ISHLT
A Society that Includes Basic Science, the Failing Heart, & Advanced Lung Disease

28 November 2023

Dear Medical Director:

The International Society for Heart and Lung Transplantation (ISHLT) is a non-profit, professional, multidisciplinary organization committed to improving the care of patients by promoting research, education, and advocacy. The Society unites a diverse range of healthcare professionals dedicated to transplantation, mechanical support, and innovative therapies. Our membership includes more than 3,400 individuals from 62 countries and 23 different specialty areas.

As such, we are writing to express our support for molecular testing of donor derived cell-free DNA (dd-cfDNA) for the assessment of allograft injury, and to request that all commercial insurance plans include coverage for this clinical tool. Current clinical evidence for dd-cfDNA, as detailed within this letter, firmly establishes its use as an evidence-based and validated instrument that should no longer be considered investigational. Based on this, prominent national and international transplant medical societies have recently issued clinical practice guidelines and consensus statements supporting the integration of dd-cfDNA into routine clinical practice for patients undergoing kidney, heart, and lung transplantation. As a result, physicians are actively employing these tests in the evaluation of heart and kidney transplant recipients, with their application now extended to include those with lung allografts.

ISHLT advocates for the equitable availability of these essential tools, supporting both physician and patients' choices to utilize them in post-transplant care. Securing commercial insurance coverage for these diagnostic tests is essential to minimize inequities in patient care and transplant outcomes.

The utility of dd-cfDNA testing has been outlined in peer-reviewed literature and consensus documents, and the value of these tests is further summarized and reflected in the MolDX local coverage determination L38568 (LCD)[1] and subsequent CMS coverage of these tools.

Clinical validation of dd-cfDNA testing is well established in kidney transplantation through peer-reviewed literature, highlighting its use as a non-invasive tool to accurately identify both ABMR and TCMR with a high negative predictive value (NPV) in both the for-cause and surveillance settings.[2-6] Dd-cfDNA outperforms other existing kidney allograft monitoring tools, including serum creatinine[2,5,6] and DSA[4], in identifying acute rejection. As such, dd-cfDNA plays an important role in identifying the need for additional follow-up procedures and tests, including allograft biopsy. The use of dd-cfDNA in kidney transplantation is now supported by multiple clinical societies including the American Society of Transplant Surgeons (ASTS)[7] and the European Society of Transplantation (ESOT)[8].

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Recently there have been clinical studies of dd-cfDNA testing in liver allograft recipients which have demonstrated its ability to identify various forms of allograft dysfunction including acute rejection (AMR and ACR). the serial elevation of dd-cfDNA identifies pre-clinical graft injury in the context of normal liver function tests and is greatest in rejection. This biomarker may help detect early signs of graft injury and rejection. [9]

The Use of dd-cfDNA testing in heart and lung transplantation is of particular interest to ISHLT, its members, and the patients we serve. The use of dd-cfDNA is supported by the following:

Heart Allograft Assessment using dd-cfDNA

- Clinical validation of dd-cfDNA testing has been established in heart transplantation through peer-reviewed literature, highlighting its use as a non-invasive tool to accurately identify both AMR and ACR with a high negative predictive value in both for-cause and surveillance settings.[10,11]
- Non-invasive tools such as dd-cfDNA help optimize the use of endomyocardial biopsies (EMB), increasing the yield and reduce the risks associated with these invasive procedures [12]. There are already transplant centers using dd-cfDNA to reduce the frequency of EMBs for allograft surveillance.
- The American Society of Transplantation has published a consensus statement[13] supporting the use of dd-cfDNA in heart transplantation, which is further supported by statements from other societies including ISHLT[14], American Society of Transplant Surgeons[7], and the European Society of Organ Transplantation[8]. The 2022 ISHLT Guidelines for the Care of Heart Transplant Recipients states that consideration should be given to remote drawing of blood samples which include gene expression profiling and donor derived cell-free DNA assays. This home-based testing can potentially reduce the need for surveillance endomyocardial biopsy and thereby limit hospital visits. Such options should be considered when applicable. [14]

Lung Allograft Assessment using dd-cfDNA

- Recently there have been multiple peer-reviewed clinical validations of dd-cfDNA testing in lung allograft recipients which have demonstrated its ability to identify various forms of allograft dysfunction including acute rejection (AMR and ACR), chronic lung allograft dysfunction (CLAD), and infection.[15-18]
- Similar to use in heart transplantation, dd-cfDNA can enable physicians to assess allograft dysfunction while avoiding unnecessary biopsies and related complications[19], of critical importance to the quality of patient care.

In summary, ISHLT reiterates the need for commercial coverage of dd-cfDNA for allograft assessment, particularly for heart and lung transplant recipients, aligned with current CMS coverage criteria under the LCD providing physicians and patients equitable access to these established and innovative non-invasive tools. ISHLT expresses the concern that inconsistency in access to this testing may lead to inequities that could potentially impact patient outcomes. Confirming commercial coverage for this technology is essential to the next steps in improving suboptimal long-term outcomes and costs for transplant recipients.

Sincerely,

Jason D. Christie MD, MS
President

Greg Schultz, CAE
Chief Executive Officer

References

1. MolDX: Molecular Testing for Solid Organ Allograft Rejection (L38568). Accessed 3/31/2023, https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=38568&ver=5

2. Sigdel T, Archila F, Constantin T, et al. Optimizing Detection of Kidney Transplant Injury by Assessment of Donor-Derived Cell-Free DNA via Massively Multiplex PCR. *Journal of Clinical Medicine*. 2018;8(1):19. doi:10.3390/jcm8010019

3. Halloran PF, Reeve J, Madill-Thomsen KS, et al. Combining Donor-derived Cell-free DNA Fraction and Quantity to Detect Kidney Transplant Rejection Using Molecular Diagnoses and Histology as Confirmation. *Transplantation*. 2022;106(12):2435-2442. doi:10.1097/tp.0000000000004212

4. Halloran PF, Reeve J, Madill-Thomsen KS, et al. Antibody-mediated Rejection Without Detectable Donor-specific Antibody Releases Donor-derived Cell-free DNA: Results From the Trifecta Study. *Transplantation*. 2023;107(3)

5. Bloom RD, Bromberg JS, Poggio ED, et al. Cell-Free DNA and Active Rejection in Kidney Allografts. *J Am Soc Nephrol*. Jul 2017;28(7):2221-2232. doi:10.1681/asn.2016091034

6. 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

7. American Society of Transplant Surgeons. ASTS Statement on donor-derived cell-free DNA (dd cf-DNA). Accessed 11/25/23, https://asts.org/docs/default-source/position-statements/dd-cfdna-position-statement.pdf

8. The European Society for Organ Transplantation. ESOT TLJ Consensus Conference Highlights Report Accessed 11/24/23, https://esot.org/wp-content/uploads/2023/03/EM012464_TLJ_3_0_Scientific_Highlights_Report_230316_V0-7_SMB.pdf

9. Levitsky J, Kandpal M, Guo K, Kleiboeker S, Sinha R, Abecassis M. Donor-derived cell-free DNA levels predict graft injury in liver transplant recipients. *Am J Transplant*. Feb 2022;22(2):532-540. doi:10.1111/ajt.16835

10. Kim PJ, Olymbios M, Siu A, et al. A novel donor-derived cell-free DNA assay for the detection of acute rejection in heart transplantation. *The Journal of Heart and Lung Transplantation*. 2022;41(7):919-927. doi:10.1016/j.healun.2022.04.002

11. Khush KK, Patel J, Pinney S, et al. Noninvasive detection of graft injury after heart transplant using donor-derived cell-free DNA: A prospective multicenter study. *American Journal of Transplantation*. 2019;19(10):2889-2899. doi:10.1111/ajt.15339

12. Agbor-Enoh S, Shah P, Tunc I, et al. Cell-Free DNA to Detect Heart Allograft Acute Rejection. *Circulation*. Mar 23 2021;143(12):1184-1197. doi:10.1161/CIRCULATIONAHA.120.049098

13. Kobashigawa J, Hall S, Shah P, et al. The evolving use of biomarkers in heart transplantation: Consensus of an expert panel. *Am J Transplant*. Jun 2023;23(6):727-735. doi:10.1016/j.ajt.2023.02.025

14. 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*. May 2023;42(5):e1-e141. doi:10.1016/j.healun.2022.10.015

15. Rosenheck JP, Ross DJ, Botros M, et al. Clinical Validation of a Plasma Donor-derived Cell-free DNA Assay to Detect Allograft Rejection and Injury in Lung Transplant. *Transplant Direct*. Apr 2022;8(4):e1317. doi:10.1097/txd.0000000000001317

16. Khush KK, De Vlaminck I, Luikart H, Ross DJ, Nicolls MR. Donor-derived, cell-free DNA levels by next-generation targeted sequencing are elevated in allograft rejection after lung transplantation. *ERJ Open Res*. Jan 2021;7(1):00462-2020. doi:10.1183/23120541.00462-2020

17. Ju C, Xu X, Zhang J, et al. Application of plasma donor-derived cell free DNA for lung allograft rejection diagnosis in lung transplant recipients. *BMC Pulm Med*. Jan 26 2023;23(1):37. doi:10.1186/s12890-022-02229-y

18. Keller M, Sun J, Mutebi C, et al. Donor-derived cell-free DNA as a composite marker of acute lung allograft dysfunction in clinical care. *J Heart Lung Transplant*. Apr 2022;41(4):458-466. doi:10.1016/j.healun.2021.12.009

19. McWilliams TJ, Williams TJ, Whitford HM, Snell GI. Surveillance Bronchoscopy in Lung Transplant Recipients: Risk versus Benefit. *The Journal of Heart and Lung Transplantation*. 2008/11/01/ 2008;27(11):1203-1209. doi: https://doi.org/10.1016/j.healun.2008.08.004