Dean Health Plan Coverage Policy

Policy Name:	**Genetic Testing: Kidney Disorders**
Effective Date:	**January 01, 2025**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by Dean Health Plan. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage.

Members may contact Dean Health Plan Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this medical policy see Provider Communications for additional information. https://deancare.com/Providers/Provider-communications

Dean Health Plan medical policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

OVERVIEW

Inherited kidney disorders and inherited disorders that indirectly affect the kidneys can be common, such as autosomal dominant polycystic kidney disease, or rare, such as Lowe syndrome and Fabry disease. Identifying the genetic cause of an inherited kidney disorder can help direct treatment, inform family members, and contribute to the overall understanding of the genetic etiology of chronic kidney disease. More advanced next-generation sequencing, such as exome sequencing and comprehensive genetic testing panels, are emerging as a first-line diagnostic method for patients with chronic kidney disease.

With the use of donor-derived cell-free DNA (ddcfDNA), biomarker tests have been developed as an alternative to more invasive procedures for post-renal transplant care to optimize graft longevity while avoiding side effects and toxicity of immunosuppressive therapies.

POLICY REFERENCE TABLE

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage.

Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

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Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Polycystic Kidney Disease				
Polycystic Kidney Disease Panels	Hereditary Cystic Kidney Diseases Panel (PreventionGenetics, part of Exact Sciences)	81404, 81405, 81406, 81407, 81408, 81479	Q61, N18	1, 2
	Polycystic Kidney Disease Panel (GeneDx)			
Comprehensive Kidney Disease Panels				
Comprehensive Kidney Disease Panels	RenaSight (Natera)	81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479	N00-N08, N10-N19, Q61, R31	3, 8
	KidneySeq Version 5 Comprehensive Testing (Iowa Institute of Human Genetics)			
	RenalZoom (DNA Diagnostic Laboratory - Johns Hopkins Hospital)			
***APOL1*-Mediated Kidney Disease**				
APOL1-Targeted Variant Analysis	Apolipoprotein L1 (APOL1) Renal Risk Variant Genotyping (Quest Diagnostics)	0355U	N00-N08, N10-N19	7
	APOL1 Genotype, Varies (Mayo Clinic Laboratories)	81479		
Donor-Derived Cell-free DNA for Kidney Transplant Rejection				
Donor-Derived Cell-free DNA for Kidney	Allosure Kidney (CareDx, Inc.)	81479	T86.11, T86.12, Z94.0	9, 10, 11
	Prospera (Natera)	0493U		

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Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Transplant Rejection	Viracor TRAC Kidney dd-cfDNA (Viracor Eurofins)	0118U		
	VitaGraft Kidney Baseline + 1st Plasma Test (Oncocyte Corporation)	0508U		
	VitaGraft Kidney Subsequent (Oncocyte Corporation)	0509U		
Other Covered Kidney Disorders				
Other Covered Kidney Disorders	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408		4, 5, 6

OTHER RELATED POLICIES

This policy document provides coverage criteria for hereditary kidney disorders. Please refer to :

- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to genetic disorders that affect multiple organ systems
- ***Genetic Testing: Hereditary Cancer Susceptibility*** for coverage criteria related to von Hippel Lindau (VHL) syndrome and other hereditary cancer syndromes.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to genetic testing for kidney disease that is not specifically discussed in this or another non-general policy, including known familial variant testing.
- ***Genetic Testing Hematologic Conditions Non-Cancerous*** for coverage criteria related to hematologic disorders that affect the kidneys.

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COVERAGE CRITERIA

POLYCYSTIC KIDNEY DISEASE PANELS

Polycystic Kidney Disease Panels

I. Genetic testing using a polycystic kidney disease panel (81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of polycystic kidney disease is considered **medically necessary** when:

A. The member has any of the following clinical features of polycystic kidney

disease:

1. Multiple bilateral renal cysts, **OR**
2. Cysts in organs other than the kidneys (especially the liver, seminal vesicles, pancreas, and arachnoid membrane), **OR**
3. Hypertension in an individual younger than age 35, **OR**
4. Bilaterally enlarged and diffusely echogenic kidneys

II. Genetic testing using polycystic kidney disease panels (81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of polycystic kidney disease is considered **investigational** for all other indications.

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COMPREHENSIVE KIDNEY DISEASE PANELS

Comprehensive Kidney Disease Panels

I. Genetic testing for kidney disease via a comprehensive kidney disease panel (81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) is considered **medically necessary** when:

A. The member has chronic kidney disease with an undetermined cause after undergoing standard-of-care workup studies (examples: history and physical examination, biochemical testing, renal imaging, or renal biopsy), **AND**

B. The member meets at least one of the following:

1. Onset of chronic kidney disease under 40 years of age, **OR**
2. One or more first- or second-degree relatives with chronic kidney disease, **OR**
3. Consanguineous family history, **OR**
4. Cystic renal disease, **OR**
5. Congenital nephropathy, **OR**
6. Syndromic/multisystem features, **OR**
7. There is a possibility of identifying a condition amenable to targeted treatment.

II. Genetic testing for kidney disease via a comprehensive kidney disease panel (81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) is considered **investigational** for all other indications.

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APOL1-MEDIATED KIDNEY DISEASE

APOL1 Targeted Variant Analysis

I. Targeted variant analysis for the *APOL1* high-risk genotype (i.e., G1/G1, G1/G2, or G2/G2) (0355U, 81479) is considered **medically necessary** when:

A. The member has kidney disease, **AND**

B. The member meets at least one of the following:

1. The member is of African ancestry, **OR**
2. The member has a family member with a confirmed *APOL1* high-risk genotype (i.e., G1/G1, G1/G2, or G2/G2).

II. Targeted variant analysis for the *APOL1* high-risk genotype (i.e., G1/G1, G1/G2, or G2/G2) (0355U, 81479) is considered **investigational** for all other indications.

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DONOR-DERIVED CELL-FREE DNA FOR KIDNEY TRANSPLANT REJECTION

Donor-Derived Cell-free DNA for Kidney Transplant Rejection

I. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation (81479, 0493U, 0118U, 0508U, 0509U) is considered **medically necessary** when:

A. The member has undergone kidney transplantation, **AND**

B. The test has not been performed in the previous 12 months, **AND**

C. The member meets at least one of the following:

1. The member has clinical signs of acute rejection, **OR**
2. A biopsy was done to check for signs of acute rejection and is inconclusive, **OR**
3. The member is being monitored for adequate immunosuppression.

II. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation (81479, 0493U, 0118U, 0508U, 0509U) is considered **investigational** for all other indications.

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OTHER COVERED KIDNEY DISORDERS

Other Covered Kidney Disorders

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

I. Genetic testing to establish or confirm one of the following genetic kidney disorders to guide management is considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below):

A. Alport Syndrome

B. C3 Glomerulopathy

C. Congenital nephrotic syndrome

D. Cystinosis

E. Cystinuria

F. Fabry Disease

G. Genetic (familial) atypical hemolytic-uremic syndrome (aHUS)

H. Primary Hyperoxaluria

II. Genetic testing to establish or confirm the diagnosis of all other kidney disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic and Molecular Testing* (see policy for coverage criteria).

*Clinical features for a specific disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference, or other scholarly source.

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PRIOR AUTHORIZATION

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

DEFINITIONS

1. **Close relatives** include first, second, and third degree blood relatives on the same side of the family:
   a. **First-degree relatives** are parents, siblings, and children
   b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
   c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

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BACKGROUND AND RATIONALE

Polycystic Kidney Disease Panels

GeneReviews: Polycystic Kidney Disease, Autosomal Dominant and Autosomal Recessive Polycystic Kidney Disease - PKHD1

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

The recommended polycystic kidney disease testing for autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) is as follows:

“ADPKD should be suspected in individuals with the following:

- Multiple bilateral renal cysts and the absence of manifestations suggestive of a different renal cystic disease
- Cysts in other organs, especially the liver, but also seminal vesicles, pancreas, and arachnoid membrane…
- Hypertension in an individual younger than age 35 years

“Autosomal recessive polycystic kidney disease – PKHD1 (ARPKD-PKHD1) should be suspected in probands with the following age-related clinical and ultrasonographic findings at presentation

Infantile presentation (age 4 weeks to 1 year)

- Bilaterally enlarged kidneys (in relation to age-, height-, or weight-based normal range) that usually retain their typical shape
  Note: (1) Bilaterally enlarged kidneys can be interspersed with macrocysts. (2) During later disease stages relative kidney length may decrease again.
- Increased echogenicity…
- High-resolution ultrasonography may demonstrate innumerable very small cysts (rarely exceeding 1-2 mm) in the cortex and medulla.

Childhood/Young Adulthood Presentation (age >1 year)

- Imaging findings typically are the following:
  - Enlarged kidneys with multiple macrocysts, increased echogenicity, and reduced or absent corticomedullary differentiation…"

Comprehensive Kidney Disease Panels

Hays et al (2020)

"We propose the following approach, based on a review of current literature and our practical experience. This approach assumes individuals have already undergone an initial nephrologic workup, including biochemical and serologic testing, imaging of the kidneys, and renal biopsy if indicated.

…[A]fter a negative or inconclusive initial workup, a patient is considered to have KDUE [kidney disease of unknown etiology] and may then be stratified according to the probability of a genetic disease. We consider higher probability patients as those with the following risk factors: early-onset disease (age <40 years), a positive family history of CKD [chronic kidney disease], consanguinity, extrarenal anomalies, cystic renal disease, or congenital nephropathy". (p. 594)

Kidney Disease: Improving Global Outcomes (KDIGO)

KDIGO developed a Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease in 2024. The guideline states the following:

"Genetic testing is emerging as a valuable component for evaluation of cause. In some studies, >10% of people with CKD, regardless of family history, were observed to carry genetic pathogenic and likely pathogenic variant(s) that represent a plausible molecular cause for the development or progression of CKD. In some cases, identification of actionable genes through genetic testing can impact the clinical management of people with CKD. A recent KDIGO Controversies Conference listed the following recommendations for when genetic testing can be particularly informative: (i) high prevalence of monogenic subtypes within the clinical category, (ii) early age of onset of CKD, (iii) syndromic/ multisystem features, (iv) consanguinity, (v) possibility of identifying a condition amenable to targeted treatment, and (vi) CKD/ kidney failure of unknown etiology when kidney biopsy would not be informative due to advanced disease." (p. S173)

Additionally, the guideline lists the following genes as examples for genetic testing evaluation: APOL1, COL4A3, COL4A4, COL4A5, NPHS1, UMOD, HNF1B, PKD1, PKD2. It goes on to say this is "evolving as a tool for diagnosis, increased utilization is expected. Recognition that genetic causes are more common and may present without classic family history". (p. S150)

APOL1 Targeted Variant Analysis

Freedman et al (2021)

A multidisciplinary group of experts and patient advocates performed a systematic review and created consensus-based guidelines in 2021 to guide health care providers in *APOL1*-associated neuropathy. The guidelines recommend the following:

"...*APOL1* testing should be considered in all patients of African ancestry with kidney disease and in any patient with kidney disease and a family member with a confirmed *APOL1* high-risk genotype." (p. 1768)
Regarding the definition of "high-risk phenotype": "Two copies of the *APOL1* variants (G1/G1, G1/G2, G2/G2) are commonly referred to as a 'high-risk' genotype…" (p. 1765)

Donor-Derived Cell-Free DNA for Kidney Transplant Rejection

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled "MolDX: Molecular Testing for Solid Organ Allograft Rejection" states the following regarding donor-derived cell-free DNA tests in individuals who have had solid organ transplantation:

"This Medicare contractor will provide limited coverage for molecular diagnostic tests used in the evaluation and management of patients who have undergone solid organ transplantation. These tests can inform decision making along with standard clinical assessments in their evaluation of organ injury for active rejection (AR).

These tests may be ordered by qualified physicians considering the diagnosis of AR affiliated with a transplant center, helping to rule in or out this condition when assessing the need for or results of a diagnostic biopsy. They should be considered along with other clinical evaluations and results and may be particularly useful in patients with significant contraindications to invasive procedures.

The intended use of the test must be:

- To assist in the evaluation of adequacy of immunosuppression, wherein a non-invasive or minimally invasive test can be used in lieu of a tissue biopsy in a patient for whom information from a tissue biopsy would be used to make a management decision regarding immunosuppression, OR
- As a rule-out test for AR in validated populations of patients with clinical suspicion of rejection with a non-invasive or minimally invasive test to make a clinical decision regarding obtaining a biopsy, OR
- For further evaluation of allograft status for the probability of allograft rejection after a physician-assessed pretest, OR
- To assess rejection status in patients that have received a biopsy, but the biopsy results are inconclusive or limited by insufficient material."

European Society of Organ Transplantation

The European Society of Organ Transplantation (ESOT, published in 2024) published a Consensus Statement on Testing for Non-Invasive Diagnosis of Kidney Allograft Rejection, which states the following:

"Recommendation 1.1: We suggest that clinicians consider measuring serial plasma dd-cfDNA in patients with stable graft function to exclude the presence of subclinical antibody mediated rejection. (p. 5)

Recommendation 2.1: We recommend that clinicians measure plasma dd-cfDNA in patients with acute graft dysfunction to exclude the presence of rejection, particularly antibody mediated rejection." (p. 6)

American Society of Transplant Surgeons (ASTS)

The ASTS issued a statement on donor derived cell-free DNA (dd-cfDNA) in 2023. At this time, there are no evidence-based screening recommendations for frequency of testing mentioned in this statement.

Concert Note

For routine monitoring of patients post-transplant, absent clear, specific and evidence-based guideline recommendations for a particular regimen of screening, a default frequency of coverage of once every 12 months will be adopted.

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Note: The Health Plan uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

	Committee/Source	Date(s)
Document Created:	Medical Policy Committee/Health Services Division	November 16, 2022
Revised:	Medical Policy Committee/Health Services Division	February 15, 2023
	Medical Policy Committee/Health Services Division	March 15, 2023
	Medical Policy Committee/Health Services Division	August 16, 2023
	Medical Policy Committee/Health Services Division	March 20, 2024
Reviewed:	Medical Policy Committee/Health Services Division	February 15, 2023
	Medical Policy Committee/Health Services Division	March 15, 2023
	Medical Policy Committee/Health Services Division	August 16, 2023
	Medical Policy Committee/Health Services Division	March 20, 2024

Original Effective Date: 03/01/2023

Re-Review Date(s): 12/19/2024- Concert Genetics Effective Date: January 01, 2025 (V.1.2025)

Administrative Update:

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