AlloSure for Kidney Transplant Rejection

MOL.TS.307.A
v1.0.2026

AlloSure for kidney transplant rejection (AlloSure Kidney) is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
AlloSure Kidney	0540U

Criteria

Requests for AlloSure Kidney testing for allograft kidney transplant rejection are reviewed using the following criteria.

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

What Is Kidney Transplant Rejection?

Kidney disease is a loss of renal function which, without treatment, leads to eventual build-up of waste and other toxic substances in the blood.[1] Treatment of advanced kidney disease, called end-stage kidney disease, consists of dialysis or renal transplant. Transplant rejection can be acute or chronic.

730 Cool Springs Blvd, Franklin, TN 37067 (800) 918-8924 www.EviCore.com

Incidence and Prevalence

According to the National Kidney Foundation, 97% of kidney transplants are functioning 1 year after transplant.[2] Between 10 and 20% of kidney transplant recipients experience at least one episode of organ rejection.[3] Organ rejection after kidney transplant is more likely in younger recipients (9.1% in recipients 18-34) than older recipients (5.9% over age 65).[2] Recipients are most likely to experience organ rejection within 6 months of transplant, but can occur at any time.[3]

Symptoms

Kidney transplant rejection can be acute (occurring suddenly and progressing quickly) or chronic (occurring slowly over time), and is typically immune system mediated. Symptoms of transplant rejection include fever and flu-like symptoms, decreased urinary output, weight gain, fatigue, and pain over the transplanted organ.[3]

Acute rejection of the donated kidney is thought to lead to tissue injury, including increased cell death in the allograft, which then leads to increased donor-derived cell free DNA (dd-cfDNA) in the bloodstream. Other investigators have reported that the fraction of cell-free DNA (cfDNA) originating from the organ grafts is approximately less than 1% and during rejection, level of dd-cfDNA increase.[4-6]

Cause

Transplanted kidneys can fail for multiple reasons:[7]

- Blood clot in the vessels leading to the kidney
- Infection
- Medication side effects
- Non-compliance with post-transplant medications and other post-surgical care
- Recurrence of the original medical problem that necessitated the kidney transplant
- Acute or chronic rejection caused by immune-mediated donor kidney damage

Diagnosis

Rise in creatinine levels is currently used to initially diagnose graft rejection, and the gold standard for initial diagnosis is histological analysis based on needle biopsy of the organ.[4-5] However, organ biopsy is invasive and often associated with complications, patient discomfort, and inconvenience. Biopsy is also prone to sampling error. Serum creatinine is one of the main markers used to monitor allograft functioning, but has been shown to lack sensitivity and specificity for graft injury and may change too late to allow prompt clinical management decisions.[8,9]

Alternatively, donor-derived cell-free DNA (dd-cfDNA) (as a fraction of the total cell-free DNA [cfDNA]) has been proposed as a noninvasive marker for detecting graft rejection and measuring allograft damage among recent kidney transplant patients.

Treatment

Rejection episodes are typically managed on an inpatient basis by altering medication dosage.[3]

Survival

The 5-year survival in individuals who have living donor transplants is over 80%.[2] Survival rates are lower with deceased donor transplants.[2] If the kidneys fail completely, survival is a few months without treatment.[1] After transplant, long-term survival is still limited, and acute rejection is a frequent complication and associated with reduced graft survival.[1]

Test Information

AlloSure Kidney is an assay designed to detect allograft rejection in kidney transplant recipients.

Description and Purpose

According to the manufacturer of AlloSure Kidney (Care Dx), the test is intended to non-invasively measure donor DNA in the blood for early detection of allograft injury and rejection.[10] AlloSure Kidney can detect antibody mediated rejection (ABMR), T cell mediated rejection (TCMR), graft injury, and de novo donor-specific antibodies (dnDSA).[10]

Test Targets

AlloSure Kidney is a targeted next-generation sequencing assay that uses 266 single-nucleotide polymorphisms (SNPs) to quantify dd-cfDNA in transplant patients.[10]

Result

The test reports an AlloSure Score (percent of donor derived DNA in the patient's blood sample) along with quality control cut-off values.[10]

Interpretation of test results:[10]

- Low risk of rejection: less than 0.5%
- Likely graft injury: 0.5-1.0%
- High risk of rejection: 1.0-2.9%

In addition, the relative change (RCV) of dd-cfDNA over time can provide additional information:[10]

- RCV less than 61%: biological variation
- RCV 149% or greater: high likelihood of graft injury.

Guidelines and evidence

American Society of Transplant Surgeons

The American Society of Transplant Surgeons (ASTS, 2024) issued a position statement on the use of dd-cfDNA in transplant recipients that stated:[11]

- "We recommend that clinicians measure dd-cfDNA levels in kidney transplant recipients with acute allograft dysfunction to exclude the presence of rejection, particularly antibody-mediated rejection (ABMR)."
- "We strongly recommend ongoing further clinical studies to clarify the scenarios and frequency in which molecular diagnostic studies should be utilized."
- "We specifically recommend that studies be carried out to evaluate the potential role of dd-cfDNA surveillance in kidney transplant recipients to improve long term allograft survival."

The Renal Association

The Renal Association Clinical Practice Guideline Post-Operative Care in the Kidney Transplant Recipient (RA, 2017, Reviewed 2022) was endorsed by the British Transplantation Society and the National Institute for Health and Care Excellence. The guideline stated:[12]

- "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)"
- "We suggest that two cores of renal tissue should be obtained at transplant biopsy since this will increase the sensitivity of the investigation. (2C)"
- "We recommend that a protocol transplant renal biopsy, defined as a biopsy performed in a stable graft without clinical evidence of acute rejection, be considered in the setting of persisting delayed graft function. (1C)"

The Transplantation Society

The Transplantation Society, via the Kidney Disease: Improving Global Outcomes (KDIGO, 2009) Transplant Work Group, states the following regarding acute rejection, renal allograft function, and renal allograft biopsy:[13]

Treatment of Acute Rejection

- "6.1: We recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment. (1C)"
- "6.2: We suggest treating subclinical and borderline acute rejection. (2D)"

Kidney Allograft Biopsy

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

Selected Relevant Publications

The available studies evaluating AlloSure Kidney provide limited evidence regarding the validity of the test for detecting renal graft rejection.[14-25] Several studies have shown an association between levels of donor derived cell-free DNA (dd-cfDNA) and kidney function, donor specific antibodies, non-immune injury, and rejection. However, these studies were hampered by several limitations including observational study designs, small sample sizes, lack of blinding, and overlapping patient populations. Additionally, the diagnostic threshold has not been definitively established, nor has the importance of absolute percentage of dd-cfDNA compared to relative changes in dd-cfDNA over time. Evidence of clinical utility for AlloSure Kidney is lacking, thus the impact of testing on clinically relevant outcomes and clinical decision-making remains unclear. Further studies are needed that demonstrate the safety of forgoing biopsies based on AlloSure Kidney results, or that demonstrate the use of AlloSure Kidney ultimately leads to improved survival or patient outcomes.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for AlloSure for kidney transplant rejection will ensure that members will not receive testing for which there is not a body of evidence demonstrating clinical utility and is therefore considered experimental, investigational, or unproven. Use of a test that does not have evidence to support clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[26] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

References

This guideline cites the following references.

1. Mayo Clinic. Chronic kidney disease. Updated September 2023. Available at: **https://www.mayoclinic.org/diseases-conditions/chronic-kidney-disease/symptoms-causes/syc-20354521** .
2. Yetman D. Are kidney transplants successful and effective? Reviewed September 2022. Available at: **https://www.healthline.com/health/kidney-transplant-success-rates**
3. Columbia University Medical Center. Renal and pancreatic transplant program: Organ rejection after renal transplant. Available at: **http://columbiasurgery.org/kidney-transplant/organ-rejection-after-renal-transplant** .
4. Beck J, Bierau S, Balzer S, et al. Digital droplet PCR for rapid quantification of donor DNA in the circulation of transplant recipients as a potential universal biomarker of graft injury. *Clin Chem.* 2013;59(12):1732-1741. doi: 10.1373/clinchem.2013.210328.
5. De Vlaminck I, Valantine HA, Snyder TM, et al. Circulating cell-free DNA enables noninvasive diagnosis of heart transplant rejection.*Sci Transl Med.* 2014;6(241):241ra277. doi: 10.1126/scitranslmed.3007803.
6. Hidestrand M, Tomita-Mitchell A, Hidestrand PM, et al. Highly sensitive noninvasive cardiac transplant rejection monitoring using targeted quantification of donor-specific cell-free deoxyribonucleic acid. *J Am Coll Cardiol.* 2014;63(12):1224-1226. doi: 10.1016/j.jacc.2013.09.029
7. National Kidney Foundation. When a Transplant Fails. Available at: **https://www.kidney.org/when-transplant-fails**
8. Cravedi P, Mannon RB. Noninvasive methods to assess the risk of kidney transplant rejection. *Expert Rev Clin Immunol*. 2009; 5(5):535-546.
9. First MR, Rose S, Schieve C, Lee D, Lewis P, et al. Value of the TruGraf blood test as a biomarker for monitoring renal transplant recipients. *InsightsBiomed*. 2018; 3(2):8.
10. CareDX. AlloSure Kidney. Updated October 2, 2023. Available at: **https://caredx.com/products-and-services/transplant-services/kidney/allosure/**
11. American Society of Transplant Surgeons. ASTS Statement on donor-derived cell-free DNA (dd-cfDNA). March 2023; Updated October 2024. Available at: **https://www.asts.org/docs/default-source/position-statements/asts-statement-on-donor-derived-cell-free-dna-(dd-cfdna)---updated-oct.-2024.pdf?sfvrsn=19314fd3_3**
12. Baker RJ, 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. doi: 10.1186/s12882-017-0553-2. Reviewed February 22. Available at: **https://ukkidney.org/sites/renal.org/files/FINAL-Post-Operative-Care-Guideline-1.pdf**
13. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am. J. Transplant.* 2009;9(Suppl 3):S1-S155.
14. Bloom RD, Bromberg JS, Poggio ED, et al. Cell-free DNA and active rejection in kidney allografts. *J Am Soc Nephrol: JASN*. 2017;28(7):2221-2232.
15. Bromberg J, Brennan DC, Poggio E, et al. Biological variation of donor-derived cell-free DNA in renal transplant recipients: Clinical implications. *JALM*. 2017;2(3):309-321.
16. Grskovic M, Hiller DJ, Eubank LA, et al. Validation of a clinical-grade assay to measure donor-derived cell-free DNA in solid organ transplant recipients. *J Mol Diag*. 2016;18(6):890-902.
17. Jordan SC, Bunnapradist S, Bromberg JS, et al. Donor-derived cell-free DNA identifies antibody-mediated rejection in donor specific antibody positive kidney transplant recipients. *Transplant Direct*. 2018;4(9):e379.
18. 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.
19. Huang E, Gillespie M, Ammerman N, et al. Donor-derived cell-free DNA combined with histology improves prediction of estimated glomerular filtration rate over time in kidney transplant recipients compared with histology alone. *Transplantation Direct.* 2020;6(8):e580. doi: 10.1097/TXD.0000000000001027.
20. Sawinski DL, Mehta S, Alhamad T, et al. Association between dd-cfDNA levels, de novo donor specific antibodies, and eGFR decline: An analysis of the DART cohort. *Clin Transplant*. 2021:e14402. doi: 10.1111/ctr.14402

730 Cool Springs Blvd, Franklin, TN 37067 (800) 918-8924 www.EviCore.com

21. Puliyanda, DP, Swinford R, Pizzo H, et al. Donor-derived cell-free DNA (dd-cfDNA) for detection of allograft rejection in pediatric kidney transplants. *Pediatr Transplant*. 2021;25(2):e13850. doi: 10.1111/petr.13850
22. Bu L, Gupta G, Pai A, et al. Clinical outcomes from the Assessing Donor-derived cell-free DNA Monitoring Insights of kidney Allografts with Longitudinal surveillance (ADMIRAL) study. *Kidney International*. 2022;101(4):793-803. doi: 10.1016/j.kint.2021.11.034
23. Dandamudi R, Gu H, Goss CW, et al. Longitudinal evaluation of donor-derived cellfree DNA in pediatric kidney transplantation. *Clin J Am Soc Nephrol*. 2022;17(11):1646-1655. doi: 10.2215/CJN.03840322
24. Huang E, Haas M, Gillespie M, et al. An assessment of the value of donor-derived cell-free DNA surveillance in patients with preserved kidney allograft function. *Transplantation*. 2023;107(1):274-282. doi: 10.1097/TP.0000000000042673
25. Aubert O, Ursule-Dufait C, Brousse R, et al. Cell-free DNA for the detection of kidney allograft rejection. *Nat Med*. 2024. doi: 10.1038/s41591-024-03087-3
26. Korenstein D, Chimonas S, Barrow B, et al. Development of a conceptual map of negative consequences for patients of overuse of medical tests and treatments. *JAMA Inter Med*. 2018;178(10):1401-1407.

730 Cool Springs Blvd, Franklin, TN 37067 (800) 918-8924 www.EviCore.com