Evidence-Based Donor-Derived Cell-free DNA for Solid Organ Transplant Rejection

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

A. Peripheral blood measurement of donor-derived cell-free DNA has not been performed in the past twelve months, **AND**

B. The member meets one of the following:

1. The member has undergone a heart transplantation, **AND**

a) The test is Allosure or Prospera, **OR**

2. The member has undergone a kidney transplantation, **AND**

a) The test is Allosure, Prospera, Viracor TRAC Kidney dd-cfDNA, VitaGraft Kidney 2.0, VitaGraft Kidney Baseline, or VitaGraft Kidney Subsequent, **AND**

(1) The member meets at least one of the following:

(a) The member has clinical signs of acute rejection, **OR**

(b) A biopsy was done to check for signs of acute rejection and is inconclusive, **OR**

(c) The member is being monitored for adequate immunosuppression, **OR**

3. The member has undergone a lung transplantation, **AND**

a) The test is Allosure or Prospera, **AND**

(1) The member meets at least one of the following:

(a) The member has clinical signs of acute rejection, **OR**

(b) A biopsy was done to check for signs of acute rejection and is inconclusive, **OR**

(c) The member is being monitored for adequate immunosuppression.

II. The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after solid organ transplantation is considered **investigational** for all other indications.

RATIONALE AND REFERENCES

Evidence-Based Donor-Derived Cell-free DNA for Solid Organ Transplant Rejection

American Society of Transplant Surgeons (ASTS)

In their position statement (2023, updated 2024), 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).

In the same updated statement, ASTS included a section on the current state of evidence supporting a frequency schedule for dd-cfDNA testing in kidney transplant recipients. Overall, the ASTS recommends “serial dd-cfDNA” testing, but 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).

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

International Society of Heart and Lung Transplantation (ISHLT)

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 (pp. E89-90, Table 13) for follow-up visits post-transplant. The 2023 updated guideline states

that noninvasive gene expression profile testing (such as Allomap) may be included in these follow-up visits but notes that the schedule “serves merely as an example”, and dd-cfDNA testing use or frequency is not addressed in the table. No clear evidence-based recommendations in ISHLT for the use of dd-cfDNA testing as a serial monitoring tool, or for a specific frequency of testing were identified.

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

Centers for Medicare and Medicaid Services (CMS)

The CMS local coverage determination (LCD) entitled “MolDX: Molecular Testing for Solid Organ Allograft Rejection” provides limited coverage for molecular testing to evaluate for active rejection in solid organ transplant recipients. The determination supports ordering of such tests when a transplant-center-affiliated physician is considering a diagnosis of active rejection (AR), particularly in patients with significant contraindications to invasive procedures.

CMS states that the intended use of the test must be one of the following:

- “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”.

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

European Society of Organ Transplantation (ESOT)

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).

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

Concert Note

For assessing rejection in patients post-transplant, absent clear, specific and evidence-based guideline recommendations for a particular regimen of testing, a default frequency of once every 12 months will be adopted.