ASTS
American Society of Transplant Surgeons

August 29, 2025

Noridian Healthcare Solutions, LLC JE Part B Contractor Medical Director(s)
Attention: Draft LCD Comments
4510 13th Ave. S, STE1
Fargo, ND 58103-6646

Submitted Electronically

Dear Sir or Madam:
As President of the American Society of Transplant Surgeons (ASTS), I write to express ASTS' concerns about the proposed Local Coverage Determination*: Molecular Testing for Solid Organ Allograft Rejection* (the "proposed LCD"). ASTS is a medical specialty society representing approximately 2,400 professionals dedicated to excellence in transplant surgery and to the patients that we serve. Our mission is the advancement of the art and science of transplant surgery through patient care, research, education, and advocacy.

We appreciate that data for the rapidly emerging field of molecular diagnostic testing are still maturing and that the global costs associated with such testing, while not insignificant, are less costly than biopsy and its associated complications or graft failure and return to dialysis (in the case of kidney) or repeat transplantation. However, molecular diagnostic testing has indisputable clinical utility and may provide massive clinical and economic benefits in the early detection and management of solid organ allograft rejection. Utilizing molecular testing for detection of allograft injury has emerged as a standard of care that can directly aid clinical decision making and may improve patient and allograft survival. We support the access of transplant patients to these diagnostic technologies and believe that continued Medicare coverage of these tools is critical. We recently issued an updated ASTS White Paper on molecular diagnostic testing (**Appendix A**), which was utilized as source material by MolDX in formulating the proposed LCD (**Appendix B**)

We note the significant changes made by MolDX to the proposed LCD relative to the prior LCD and congratulate them for the wise removal of the linkage of molecular testing to tissue biopsy. We note that the proposed LCD recognizes the clinical utility of both surveillance and for-cause testing. We are heartened by the progress made and confident that those changes will benefit patients. However, we have scientific, ethical, and process-related concerns about the proposed LCD which are enumerated below.

We are puzzled that the coverage limitations in the proposed LCD have been put forward at a time when CMS has clearly acknowledged that transplantation is the best, and most cost-effective, treatment option for those with ESRD, and without apparent consideration of the potential impact on innovation in the field or on patient care.

The proposed local coverage determination (LCD):

1) Specifically constrains clinicians' ability to surveil their kidney transplant recipients for rejection utilizing molecular testing by limiting surveillance testing in kidney transplant recipients to four tests in the first year after transplant and two tests per year in subsequent years.
2) Specifically constrains clinicians' ability to surveil their heart transplant recipients for rejection utilizing molecular testing by limiting surveillance testing to twelve tests in the first year after transplant and two tests per year in subsequent years.
3) Specifically constrains clinicians' ability to surveil their lung transplant recipients for rejection utilizing molecular testing by limiting surveillance testing to twelve tests in the first year after transplant and two tests per year in subsequent years.
4) Does not provide support for the utilization of molecular testing in recipients of simultaneous kidney and pancreas transplants or recipients of repeat kidney transplants despite evidence of analytical validity (AV) and clinical validity (CV) in this patient population.
5) Does not support multimodality or combination testing or concomitant use of multiple tests in heart transplant recipients.

We feel that these features of the proposed LCD may substantively compromise patient care as detailed below. Our concerns regarding the surveillance testing limits in the proposed LCD extend to abdominal and thoracic transplant organs.

1. **The proposed LCD's limits on the frequency of surveillance testing are too low.**

The primary purpose of surveillance (or protocol) biopsies in kidney transplant recipients is the detection of subclinical acute rejection (subAR), i.e., rejection occurring in the absence of overt clinical symptoms or laboratory abnormalities. The role of routine surveillance biopsies in the era of modern immunosuppression has come into question, and the utilization of such biopsy protocols has decreased over the years. [1, 2] In a survey of US transplant programs in 2017, only a minority (38%) reported performing any surveillance biopsies, with very few (17%) doing so in a universal, non-risk stratified fashion. [3] The most recent KDIGO guidelines on the management of kidney transplant recipients, published in 2009, do not recommend surveillance biopsies, instead concluding that "RCTs are needed to determine when the benefits of protocol biopsies outweigh harm." [4] However, the same guidelines recommend treating subAR recognizing its association with eGFR decline, chronic graft injury, and graft loss, along with evidence that treatment may ameliorate the risk of these adverse outcomes. [4-9] This is inherently conflicting guidance, as subAR treatment is advised, but none of the modalities endorsed in the KDIGO guidelines for monitoring graft function (urine volume, urine protein excretion, serum creatinine, or ultrasound) are useful for its detection and the surveillance biopsies that historically have revealed the presence of subAR are not recommended. [4]

Molecular testing with donor-derived cell-free DNA (dd-cfDNA) provides an ideal solution to this conundrum. Several studies have demonstrated a strong correlation between dd-cfDNA and the finding of histologic rejection identified on surveillance biopsies, establishing a non-invasive

alternative for detection of clinically relevant subAR. [10, 11] Furthermore, the superior correlation between dd-cfDNA and molecular histology offers the possibility of detecting subAR that may not yet be apparent on traditional histologic tissue examination. [11]

The proposed LCD tethers the ability to perform reimbursable surveillance testing with dd-cfDNA to published surveillance biopsy protocols, limiting patient access and essentially conflating the risk/benefit calculations for a non-invasive blood test with a resource-intensive interventional procedure (tissue biopsy) that is neither guideline-endorsed nor broadly utilized for kidney allograft surveillance (as opposed to for-cause use) in clinical practice.[3, 4] We maintain that transplant professionals, in partnership with patients, require the exercise of clinical discretion in determining the frequency of molecular surveillance testing in these challenging patients. We are also cognizant of the need for all transplant stakeholders to be responsible stewards of scarce resources. Guardrails on surveillance testing frequencies are logical, and we have openly advocated for transplant professionals utilizing these testing modalities to enshrine practice patterns or protocols that prevent inadvertent overutilization. By the same token, the cost of inadequate surveillance can be measured in organs and lives lost, and those losses are both tragic and inordinately expensive.

Testing frequency should therefore be based on relevant patient-centric factors, including the immunologic risk of a particular patient, the risks of biopsy in that patient, and their clinical judgement regarding the time points post-transplant at which such surveillance are warranted. Molecular testing is non-invasive and carries a diametrically different risk-benefit profile than invasive tissue biopsy. The robust clinical validity of molecular testing and its utility in clinical decision-making suggest that surveillance testing frequencies should parallel those of other non-invasive surveillance tests. While the optimal surveillance testing frequency is unknown, the most robust clinical validation study for kidney allograft surveillance testing comes from the DART study, which utilized the so-called “ARTS” surveillance testing schedule. This protocol recommended testing at monthly intervals from month one through four, and then quarterly thereafter. This would suggest a reasonable kidney allograft surveillance frequency of seven tests in the first-year post-transplant and four tests per year thereafter.

This schedule was developed empirically based on the KDIGO recommended testing frequencies for other noninvasive post-transplant tests and temporally correlates the highest testing frequency with the period of highest immunologic risk and recommending decreased frequencies later in the post-transplant course. Importantly, longitudinal surveillance testing at this frequency provides an early baseline for the allograft and then captures data at critical post-transplant immunologic timepoints.[12] This correlates with existing molecular testing surveillance protocols at many transplant centers and would alleviate patient and transplant provider concerns about the proposed LCDs stringent limits on surveillance test frequency.

Surveillance of renal transplant recipients does not only serve the clinical imperative of detecting subAR. The other critical importance of allograft surveillance is to facilitate individualization of the immunosuppressive burden faced by patients. One of the reasons for the paucity of improvement in long-term outcomes is that the burden of over immunosuppression carries significant risk of morbidity and mortality for patients. Surveillance of clinically stable patients allows for a data-

driven approach to the careful decrease of immunosuppressive burden in these patients. Again, the surveillance testing frequency stipulated in the proposed LCD is inadequate for that long-term follow up goal.

The types of kidneys utilized, and the types of recipients transplanted continue to change in ways that increase the need for robust surveillance frequencies and the need for clinically validated tools for that surveillance. The Centers for Medicare and Medicaid Innovation (CMMI) IOTA model started in July of this year and is specifically designed to increase the utilization of kidneys at elevated risk of discard, including many biologically marginal, high-KDPI organs. IOTA is a mandatory model into which approximately half of the nation's kidney transplant programs have been enrolled by CMS. The model will predictably, and by intent, result in higher incidences of delayed graft function (DGF) and higher prevalence of suboptimal allograft function. While many aspects of the IOTA model are laudatory, achieving IOTA objectives while protecting patients will likely require more frequent surveillance and closer monitoring.

Surveillance of renal transplant recipients is bound by the basic clinical tenant that rejection risk persists for the life of the allograft. While the risk of acute rejection, and therefore subAR, is highest in the first year after transplant, a sudden, steplike decrease in risk to the allograft, and thus the patient, does not occur at the transition from post-transplant month-12 to post-transplant month-13. As we have detailed above, kidney recipient surveillance testing frequencies should accommodate a minimum of seven tests in year one and four annual tests thereafter.

The proposed LCD limits surveillance testing frequencies for heart and lung recipients to 12 tests in year one, and 2 tests in all subsequent years. All organ transplant recipients remain at risk for rejection for the life of their allografts.[13,14] The prognosis of cardiac allograft rejection worsens when it is recognized at a more advanced stage, and more timely treatment of mild forms of rejection yields a more favorable prognosis.[15,16] Thus, efficacious and timely surveillance for rejection is a critical component in the management of cardiac transplant patients and a significant determinant of long-term survival rates.[13] Importantly, rejection surveillance utilizing molecular testing may also allow safe, monitored, individualization of immunosuppression for transplant patients.[13] Molecular testing shows promise in its ability to allow clinicians to safely lower immunosuppression in stable cardiac transplant recipients. Molecular testing surveillance techniques provide adequate sensitivity and specificity to provide early detection of allograft injury and allow timely treatment while avoiding the dangers of myocardial biopsy.[17]

Historically, while only biopsies provided sufficient sensitivity to detect early rejection, it is now clear that biopsies, in fact, may cause harm. Unavoidable risks of biopsies include bleeding, infection, pain, and anxiety. Biopsy-related complications can be devastating to patients as well as enormously expensive for payers. [13,18-21] In an actively surveilled population receiving modern immunosuppression the yield of biopsies is quite low.[13] Finally, it has also increasingly been recognized that biopsies are severely limited in their real-world sensitivity and specificity, due to both significant interobserver variability and sampling error.[16,22,23] Because of these limitations, over the years, transplant centers have reduced the utilization of surveillance (protocol) biopsies while not reducing the frequency or duration of other forms of non-invasive surveillance, including molecular diagnostic testing.[13] Importantly, the risk of heart allograft rejection, and the intensity of

surveillance needed to monitor for it, do not decrease as precipitously over time as the surveillance testing frequencies allowed in the proposed LCD would imply or safely allow.

Surveillance molecular testing is not associated with pain, anxiety or life-threatening complications and can even be done at the patient's home, sparing exposure of patients to hospital pathogens and limiting hospital resource consumption.[13,18,21] Furthermore, molecular testing is not subject to interobserver variability or sampling errors and therefore, may in fact have superior sensitivity and specificity than biopsies.[24] Therefore, molecular testing, performed at an adequate frequency, suitably replaces most cardiac surveillance biopsies. Specifically, extended surveillance with molecular testing is now reasonable both to detect late rejection and allow clinicians the ability to provide individualization of immunosuppression regimens throughout the transplant recipient's lifetime.

2. **The proposed LCD makes no provision for the use of molecular testing in simultaneous pancreas and kidney (SPK) recipients nor in kidney transplant recipients who have received one or more prior kidney transplants.**

While the number of simultaneous pancreas and kidney (SPK) transplants performed nationally remains small, the risks to allograft health faced by these patients are more significant than in kidney alone recipients, and the risks of allograft pancreas biopsy are much higher than those associated with kidney biopsy. Importantly, acute rejection can occur in the pancreatic allograft of an SPK recipient discordantly from rejection in that recipient's renal allograft. That makes the utilization of molecular testing for allograft surveillance critically important in these patients. Fortunately, data supporting the clinical utility of molecular testing utilizing dd-cfDNA continues to accrue. An observational, prospective single center study of SPK recipients conducted by Williams et al demonstrated that dd-cfDNA levels were significantly different (p=0.0006) between patients with rejection (median 2.25%) versus those with allograft injury (median 0.36%) or quiescence (median 0.18%). Among patients without rejection, 97% had dd-cfDNA <0.5%. This finding was consistent with published data in kidney transplantation. Biopsy-confirmed rejection was associated with elevations in dd-cfDNA levels with a median level of 2.4%. a median dd-cfDNA of 2.4%.[25]

Yoo et al. demonstrated that dd-cfDNA values differed between SPK patients with rejection or infection (median 0.56%) versus those who were stable (median 0.28%). Of the SPK recipients with dd-cfDNA > 1.0%, 36.8% had evidence of infection or rejection. 100% of recipients without infection or rejection had dd-cfDNA levels <1.0%, consistent with the previously published rejection threshold of 1.0% for kidney transplant recipients.[26] These and other studies support the clinical utility of dd-cfDNA in SPK recipients, and we urge MolDX to incorporate that emerging standard of care in the proposed LCD.

Kidney recipients facing the need for retransplantation already represent a sizeable proportion of all kidney transplant candidates, and the prevailing trend of more aggressive utilization of biologically challenged and high-KDPI kidneys will likely increase that proportion. A total of 27,759 kidneys were transplanted in the US in 2024. Of those, 2,614 kidneys were transplanted into prior kidney recipients. Over the past decade, approximately 10% of patients who received kidney transplants had a prior kidney transplant that had failed.[27] The ADMIRAL Study evaluated dd-cfDNA

in 1,092 kidney transplant recipients from seven US transplant centers, 8% of these recipients had a prior kidney transplant.[28] Aubert evaluated 2,882 kidney transplant recipients from the US and Europe, 447 (15.5%) of which had had a prior kidney transplant.[29] Both of these large studies demonstrated that the performance of dd-cfDNA was similar in de novo and repeat kidney transplant recipients and clearly differentiated immunologic quiescent and rejection in both groups. The proposed LCD should contain language, and reference data, supporting surveillance and for-cause testing kidney recipients who have had prior kidney transplants.

3. **The proposed LCD inappropriately restricts multimodality testing and concomitant use of multiple tests.**

Multi-modality molecular surveillance testing using gene expression profiling (GEP) and dd-cfDNA provides complementary, not redundant, information about a transplant recipient. Gene expression profiling measures mRNA levels of peripheral blood mononuclear cells while dd-cfDNA measures levels of circulating DNA released by an injured allograft.[23] Multimodal assessment utilizing both dd-cfDNA and GEP in heart transplant recipients provides additional clinical utility over their use in isolation. Combined dd-cfDNA and GEP testing provides information on distinct biologic processes, with dd-cfDNA providing insight about graft injury, and GEP providing insight about recipient immune system activation. In the context of rejection surveillance, where the prevalence of disease is low, it is generally accepted that the most important characteristic of a surveillance test is its ability to predict which of the surveilled patients are most likely to have rejection.[30,31] The characteristics of the test that closely aligns with this objective is the positive likelihood ratio. For patients undergoing surveillance for acute cellular rejection, the magnitude of the positive likelihood ratio of any one commercially available molecular test using recommended thresholds is modest and at most 2.9.[31,32,35,36] When results in a transplant recipient exceed normal thresholds for both GEP and dd-cfDNA the likelihood ratio is approximately 4, which provides a robust ability to accurately identify patients with underlying acute cellular rejection.[35] The clinical utility achieved by using dd-cfDNA and GEP concomitantly allows clinicians to dramatically reduce their use of biopsies, with attendant benefits for patients.[33,34,35] Importantly, the SHORE study, published by Kush et al., was not available at the time we published the most recent version of our molecular diagnostics position statement. It is an exceptionally large multi-center study in the cardiac transplant space with convincing clinical validity and utility data supporting the clinical utility of combination GEP and dd-cfDNA testing in heart transplant recipients.

We recognize that results obtained utilizing legacy surveillance techniques are suboptimal. Further, the persistent failure to achieve meaningfully better long-term renal allograft survival despite massive improvements in short-term patient and allograft survival remains one of the cardinal failures of the transplant endeavor. Molecular testing is a standard of care that holds the promise of changing kidney allograft surveillance and for-cause testing paradigms. Molecular diagnostic testing may allow us to unlock long sought and badly needed gains in long-term patient and allograft survival in kidney transplant recipients. This technology is already a standard of care in the management of our patients, and the limitation of patient access to these platforms stipulated in the proposed LCD will be detrimental to advancement of the field in general and the care of these vulnerable patients specifically. We respectfully and strongly urge MolDX to increase or eliminate the surveillance testing frequency limits in the proposed LCD and to stipulate coverage for SPK and retransplant patients as well as multimodal testing of GEP/dd-cfDNA in heart

transplants. We are deeply appreciative of the opportunity to submit a public comment on this issue and welcome future dialogue.

If you have any questions about these comments, please do not hesitate to contact Associate Director, Advocacy & Professional Practices, Emily Besser, at Emily.Besser@asts.org

Sincerely,

James F. Markmann, MD, PhD

Appendices:

Appendix A.

Link to the American Society of Transplant Surgeons (ASTS) Position Statement on Molecular Diagnostic Testing:

ASTS Statement on donor derived cell-free DNA (dd-cfDNA) accessed on 8/10/2025

Appendix B.

Link to the MolDX proposed LCD:

https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=40059

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References

1. Wilkinson, A., *Protocol transplant biopsies: are they really needed?* Clin J Am Soc Nephrol, 2006. **1**(1): p. 130-7.
2. Rush, D., et al., *Lack of benefit of early protocol biopsies in renal transplant patients receiving TAC and MMF: a randomized study.* Am J Transplant, 2007. **7**(11): p. 2538-45.
3. Mehta, R., et al., *Kidney allograft surveillance biopsy practices across US transplant centers: A UNOS survey.* Clin Transplant, 2017. **31**(5).
4. Kidney Disease: Improving Global Outcomes Transplant Work, G., *KDIGO clinical practice guideline for the care of kidney transplant recipients.* Am J Transplant, 2009. **9 Suppl 3**: p. S1-155.
5. Seifert, M.E., et al., *Impact of Subclinical Borderline Inflammation on Kidney Transplant Outcomes.* Transplant Direct, 2021. **7**(2): p. e663.
6. Mehta, R.B., et al., *Early subclinical tubulitis and interstitial inflammation in kidney transplantation have adverse clinical implications.* Kidney International, 2020. **98**(2): p. 436-447.
7. Rush, D., et al., *Beneficial effects of treatment of early subclinical rejection: a randomized study.* Journal of the American Society of Nephrology, 1998. **9**(11): p. 2129-2134.
8. Nankivell, B.J. and J.R. Chapman, *The significance of subclinical rejection and the value of protocol biopsies.* Am J Transplant, 2006. **6**(9): p. 2006-12.
9. Kee, T.Y., et al., *Treatment of subclinical rejection diagnosed by protocol biopsy of kidney transplants.* Transplantation, 2006. **82**(1): p. 36-42.
10. Bu, L., et al., *Validation and clinical outcome in assessing donor-derived cell-free DNA monitoring insights of kidney allografts with longitudinal surveillance (ADMIRAL) study.* Kidney Int, 2021.
11. Gupta, G., et al., *Correlation of Donor-derived Cell-free DNA With Histology and Molecular Diagnoses of Kidney Transplant Biopsies.* Transplantation, 2022. **106**(5): p. 1061-1070.
12. Pai, A. et al. Clinical Rationale for a Routine testing Schedule Using Donor-Derived Cell-Free DNA After Kidney Transplantation. Annals of Transplantation. 2021 July
13. Velleca, A., 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): p. e1-e141.
14. Khush, K.K., et al., *The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report - 2019; focus theme: Donor and recipient size match.* J Heart Lung Transplant, 2019. **38**(10): p. 1056-1066.
15. Mills, R.M., et al., *Heart transplant rejection with hemodynamic compromise: a multiinstitutional study of the role of endomyocardial cellular infiltrate. Cardiac Transplant Research Database.* J Heart Lung Transplant, 1997. **16**(8): p. 813-21.
16. Everitt, M.D., et al., *Rejection with hemodynamic compromise in the current era of pediatric heart transplantation: a multi-institutional study.* J Heart Lung Transplant, 2011. **30**(3): p. 282-8.
17. Dobrow, M.J., et al., *Consolidated principles for screening based on a systematic review and consensus process.* CMAJ, 2018. **190**(14): p. E422-E429.

18. Amadio, J.M., et al., *Sparing the Prod: Providing an Alternative to Endomyocardial Biopsies With Noninvasive Surveillance After Heart Transplantation During COVID-19*. CJC Open, 2022. **4**(5): p. 479-487.

19. Wong, R.C., et al., *Tricuspid regurgitation after cardiac transplantation: an old problem revisited*. J Heart Lung Transplant, 2008. **27**(3): p. 247-52.

20. Hull, J.V., et al., *Risks of Right Heart Catheterization and Right Ventricular Biopsy: A 12-year, Single-Center Experience*. Mayo Clin Proc, 2023. **98**(3): p. 419-431.

21. Jamil, A.K., et al., *Heart transplant Recipients' perspectives on invasive versus Non-invasive graft failure surveillance Methods*. Heart Lung, 2022. **57**: p. 41-44.

22. Crespo-Leiro, M.G., et al., *Clinical usefulness of gene-expression profile to rule out acute rejection after heart transplantation: CARGO II*. Eur Heart J, 2016. **37**(33): p. 2591-601.

23. Holzhauser, L., et al., *The End of Endomyocardial Biopsy?: A Practical Guide for Noninvasive Heart Transplant Rejection Surveillance*. JACC Heart Fail, 2023. **11**(3): p. 263-276.

24. Agbor-Enoh, S., et al., *Cell-Free DNA to Detect Heart Allograft Acute Rejection*. Circulation, 2021. **143**(12): p. 1184-1197.

25. Williams MD, Fei M, Schadde E, et al. Early experience using donor-derived cell-free DNA for surveillance of rejection following simultaneous pancreas and kidney transplantation. Transplantation Direct 2022; 8:e1321.

26. Yoo A, Riedel A, Qian I, et al. An initial analysis of the baseline levels of dd-cfDNA after pancreas transplantation: a prospective study from high-volume centers in the United States. Transplantation Direct 2023; 9:e1459.

27. https://unos.org/data/tranplant-trends/ Accessed on June 18, 2025

28. Bu 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.

29. Aubert et al. Cell-free DNA for the detection of kidney allograft rejection. Nature Medicine (2024); 30:2320-2317.

30. Kobashigawa, J., et al., The evolving use of biomarkers in heart transplantation: Consensus of an expert panel. Am J Transplant, 2023. 23(6): p. 727-735.

31. Kim, P.J., et al., A novel donor-derived cell-free DNA assay for the detection of acute rejection in heart transplantation. J Heart Lung Transplant, 2022. 41(7): p. 919-927.

32. Khush, K.K., et al., Noninvasive detection of graft injury after heart transplant using donor-derived cell free DNA: A prospective multicenter study. Am J Transplant, 2019. 19(10): p. 2889-2899.

33. Gondi, K.T., et al., Single-center utilization of donor-derived cell-free DNA testing in the management of heart transplant patients. Clin Transplant, 2021. 35(5): p. e14258.

34. Henricksen, E.J., et al., Combining donor derived cell free DNA and gene expression profiling for non invasive surveillance after heart transplantation. Clin Transplant, 2022: p. e14699

35. Khush K, Hall S, Kao A, et al. Surveillance with dual noninvasive testing for acute cellular rejection after heart transplantation: Outcomes from the Surveillance HeartCare Outcomes Registry. J Heart Lung Transplant 2024;43(9):1409-1421. (In eng). DOI: 10.1016/j.healun.2024.05.003.
36. Moayedi Y, Teuteberg JJ. Rejection Surveillance After Heart Transplantation: Is Paired Noninvasive Testing the New Gold Standard? Transplantation 2024 (In eng). DOI: 10.1097/TP.0000000000005113.