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American Society of Transplant Surgeons®

September 20, 2023

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

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 massive 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 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 provides additional background that was not made public in time to be taken into consideration by MoIDX when it formulated *Article - Billing and Coding: MoIDX: Molecular Testing for Solid Organ Allograft Rejection (A58019)* (the "Billing Article"), which appears to be the basis for the proposed LCD (**Appendix B**)

We have scientific, ethical, and process-related concerns about the proposed LCD which 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, and without consideration of the potential chilling impact on innovation in the field or continuity of care for patients. We thank you for utilizing revision of the existing LCD, which affords public comment, and also are appreciative of the admission that the Billing Article was not the appropriate mechanism with which to introduce significant changes to the 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. **We request that MoIDX reject the proposed LCDs in favor of the mandates codified in the LCD prior to issuance of the Billing Article (Appendix C).**

The proposed local coverage determination (LCD) 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.

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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 by Limiting it to Direct Replacement of Pre-existing Surveillance Biopsy Protocols**

The primary purpose of a surveillance (or protocol) biopsy in kidney transplant recipients is the detection of subclinical rejection (SCR), 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.<sup>1,2</sup> 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.<sup>3</sup> Not surprisingly, the most current KDIGO guidelines on the management of kidney transplant recipients (2009) do not recommend surveillance biopsies, instead concluding that “RCTs are needed to determine when the benefits of protocol biopsies outweigh harm.”<sup>4</sup> However, the same guidelines formally recommend treating SCR, 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.<sup>4-9</sup> This is inherently conflicting guidance, because SCR treatment is advised, but none of the modalities endorsed 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 SCR are not recommended.<sup>4</sup>

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 SCR.<sup>10,11</sup> Furthermore, the superior correlation between dd-cfDNA and molecular histology offers the possibility of detecting SCR that may not yet be apparent on traditional histologic tissue examination.<sup>11</sup>

The proposed LCD tethers the ability to perform reimbursable surveillance testing with dd-cfDNA to a transplant center’s established surveillance biopsy protocol, limiting patient access and essentially conflating the risk/benefit calculations for a non-invasive blood test with a resource-intensive interventional procedure that is neither guideline-endorsed nor broadly utilized for surveillance (as opposed to for-cause use) in clinical practice.<sup>3,4</sup> We advocate for the transplant professional, in partnership with patients, to have the discretion to determine the frequency of molecular surveillance testing in these challenging patients. Testing frequency should 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.

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

While dd-cfDNA is an emerging standard-of-care in for-cause settings to help guide the decision to pursue biopsy, dd-cfDNA has also been studied and utilized in a variety of other clinical contexts, including those where histologic assessment via biopsy was recently performed or is being planned. Levels of dd-cfDNA obtained concurrently with biopsies demonstrating borderline T-cell mediated rejection (BL-TCMR) or Banff TCMR1A have demonstrated utility in predicting subsequent eGFR decline, development of de-novo donor specific antibodies (dnDSA), and development of recurrent

rejection.<sup>12</sup> Biopsy-paired dd-cfDNA results also have shown utility in improving the performance of histology-based predictive models of graft function.<sup>13</sup> Obtaining dd-cfDNA levels concomitantly with biopsy can also help establish a tighter cross-sectional correlation between histologic findings and dd-cfDNA results; at centers where response to therapy is assessed using dd-cfDNA (in lieu of biopsy), having a result temporally closer to start of treatment can better help evaluate the adequacy of response to rejection treatment and preclude the need for follow-up histologic assessment.<sup>11</sup>

The proposed LCD cites settings where biopsy was either recently performed or already planned as examples where molecular diagnostics would not inform clinical decision making, however, as the cited studies demonstrate, information from concurrent molecular & histologic testing can help clinicians make decisions about immunosuppression management, long-term prognostication, and need for or timing of repeat biopsies.<sup>11-13</sup>

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

Definitive diagnosis and characterization of disease states frequently requires comprehensive and multimodal laboratory investigation. For example, guideline-based assessment of anemia in chronic kidney disease requires a complete blood count (CBC), absolute reticulocyte count, serum ferritin level, serum transferrin saturation (TSAT), as well as vitamin B12 and folate levels.<sup>14</sup> Each analyte provides distinct and non-interchangeable information that can help characterize the etiology of anemia. In the case of iron deficiency anemia, a combination of findings (low mean corpuscular volume (MCV), low TSAT, and low ferritin) provides much more diagnostic certainty about the underlying diagnosis than any of the abnormalities in isolation. Multimodal assessment utilizing dd-cfDNA and gene expression profiling (GEP) in solid organ transplantation offer similar clinical utility, providing information on distinct biologic processes, with dd-cfDNA providing insight about graft injury, and GEP providing insight about recipient immune system activation. Paired testing (dd-cfDNA and GEP) results demonstrate better diagnostic performance for active rejection than either test type alone and provide enhanced utility for clinician decision-making, including whether invasive assessment with biopsy is warranted or can be safely avoided.<sup>15, 16</sup>

The proposed LCD emphasizes that various molecular tests have “...different strengths and weaknesses,” acknowledging for instance that “...some GEP tests have high negative predictive value for the likelihood of AR, but may be limited in their ability as a positive predictor for ACR or even detecting AMR [sic].” However, rather than recognizing the potential value in pairing molecular tests that can yield complementary information, the proposed LCD restricts such use. This limitation is likely to increase the rate of observed false positives and false negatives even when test selection is optimally tailored to the immunologic risk and clinical situation of the patient being evaluated.

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 holds the promise of changing the kidney allograft surveillance paradigm. Molecular diagnostic testing may allow us to unlock significant gains in long-term patient and allograft survival in kidney transplant recipients. This technology is already an emerging standard of care in the management of our patients, and onerous limitation of patient access to these platforms will be detrimental to advancement of the field in general and the care of these

vulnerable patients specifically. We respectfully and strongly urge MoIDX 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 MoIDX 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](mailto:Emily.Besser@asts.org).

Sincerely,

A handwritten signature in black ink that reads "Elizabeth A. Pomfret". The signature is written in a cursive style with a large initial "E".

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: MoDX: 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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