MOLECULAR DIAGNOSTIC TESTING FOR ACUTE REJECTION IN HEART OR LUNG ALLOGRAFTS

List has been updated

See publications in italicized text

Selected Clinical Literature List

Below is the list of selected literature (organized by organ and test) for the Kidney or Liver CAC discussion. For select tests, there is a paucity of evidence. Therefore, additional searches on manufacturer's websites were conducted to ensure that all relevant information was included. Results from these searches and rationale for exclusion are included in the Appendices.

Selected Clinical Literature List

Below is the list of selected literature (organized by organ and test) for the Heart or Lung CAC discussion. For select tests, there is a paucity of evidence. Therefore, additional searches on manufacturer's websites were conducted to ensure that all relevant information was included. Results from these searches and rationale for exclusion are included in the Appendices.

Transplant Organ: Heart

AlloMap

1. Deng MC, Eisen HJ, Mehra MR, et al.; CARGO Investigators. Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. Am J Transplant. 2006 Jan;6(1):150-60.
2. Crespo-Leiro MG, Stypmann J, Schulz U, et al. Clinical usefulness of gene-expression profile to rule out acute rejection after heart transplantation: CARGO II. Eur Heart J. 2016 Sep 1;37(33):2591-601.
3. Crespo-Leiro MG, Stypmann J, Schulz U, et al. Performance of gene-expression profiling test score variability to predict future clinical events in heart transplant recipients. BMC Cardiovasc Disord. 2015 Oct 9;15:120.
4. Moayedi Y, Fan CS, Miller RJH, et al. Gene expression profiling and racial disparities in outcomes after heart transplantation. J Heart Lung Transplant. 2019 Aug;38(8):820-829.
5. Pham MX, Teuteberg JJ, Kfoury AG, et al; IMAGE Study Group. Gene-expression profiling for rejection surveillance after cardiac transplantation. N Engl J Med. 2010 May 20;362(20):1890-900.

6. Costanzo MR, Dipchand A, Starling R, et al.; International Society of Heart and Lung Transplantation Guidelines. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2010 Aug;29(8):914-56.
7. Chih S, McDonald M, Dipchand A, et al. Canadian Cardiovascular Society/Canadian Cardiac Transplant Network Position Statement on Heart Transplantation: Patient Eligibility, Selection, and Post-Transplantation Care, Canadian Journal of Cardiology, Volume 36, Issue 3, 2020, p. 335-356.
8. U.S. Food and Drug Administration. Washington (DC): FDA; Premarket notification 510(k); cited 2022 Oct 06. Available from this hyperlink.

AlloSure

1. 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. Am J Transplant. 2019 Oct;19(10):2889-2899.

AlloMap and AlloSure

1. Henricksen EJ, Moayedi Y, Purewal S, et al. Combining donor derived cell free DNA and gene expression profiling for non-invasive surveillance after heart transplantation. Clin Transplant. 2022 May 12:e14699.

Prospera

1. 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. J. Heart Lung Transplant. April 2022.

Viracor TRAC

The literature review returned no publications that assessed the clinical utility or utility of Viracor TRAC in heart transplant recipients.

Transplant Organ: Lung

AlloSure

1. Khush KK, De Vlaminck I, Luikart H, et al. Donor-derived, cell-free DNA levels by next-generation targeted sequencing are elevated in allograft rejection after lung transplantation. ERJ Open Res. 2021 Jan 25;7(1):00462-2020.
2. Sayah D, Weigt SS, Ramsey A, Ardehali A, Golden J, Ross DJ. Plasma Donor-derived Cell-free DNA Levels Are Increased During Acute Cellular Rejection After Lung Transplant: Pilot Data. Transplant Direct. 2020 Sep 24;6(10):e608.

3. Keller M, Mutebi C, Shah P, Levine D, Aryal S, Iacono A, Timofte I, Mathew J, Varghese A, Giner C, Agbor-Enoh S. Biological Variation of Donor-Derived Cell-Free DNA in Stable Lung Transplant Recipients. J Appl Lab Med. 2022 Jun 30;7(4):901-909.
4. Keller M, Sun J, Mutebi C, Shah P, Levine D, Aryal S, Iacono A, Timofte I, Mathew J, Varghese A, Giner C, Agbor-Enoh S. Donor-derived cell-free DNA as a composite marker of acute lung allograft dysfunction in clinical care. J Heart Lung Transplant. 2022 Apr;41(4):458-466.

Prospera

1. Rosenheck JP, Ross DJ, Botros M, Wong A, Sternberg J, Chen YA, Liang N, Baer A, Ahmed E, Swenerton R, Zimmermann BG, Fehringer G, Demko ZP, Olymbios M, Billings PR, Keller BC. Clinical Validation of a Plasma Donor-derived Cell-free DNA Assay to Detect Allograft Rejection and Injury in Lung Transplant. Transplant Direct. 2022 Mar 25;8(4):e1317.

Viracor TRAC

The literature review returned no publications that assessed the clinical validity or utility of Viracor TRAC in lung transplant recipients.

Appendix A

Organ: Heart

AlloSure

Due to the paucity of literature on the use of AlloSure in heart transplant recipients, an additional search on CareDx's website was conducted. CareDx's HeartCare webpage cites the following references:

Rationale for exclusion	Reference
This is a reference to unpublished raw data.	AlloMap results were considered High for scores >30 (<6 months post-transplant) or >34. AlloSure Heart results were considered High for 0.2% dd-cfDNA or greater. Data are a combination of CARGO II and DOAR outcomes CARGO II and DOAR. Unpublished raw data. Endpoints measured were rejection episodes.
An RCT, which is cited in the list above.	Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-Expression Profiling for Rejection Surveillance after Cardiac Transplantation. *New England Journal of Medicine* 2010;20:1890–1900.

Rationale for exclusion	Reference
The CARGO study, which is cited in the list above.	Crespo-Leiro MG, Stypmann J, Schulz U, et al. Clinical usefulness of gene-expression profile to rule out acute rejection after heart transplantation: CARGO II. Eur Heart J. 2016 Sep 1;37(33):2591-601.
This is an abstract.	Crespo-Leiro MG, et al. Abstract of "Increased Plasma Levels of Donor-Derived Cell-Free DNA Correlate with Rejection in Heart Transplant Recipients: The CARGO II Multicenter Trial." International Society for Heart and Lung Transplantation (ISHLT), 35th Annual Meeting and Scientific Sessions April 15 – 18, 2015. Nice, France.

Prospera

Due to the paucity of literature on the use of Prospera in heart transplant recipients, an additional search of Natera's website was conducted. Natera's Prospera Heart webpage cites the following references:

Rationale for exclusion	Reference
This is a reference to a submitted manuscript.	Natera validation data; manuscript submitted. Data on file.
This study assessed the use of Prospera in kidney (not heart) transplant recipients.	Sigdel TK, Archila FA, Constantin T, et al. Optimizing detection of kidney transplant injury by assessment of donor-derived cell-free DNA via massively multiplex PCR. J Clin Med. 2018 (per published article);8(1):19.
This was an analytical validation study for detection of rejection in kidney (not heart) transplant recipients.	Altug Y, Liang N, Ram R, et al. Analytical validation of a single-nucleotide polymorphism-based donor-derived cell-free DNA assay for detecting rejection in kidney transplant patients. Transplantation. 2019;103(12):2657-2665.
This was an analytical validation study for the detection of rejection in heart and kidney recipients that was conducted using AlloSure rather than Prospera Heart.	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 Diagn. 2016;18(6):890-902.

Rationale for exclusion	Reference
This is a reference for organ transplant data cited.	Data from the U.S. Department of Health & Human Services: Health Resources and Services Administration. Scientific Registry of Transplant Recipients (SRTR): Organ Procurement and Transplantation Network (OPTN)/SRTR.
A brief that includes 4 case reports. Discusses the indications for, and outcomes of, heart and lung transplant recipients.	Toyoda Y, Toyoda Y. Heart-lung transplantation: adult indications and outcomes. J Thorac Dis. 2014;6(8):1138-1142.

A search of Natera's Prospera Heart Physician Brochure was conducted. However, only one study, Kim 2022 (listed above) reported the performance of Prospera Heart to detect rejection. The other cited publications were used to support background information.

Viracor TRAC

An additional search of Eurofins' website was performed. Eurofins' Viracor TRAC Heart dd-cfDNA webpage cites the following references:

Rationale for exclusion	Reference
This study evaluated AlloSure (not Viracor TRAC) in renal (not heart) transplant recipients.	Bromberg JS, Brennan DC, et. al. Biological Variation of Donor-Derived Cell-Free DNA in Renal Transplant Recipients: Clinical Implications. Journal of Applied Laboratory Medicine (2017, September); 2:02, 1-13.
This study is a narrative review. It is labeled as a "Minireview" and discusses dd cf DNA measurement methods and several observational studies.	Gielis EM, Ledeganck KJ, De Winter BY, et. al. Cell-Free DNA: An Upcoming Biomarker in Transplantation. American Journal of Transplantation (2015); 15: 2541-2551.
This study evaluated lung (not heart) transplant recipients and measured dd cf DNA by shotgun sequencing. Eurofins states that Viracor TRAC Heart "analyzes NGS and genome-wide recipient genotype data to determine the percentage of dd cfDNA present….", which is a different measurement method.	De Vlaminick I, Martin L, Kertesz M, et. al. Noninvasive monitoring of infection and rejection after lung transplantation. Proceedings of the National Academy of Sciences (2015, October 27); 112:43, 13336-13341.

Rationale for exclusion	Reference
This was an analytical validation study for the detection of rejection in heart and kidney recipients and conducted using AlloSure rather than Viracor TRAC Heart.	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. The Journal of Molecular Diagnostics (2016, November); 18:6, 890-902.

Appendix B

Organ: Lung

AlloSure

An additional search of CareDx's website was conducted. CareDx's AlloSure – Lung webpage cites the following references:

Rationale for exclusion	Reference
This is a reference for organ transplant data cited.	OPTN data (01/29/2021)
This study measured dd cf DNA by shotgun sequencing. CareDx states (in their AlloSure Lung Interpretive Guide) that AlloSure "…is a clinical grade, targeted, next generation sequencing (NGS) assay that measures single-nucleotide polymorphism (SNPs) to accurately quantify donor-derived cell-free DNA….), which is a different measurement method.	Agbor-Enoh S, Jackson AM, Tunc I, et al. Late manifestation of alloantibody-associated injury and clinical pulmonary antibody-mediated rejection: Evidence from cell-free DNA analysis. J Heart Lung Transplant. 2018 Jul;37(7):925-932.
This study measured dd cf DNA by shotgun sequencing, which is a different measurement method than what is used with AlloSure.	Agbor-Enoh S, Wang Y, Tunc I, et al. Donor-derived cell-free DNA predicts allograft failure and mortality after lung transplantation. EBioMedicine. 2019 Feb;40:541-553.
This was a Letter to Editor, which described a single center's experience with AlloSure in lung transplant recipients.	Levine et al. (2020). Single Center "Snapshot" Experience with Donor-Derived Cell-Free DNA After Lung Transplantation. Biomarker Insights, 15, 1177271920958704.
This study measured dd cf DNA by shotgun sequencing, which is a different measurement method than what is used with AlloSure.	De Vlaminck I, Martin L, Kertesz M, et al. Noninvasive monitoring of infection and rejection after lung transplantation. Proc Natl Acad Sci U S A. 2015 Oct 27;112(43):13336-41.

Rationale for exclusion	Reference
This was an abstract.	Keller, M., Mutebi, C., Shah, P.D., et al. Performance of Donor Derived Cell-Free DNA in Routine Clinical Care of Lung Transplant Recipients, a Multi-Center Study. Journal of Heart and Lung Transplantation, 40 No 4S, 2021.

Prospera

An additional search of Natera's website was conducted. Natera's Prospera – Lung webpage cites the following references:

Rationale for exclusion	Reference
This is a reference to a submitted manuscript.	Natera validation data; manuscript submitted. Data on file.
This study assessed the use of Prospera in kidney (not lung) transplant recipients.	Sigdel TK, Archila FA, Constantin T, et al. Optimizing detection of kidney transplant injury by assessment of donor-derived cell-free DNA via massively multiplex PCR. J Clin Med. 2018 (per published article);8(1):19.
This was an analytical validation study for detection of rejection in kidney (not lung) transplant recipients.	Altug Y, Liang N, Ram R, et al. Analytical validation of a single-nucleotide polymorphism-based donor-derived cell-free DNA assay for detecting rejection in kidney transplant patients. Transplantation. 2019;103(12):2657-2665.
This was an analytical validation study for the detection of rejection in heart and kidney recipients that was conducted using AlloSure rather than Prospera Lung.	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 Diagn. 2016;18(6):890-902.
This is a reference for organ transplant data cited.	Data from the U.S. Department of Health & Human Services: Health Resources and Services Administration. Scientific Registry of Transplant Recipients (SRTR): Organ Procurement and Transplantation Network (OPTN)/SRTR.
A brief that includes 4 case reports. Discusses the indications for, and outcomes of, heart and lung transplant recipients.	Toyoda Y, Toyoda Y. Heart-lung transplantation: adult indications and outcomes. J Thorac Dis. 2014;6(8):1138-1142.

In addition, a search of Natera's Prospera Lung Physician Brochure was conducted. The brochure cites some performance indices from the VALID study however, it states that the publication is pending. The brochure references did not provide any additional information on the clinical validity or utility of Prospera Lung.

Viracor TRAC

An additional search of Eurofins' website was performed. Eurofins' Viracor TRAC Lung dd-cfDNA webpage cites the following references:

Rationale for exclusion	Reference
This study evaluated AlloSure (not Viracor TRAC) in renal (not lung) transplant recipients.	Bromberg JS, Brennan DC, et. al. Biological Variation of Donor-Derived Cell-Free DNA in Renal Transplant Recipients: Clinical Implications. Journal of Applied Laboratory Medicine (2017, September); 2:02, 1-13.
This study is a narrative review. It is labeled as a "Minireview" and discusses dd cf DNA measurement methods and several observational studies.	Gielis EM, Ledeganck KJ, De Winter BY, et. al. Cell-Free DNA: An Upcoming Biomarker in Transplantation. American Journal of Transplantation (2015); 15: 2541-2551.
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This was an analytical validation study for the detection of rejection in heart and kidney (not lung) recipients and conducted using AlloSure rather than Viracor TRAC Lung.	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. The Journal of Molecular Diagnostics (2016, November); 18:6, 890-902.