| BSC_CON_2.22 | Genetic Testing: Kidney Disorders | | |
|---|---|---|---|
| **Original Policy Date:** | April 1, 2024 | **Effective Date:** | November 1, 2024 |
| **Section:** | 2.0 Medicine | **Page:** | Page 1 of 15 |

## Example Test 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. Please see the Concert Genetics Platform for a comprehensive list of registered tests.

| Policy Statement Locations | Example Tests, Labs | Common CPT Codes |
|---|---|---|
| **Polycystic Kidney Disease** | | |
| Targeted Variant Analysis | Targeted Mutation Analysis for a Known Familial Variant | 81403 |
| Single gene or Multigene Panel | Autosomal Dominant Polycystic Kidney Disease via the PKD1 Gene (PreventionGenetics, part of Exact Sciences) | 81407, 81479 |
| | PKD2 Full Gene Sequencing and Deletion/Duplication (Invitae) | 81406, 81479 |
| | Autosomal Recessive Polycystic Kidney Disease (ARPKD) via the PKHD1 Gene (PreventionGenetics, part of Exact Sciences) | 81408, 81479 |
| | Autosomal Dominant Polycystic Kidney Disease (ADPKD) via the GANAB Gene (PreventionGenetics, part of Exact Sciences) | 81479 |
| | Autosomal Dominant Polycystic Kidney Disease (ADPKD) via the DNAJB11 Gene (PreventionGenetics, part of Exact Sciences) | |
| | Hereditary Cystic Kidney Diseases Panel (PreventionGenetics, part of Exact Sciences) | 81404, 81405, 81406, 81407, 81408, 81479 |
| | Polycystic Kidney Disease Panel (GeneDx) | |
| **Comprehensive Kidney Disease Panels** | | |
| Comprehensive Kidney Disease Panels | RenaSight (Natera) | 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479 |
| | KidneySeq Version 5 Comprehensive Testing (Iowa Institute of Human Genetics) | |
| | RenalZoom (DNA Diagnostic Laboratory - Johns Hopkins Hospital) | |
| ***APOL1*-Mediated Kidney Disease** | | |
| *APOL-1* Targeted Variant Analysis | Apolipoprotein L1 (APOL1) Renal Risk Variant Genotyping (Quest Diagnostics) | 0355U |
| | APOL1 Genotype, Varies (Mayo Clinic Laboratories) | 81479 |

| Policy Statement Locations | Example Tests, Labs | Common CPT Codes |
|---|---|---|
| **Donor-Derived Cell Free DNA for Kidney Transplant Rejection** | | |
| Donor-Derived Cell Free DNA for Kidney Transplant Rejection | Allosure Kidney (CareDx, Inc.) | 81479 |
| | Prospera Kidney (Natera) | |
| | 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 in policy statement section | 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 0268U |

## Policy Statement

**Polycystic Kidney Disease**
**Targeted Variant Analysis**

I. *PKD1*, *PKD2*, *GANAB*, or *DNAJB11* targeted variant analysis (81403) to establish a diagnosis of autosomal dominant polycystic kidney disease may be considered **medically necessary** when:
   A. The member has a close relative with a known pathogenic or likely pathogenic variant in *PKD1*, *PKD2*, *GANAB*, or *DNAJB11.*

II. *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal recessive polycystic kidney disease may be considered **medically necessary** when:
   A. The member has a biological full sibling with known biallelic pathogenic or likely pathogenic variants in *PKHD1.*

III. *PKD1*, *PKD2*, *GANAB*, *DNAJB11,* or *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal dominant or autosomal recessive polycystic kidney disease is considered **investigational** for all other indications.

**Single Gene or Multigene Panel**

IV. *PKD1* (81407, 81479), *PKD2* (81406, 81479), *GANAB* (81479), *DNAJB11* (81479), *PKHD1* (81408, 81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of polycystic kidney disease may be considered **medically necessary** when:
   A. The member has **any** of the following clinical features of polycystic kidney disease:
      1. Multiple bilateral renal cysts
      2. Cysts in organs other than the kidneys (especially the liver, seminal vesicles, pancreas, and arachnoid membrane)
      3. Hypertension in an individual younger than age 35
      4. Intracranial aneurysm
      5. Bilaterally enlarged and diffusely echogenic kidneys
      6. Poor corticomedullary differentiation
      7. Hepatobiliary abnormalities with progressive portal hypertension
      8. Congenital hepatic fibrosis (CHF) with portal hypertension.

V. *PKD1* (81407, 81479), *PKD2* (81406, 81479), *GANAB* (81479), *DNAJB11* (81479), *PKHD1* (81408, 81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of polycystic kidney disease is considered **investigational** for all other indications.

**Comprehensive Kidney Disease Panels**

VI. Genetic testing for kidney disease via a comprehensive kidney disease panel (81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) may be considered **medically necessary** when **both** of the following criteria are met:
   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)
   B. The member meets at least **one** of the following:
      1. Onset of chronic kidney disease under 40 years of age
      2. One or more first- or second-degree relatives with chronic kidney disease
      3. Consanguineous family history
      4. Cystic renal disease
      5. Congenital nephropathy.

VII. 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.

***APOL1*-Mediated Kidney Disease**

***APOL-1* Targeted Variant Analysis**

VIII. Targeted variant analysis for the *APOL1* high-risk genotype (i.e., G1/G1, G1/G2, or G2/G2) (0355U, 81479) may be considered **medically necessary** when **both** of the following criteria are met:
   A. The member has kidney disease
   B. The member meets at least **one** of the following:
      1. The member is of African ancestry
      2. The member has a family member with a confirmed *APOL1* high-risk genotype (i.e., G1/G1, G1/G2, or G2/G2).

IX. 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.

**Donor-Derived Cell-Free DNA For Kidney Transplant Rejection**

X. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation (81479, 0118U, 0508U, 0509U) may be considered **medically necessary** when:
   A. The member has undergone kidney transplantation, **AND**
      1. The member has clinical signs of acute rejection, **OR**
      2. A biopsy was done to check for signs of acute rejection and is non-diagnostic, **OR**
      3. The member is being monitored for adequate immunosuppression, **AND**
         a. The test has not been performed in the last 12 months.

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

**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.

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

XIII. 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.

**NOTE**: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

## Policy Guidelines

### 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
2. **Full siblings** are individuals who share the same biological parents.

### Coding

See the Codes table for details.

## Description

Inherited kidney disorders and inherited disorders that indirectly affect the kidneys can be more common, such as autosomal dominant polycystic kidney disease, or more rarely 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.

## 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 ***(to be published)***
- ***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.

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

**State:**
SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

## Rationale

**Polycystic Kidney Disease - Targeted Variant Analysis**
***Genetic Support Foundation***
The Genetic Support Foundation's Genetics 101 information on genetic testing says the following about testing for familial pathogenic variants:

> Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members of the family to see who is also at risk.

**GeneReviews: Polycystic Kidney Disease, Autosomal Dominant and Polycystic Kidney Disease, Autosomal Recessive**
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.

Per GeneReviews, autosomal recessive polycystic kidney disease (ARPKD) is due to biallelic mutations in the PKHD1 gene. Testing is possible for siblings of an affected individual in whom both of the causative mutations are identified

### Polycystic Kidney Disease - Single Gene or Multigene Panel

***GeneReviews: Polycystic Kidney Disease, Autosomal Dominant and Polycystic Kidney Disease, Autosomal Recessive***

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
- An intracranial aneurysm…"

"Autosomal recessive polycystic kidney disease (ARPKD) should be suspected in individuals with bilaterally enlarged, diffusely echogenic kidneys…[and] one or more of the following:…Clinical/laboratory signs of congenital hepatic fibrosis (CHF) that leads to portal hypertension…"

"The renal diagnostic criteria for ARPKD detected by ultrasonography are:

- Increased renal size (in relation to normative size based on age and size of the affected individual);
- Increased echogenicity;
- Poor corticomedullary differentiation"

"[In] Childhood and young adulthood…The hepatobiliary abnormalities with progressive portal hypertension are often the prominent presenting features."

### 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)

### *APOL1*-Mediated Kidney Disease

*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

*Knight et al (2019)*
A publication in the journal Transplantation entitled "Donor-specific Cell-free DNA as a Biomarker in Solid Organ Transplantation. A Systematic Review" stated the following:

> In summary, donor-derived cfDNA shows promise as a biomarker for the detection of acute transplant graft injury. It has potential to reduce the need for protocol biopsy surveillance, allowing for a more targeted diagnostic approach. Detection of injury occurs before clinical manifestation, meaning that there is a window for earlier detection and treatment of AR [acute rejection] and other causes of graft injury with the potential to improve outcomes. It may also facilitate the detection of under immunosuppression and find use as a tool for monitoring during immunosuppression minimization. Further studies are required to validate the thresholds for further investigation and intervention, determine the optimum frequency for monitoring, and to identify whether prospective monitoring using dd-cfDNA can indeed improve transplant outcomes compared to current practice. (p. 280)

*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.

## References

1. Harris PC, Torres VE. Polycystic Kidney Disease, Autosomal Dominant. 2002 Jan 10 [Updated 2022 Sep 29]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1246/
2. Sweeney WE, Avner ED. Polycystic Kidney Disease, Autosomal Recessive. 2001 Jul 19 [Updated 2019 Feb 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1326/
3. Hays T, Groopman EE, Gharavi AG. Genetic testing for kidney disease of unknown etiology. Kidney Int. 2020;98(3):590-600. doi:10.1016/j.kint.2020.03.031
4. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
5. Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
6. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.
7. Knight SR, Thorne A, Lo Faro ML. Donor-specific cell-free DNA as a biomarker in solid organ transplantation. A systematic review. *Transplantation*. 2019;103(2):273-283.
8. Genetic Support Foundation. Genetics 101 Genetic Testing: Familial Pathogenic Variant. Accessed 10/4/2022. https://geneticsupportfoundation.org/genetics-101/#
9. Freedman BI, Burke W, Divers J, et al. Diagnosis, education, and care of patients with APOL1-associated nephropathy: a Delphi consensus and systematic review. JASN. 2021;32(7):1765-1778.
10. Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Molecular Testing for Solid Organ Allograft Rejection (L38582). Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38582
11. Park S, Sellares J, Tinel C, Anglicheau D, Bestard O, Friedewald JJ. European Society of Organ Transplantation Consensus Statement on Testing for Non-Invasive Diagnosis of Kidney Allograft Rejection. *Transpl Int*. 2024;36:12115. Published 2024 Jan 4. doi:10.3389/ti.2023.12115

## Documentation for Clinical Review

**Please provide the following documentation:**

- Name of the test being requested or the Concert Genetics GTU identifier. The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

**Post Service (in addition to the above, please include the following):**

- Results/reports of tests performed

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

| Type | Code | Description |
|---|---|---|
| CPT® | 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 |
| | 0268U | Hematology (atypical hemolytic uremic syndrome [aHUS]), genomic sequence analysis of 15 genes, blood, buccal swab, or amniotic fluid |
| | 0355U | POL1 (apolipoprotein L1) (e.g., chronic kidney disease), risk variants (G1, G2) |
| | 0508U | Transplantation medicine, quantification of donor-derived cell-free DNA using 40 singlenucleotide polymorphisms (SNPs), plasma, and urine, initial evaluation reported as percentage of donor-derived cellfree DNA with risk for active rejection ***(Code effective 10/1/2024)*** |
| | 0509U | Transplantation medicine, quantification of donor-derived cell-free DNA using up to 12 single-nucleotide polymorphisms (SNPs) previously identified, plasma, reported as percentage of donor-derived cell-free DNA with risk for active rejection ***(Code effective 10/1/2024)*** |

| Type | Code | Description |
|---|---|---|
| | 81400 | Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis) |
| | 81401 | Molecular pathology procedure, Level 2 (e.g., 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) |
| | 81402 | Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) |
| | 81403 | Molecular pathology procedure, Level 4 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons) |
| | 81407 | Molecular pathology procedure, Level 8 (e.g., 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 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis) |
| | 81479 | Unlisted molecular pathology procedure |
| HCPCS | None | |

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

| Effective Date | Action |
|---|---|
| 04/01/2024 | New policy. |
| 07/01/2024 | Policy statement, literature and references updated. |
| 11/01/2024 | Coding update. |

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished

primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

## Appendix A

| POLICY STATEMENT | |
|---|---|
| **BEFORE** | **AFTER** |
| **Genetic Testing: Kidney Disorders BSC_CON_2.22**<br><br>**Policy Statement:**<br>**Polycystic Kidney Disease**<br>**Targeted Variant Analysis**<br>I. *PKD1*, *PKD2*, *GANAB*, or *DNAJB11* targeted variant analysis (81403) to establish a diagnosis of autosomal dominant polycystic kidney disease may be considered **medically necessary** when:<br>A. The member has a close relative with a known pathogenic or likely pathogenic variant in *PKD1*, *PKD2*, *GANAB*, or *DNAJB11*.<br><br>II. *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal recessive polycystic kidney disease may be considered **medically necessary** when:<br>A. The member has a biological full sibling with known biallelic pathogenic or likely pathogenic variants in *PKHD1*.<br><br>III. *PKD1*, *PKD2*, *GANAB*, *DNAJB11,* or *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal dominant or autosomal recessive polycystic kidney disease is considered **investigational** for all other indications.<br><br>**Single Gene or Multigene Panel**<br>IV. *PKD1* (81407, 81479), *PKD2* (81406, 81479), *GANAB* (81479), *DNAJB11* (81479), *PKHD1* (81408, 81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of polycystic kidney disease may be considered **medically necessary** when:<br>A. The member has **any** of the following clinical features of polycystic kidney disease:<br>a. Multiple bilateral renal cysts | **Genetic Testing: Kidney Disorders BSC_CON_2.22**<br><br>**Policy Statement:**<br>**Polycystic Kidney Disease**<br>**Targeted Variant Analysis**<br>I. *PKD1*, *PKD2*, *GANAB*, or *DNAJB11* targeted variant analysis (81403) to establish a diagnosis of autosomal dominant polycystic kidney disease may be considered **medically necessary** when:<br>A. The member has a close relative with a known pathogenic or likely pathogenic variant in *PKD1*, *PKD2*, *GANAB*, or *DNAJB11.*<br><br>II. *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal recessive polycystic kidney disease may be considered **medically necessary** when:<br>A. The member has a biological full sibling with known biallelic pathogenic or likely pathogenic variants in *PKHD1*.<br><br>III. *PKD1*, *PKD2*, *GANAB*, *DNAJB11,* or *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal dominant or autosomal recessive polycystic kidney disease is considered **investigational** for all other indications.<br><br>**Single Gene or Multigene Panel**<br>IV. *PKD1* (81407, 81479), *PKD2* (81406, 81479), *GANAB* (81479), *DNAJB11* (81479), *PKHD1* (81408, 81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of polycystic kidney disease may be considered **medically necessary** when:<br>A. The member has **any** of the following clinical features of polycystic kidney disease:<br>1. Multiple bilateral renal cysts |

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| b. Cysts in organs other than the kidneys (especially the liver, seminal vesicles, pancreas, and arachnoid membrane)<br>c. Hypertension in an individual younger than age 35<br>d. Intracranial aneurysm<br>e. Bilaterally enlarged and diffusely echogenic kidneys<br>f. Poor corticomedullary differentiation<br>g. Hepatobiliary abnormalities with progressive portal hypertension<br>h. Congenital hepatic fibrosis (CHF) with portal hypertension. | 2. Cysts in organs other than the kidneys (especially the liver, seminal vesicles, pancreas, and arachnoid membrane)<br>3. Hypertension in an individual younger than age 35<br>4. Intracranial aneurysm<br>5. Bilaterally enlarged and diffusely echogenic kidneys<br>6. Poor corticomedullary differentiation<br>7. Hepatobiliary abnormalities with progressive portal hypertension<br>8. Congenital hepatic fibrosis (CHF) with portal hypertension. |
| V. *PKD1* (81407, 81479), *PKD2* (81406, 81479), *GANAB* (81479), *DNAJB11* (81479), *PKHD1* (81408, 81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of polycystic kidney disease is considered **investigational** for all other indications. | V. *PKD1* (81407, 81479), *PKD2* (81406, 81479), *GANAB* (81479), *DNAJB11* (81479), *PKHD1* (81408, 81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of polycystic kidney disease is considered **investigational** for all other indications. |
| **Comprehensive Kidney Disease Panels**<br>VI. Genetic testing for kidney disease via a comprehensive kidney disease panel (81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) may be considered **medically necessary** when **both** of the following criteria are met:<br>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)<br>B. The member meets at least **one** of the following:<br>a. Onset of chronic kidney disease under 40 years of age<br>b. One or more first- or second-degree relatives with chronic kidney disease<br>c. Consanguineous family history<br>d. Cystic renal disease<br>e. Congenital nephropathy. | **Comprehensive Kidney Disease Panels**<br>VI. Genetic testing for kidney disease via a comprehensive kidney disease panel (81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) may be considered **medically necessary** when **both** of the following criteria are met:<br>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)<br>B. The member meets at least **one** of the following:<br>1. Onset of chronic kidney disease under 40 years of age<br>2. One or more first- or second-degree relatives with chronic kidney disease<br>3. Consanguineous family history<br>4. Cystic renal disease<br>5. Congenital nephropathy. |

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| VII. 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. | VII. 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. |
| ***APOL1*-Mediated Kidney Disease**<br>**APOL-1 Targeted Variant Analysis**<br>VIII. Targeted variant analysis for the *APOL1* high-risk genotype (i.e., G1/G1, G1/G2, or G2/G2) (0355U, 81479) may be considered **medically necessary** when:<br>A. The member has kidney disease<br>B. The member meets at least **one** of the following:<br>a. The member is of African ancestry<br>b. The member has a family member with a confirmed *APOL1* high-risk genotype (i.e., G1/G1, G1/G2, or G2/G2). | ***APOL1*-Mediated Kidney Disease**<br>***APOL-1* Targeted Variant Analysis**<br>VIII. Targeted variant analysis for the *APOL1* high-risk genotype (i.e., G1/G1, G1/G2, or G2/G2) (0355U, 81479) may be considered **medically necessary** when **both** of the following criteria are met:<br>A. The member has kidney disease<br>B. The member meets at least **one** of the following:<br>1. The member is of African ancestry<br>2. The member has a family member with a confirmed *APOL1* high-risk genotype (i.e., G1/G1, G1/G2, or G2/G2). |
| IX. 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. | IX. 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. |
| **Donor-Derived Cell-Free DNA For Kidney Transplant Rejection**<br>X. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation (81479, 0118U) may be considered **medically necessary** when:<br>A. The member has undergone kidney transplantation, **AND**<br>1. The member has clinical signs of acute rejection, **OR**<br>2. A biopsy was done to check for signs of acute rejection and is non-diagnostic, **OR**<br>3. The member is being monitored for adequate immunosuppression, **AND**<br>a. The test has not been performed in the last 12 months. | **Donor-Derived Cell-Free DNA For Kidney Transplant Rejection**<br>X. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation (81479, 0118U) may be considered **medically necessary** when:<br>A. The member has undergone kidney transplantation, **AND**<br>1. The member has clinical signs of acute rejection, **OR**<br>2. A biopsy was done to check for signs of acute rejection and is non-diagnostic, **OR**<br>3. The member is being monitored for adequate immunosuppression, **AND**<br>a. The test has not been performed in the last 12 months. |
| XI. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation (81479, 0118U) is considered **investigational** for all other indications. | XI. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation (81479, 0118U) is considered **investigational** for all other indications. |

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| **Other Covered Kidney Disorders**<br>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.<br>XII. Genetic testing to establish or confirm one of the following genetic kidney disorders to guide management may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see XIII below):<br>A. Alport Syndrome<br>B. C3 Glomerulopathy<br>C. Congenital nephrotic syndrome<br>D. Cystinosis<br>E. Cystinuria<br>F. Fabry Disease<br>G. Genetic (familial) atypical hemolytic-uremic syndrome (aHUS)<br>H. Primary Hyperoxaluria<br><br>XIII. 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).<br><br>*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 | **Other Covered Kidney Disorders**<br>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.<br>XII. Genetic testing to establish or confirm one of the following genetic kidney disorders to guide management may be considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see XIII below):<br>A. Alport Syndrome<br>B. C3 Glomerulopathy<br>C. Congenital nephrotic syndrome<br>D. Cystinosis<br>E. Cystinuria<br>F. Fabry Disease<br>G. Genetic (familial) atypical hemolytic-uremic syndrome (aHUS)<br>H. Primary Hyperoxaluria<br><br>XIII. 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).<br><br>*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. |