Clinical Policy: Genetic Testing Kidney Disorders

Reference Number: CP.MP.227
Date of Last Revision: 02/22

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 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.

Below is a list of higher volume tests and the associated laboratories for each criteria section. This list is not all inclusive.

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81403	PKD1 Targeted Mutation Analysis PKD2 Targeted Mutation Analysis PKHD1 Targeted Mutation Analysis	Targeted Variant Analysis	Q61, N18
81406,81407, 81479	PKD1 Sequencing Analysis PKD2 Sequencing Analysis PKHD1 Sequencing Analysis	Simple-gene or Multigene Panel Analysis	Q61, N18
81404,81405, 81406,81407, 81408, 81479	Autosomal Dominant and Recessive Polycystic Kidney Disease (ADPKD and ARPKD) Panel (PreventionGenetics)	Simple-gene or Multigene Panel Analysis	Q61, N18
81404,81405, 81406,81407, 81408, 81479	Expanded Polycystic Kidney Disease NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics)	Simple-gene or Multigene Panel Analysis	Q61, N18
81401,81402, 81403,81404, 81405,81406,	RenaSight (Natera)	Comprehensive Kidney Disease Panels	N00-N08, N10-N16, N17-N19, Q61, R31

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81407,81408, 81479	KidneySeq Version 4 Comprehensive Testing (Iowa Institute of Human Genetics) Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT) Panel (PreventionGenetics) RenalZoom (DNA Diagnostic Laboratory - Johns Hopkins Hospital)		
81479	Allosure Kidney (CareDx, Inc.) Prospera (Natera)	Donor-Derived Cell Free DNA for Kidney Transplant Rejection	T86.11, T86.12, Z94.0
0118U	Viracor TRAC dd-cfDNA (Viracor Eurofins)	Donor-Derived Cell Free DNA for Kidney Transplant Rejection	T86.11, T86.12, Z94.0
81400-81408	See list below	Other Kidney Disorders	N/A

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

- ***CP.MP.230 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to genetic disorders that affect multiple organ systems
- ***CP.MP.225 Genetic Testing: Hereditary Cancer Susceptibility*** for criteria related to von Hippel Lindau (VHL) syndrome and other hereditary cancer syndromes.
- ***CP.MP.222 Genetic Testing: General Approach to Genetic Testing*** for criteria related to genetic testing for kidney disease that is not specifically discussed in this or another non-general policy.

Policy/Criteria

Polycystic Kidney Disease

Targeted Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *PKD1*, *PKD2*, *GANAB*, *DNAJB11* or *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal dominant polycystic kidney disease is considered **medically necessary** when:

A. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant in *PKD1*, *PKD2*, *GANAB*, *DNAJB11*, *or PKHD1*.

II. It is the policy of health plans affiliated with Centene Corporation® that *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal recessive polycystic kidney disease is considered **medically necessary** when:

A. The member/enrollee has a sibling with known biallelic pathogenic or likely pathogenic variants in *PKHD1*.

III. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *PKD1*, *PKD2*, *GANAB*, *DNAJB11*, or *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal dominant or autosomal recessive polycystic kidney disease for all other indications.

Single Gene or Multigene Panel Analysis

I. It is the policy of health plans affiliated with Centene Corporation® that *PKD1* (81407), *PKD2* (81406), *GANAB* (81479), *DNAJB11* (81479), *PKHD1* (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 **medically necessary** when:

A. The member/enrollee has any of the following clinical features of polycystic kidney disease:

1. Multiple bilateral renal cysts
2. Cysts in other organs (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,

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *PKD1* (81407), *PKD2* (81406), *GANAB* (81479), *DNAJB11* (81479), *PKHD1* (81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81405, 81406, 81407, 81408, 81409, 81479) to confirm or establish a diagnosis of polycystic kidney disease for all other indications.

Comprehensive Kidney Disease Panels

I. It is the policy of health plans affiliated with Centene Corporation® that 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 meeting all of the following:

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

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

      1. Onset of chronic kidney disease under 40 years of age,

      2. One or more first[1a]- or second-degree[1b] relatives with chronic kidney disease,

      3. Consanguineous family history,

   C. The member/enrollee is being considered for a kidney transplant.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support genetic testing for kidney disease via a comprehensive kidney disease panel (81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) for all other indications.

Donor-Derived Cell-Free DNA For Kidney Transplant Rejection

I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation(81479, 0118U) (e.g., Allosure Kidney, Viracor TRAC) for all indications, including but not limited to:

   A. Detection of acute renal transplant rejection
   B. Detection of renal transplant graft dysfunction

Other Kidney Disorders

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

I. It is the policy of health plans affiliated with Centene Corporation® that genetic testing to establish or confirm one of the following genetic kidney disorders to guide management is considered **medically necessary** when the member/enrollee 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. It is the policy of health plans affiliated with Centene Corporation® that 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 *CP.MP.222 General Approach to Genetic Testing* (see policy for 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.

Notes and 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

Background

Kidney Disease Improving Global Outcomes (KDIGO)
The Kidney Disease Improving Global Outcomes (2009) issued guidelines for the care of kidney transplant recipients. The guidelines included the following recommendations:

- "We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine. (1C)"
- "We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection. (2D)"
- "We suggest kidney allograft biopsy every 7-10 days during delayed function. (2C)"
- "We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1-2 months after transplantation. (2D)"
- "We suggest kidney allograft biopsy when there is new onset of proteinuria. (2C)"
- "We suggest kidney allograft biopsy when there is unexplained proteinuria ≥3.0 g/g creatinine or ≥3.0 g per 24 hours. (2C)"

Renal Association

The Renal Association (2017) published clinical practice guidelines for the care of patients from the period following kidney transplantation until the transplant is no longer working or the patient dies, which included the following:

- Guideline 4.1 – "We recommend that a transplant renal biopsy should be carried out before treating an acute rejection episode unless this will substantially delay treatment or pose a significant risk to the patient (1C)"
- Guideline 4.6 – "We suggest that a serum sample be sent at the time of renal biopsy (for graft dysfunction) to look for human leukocyte antigen (HLA)-specific antibodies (2C)"
- Guideline 5.1 – "We recommend that early identification of graft injury is desirable to maximise the potential for intervention. A proactive and systematic approach should employed to manage graft dysfunction (1C)"
- Guideline 5.2 – "We suggest that renal function should be monitored at each clinic visit by assessment of serum creatinine and qualitative evaluation of urine protein excretion by dipstick, supplemented by spot protein:creatinine ratio (PCR) or albumin:creatinine ratio (ACR) if positive (2C)"
- Guideline 5.3 – "We suggest that renal biopsy is the optimal investigation for parenchymal causes of graft dysfunction where the cause is uncertain (2C)"

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2021, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	02/22	02/22

References

1. Harris PC, Torres VE. Polycystic Kidney Disease, Autosomal Dominant. 2002 Jan 10 [Updated 2018 Jul 19]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. 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; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1326/

3. Groopman EE, Marasa M, Cameron-Christie S, et al. Diagnostic Utility of Exome Sequencing for Kidney Disease. N Engl J Med. 2019;380(2):142-151. doi:10.1056/NEJMoa1806891
4. Cocchi E, Nestor JG, Gharavi AG. Clinical Genetic Screening in Adult Patients with Kidney Disease. Clin J Am Soc Nephrol. 2020;15(10):1497-1510. doi:10.2215/CJN.15141219
5. Benson KA, Murray SL, Doyle R, et al. Diagnostic utility of genetic testing in patients undergoing renal biopsy. Cold Spring Harb Mol Case Stud. 2020;6(5):a005462. Published 2020 Oct 7. doi:10.1101/mcs.a005462Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8(8):1308-1339. doi:10.1016/j.hrthm.2011.05.020
6. de Haan A, Eijgelsheim M, Vogt L, Knoers NVAM, de Borst MH. Diagnostic Yield of Next-Generation Sequencing in Patients With Chronic Kidney Disease of Unknown Etiology. Front Genet. 2019;10:1264. Published 2019 Dec 13. doi:10.3389/fgene.2019.01264
7. Stokman MF, Renkema KY, Giles RH, Schaefer F, Knoers NV, van Eerde AM. The expanding phenotypic spectra of kidney diseases: insights from genetic studies. Nat Rev Nephrol. 2016;12(8):472-483. doi:10.1038/nrneph.2016.87
8. Kashtan CE. Alport Syndrome. 2001 Aug 28 [Updated 2019 Feb 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1207/
9. Bloom RD, Bromberg JS, Poggio ED, et al. Cell-Free DNA and Active Rejection in Kidney Allografts. J Am Soc Nephrol. 2017;28(7):2221-2232. doi:10.1681/ASN.2016091034
10. Huang E, Sethi S, Peng A, et al. Early clinical experience using donor-derived cell-free DNA to detect rejection in kidney transplant recipients. Am J Transplant. 2019;19(6):1663-1670. doi:10.1111/ajt.15289
11. Kasiske BL, Zeier MG, Chapman JR, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. Kidney Int. 2010;77(4):299-311. doi:10.1038/ki.2009.377
12. Baker RJ, Mark PB, Patel RK, Stevens KK, Palmer N. Renal association clinical practice guideline in post-operative care in the kidney transplant recipient. BMC Nephrol. 2017;18(1):174. Published 2017 Jun 2. doi:10.1186/s12882-017-0553-2
13. Jayasinghe K, Stark Z, Kerr PG, et al. Clinical impact of genomic testing in patients with suspected monogenic kidney disease. Genet Med. 2021;23(1):183-191. doi:10.1038/s41436-020-00963-4
14. Thomas CP, Freese ME, Ounda A, et al. Initial experience from a renal genetics clinic demonstrates a distinct role in patient management [published correction appears in Genet Med. 2020 Oct 6;:]. Genet Med. 2020;22(6):1025-1035. doi:10.1038/s41436-020-0772-y
15. 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
16. Schrezenmeier E, Kremerskothen E, Halleck F, et al. The underestimated burden of monogenic kidney disease in adults waitlisted for kidney transplantation [published online

ahead of print, 2021 Mar 12]. Genet Med. 2021;10.1038/s41436-021-01127-8. doi:10.1038/s41436-021-01127-8

17. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
18. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
19. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.
20. Gimpel C, Bergmann C, Bockenhauer D, et al. International consensus statement on the diagnosis and management of autosomal dominant polycystic kidney disease in children and young people. Nat Rev Nephrol. 2019;15(11):713-726. doi:10.1038/s41581-019-0155-2
21. Dudley J, Winyard P, Marlais M, et al. Clinical practice guideline monitoring children and young people with, or at risk of developing autosomal dominant polycystic kidney disease (ADPKD). BMC Nephrol. 2019;20(1):148. Published 2019 Apr 30. doi:10.1186/s12882-019-1285-2

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, member/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, member/enrollees and their representatives agree to be bound by such terms and conditions by providing services to member/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.

©2016 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.