General Genetic Testing, Germline Disorders

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Line(s) of Business: HMO; PPO; QUEST Integration	Precertification: Required

I. Policy Description

Germline variants or mutations are defined as genetic alterations that occur within the germ cells (egg or sperm), such that the alteration becomes incorporated into the DNA of every cell in the body of the offspring. It may also be called hereditary mutation.

Genetic testing refers to the use of technologies that identify genetic variation, which include genomic, transcriptional, proteomic, and epigenetic alterations, for the prevention, diagnosis, and treatment of disease.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in Section VIII of this policy document.

1) Genetic counseling **MEETS COVERAGE CRITERIA AND IS REQUIRED** (IF TESTING IS NOT BEING ORDERED BY A SPECIALIST IN THE DISEASE PROCESS IN QUESTION (e.g. endocrinologist and maturity onset diabetes of youth gene evaluation)) for individuals prior to and after undergoing genetic testing for diagnostic, carrier, and/or risk assessment purposes.

2) Genetic testing of the individual's genome for inherited diseases **MEETS COVERAGE CRITERIA**, once per patient lifetime, when the following criteria are met:

   a) The individual for whom the test is requested is either:

      i) Is currently symptomatic with suspicion of a known genetic disease where knowledge of mutation will assist in diagnosis, treatment, or procreative management, **OR**

      ii) Is currently asymptomatic but is judged to be at significant risk for an inherited disorder or cancer risk factor based on family history and/or ethnicity, **AND**, if being tested for risk of an adult-onset condition is at or above the age of majority, (e.g., 18 years), unless there is documented evidence that early intervention during childhood may prevent disease severity or time of disease onset, **OR**

      iii) Is asymptomatic but judged to be at risk as a carrier of an inherited disorder or cancer risk factor based on family history and/or ethnicity **AND** would benefit from procreative management

   b) Regarding the test being considered ALL the following are MET:

      i) Scientific literature shows association of specific a gene mutation (or mutations) is associated with the disease in question and is clinically actionable (there is clinical utility) with non-investigational treatment; **AND**

ii) Other testing for the disease is equivocal or does not exist and confirmation of gene mutation is standard of care for the disease state; **AND**

iii) Disease in question is associated with significant morbidity and/or mortality; **AND**

iv) Results of testing can impact clinical management via surveillance or treatment strategies and will guide decisions on healthcare management to mitigate symptoms or progression of the disorder.

3) Germline multi-gene panel testing (See Note 1), defined as multiple gene tests for a medical condition or symptoms/non-specific presentation run on one testing platform, **MEETS COVERAGE CRITERIA** according to the guidelines in the preceding coverage criteria and the reimbursement limitations (see section regarding Reimbursement below).

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

4) Genetic testing of an individual's genome for inherited diseases **DOES NOT MEET COVERAGE CRITERIA** in the following situations:

a) For risk assessment of an individual's genome when the criteria defined in the "MEETS COVERAGE CRIERIA" criteria above are not met

b) For inherited disease diagnosis or carrier assessment using panels of genes that include genes outside of those specifically related to the disease being investigated

c) Repeat germline testing of a unique gene using the identical method of gene analysis

d) Testing as a screening tool in the general population

e) Direct-to-consumer genetic testing (e.g. mail order, online ordering, pharmacy, retail)

Note 1: For references regarding the clinical application of genomic sequencing and for appropriate medical coding, please refer to.

III. Reimbursement

1. If a procedure code is available for the multi-gene panel test, then this code is to be utilized (i.e. 81442 Noonan spectrum disorders genomic sequence analysis panel).

2. If there is not a specific next generation sequencing procedure code that represents the requested test, the procedure may be represented by a maximum of **ONE** unit of 81479 [unlisted molecular pathology procedure] (i.e. 81479 X 1 should account for all remaining gene testing) **OR** All genes tested on the panel must be represented by ALL appropriate Molecular Pathology Tier 1 or 2 procedure codes (with exception of 81479 x 1 only being listed once if it appropriately represents more than one gene in the panel)

3. **ALL** gene tests in the panel must be listed on the request and rationale for the clinical utility for the gene test must come from the **ordering** provider.

4. If **ALL** codes that represent the testing of the panel are not submitted, the test will be denied as not medically necessary due to incorrect coding process as neither laboratory or clinical reviewer should assign meaning to incomplete unspecified panel codes.

IV. Table of Terminology

Term	Definition
ACMG	American College of Medical Genetics and Genomics
AMP	Association For Molecular Pathology
APC	*Adenomatous polyposis coli*
ASCO	American Society of Clinical Oncology
ATM	*Ataxia telangiectasia mutated*
BRCA1/2	*Breast cancer gene 1/2*
CAP	College Of American Pathologists
CDH1	*Cadherin-1*
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
CNV	Copy number variant
FDA	Food and Drug Administration
LDTs	Laboratory developed tests
LOF	Loss of function
MGPT	Multigene panel testing
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
PALB2	*Partner and localizer of BRCA2*
PTEN	*Phosphatase and tensin homolog*
PVG	Pathogenic germline variants
smMIPS	Single molecule molecular inversion probes
SNPs	Single nucleotide polymorphisms
TP53	*Tumor protein P53*

V. Scientific Background

Gene mutations are referred to as "germline" if they are within gametes (ova and sperm). Therefore, these mutations may be passed on from parent to offspring. There are many different types of germline mutations, such as single nucleotide polymorphisms (SNPs), structural variations such as deletions, inversions, or translocations, as well as smaller chromosomal abnormalities such as short tandem repeats, or gene fusions. Mutations may not necessarily result in disease.

SNPs are the most common type of genetic mutation, such as missense mutations. These mutations are single base-pair changes where one nucleotide is replaced with a different nucleotide. Millions of individual SNPs have been identified through genome-wide association studies, with approximately 4000 SNPs with potential association with disease. Insertion/deletion (indel) polymorphisms are often a single nucleotide but may be up to four nucleotides. SNPs often lead to frameshift mutations, which can cause premature stop codons and the failure of the allele.

Structural variations are usually classified as larger than 1000 base pairs. These include deletions, duplications, inversions, translocations, or ring chromosome formation. Due to the large number of bases affected, these variations may lead to severe genetic abnormalities. For example, a major cause of Duchenne muscular dystrophy is the deletion of large portions of exons (coding portions of genes). The most common structural variation is the copy number variant (CNV), which refers to differing amounts of DNA segments in different individuals. For example, one person may have three copies of a specific segment whereas another may only have two. These variations may lead to dysregulation, gain-of-function, or loss-of-function of the affected genes. The sensitive genes that require or produce precise amounts of a protein product tend to suffer more from these variations.

Germline mutations are unique in that the risk for certain conditions, including many forms of cancer, may be passed from parent to offspring. Testing for these conditions will often involve testing entire families if one member is found to have a germline mutation; for example, the National Comprehensive Cancer Network (NCCN) guidelines for hereditary cancer recommend testing for *BRCA1/2, CDH1, PALB2, PTEN and TP53* mutations if any blood relative has a known or likely pathogenic variant in a cancer susceptibility gene. Wilson et al. (2020) estimate that 21,800 adult survivors of childhood cancer in the United States carry a pathogenic or likely pathogenic variant in one of 156 cancer predisposition genes.

Other types of mutations are unique to germline mutations. Errors in chromosome number (aneuploidy) are typically caused by non-disjunctions in meiosis, causing either a monosomic (one chromosome) or a trisomic (three chromosomes) set of chromosomes. Some aneuploidies, trisomy 21, or Down Syndrome, being most notable, are compatible with life. Aneuploidies may also result with sex chromosomes, resulting in conditions such as Turner's Syndrome (one X chromosome) or Klinefelter's Syndrome (XXY).

Any size mutation may be pathogenic and must be classified as to how likely they are to cause disease. The American College of Medical Genetics and Genomics (ACMG) has classified mutations in five categories, which are as follows: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. The "likely pathogenic" and "likely benign" refer to weaker evidence than their respective pathogenic and benign categories, and "uncertain significance" refers to evidence that does not meet criteria for benignity or pathogenicity or has conflicting evidence from both sides. Prediction algorithms have been used to interpret variants and to predict whether a variant will affect the gene function or splicing of the gene. These algorithms are publicly available but have a tendency of predicting harmful impact of a variant. The specificity of these databases has been estimated at 60-80%.

Due to the enormous number of variants, as well as the rate that variants are discovered, comprehensive databases of genetic variants have been published and are easily available. For example, the Haplotype Reference Consortium contains over 40 million identified SNPs. Databases focusing on cancer-specific variants, reference sequences, and the general population are all available publicly.

For many years, single-gene testing was the standard approach for germline mutation testing. In recent years, multigene panel testing (MGPT) has been introduced and widely accepted as the first-tier test. MGPT increases the probability of identifying pathogenic mutations and represents an affordable application of next-generation sequencing (NGS) into clinical practice. However, the clinical utility of MGPT is not well established, especially in cases where more than one pathogenic variant is identified. The risk for a specific malignancy is complex and if a gene panel discovers a mutation incidentally, management can be difficult. Many guidelines call for radical procedures for these disease states and it

may cause unnecessary harm for the patient concerned about predisposition to the disease. Additionally, a combination of mutations may interact to alter the profile of the disease. For instance, certain combinations of mutations may be detrimental and increase the overall risk of cancer malignancy, while other combinations may reduce overall risk of malignancy. In this regard, identifying clinically actionable mutations may be unclear with MGPT.

Clinical Utility and Validity

Genetic testing for germline mutations "can be conducted on virtually any tissue type," although many laboratories prefer blood samples, check swabs or saliva samples. Advancements in technology and availability of sequencing, previously constrained by limitations of sequential single-gene testing on limited patient samples, have led to significant strides in the understanding of the genetic basis of inherited and somatic conditions.

Variants detected by genetic testing include inherited germline variants and somatic mutations; next generation sequencing (NGS) has allowed for superior detection for these mutations. The accuracy of NGS varies depending on how many genes are sequenced; fewer genes tend to result in higher accuracy since there will be more "probe-template overlap." Although Sanger sequencing remains the most accurate at >99.99% accuracy, it cannot sequence a large quantity of genes in a timely fashion and is best used for sequencing of a specific gene. Pogoda et al. (2019) identified rare variants in the *ATM* gene by using single molecule Molecular Inversion Probes (smMIPSs), an NGS-based screening method. A total of 373 patients with dystonia and six positive controls with previously identified *ATM* variants participated in this study. Results generated by the smMIPs "produced similar results as routinely used NGS-based approaches" (Pogoda et al., 2019). This suggests that *ATM* screening should be routinely used when genetic testing dystonia patients. Further, smMIPs may be an important technique for the germline screening for all rare neurodegenerative disorders.

The clinical validity of a genetic test depends primarily on the expressivity and penetrance of a given phenotype. Penetrance refers to the likelihood of developing a disease when the pathogenic mutation is present, and expressivity refers to the variations in the way the disease is expressed. For example, virtually any mutation in the *APC* gene will cause symptoms of familial adenomatous polyposis, thereby increasing the clinical validity of an *APC* assessment while other conditions may not clinically manifest at all despite a mutated genotype.

The clinical utility of a genetic test generally relies on available treatments for a condition. Conditions such as Huntington Disease that do not have many options for treatment will have limited clinical utility compared to another condition even though the actual test is highly valid. Factors, such as severity of the disease and management options, affect the clinical utility of a genetic test.

Lincoln et al. (2020) performed a retrospective study to investigate the yield and utility of germline testing on cancer patients following tumor DNA sequencing. The authors calculated the prevalence of pathogenic germline variants (PVG) and the potential actionability of the PVGs in 2023 cancer patients. 30.5% (n=617) of participants had PVGs. Participants with PVGs spanned all ages and cancer types. Tumor DNA sequencing missed 8.1% of PGVs. 11.2% of missed PVGs were only detected after developing a second primary cancer. The results suggest that missed PVGs could have been detected earlier and the second cancer could have been treated earlier or prevented. The authors concluded that germline testing following tumor DNA sequencing can result in important findings that can impact patient care.

VI. Guidelines and Recommendations

American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP)

The ACMG and AMP released criteria on the types and severity of mutations, which are as follows:

- **Very strong evidence of pathogenicity**: Null variants (nonsense, frameshifts, canonical +/- 1-2 splice sites, initiation codon, exon deletions) in a gene where loss of function (LOF) is a known mechanism of disease. The guidelines note to use caution in genes where LOF is not a mechanism, if LOF variants are at the 3' end, if exon skipping occurs, and if multiple transcripts are present.
- **Strong:** Amino acid change to a pathogenic version, de novo mutations, established studies supporting a damaging gene or gene product, or if the prevalence of the variant is increased in affected individuals compared to healthy controls. The guidelines note to be careful of changes impacting splicing and if only the paternity has been confirmed.
- **Moderate:** Located in a mutational hot spot or well-established functional domain (e.g., active site of an enzyme) without a benign variation, absent from controls in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium, detected in *trans* with pathogenic variants for a recessive disorder, protein length changes, novel missense changes where a different missense change has been pathogenic before, and a possible de novo mutation.
- **Supporting:** Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease, missense variant in a gene with low rate of benign missense variation, if the mutation has evidence that it is deleterious, or if the patient's phenotype is highly specific for disease with a single genetic cause.

The guidelines also list criteria for benign gene variants.

- **Stand-alone evidence of benignity:** Allele frequency is >5% in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium
- **Strong:** Allele frequency is greater than expected for disorder, observed in healthy adult with full penetrance at early age, lack of segregation in affected family members (although pathogenic variants may masquerade as nonsegregated), or well-established studies that show no damaging effect on protein production.
- **Supporting:** Missense variant of a gene for which truncating mutations are pathogenic, indels in repetitive region of unknown function, silent variants, variants of unknown significance, or a *trans* version of a *cis* mutation.

National Comprehensive Cancer Network (NCCN)

Multiple germline mutations have been incorporated into the diagnostic workups recommended by the NCCN. Furthermore, the NCCN has several guidelines which recommend that gene expression profiling, or multiple gene testing, may be helpful, more efficient and/or cost-effective for selected patients. Please see the individual policies.

Association for Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO), and College of American Pathologists (CAP)

The Joint Commission noted that germline variants should focus on the pathogenicity of a given variant rather than their impact on clinical care. The guidelines recommend reporting germline variants with known clinical impact, such as *BRCA1* or 2. A genetic counseling recommendation should also be provided if a pathogenic germline mutation is found.

The guidelines note that it is critical to identify a somatic vs a germline mutation as the type of mutation may have significant clinical consequences.

American Society of Clinical Oncology (ASCO)

The ASCO published guidelines regarding genetic and genomic testing for cancer susceptibility. These guidelines state that the "ASCO recognizes that concurrent multigene testing (ie, panel testing) may be efficient in circumstances that require evaluation of multiple high-penetrance genes of established clinical utility as possible explanations for a patient's personal or family history of cancer. Depending on the specific genes included on the panel employed, panel testing may also identify mutations in genes associated with moderate or low cancer risks and mutations in high-penetrance genes that would not have been evaluated on the basis of the presenting personal or family history… ASCO affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history."

ASCO released guidelines regarding germline testing for ovarian cancer. ASCO recommends that "all women diagnosed with epithelial ovarian cancer should be offered germline genetic testing for *BRCA1, BRCA2*, and other ovarian cancer susceptibility genes, irrespective of their clinical features or family cancer history. In addition, "first- or second-degree blood relatives of a patient with ovarian cancer with a known germline pathogenic cancer susceptibility gene mutation or variant should be offered individualized genetic risk evaluation, counseling, and genetic testing." Lastly, "clinical decisions should not be based on a variant of uncertain significance (VUS)." In this case, the patient's clinical features and family history should be taken into consideration and should inform clinical decision making.

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), or for QUEST Integration members under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

IX. Evidence-based Scientific References

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X. Policy History

Action Date	Action
06/01/2023	Initial policy implementation
11/21/2023	Policy approved by Medical Directors
12/15/2023	Policy approved at UMC
2/01/2025	Policy effective date following notification period