American Society of Transplant Surgeons®

*Saving and improving lives with transplantation.*

September 20, 2023

**Re: ASTS Written Response to Proposed Revisions to DL389568 and DL 38629: Molecular Testing for Solid Organ Allograft Rejection (Heart)**

As President of the American Society of Transplant Surgeons (ASTS), I write to express ASTS' deep concerns about the proposed revisions to the Local Coverage Determination*: Molecular Testing for Solid Organ Allograft Rejection* (DL389568 and DL38629) (the "proposed LCD"). ASTS is a medical specialty society representing approximately 2,000 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 is still maturing and that the global costs associated with such testing are significant. However, we feel strongly that molecular diagnostic testing may provide significant clinical and economic benefits in the early detection and management of solid organ allograft rejection. Utilizing molecular testing for detection of allograft injury is an emerging standard of care that can directly aid in clinical decision making and may improve patient and allograft survival. We support the access of heart transplant patients to these diagnostic technologies and believe that continued Medicare coverage of these tools is critical to further refine their utility and cost effectiveness**.** We recently issued an ASTS White Paper on molecular diagnostic testing (Appendix A), which provided additional background that was not made public in time to be taken into consideration by MolDX when it formulated *Article - Billing and Coding: MolDX: Molecular Testing for Solid Organ Allograft Rejection (A58019)* (the "Billing Article"), which appears to be the basis for the proposed LCD (Appendix B)

Our scientific and ethical concerns about the proposed LCD are enumerated below. We are puzzled that the coverage limitations that would be enshrined 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, while heart transplantation is an established, successful, and life-saving therapy for those in need. Furthermore, MolDX seems to have embarked on this process without due consideration of the negative impact the proposed LCD would impose on innovation in the field or continuity of care for patients. We thank you for utilizing the correct process of proposing revision of the existing LCD, which affords public comment, and appreciate the admission that the Billing Article was not the appropriate mechanism with which to introduce significant changes to the prior LCD. However, we note that the revised Billing Article remains in effect, which appears at odds with both transparency and with the public comment process, as well as with community feedback you have received. **We request that MolDX reject the proposed LCDs in favor of the mandates codified in the LCD prior to issuance of the Billing Article** (Appendix C)**.**

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The proposed local coverage determination (LCD) clearly seeks to change coverage in that it:

1) Enforces a *de facto* limitation on clinicians' ability to surveil their patients for rejection by requiring an attestation that the molecular surveillance is replacing a center protocol biopsy.
2) Prohibits use of molecular testing at the time a biopsy is obtained.
3) Prohibits use of two molecular tests during the same patient encounter.

The changes in the proposed LCD may substantively compromise patient care as outlined below.

**1. The Proposed LCD Restricts the Frequency of Molecular Surveillance Testing**

All organ transplant recipients remain at risk for rejection for the life of their allografts.[1,2] The prognosis of rejection worsens when it is recognized at a more advanced stage, and mild forms of rejection when treated have a favorable prognosis.[3,4] Thus, efficacious surveillance for rejection will always remain a critical component in the management of transplant patients and a significant determinant of long-term allograft survival rates.[1] Importantly, rejection surveillance utilizing molecular testing may also allow safe, monitored, individualization of immunosuppression for transplant patients. [1] Molecular testing shows promise in its ability to allow clinicians to safely lower immunosuppression in stable transplant recipients. Clinically useful surveillance techniques must have adequate sensitivity and specificity to provide early detection of allograft injury and immune activation to allow timely interventions while being safe enough to allow frequent monitoring for patients. [5]

Historically, while only biopsies provided sufficient sensitivity to detect early rejection, it is now well established that biopsies, in fact, do cause harm. Biopsies can cause bleeding, infection, pain and anxiety, and biopsy-related complications can be devastating to patients as well as enormously expensive for payers. [1,6-9] In an actively surveilled population receiving modern immunosuppression the yield of biopsies is quite low. [1] 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. [4,10,11] 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. [1]

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. [1,6,9] Furthermore, molecular testing is not subject to interobserver variability or sampling errors and therefore, may in fact have superior sensitivity and specificity than biopsies. [12] Therefore, molecular testing is a suitable candidate to replace most surveillance biopsies and to allow surveillance testing when biopsies were not typically performed due to a dramatically more favorable risk benefit ratio. Specifically, extended surveillance with molecular testing is now reasonable both to detect late rejection but also to allow clinicians the opportunity to provide data-drive individualization of immunosuppression regimens throughout the transplant recipient's lifetime.

**2. The Proposed LCD Restricts Molecular Testing Based on Timing Relative to Biopsy**

While the most important benefit of molecular testing in current clinical practice is the utility of such testing in decreasing the need for endomyocardial biopsies, there are instances where concomitant use of molecular testing and biopsy provides complementary information and should appropriately be performed together. Currently, molecular testing cannot be used to determine the exact etiology of rejection and therefore in patients presenting with overt signs and symptoms of rejection, biopsies remain the gold standard for diagnosis of rejection.[11] However, the observation that dd-cfDNA levels fall back to baseline with successful therapy of rejection has been well documented. [12,13] Therefore, a dd-cfDNA level obtained at the same time as a biopsy in a

patient presenting with overt clinical signs of rejection may obviate the need for a second biopsy that otherwise would need to be obtained to assess the adequacy of rejection therapy.

### 3. The Proposed LCD Restricts Multimodality Testing/Concomitant Use of Multiple Tests

Multi-modality molecular surveillance testing using gene expression profiling (GEP) and dd-cfDNA provides complementary and 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 graft. [11] Multimodal assessment utilizing both dd-cfDNA and GEP in heart recipients provides additional clinical utility over their use in isolation. Combined dd-cfDNA and GEP testing provide 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. [14,15] 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 2.5. [10,16,17] When results in a transplant recipient exceed normal thresholds for both GEP and dd-cfDNA the likelihood ratio is approximately 5, which provides a robust ability to accurately identify patients with underlying acute cellular rejection. [15] 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. [18,19]

We recognize that results obtained utilizing legacy kidney recipient surveillance techniques are suboptimal. Further, the failure of the transplant community to meaningfully improve long-term renal allograft survival despite massive improvements in short-term patient and allograft survival remains one of the rare cardinal failures of the transplant endeavor. Molecular testing is an emerging standard of care that has already changed the landscape of post-transplant care for heart transplant recipients. Molecular diagnostic testing may allow us to unlock significant gains in long-term patient and allograft recipients of multiple organ types. This technology is already a standard of care in the management of our heart transplant patients, and limitation of patient access to these platforms will be detrimental to advancement of the field in general and the care of these vulnerable patients in particular. We respectfully and strongly urge MolDX to reconsider the limits on access to critical molecular testing that were implemented under the Billing Article and would be codified in the proposed changes to the LCD. **We respectfully urge MolDX to reject the proposed LCD in favor of the coverage determinations codified in the LCD prior to issuance of the Billing Article.**

If you have any questions, please do not hesitate to contact Emily Besser, MA, CAE, Associate Director, Advocacy, at Emily.Besser@asts.org.

Sincerely,

Elizabeth A. Pomfret, MD, PhD
President, ASTS

**Appendices:**

**Appendix A.**

American Society of Transplant Surgeons Position Statement on Molecular Diagnostic Testing
https://asts.org/docs/default-source/position-statements/dd-cfdna-position-statement.pdf

**Appendix B.**

MolDX proposed Billing Article
Article - Billing and Coding: MolDX: Molecular Testing for Solid Organ Allograft Rejection (A58061)

**Appendix C.**

MolDX Local Coverage Determination: Molecular Testing for Solid Organ Allograft Rejection
https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=38568&ver=5

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