbors a mutation has direct implications on treatment and surveillance. Given the inability to clinically discern which specific gene mutation may be present, the use of gene panels allows for an accurate and rapid determination of the most appropriate clinical approach to patients.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers panel genetic testing for thoracic and abdominal inherited aortopathy disorders (TAAD) when either I or II are met:

I. Select Health considers panel genetic testing for TAAD as medically necessary, if recommended by Intermountain Heart Institute. (Genes include, but are not limited to: *FBN1*, *LOX*, *COL3A1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *ACTA2*, *MYH11*, *MYLK*, and *PRKG1*);

OR

II. For all other clinicians, Select Health considers panel genetic testing for TAAD as medically necessary, when the following criteria are met:

Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: INHERITABLE COLORECTAL CANCER

Policy # 222

Implementation Date: 4/20/04

Review Dates: 4/14/05, 6/22/06, 7/12/07, 6/11/09, 6/17/10, 8/16/11, 8/16/12, 8/15/13, 6/19/14, 6/11/15, 6/16/16, 9/25/17, 9/17/18, 10/15/19, 1/31/23, 7/12/24

Revision Dates: 6/19/08, 1/16/16, 5/2/17, 9/25/17, 10/2/18, 7/1/23, 7/22/24, 10/29/24, 12/20/24, 1/27/25

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Of the nearly 150,000 cases of colorectal cancer expected to be diagnosed this year in the US, about 5% are inherited. In these cases, mutations in key genes dramatically increase cancer risk. These mutations give rise to multiple colorectal cancer syndromes, including:

- Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer [HNPCC])
- Familial adenomatous polyposis (FAP)
- Attenuated familial adenomatous polyposis (AFAP), a variation of FAP
- MUTYH-associated polyposis (MAP)

Lynch syndrome, the most common syndrome, is caused by a mutation in one of the specific genes responsible for proteins that repair DNA mismatches. Microsatellite instability is a marker for this syndrome. Usually, the colon cancers are located on the right side of the colon. Familial adenomatous polyposis (FAP) and attenuated AFP (AFAP) are the result of mutations in the gene that codes for the key tumor-suppressor protein adenomatous polyposis coli (APC). MUTYH-associated polyposis (MAP) results from mutations in the MUTYH gene that codes for adenine DNA glycosylase which plays a major role in DNA base excision repair. Unlike Lynch syndrome, FAP and AFAP, which are dominantly inherited conditions, MAP is inherited in a recessive manner.

Although Lynch Syndrome, FAP/AFAP, and MAP are biologically different, families affected with these syndromes exhibit accelerated and amplified colorectal carcinogenesis. This is most obvious in the family's history, which features frequent early-onset colorectal cancer. In the case of MAP, however, the family history may not be significant for multiple cases of colorectal cancer. Screening, early prophylactic surgery, close follow-up, and chemoprevention (when appropriate) are important in managing the disease in individual patients. Gene-based tests are used to diagnose susceptibility to these hereditary colorectal cancer syndromes, specifically Lynch syndrome, Familial adenomatous polyposis (FAP), Attenuated FAP (A-FAP), or MUTYH-associated polyposis (MAP).

Multiple molecular testing laboratories offer colon cancer multi-gene panels specific to the needs of a given patient based on personal or family cancer history. These tests include: (1) panels for Lynch Syndrome that includes gene sequence analysis of the MLH1, MSH2, MSH6, EPCAM and PMS2 genes; (2) panels for polyposis syndromes (FAP, AFAP and MAP) that include the APC and MUTYH genes; (3) single site mutation analyses for individuals with known colon cancer gene mutations via previous testing in a family member.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.



Genetic Testing Policies, Continued

Genetic Testing: Inheritable Colorectal Cancer, continued

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

3. Select Health covers multi-gene panel testing for hereditary colorectal cancer (CRC) syndromes* when any of the following criteria are met:

- A. Individuals with personal or family history^a of, at the time of a colonoscopy:

1) ≥ 10 adenomatous polyps

or

2) ≥ 2 hamartomatous polyps

or

3) ≥ 5 serrated polyps/lesions proximal to the rectum

- B. Personal history of:

1) a Lynch syndrome (LS)-related cancer^b or

2) a personal history of a tumor with deficient mismatch repair (dMMR)^c, or

3) a pathogenic/likely pathogenic variant identified on tumor genomic testing clinical implications if also identified in the germline

4) a Lynch syndrome-related cancer with a diagnosis of a second Lynch syndrome-related cancer in the same individual, regardless of age.

OR

- C. Family history of:

1) Colon and/or uterine cancer under age 50^b or

2) a personal history of a tumor with deficient mismatch repair (dMMR)^c, or

3) a pathogenic/likely pathogenic mutation in LS associated genes, or

4) an individual with a Lynch syndrome-related cancer with a diagnosis of a second Lynch syndrome-related cancer in the same individual, regardless of age.

OR

- D. Two or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer, one of whom was diagnosed before age 50.

OR

- E. Three or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer, regardless of age.

OR

- F. Personal or family history of one or more of the following: congenital hypertrophy of retinal pigment

Genetic Testing Policies, Continued

Genetic Testing: Inheritable Colorectal Cancer, continued

epithelium (CHRPE), desmoid tumor, or papillary thyroid cancer.

- a- Personal or family history of polyps is based on cumulative lifetime history of adenomas, hamartomas, and/or serrated polyps/lesions in the proband or a single family member.
- b- LS-related cancers include colorectal and endometrial cancer under or at age 50, gastric, ovarian, pancreas, urothelial, brain (usually glioblastoma and medulloblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.
- c- Any tumor at any age that 1) is microsatellite instability-high (MSI-H) by polymerase chain reaction (PCR) or next-generation sequencing (NGS); or 2) has abnormal/ deficient MMR protein expression (dMMR) on immunohistochemistry(IHC) without concurrent MLH1 promoter hypermethylation or BRAF 600E mutation.

***Associated CRC Syndromes:**

- Lynch syndrome
- Classical familial adenomatous polyposis (FAP),
- Attenuated FAP (AFAP), BMPR1A, MUTYH-associated polyposis (MAP)
- Rare genetic causes of multiple adenomatous polyps
- Colonic adenomatous polyposis of unknown etiology (CPUE)
- Puerz-Jeghers syndrome (PJS), Juvenile polyposis syndrome (JPS)
- Cowden/PTEN hamartoma syndrome

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

The evidence related to the effectiveness of gene-based testing for diagnosis, prognosis, and prediction of increased risk of colorectal cancer has been previously reviewed (SelectHealth Tech Assessment November 2001). Additional information obtained from discussions with genetic testing experts since then continues to support these conclusions.

It is now known that Lynch syndrome results from an inherited mutation in 1 of the mismatch repair (MMR) genes. Normally, MMR genes produce proteins that identify and correct base-pairing mismatches that can occur during DNA replication. Consequently, a mutation that inactivates an MMR gene leads to accumulation of other mutations which significantly increases the likelihood of developing cancer. Mutations that disrupt the function of MMR genes (mutations in MLH1, MSH2, MSH6, EPCAM and PMS2) have been linked to Lynch syndrome.

It has been known that germline mutations in MLH1, MSH2, and MSH6 account for most detected mutations in families with Lynch syndrome. More recently it has been discovered that PMS2 and EPCAM also play an important role in Lynch syndrome.

Genetic Testing Policies, Continued

Genetic Testing: Inheritable Colorectal Cancer, continued

As 1 of the 4 primary mismatch repair genes associated with Lynch syndrome, the functional importance of PMS2 has been clear, but its total contribution to Lynch syndrome was historically considered to be quite low. More recent studies suggest that the prevalence of PMS2 mutations is comparable to MSH6, with as much as 15% of all Lynch syndromes attributable to PMS2.

Finally, the EPCAM gene is a recently discovered contributor to Lynch syndrome, accounting for an estimated 1–3% of all detectable Lynch syndrome mutations. Studies indicate that large deletions in the end of this gene, which is located directly "upstream" of MSH2, can lead to a loss of MSH2 expression and result in Lynch syndrome.

Billing/Coding Information

CPT CODES

- 0069U** Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score
- 0101U** Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated [15 genes (sequencing and deletion/duplication), EPCAM and GREM1 (deletion/duplication only)]
- 0130U** Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure)
- 0157U** APC (APC regulator of WNT signaling pathway) (eg, familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0158U** MLH1 (mutL homolog 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0159U** MSH2 (mutS homolog 2) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0160U** MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0161U** PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
- 0162U** Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure)
- 0229U** BCAT1 (Branched chain amino acid transaminase 1) and IKZF1 (IKAROS family zinc finger 1) (eg, colorectal cancer) promoter methylation analysis
- 0235U** PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
- 0238U** Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions

Genetic Testing Policies, Continued

Genetic Testing: Inheritable Colorectal Cancer, continued

- 81201** APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202 APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203 APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81210 BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81288 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81292 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293 ;known familial variants
81294 ;duplication/deletion variants
81295 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296 ;known familial variants
81297 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary duplication/deletion variants duplication/deletion variants
81298 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299 ;known familial variants
81300 ;duplication/deletion variants
81301 Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81309 PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
81317 PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318 ;known familial variants
81319 ;duplication/deletion variants
81321 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322 PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81327 SEPT9 (Septin9) (eg, colorectal cancer) promoter methylation analysis
81401 Molecular pathology procedure, Level 2
81403 Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons): EPCAM (epithelial cell adhesion molecule) (eg, Lynch syndrome), duplication/deletion analysis

Genetic Testing Policies, Continued

Genetic Testing: Inheritable Colorectal Cancer, continued

- 81406** Molecular pathology procedure, Level 7
- 81435** Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
- 81436**; duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11
- 81445** Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
- 81449** Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
- 81455** Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
- 81456** Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
- 81479** Unlisted molecular pathology procedure
- 81528** Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result

Key References

1. NCCN Guidelines. Colorectal Cancer Screening. Version 3.2022 – September 30, 2022.
2. NCCN Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. Versions 2.2023 – October 30, 2023.
3. NCCN Guidelines. Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 2.2024 — October 3, 2024.

Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards.
7/22/24	For Commercial Plan Policy, clarified age requirement for qualifying factor of personal history of colorectal cancer: “Personal history of CRC age 50 or under ” and also updated other personal/family history requirements in coverage criteria to align with current clinical standards.
10/29/24	For Commercial Plan Policy, added criterion #B-4, added new criterion #C-1 and #C-2, thereby, making the previous criterion #C-1 and #C-2 as

Genetic Testing Policies, Continued

Genetic Testing: Inheritable Colorectal Cancer, continued

	#C-3 and #C-4, and added new criteria for sections D and E, as well as new criteria section F, to align with NCCN updates.
12/20/24	For Commercial Plan Policy, modified requirements in criterion #1 in first section: "Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history. Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing."

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: LACTOSE INTOLERANCE

Policy # 318

Implementation Date: 8/10/06

Review Dates: 8/23/07, 8/21/08, 8/13/09, 8/19/10, 9/15/11, 11/29/12, 12/19/13, 12/18/14, 12/10/15, 12/15/16, 12/21/17, 12/4/18, 2/14/23, 2/15/24

Revision Dates: 7/1/23

Disclaimer:

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Adult-type hypolactasia (primary lactose malabsorption) is determined by a genetically programmed reduction in lactase activity at the intestinal brush border. It affects most of the world's human population and limits the use of fresh milk due to lactose intolerance. The incidence of lactose malabsorption ranges from 11%–60% in Europe and this condition can cause gastrointestinal symptoms such as abdominal pain, bloating, flatulence, and diarrhea. Lactose intolerance can cause bloating and indigestion from consuming milk or milk products. More than 30 million Americans, mostly African-American or Asian, are prone to the condition. However, the correlation between lactose malabsorption and clinical symptoms is unclear: many malabsorbers are in fact able to tolerate a certain quantity of milk without presenting symptoms, while many cases of self-reported milk-intolerance remain asymptomatic after lactose oral load. The diagnosis of adult-type hypolactasia has been difficult to establish because of unsatisfactory diagnostic methods.

C/T(-13910) single nucleotide polymorphism residing 13910 base pairs from the 5' end of the lactase gene has been shown to be associated with lactase deficiency.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does not cover genetic testing for lactose intolerance as there is a lack of clinical utility as it relates to this testing; this meets the plan's definition of experimental/investigational.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit

Genetic Testing Policies, Continued

Genetic Testing: Lactose Intolerance, continued

their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

Carroccio et al., in their study of 323 subjects in 1998 demonstrated the difficulties identifying patients who have lactose malabsorption but no tolerants, and who have lactose malabsorption and intolerants. They concluded that in studies of the general population, the frequency of lactose intolerance is much lower than that of lactose malabsorption. Gastrointestinal symptoms after lactose load in self-reported milk-intolerants are found in only a very low number of these subjects. However, the lay public is very aware of lactose intolerance as a cause of gastrointestinal distress and often adjusts their diet due to concern about this phenomenon risking inadequate nutritional and calcium intake.

Additionally, the symptoms of lactose malabsorption can be ill-defined dependent upon the level of lactase enzyme activity persisting in an individual. These symptoms are the same presenting symptoms seen in Celiac disease (Sprue), early inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS).

Measurement of lactase and sucrase levels in intestinal biopsy specimens is required for a definitive diagnosis of the condition. However, due to the invasive and costly manner of obtaining these specimens, the diagnosis of intestinal malabsorption of lactose has been confirmed by a test of absorption (e.g., lactose absorption test) or malabsorption (lactose breath hydrogen test). Less direct tests, such as low fecal pH or reducing substances in the stool, are only valid when lactose has been ingested, intestinal transit time is rapid, stools are collected fresh, assays are performed immediately, and bacterial metabolism of colonic carbohydrate is incomplete. These tests, however, had significant limits impairing diagnostic accuracy.

The utility of the lactose tolerance test is limited by many false negative results that may occur in patients with diabetes or bacterial overgrowth. Abnormal gastric emptying also can lead to spurious results; the blood glucose may be relatively higher with rapid emptying and depressed with delayed gastric emptying. In adults, the lactose tolerance test has a sensitivity of 75% and a specificity of 96%. However, it is cumbersome (particularly in children), and time-consuming, and has largely been replaced by the lactose breath hydrogen test.

The lactose breath hydrogen test measures lactose non-absorption. It is simple to perform, noninvasive, and has a sensitivity and specificity that are superior to the absorption test. Both false-positive and false-negative results can occur. False-positive results are seen with inadequate pretest fasting or recent smoking; false-negative results can be seen after the recent use of antibiotics, in patients with lung disorders, or in the approximately 1% of subjects who are nonhydrogen producers. A normal breath hydrogen test does not rule out an intestinal mucosal lesion and should not be used to avoid an intestinal biopsy. A significant proportion of patients with symptoms suggestive of lactose intolerance have normal breath hydrogen tests. In 2 series described above, for example, 30%–42% of subjects with severe symptoms of milk intolerance had normal tests. Other possibilities that must be considered include psychologic factors and intolerance to other factors in milk.

In 2002, Enattah et al. published their findings identifying a DNA variant, C/T-13910, roughly 14 kb upstream from the LCT locus, that completely associates with biochemically verified lactase non-persistence in Finnish families and a sample set of 236 individuals from 4 different populations. A second variant, G/A-22018, 8 kb telomeres to C/T-13910, is also associated with the trait in 229 of 236 cases. Prevalence of the C/T-13910 variant in 1,047 DNA samples is consistent with the reported prevalence of adult-type hypolactasia in 4 different populations.

Rasinpera et al. confirmed this finding in their study published in *Gut* in 2004. In a comparison with lactase enzyme levels obtained during duodenal biopsies as the "gold standard" of lactose malabsorption, the genetic variant with C/C-13910 was associated with low lactase enzyme in the majority of 8-year-old and all children 12 years of age. Sensitivity and specificity were 93% and 100%, respectively, which is comparable to the accuracy of the lactose tolerance test and breath hydrogen tests.

Hogenauer et al., in 2005, confirmed this sensitivity and specificity in their prospective trial comparing the DNA testing to lactose hydrogen breath test. In this study, 97% of patients testing positive for the CC genotype of the -13910 T>C polymorphism suggesting lactase non-persistence also had a positive hydrogen test, 86% with either a TC or a TT genotype suggestive of lactase persistence tested negative

Genetic Testing Policies, Continued

Genetic Testing: Lactose Intolerance, continued

on the hydrogen test. They concluded that DNA testing had an excellent correlation between a CC genotype and a positive hydrogen test, whereas the correlation between a TC or TT genotype and a negative hydrogen test result is less strong. Analysis of the -13910 T/C variant can be considered a good test for predicting the presence of lactase non-persistence in a patient population with suspected lactose malabsorption.

This testing is only available in the U.S. through Prometheus Laboratories Inc. under the name Lacto *TYPE*, as they have an exclusive marketing arrangement with the National Public Health Institute, Finland, who hold the patent on this genetic test.

A November 2015 review of the literature found no new studies to change the recommendation. One study of note was found. Sontonocito and coworkers examined over 1,400 patients and concluded that use of the variants upstream of LPH (C/T-13910 and G/A-22018 mutations) are not useful for routine screening, support the policy stipulation for use in atypical patients who have not been diagnosed by other means.

Billing/Coding Information

CPT CODES

81400 Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)

HCPCS CODES

G0452 Molecular pathology procedure; physician interpretation and report

Key References

1. Carroccio, MD, G. Montalto, G. Cavera, MD, A. Notarbatolo, MD and the Lactase Deficiency Study Group. Lactose Intolerance and Self-Reported Milk Intolerance: Relationship with Lactose Malabsorption and Nutrient Intake. *Journal of the American College of Nutrition*, Vol. 17, No. 6, 631-636 (1998).
2. Chitkara DK, Montgomery RK, Grand RJ, Buler HA. Lactose intolerance. UpToDate ©2006 Last updated July 27, 2005.
3. Enattah NS, Sahl T, Savilahti E, Terwilliger JD, Peltonen L, Jarvela I. Identification of a variant associated with adult-type hypolactasia. *Nat Genet*. 2002 Feb;30(2):233-7. Epub 2002 Jan 14 PMID: 11788828
4. Hogenauer C, Hammer HF, Mellitzer K, Renner W, Krejs GJ, Toplak H. Evaluation of a new DNA test compared with the lactose hydrogen breath test for the diagnosis of lactase non-persistence. *Eur J Gastroenterol Hepatol*. 2005 Mar;17(3):371-6 PMID: 15716664
5. Jarvela IE. Molecular genetics of adult-type hypolactasia. *Ann Med*. 2005;37(3):179-85. PMID: 16019716
6. John R Saltzman, Robert M Russell, Barbara Golner, Susan Barakat, Gerard E Dallal and Barry R Goldin. A randomized trial of Lactobacillus acidophilus BG2FO4 to treat lactose intolerance. *American Journal of Clinical Nutrition*, Vol. 69, No. 1, 140-146, January 1999.
7. Johnson AO, Semenza JG, Buchowski MS, et al. Correlation of lactose malabsorption, lactose intolerance, and milk intolerance. *Am J Clin Nutr* 1993; 57:399.
8. Joseph F, Rosenberg AJ. Identifying lactose malabsorbers through breath hydrogen measurements. *Lab Med* 1986; 17:85.
9. Newcomer AD, McGill DB, Thomas PJ, Hofmann AF. Prospective comparison of indirect methods for detecting lactose deficiency. *N Engl J Med* 1975; 293:1232.
10. Rasinpera H, Savilahti E, Enattah NS, Kuokkanen M, Totterman N, Lindahl H, Jarvela I, Kolho KL. A genetic test which can be used to diagnose adult-type hypolactasia in children. *Gut*. 2004 Nov;53(11):1571-6. PMID: 15479673
11. Santonocito, C., et al. (2015). "Lactose intolerance genetic testing: is it useful as routine screening? Results on 1426 south-central Italy patients." *Clin Chim Acta* 439: 14-17.
12. Suarez FL, Savaiano DA, Levitt MD. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N Engl J Med* 1995; 333:1.
13. Suarez FL, Savaiano D, Arbisi P, Levitt MD. Tolerance to the daily ingestion of two cups of milk by subjects claiming lactose intolerance. *Am J Clin Nutr* 1997; 65:1502.
14. Vesa TH, Seppo LM, Marteau PR, et al. Role of irritable bowel syndrome in subjective lactose intolerance. *Am J Clin Nutr* 1998; 67:710.

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Genetic Testing Policies, Continued

Genetic Testing: Lactose Intolerance, continued

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

Policy # 356

Implementation Date: 6/23/07

Review Dates: 6/19/08, 6/11/09, 6/17/10, 8/16/11, 8/12/12, 8/15/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 6/16/18, 6/8/19, 2/21/23, 2/15/24

Revision Dates: 2/21/19, 7/1/23

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Leber's hereditary optic neuropathy (LHON) is a bilateral optic neuropathy that typically produces severe and permanent visual loss. The disorder occurs predominantly in young adult males. The initial symptoms include visual dysfunction with blurring of vision and loss of central vision, most often beginning in the late teens. Painless vision loss is typically the only symptom of LHON. Affected individuals are usually entirely asymptomatic, until they develop visual blurring and clouding, affecting the central visual field (i.e., a centrocecal scotoma or "blind spot"). These vision problems may begin in one eye or simultaneously in both eyes. However, if vision loss starts in one eye, the other eye is usually affected within several weeks or months. Over time, the blind spot enlarges and vision in both eyes worsens with a severe loss of visual acuity and color vision. Visual acuity is typically reduced to finger-counting in most cases. Although central vision gradually improves in a small percentage of cases, in most cases, the vision loss is profound and permanent.

LHON has a mitochondrial pattern of inheritance. This inheritance pattern applies to genes contained in mitochondrial DNA. Because human egg cells, but not sperm cells, contribute mitochondria to the developing embryo, only females pass mitochondrial conditions to their children. Pathogenic variants in the following genes have been associated with LHON: *MT-ND1*, *MT-ND2*, *MT-ND3*, *MT-ND4*, *MT-ND4L*, *MT-ND5*, *MT-ND6*, *MT-ATP6*, *MT-CO3*, *MT-CO1*, *MT-ATP6*, and *MT-CYB*.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers genetic testing for Leber's hereditary optic neuropathy (LHON) in limited circumstances when standard clinical exams, genetic counseling, and conventional diagnostic studies do not provide a definitive diagnosis.



Genetic Testing Policies, Continued

Genetic Testing: Leber's Hereditary Optic Neuropathy (LHON), continued

Any other circumstances for this testing meet the plan's definition of experimental/investigational.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

The limited research evidence examining the clinical use of genetic testing for LHON suggests that this testing may be most useful in specific situations involving atypical symptoms without a clear pattern of maternal inheritance. For patients with typical signs and maternal inheritance, genetic testing is likely unnecessary for establishing a diagnosis of LHON. In terms of predictive testing, the incomplete penetrance of LHON mutations limits the prognostic value of positive test results, particularly in females in whom penetrance is only about 10%. Penetrance is higher in males, though, still only around 50%. De novo mutations are rare in LHON and confer no risk to siblings or parents. A male (affected or unaffected) with a primary LHON-causing mtDNA mutation cannot transmit the mutation to any of his offspring. A female (affected or unaffected) with a primary LHON-causing mtDNA mutation will transmit the mutation to all of her offspring. But again, presence of a mutation in an asymptomatic individual does not predict occurrence, age of onset, or severity of diseases. A negative test result confers a high likelihood of not developing symptoms, and thus, may be informative in cases where a clear family history is not evident. In most cases, however, clinical and family history are likely sufficient to establish risk for developing LHON.

Billing/Coding Information

CPT CODES

- | | |
|--------------|--|
| 81401 | Molecular Path Level 2: includes the following genes: MT-TS1, MT-RNR1, MT-ATP6, MT-ND4, MT-ND6, MT-ND5, MT-TL1, MT-TS1, MT-RNR1 |
| 81403 | Molecular Path Level 4: includes the following genes: MT-RNR1, MT-TS1 |
| 81434 | Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A |
| 81460 | Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection |

Genetic Testing Policies, Continued

Genetic Testing: Leber's Hereditary Optic Neuropathy (LHON), continued

HCPCS CODES

G0452 Molecular pathology procedure; physician interpretation and report

Key References

1. Achilli, A., et al. (2012). "Rare primary mitochondrial DNA mutations and probable synergistic variants in Leber's hereditary optic neuropathy." *PLoS One*, 7(8): e42242.
2. Cavelier L, Gyllensten U, Dahl N. "Intrafamilial variation in Leber hereditary optic neuropathy revealed by direct mutation analysis." *Clin Genet*, 43.2 (1993): 69-72.
3. . Hereditary neuropathies associated with hereditary disorders. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Available: <https://www.uptodate.com/contents/hereditary-disorders-associated-with-hereditary-disorders>. Date Accessed: February 15, 2024.
4. MedlinePlus Genetics. Leber hereditary optic neuropathy. 2007. National Library of Medicine. Available: <https://medlineplus.gov/genetics/condition/leber-hereditary-optic-neuropathy/>. Date Accessed: February 15, 2024.
5. Harding AE, Sweeney MG, Govan GG, Riordan-Eva P. "Pedigree analysis in Leber hereditary optic neuropathy families with a pathogenic mtDNA mutation." *Am J Hum Genet*, 57.1 (1995): 77-86.
6. Macmillan C, Kirkham T, Fu K, et al. "Pedigree analysis of French Canadian families with T14484C Leber's hereditary optic neuropathy." *Neurology*, 50.2 (1998): 417-22.
7. Man PY, Turnbull DM, Chinnery PF. "Leber hereditary optic neuropathy." *J Med Genet* 39.3 (2002): 162-9.
8. Seedorff T. "The inheritance of Leber's disease. A genealogical follow-up study." *Acta Ophthalmol (Copenh)*, 63.2 (1985): 135-45.
9. Yu-Wai-Man P, Chinnery PF. Leber Hereditary Optic Neuropathy. 2000 Oct 26 [Updated 2021 Mar 11]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available: <https://www.ncbi.nlm.nih.gov/books/NBK1174/> Date Accessed: February 15, 2024.

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: LONG QT SYNDROME

Policy # 385

Implementation Date: 11/12/07

Review Dates: 10/23/08, 12/17/09, 10/21/10, 10/13/11, 11/29/12, 12/19/13, 12/10/15, 6/15/17, 7/20/18, 6/13/19, 2/21/23, 2/15/24

Revision Dates: 12/29/15, 6/30/16, 7/1/23, 12/6/23, 7/26/24

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG) and an increased risk of sudden cardiac death. A range of dysrhythmias can occur with LQTS, the most common being torsade de pointes (TdP), a form of polymorphic ventricular tachycardia (VT). In the specific case of TdP, these variations take the form of a progressive, sinusoidal, cyclic alteration of the QRS axis. The peaks of the QRS complexes appear to twist around the isoelectric line of the recording; hence the name torsade de pointes or "twisting of the points."

Bradycardia (a resting heart rate less than 60 beats/min) is also common in patients with LQTS (20%–31% in recent registry studies). Bradycardia appears to be more common in children during the first 3 years of life and has been reported in fetuses and neonates with LQTS.

Long QT syndrome may be either genetic or acquired. Acquired LQTS usually results from drug therapy, hypokalemia, or hypomagnesemia. Congenital LQTS is associated with 13 genes and two clinical phenotypes have been described that vary with the type of inheritance and the presence or absence of sensorineural hearing loss.

- The more common, autosomal dominant form, **Romano-Ward syndrome**, is characterized by QT prolongation and T-wave abnormalities on the ECG, associated with tachyarrhythmias that include the ventricular tachycardia TdP, which may degenerate into ventricular fibrillation. TdP is usually self-terminating, thus, causing a syncopal event, the most common symptom in Romano-Ward syndrome.
- **Jervell and Lange-Nielsen syndrome (JLNS)**, the autosomal recessive form of LQTS, is characterized by congenital profound bilateral sensorineural hearing loss and long QTc, usually greater than 500 ms. Prolongation of the QTc interval is associated with tachyarrhythmias, including ventricular tachycardia, episodes of TdP tachycardia, and ventricular fibrillation, which may culminate in syncope or sudden death. The classic presentation of JLNS is a deaf child who experiences syncopal episodes during periods of stress, exercise, or fright. 50% of individuals had cardiac events before age 3 years.

Prolonged QT interval is an essential component of the diagnosis of LQTS. Under normal circumstances, the duration of repolarization depends upon the heart rate. The QT interval is longer at slower rates and shorter at faster rates. As a result, the QT interval is often corrected for heart rate (or the duration of the R-R interval) using a common formula: Corrected QT (QTc) = QT interval ÷ square root of the R-R interval (in sec). While there are many ways of calculating the QTc, the most common method is the Bazett formula as described above.



Genetic Testing Policies, Continued

Genetic Testing: Long QT Syndrome, continued

Testing should be performed using the updated Heart Rhythm Society/European Heart Rhythm Association Expert Consensus Recommendations on LQTS Genetic Testing.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers genetic testing for long QT syndrome (LQTS) when either I or II are met:

I. Select Health considers genetic testing for LQTS as medically necessary, if recommended by Intermountain Heart Institute;

OR

II. For all other clinicians, Select Health considers genetic testing for LQTS as medically necessary, when the following criteria are met:

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

AND when the following criteria are met:

3. Select Health covers genetic testing for LQTS in *limited* clinical circumstances. Clinical circumstances in which LQTS Genetic Testing is covered, include any of the following:

- A. Comprehensive LQTS genetic testing by multi-gene next generation sequencing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype; or
- B. Comprehensive LQTS genetic testing is recommended for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, medications, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc > 450 ms in individuals assigned male at birth or children 12 years and younger and > 460 ms in individuals assigned female at birth; or
- C. Testing for a known pathogenic familial variant in appropriate relatives.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp> or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health

Genetic Testing Policies, Continued

Genetic Testing: Long QT Syndrome, continued

Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

There exist few articles discussing the relevance of genetic testing for Long QT Syndrome. The most significant articles are: *The Long QT Family of Cardiac Ion Channelopathies and Genetic Testing in the Long QT syndrome*. Both articles focus on the insensitivity of the routine ECG in accurately diagnosing a prolonged QTc. The availability of clinical studies on a large series of genotyped patients with LQTS has highlighted major locus specific differences in the prognosis, and in response to therapy it has shown that carriers of LQTS mutations with a normal QTc who cannot be identified by clinical evaluation have a 10% probability of cardiac events by age 40 years if they are not appropriately treated. These data provide a rational for moving genetic analysis from research to diagnostic laboratories and highlight the need for defining optimal screening strategies to make genetic analysis clinically available, efficient, and potentially affordable.

A recent American College of Cardiology/American Heart Association position paper states that the use of β-blocker therapy is appropriate in patients whose molecular testing is positive, thus, supporting the use of genetic testing in this syndrome. Even though the accuracy of genetic testing is 70% in the most common genotypes, the authors suggest that this test is much more predictive than other older tests which have a high false-negative rate.

Billing/Coding Information

Covered: *For the conditions outlined above*

CPT CODES

Effective 1/01/17 Possibly covered for Commercial, Covered PA for Medicare & Not Covered for Medicaid

0237U	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) [when specified as the following]: F2 (coagulation factor 2) (eg, hereditary hypercoagulability), 1199G>A variant
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) [when specified as the following]: CFH/ARMS2 (complement factor H/age-related maculopathy susceptibility 2) (eg, macular degeneration), common variants (eg, Y402H [CFH], A69S [ARMS2])
81402	Tier 2 Molecular Pathology Procedures
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) [when specified as the following]: ANG (angiogenin, ribonuclease, RNase A family, 5) (eg, amyotrophic lateral sclerosis), full gene sequence GJB1 (gap junction protein, beta 1) (eg, Charcot-Marie-Tooth X-linked), full gene sequence
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) [when specified as the following]: EGR2 (early growth response 2) (eg, Charcot-Marie-Tooth), full gene sequence HSPB1 (heat shock 27kDa protein 1) (eg, Charcot-Marie-Tooth disease), full gene sequence LITAF (lipopolysaccharide-induced TNF factor) (eg, Charcot-

Genetic Testing Policies, Continued

Genetic Testing: Long QT Syndrome, continued

- Marie-Tooth), full gene sequence SCN1B (sodium channel, voltage-gated, type 1, beta) (eg, Brugada syndrome), full gene sequence SOD1 (superoxide dismutase 1, soluble) (eg, amyotrophic lateral sclerosis), full gene sequence
- 81405** Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) [when specified as the following]: ANKRD1 (ankyrin repeat domain 1) (eg, dilated cardiomyopathy), full gene sequence GDAP1 (ganglioside-induced differentiation-associated protein 1) (eg, Charcot-Marie-Tooth disease), full gene sequence HTRA1 (HtrA serine peptidase 1) (eg, macular degeneration), full gene sequence MPZ (myelin protein zero) (eg, Charcot-Marie-Tooth), full gene sequence NEFL (neurofilament, light polypeptide) (eg, Charcot-Marie-Tooth), full gene sequence PRX (periaxin) (eg, Charcot-Marie-Tooth disease), full gene sequence PSEN1 (presenilin 1) (eg, Alzheimer disease), full gene sequence RAB7A (RAB7A, member RAS oncogene family) (eg, Charcot-Marie-Tooth disease), full gene sequence TARDBP (TAR DNA binding protein) (eg, amyotrophic lateral sclerosis), full gene sequence
- 81406** Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]: APP (amyloid beta [A4] precursor protein) (eg, Alzheimer disease), full gene sequence CACNB2 (calcium channel, voltage-dependent, beta 2 subunit) (eg, Brugada syndrome), full gene sequence FIG4 (FIG4 homolog, SAC1 lipid phosphatase domain containing [S. cerevisiae]) (eg, Charcot-Marie-Tooth disease), full gene sequence FUS (fused in sarcoma) (eg, amyotrophic lateral sclerosis), full gene sequence GARS (glycyl-tRNA synthetase) (eg, Charcot-Marie-Tooth disease), full gene sequence GRN (granulin) (eg, frontotemporal dementia), full gene sequence JUP (junction plakoglobin) (eg, arrhythmogenic right ventricular dysplasia/ cardiomyopathy 11), full gene sequence LDB3 (LIM domain binding 3) (eg, familial dilated cardiomyopathy, myofibrillar myopathy), full gene sequence MAPT (microtubule-associated protein tau) (eg, frontotemporal dementia), full gene sequence MFN2 (mitofusin 2) (eg, Charcot-Marie-Tooth disease), full gene sequence OPTN (optineurin) (eg, amyotrophic lateral sclerosis), full gene sequence PSEN2 (presenilin 2 [Alzheimer disease 4]) (eg, Alzheimer disease), full gene sequence SH3TC2 (SHE domain and tetratricopeptide repeats 2) (eg, Charcot-Marie-Tooth disease), full gene sequence
- 81407** Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) [when specified as the following]: APOB (apolipoprotein B) (eg, familial hypercholesterolemia type B), full gene sequence MYBPC3 (myosin binding protein C, cardiac) (eg, familial hypertrophic cardiomyopathy), full gene sequence [for HCM, DCM testing] MYH7 (myosin, heavy chain 7, cardiac muscle, beta) (eg, familial hypertrophic cardiomyopathy, Liang distal myopathy), full gene sequence [for HCM testing] SCN5A (sodium channel, voltage-gated, type V, alpha subunit) (eg, familial dilated cardiomyopathy), full gene sequence [for long QT and Brugada syndrome testing only] TSC2 (tuberous sclerosis 2) (eg, tuberous sclerosis), full gene sequence
- 81408** Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) [when specified as the following]: FBN1 (fibrillin 1) (eg, Marfan syndrome), full gene sequence RYR1 (ryanodine receptor 1, skeletal) (eg, malignant hyperthermia), full gene sequence RYR2 (ryanodine receptor 2 [cardiac]) (eg, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia), full gene sequence or targeted sequence analysis of >50 exons [for CPVT testing only]
- 81413** Cardiac ion channelopathies (e.g, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence

Genetic Testing Policies, Continued

Genetic Testing: Long QT Syndrome, continued

	analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
81414	Cardiac ion channelopathies (e.g. Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ
81479	Unlisted molecular pathology procedure

HCPCS CODES

No specific codes identified

Key References

1. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin Wilde AAM, Semsari C, Marquez MF, et al. (2022). American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. *J Arrhythm.* 38(4):491-553.
2. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. (2022). 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J.* 43(40):3997-4126.
3. Al-Khatib, SM, Stevenson, WG, Ackerman, MJ, et al. (2018). 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Circulation.* 138:e272–e391
4. Krahn, AD, Laksman, Z, Sy, RW, et al. (2022). Congenital Long QT Syndrome. *JACC Clin Electrophysiol.* 8(5):687-706.
5. Tranebjærg, L, Samson, RA, Green, GE. Jervell and Lange-Nielsen Syndrome. 2002 Jul 29 [Updated 2017 Aug 17]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1405/> Date Accessed: February 15, 2024.
6. Alders, M, Bikker, H, Christiaans, I. Long QT Syndrome. 2003 Feb 20 [Updated 2018 Feb 8]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle; 1993-2024. Available: <https://www.ncbi.nlm.nih.gov/books/NBK1129/> Date Accessed: February 15, 2024
7. Wilde, AAM, Amin, AS, Postema, PG. (2022). Diagnosis, management and therapeutic strategies for congenital long QT syndrome. *108(5):332-338.*
8. Michell, LB. (2023). Long QT Interval Syndromes. In *Merck Manual Professional Version*. Merck & Co., Inc. Available: <https://www.merckmanuals.com/professional/cardiovascular-disorders/arrhythmogenic-cardiac-disorders/isolated-progressive-cardiac-conduction-disease> Accessed: February 15, 2024
9. Priori SG, Wilde AA, Horie M, Cho Y, et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europac.* 2013 Oct;15(10):1389-406.
10. Priori, S, Napolitano, C., Schwartz, PJ., Grillo, M., Bloise, R., Ronchetti, E., et al. (2004). Association of long QT syndrome loci and cardiac events among patients treated with beta blockers. *JAMA.* 292. 11:1341-1344.
11. Schwartz, P, Priori, SG., Spazzolini, C., Moss, AJ., Vincent, GM., Napolitano, C., Denjoy I., et al. (2001). Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation.* 103. 1:89-95.
12. Schwartz, PJ. (2005). Management of long QT syndrome. *Nat Clin Pract Cardiovasc Med.* 2. 7:346-51.
13. Schwartz PJ, Ackerman MJ, George AL Jr, Wilde AA. Impact of genetics on the clinical management of channelopathies. *J Am Coll Cardiol.* 2013 Jul 16;62(3):169-80.
14. Schwartz, PJ, Ackerman, MJ.. Congenital long QT syndrome: Epidemiology and clinical manifestations. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Available: <https://www.uptodate.com/contents/congenital-long-qt-syndrome-epidemiology-and-clinical-manifestations> Accessed Date: February 15, 2024
15. Schwartz, PJ, Ackerman, MJ. Congenital long QT syndrome: Diagnosis. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Available: <https://www.uptodate.com/contents/congenital-long-qt-syndrome-diagnosis> Accessed Date: February 15, 2024
16. Ackerman, MJ, Schwartz, PJ. Congenital long QT syndrome: Pathophysiology and genetics. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Available: <https://www.uptodate.com/contents/1009#> Date Accessed: February 15, 2024
17. Berul, CI. Acquired long QT syndrome: Definitions, pathophysiology, and causes. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Available: <https://www.uptodate.com/contents/acquired-long-qt-syndrome-definitions-pathophysiology-and-causes>. Date Accessed: February 15, 2024.
18. Berul, CI. Acquired long QT syndrome: Clinical manifestations, diagnosis, and management. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Available: <https://www.uptodate.com/contents/acquired-long-qt-syndrome-clinical-manifestations-diagnosis-and-management> Date Accessed: February 15, 2024.

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Genetic Testing Policies, Continued

Genetic Testing: Long QT Syndrome, continued

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: LYMPHOPROLIFERATIVE DISORDERS

Policy # 685

Implementation Date: 8/14/24

Review Dates:

Revision Dates:

Related Medical Policies:

[#668: Genetic Testing: Myeloid Neoplasms](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Lymphoproliferative disorders encompass a large and diverse group of clonal lymphoid neoplasms with distinct clinicopathologic features. Current classification schemes (WHO 5th edition, ICC 2022) incorporate a combination of morphologic, immunophenotypic, cytogenetic, and molecular features to classify these entities, allowing for more accurate prognostication and therapeutic decisions. Current classification systems group these disease entities into multiple categories of which broadly include: 1) Small B-cell lymphomas, 2) plasma cell neoplasms, 3) large B-cell lymphomas, 4) mature T-cell and NK-cell lymphomas, 5) Hodgkin lymphomas, and 6) precursor B-cell and T-cell leukemias/lymphomas (i.e., acute lymphoblastic leukemias/lymphomas). For the purposes of this policy only neoplasms that commonly require molecular studies will be included/discussed.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when recommended by a genetic counselor, medical geneticist, or other provider with recognized expertise in this area; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers the following groups of molecular studies when the following criteria are met for each group:

A. Small B-Cell Lymphomas

Select Health covers the following molecular studies in the workup of small B-cell lymphomas (e.g., follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone lymphoma (MZL), Hairy cell leukemia (HCL), splenic B-cell lymphomas, lymphoplasmacytic lymphoma (LPL), mantle cell lymphoma (MCL)):

1. IGHV (immunoglobulin heavy chain variable region genes) mutation analysis by sequencing (MCL, CLL/SLL, HCL).
2. TP53 somatic mutation testing (MCL, CLL/SLL).
 - a. May be performed as an individual standalone test or as part of a small lymphoid-specific NGS panel (e.g., CLL NGS panel at ARUP, NeoTYPE CLL profile).

Genetic Testing Policies, Continued

Genetic Testing: Lymphoproliferative Disorders, continued

- b. NeoTYPE CLL profile may be performed with and without the FISH probes. The FISH probes are most appropriate in cases of CLL/SLL, though they may be helpful when the differential includes both CLL/SLL and MCL.
3. BRAF V600 mutation detection by PCR (HCL).
4. MYD88 L265P by PCR (LPL, MZL, IgM MGUS)
 - a. MYD88 L265P is present in most cases of LPL but may be used to assist in the workup when the differential includes both MZL and LPL)
 - b. CLL mutation panel by NGS or other similar panel that includes MYD88 and CXCR4 is considered acceptable
5. CXCR4 mutation analysis (LPL/Waldenstroms macroglobulinemia).
 - a. CLL mutation panel by NGS or other similar panel that includes MYD88 and CXCR4 is considered acceptable

B. Mature T-Cell lymphomas

Select Health covers the following studies in the work-up for mature T-cell lymphomas that may include, but are not limited to T-cell large granular lymphocytic leukemia (T-cell LGL) and peripheral T-cell lymphomas:

1. T-cell clonality screening by PCR (acceptable for all suspected T-cell neoplasms).
2. NGS panel that includes STAT3 and STAT5B (T-cell LGL).

C. B-Lymphoblastic Leukemia/Lymphoma

Select Health covers the following molecular studies in the work-up for B-lymphoblastic leukemia/lymphoma (B-ALL):

1. BCR-ABL1, quantitative and/or qualitative RT-PCR studies.
2. Cytogenomic SNP microarray.
3. ClonoSeq ID and MRD testing.
4. Comprehensive NGS* panel that includes both DNA and RNA sequencing.
 - a. If a recurrent fusion is detected then quantitative RT-PCR studies should be covered, if available, as they may be used in the monitoring of minimal residual disease.

*Given the importance of identifying recurrent fusions in this disease category the utilization of an NGS panel that detects fusion events is required (i.e., NeoGenomics Neo Comprehensive-Heme cancers, FoundationOne Heme panel).

D. T-Lymphoblastic Leukemia/Lymphoma

Select Health covers the following molecular studies in the work-up of patients with T-lymphoblastic leukemia/lymphoma.

1. Cytogenomic SNP microarray.
2. Comprehensive NGS* panel that includes both DNA and RNA sequencing.
 - a. If a recurrent fusion is detected then quantitative RT-PCR studies should be covered, if available, as they may be used in the monitoring of minimal residual disease.

*Given the importance of identifying recurrent fusions in this disease category the utilization of an NGS panel that detects fusion events is required (i.e., NeoGenomics Neo Comprehensive-Heme cancers, FoundationOne Heme panel).

Genetic Testing Policies, Continued

Genetic Testing: Lymphoproliferative Disorders, continued

E. Acute Leukemia of Mixed or Ambiguous Lineage

Select Health covers the following studies in the work-up of acute myeloid leukemia that is of mixed or ambiguous lineage:

1. Comprehensive NGS panel that includes both DNA and RNA sequencing (e.g., NeoGenomics Neo Comprehensive-Heme cancers, FoundationOne Heme panel)
2. If a recurrent fusion is detected then quantitative RT-PCR studies should be covered, if available, as they may be used in the monitoring of minimal residual disease.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Billing/Coding Information

CPT CODES

0171U Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence

0306U Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient-specific panel for future comparisons to evaluate for MRD

0307U Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD

0340U Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence

0364U Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate

81206 BCR/ABL (T(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative

81207 BCR/ABL1 (T(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative

Genetic Testing Policies, Continued

Genetic Testing: Lymphoproliferative Disorders, continued

81208 BCR/ABL1 (T(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative

81210 BRAF (V-RAF murine sarcoma viral oncogene homolog B1) (eg, colon cancer) gene analysis, V600 variant

81229 Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis

81261 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)

81263 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis

81264 IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

81277 Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities

81278 IGH@/BCL2 (t(14;18)) (eg, follicular lymphoma) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints, qualitative or quantitative

81305 MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant

81342 TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

81351 TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence

81352 TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)

81353 TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant

81404 Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)

81405 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)

81445 Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

81449 Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis

Genetic Testing Policies, Continued

Genetic Testing: Lymphoproliferative Disorders, continued

81450 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed

81451 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

81456 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

81479 Unlisted molecular pathology procedure

Key References

1. Intermountain Precision Genomics. Genetic Testing for Myeloproliferative Neoplasms. June 2023.

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MEDICAL POLICY

GENETIC TESTING: METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) POLYMORPHISMS IN CANCER, CARDIOVASCULAR DISEASE, AND NEURAL TUBE DEFECTS

Policy # 426

Implementation Date: 10/12/09

Review Dates: 2/17/11, 2/16/12, 4/25/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 12/19/18, 3/1/23, 6/6/24

Revision Dates: 7/1/23

Related Medical Policies:

[#123 Gene Therapy, Testing, and Counseling](#)

[#590 Pharmacogenomic Testing for Drug Metabolism](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme encoded by the MTHFR gene which is involved in the folate metabolism pathway. Autosomal recessive pathogenic mutations in the MTHFR gene can cause MTHFR deficiency (homocystinuria), a rare disorder characterized by reduced homocysteine levels, developmental delay, and neurological problems (such as seizures).

Two common *MTHFR* polymorphisms in the general population, C677T and A1298C, have been proposed as risk factors for a variety of complex medical conditions including folate metabolism (neural tube defects, pregnancy loss), cardiovascular disease (specifically thromboembolism), cancer risk.

The American College of Medical Genetics and Genomics (ACMG) issued a practice guideline stating that there is a lack of evidence for MTHFR polymorphism testing in the setting of thrombophilia, a family member with a known polymorphism, or dosing of folic acid supplementation in pregnancy*. Additionally, this testing was not recommended as part of the Choosing Wisely campaign. The American College of Obstetrics and Gynecologists (ACOG) does not recommend MTHFR polymorphism testing in pregnancy.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover genetic testing for the methylenetetrahydrofolate reductase (MTHFR) polymorphisms. There is a lack of clinical outcome data demonstrating the clinical utility of MTHFR polymorphism testing; therefore, this is considered experimental/investigational.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website

Genetic Testing Policies, Continued

Genetic Testing: Methylenetetrahydrofolate Reductase (MTHFR) Polymorphisms In Cancer, Cardiovascular Disease, and Neural Tube Defects. continued

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

One systematic review addressed one aspect of the MTHFR mutation. Their focus was on the role of the enzyme in thromboembolism and homocysteinemia. Homocysteinemia has been proposed to increase the rate of thromboembolism.

Pertinent literature discussing the comparative testing approach for homocysteinemia using MTHFR or other biochemical end products, which include homocysteine, are not available. Most of the literature discusses the potential role of homocysteine as a mediator in cardiovascular disease, cancer, and neural tube defects. It is noted the literature poses unanswered questions related to the need for MTHFR testing as there is the lack of scientific evidence to explain the clinical outcomes observed in patients with polymorphisms. Specifically, questions remain unanswered as to how MTHFR polymorphisms are associated with an increase in the rate of NT defects; the role of homocysteine in the process is unclear.

Articles concerning cancer and MTHFR polymorphisms demonstrate both an increase and decrease in cancer rates/risk depending on the circumstance. Regardless of the association between MTHFR polymorphisms and cancer risk, there are currently no clear clinical pathways leading to improvements in patient outcomes. Outcome studies comparing genetic testing with biochemical markers are not available.

A 2014 review of the literature found limited new data regarding the utility of MTHFR testing. Cohen et al. (2013), in a study of over-utilization of MTHFR genotyping took as fact that: "The methylene tetrahydrofolate reductase (MTHFR) C677T variant has been demonstrated to have negligible utility in patient management" based on expert practice guidelines from the College of American Pathologists (Eldibany et al., 2007) and the American College of Medical Genetics (Hickey et al., 2013) that recommend against MTHFR testing in thrombophilia. Additionally, the expert consensus recommendations from American Heart Association continue to suggest that testing may be appropriate only in the setting of hyperhomocysteinemia (Varga et al., 2005), however no new evidence to support this has been published. No new publications demonstrating utility in neural tube defects or cancer were found. Thus, evidence remains insufficient to recommend coverage of MTHFR for any condition.

Billing/Coding Information

Not covered: Experimental/Investigational/Unproven for this indication

CPT CODES

0078U	Pain management (opioid-use disorder) genotyping panel, 16 common variants (ie, ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A, HTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder
81291	MTHFR (5, 10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report
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Key References

1. ACOG Practice Bulletin No. 138: Inherited thrombophilias in pregnancy. *Obstet Gynecol*, 2013. 122:706–717.
2. Eldibany, M. M. and J. A. Caprini (2007). "Hyperhomocysteinemia and thrombosis: an overview." *Arch Pathol Lab Med* 131(6): 872-884.
3. Hickey, S. E., et al. American College of Medical Genetics and Genomics Practice Guideline: lack of evidence for MTHFR polymorphism testing, *Genet Med* 2013;15(2):153–156). <https://www.acmg.net/docs/MTHFRgm2012165aFeb2013.pdf>.

Genetic Testing Policies, Continued

Genetic Testing: Methylenetetrahydrofolate Reductase (MTHFR) Polymorphisms In Cancer, Cardiovascular Disease, and Neural Tube Defects, continued

4. Levin BL, Varga E. MTHFR: Addressing Genetic Counseling Dilemmas Using Evidence-Based Literature. *J Genet Couns.* 2016 Oct;25(5):901-11. PMID: 27130656.
5. Moll S, Varga EA. Homocysteine and MTHFR Mutations. *Circulation.* 2015 Jul 7;132(1): e6-9. doi: 10.1161/CIRCULATIONAHA.114.013311. PMID: 26149435.
6. Varga, E. A., et al. (2005). "Cardiology patient pages. Homocysteine and MTHFR mutations: relation to thrombosis and coronary artery disease." *Circulation* 111(19): e289-293.

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: MINIMAL RESIDUAL DISEASE (MRD) ASSESSMENT

Policy # 673

Implementation Date: 7/21/23

Review Dates:

Revision Dates:

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Minimal residual disease, also called measurable residual disease or MRD, refers to the subclinical levels of residual diseases, such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and multiple myeloma (MM). MRD is a postdiagnosis, prognostic indicator that can be used for risk stratification and to guide therapeutic options when used alongside other clinical and molecular data. Many different techniques have been developed to detect residual disease. However, PCR-based techniques, multicolor flow cytometry, and deep sequencing based MRD generally provide better sensitivity, specificity, reproducibility, and applicability than other techniques, such as fluorescence in situ hybridization (FISH), Southern blotting, or cell culture.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.
3. Select Health covers minimal residual disease (MRD) assessment for specific hematologic malignancies, including:
 - a) acute myeloid leukemia (AML)
 - b) acute lymphoblastic leukemias
 - c) chronic lymphocytic leukemia (CLL)
 - d) chronic myeloid leukemia (CML)
 - e) multiple myeloma
4. Select Health will also cover MRD assessment in other similar clinical circumstances (such as in the context of clinical trials) in other hematologic malignancies (e.g., hairy cell leukemia, some myeloid/lymphoid neoplasms with eosinophilia, follicular lymphoma, and mantle cell lymphoma).

Genetic Testing Policies, Continued

Genetic Testing: Minimal Residual Disease (MRD) Assessment, continued

The use of MRD assessment is considered experimental/investigational for other conditions, including breast and colon cancer.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the **Select Health Commercial policy applies**. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the **Select Health Commercial criteria will apply**. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Billing/Coding Information

CPT CODES

Covered for the indications listed above when criteria are met

- 81479** Unlisted molecular pathology procedure [when specified as NGS tumor DNA testing for MRD]
- 81599** Unlisted multianalyte assay with algorithmic analysis [when specified as NGS tumor DNA testing for MRD]
- 0364U** Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate clonoSEQ® Assay, Adaptive Biotechnologies
- 0306U** Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient-specific panel for future comparisons to evaluate for MRD
- 0307U** Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD

Not Covered for the indications listed above

- 0340U** Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate
- 0453U** Oncology (colorectal cancer), cellfree DNA (cfDNA), methylationbased quantitative PCR assay (SEPTIN9, IKZF1, BCAT1, Septin9-2, VAV3, BCAN), plasma, reported as presence or absence of circulating tumor DNA (ctDNA)

Genetic Testing Policies, Continued

Genetic Testing: Minimal Residual Disease (MRD) Assessment, continued

Key References

1. ARUP Laboratories. Minimal Residual Disease Testing. Available at: <https://arupconsult.com/content/minimal-residual-disease-testing>
2. Horton, T. M., & Steuber, C. P. (2022, June 10). Risk group stratification and prognosis for acute lymphoblastic leukemia/lymphoblastic lymphoma in children and adolescents. Available at: <https://www.uptodate.com/contents/risk-group-stratification-and-prognosis-for-acute-lymphoblastic-leukemia-lymphoblastic-lymphoma-in-children-and-adolescents>
3. Larson, R. A. (2020, April 17). Remission criteria in acute myeloid leukemia and monitoring for residual disease. Available at: <https://www.uptodate.com/contents/remission-criteria-in-acute-myeloid-leukemia-and-monitoring-for-residual-disease>
4. Rajkumar, S. V. (2022, May 27). Multiple myeloma: Evaluating response to treatment. Available at: <https://www.uptodate.com/contents/multiple-myeloma-evaluating-response-to-treatment>
5. Stock, W., & Estrov, Z. (2020a, 02/14/2020). Clinical use of measurable residual disease detection in acute lymphoblastic leukemia. Available at: <https://www.uptodate.com/contents/clinical-use-of-measurable-residual-disease-detection-in-acute-lymphoblastic-leukemia>
6. Stock, W., & Estrov, Z. (2020b, 04/21/2020). Detection of measurable residual disease in acute lymphoblastic leukemia. Available at: <https://www.uptodate.com/contents/detection-of-measurable-residual-disease-in-acute-lymphoblastic-leukemia>
7. Stock, W., & Estrov, Z. (2020b, 04/21/2020). Detection of measurable residual disease in acute lymphoblastic leukemia. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10092948/>

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MEDICAL POLICY

GENETIC TESTING: MYELOID NEOPLASMS

Policy # 668

Implementation Date: 7/1/23

Review Dates: 7/16/24

Revision Dates: 11/8/23, 7/22/24, 9/30/24, 10/29/24

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Myeloid neoplasms encompass a large and diverse group of clonal myeloid neoplasms with distinct clinicopathologic features. Current classification schemes (WHO 5th edition, ICC 2022) incorporate a combination of clinical, morphological, immunophenotypic, cytogenetic, and molecular features to classify these entities allowing for more accurate prognostication and therapeutic decisions. Current classification systems group these disease entities into categories of which include: 1) myeloproliferative neoplasms, 2) mastocytosis, 3) myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement, 4) myelodysplastic/myeloproliferative neoplasms, 5) myelodysplastic syndromes, 6) acute myeloid leukemia and related precursor neoplasms, and 7) acute leukemia is of mixed or ambiguous lineage.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when recommended by a genetic counselor, medical geneticist, or other provider with recognized expertise in this area; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Select Health covers the following groups of molecular studies when the following criteria are met for each group:

A. Myeloproliferative Neoplasms

Select Health covers the following molecular studies in the workup and monitoring of myeloproliferative neoplasms:

1. Qualitative and quantitative RT-PCR studies for BCR-ABL1 fusion transcripts
2. BCR-ABL1 mutation analysis for TKI resistance by NGS
3. i. JAK2 V617F mutation by ddPCR, or
ii. JAK2 V617F mutation by ddPCR with reflex to JAK2 exon 12 mutation analysis; also applicable for abdominal thrombosis evaluation
4. The NGS panel must at a minimum include the following genes: **ASXL1, CALR, CBL, CSF3R, DNMT3A, EZH2, IDH1, IDH2, JAK2, KRAS, MPL, NRAS, PTPN11, RUNX1, SRSF2, SF3B1, SH2B3, TP53, and U2AF1.**

Genetic Testing Policies, Continued

Genetic Testing: Myeloproliferative Neoplasms, continued

5. A limited panel that only includes **JAK2, CALR, and MPL**, while not preferred, is considered acceptable.

B. Mastocytosis

Select Health covers the following studies in the workup for systemic mastocytosis:

1. Molecular testing for KIT D816V using an assay with high-sensitivity (i.e., ddPCR).
2. Multigene NGS panel that includes genes such as SRSF2, ASXL1, and RUNX1 (e.g., myeloid-specific NGS panel).
 - a. The NGS panel must, at a minimum, include the following genes: **ASXL1, CBL, DNMT3A, EZH2, JAK2, KIT, KRAS, NRAS, RUNX1, SRSF2, TET2**.
 - b. The presence of KIT in an NGS panel does not replace the need for KIT D816V mutation testing by a more sensitive method (i.e., ddPCR).

C. Myeloid/Lymphoid Neoplasms with Eosinophilia and Gene Rearrangement

Select Health covers the following studies in the workup for myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement:

1. T-cell clonality studies by PCR
2. Myeloid mutation panel by next generation sequencing* (e.g., myeloid-specific panel).
 - a. The panel should at a minimum include the following genes: **ABL1, ETV6, FLT3, PCM1, JAK2, PDGFRA, PDGFRB, FIP1L1, FGFR1, ZMYM2**.

*Given the importance of identifying recurrent fusions in this disease category the utilization of an NGS panel that detects fusion events may be favored (i.e., NeoGenomics Neo Comprehensive-Heme cancers, FoundationOne Heme panel). If a recurrent fusion is detected then quantitative RT-PCR studies should be covered, if available, as they may be used in the monitoring of minimal residual disease.

D. Myelodysplastic Neoplasms/Myelodysplastic Syndromes and Clonal Hematopoiesis

Select Health covers the following molecular studies in the workup of patients with persistent and unexplained cytopenias:

1. Myeloid-specific next generation sequencing panel
 - a. The panel should at a minimum include the following genes: **ANKRD26, ASXL1, BCOR, CALR, CBL, CSF3R, DDX41, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, KRAS, MPL, NRAS, NPM1, PHF6, PPM1D, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TP53, TET2, UBA1, U2AF1, WT1, ZRSR2**.
2. Cytogenomic SNP microarray-oncology.
3. Qualitative/quantitative RT-PCR studies for BCR-ABL1

E. Myelodysplastic/Myeloproliferative Neoplasms

Select Health covers the following molecular studies in the workup of myelodysplastic/myeloproliferative neoplasms:

1. Myeloid-specific next generation sequencing panel
 - a. The panel should at a minimum include the following genes: **ANKRD26, ASXL1, BCOR, CALR, CBL, CSF3R, DDX41, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, KRAS, MPL, NRAS, NPM1, PHF6, PPM1D, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TP53, TET2, UBA1, U2AF1, WT1, ZRSR2**.
2. Cytogenomic SNP microarray-oncology.
3. Qualitative/quantitative RT-PCR studies for BCR-ABL1

Genetic Testing Policies, Continued

Genetic Testing: Myeloproliferative Neoplasms, continued

F. Acute Myeloid Leukemia

Select Health covers the following studies should in the workup of acute myeloid leukemia:

1. Myeloid-specific next generation sequencing panel
 - a. The panel should at a minimum include the following genes: **ANKRD26, ASXL1, BCOR, CALR, CBL, CEBPA, DDX41, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, KIT, KRAS, KMT2A (MLL), MPL, NRAS, NPM1, PHF6, PPM1D, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TP53, TET2, U2AF1, WT1, ZRSR2.**
 - b. Rapid NGS panels will be covered only at diagnosis to facilitate immediate management of newly diagnosed AML patients. Rapid NGS panels are typically more limited in scope to facilitate a rapid return of results. Therefore, more comprehensive myeloid-specific NGS panels will also be covered at diagnosis to allow for further risk stratification at diagnosis. A rapid AML NGS panel should, at a minimum, include the following set of genes: **CEBPA, FLT3, IDH1, IDH2, KIT, KRAS, NPM1, NRAS, and TP53.**
2. Cytogenomic SNP microarray-oncology.
3. FLT3 ITD and TKD mutation analysis by PCR
4. Quantitative RT-PCR for CBFB-MYH11 inv(16) if detected by FISH or karyotype
5. Quantitative RT-PCR for RUNX1-RUNX1T1 t(8;21) if detected by FISH or karyotype
6. Quantitative RT-PCR for NPM1 if detected by NGS
7. Quantitative RT-PCR for PMIL-RAR α t(15;17) if detected by FISH or karyotype
8. Qualitative/Quantitative RT-PCR for BCR-ABL1 if detected by FISH or Karyotype
9. KIT mutations in AML by fragment analysis and sequencing or equivalent assay if t(8;21) or inv(16)/t(16;16) detected.
10. Quantitative RT-PCR studies will be covered at diagnosis and during treatment and disease monitoring stages.

G. Acute Myeloid Leukemia of Mixed or Ambiguous Lineage

Select Health covers the following studies in the workup of acute myeloid leukemia that is of mixed or ambiguous lineage:

1. Comprehensive NGS panel that includes both DNA and RNA sequencing (e.g., NeoGenomics Neo Comprehensive-Heme cancers, FoundationOne Heme panel)
2. If a recurrent fusion is detected then quantitative RT-PCR studies should be covered, if available, as they may be used in the monitoring of minimal residual disease.

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For this policy, specifically, there are no CMS criteria available; therefore, the Select Health Commercial policy or InterQual criteria apply. Select Health applies these requirements after careful review of the evidence that supports the clinical benefits outweigh the clinical risks. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [http://www.cms.gov/medicare-coverage-database/coverage-and-qualifying-criteria/coverage-and-qualifying-criteria.aspx](#).

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health

Genetic Testing Policies, Continued

Genetic Testing: Myeloproliferative Neoplasms, continued

Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Billing/Coding Information

CPT CODES

- 81206** BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
- 81207** BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
- 81208** BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
- 81245** FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
- 81246** FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
- 81273** KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
- 81277** Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities
- 81310** NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
- 81315** PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
- 81342** TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
- 81401** Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
- 81450** Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, 11 NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
- 81455** Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
- 81219** CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9

Genetic Testing Policies, Continued

Genetic Testing: Myeloproliferative Neoplasms, continued

- 81270 JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
- 81279 JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
- 81339 MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10
- 81338 MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)
- 81236 EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
- 81175 ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
- 81176 ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)
- 81237 EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
- 0027U JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15
- 0171U Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence
- 0040U BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
- 0016U Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
- 81348 SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L)
- 81272 KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
- 81316 PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
- 81233 BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)

Genetic Testing Policies, Continued

Genetic Testing: Myeloproliferative Neoplasms, continued

- 81218** CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
- 81305** MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, pLeu265Pro (L265P) variant
- 81347** SF3B1 (splicing factor [3b] subunit B1) (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L)
- 81357** U2AF1 (U2 small nuclear RNA auxiliary factor 1) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, S34F, S34Y, Q157R, Q157P)
- 81360** ZRSR2 (zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variant(s) (eg, E65fs, E122fs, R448fs)
- 81348** SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L)
- 81320** PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F)
- 81175** ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
- 81263** IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
- 81272** KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
- 81176** ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)
- 0049U** NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative
- 0050U** Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements
- 0040U** BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
- 0046U** FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative
- 0023U** Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.l836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin

Genetic Testing Policies, Continued

Genetic Testing: Myeloproliferative Neoplasms , continued

Key References

1. Intermountain Precision Genomics. Genetic Testing for Myeloproliferative Neoplasms. June 2023.

Revision History

Revision Date	Summary of Changes
11/8/23	For Commercial Plan Policy, modified coverage criterion #3B: “i. JAK2 V617F mutation by ddPCR, or ii. JAK2 V617F mutation by ddPCR with reflex to JAK2 exon 12 mutation analysis; also applicable for abdominal thrombosis evaluation. ”
7/22/24	Modified title of policy, was previously titled as [Genetic Testing: Myeloproliferative Neoplasms], and for Commercial Plan Policy, added Section G with coverage criteria for “Acute Myeloid Leukemia of Mixed or Ambiguous Lineage.”
9/30/24	For Commercial Plan Policy, added new criterion #5 to criteria section #A (Myeloproliferative Neoplasms), “A limited panel that only includes JAK2, CALR, and MPL , while not preferred, is considered acceptable.” Also, added new criterion #1-b to criteria section #F (Acute Myeloid Leukemia), “Rapid NGS panels will be covered only at diagnosis to facilitate immediate management of newly diagnosed AML patients. Rapid NGS panels are typically more limited in scope to facilitate a rapid return of results. Therefore, more comprehensive myeloid-specific NGS panels will also be covered at diagnosis to allow for further risk stratification at diagnosis. A rapid AML NGS panel should, at a minimum, include the following set of genes: CEBPA, FLT3, IDH1, IDH2, KIT, KRAS, NPM1, NRAS, and TP53. ”
10/29/24	For Commercial Plan Policy, removed the NF1 gene as part of a required panel of genes to qualify for genetic testing associated with sections A, D, E, and F.

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Genetic Testing Policies, Continued

Genetic Testing: Myeloproliferative Neoplasms , continued

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MEDICAL POLICY

GENETIC TESTING: NOTCH3 TESTING FOR CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY (CADASIL)

Policy # 353

Implementation Date: 6/23/07

Review Dates: 6/11/09, 6/17/10, 8/16/11, 8/16/12, 8/15/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 9/12/18, 8/7/19, 2/14/23, 2/15/24

Revision Dates: 6/19/08, 2/26/19, 7/1/23, 7/25/24

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)

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1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited form of angiopathy affecting small blood vessels. All arteries are affected but the brain is most severely affected. Patients with CADASIL may also be at increased risk of myocardial infarction because of damaged blood vessels in the heart. Most patients with CADASIL do not have the common risk factors for stroke and heart attack, such as high blood pressure and high cholesterol, although in some cases these features may also be present.

Transient ischemic attacks (TIAs) and stroke at a young age (mean age of onset = 46 years) are the most common presentation, occurring in 85%. Cognitive disturbances (dysexecutive syndrome), the second most frequent feature, are observed in about 60% of symptomatic individuals—these disturbances may start as early as age 35 years—and about 75% of affected individuals develop dementia. Migraine occurs in about 40% of individuals, and 90% of individuals with migraine have migraine with aura. Psychiatric disturbance is observed in 30% of individuals with CADASIL, varying from personality changes to severe depression.

Genetic variants in NOTCH3 (located on chromosome 19p13.2) cause CADASIL. CADASIL is inherited in an autosomal dominant pattern (i.e., only 1 affected allele is sufficient to cause the disorder). In most cases, an affected person has one parent with the condition. In rare cases, a family history is not evident, and a new mutation in the NOTCH3 gene is identified. Penetrance of the disease approaches 100%, however, pathogenic variants in domains 7-34 are more common and may be associated with milder disease and possibly even reduced penetrance.

A more recently recognized form of CADASIL, type 2, is caused by genetic variants affecting one copy of the HTRA1 gene. While this form of CADASIL has significant overlap in presentation, the age of onset tends to be later (50-70 years) and additional clinical features such as alopecia, spondylosis, and lower back pain have been reported.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

POLICY #353 – GENETIC TESTING: NOTCH3 TESTING FOR CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY (CADASIL)



Genetic Testing Policies, Continued

Genetic Testing: *Notch3* Testing for CADASIL, continued

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested; and
3. **Select Health covers NOTCH3 testing for CADASIL, either as a single gene test or as part of a focused panel, under limited circumstances, when all the criteria below have been met.**

Criteria required for coverage:

- A. When the family history is suggestive of an autosomal dominant pattern of inheritance, or there is a strong suspicion of CADASIL; and
- B. Personal or family history of transient ischemic attacks (TIA), cerebral vascular accidents (CVA), and/or vascular dementia; and
- C. MRI brain scan shows unexplained white matter hyperintensities.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

The medical and empirical literature reviewed suggests that NOTCH3 testing provides valuable information confirming the clinical utility of this testing in patients suspected to have CADASIL. This was best identified by Markus et al. in 2002. In this study, the associated mutations were noted to be 100% penetrant with variable expressivity. Additionally, it was identified that this testing had higher sensitivity than the gold standard for diagnosing CADASIL, skin biopsy. This confirmed the findings noted by Joutel et al. in 2001.

CADASIL is an extremely rare disorder, suggesting that NOTCH3 testing is only appropriate in cases when other more likely diagnoses have been excluded. In symptomatic patients with a clear family history, NOTCH3 appears to be more reliable than skin biopsy at diagnosing CADASIL. The high penetrance and the fact that children of individuals with a NOTCH3 mutation have a 50% chance of inheriting the mutation suggests a potential use for presymptomatic testing in these individuals, though, the utility of this indication has not yet been evaluated in the literature.

Lack of clinical guidance is apparent in the literature, but a decrease in extensive laboratory testing may occur if genetic testing for CADASIL is permitted. NOTCH3 testing may be used as a diagnostic, predictive, or prenatal test. Positive test results are diagnostic for CADASIL. As a predictive test in asymptomatic individuals, testing is not useful in predicting age of onset, severity, type of symptoms, or

Genetic Testing Policies, Continued

Genetic Testing: *Notch3* Testing for CADASIL, continued

rate of progression. Predictive testing of at-risk individuals should be preceded by testing an affected family member to confirm that the mutation is identifiable by currently available techniques. The mutation detection rate ranges from 57%–96% in individuals with well-defined or biopsy-proven CADASIL. Most authors agree that sensitivity exceeds 90%.

Prenatal testing is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis performed at 15–18 weeks' gestation or chorionic villus sampling at about 10–12 weeks. As with predictive testing, a disease-causing mutation must be identified in an affected family member before prenatal testing can be performed.

Recent literature identified one study by Stojanov et al. (2014) which described a case of a de novo NOTCH3 mutation in a patient with CADASIL, supporting testing in rare instances even when a family history is absent.

Billing/Coding Information

Covered: Under the circumstances listed above

CPT CODES

81406 Molecular pathology procedure, Level 7

HCPCS CODES

G0452 Molecular pathology procedure; physician interpretation and report

Key References

1. Brulin P, Godfraind C, Leteurtre E, Ruchoux MM. "Morphometric analysis of ultrastructural vascular changes in CADASIL: analysis of 50 skin biopsy specimens and pathogenic implications." *Acta Neuropathol (Berl)* 104.3 (2002): 241-8.
2. Dichgans M. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). 2006. UpToDate. Available: <https://www.uptodate.com/contents/cerebral-autosomal-dominant-arteriopathy-with-subcortical-infarcts-and-leukoencephalopathy-cadasil>. Date Accessed: February 15, 2024.
3. Furby A, Vahedi K, Force M, et al. "Differential diagnosis of a vascular leukoencephalopathy within a CADASIL family: use of skin biopsy electron microscopy study and direct genotypic screening." *J Neurol* 245.11 (1998): 734-40.
4. Hack RJ, Rutten J, Lesnik Oberstein SAJ. CADASIL. 2000 Mar 15 [Updated 2019 Mar 14]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available: <https://www.ncbi.nlm.nih.gov/books/NBK1500/> Date Accessed: February 15, 2024.
5. Joutel A, Favrole P, Labauge P, et al. "Skin biopsy immunostaining with a Notch3 monoclonal antibody for CADASIL diagnosis." *Lancet* 358.9298 (2001): 2049-51.
6. Khan, M. T., A. Murray and M. Smith (2016). "Successful Use of Intravenous Tissue Plasminogen Activator as Treatment for a Patient with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy: A Case Report and Review of Literature." *J Stroke Cerebrovasc Dis* 25(4): e53-57.
7. Markus HS, Martin RJ, Simpson MA, et al. "Diagnostic strategies in CADASIL." *Neurology* 59.8 (2002): 1134-8.
8. MedlinePlus Genetics. CADASIL. 2007. National Library of Medicine. Available: <https://medlineplus.gov/genetics/condition/cerebral-autosomal-dominant-arteriopathy-with-subcortical-infarcts-and-leukoencephalopathy/>. Date Accessed: February 15, 2024.
9. Personal Communication. Williams J, 2007
10. Peters N, Opherk C, Bergmann T, Castro M, Herzog J, Dichgans M. "Spectrum of mutations in biopsy-proven CADASIL: implications for diagnostic strategies." *Arch Neurol* 62.7 (2005): 1091-4.
11. Stojanov, D., et al. (2014). "De novo mutation in the NOTCH3 gene causing CADASIL." *Bosn J Basic Med Sci* 14(1): 48-50.
12. Rutten, J. W., et al. (2014). "Interpretation of NOTCH3 mutations in the diagnosis of CADASIL." *Expert Rev Mol Diagn* 14(5): 593-603.
13. United Leukodystrophy Association. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL). 2006. Available: <https://ulf.org/leukodystrophies/cerebral-autosomal-dominant-arteriopathy-with-subcortical-infarcts-and-leukoencephalopathy-cadasil/>. Date Accessed: February 15, 2024.

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Genetic Testing Policies, Continued

Genetic Testing: Notch3 Testing for CADASIL, continued

refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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MEDICAL POLICY

GENETIC TESTING FOR SCREENING AND DETECTION OF PROSTATE CANCER

Policy # 510

Implementation Date: 9/3/12

Review Dates: 10/24/13, 10/23/14, 10/18/14, 10/15/15, 10/20/16, 10/19/17, 3/16/23, 5/15/24

Revision Dates: 7/1/23, 8/7/23, 9/21/23, 9/13/24

Related Medical Policies:

[#544 Genetic Testing for Prostate Cancer Prognosis](#)

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1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Prostate cancer (PCa) is the second leading cause of cancer death in men, exceeded only by lung cancer; a man's lifetime risk of PCa is 1 in 6. Not everyone experiences symptoms of prostate cancer. Many times, signs of PCa are first detected by a doctor during a routine check-up. Part of the annual exam that men over the age of 50 undergo includes a digital rectal exam (DRE) to feel the prostate and a PSA to screen for asymptomatic prostate cancer. Use of the PSA has become controversial in the last couple of years due to the low sensitivity in screening for prostate cancer. Consequently, new tests which may be more sensitive and specific for identifying early or aggressive prostate cancer are being developed.

Prostate cancer is the most common cancer among men, with over 200,000 new cases identified each year in the United States. The median age at diagnosis is 66 years. Older men are more likely to be affected than younger men, and African American men have higher rates compared to men of other ethnic backgrounds.

Screening programs for prostate cancer allow for its early detection. Screening is typically performed by prostate-specific antigen (PSA) test and digital rectal examination (DRE). Diagnosis is confirmed by prostate biopsy. Biopsy is typically performed by collection of approximately 12 needle biopsy cores. Initial biopsies only detect 65-77% of prostate cancers, and repeat biopsies are frequently performed.^{9,10} The false negative rate of biopsy may be as high as 25%

The ConfirmMDx test (MDx Health) is a proprietary epigenetic assay that measures gene methylation associated with the presence of cancer. Results are intended to assist in determining which patients likely have a true negative biopsy, and which patients are at increased risk for occult cancer. Results may prevent unnecessary repeat biopsies in unaffected men, and triage higher risk patients for repeat biopsies and treatment, as needed.

SelectMDx is a proprietary test that is designed to identify an individual's risk of prostate cancer without the need for a biopsy. SelectMDx is a urine-based assay that measures mRNA levels of DLX1 and HOXC6 to determine an individual's risk of prostate cancer.

Another test is the urine Progensa PCA3 test. PCA3 (or Prostate Cancer Antigen-3, formerly known as DD3) is a prostate-tissue-specific, noncoding messenger RNA (mRNA) that is over-expressed in virtually all prostate carcinoma specimens compared to normal prostate tissue. These attributes of PCA3 mRNA expression make it a promising prostate-cancer-specific marker. Collecting the specimen is a bit more complicated than simply drawing blood as is done with a PSA test. After massaging each lobe of the prostate 3 times, a urine sample is collected and the amount of PCA3 in the sample is analyzed. The

Genetic Testing Policies, Continued

Genetic Testing: PCA3 Testing for Prostate Cancer, continued

result is reported as an absolute value but also as positive or negative based upon achieving a pre-specified threshold of 35. Based on the results, a patient's physician may decide whether to continue to biopsy or if active surveillance is more appropriate.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.
3. Select Health considers prostate cancer risk assessment and diagnostic algorithmic tests with sufficient evidence of clinical validity and utility to be medically necessary in the following situations:

i. The member has not had a prostate biopsy, and the member has at least one of the following:

- a) Prostate specific antigen (PSA) of > 3 ng/ml, OR
- b) A digital rectal exam (DRE) that is very suspicious for cancer, AND
- c) The test is one of the following:
 - Prostate Health Index (PHI)
 - SelectMDx
 - 4Kscore
 - ExoDx Prostate Test
 - MyProstateScore (MPS)
 - IsoPSA

OR

ii. The member has had a prostate biopsy, and the result is one of the following:

- a) Atypia, suspicious for cancer, OR
- b) High-grade prostatic intraepithelial neoplasia (PIN), OR
- c) Benign, AND
- d) The test is one of the following:
 - Prostate Health Index (PHI)
 - 4Kscore
 - ExoDx Prostate Test
 - MyProstateScore (MPS)
 - IsoPSA
 - ConfirmMDx
 - PCA

The use of prostate cancer risk assessment and diagnostic algorithmic tests with sufficient evidence of clinical validity and utility are for all other indications is considered experimental/investigational.

SELECT HEALTH MEDICARE

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage,

Genetic Testing Policies, Continued

Genetic Testing: PCA3 Testing for Prostate Cancer, continued

please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

A Medical Technology Assessment performed in August 2012 identified 5 systematic reviews and 30 peer-reviewed journal articles concerning PCA3 testing for PCa indications. The literature spans the years 2006–2012 where more than 9,670 (mean per study ≈322) men were studied. Though the systematic reviews are dated, the addition of more current peer-reviewed literature adds or subtracts very little from the conclusions drawn by the authors of the reviews. Three key points frequently discussed in the literature include: 1) the clinical utility of PCA3, 2) defining the appropriate cut-off value for the PCA3 test, and 3) appropriate patient selection for use of the PCA3 assay.

Clinical Utility: The Hayes GTE update in July 2011 noted that PCA3 detection may be useful for guiding biopsy decisions and that it could possibly improve treatment decision-making in the clinic. This conclusion is largely based on their finding that the diagnostic accuracy of the PCA3 detection test (the ability of the test to predict biopsy outcome) is greater than that of PSA screening. Ultimately, the Hayes GTE report did not find PCA3 testing to be a viable screening test for men considering biopsy, for general population screening, or for disease monitoring, giving it a 'D2' rating. The 2009 BCBS TEC assessment echoes the concerns brought forth in the Hayes review, noting the most significant and persistent finding among all the literature identified for this review, that being: "PCA3 results have not been standardized and clinical utility studies of decision-making for initial biopsy, repeat biopsy or treatment have not been reported."

Similarly, Auprich et al., Henderson et al., Hessel et al., and others have all noted that the exact place of PCA3 as a prognostic test for PCa remains the subject of investigation and that no evidence for the usefulness of PCA3 in active surveillance programs has been presented.

Cut-Off Value: The issue of what constitutes an appropriate cut-off value was addressed throughout the studies (patients whose assay scores are above that cut-off would be qualified as high risk of having PCa). Of note, are the comments by van Poppel et al. who showed that a PCA3 cut-off of < 20 may be the most suitable to select men with clinically insignificant PCa in whom active surveillance may be appropriate. A PCA3 score threshold of 50 may be used to identify men at risk of harboring insignificant prostate cancer. Chun et al. was the only other study that stratified cut-offs correlating to predictive accuracy of PCa upon completion of biopsy. In all, twelve papers used cut-offs of between 17 and 66 with the average being 35. This, once again, points to the fact that PCA3 results and methods have not been stratified in large, prospective, blinded studies.

Where PSA has a relatively high sensitivity and low specificity, PCA3 has a relatively high specificity and low sensitivity. Combining the use of these 2 tests may be postulated to result in improved diagnostic performance. Aubin et al., Ochiai et al., and Pepe et al., all showed that when used in conjunction with PSA, PCA3 testing improves diagnostic accuracy of prostate biopsy for PCa. Only Nyberg et al. showed otherwise. These results came after studying 1,251 patients in total. Despite this, these studies only show potential clinical utility in 13% of all patients reported in this review. It has not been determined, as per the literature, if defining cut-off values for the PCA3 test will raise the sensitivity and specificity of the test to a clinically useful level.

Patient Selection: Though many of the papers illustrated promising outcomes, especially when compared to PSA screening, there is little evidence that PCA3 testing improves patient outcomes because of the lack of standardization and patient segmentation delineating for whom this test is most appropriate. The various studies used different populations and different primary endpoints. This, again, clouds the question as to the clinical utility of this test.

Genetic Testing Policies, Continued

Genetic Testing: PCA3 Testing for Prostate Cancer, continued

Though PCA3 testing has been shown to have better specificity, AUC, and odds ratio than PSA, currently there is no consensus among societies or authors regarding in whom this test should be performed, what cut-off value should be used to stratify risk or need for biopsy, and under what clinical constraints.

An AHRQ evaluation (Gutman et al., 2013) suggests that further comparative effectiveness research is needed to demonstrate utility of PCA3. Also, in 2013, a report from the EGAPP Working Group found insufficient evidence to recommend PCA3 testing to inform decisions about initial or re-biopsy for prostate cancer in at-risk men. They deemed the clinical validity and net health benefit "low" and recommended against use until additional evidence supports improved outcomes.

Wei et al. in 2014 studied 859 men (mean age, 62 years) from 11 centers who underwent prostate biopsy from 2009–2011 to assess whether PCA3 could improve the positive predictive value (PPV) for an initial biopsy (at a score > 60) and the negative predictive value (NPV) for a repeat biopsy (at a score < 20). PPV was 80% (95% CI, 72% to 86%) in the initial biopsy group, and NPV was 88% (95% CI, 81% to 93%) in the repeat biopsy group.

Recent NCCN Guidelines recommend use of the PCA3 assay in the screening and detection of prostate cancer: "Tests that improve specificity in the post-biopsy setting- including the Sentinel Prostate Cancer Test, percent-free PSA, 4KScore, PHI, PCA3, and ConfirmMDx should be considered in patients thought to be at higher risk despite a negative prostate biopsy." (NCCN Guidelines for Prostate Cancer Early Detection V.1.2022)

Billing/Coding Information

CPT CODES

Covered for the indications listed above when criteria are met

0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and urine, algorithms to predict high-grade prostate cancer risk
0021U	Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score
0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score
0228U	Oncology (prostate), multianalyte molecular profile by photometric detection of macromolecules adsorbed on nanosponge array slides with machine learning, utilizing first morning voided urine, algorithm reported as likelihood of prostate cancer
0339U	Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer
0359U	Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer.
0403U	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch post-digital rectal examination urine (or processed first-catch urine), algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)

Genetic Testing Policies, Continued

Genetic Testing: PCA3 Testing for Prostate Cancer, continued

- 81479** Unlisted molecular pathology procedure
- 81539** Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and Human Kallikrein-2 [HK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score
- 81551** Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy
- 81599** Unlisted multianalyte assay with algorithmic analysis

HCPCS CODES

No specific codes identified

Not covered: the following codes are considered experimental/investigational

- 0343U** Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (snRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer

Key References

1. Abdellaoui, A. (2011). Imaging in Prostate Cancer. Medscape. Last Update: Available: <http://www.medscape.com/viewarticle/742986>. Date Accessed: June 13, 2011.
2. American Cancer Society (ACS). (2012). Prostate Cancer. American Cancer Society (ACS). Last Update: February 27, 2012. Available: <http://www.cancer.org/acs/groups/cid/documents/webcontent/003134-pdf.pdf>. Date Accessed: February 20, 2012.
3. Aubin, SM, Reid, J, Samo, MJ, et al. (2010). PCA3 molecular urine test for predicting repeat prostate biopsy outcome in populations at risk: validation in the placebo arm of the dutasteride REDUCE trial. *J Urol.* 184. 5:1947-52.
4. Auprich, M, Bjartell, A, Chun, FK, et al. (2011). Contemporary role of prostate cancer antigen 3 in the management of prostate cancer. *Eur Urol.* 60. 5:1045-54.
5. Auprich, M, Chun, FK, Ward, JF, et al. (2011). Critical assessment of preoperative urinary prostate cancer antigen 3 on the accuracy of prostate cancer staging. *Eur Urol.* 59. 1:96-105.
6. Auprich, M, Haese, A, Walz, J, et al. (2010). External validation of urinary PCA3-based nomograms to individually predict prostate biopsy outcome. *Eur Urol.* 58. 5:727-32.
7. Benway, BM. (2012). Prostate biopsy. Up to Date. Last Update: June 4, 2012. Available: http://www.uptodate.com/contents/prostate-biopsy?source=search_result&search=prostate+biopsy&selectedTitle=1~33. Date Accessed: July 31, 2012. 2012.
8. Brawer, MK, Chetner, MP, Beatie, J, et al. (1992). Screening for prostatic carcinoma with prostate specific antigen. *J Urol.* 147. 3 Pt 2:841-5.
9. Carroll, P. R., J. K. Parsons, G. Andriole, R. R. Bahnson, E. P. Castle, W. J. Catalona, D. M. Dahl, J. W. Davis, J. I. Epstein, R. B. Etzioni, T. Farrington, G. P. Hemstreet, 3rd, M. H. Kawachi, S. Kim, P. H. Lange, K. R. Loughlin, W. Lowrance, P. Maroni, J. Mohler, T. M. Morgan, K. A. Moses, R. B. Nadler, M. Poch, C. Scales, T. M. Shaneyfelt, M. C. Smaldone, G. Sonn, P. Sprengle, A. J. Vickers, R. Wake, D. A. Shead and D. A. Freedman-Cass (2016). "NCCN Guidelines Insights: Prostate Cancer Early Detection, Version 2.2016." *J Natl Compr Canc Netw* 14(5): 509-519.
10. Catalona, WJ, Richie, JP, Ahmann, FR, et al. (1994). Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol.* 151. 5:1283-90.
11. Chun, FK, de la Taille, A, van Poppel, H, et al. (2009). Prostate cancer gene 3 (PCA3): development and internal validation of a novel biopsy nomogram. *Eur Urol.* 56. 4:659-67.
12. Cirillo, S, Petracchini, M, Della Monica, P, et al. (2008). Value of endorectal MRI and MRS in patients with elevated prostate-specific antigen levels and previous negative biopsies to localize peripheral zone tumours. *Clin Radiol.* 63. 8:871-9.
13. Clements, R. (2001). Ultrasonography of prostate cancer. *Eur Radiol.* 11. 11:2119-25.
14. Dahnhert, WF, Hamper, UM, Eggleston, JC, et al. (1986). Prostatic evaluation by transrectal sonography with histopathologic correlation: the echogenic appearance of early carcinoma. *Radiology.* 158. 1:97-102.
15. de la Taille, A, Irfani, J, Graefen, M, et al. (2011). Clinical evaluation of the PCA3 assay in guiding initial biopsy decisions. *J Urol.* 185. 6:2119-25.
16. Deras, IL, Aubin, SM, Blase, A, et al. (2008). PCA3: a molecular urine assay for predicting prostate biopsy outcome. *J Urol.* 179. 4:1587-92.
17. Draisma, G, Boer, R, Otto, SJ, et al. (2003). Lead times and overdiagnosis due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst.* 95. 12:868-78.
18. Draisma, G, Etzioni, R, Tsodikov, A, et al. (2009). Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst.* 101. 6:374-83.
19. Etzioni, R, Penson, DF, Legler, JM, et al. (2002). Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. *J Natl Cancer Inst.* 94. 13:981-90.
20. Evaluation of Genomic Applications in, P. and G. Prevention Working (2013). "Recommendations from the EGAPP Working Group: does PCA3 testing for the diagnosis and management of prostate cancer improve patient health outcomes?" *Genet Med.*

Genetic Testing Policies, Continued

Genetic Testing: PCA3 Testing for Prostate Cancer, continued

21. EviCore. ConfirmMDX for Prostate Cancer Risk Assessment. V.1.0.2020.
22. Food and Drug Association (FDA). (2012). Premarket Approval (PMA) Approval Summary for PROGENSA PSA3 Assay. US Department of Health & Human Services. Last Update: July 16, 2012. Available: http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100033A.pdf. Date Accessed: August 6. 2012.
23. Galasso, F, Giannella, R, Bruni, P, et al. (2010). PCA3: a new tool to diagnose prostate cancer (PCa) and a guidance in biopsy decisions. Preliminary report of the UrOP study. Arch Ital Urol Androl. 82. 1:5-9.
24. Gen-Probe. (2012). Progensa PCA3. Gen-Probe. Last Update: Available: <http://www.gen-probe.com/products-services/progensa-pca3>. Date Accessed: February 22. 2012.
25. Gulati, R, Wever, EM, Tsodikov, A, et al. (2011). What If I Don't Treat My PSA-Detected Prostate Cancer? Answers from Three Natural History Models. Cancer Epidemiol Biomarkers Prev. 20. 5:740-50.
26. Gutman, S. I., D. M. Oliansky, et al. (2013). PCA3 Testing in the Diagnosis and Management of Prostate Cancer: Future Research Needs: Identification of Future Research Needs From Comparative Effectiveness Review No. 98. Rockville (MD).
27. Haese, A, de la Taille, A, van Poppel, H, et al. (2008). Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy. Eur Urol. 54. 5:1081-8.
28. Hamper, UM, Sheth, S, Walsh, PC, et al. (1990). Bright echogenic foci in early prostatic carcinoma: sonographic and pathologic correlation. Radiology. 176. 2:339-43.
29. Hayes GTE Report. (2009) PCA3 Detection Test for Prostate Cancer. Winifred S. Hayes Inc. August 9. Updated Search: July 15, 2011.
30. Henderson, J, Ghani, KR, Cook, J, et al. (2010). The role of PCA3 testing in patients with a raised prostate-specific antigen level after Greenlight photoselective vaporization of the prostate. J Endourol. 24. 11:1821-4.
31. Hessel, D, van Gils, MP, van Hooij, O, et al. (2010). Predictive value of PCA3 in urinary sediments in determining clinicopathological characteristics of prostate cancer. Prostate. 70. 1:10-6.
32. Hoffman, RM. (2012). Screening for prostate cancer. Up to Date. Last Update: Available: http://www.uptodate.com/contents/screening-for-prostate-cancer?source=search_result&search=search+result&selectedTitle=4~31#H988952102. Date Accessed: March 7. 2012.
33. Jones, JS. (2012). Prostate Biopsy. Medscape. Last Update: May 16, 2012. Available: <http://emedicine.medscape.com/article/1949728-overview#aw2aab6b2b2>. Date Accessed: August 1. 2012.
34. Klecka, J, Holubec, L, Pesta, M, et al. (2010). Differential display code 3 (DD3/PCA3) in prostate cancer diagnosis. Anticancer Res. 30. 2:665-70.
35. Lee, GL. (2011). Prostate Cancer: Diagnostic Performance of the PCA3 Urine Test. Medscape News. Last Update: Available: <http://www.medscape.com/viewarticle/738934>. Date Accessed: February 22. 2012.
36. Liss, MA, Santos, R, Osann, K, et al. (2011). PCA3 molecular urine assay for prostate cancer: association with pathologic features and impact of collection protocols. World J Urol. 29. 5:683-8.
37. Marks, LS, Fradet, Y, Deras, IL, et al. (2007). PCA3 molecular urine assay for prostate cancer in men undergoing repeat biopsy. Urology. 69. 3:532-5.
38. Nakanishi, H, Groskopf, J, Fritzsche, HA, et al. (2008). PCA3 molecular urine assay correlates with prostate cancer tumor volume: implication in selecting candidates for active surveillance. J Urol. 179. 5:1804-9; discussion 1809-10.
39. National Cancer Institute. (2011). Genetics of Prostate Cancer. National Cancer Institute. Last Update: May 13, 2011. Available: <http://www.cancer.gov/cancertopics/pdq/genetics/prostate/HealthProfessional>. Date Accessed: May 23, 2011.
40. National Cancer Institute. (2012). Prostate-Specific Antigen (PSA) Test. National Institutes of Health. Last Update: March 3, 2009. Available: <http://www.cancer.gov/cancertopics/factsheet/detection/PSA>. Date Accessed: February 22. 2012.
41. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines). (2011). Prostate Cancer Early Detection. National Comprehensive Cancer Network (NCCN). Last Update: June 6, 2011. Available: http://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf. Date Accessed: February 20. 2012.
42. National Horizon Scanning Centre (NHSC). (2006) Prostate cancer gene 3 (Progensa PCA3) assay in the diagnosis of prostate cancer. University of Bellingham (UK). December.
43. NCCN Guidelines for Prostate Cancer Early Detection V.1.2022.
44. Norberg, M, Holmberg, L, Busch, C, et al. (1996). Multiple transrectal ultrasound-guided biopsies for the detection of prostate cancer and determination of tumor volume, grade, and seminal vesicle invasion. Eur Radiol. 6. 1:56-61.
45. Nyberg, M, Ullmert, D, Lindgren, A, et al. (2010). PCA3 as a diagnostic marker for prostate cancer: a validation study on a Swedish patient population. Scand J Urol Nephrol. 44. 6:378-83.
46. Ochiai, A, Okihara, K, Kamoi, K, et al. (2011). Prostate cancer gene 3 urine assay for prostate cancer in Japanese men undergoing prostate biopsy. Int J Urol. 18. 3:200-5.
47. Pashayan, N, Duffy, SW, Pharoah, P, et al. (2009). Mean sojourn time, overdiagnosis, and reduction in advanced stage prostate cancer due to screening with PSA: implications of sojourn time on screening. Br J Cancer. 100. 7:1198-204.
48. PCA3.org. (2010). PCA3 Materials & News. PCA3.org. Last Update: October 12, 2010. Available: <http://www.pca3.org/pro/content/pca3-assay-indications-use-clinical-practice>. Date Accessed: February 22. 2012.
49. Pepe, P, Aragona, F. (2011). PCA3 score vs PSA free/total accuracy in prostate cancer diagnosis at repeat saturation biopsy. Anticancer Res. 31. 12:4445-9.
50. Ploussard, G, Durand, X, Xylinas, E, et al. (2011). Prostate cancer antigen 3 score accurately predicts tumour volume and might help in selecting prostate cancer patients for active surveillance. Eur Urol. 59. 3:422-9.
51. Ploussard, G, Haese, A, Van Poppel, H, et al. (2010). The prostate cancer gene 3 (PCA3) urine test in men with previous negative biopsies: does free-to-total prostate-specific antigen ratio influence the performance of the PCA3 score in predicting positive biopsies? BJU Int. 106. 8:1143-7.
52. Prezelin, Y, Ronsin, C, Celhay, O, et al. (2011). [Variation of urinary PCA3 following transrectal ultrasound-guided prostate biopsy]. Prog Urol. 21. 6:412-6.
53. Prostate Cancer Foundation. (2011). Understanding the Prostate: About the Prostate. Prostate Cancer Foundation. Last Update: 2011. Available: http://www.pcf.org/site/c.leJRIOREpH/b.5802023/k.B322>About_the_Prostate.htm. Date Accessed: May 23. 2011.
54. Rigau, M, Morote, J, Mir, MC, et al. (2010). PSGR and PCA3 as biomarkers for the detection of prostate cancer in urine. Prostate. 70. 16:1760-7.

Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: PCR FOR BCR-ABL IN CHRONIC MYELOGENOUS LEUKEMIA (CML)

Policy # 340

Implementation Date: 3/22/07

Review Dates: 2/21/08, 2/26/09, 2/17/11, 2/16/12, 4/25/13, 2/20/14, 2/11/16, 2/16/17, 2/15/18, 2/18/19, 2/14/23, 2/15/24

Revision Dates: 7/16/13, 9/17/18, 7/1/23

Related Medical Policies:
[#123 Gene Therapy, Testing, and Counseling](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Chronic myelogenous leukemia (CML) is a disorder characterized by uncontrolled production of immature granulocytes (white blood cells). The presence of a greater percentage of immature granulocytes over more mature granulocytes ("leukemic hiatus") is one of the classic findings in CML.

Chronic myelogenous leukemia is distinguished from other leukemias by the presence of a specific acquired cytogenetic abnormality; the Philadelphia chromosome (Ph^1). Ph^1 is an abnormally short chromosome that results from a balanced translocation between the distal ends of chromosomes 9 and 22. The breakage on chromosome 22 involves a gene called "BCR" (for breakpoint cluster region), while the breakage on chromosome 9 mutates the Abelson (ABL) gene. This mutated gene is translocated to chromosome 22 and fused with the remaining part of the BCR gene. This fusion between BCR and ABL leads to an abnormal fused gene, called BCR-ABL.

In the past, the diagnosis of CML was based largely upon clinical and laboratory criteria. However, current diagnostic criteria from the National Comprehensive Network (NCCN) require detection of Ph^1 or its products. The BCR-ABL fusion mRNA or the BCR-ABL protein for a diagnosis of CML to be made. The NCCN guidelines also recommend testing for BCL-ABL in monitoring treatment for CML, follow-up during remission, and to monitor progress when recurrence is evident. Ph^1 and its products may be detected through several methods, including cytogenetic examination of bone marrow cells, fluorescence in situ hybridization (FISH), and quantitative and qualitative reverse transcriptase polymerase chain reaction (RT-PCR). RY-PCR may also be used to detect specific ABL kinase domain (KD) mutations.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

Genetic Testing Policies, Continued

Genetic Testing: PCR for BCR-ABL in Chronic Myelogenous Leukemia (CML), continued

Select Health covers BCR-ABL testing when the following criteria are met:

- A. BCR-ABL kinase domain point mutation analysis is considered medically necessary in the monitoring of chronic myeloid leukemia (CML) in any of the following circumstances:

1) Evaluation of individuals with chronic myelogenous leukemia to evaluate treated individuals who manifest suboptimal response to tyrosine kinase inhibitor therapy indicated by:

- i. Lack of a partial hematologic or cytogenetic response at 3 months or greater after treatment onset
- ii. Less than a complete hematologic and cytogenetic response at 12 months
- iii. Disease progression to accelerated or blast phase

Select Health does NOT cover other BCR-ABL mutation analysis, as its clinical utility has not been established, and its use meets the plan's definition of experimental/investigational

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

Chronic myelogenous leukemia results from a somatic mutation (i.e., not inherited) to DNA of a stem cell in the bone marrow. The mutation confers a growth and survival advantage on the malignant stem cell. The result of this injury is the uncontrolled growth of white cells leading, if unchecked, to a massive increase in their concentration in the blood. Unlike acute myelogenous leukemia (AML), CML allows some white blood cells to mature and function normally, which accounts for the less severe early course of the disease.

Chronic myelogenous leukemia has a triphasic clinical course. Approximately 85%–90% of patients present at the time of diagnosis with relatively indolent disease (chronic phase), which is easily controlled with oral chemotherapy. Untreated, however, CML progresses from a chronic phase to a rapidly fatal blast phase, generally over 3–5 years. Two-thirds of patients will also experience a transition period called the accelerated phase, during which time disease control is more difficult to achieve.

Overall, the literature suggests that BCR-ABL testing using quantitative and/or qualitative PCR is an accurate method of monitoring response to Gleevec therapy and for assessing remission in post-transplant patients. BCR-ABL transcript analysis appears to be more accurate than cytogenetic testing, resulting in fewer false negatives. These test results also impact management decisions regarding initiation or change in treatment modalities. Most of the available literature reports on PCR testing in the context of monitoring for recurrence after stem cell transplantation. Thus, conclusions about this testing in other pre-transplant patients are more limited. Moreover, whether early detection with BCR-ABL testing would prevent blast

Genetic Testing Policies, Continued

Genetic Testing: PCR for BCR-ABL in Chronic Myelogenous Leukemia (CML), continued

crises and/or future stem-cell transplantation is unknown. Nevertheless, The National Comprehensive Cancer Network (NCCN) guidelines require BCR-ABL transcript analysis in diagnosis and monitoring of CML. Likewise, an extensive systematic review from the Medical Services Advisory Committee of Australia concluded that BCR-ABL transcript analysis is an accurate and cost-effective method of diagnosing and monitoring CML.

The clinical value of testing for specific BCR-ABL mutations is more controversial and less well-supported in the literature. The NCCN recommends ABL kinase domain (KD) mutation analysis in the event of inadequate treatment response. However, the literature is unclear as to the significance of specific ABL mutations, and whether identification of a particular mutation improves clinical outcomes or changes treatment decisions. The exception to this is the T315I mutation analysis. Both dasatinib and nilotinib are effective against most of the known BCR-ABL mutations. Their clinical effectiveness, along with that of imatinib and bosutinib is markedly diminished in the presence of the T315I mutation. Ponatinib, however, retains its clinical effectiveness in the presence of this mutation. Thus, for patients with this mutation, the choice of agent will alter clinical outcomes and thus clinical utility has been established. For the other BCR-ABL mutations, their clinical utility is not well-supported in the literature.

A phase II trial of 34 Ph-positive relapsed patients (Benjamini et al., 2014) showed high efficacy of treatment using a regimen that included Desatinib in imatinib resistant patients and depended on genotyping of BCR-ABL genotyping beyond just T315I.

More significantly, a multicenter study of TKI resistance (Zabriske et al., 2014) found that different mutations in BCR-ABL confer different resistance and that compound mutations in the fusion gene let to resistance even to Ponatinib (which had been effective in all single mutations) necessitating complete fusion gene genotyping for rational treatment TKI selection to optimize clinical outcome. These developments show that use of Ponatinib will not be effective against all mutations and mutational analysis will be needed to guide optimal TKI choice.

In the wake of these findings, the NCCN now includes complete mutation analysis in their latest (2015.1) guideline on diagnosis and treatment of CML.

Billing/Coding Information

CPT CODES

0016U	Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
0040U	BCR/ABL1 (t (9;22)) (e.g., chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
81206	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	; minor breakpoint, qualitative or quantitative
81208	; other breakpoint, qualitative or quantitative
81401	Molecular pathology procedure Level 2

HCPCS CODES

No specific codes identified

Key References

1. American Cancer Society. Treatment of Chronic Myeloid Leukemia by Phase. 2006. American Cancer Society. Available: http://www.cancer.org/docroot/CRI/content/CRI_2_4_4x_Treatment_of_Chronic_Myeloid_Leukemia_by_Phase_CML.asp?sitearea=CRI&viewmode=print&. Date Accessed: January 17, 2007.
2. Benjamini, O., et al. (2014). "Phase II trial of hyper CVAD and dasatinib in patients with relapsed Philadelphia chromosome

Genetic Testing Policies, Continued

Genetic Testing: PCR for BCR-ABL in Chronic Myelogenous Leukemia (CML), continued

- positive acute lymphoblastic leukemia or blast phase chronic myeloid leukemia." *Am J Hematol* 89(3): 282-287.
3. Branford S, Rudzki Z, Walsh S, et al. "Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor prognosis." *Blood* 102.1 (2003): 276-83.
 4. Branford, S. and T. P. Hughes (2011). "Mutational analysis in chronic myeloid leukemia: when and what to do?" *Curr Opin Hematol* 18(2): 111-116.
 5. Cortes J, Talpaz M, O'Brien S, et al. "Molecular responses in patients with chronic myelogenous leukemia in chronic phase treated with imatinib mesylate." *Clin Cancer Res* 11.9 (2005): 3425-32.
 6. Cortes, J. E., et al. (2013). "A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias." *N Engl J Med* 369(19): 1783-1796.
 7. Drobyski WR, Endean DJ, Klein JP, Hessner MJ. "Detection of BCR/ABL RNA transcripts using the polymerase chain reaction is highly predictive for relapse in patients transplanted with unrelated marrow grafts for chronic myelogenous leukaemia." *Br J Haematol* 98.2 (1997): 458-66.
 8. Druker, B. J. (2006). "Circumventing resistance to kinase-inhibitor therapy." *N Engl J Med* 354(24): 2594-2596.
 9. Emig M, Saussele S, Wittor H, et al. "Accurate and rapid analysis of residual disease in patients with CML using specific fluorescent hybridization probes for real time quantitative RT-PCR." *Leukemia* 13.11 (1999): 1825-32.
 10. Giles, F. J., J. Cortes, et al. (2007). "MK-0457, a novel kinase inhibitor, is active in patients with chronic myeloid leukemia or acute lymphocytic leukemia with the T315IBCR-ABL mutation." *Blood* 109(2): 500-502.
 11. Gontarewicz, A., S. Balabanov, et al. (2008). "Simultaneous targeting of Aurora kinases and Bcr-Abl kinase by the small molecule inhibitor PHA-739358 is effective against imatinib-resistant BCR-ABL mutations including T315I." *Blood*, 111(8): 4355-4364.
 12. Hughes T, Deininger M, Hochhaus A, et al. "Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results." *Blood* 108.1 (2006): 28-37.
 13. Jabbour E, Kantarjian H, Jones D, et al. "Frequency and clinical significance of BCR-ABL mutations in patients with chronic myeloid leukemia treated with imatinib mesylate." *Leukemia* 20.10 (2006): 1767-73.
 14. Kantarjian HM, Talpaz M, Cortes J, et al. "Quantitative polymerase chain reaction monitoring of BCR-ABL during therapy with imatinib mesylate (ST1571; gleevec) in chronic-phase chronic myelogenous leukemia." *Clin Cancer Res* 9.1 (2003): 160-6.
 15. Khorashad JS, Anand M, Marin D, et al. "The presence of a BCR-ABL mutant allele in CML does not always explain clinical resistance to imatinib." *Leukemia* 20.4 (2006): 658-63.
 16. Kim YJ, Kim DW, Lee S, et al. "Comprehensive comparison of FISH, RT-PCR, and RQ-PCR for monitoring the BCR-ABL gene after hematopoietic stem cell transplantation in CML." *Eur J Haematol* 68.5 (2002): 272-80.
 17. Kim YJ, Kim DW, Lee S, et al. "Early prediction of molecular remission by monitoring BCR-ABL transcript levels in patients achieving a complete cytogenetic response after imatinib therapy for posttransplantation chronic myelogenous leukemia relapse." *Biol Blood Marrow Transplant* 10.10 (2004): 718-25.
 18. Laboratory Corporation of America. BCR-ABL1 Kinase Domain Mutation Analysis. 2007. Available: <http://www.labcorp.com/datasets/labcorp/html/chapter/mono/mo003100.htm>.
 19. Lee, T. S., S. J. Potts, et al. (2008). "Molecular basis explanation for imatinib resistance of BCR-ABL due to T315I and P-loop mutations from molecular dynamics simulations." *Cancer* 112(8): 1744-1753.
 20. McKusick VA. Leukemia, Chronic Myeloid; CML. 2003. Online Mendelian Inheritance in Man (OMIM) Gene Records. Available: <http://www.ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=608232>. Date Accessed: January 27, 2007.
 21. Medical Services Advisory Committee. Polymerase chain reaction in the diagnosis and monitoring of patients with BCR-ABL gene rearrangement in chronic myeloid leukaemia. 2003. Commonwealth of Australia. Available: [http://www.msac.gov.au/internet/msac/publishing.nsf/Content/ref09ai-1/\\$FILE/msacref9ai.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/ref09ai-1/$FILE/msacref9ai.pdf). Date Accessed: January 17, 2007.
 22. Merx K, Muller MC, Kreil S, et al. "Early reduction of BCR-ABL mRNA transcript levels predicts cytogenetic response in chronic phase CML patients treated with imatinib after failure of interferon alpha." *Leukemia* 16.9 (2002): 1579-83.
 23. National Comprehensive Cancer Network. Chronic Myelogenous Leukemia. 2007. National Comprehensive Cancer Network, Inc. Available: http://www.nccn.org/professionals/physician_gls/PDF/cml.pdf. Date Accessed: January 19, 2007.
 24. Nicolinii FE, Corm S, Le QH, et al. "Mutation status and clinical outcome of 89 imatinib mesylate-resistant chronic myelogenous leukemia patients: a retrospective analysis from the French intergroup of CML (Fi(phi)-LMC GROUP)." *Leukemia* 20.6 (2006): 1061-6.
 25. Novartis Pharma AG. Gleevec Labeling. 2002. Available: <http://www.fda.gov/cder/foi/label/2002/021335s004lbl.pdf>. Date Accessed: January 17, 2007.
 26. Novartis Pharma AG. (2006).
 27. O'Hare, T., C. A. Eide, et al. (2008). "SGX393 inhibits the CML mutant Bcr-AblT315I and preempts in vitro resistance when combined with nilotinib or dasatinib." *Proc Natl Acad Sci U S A* 105(14): 5507-5512.
 28. Olavarria E, Kanfer E, Szydlo R, et al. "Early detection of BCR-ABL transcripts by quantitative reverse transcriptase-polymerase chain reaction predicts outcome after allogeneic stem cell transplantation for chronic myeloid leukemia." *Blood* 97.6 (2001): 1560-5.
 29. Paschka P, Muller MC, Merx K, et al. "Molecular monitoring of response to imatinib (Glivec) in CML patients pretreated with interferon alpha. Low levels of residual disease are associated with continuous remission." *Leukemia* 17.9 (2003): 1687-94.
 30. Press RD, Love Z, Tronnes AA, et al. "BCR-ABL mRNA levels at and after the time of a complete cytogenetic response (CCR) predict the duration of CCR in imatinib mesylate-treated patients with CML." *Blood* 107.11 (2006): 4250-6.
 31. Preudhomme C, Chams-Eddine L, Roumier C, et al. "Detection of BCR-ABL transcripts in chronic myeloid leukemia (CML) using an in situ RT-PCR assay." *Leukemia* 13.5 (1999): 818-23.
 32. Preudhomme C, Revillion F, Merlat A, et al. "Detection of BCR-ABL transcripts in chronic myeloid leukemia (CML) using a 'real time' quantitative RT-PCR assay." *Leukemia* 13.6 (1999): 957-64.
 33. Shi, X., Y. Jin, et al. (2009). "Triptolide inhibits Bcr-Abl transcription and induces apoptosis in ST1571-resistant chronic myelogenous leukemia cells harboring T315I mutation." *Clin Cancer Res* 15(5): 1686-1697.
 34. Soverini S, Martinelli G, Rosti G, et al. "ABL mutations in late chronic phase chronic myeloid leukemia patients with up-front cytogenetic resistance to imatinib are associated with a greater likelihood of progression to blast crisis and shorter survival: a

Genetic Testing Policies, Continued

Genetic Testing: PCR for BCR-ABL in Chronic Myelogenous Leukemia (CML), continued

- study by the GIMEMA Working Party on Chronic Myeloid Leukemia." *J Clin Oncol* 23.18 (2005): 4100-9.
- 35. Soverini, S., G. Martinelli, et al. (2006). "Presence or the emergence of a F317L BCR-ABL mutation may be associated with resistance to dasatinib in Philadelphia chromosome-positive leukemia." *J Clin Oncol* 24(33): e51-52.
 - 36. Tbakhi A, Pettay J, Sreenan JJ, et al. "Comparative analysis of interphase FISH and RT-PCR to detect *bcr-abl* translocation in chronic myelogenous leukemia and related disorders." *Am J Clin Pathol* 109.1 (1998): 16-23.
 - 37. The Leukemia & Lymphoma Society. Chronic Myelogenous Leukemia. 2006. The Leukemia & Lymphoma Society. Available: http://www.leukemia-lymphoma.org/all_page?item_id=8501. Date Accessed: January 17, 2007.
 - 38. Van Etten RA. Clinical manifestations and diagnosis of chronic myelogenous leukemia. 2006. UpToDate. Available: <http://www.utdol.com/utd/content/topic.do?topicKey=leukemia/9368&type=A&selectedTitle=1~33>. Date Accessed: January 17, 2007.
 - 39. Van Etten RA. Overview of the treatment of chronic myelogenous leukemia. 2006. UpToDate. Available: <http://www.utdol.com/utd/content/topic.do?topicKey=leukemia/15171&type=A&selectedTitle=3~33>. Date Accessed: January 17, 2007.
 - 40. Van Etten RA. Molecular genetics of chronic myelogenous leukemia. 2006. UpToDate. Available: <http://www.utdol.com/utd/content/topic.do?topicKey=leukemia/7803&type=A&selectedTitle=2~20>. Date Accessed: January 17, 2007.
 - 41. von Bubnoff, N., P. W. Manley, et al. (2006). "Bcr-Abl resistance screening predicts a limited spectrum of point mutations to be associated with clinical resistance to the Abl kinase inhibitor nilotinib (AMN107)." *Blood* 108(4): 1328-1333.
 - 42. Willis SG, Lange T, Demehri S, et al. "High-sensitivity detection of BCR-ABL kinase domain mutations in imatinib-naïve patients: correlation with clonal cytogenetic evolution but not response to therapy." *Blood* 106.6 (2005): 2128-37.
 - 43. Zabriskie, M. S., et al. (2014). "BCR-ABL1 compound mutations combining key kinase domain positions confer clinical resistance to ponatinib in Ph chromosome-positive leukemia." *Cancer Cell* 26(3): 428-442.

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: PTEN MUTATION ANALYSIS

Policy # 438

Implementation Date: 3/22/10

Review Dates: 4/21/11, 6/21/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 9/18/18, 8/8/19, 3/14/23, 6/12/24

Revision Dates: 7/1/23, 7/15/24

Related Medical Policies:

[#123 Gene Therapy, Testing, and Counseling](#)

[#664 Genetic Testing: Breast Cancer](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Colorectal cancer (CRC) and breast cancer are two of the most common cancers in the United States. Although recent improvements in screening and increased understanding of the genetics involved with these cancers has reduced the incidence of these cancers, the morbidity and mortality associated with CRC and breast cancer remains significant. Surgery is the usual approach for tumors that have not metastasized and may be curative. However, chemotherapy, sometimes with radiotherapy, is given to patients with stage III or IV (metastatic) cancer.

PTEN mutations have also been identified in a subset of patients for the PTEN hemartoma tumor syndromes (PHTS). PHTS encompasses many several disorders including Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Lhermitte-Duclos disease, Proteus syndrome (PS), Proteus-like syndrome, and autism spectrum disorder.

CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, kidney, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules, and present by the late 20s. The lifetime risk of developing breast cancer is 85%, with an average age of diagnosis between 38 and 46 years. The lifetime risk for thyroid cancer (usually follicular, rarely papillary, but never medullary thyroid cancer) is approximately 35%. The lifetime risk for renal cell cancer (predominantly of papillary histology) is 34%. The risk for endometrial cancer may approach 28%.

BRRS is a congenital disorder characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, and pigmented macules of the glans penis. PS is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses.

Proteus-like syndrome is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS. The targeted therapy Truqap (capivasertib) is a type of drug known as an AKT inhibitor. AKT inhibitors may work better in people with PTEN mutations.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Genetic Testing Policies, Continued

Genetic Testing: PTEN Mutation Analysis, continued

1. Select Health orders genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.
- 3. Select Health covers germline testing for PTEN gene mutations and deletions as a diagnostic tool for ruling out Cowden's syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), or another PTEN-related hamartoma syndrome (PHTS).** PTEN gene testing may be considered in individuals with a suspected or known clinical diagnosis of Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), or another PTEN-related hamartoma syndrome; or who have a known family history* of a PTEN mutation.

*Known deleterious family mutation in PTEN identified in 1st, 2nd, or 3rd degree biologic relative.

4. Testing is clinically indicated in the following scenarios:

- a) Individual from a family with a known PTEN P/LP variant
- b) Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- c) Individual meeting clinical diagnostic criteria for CS/PHTS
- d) Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of:
 - i. Adult Lhermitte-Duclos disease (cerebellar tumors); or
 - ii. Autism spectrum disorder and macrocephaly; or
 - iii. Two or more biopsy-proven trichilemmomas; or
 - iv. Two or more major criteria** (one must be macrocephaly); or
 - v. Three major criteria, without macrocephaly; or
 - vi. One major criterion and ≥ 3 minor criteria***; or
 - vii. ≥ 4 minor criteria
- e) Individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed; individual must have one of the following:
 - i. Any one major criterion; or
 - ii. Two minor criteria
- f) PTEN P/LP variant detected by tumor genomic testing on any tumor type in the absence of germline analysis

For breast cancer germline testing for PTEN see SH MP 664.

Select Health does NOT cover PTEN gene testing on tumor tissue in breast or colorectal cancer when used for the purpose of guiding treatment decisions. There is a lack of direct evidence regarding the role of PTEN somatic testing in these clinical settings. This meets the plan's definition of experimental/investigational.

Genetic Testing Policies, Continued

Genetic Testing: PTEN Mutation Analysis, continued

****Major criteria:** • Breast cancer • Endometrial cancer • Follicular thyroid cancer • Multiple GI hamartomas or ganglioneuromas • Macrocephaly (megalcephaly) (i.e., ≥ 97%, 58 cm in adult female, 60 cm in adult male) • Macular pigmentation of glans penis • Mucocutaneous lesions One biopsy-proven trichilemmoma Multiple palmoplantar keratoses Multifocal or extensive oral mucosal papillomatosis Multiple cutaneous facial papules (often verrucous)

****Minor criteria:** • Autism spectrum disorder • Colon cancer • ≥ 3 esophageal glycogenic acanthoses • Lipomas • Intellectual disability (i.e., IQ ≤ 75) • Papillary or follicular variant of papillary thyroid cancer • Thyroid structural lesions (e.g., adenoma, nodule[s], goiter) • Renal cell carcinoma • Single GI hamartoma or ganglioneuroma • Testicular lipomatosis • Vascular anomalies (including multiple intracranial developmental venous anomalies)

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp> or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

No systematic reviews on the role of PTEN (somatic) testing of tumor tissue for any clinical question were identified for this report. There is limited published evidence concerning the clinical utility of PTEN somatic testing in colorectal or breast cancer.

In CRC, Perrone et al. evaluated, retrospectively, multiple molecular markers in patients who did not respond to cetuximab; 13% of patients showed a decreased PTEN gene copy number and none of these patients responded to cetuximab. Unfortunately, the study is small; uncontrolled (i.e., single-arm only), and PTEN gene status was evaluated for copy number (by FISH) rather than protein expression (by IHC). Reviews of PTEN testing in CRC state inconsistencies in IHC testing methodology are at least partially responsible for the equivocal clinical results in CRC. While there is a substantial evidence base on PTEN gene/protein status, it is currently immature and extremely heterogeneous.

In breast cancer, a study by Capodanno et al. showed a 12.5% incidence of reduced PTEN expression (by IHC) in node negative breast carcinoma (n = 72). HER2 was expressed in 30% of the patients. Lack of PTEN expression was not associated with main clinicopathologic or biological parameters. A multivariate analysis showed that PTEN dysregulation was predictive of disease recurrence. This study was also uncontrolled so can only address prognostic value of measured markers. Studies comparing the PTEN mutation and other prognostic tests such as Oncotype DX are not available. Studies evaluating the PTEN mutation status and chemotherapy in early-stage breast cancer with clinical outcomes are not available. The evidence base is even larger with PTEN and breast cancer, and even more diverse. Clinical questions and settings addressed in published studies are nearly as numerous as the studies themselves, often with conflicting results.

In both diseases, interpretation of evidence is complicated by the many ways PTEN status is being measured, and includes gene mutations, gene copy number, deletions and duplications, polymorphisms, DNA expression, protein expression, various esoteric RNA moieties, and "systems biology" approaches. Additionally, measurement can be performed either on primary tumor or secondary/metastatic tissue, with widely varying concordance depending on what is being measured and stage of disease.

Genetic Testing Policies, Continued

Genetic Testing: PTEN Mutation Analysis, continued

As with BRAF and other molecular markers, determination of the predictive value of a biomarker requires, at minimum, retrospective validation (prospectively planned) on a well-designed and conducted RCT. Such a study, which has not yet been published, would then provide sufficient evidence, preferably duplicated in another quality study, to warrant performing a prospective RCT in a practical setting that includes the most appropriate patient-oriented outcome compared to current best practice.

The current published literature fails to answer key questions regarding the specific role of PTEN somatic (tumor) testing. Remaining questions include the role of the multiple additional molecular markers, the role of clinical markers (and their relationships with molecular markers), standardization and reliability of test assays, the value of testing the primary tumor versus or in addition to metastatic tumor tissue, the timing of biomarker measurement, and the most appropriate outcomes to assess the success and failure of decision-treatment protocols. As such, conclusions regarding the role of PTEN somatic testing in guiding colorectal or breast cancer treatment cannot be made.

Billing/Coding Information

CPT CODES

- | | |
|--------------|--|
| 0235U | PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions |
| 81321 | PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis |
| 81322 | PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant |
| 81323 | PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant |

HCPCS CODES

No specific codes identified

Key References

1. Bardelli A, Siena S. "Molecular Mechanisms of Resistance to Cetuximab and Panitumumab in Colorectal Cancer." *J Clin Oncol.*
2. Capodanno A, Camerini A, Orlandini C, et al. "Dysregulated PI3K/Akt/PTEN pathway is a marker of a short disease-free survival in node-negative breast carcinoma." *Hum Pathol* 40.10 (2009): 1408-17.
3. Christodoulou C, Kostopoulos I, Kalofonos HP, et al. "Trastuzumab combined with pegylated liposomal doxorubicin in patients with metastatic breast cancer. phase II Study of the Hellenic Cooperative Oncology Group (HeCOG) with biomarker evaluation." *Oncology* 76.4 (2009): 275-85.
4. Colakoglu T, Yildirim S, Kayaselcuk F, et al. "Clinicopathological significance of PTEN loss and the phosphoinositide 3-kinase/Akt pathway in sporadic colorectal neoplasms: is PTEN loss predictor of local recurrence?" *Am J Surg* 195.6 (2008): 719-25.
5. Evaluation of Genomic Applications in, P. and G. Prevention Working (2013). "Recommendations from the EGAPP Working Group: can testing of tumor tissue for mutations in EGFR pathway downstream effector genes in patients with metastatic colorectal cancer improve health outcomes by guiding decisions regarding anti-EGFR therapy?" *Genet Med* 15(7): 517-527.
6. Faratian D, Goltssov A, Lebedeva G, et al. "Systems biology reveals new strategies for personalizing cancer medicine and confirms the role of PTEN in resistance to trastuzumab." *Cancer Res* 69.16 (2009): 6713-20.
7. Frattini M, Salotti P, Romagnani E, et al. "PTEN loss of expression predicts cetuximab efficacy in metastatic colorectal cancer patients." *Br J Cancer* 97.8 (2007): 1139-45.
8. Garcia-Saenz JA, Sastre J, Diaz-Rubio Garcia E. "Biomarkers and anti-EGFR therapies for KRAS wild-type metastatic colorectal cancer." *Clin Transl Oncol* 11.11 (2009): 737-47.
9. Gori S, Sidoni A, Colozza M, et al. "EGFR, pMAPK, pAkt and PTEN status by immunohistochemistry: correlation with clinical outcome in HER2-positive metastatic breast cancer patients treated with trastuzumab." *Ann Oncol* 20.4 (2009): 648-54.
10. Jang KS, Song YS, Jang SH, et al. "Clinicopathological significance of nuclear PTEN expression in colorectal adenocarcinoma." *Histopathology* 56.2: 229-39.
11. Kendall A, Lord R, Maisey N. "Anti-Epidermal Growth Factor Receptor Antibodies in the Treatment of Metastatic Colorectal Cancer." *Recent Pat Anticancer Drug Discov* (2009).
12. Laurent-Puig P, Cayre A, Manceau G, et al. "Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer." *J Clin Oncol* 27.35 (2009): 5924-30.

Genetic Testing Policies, Continued

Genetic Testing: PTEN Mutation Analysis, continued

13. Li XH, Zheng HC, Takahashi H, Masuda S, Yang XH, Takano Y. "PTEN expression and mutation in colorectal carcinomas." *Oncol Rep* 22.4 (2009): 757-64.
14. Loupakis F, Pollina L, Stasi I, et al. "PTEN expression and KRAS mutations on primary tumors and metastases in the prediction of benefit from cetuximab plus irinotecan for patients with metastatic colorectal cancer." *J Clin Oncol* 27.16 (2009): 2622-9.
15. Mandrekar SJ, Sargent DJ. "Clinical trial designs for predictive biomarker validation: theoretical considerations and practical challenges." *J Clin Oncol* 27.24 (2009): 4027-34.
16. Molinari F, Martin V, Saletti P, et al. "Differing deregulation of EGFR and downstream proteins in primary colorectal cancer and related metastatic sites may be clinically relevant." *Br J Cancer* 100.7 (2009): 1087-94.
17. Negri FV, Bozzetti C, Lagrasta CA, et al. "PTEN status in advanced colorectal cancer treated with cetuximab." *Br J Cancer* 102.1: 162-4.
18. Perrone F, Lampis A, Orsenigo M, et al. "PI3KCA/PTEN deregulation contributes to impaired responses to cetuximab in metastatic colorectal cancer patients." *Ann Oncol* 20.1 (2009): 84-90.
19. Planchon SM, Waite KA, Eng C. "The nuclear affairs of PTEN." *J Cell Sci* 121.Pt 3 (2008): 249-53.
20. Razis E, Brasoulis E, Vrettou E, et al. "Potential value of PTEN in predicting cetuximab response in colorectal cancer: an exploratory study." *BMC Cancer* 8 (2008): 234.
21. Rychahou PG, Kang J, Gulhati P, et al. "Akt2 overexpression plays a critical role in the establishment of colorectal cancer metastasis." *Proc Natl Acad Sci U S A* 105.51 (2008): 20315-20.
22. Sartore-Bianchi A, Di Nicolantonio F, Nichelatti M, et al. "Multi-determinants analysis of molecular alterations for predicting clinical benefit to EGFR-targeted monoclonal antibodies in colorectal cancer." *PLoS One* 4.10 (2009): e7287.
23. Sartore-Bianchi A, Martini M, Molinari F, et al. "PIK3CA mutations in colorectal cancer are associated with clinical resistance to EGFR-targeted monoclonal antibodies." *Cancer Res* 69.5 (2009): 1851-7.
24. Sawai H, Yasuda A, Ochi N, et al. "Loss of PTEN expression is associated with colorectal cancer liver metastasis and poor patient survival." *BMC Gastroenterol* 8 (2008): 56.
25. Swart R, Downey L, Lang J, Thompson P, Livingston RB, Stopeck A. *Breast Cancer*. February 10, 2010. eMedicine. Available: <http://emedicine.medscape.com/article/283561-overview>. Date Accessed: February 3, 2010.
26. Therkildsen, C., et al. (2014). "The predictive value of KRAS, NRAS, BRAF, PIK3CA and PTEN for anti-EGFR treatment in metastatic colorectal cancer: A systematic review and meta-analysis." *Acta Oncol*.
27. Wee S, Jagani Z, Xiang KX, et al. "PI3K pathway activation mediates resistance to MEK inhibitors in KRAS mutant cancers." *Cancer Res* 69.10 (2009): 4286-93.
28. Yonemori K, Tsuta K, Shimizu C, et al. "Immunohistochemical expression of PTEN and phosphorylated Akt are not correlated with clinical outcome in breast cancer patients treated with trastuzumab-containing neo-adjuvant chemotherapy." *Med Oncol* 26.3 (2009): 344-9.

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: RETT SYNDROME

Policy # 586

Implementation Date: 6/6/16

Review Dates: 8/17/17, 8/13/18, 10/13/19, 4/5/23, 6/12/24

Revision Dates: 9/24/18, 7/1/23, 7/15/24

Related Medical Policies:

[#123 Gene Therapy, Testing, and Counseling](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Rett syndrome is an X-linked dominant genetic neurodevelopmental disorder. There is wide variability in the rate of progression and severity of the disease. Over 80% of patients with classical Rett have pathogenic mutations in the *MECP2* gene. More than 200 mutations in *MECP2* have been associated with Rett. However, 8 of the most commonly occurring missense and nonsense mutations account for almost 70% of all cases. Small C-terminal deletions account for approximately 10%; and large deletions, 8% to 10%. *MECP2* mutation type is associated with disease severity. Whole duplications of the *MECP2* gene have been associated with severe X-linked intellectual disability with progressive spasticity, no or poor speech acquisition, and acquired microcephaly. In addition, the pattern of X-chromosome inactivation influences the severity of the clinical disease in females.

This disorder primarily affects individuals assigned female at birth (AFAB) with an incidence of 1:10,000 AFAB births, making it one of the most common genetic causes of intellectual disability in individuals assigned female at birth. In AFAB, classic Rett syndrome is characterized by apparently normal psychomotor development during the first six to 18 months of life, followed by a short period of developmental stagnation, then rapid regression in language and motor skills, followed by long-term stability. During the phase of rapid regression, repetitive, stereotypic hand movements replace purposeful hand use. Additional findings include fits of screaming and inconsolable crying, autistic features, panic-like attacks, bruxism, episodic apnea and/or hyperpnea, gait ataxia and apraxia, tremors, seizures, and acquired microcephaly. In individuals assigned male at birth (AMAB), this condition presents as severe neonatal-onset encephalopathy characterized by a relentless clinical course that follows a metabolic-degenerative type of pattern, abnormal tone, involuntary movements, severe seizures, and breathing abnormalities. Death often occurs before age two years.

The diagnosis of Rett remains a clinical one, using diagnostic clinical criteria that have been established for the diagnosis of classic and variant Rett syndrome. Rett syndrome is usually caused by mutations in the *MECP2* (methyl-CpG-binding protein 2) gene. Genetic testing is available to determine whether a pathogenic mutation exists in a patient with clinical features of Rett syndrome, or in a patient's family member.

Approximately 99.5% of cases of Rett are sporadic, resulting from a de novo mutation, which arise almost exclusively on the paternally derived X chromosome. The remaining 0.5% of cases are familial and usually explained by germline mosaicism or favorably skewed X-chromosome inactivation in the carrier mother that results in her being unaffected or only slightly affected (mild intellectual disability). In the case of a carrier mother, the recurrence risk of RTT is 50%. If a mutation is not identified in leukocytes of the mother, the risk to a sibling of the proband is below 0.5% (since germline mosaicism in either parent cannot be excluded).

Genetic Testing Policies, Continued

Genetic Testing: Rett Syndrome, continued

There are currently no specific treatments that halt or reverse the progression of the disease, and there are no known medical interventions that will change the outcome of patients with Rett. Management is mainly symptomatic and individualized, focusing on optimizing each patient's abilities. A multidisciplinary approach is usually used, with specialist input from dietitians, physiotherapists, occupational therapists, speech therapists, and music therapists. Regular monitoring for scoliosis (seen in about 87% of patients by age 25 years) and possible heart abnormalities may be recommended. Spasticity can have a major impact on mobility; physical therapy and hydrotherapy may prolong mobility. Occupational therapy can help children develop communication strategies and skills needed for performing self-directed activities (such as dressing, feeding, practicing arts, and crafts).

Pharmacologic approaches to managing problems associated with RTT include melatonin for sleep disturbances and several agents for the control of breathing disturbances; seizures; and stereotypic movements. Rett patients have an increased risk of life-threatening arrhythmias associated with a prolonged QT interval, and avoidance of a number of drugs is recommended, including prokinetic agents, antipsychotics, tricyclic antidepressants, antiarrhythmics, anesthetic agents, and certain antibiotics.

The identification of a mutation in *MECP2* does not necessarily equate to a diagnosis of Rett. Rare cases of *MECP2* mutations have also been reported in other clinical phenotypes, including individuals with an Angelman-like picture, non-syndromic X-linked intellectual disability, PPM-X syndrome (an X-linked genetic disorder characterized by psychotic disorders [most commonly bipolar disorder], parkinsonism, and intellectual disability], autism, and neonatal encephalopathy.

A proportion of patients with a clinical diagnosis of Rett do not appear to have mutations in the *MECP2* gene. Two other genes, *CDKL5* and *FOXP1*, have been shown to be associated with atypical variants.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.
3. Select Health covers genetic testing for potential carriers and patients suspected of having Rett syndrome.

Rett syndrome should NOT be suspected if an individual has a history of:

- Brain injury secondary to peri- or postnatal trauma, neurometabolic disease, or severe infection that causes neurologic problems
- Grossly abnormal psychomotor development in the first six months of life, with early milestones not being met

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the **Select Health Commercial policy applies**. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website

Genetic Testing Policies, Continued

Genetic Testing: Rett Syndrome, continued

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

According to a large reference laboratory, MECP2 testing for RTT has an analytic sensitivity for sequencing of 99% and for MLPA, 90%; analytic specificity is 99% for sequencing and for MLPA, 98%.

Huppke et al (2000) analyzed the MECP2 gene in 31 female patients diagnosed clinically with RTT. (13) Sequencing revealed mutations in 24 of the 31 patients (77%). Of the 7 patients in whom no mutations were found, 5 fulfilled criteria for classical RTT. In this study, 17 different mutations were detected, 11 of which had not been previously described. Several females carrying the same mutation displayed different phenotypes, suggesting that factors other than the type or position of mutations influenced the severity of RTT.

Cheadle et al (2000) analyzed mutations in 48 females with classical sporadic RTT, 7 families with possible familial RTT, and 5 sporadic females with features suggestive, but not diagnostic, of RTT. (14) The entire MECP2 gene was sequenced in all cases. Mutations were identified in 44 (80%) of 55 unrelated classical sporadic and familial RTT patients. Only 1 (20%) of 5 sporadic cases with suggestive but nondiagnostic features of RTT had mutations identified. Twenty-one different mutations were identified (12 missense, 4 nonsense, and 5 frame-shift mutations); 14 of the mutations identified were novel. Significantly milder disease was noted in patients carrying missense mutations as compared with those with truncating mutations.

The 2 studies previously outlined were included in a summary of 6 articles by Lotan et al (2006) who attempted to disclose a genotype-phenotype correlation (3). The authors found that these studies have yielded inconsistent results and that further controlled studies are needed before valid conclusions can be drawn about the effect of mutation type on phenotypic expression. Two subsequent studies (15, 16) used the InterRett database to examine genotype and RTT severity. Of 357 girls with epilepsy who had MECP2 genotype recorded, those with large deletions were more likely than those with 10 other common mutations to have active epilepsy (odds ratio [OR], 3.71; 95% confidence interval [CI], 1.13 to 12.17; p=0.03) and had the earliest median age at epilepsy onset (3 years, 5 months). Among all girls in the database, those with large deletions were more likely to have never walked (OR=0.42; 95% CI, 0.22 to 0.79; p=0.007). Of 260 girls with classic RTT enrolled in the multicenter RTT Natural History study (NCT00299312), those with the R133C substitution mutation had clinically less severe disease, assessed by the Clinical Severity, Motor Behavior Analysis, and Physician Summary scales. Fabio et al (2014) reported similar genotype-phenotype correlations among 144 patients with RTT in Italy.

Evidence from several small studies has indicated that the clinical sensitivity of genetic testing for classical RTT is reasonably high, in the range of 75% to 80%. However, sensitivity may be lower when classic RTT features are absent. Clinical specificity is unknown, but also is likely to be high, as only rare cases of MECP2 mutations have been reported in other clinical phenotypes, including individuals with an Angelman-like picture, non-syndromic X-linked intellectual disability, PPM-X syndrome, autism, and neonatal encephalopathy.

The clinical utility of genetic testing can be considered in the following clinical situations: (1) individuals with suspected RTT, (2) family members of individuals with RTT, and (3) prenatal testing for mothers with a previous RTT child. These situations will be discussed separately next.

The clinical utility for these patients depends on the ability of genetic testing to make a definitive diagnosis and for that diagnosis to lead to management changes that improve outcomes. No studies were identified that described how a molecular diagnosis of RTT changed patient management. Therefore, there is no direct evidence for the clinical utility of genetic testing in these patients.

Genetic Testing Policies, Continued

Genetic Testing: Rett Syndrome, continued

There is no specific treatment for RTT, so making a definitive diagnosis will not lead to treatment that alters the natural history of the disorder. There are several potential ways in which adjunctive management might be changed after genetic confirmation of the diagnosis:

- Further diagnostic testing may be avoided
- Referral to a specialist(s) may be made
- Heightened surveillance for Rett-associated clinical manifestations, such as scoliosis or cardiac arrhythmias may be performed
- More appropriate tailoring of ancillary treatments such as occupational therapy may be possible

Billing/Coding Information

CPT CODES

0234U	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
81302	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants
81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81471	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81479	Unlisted molecular pathology procedure

HCPCS CODES

No specific codes identified

Key References

1. AAP publications retired and reaffirmed. Pediatrics. Dec 2007, reaffirmed in 2010 and 2014; 126: e1622. PMID 18056790
2. Amir RE, Sutton VR, Van den Veyver IB. Newborn screening and prenatal diagnosis for Rett syndrome: implications for therapy. J Child Neurol. Sep 2005; 20(9):779-783. PMID 16225835
3. Archer H, Evans J, Leonard H, et al. Correlation between clinical severity in patients with Rett syndrome with a pR168X or pT158M MECP2 mutation, and the direction and degree of skewing of X-chromosome inactivation. J Med Genet. Feb 2007;44(2):148-152. PMID 16905679
4. ARUP Laboratories. Rett Syndrome (MECP2): sequencing and deletion/duplication. <http://ltd.aruplab.com/Tests/Pub/0051614>. Accessed August 2014.
5. ARUP Laboratories. Rett Syndrome (MECP2): sequencing and deletion/duplication. <http://ltd.aruplab.com/Tests/Pub/0051614>. Accessed November 2015
6. Bao X, Downs J, Wong K, et al. Using a large international sample to investigate epilepsy in Rett syndrome. Dev Med Child Neurol. Jun 2013; 55(6):553-558. PMID 23421866
7. Bebbington A, Downs J, Percy A, et al. The phenotype associated with a large deletion on MECP2. Eur J Hum Genet. Sep 2012; 20(9):921-927. PMID 22473088
9. Cheadle JP, Gill H, Fleming N, et al. Long-read sequence analysis of the MECP2 gene in Rett syndrome patients: correlation of disease severity with mutation type and location. Hum Mol Genet. Apr 12, 2000; 9(7):1119-1129. PMID 10767337

Genetic Testing Policies, Continued

Genetic Testing: Rett Syndrome, continued

10. Cuddapah VA, Pillai RB, Shekar KV, et al. Methyl-CpG-binding protein 2 (MECP2) mutation type is associated with disease severity in Rett syndrome. *J Med Genet.* Mar 2014;51(3):152-158. PMID 24399845
11. Fabio RA, Colombo B, Russo S, et al. Recent insights into genotype-phenotype relationships in patients with Rett syndrome using a fine grain scale. *Res Dev Disabil.* Aug 11, 2014;35(11):2976-2986. PMID 25124696
12. Guy J, Gan J, Selfridge J, et al. Reversal of neurological defects in a mouse model of Rett syndrome. *Science.* Feb 23, 2007; 315(5815):1143-1147. PMID 17289941
13. Huppke P, Laccone F, Kramer N, et al. Rett syndrome: analysis of MECP2 and clinical characterization of 31 patients. *Hum Mol Genet.* May 22, 2000; 9(9):1369-1375. PMID 10814718
14. Johnson CP, Myers SM. Identification and evaluation of children with autism spectrum disorders. *Pediatrics.* Nov 2007;120(5):1183-1215. PMID 17967920
15. Kaur, S. & Christodoulou, M. P. MECP2 Disorders. National Library Medicine. <https://www.ncbi.nlm.nih.gov/sites/books/NBK1497/>
16. Lane JB, Lee HS, Smith LW, et al. Clinical severity and quality of life in children and adolescents with Rett syndrome. *Neurology.* Nov 15, 2011; 77(20):1812-1818. PMID 22013176
17. Liyanage VR, Rastegar M. Rett syndrome and MeCP2. *Neuromolecular Med.* Jun 2014;16(2):231-264. PMID 24615633
18. Lotan M, Ben-Ze'ev B. Rett syndrome. A review with emphasis on clinical characteristics and intervention. *ScientificWorldJournal.* 2006; 6:1517-1541. PMID 17160339
19. Michelson DJ, Shevell MI, Sherr EH, et al. Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* Oct 25, 2011; 77(17):1629-1635. PMID 21956720
20. Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol.* Dec 2010;68(6):944-950. PMID 21154482
21. Robinson L, Guy J, McKay L, et al. Morphological and functional reversal of phenotypes in a mouse model of Rett syndrome. *Brain.* Sep 2012; 135(Pt 9):2699-2710. PMID 22525157
22. Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. *Genet Med.* May 2013;15(5):399-407. PMID 23519317
23. Suter B, Treadwell-Deering D, Zoghbi HY, et al. Brief report: MECP2 mutations in people without Rett syndrome. *J Autism Dev Disord.* Mar 2014;44(3):703-711. PMID 23921973
24. Weaving LS, Williamson SL, Bennetts B, et al. Effects of MECP2 mutation type, location and X-inactivation in modulating Rett syndrome phenotype. *Am J Med Genet A.* Apr 15, 2003;118A(2):103-114. PMID 12655490
25. Williamson SL, Christodoulou J. Rett syndrome: new clinical and molecular insights. *Eur J Hum Genet.* Aug 2006; 14(8):896-903. PMID 16865103

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Genetic Testing Policies, Continued



MEDICAL POLICY

GENETIC TESTING: SPINAL MUSCULAR ATROPHY

Policy # 600

Implementation Date: 11/14/16

Review Dates: 12/21/17, 12/11/18, 4/5/23, 5/10/24

Revision Dates: 9/17/18, 7/1/23, 7/25/24

Related Medical Policies:

[#123 Gene Therapy, Testing, and Counseling](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Spinal muscular atrophy (SMA) disorders are characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem. These diseases are classified as types 0 through IV depending upon the age of onset and clinical course.

- SMA 0 has prenatal onset of severe hypotonia, weakness, and areflexia. This can present as decreased fetal movements during pregnancy. Other findings include arthrogryposis, atrial septal defects, facial diplegia, and respiratory failure at birth. Lifespan is typically less than 6 months.
- SMA I, also known as infantile spinal muscular atrophy or Werdnig-Hoffmann disease, is the most common and severe type of SMA. It typically presents in the neonatal period with loss of head control, joint contractures, and variable difficulties with sucking and swallowing. Symptoms progress rapidly, with median survival reported as ranging from 8-24 months.
- SMA II presents between 6 and 18 months of age. Poor muscle tone is often the first symptom and motor milestones, such as sitting independently, are slowly gained until around five years old. Affected individuals typically have a slow decline in motor function with progressive respiratory muscle weakness leading to restrictive lung disease. Scoliosis and finger tremors are also frequently seen. Life expectancy estimates are not established; one study reported 68% of individuals with SMA II alive at 25 years old.
- SMA III typically presents after 18 months. Affected individuals often can walk independently although, over time, may have trouble with frequent tripping and difficulty with stairs. Similar to SMA II, there is a slow decline in motor function, although respiratory muscle weakness is less common. A retrospective study found no difference in life expectancy between individuals with SMA III and the general population.
- SMA IV usually presents in adulthood. Though manifesting with some muscular weakness and gait dysfunction, loss of ambulation is not usually until after the fifth decade, and these individuals tend to have a normal lifespan.

The inheritance pattern of SMA is autosomal recessive, resulting from biallelic variants in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13.2. Approximately 95% of individuals with SMA have homozygous deletions of exon 7, while the remaining 5% are compound heterozygous for an exon 7 deletion and a *SMN1* sequence variant. SMN protein appears to play a role in mRNA synthesis in motor neurons and may also inhibit apoptosis. The level of SMN protein tends to correlate with the severity of the clinical manifestations.

The *SMN2* gene also encodes for the SMN protein, although it makes several versions of the protein and only one is functional while the others are quickly degraded. While most people have two copies of the



Genetic Testing Policies, Continued

Genetic Testing: Spinal Muscularatrophy, continued

SMN2 gene, the number of copies can vary. For individuals with SMA, having multiple copies of *SMN2* is often associated with less severe disease as the *SMN2* gene compensates for some of the *SMN* protein deficiency resulting from the *SMN1* deletion or sequence variant.

Genetic testing is done to confirm a diagnosis of SMA. Definitive diagnosis may allow for more appropriate therapy beyond supportive care, especially for individuals with SMA I and SMA II.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

3. Select Health covers genetic testing for spinal muscular atrophy (*SMN1* and *SMN2*) for any of the following groups:

- A. Individuals suspected of having spinal muscular atrophy (SMA) who have manifested symptoms suggestive of the disorder; or
- B. Couples seeking prenatal care; or
- C. Couples who are planning a pregnancy; or
- D. Individuals with a family history of SMA; or
- E. Individuals with a first-degree relative identified as an SMA carrier.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Summary of Medical Information

Spinal muscular atrophy (SMA) is the second most common fatal autosomal recessive disorder after cystic fibrosis, with an estimated carrier frequency of 1/40 to 1/60 in the general population. SMA affects alpha motor neurons in the spinal cord; degeneration of these neurons leads to severe, progressive proximal muscle weakness. Based on age of onset and clinical course, five phenotypes are observed: SMA 0 has prenatal onset of severe weakness and hypotonia with respiratory distress at birth; lifespan is typically weeks to months. SMA I (Werdnig-Hoffmann) presents with severe, generalized muscle weakness and hypotonia are present by six months of age, and death from respiratory failure usually

Genetic Testing Policies, Continued

Genetic Testing: Spinal Muscular Atrophy, continued

occurs before age 2 years. In SMA II, children can sit, although they are unable to stand or walk unaided; survival is typically into early adulthood. SMA III (Kugelberg-Welander) is a milder form—patients can walk unaided—with onset after 18 months of age. SMA IV manifests in adulthood and may result in increased muscular weakness but usually has no impact on lifespan.

ACMG's 2008 guideline, reaffirmed in 2013, recommends carrier testing for SMA in all couples regardless of race or ethnicity. ACOG's 2017 Committee Opinion states: "Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant."

The evidence for carrier testing in individuals who are asymptomatic but at risk for having an offspring with a genetic disease includes mutation prevalence studies, general principles of carrier testing, and accepted practice guidelines from major medical societies; the evidence provides a framework for evaluating these tests because direct evidence on outcomes with carrier testing is lacking. Relevant outcomes are test accuracy, test validity, and changes in reproductive decision making. Reported analytic validity (technical accuracy) of targeted carrier screening tests is high. Changes in management involve family planning. Results of genetic testing can be used to assist individuals with reproductive decisions such as avoidance of pregnancy, preimplantation genetic testing, and adoption. Therefore, the evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Billing/Coding Information

CPT CODES

0236U	SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications, deletions, and mobile element
81336	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence
81337	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s)
81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed

HCPCS CODES

G0452	Molecular pathology procedure; physician interpretation and report
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Key References

1. Carrier screening for genetic conditions. Committee Opinion No. 691. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2017; 129:341–55.
2. Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. 2000 Feb 24 [Updated 2020 Dec 3]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1352/>
3. UpToDate – Spinal Muscular Atrophy; accessed on 11/4/16.

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Genetic Testing Policies, Continued

Genetic Testing: Spinal Muscularatrophy, continued

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Genetic Testing Policies, Continued



MEDICAL POLICY

PHARMACOGENOMIC TESTING FOR DRUG METABOLISM

Policy # 590

Implementation Date: 1/16/17

Review Dates: 12/21/17, 12/13/18, 4/26/23, 7/31/24

Revision Dates: 9/17/18, 7/1/23, 1/24/24, 8/29/24

Related Medical Policies:

[#123 Gene Therapy, Testing, and Counseling](#)

[#426 Genetic Testing: \(MTHFR\) Polymorphisms in Cancer, Cardiovascular Disease, and Neural Tube Defects](#)

[#594 Genetic Testing: 5-Fluorouracil Testing in Cancer Patients](#)

Disclaimer:

1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Pharmacogenomics (PGx) is the study of gene variations within an individual's DNA and how these differences influence an individual's response to medications. An individual's unique genetic makeup helps determine how they respond to a drug and whether side effects or adverse reactions may be experienced. Variations in genes may also cause an individual to metabolize a drug more quickly, more slowly or at the same rate as anticipated, based on dosage.

Various factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, ethnicity, and drug-drug interactions. Inherited (germline) DNA sequence variations (or, polymorphisms) in genes coding for drug metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse effects, and decrease medical costs.

PGx tests are indicated when medications are being considered for use (or already prescribed) that are medically necessary, appropriate, and approved for use in the patient's condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable as defined by the FDA (PGx information required for safe drug administration) or Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines (category A or B).

The selection of the medications in question must be derived from clinical factors/necessity rather than from a PGx test. Once the putative therapeutic agents are selected, and those agents are known to have gene-drug interactions as identified above, then a PGx test may be considered reasonable and necessary as the result of that test would aid physician's prescribing or dosing decisions.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.

Select Health also recommends submitting documentation that shows a review of clinical



Genetic Testing Policies, Continued

Pharmacogenomic Testing for Drug Metabolism, continued

literature or guidelines which would support this genetic testing; and

2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

PGx test may be considered reasonable and necessary:

- 1) When the result of that test is necessary for the physician's decision-making process regarding safely administering or dosing the drug.
- 2) The selection of the medications in question must be derived from clinical factors/necessity and have been demonstrated to be clinically actionable as defined by the FDA (PGx information required for safe drug administration) or Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines (category A and B).

The following pharmacogenomic tests and indications are covered when the member meets the applicable criteria below:

SINGLE GENE: The clinical record must clearly show the use of, or intent to prescribe, a drug that has known drug-gene interactions that require a PGx test (based on CPIC level A or B guidelines) to be ordered to define the safe use of that drug in that patient:

- a. If two or more single genes are tested, then the record must reflect that a clinician individually ordered each gene, and each single gene must individually be reasonable and necessary at the time they are ordered.

A multi-gene panel is not considered medically necessary because it is unproven to improve health outcomes.

See Select Health Medical Policy 426: MTHFR, for panels or tests ordered solely for MTHFR testing.

PGx testing is covered for single genes for the following gene-drug pairs:

Gene	Drug	CPIC Level
Abacavir	<i>HLA-B</i>	A
Allopurinol	<i>HLA-B</i>	A
Amitriptyline	<i>CYP2C19</i>	A
	<i>CYP2D6</i>	A
Atomoxetine	<i>CYP2D6</i>	A
Azathioprine	<i>TPMT</i>	A
	<i>NUDT15</i>	A
Capecitabine	<i>DPYD</i>	A
Carbamazepine	<i>HLA-B</i>	A
	<i>HLA-A</i>	A
Celecoxib	<i>CYP2C9</i>	A
Citalopram	<i>CYP2C19</i>	A
Clomipramine	<i>CYP2D6</i>	A
	<i>CYP2C19</i>	A
Clopidogrel	<i>CYP2C19</i>	A
Codeine	<i>CYP2D6</i>	A
Desipramine	<i>CYP2D6</i>	B
Dexlansoprazole	<i>CYP2C19</i>	B
Doxepin	<i>CYP2C19</i>	B
	<i>CYP2D6</i>	B
Efavirenz	<i>CYP2B6</i>	A
Escitalopram	<i>CYP2C19</i>	A

Genetic Testing Policies, Continued

Pharmacogenomic Testing for Drug Metabolism, continued

Fluorouracil	<i>DPYD</i>	A
Flurbiprofen	<i>CYP2C9</i>	A
Fluvoxamine	<i>CYP2D6</i>	A
Ibuprofen	<i>CYP2C9</i>	A
Imipramine	<i>CYP2C19</i>	B
	<i>CYP2D6</i>	B
Meloxicam	<i>CYP2C9</i>	A
Mercaptopurine	<i>TPMT</i>	A
	<i>NUDT15</i>	A
Nortriptyline	<i>CYP2D6</i>	A
Omeprazole	<i>CYP2C19</i>	A
Oxcarbazepine	<i>HLA-A</i>	C
	<i>HLA-B</i>	A
Pantoprazole	<i>CYP2C19</i>	A
Paroxetine	<i>CYP2D6</i>	A
Piroxicam	<i>CYP2C9</i>	A
Simvastatin	<i>SLCO1B1</i>	A
Succinylcholine	<i>CACNA15</i>	A
	<i>RYR1</i>	A
Tacrolimus	<i>CYP3A5</i>	A
Tamoxifen	<i>CYP2D6</i>	A
Thioguanine	<i>TPMT</i>	A
	<i>NUDT15</i>	A
Tramadol	<i>CYP2D6</i>	A
Trimipramine	<i>CYP2D6</i>	B
	<i>CYP2C19</i>	B
Voriconazole	<i>CYP2C19</i>	A
Warfarin	<i>CYP2C9</i>	A
	<i>CYP4F2</i>	A
	<i>VKORC1</i>	A

Other Considerations

For pharmacogenomic tests that look for changes in germline DNA (i.e., not tumor DNA or viral DNA), **testing will be allowed once per lifetime per gene.** Exceptions may be considered if technical advances in testing or the discovery of novel genetic variants demonstrate significant advantages that would support a medical need to retest.

Testing performed in a CLIA-certified laboratory will be considered for coverage. The use of a specific FDA approved companion diagnostic is not necessary for coverage to be considered.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the manual website [the manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Genetic Testing Policies, Continued

Pharmacogenomic Testing for Drug Metabolism, continued

Summary of Medical Information

Current evidence regarding the use of genotyping tests for the determination of drug metabolizer status indicates that while available testing methods may accurately identify genetic variations in an individual, there is insufficient data to demonstrate that such testing, and the clinical decisions made based on the testing, results in a significant impact on health outcomes. Specifically, clinical trials have not yet adequately demonstrated that such testing results in either enhanced clinical effectiveness, or in decreased short-term or long-term serious adverse events.

A particular variant is not always phenotype specific in that it may have a different impact depending on the drug in question (National Academy of Clinical Biochemistry [NACB], 2010). Racial and ethnic differences in the frequency and nature of genetic variants are also possible and should be recognized in translating outcomes from one population to another. The relation of a gene or gene biomarker and a drug target must be validated for each therapeutic indication in different racial and ethnic groups, as well as in different treatment and disease contexts (Kager and Evans, 2012). Pharmacogenetic testing is not currently recommended for general population screening (National Academy for Clinical Biochemistry [NACB], 2010).

Recently, the FDA has added language to the labels of many approved drugs to include pharmacogenomic information. Wang and colleagues published a study evaluating the evidence that supports pharmacogenomic biomarker testing in drug labels and how frequently testing is recommended (2014). Their analysis found that of the 119 drug-biomarker combinations identified, only 43 (36.1%) had labels that provided convincing clinical validity evidence supporting pharmacogenomic testing related to a specific drug. Furthermore, only 18 (15.1%) provided convincing evidence of clinical utility.

Recommendations on the manner of clinical decisions based on the results of a biomarker test were made on 61 labels (51.3%); but only 36 (30.3%) of these contained convincing clinical utility data. A full description of the supporting studies for these recommendations was included in 13 labels (10.9%). The authors found that less than one-sixth of drug labels contained or referenced convincing evidence of clinical utility of biomarker testing, whereas more than half made recommendations based on biomarker test results. They concluded that it may be premature to include biomarker testing recommendations in drug labels when convincing data that link testing to health outcomes do not exist.

Critical elements of assessing the effectiveness of such genetic tests include: (1) analytic (diagnostic) validity; (2) clinical validity; and (3) clinical utility. Analytic validity measures the technical performance of the test, in terms of accurately identifying the genetic markers to be measured. Clinical validity measures the strength of association between genetic test results and clinical parameters such as dose, therapeutic efficacy, or adverse events. Clinical utility, the ultimate goal of genetic testing, measures the ability of the test to improve clinical outcomes, such as whether prescribing or dosing based on information from genetic testing improves therapeutic efficacy or adverse event rate as compared with treatment without genetic testing.

Testing for genetic polymorphisms has also been proposed for a wide array of drugs, involving many different conditions and enzymes. At this time, the available literature addressing such testing is limited and insufficient to allow any assessment of clinical utility in the treatment of individuals. The outcomes that require further research attention include major adverse events, utilization of health resources, and time to clinically significant changes in condition using appropriate and validated measures.

While the potential of pharmacogenomics is intriguing for many clinical applications, it is not yet clear which are most likely to yield clinical benefit in the near future. As this field evolves and matures, and if pre-prescription testing can be shown to be of clinical utility for specific drugs and individuals, it will be imperative to establish evidence-based guidelines for health care professionals delineating the most effective courses of action based on such genotype testing results.

Several commercial laboratories market multi-test panels for genetic polymorphisms related to drug metabolizer status. While the use of some individual tests included in these test panels may be reasonable under specific circumstances, the use of all the tests within a panel is rarely justified unless there is clinical evidence that the panel provides information that leads to meaningful impact on treatment. At this time, the available published evidence addressing the use of such test panels is limited to a few panel- and condition-specific studies (Altar, 2015; Hall-Flavin 2012, 2013; Winner, 2013a, 2013b). The results of these studies are limited by the study designs utilized by the investigators, with each having some combination of no blinding, small study population, retrospective methodology, selection bias, short

Genetic Testing Policies, Continued

Pharmacogenomic Testing for Drug Metabolism, continued

follow-up periods, and subjective study outcomes. The data from these studies is weak, and further investigation is warranted using better designed, larger study samples and double-blind randomized controlled methodology.

Billing/Coding Information

CPT CODES

- 0029U** Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
- 0078U** Pain management (opioid-use disorder) genotyping panel, 16 common variants (i.e., ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A, HTTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder
- 0173U** Psychiatry (i.e., depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes
- 0175U** Psychiatry (e.g., depression, anxiety), genomic analysis panel, variant analysis of 15 genes
- 0286U** CEP72 (centrosomal protein, 72-KDa), NUDT15 (nudix hydrolase 15) and TPMT (thiopurine Smethyltransferase) (e.g., drug metabolism) gene analysis, common variants
- 0290U** Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score
- 0291U** Psychiatry (mood disorders), mRNA, gene expression profiling by RNA sequencing of 144 genes, whole blood, algorithm reported as predictive risk score
- 0292U** Psychiatry (stress disorders), mRNA, gene expression profiling by RNA sequencing of 72 genes, whole blood, algorithm reported as predictive risk score
- 0293U** Psychiatry (suicidal ideation), mRNA, gene expression profiling by RNA sequencing of 54 genes, whole blood, algorithm reported as predictive risk score
- 0345U** Psychiatry (e.g., depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
- 0347U** Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes
- 0348U** Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes
- 0349U** Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis, including reported phenotypes and impacted gene-drug interactions
- 0350U** Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes
- 0380U** Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis, 20 gene variants and CYP2D6 deletion or duplication analysis with reported genotype and phenotype
- 81418** Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
- 0031U** CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7)

Genetic Testing Policies, Continued

Pharmacogenomic Testing for Drug Metabolism, continued

0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, common and select rare variants (ie, *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure)
0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
0074U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure)
0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication) (List separately in addition to code for primary procedure)
0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/ multiplication) (List separately in addition to code for primary procedure)
0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823)
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81291	MTHFR (5, 10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639G>A, c.173+1000C>T)
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each
81400	Molecular pathology procedure level 1
81401	Molecular pathology procedure level 2
81404	Molecular pathology procedure level 5
81405	Molecular pathology procedure level 6
81406	Molecular pathology procedure level 7
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis

Genetic Testing Policies, Continued

Pharmacogenomic Testing for Drug Metabolism, continued

HCPCS CODES

G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)
G0452	Molecular pathology procedure; physician interpretation and report

Not covered: the following codes are considered experimental/investigational

0516U	Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and CYP2D6 copy number variant analysis, reported as metabolizer status
0533U	Drug metabolism (adverse drug reactions and drug response), genotyping of 16 genes (ie, ABCG2, CYP2B6, CYP2C9, CYP2C19, CYP2C, CYP2D6, CYP3A5, CYP4F2, DPYD, G6PD, GGCX, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1), reported as metabolizer status and transporter function

Key References:

1. Centers for Medicare & Medicaid Services (CMS). LCD – MolDX: Pharmacogenomics Testing (L38294).
2. CPIC. Guidelines. <https://cpicpgx.org/guidelines/>
3. PHARMGKB. Pharmacogenomics. <https://www.pharmgkb.org/>

Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated this medical policy after Select Health and Intermountain Precision Genomics reacquired responsibility for evaluating genetic testing claims; and updated overall coverage criteria to align with current clinical standards.
1/24/24	For Commercial Plan Policy, clarified that both TPMT and NUDT15 are covered without restriction.
8/29/24	For Commercial Plan Policy, updated overall coverage criteria to align with current clinical standards, including providing more specific requirements for determining the eligibility of single-gene tests; and added the following exclusion: "A multi-gene panel is not considered medically necessary because it is unproven to improve health outcomes."

Disclaimer

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The codes for treatments and procedures applicable to this policy are included for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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Members may contact Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Coverage Policy may call Select Health Provider Relations at (801) 442-3692.

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MEDICAL POLICY

WHOLE GENOME SEQUENCING (WGS)/WHOLE EXOME SEQUENCING (WES)

Policy # 514

Implementation Date: 11/9/12

Review Dates: 12/19/13, 12/8/14, 4/21/17, 6/21/18, 4/17/19, 1/7/23, 2/15/24

Revision Dates: 4/14/16, 10/11/18, 7/1/23, 8/17/23, 8/28/23, 7/23/24

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2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Whole genome sequencing (WGS) in the outpatient setting has evidence and support for use as a first-line test for children with multiple congenital anomalies, neurodevelopmental delays, and for health conditions where there is a need for a timely and efficient diagnostic pathway.

First-line use of WGS reduces costs, avoids redundant or wasteful testing, reduces time to diagnosis, reduces disparities in diagnosis, reduces referrals and multiple visits with different specialists, and provides earlier access to treatment options. WGS is currently available at the same or lower cost compared to genetic panel testing or whole exome sequencing (WES). Studies support that the use of trio-based WGS decreases the likelihood of receiving variants of uncertain significance that require further evaluation, in comparison to many phenotype-based gene panels.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1. Select Health covers genetic testing when ordered or recommended by a medical geneticist, a genetic counselor, or a provider with recognized expertise in the area being assessed; or a provider who has submitted clinical rationale based upon the patient's personal and family history.
Select Health also recommends submitting documentation that shows a review of clinical literature or guidelines which would support this genetic testing; and
2. Testing results will directly impact clinical decision-making and/or clinical outcome for the individual being tested.

I. Whole Genome/Whole Exome Sequencing

- A. Select Health considers whole genome sequencing (WGS) or whole exome sequencing (WES) medically necessary when the member meets all the following criteria in A, and one of the following (B or C):

- 1) No other causative circumstances (e.g., environmental exposures, injury, prematurity, infection) can explain symptoms; and

Genetic Testing Policies, Continued

Whole Genome Sequencing (WGS)/Whole Exome Sequencing (WES), continued

- 2) Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available; and
- 3) The differential diagnosis list and/or phenotype warrant testing of multiple genes and one of the following (i or ii):
 - i. WES/WGS is more practical than the separate single gene tests or panels that would be recommended based on the differential diagnosis; or
 - ii. WES/WGS results may preclude the need for multiple and/or invasive procedures, follow-up, or screening that would be recommended in the absence of testing.

AND

B. WGS/WES will be considered medically necessary for any of the following conditions:

- 1) Unexplained multiple congenital anomalies including structural brain or organ abnormalities; or
- 2) Neurodevelopmental disorders, including intellectual disability and autism spectrum disorder; or
- 3) Unexplained conditions with significant potential for influencing medical management and clinical outcomes with need for timely diagnosis, including but not limited to:
 - i. Significant or refractory epilepsy and/or EEG or exam consistent with encephalopathy; or
 - ii. Abnormal labs and/or presentation concerning for metabolic or mitochondrial disorder; or
 - iii. Developmental regression or neurological findings suspicious for a progressive disorder including but not limited to white matter disease, cerebellar atrophy, movement disorders; or
 - iv. Unexplained cytopenias, immune dysregulation, and bone marrow failure, as well as a significant family history of multiple family members with cancer or autoimmunity not detected by standard, focused screening.

OR

C. WGS/WES is allowed for fetal testing, when all the following criteria are met:

- 1) Standard diagnostic genetic testing (chromosomal microarray analysis (CMA) and/or karyotype) of the fetus has been performed and is uninformative; and
- 2) Testing is performed on direct amniotic fluid/chorionic villi, cultured cells from amniotic fluid/chorionic villi or DNA extracted from fetal blood or tissue; and
- 3) At least one of the following is present:
 - i. multiple fetal structural anomalies affecting unrelated organ systems
 - ii. fetal hydrops of unknown etiology
 - iii. a fetal structural anomaly affecting a single organ system and family history strongly suggests a genetic etiology

II. Whole Exome/Genome Reanalysis: Reanalysis of previously obtained uninformative whole exome or whole genome sequence data is considered medically necessary when the above criteria (A plus B or C) for whole exome/genome sequencing are met, AND

- 1) When any of the following conditions (i–iii) are met:
 - i. Onset of additional symptoms that broadens the phenotype assessed during the original exome/genome evaluation, or
 - ii. Birth or diagnosis of a similarly affected first-degree relative that has expanded the clinical picture, or
 - iii. At least 18 months have passed since the last analysis (meaning there could now be new scientific knowledge that would impact the patient's result interpretation).

Genetic Testing Policies, Continued

Whole Genome Sequencing (WGS)/Whole Exome Sequencing (WES), continued

*Providers should utilize any no-charge analysis offered by the laboratory prior to submitting a request to Select Health for payment of reanalysis.

WGS/WES for cardiac arrhythmias and cardiomyopathies is considered experimental/investigational.

III. Ultra Rapid/Rapid Genome Sequencing

- A. **Select Health covers Ultra Rapid or Rapid Genome Sequencing for acutely-ill infants 12 months of age or younger in the hospital setting**, when all the following criteria (1–4) are met:
- 1) The etiology of the infant's features is unknown, and a genetic etiology is considered a likely explanation for the phenotype, based on either of the following:
 - i. Multiple congenital abnormalities affecting unrelated organ systems,
or
 - ii. Two of the following criteria are met:
 - a) Abnormality affecting at minimum a single organ system
 - b) Encephalopathy
 - c) Symptoms of a complex neurodevelopmental disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia)
 - d) Family history strongly suggestive of a genetic etiology, including consanguinity
 - e) Laboratory findings suggestive of an inborn error of metabolism
 - f) Abnormal response to therapy;
 - AND**
 - 2) Alternate etiologies have been considered and ruled out, when possible (e.g., environmental exposure, injury, infection, isolated prematurity);
AND
 - 3) Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted panel testing is available;
AND
 - 4) A diagnosis cannot be made in a timely manner by standard clinical evaluation.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the **Select Health Commercial policy applies**. For the most up-to-date Medicare policies and coverage, please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or the [manual website](#)

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

Genetic Testing Policies, Continued

Whole Genome Sequencing (WGS)/Whole Exome Sequencing (WES), continued

Billing/Coding Information

Covered for the indications listed above when criteria are met:

CPT Codes

- 0094U** Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
- 0454U** Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
- 0469U** Rare diseases (constitutional/heritable disorders), whole genome sequence analysis for chromosomal abnormalities, copy number variants, duplications/deletions, inversions, unbalanced translocations, regions of homozygosity (ROH), inheritance pattern that indicate uniparental disomy (UPD), and aneuploidy, fetal sample (amniotic fluid, chorionic villus sample, or products of conception), identification and categorization of genetic variants, diagnostic report of fetal results based on phenotype with maternal sample and paternal sample, if performed, as comparators and/or maternal cell contamination
- 81415** Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
- 81416** Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)
- 81417** Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
- 81425** Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
- 81426** Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)
- 81427** Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)
- 96040** Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

HCPCS Codes

- S0265** Genetic counseling, under physician supervision, each 15 minutes

Not covered: considered experimental/investigational/unproven or not medically necessary

CPT Codes

- 0019U** Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents
- 0036U** Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
- 0212U** Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem

Genetic Testing Policies, Continued

Whole Genome Sequencing (WGS)/Whole Exome Sequencing (WES), continued

repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband

- 0213U** Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent, sibling)
- 0214U** Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
- 0215U** Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (eg, parent, sibling)
- 0260U** Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
- 0264U** Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
- 0265U** Rare constitutional and other heritable disorders, whole genome and mitochondrial DNA sequence analysis, blood, frozen and formalin-fixed paraffin embedded (FFPE) tissue, saliva,buccal swabs or cell lines, identification of single nucleotide and copy number variants
- 0266U** Unexplained constitutional or other heritable disorders or syndromes, tissue-specific gene expression by whole-transcriptome and next-generation sequencing, blood, formalin-fixed paraffin-embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression changes
- 0267U** Rare constitutional and other heritable disorders, identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping and whole genome sequencing
- 0297U** Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification
- 0298U** Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification
- 0300U** Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification
- 0329U** Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations

Genetic Testing Policies, Continued

Whole Genome Sequencing (WGS)/Whole Exome Sequencing (WES), continued

- 0335U** Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, fetal sample, identification and categorization of genetic variants
- 0336U** Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent)
- 0460U** Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes
- 0532U** Rare diseases (constitutional disease/hereditary disorders), rapid whole genome and mitochondrial DNA sequencing for singlenucleotide variants, insertions/deletions, copy number variations, peripheral blood, buffy coat, saliva, buccal or tissue sample, results reported as positive or negative
- 81349** Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
- 81479** Unlisted molecular pathology procedure

Key References

1. Bick D, Fraser PC, Gutzeit MF, et al. Successful Application of Whole Genome Sequencing in a Medical Genetics Clinic. *J Pediatr Genet.* 2017 Jun;6(2):61-76. PMID: 28496993
2. Evans L.J., et al. Whole exome and genome sequencing in mendelian disorders: a diagnostic and health economic analysis. *Eur J Hum Genet.* 2022 Oct; 30(10):1121-1131. doi: 10.1038/s41431-022-01162-2. Epub 2022 Aug 15. PMID: 35970915; PMCID: PMC9553973.
3. Manickam K, McClain MR, Demmer LA, Biswas S, Kearney HM, Malinowski J, Massingham LJ, Miller D, Yu TW, Hisama FM; ACMG Board of Directors. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2021 Nov;23(11):2029-2037. doi: 10.1038/s41436-021-01242-6. Epub 2021 Jul 1. PMID: 34211152.
4. Nazeha N., et al. Reduced resource utilization with early use of next-generation sequencing in rare genetic diseases in an Asian cohort. *Am J Med Genet A.* 2022 Dec;188(12):3482-3491. doi: 10.1002/ajmg.a.62974. Epub 2022 Sep 25. PMID: 36156406.
5. Nurchis, M. C., Incremental net benefit of whole genome sequencing for newborns and children with suspected genetic disorders: Systematic review and meta-analysis of cost-effectiveness evidence. *Health Policy.* 2022 Apr;126(4):337-345. doi: 10.1016/j.healthpol.2022.03.001. Epub 2022 Mar 4. PMID: 35317923.
6. Smith HS, Swint JM, Lalani SR, Yamal JM, de Oliveira Otto MC, Castellanos S, Taylor A, Lee BH, Russell HV. Clinical Application of Genome and Exome Sequencing as a Diagnostic Tool for Pediatric Patients: a Scoping Review of the Literature. *Genet Med.* 2019 Jan;21(1):3-16. PMID: 29760485
7. Smith L, Malinowski J, Ceulemans S, Peck K, Walton N, Sheidley BR, Lippa N. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. *J Genet Couns.* 2023 Apr;32(2):266-280. doi: 10.1002/jgc4.1646. Epub 2022 Oct 24. PMID: 36281494.

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