HeartCare®

Go Beyond Surveillance Biopsies with HeartCare

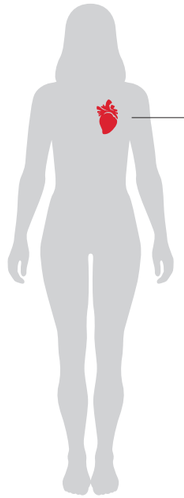
The first multimodal test with studies demonstrating a significant reduction in biopsies, resulting in more patient-centric clinical decision making

Sam D, heart transplant recipient, and his wife

HeartCare Offers a **Comprehensive Approach** to **Post-transplant Surveillance**

HeartCare®

A non-invasive surveillance tool with the dual power of cell-free DNA and gene expression profiling



AlloMap® HEART

- Measures mRNA of the recipient
- Measures immune response
- Originates from WBCs

AlloSure® HEART

- Measures dd-cfDNA from the transplanted heart
- Originates from the graft

HeartCare Has Proven Validation and Clinical Utility for Heart Transplant Rejection Surveillance

2006	2010	2015	2016	2019	2019	2024
CARGO	IMAGE	eIMAGE	CARGO II	OAR	D-OAR	SHORE (1st publication)

Now published: the inaugural publication from SHORE in JHLT[2]

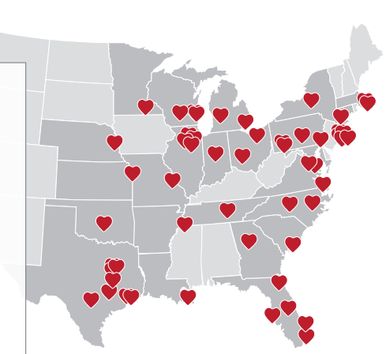
Surveillance HeartCare Outcomes Registry
S.H.O.R.E

67 Transplant Centers
across the United States of America

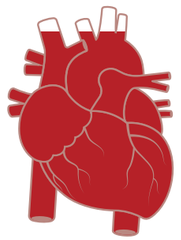
2732 Transplant Patients
monitored between 2018 and 2021

Real-World Evidence
Represents US Transplant demographics

Surveillance Testing
6,363 Samples of HeartCare



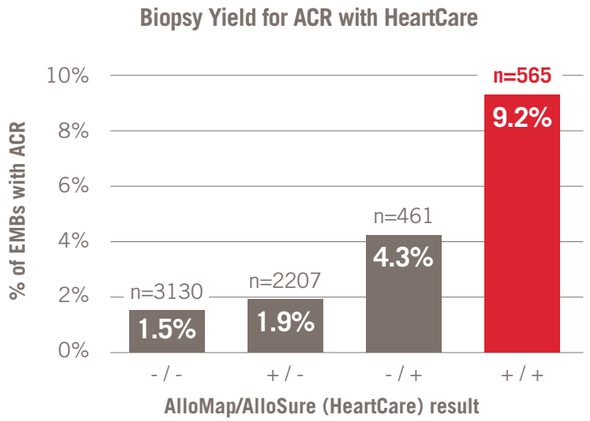
Patients surveilled with HeartCare in SHORE had excellent outcomes[2]



At 2-Years Post Transplant:

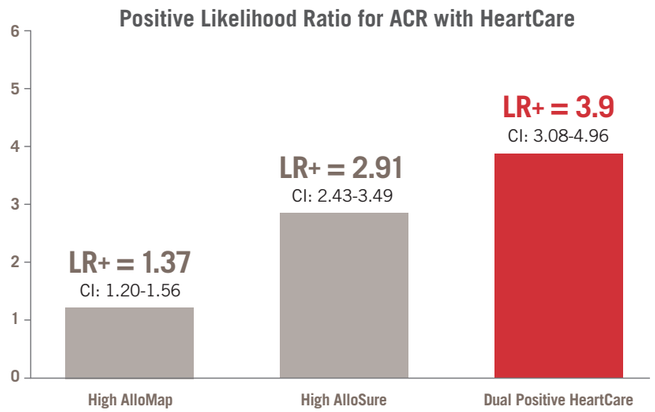
- ✓ **94.9%** survival rate
- ✓ **97.3%** of surviving patients had normal graft function
- ✓ **61%** mean LVEF for surviving patients

Dual Positive HeartCare Results **Better Identify ACR than A Single Test Alone**[2]



HeartCare improves biopsy yield for acute cellular rejection, with **most biopsies revealing ACR with dual positive HeartCare results.**

Dual Positive HeartCare Results **Increased the Odds of ACR by ~4X**[2]



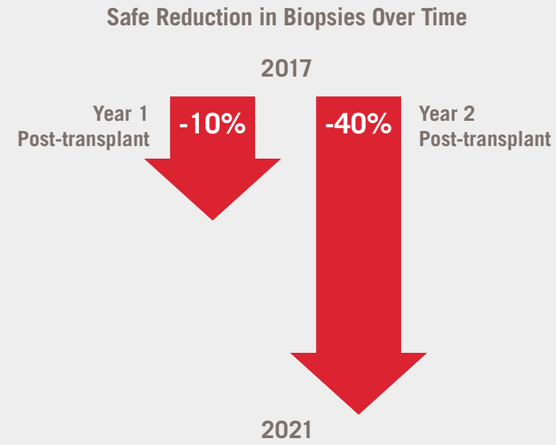
The chance of a biopsy revealing ACR is **greater with a dual positive HeartCare** than with either a high AlloMap or a high AlloSure alone

Positive Likelihood Ratio gives the change in the odds of having a diagnosis in patients with a positive test. A LR+ is mathematically defined as sensitivity / (1-specificity)

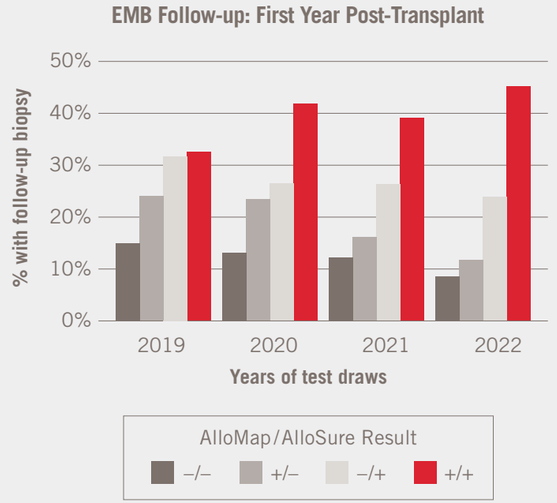
High AlloMap is: ≥30 for 2-6 months or ≥34 for >6 months | High AlloSure is ≥0.20%

HeartCare Interpretation Improved Over Time, Resulting in **More Patient-Centric Biopsy Decision Making**

Patients monitored with HeartCare had fewer biopsies over time, with fewest biopsies occurring in patients without dual positive HeartCare results.



AlloMap was defined as a value ≥30 in the first 6 months or ≥34 beyond 6 months post-transplant
AlloSure was defined as a level ≥0.20% at any time post-transplant



Clinical Interpretation for HeartCare - **ACR Surveillance**[2]

HeartCare helps clinicians precisely identify patients who are at higher risk of ACR

HIGH ALLOMAP / LOW ALLOSURE

A biopsy is unlikely to reveal ACR (ACR positivity in SHORE[2] = 1.9%)

Consider biopsy or repeat HeartCare testing earlier if:

- AlloSure level is close to threshold and increased from prior measurement

Consider other pathological causes of an increased AlloMap:

- CMV infection

Medication adherence review recommended

DUAL POSITIVE HEARTCARE (High AlloSure / High AlloMap)

A biopsy is more likely to reveal ACR
(ACR positivity in SHORE[2] = 9.2%)

- Biopsy should be considered

Medication adherence review recommended

DUAL NEGATIVE HEARTCARE (Low AlloSure / Low AlloMap)

A biopsy is unlikely to reveal ACR
(ACR positivity in SHORE[2] = 1.5%)

- Continue protocol immuno-optimization

LOW ALLOMAP / HIGH ALLOSURE

A biopsy is unlikely to reveal ACR (ACR positivity in SHORE[2] = 4.3%)

Consider a biopsy or repeat HeartCare testing earlier if:

- AlloMap is close to threshold and AlloSure has increased by ≥0.20% from prior measurement
- Recent treatment for rejection (<21 days) or current prednisone >20 mg
- At risk of Antibody Mediated Rejection/markedly elevated AlloSure

Consider other possible pathological causes of an increased AlloSure:

- Cardiac allograft vasculopathy
- Severe infection
- Antibody Mediated Rejection (AMR) / Donor specific antibodies

Medication adherence review recommended

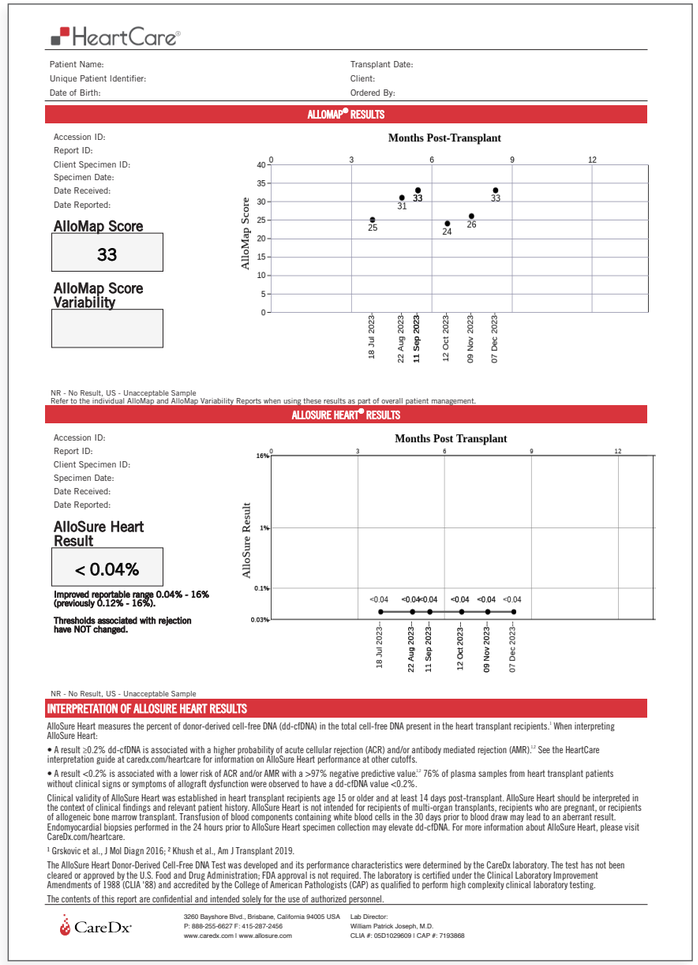
The table is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, current guidelines, and assessment of the patient. Please refer to publications for detailed clinical discussion. Clinical interpretation of AlloSure in Heart Transplantation graph is based on data from all commercial samples.

This table is designed for the context of surveillance testing for ACR; For patients that are at risk of AMR or being tested in other clinical context, different guidance may apply.

High AlloMap is ≥30 for 2-6 months or ≥34 for >6 months | High AlloSure is ≥0.20%

HeartCare Sample Report Offers an **Integrated View** to **Drive Informed Decisions**

- Individual test results (AlloMap or AlloSure Heart) are released when available on individual reports
- Combined HeartCare results are provided on an integrated report that includes both AlloMap and AlloSure Heart when both test results are available



HeartCare®

Patient Name:
Unique Patient Identifier:
Date of Birth:
Transplant Date:
Client:
Ordered By:

ALLOMAP® RESULTS

Accession ID:
Report ID:
Client Specimen ID:
Specimen Date:
Date Received:
Date Reported:

AlloMap Score
33

AlloMap Score Variability

Months Post-Transplant

AlloMap Score

18 Jul 2023	22 Aug 2023	11 Sep 2023	12 Oct 2023	09 Nov 2023	07 Dec 2023
25	31	33	24	26	33

NR - No Result, US - Unacceptable Sample
Refer to the individual AlloMap and AlloMap Variability Reports when using these results as part of overall patient management.

ALLOSURE HEART® RESULTS

Accession ID:
Report ID:
Client Specimen ID:
Specimen Date:
Date Received:
Date Reported:

AlloSure Heart Result
< 0.04%

Improved reportable range 0.04% - 16% (previously 0.12% - 16%).

Thresholds associated with rejection have NOT changed.

Months Post Transplant

AlloSure Result

18 Jul 2023	22 Aug 2023	11 Sep 2023	12 Oct 2023	09 Nov 2023	07 Dec 2023
<0.04	<0.04	<0.04	<0.04	<0.04	<0.04

NR - No Result, US - Unacceptable Sample

INTERPRETATION OF ALLOSURE HEART RESULTS

AlloSure Heart measures the percent of donor-derived cell-free DNA (dd-cfDNA) in the total cell-free DNA present in the heart transplant recipients.[1] When interpreting AlloSure Heart:

- A result ≥0.2% dd-cfDNA is associated with a higher probability of acute cellular rejection (ACR) and/or antibody mediated rejection (AMR).[1,2] See the HeartCare interpretation guide at caredx.com/heartcare for information on AlloSure Heart performance at other cutoffs.
- A result <0.2% is associated with a lower risk of ACR and/or AMR with a >97% negative predictive value.[1,2] 76% of plasma samples from heart transplant patients without clinical signs or symptoms of allograft dysfunction were observed to have a dd-cfDNA value <0.2%.

Clinical validity of AlloSure Heart was established in heart transplant recipients age 15 or older and at least 14 days post-transplant. AlloSure Heart should be interpreted in the context of clinical findings and relevant patient history. AlloSure Heart is not intended for recipients of multi-organ transplants, recipients who are pregnant, or recipients of allogeneic bone marrow transplant. Transfusion of blood components containing white blood cells in the 30 days prior to blood draw may lead to an aberrant result. Endomyocardial biopsies performed in the 24 hours prior to AlloSure Heart specimen collection may elevate dd-cfDNA. For more information about AlloSure Heart, please visit CareDx.com/heartcare.

[1] Grskovic et al., J Mol Diagn 2016; [2] Khush et al., Am J Transplant 2019.

The AlloSure Heart Donor-Derived Cell-Free DNA Test was developed and its performance characteristics were determined by the CareDx laboratory. The test has not been cleared or approved by the U.S. Food and Drug Administration; FDA approval is not required. The laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88) and accredited by the College of American Pathologists (CAP) as qualified to perform high complexity clinical laboratory testing.

The contents of this report are confidential and intended solely for the use of authorized personnel.

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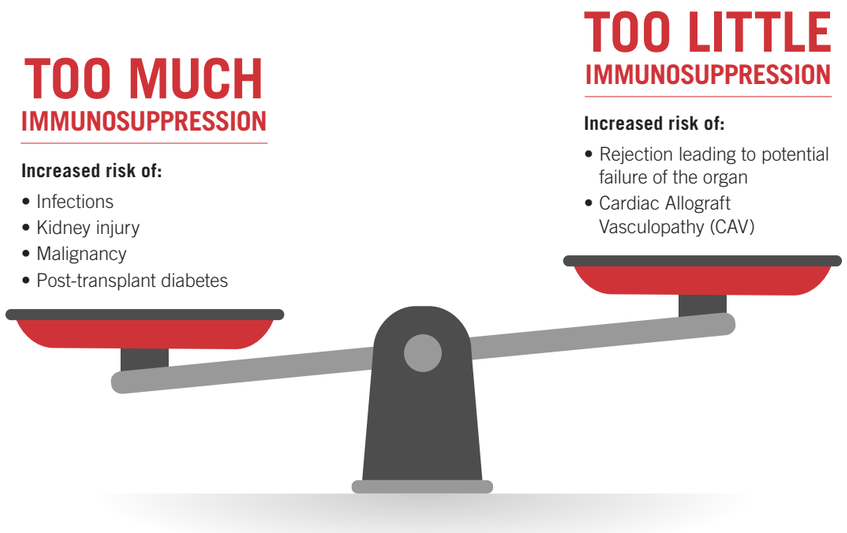
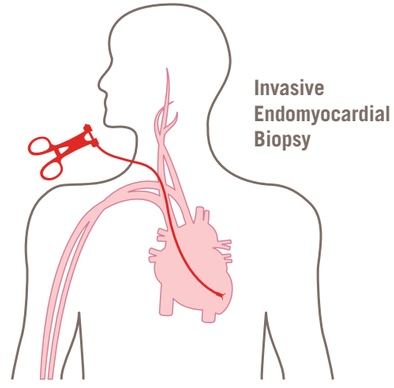
HeartCare Helps Patient Management **Without the Limitations** of Traditional Biopsies

Heart transplant surveillance is complex



Traditional biopsies have significant limitations for rejection surveillance

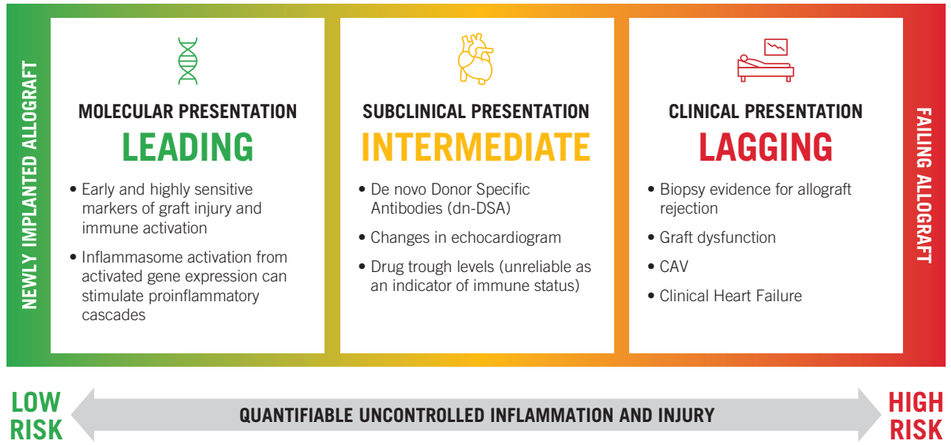
- Resource intensive
- Risk of exposure to pathogens
- Sampling errors and limitations
- Invasive, painful, and frequent (sometimes >10 Biopsies in the 1st year post-transplant)
- Interobserver variability in interpretation



Almost 40% of rejections called by local pathologists were downgraded when reviewed by a panel of central pathologists

Agreement between local and central pathology for rejection[1]		
	Central Grades	
Local Grades	2R Rejection	< 2R Rejection
2R Rejection	46/76 (60.5%)	**30/76 (39.5%)**
< 2R	63/862 (7.3%)	799/862 (92.7%)

Traditional tools for surveillance monitoring may not allow for early intervention



2023 ISHLT guidelines support use of HeartCare in routine monitoring of heart transplant patients

THE 2023 ISHLT GUIDELINES[6] RECOMMEND:

Use of AlloMap Heart starting at two months post-transplant

Use of AlloMap and donor-derived cell-free DNA (AlloSure) for routine post-transplant monitoring

Remote use of AlloMap and donor-derived cell-free DNA (AlloSure) for heart transplant surveillance

References to ISHLT are offered solely to support AlloMap's FDA indications and should not be construed as supporting any other use. AlloMap should be solely used in conjunction with standard clinical assessment

A Suite of **Innovative Transplant Management Solutions**, Enabling More Cohesive Care

CareDx is dedicated to patients and providers throughout the transplant journey

The transplant journey is complex.

Centers and providers are on a constant quest to deliver better outcomes while navigating the reality of operational challenges and fragmentation along the way.

CareDx provides a connected and innovative set of transplant management solutions to enable more cohesive care.

Patient Management

Solutions enabling providers to engage patients in their own care at every stage in the transplant journey

TransplantPharmacy™

Specialty pharmacy dedicated to the unique needs of pre/post-transplant patients

MedActionPlan®

Medication management, education and adherence platform

AlloCare®

Free pre-to-post transplant app that provides medication management and biometric tracking to patients and is fully integrated with AlloHome and TxAccess

AlloHome™

Customizable remote patient monitoring platform and monitoring service

Operational Support

Administrative and workflow support that enable process excellence and reduce inefficiencies and errors

XynCare™

Customizable administrative service

TxAccess™

Referral management and communication tool

Quality Improvement

Advanced algorithms, predictive analytics and quality program tracking to help improve patient outcomes

XynQAPI®

Comprehensive transplant quality management software

Informed Decision Support

Data-driven insights that help providers assess individual patient's status and deliver tailored care

AiCAV™

AiCAV helps to stratify patients based on their risk of developing CAV, a leading cause of heart transplant failure [In development]

Laboratory Management

Software and interoperability solutions for the histocompatibility and immunogenetics community

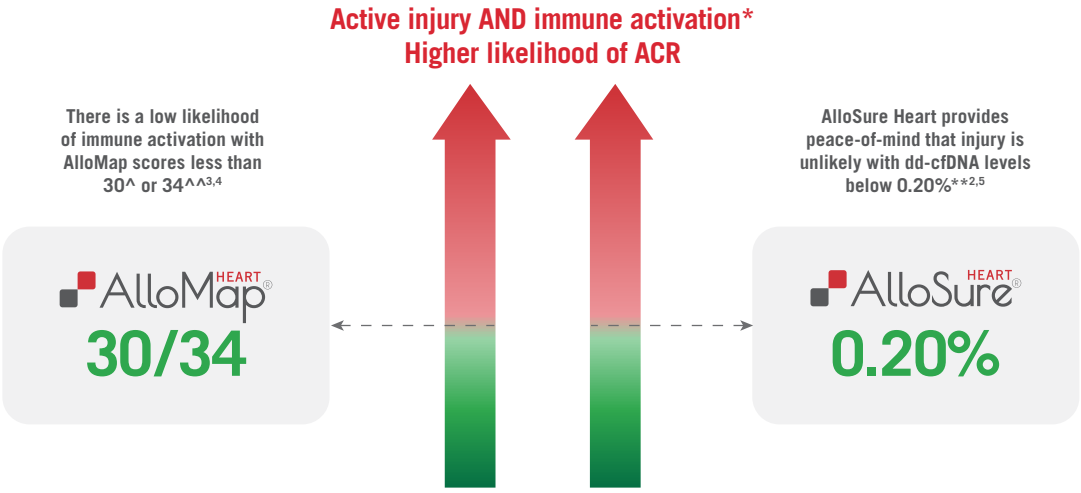
mTilda™

Laboratory Information Management System (LIMS) purpose-built for the world of histocompatibility and immunogenetics

References

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 [published online ahead of print, 2022 May 12]. *Clin Transplant*. 2022;e14699. doi:10.1111/ctr.14699.
2. Khush KK, Hall S, Kao A, et. al. Surveillance with Dual Non-invasive Testing for Acute Cellular Rejection After Heart Transplantation: Outcomes from the Surveillance HeartCare Outcomes Registry (SHORE). *J Heart Lung Transplant*. 2024. https://doi.org/10.1016/j.healun.2024.05.003
3. Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-expression profiling for rejection surveillance after cardiac transplantation. *N Engl J Med*. 2010;362(20):1890-1900. doi:10.1056/ NEJMoa0912965.
4. Kobashigawa J, Patel J, Azarbal B, et al. Randomized pilot trial of gene expression profiling versus heart biopsy in the first year after heart transplant: early invasive monitoring attenuation through gene expression trial. *Circ Heart Fail*. 2015;8(3):557-564. doi:10.1161/CIRCHEARTFAILURE.114.001658.
5. 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;19(10):2889-2899. doi:10.1111/ajt.15339. ; D-OAR is a sub-study of the Outcomes AlloMap Registry (OAR).
6. 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*. 2023;42(5):e1-e141. doi:10.1016/j.healun.2022.10.015

HeartCare Provides **Actionable Information** During Surveillance



^ Post-transplant period 2-6 months
^^ Post-transplant period > 6months

* clinical correlation is required
** as defined by their institutional protocol

HeartCare Has Been **Clinically Validated in Multi-Center Prospective Studies** Including >4,500 Patients

2006	**Cardiac Allograft Rejection Gene Expression Observation (CARGO)** First multicenter validation of GEP test to identify heart transplant patients at low risk mod/severe rejection	*AJT*	N = 222
2010	**Invasive Monitoring Attenuation through Gene Expression (IMAGE)** Prospective, randomized, controlled, multi-center trial where Surveillance for rejection with AlloMap (gene expression profiling) was compared to routine biopsy (standard of care)	*NEJM*	N = 602
2015	**Early Invasive Monitoring Attenuation through Gene Expression (eIMAGE)** Randomized controlled trial comparing GEP to EMB as early as 55 days post transplant	*Circ: Heart Fail.*	N = 60
2016	**CARGO II** The CARGO II study validated the CARGO I study findings of GEP score performance in a predominantly European based cohort	*Eur Heart J.*	N = 472
2019	**Outcomes AlloMap® Registry (OAR)** Registry 5-year follow-up of patients from 2013-2019	*JHLT*	N = 1,504
2019	**Donor-derived cell free DNA Outcomes AlloMap Registry (D-OAR)** Subset of patients co-enrolled in OAR Prospective, multi-center registry with 26 centers to determine whether dd-cfDNA level in heart transplant recipients' blood can differentiate rejection from no rejection	*AJT*	N = 740
2024	**Surveillance HeartCare Outcomes Registry (SHORE)** Prospective registry captured events in patients during their first 5 years post-transplant	*JHLT*	N = 2732

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