BSC_CON_2.22	Genetic Testing: Kidney Disorders		
Original Policy Date:	April 1, 2024	**Effective Date:**	January 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 14

Example Test Table

The tests, associated laboratories, CPT codes, 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 Platform for a comprehensive list of registered tests.

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
Polycystic Kidney Disease		
Polycystic Kidney Disease Panels	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
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)	0493U
	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,

Policy Statement

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 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. 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.

Comprehensive Kidney Disease Panels

III. 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
      6. Syndromic/multisystem features
      7. There is a possibility of identifying a condition amenable to targeted treatment.

IV. 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

APOL1 Targeted Variant Analysis

V. 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).

VI. 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

VII. 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) may be 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.

VIII. 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.

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.

IX. 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 X 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

X. 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

Coding

See the Codes table for details.

Description

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.

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.

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 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.

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; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1246/
2. Burgmaier K, Gimpel C, Schaefer F, Liebau M. . Autosomal Recessive Polycystic Kidney Disease - *PKHD1* 2001 Jul 19 [Updated 2024 Apr 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. 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; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
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6. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.
7. 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.
8. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International (2024). Volume 105 (Suppl 4S), S117–S314. https://kdigo.org/wp-content/uploads/2024/03/KDIGO-2024-CKD-Guideline.pdf
9. 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

10. 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
11. ASTS Statement on donor derived cell-free DNA (dd-cfDNA), ASTS.org, Approved March 6, 2023.https://asts.org/docs/default-source/position-statements/dd-cfdna-position-statement.pdf

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
	0355U	POL1 (apolipoprotein L1) (e.g., chronic kidney disease), risk variants (G1, G2)
	0493U	Transplantation medicine, quantification of donor-derived cell-free DNA (cfDNA) using next-generation sequencing, plasma, reported as percentage of donor-derived cell-free DNA ***(Code effective 10/1/2024)***
	0508U	Transplantation medicine, quantification of donor-derived cell-free DNA using 40 singlenucleotide polymorphisms (SNPs), plasma, and

Type	Code	Description
		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)***
	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.
01/01/2025	Annual update. Policy statement, literature and references updated.

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 Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Genetic Testing: Kidney Disorders BSC_CON_2.22 **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	**Genetic Testing: Kidney Disorders BSC_CON_2.22** **Policy Statement:** **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 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,

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
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.	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. Bilaterally enlarged and diffusely echogenic kidneys
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.	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.
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.	**Comprehensive Kidney Disease Panels** III. 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 6. Syndromic/multisystem features 7. There is a possibility of identifying a condition amenable to targeted treatment.

POLICY STATEMENT	
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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.	IV. 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).	***APOL1*-Mediated Kidney Disease** **APOL1 Targeted Variant Analysis** V. 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.	VI. 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.	**Donor-Derived Cell-Free Dna For Kidney Transplant Rejection** VII. 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) may be 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.

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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.	VIII. 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.
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.	**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	IX. 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 X 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).	X. 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.	*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.