Concert Genetic Testing: Transplant

Reference Number: V2.2025 **Coding implications**
Date of Last Revision 04/26 **Revision Log**

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

OVERVIEW

This policy addresses the use of tests for diagnosis and screening during the process of solid organ transplantation, either using tissue or peripheral blood.

For additional information see the Rationale section.

POLICY REFERENCE TABLE

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 2024, 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.

The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their inclusion does not represent a guarantee of coverage or non-coverage. Please see the Concert Platform for additional registered tests.

> **NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.**

CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Heart Transplant Tests			
Donor-Derived Cell-free DNA for Heart Transplant Rejection	AlloSure (CareDx)	81479, 0055U*, 0118U*, 0493U*, Z48.21, Z94.1	7, 8
	Prospera - 0493U (Natera)		
	myTAIHEART - 0055U (TAI Diagnostics)		
	Viracor TRAC Heart dd-cfDNA - 0118U (Eurofins)		
Post Heart Transplant Gene Expression Panels for Rejection Risk via Peripheral Blood	AlloMap - 81595 (CareDx)	81595*, Z48.21, Z94.1	7
Post Heart Transplant Gene Expression Panels for Rejection Risk via Tissue	Molecular Microscope MMDX - Heart - 0087U (Kashi Clinical Laboratories)	0087U*, Z48.21, Z94.1	7
Kidney Transplant Tests			
Donor-Derived Cell-free DNA for Kidney Transplant Rejection	Allosure Kidney (CareDx, Inc.)	81479, 0118U*, 0493U*, 0508U*, 0509U*, T86.11, T86.12, Z94.0	6, 8, 9
	Prospera - 0493U (Natera)		
	Viracor TRAC Kidney dd-cfDNA - 0118U (Viracor Eurofins)		
	VitaGraft Kidney Baseline + 1st Plasma Test - 0508U (Oncocyte Corporation)		
	VitaGraft Kidney Subsequent - 0509U (Oncocyte Corporation)		
Lung Transplant Tests			

Evidence-Based Donor-Derived Cell-free DNA for Lung Transplant Rejection	Prospera Lung (Natera) AlloSure Lung (CareDx)	81479, T86.810, Z48.24, Z94.2	6
Emerging Evidence Donor-Derived Cell-free DNA for Lung Transplant Rejection	Eurofins TRAC dd-cfDNA - 0118U (Transplant Genomics Inc)	0118U*, T86.810, Z48.24, Z94.2	6
HLA Typing for Transplantation			
HLA Typing for Transplantation	HLA-A,B Intermediate Resolution (Versiti) HLA-B Low Resolution (Versiti)	81370*, 81371*, 81372*, 81373*, 81376*, 81378*, 81379*, 81380, 81382, C25, C81-C96, D46, D61, Z52.20, Z52.3, Z52.4 Z52.89, N17, N18, N19, I12, E08-E13	1, 2, 3, 4, 5
	HLA-DQB1,DQA1 Intermediate Resolution (Versiti)		
	HLA-A, B, C, DRB1 and DQ High Resolution (Quest Diagnostics)		
	HLA A,B,C Profile (High Resolution) (Labcorp) HLA-A High Resolution (Versiti)		

RELATED POLICIES

This policy document provides criteria for testing related to transplantation. Please refer to:

- ***Oncology Testing: Hematologic Malignancy Molecular Diagnostics*** **for criteria related to molecular profiling of a known or suspected blood cancer (e.g. broad molecular profiling, including Minimal Residual Disease (MRD) Testing, Tumor Mutational Burden (TMB), and cytogenetic / fusion testing).**
- ***Oncology Testing: Solid Tumor Molecular Diagnostics*** **for criteria related to molecular profiling of a known or suspected cancer (e.g. broad molecular profiling, including Minimal Residual Disease (MRD) Testing, Tumor Mutational Burden (TMB), and cytogenetic / fusion testing).**
- ***Specialty Testing: Cardiovascular*** **for criteria related to diagnostic tests for inherited and sporadic cardiovascular conditions.**

- ***Specialty Testing: Nephrology*** **for criteria related to diagnostic tests for suspected kidney disorders, including testing of asymptomatic potential living donors.**
- ***Specialty Testing: Respiratory*** **for criteria related to diagnostic tests for disorders that affect the lungs, including cystic fibrosis.**
- ***General Approach to Laboratory Testing*** **for criteria related to transplantation, that is not specifically discussed in this or another non-general policy.**

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CRITERIA

HEART TRANSPLANT TESTS

Donor-Derived Cell-free DNA for Heart Transplant Rejection

I. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after heart transplantation is considered medically necessary when:

A. The member/enrollee has undergone a heart transplant, AND

B. Peripheral blood measurement of donor-derived cell-free DNA testing has not been performed in the past twelve months.

II. Current evidence does not support the use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after heart for all other indications.

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Post Heart Transplant Gene Expression Panels for Rejection Risk via Peripheral Blood

I. The use of post heart transplant gene expression panels for rejection risk via peripheral blood to determine management of patients after heart transplantation is considered medically necessary when:

A. The member/enrollee is age 18 or older, AND

B. The member/enrollee has undergone heart transplant, AND

C. The member/enrollee is at low-risk for organ rejection, AND

D. The member/enrollee's heart transplant was performed at least 2 months ago and less than 5 years ago.

II. Current evidence does not support the use of post heart transplant gene expression panels for rejection risk via peripheral blood to determine management of patients after heart transplantation for all other indications.

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Post Heart Transplant Gene Expression Panels for Rejection Risk via Tissue

I. Current evidence does not support the use of post heart transplant gene expression panels for rejection risk via tissue for all indications.

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KIDNEY TRANSPLANT TESTS

Donor-Derived Cell-free DNA for Kidney Transplant Rejection

I. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation is considered medically necessary when:

A. The member/enrollee has undergone kidney transplantation, AND

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

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

1. The member/enrollee 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/enrollee is being monitored for adequate immunosuppression.

II. 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 for all other indications.

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LUNG TRANSPLANT TESTS

Evidence-Based Donor-Derived Cell-free DNA for Lung Transplant Rejection

I. The use of peripheral blood measurement of donor-derived cell-free DNA tests with sufficient evidence of clinical utility and validity in the management of patients after lung transplantation is considered medically necessary when:

   A. The member/enrollee has undergone lung transplantation, AND

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

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

      1. The member/enrollee has clinical signs of acute rejection, OR

      2. A biopsy was done and is inconclusive for rejection, OR

      3. The member/enrollee is being monitored for adequate immunosuppression.

II. Current evidence does not support the use of peripheral blood measurement of donor-derived cell-free DNA tests in the management of patients after lung for all other indications.

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Emerging Evidence Donor-Derived Cell-free DNA for Lung Transplant Rejection

I. Current evidence does not support donor-derived cell-free DNA tests with insufficient evidence of clinical validity in the management of patients after lung transplantation for all indications.

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HLA TYPING FOR TRANSPLANTATION

HLA Typing for Transplantation

I. HLA typing for transplantation is considered medically necessary when the member/enrollee meets the following:

A. **The member/enrollee is being considered for any of the following:**

1. **Recipient of bone marrow transplantation, OR**
2. **Donor for bone marrow transplantation, OR**
3. **Recipient of solid organ transplantation, OR**
4. **Donor for solid organ transplantation.**

II. **Current evidence does not support HLA typing for all other indications.**

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RATIONALE

Donor-Derived Cell-free DNA for Heart Transplant Rejection

American Society of Transplant Surgeons

In their position statement approved in March 2023 and updated October 2024, the American Society of Transplant Surgeons (ASTS) stated the following: "We recommend that dd-cfDNA [donor-derived cell-free DNA] may be utilized to rule out subclinical rejection for heart transplant recipients" (p. 5).

International Society of Heart and Lung Transplantation

The 2023 ISHLT guidelines were reviewed to assess the recommended frequency for dd-cfDNA testing. Included in the guidelines is an example of a biopsy schedule for follow-up visits post-transplant. The 2023 updated guideline states that noninvasive testing (such as Allomap) may be included in these follow-up visits. However, we did not identify any clear evidence-based recommendations in ISHLT for the use of dd-cfDNA testing as a serial monitoring tool.

Concert Note

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

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Post Heart Transplant Gene Expression Panels for Rejection Risk via Peripheral Blood

International Society of Heart and Lung Transplantation

The 2023 International Society of Heart and Lung Transplantation (ISHLT) Guidelines for the Care of Heart Transplant Patients include recommendations for the non-invasive monitoring of acute cellular rejection (ACR) after heart transplant [HT]. They specifically address Allomap and state that peripheral blood testing "can be used in low-risk patients between 2 months and 5 years after HT to identify adult recipients who have low risk of current ACR to reduce the frequency of EMB [endomyocardial biopsy]". At this time, the recommendation is specific to adults given data in children does not allow for a general recommendation for GEP (p. e38).

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Post Heart Transplant Gene Expression Panels for Rejection Risk via Tissue

International Society of Heart and Lung Transplantation

The 2023 International Society of Heart and Lung Transplantation (ISHLT) guidelines for the Care of Heart Transplant Patients states that gene expression testing of allograft tissue (e.g., Molecular Microscope, MMDx) may allow for "improved discrimination between T-cell mediated or antibody mediated rejection and tissue injury". However, the test is not routinely used or may not be clinically available at this time (p. e33-34).

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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 (2024)

The European Society of Organ Transplantation (ESOT) 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 an updated statement on donor derived cell-free DNA (dd-cfDNA) in October of 2024. Included in the statement is a section on the current state of evidence supporting a frequency schedule for dd-cfDNA testing in kidney transplant recipients. Overall, the ASTS states that "the optimal surveillance testing frequency is unknown". In their summary of evidence, they state that additional research is needed to determine the optimal frequency for dd-cfDNA surveillance testing (p. 3-4).

Concert Note

Although the ASTS recommendations include a suggestion for "serial dd-cfDNA" testing in kidney transplant recipients, there is currently not a clear, specific, and evidence-based guideline recommendation for a particular regimen of screening. Therefore, a default frequency of coverage of once every 12 months will be adopted.

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Evidence-Based Donor-Derived Cell-free DNA for Lung 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."**

Concert Note

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

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Emerging Evidence Donor-Derived Cell-free DNA for Lung Transplant Rejection

Tests that have limited established clinical utility or validity as defined in the Concert policy for General Approach to Genetic and Molecular testing do not meet the threshold for coverage. Evidence for validity may include a Technology Assessment conducted by an independent third party (e.g.MolDx Tech, ECRI, Optum Genomic) and/or evidence-based guidelines published by professional societies. Such evidence was not identified for the tests referenced by this policy.

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HLA Typing for Transplantation

UpToDate: Human leukocyte antigens (HLA): A roadmap

For patients who are undergoing or being evaluated for hematopoietic stem cell transplantation, full HLA typing is required.

UpToDate: Donor selection for hematopoietic cell transplantation

Donor and recipient HLA typing for HLA-A, -B, -C, and -DR is an important and necessary part of successful hematopoietic cell transplantation (HCT). T

NMDP, formerly known as the National Marrow Donor Program and Be The Match

"These guidelines were developed jointly by NMDP and the American Society for Transplantation and Cellular Therapy (ASTCT). The guidelines are based on current clinical practice, medical literature, National Comprehensive Cancer Network (NCCN) Guidelines for the treatment of cancer and evidence-based reviews."

"If allogeneic transplant is potentially indicated, you should perform HLA typing of the patient and potential family donors at diagnosis. In addition, a preliminary unrelated donor search of the NMDP Registry should be completed."

Organ Procurement and Transplantation Network (OPTN)

The OPTN (effective date: 10/31/2024) includes a section titled "Requirements for Performing and Reporting HLA Typing", in which it states:

"Laboratories must perform HLA typing on a kidney, kidney-pancreas, pancreas, or pancreas islet candidate and report results for HLA A, B, Bw4, Bw6, and DR to the transplant program prior to registration on the waiting list" (p. 52).

Additionally, the document states:

"Laboratories performing histocompatibility testing for kidney transplants or multi-organ transplants in which a kidney is to be transplanted must perform a final crossmatch and report the results to the Transplant Program before transplant (p. 55).

Tait, et al

In 2013, Tait et al. created a list of technical test recommendations for pre and post solid organ transplantation. Per the article:

"HLA typing of donor and recipient must be performed at a level required for accurate antibody interpretation. When a patient is sensitized, precise characterization of HLA antibodies and complete HLA typing of the donor pretransplantation must be performed" (p. 37).

Of note, there is no mention of performing HLA Typing post-transplantation.

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
New policy developed from criteria previously in other policies- criteria for Donor-Derived Cell Free DNA for Heart Transplant Rejection, Post Heart Transplant Gene Expression Panels for Rejection Risk via Peripheral Blood, and Post Heart Transplant Gene Expression Panels For Rejection Risk via Tissue incorporated from Concert Genetic Testing: Cardiac Disorders; Donor-Derived Cell-free DNA for Kidney Transplant Rejection criteria incorporated from Concert Genetic Testing: Kidney Disorders; criteria for Emerging Evidence Donor-Derived Cell-free DNA for Lung Transplant Rejection and Evidence-Based Donor-Derived Cell-free DNA for Lung Transplant Rejection incorporated from Concert Genetic Testing: Lung Disorders; criteria for HLA Typing for Transplantation incorporated from Concert Oncology Genetic Testing: Molecular Analysis of Solid Tumors and Hematologic Malignancies. Post Heart Transplant Gene Expression Panels for Rejection Risk via Peripheral Blood criteria: Added criterion stating that the member must be age 18 years or older, in alignment with guidelines. Post Heart Transplant Gene Expression Panels for Rejection Risk via Tissue: Added the term "for all indications" to the criteria set to be consistent throughout the policy. Emerging Evidence Donor-Derived Cell-free DNA for Lung Transplant Rejection: Added "for all indications." Replaced "investigational" policy statements with "current evidence does not support." Policy reference table, rationale, background, and references updated.	04/26	

REFERENCES

1. Viatte, MD, PhD, et al. Human leukocyte antigens (HLA): A roadmap. In: UpToDate, Connor RF (ed), Wolters Kluwer (Accessed on May 8, 2024). https://www.uptodate.com/contents/human-leukocyte-antigens-hla-a-roadmap
2. Negrin, R.S., MD, et al. Donor selection for hematopoietic cell transplantation. In: UpToDate, Connor, RF (ed), Wolters Kluwer (Accessed May 8, 2024). https://www.uptodate.com/contents/donor-selection-for-hematopoietic-cell-transplantation
3. 2024 CONSULTATION GUIDELINES Recommended Timing for Transplant Consultation. Published jointly by NMDPSM and the American Society for Transplantation and Cellular Therapy (ASTCT). Available at: https://www2.bethematchclinical.org/ConsultationGuidelines
4. Tait BD, Süsal C, Gebel HM, et al. Consensus guidelines on the testing and clinical management issues associated with HLA and non-HLA antibodies in transplantation. *Transplantation*. 2013;95(1):19-47. doi:10.1097/TP.0b013e31827a19cc
5. "Requirements for Performing and Reporting HLA Typing" OPTN (Effective Date: 10/31/2024). Available at: https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf
6. 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
7. Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. 2023;42(5):e1-e141. doi:10.1016/j.healun.2022.10.015
8. ASTS Statement on donor-derived cell-free DNA (dd-cf-DNA). Published online March 6, 2023, Updated October 2024. American Society of Transplant Surgeons. https://www.asts.org/docs/default-source/position-statements/asts-statement-on-donor-derived-cell-free-dna-(dd-cfdna)---updated-oct.-2024.pdf
9. 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

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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. LHCC 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.
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 LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. 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. LHCC 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.

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