

CareDx at ISHLT April 27 – 30, 2016 Washington, DC



Speaker Programs
Outcomes AlloMap Registry (OAR) Meeting
Clinical Presentations

CareDx Lunchtime Program

The Baylor Experience with AlloMap: A Genomic Test for Heart Transplant Patients.

SPEAKER:

Sandra A. Carey, PhD, ANP-BC
Advanced Heart and Lung, Baylor University Medical Center, Dallas, TX.

DISCUSSION:

Adoption of AlloMap® in post transplant care

Case Studies

Mobile phlebotomy services

Current research initiatives

CareDx Symposium

Detecting Rejection and Surveillance in Cardiac Transplantation: Applications of Genomic Medicine.

MODERATORS:

Jon Kobashigawa, MD, Cedars-Sinai Medical Center, Los Angeles, CA.

Kiran Khush, MD, MAS, Stanford University School of Medicine, Palo Alto, CA.

LECTURES:

Surveillance with gene-expression profiling test: 10 years experience with AlloMap and future directions

Intragraft mRNA as signatures for true rejection: Getting it right in heart biopsies.

MicroRNA as viable biomarkers in the detection of both acute and chronic rejection.

Can dd-cfDNA become a reality in heart transplantation?

CareDx Outcomes AlloMap® Registry (OAR) Investigator Meeting

- OAR is a prospective, ongoing, observational registry for heart transplant patients being managed with gene expression profiling (GEP).
- OAR is the first heart transplant registry to focus on GEP, allowing insights into the real world long-term outcomes of patients managed with GEP as a part of the surveillance strategy
- OAR Steering Committee Members:

Name	Institution
Jon Kobashigawa, Chair	Cedars-Sinai Medical Center
Kiran Khush, MD	Stanford University
Farhana Latif, MD	Columbia University/NY Presbyterian
Srinivas Murali, MD	Allegheny General Hospital
Nasir Sulemanjee, MD	Aurora St. Luke's
Jeffrey Teuteberg, MD	University of Pittsburg Medical Center

CareDx at ISHLT: clinical data presentations

1. **Impact of Cytomegalovirus (CMV) Infection on Longitudinal Gene-expression Profiling (GEP) Score: Results from the Outcomes AlloMap Registry.** Kanwar et al.
2. **Our Experience with the Use of AlloMap in Multi Organ Recipients.** Carey et al.
3. **Higher Rate of Hospitalizations for Infection and Cancer than Rejection in Low Risk Heart Transplant Patients Followed by Gene Expression Profiling.** Teuteberg et al.
4. **Initial Analysis of the D-OAR Study: Donor-Derived cfDNA and Gene-expression Profiling Scores in Heart Transplant Recipients Undergoing Surveillance for Rejection.** Kobashigawa et al.
5. **Utility of Gene Expression (AlloMap Score) in Antibody Mediated Rejection Detection.** Uriel et al.
6. **Outcomes with Gene Expression in Profiling for Heart Transplant Recipients Within North America.** Shah et al.
7. **Monocyte Gene Expression before and after LVAD Implantation.** Uriel et al.

1. Impact of Cytomegalovirus (CMV) Infection on Longitudinal Gene-expression Profiling (GEP) Score: Results from the Outcomes AlloMap Registry (OAR)

M. Kanwar, MD¹, J. Yee, MD PhD², G. Ewald, MD³, S. Murali, MD¹

Presentation at the 37th Annual ISHLT Meeting, Washington DC, April 28th 6:10-6:15pm

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¹ Allegheny General Hospital, Pittsburgh, PA

² CareDx, Inc., Brisbane, CA

³ Washington University School of Medicine, St. Louis, MO

1. Impact of Cytomegalovirus (CMV) Infection on Longitudinal Gene-expression Profiling (GEP) Score: Results from the Outcomes AlloMap Registry (OAR)

Background:

- Cytomegalovirus (CMV) is one of the most common post-transplant complications with significant morbidity and occasional mortality;
- CMV infection has a latent effect on the GEP scores (IMAGE STUDY: D+ or R+ serologies had higher mean GEP scores than D-/R- patients);
- Data previously reported an increase in GEP score (33.9 vs. 29.1, $p=0.0048$) $N=11$

Data:

- 32(5.4%) had a diagnosis of CMV infection reported. CMV infection was defined as any positive CMV serology. 30 (94%) had CMV serology at time of transplant, time of infection and at least one GEP score.

Results:

- CMV infections in cardiac transplant recipients are associated with an **increase in GEP** score that is independent of acute cellular rejection with a **trend towards decrease** in score when viremia is resolved;
- The likely mechanism is immune activation/modulation of one or more of the 11 genes in the GEP signature;
- Newly elevated AlloMap scores in the absence of ACR may signal CMV infection.

2. Our Experience with the Use of AlloMap in Multiple Organ Recipients

S. Carey PhD¹, G. Saracino MS², A. Jamil MPH¹, Shelley Hall MD¹

Presentation at the 37th Annual ISHLT Meeting, Washington DC, April 27th 6:00 -7:00 PM

¹ Advanced Heart and Lung, Baylor University Medical Center, Dallas TX

² Baylor University Medical Center, Dallas TX

2. Our Experience with the Use of AlloMap in Multiple Organ Recipients

Background:

- Limited information is available on the use of gene-expression profiling as a part of post transplant surveillance in multiple organ recipients;
- Current mid- and long-term outcomes of multiple-organ transplantation are comparable to those of single-organ transplantation.

Data:

- Retrospective analysis of 15 adult multiple-organ transplant recipients (heart/kidney and heart/liver) performed from January 1, 2007 - September 30, 2015;

Results:

- No differences in AlloMap scores were observed between heart only and multi-organ patients with EMB proven rejection;
- CMV Viremia was associated with higher AlloMap Scores (35 vs.28, $p < 0.025$);
- Serial AlloMap scores in multiple organ recipients were not found to be significantly different when compared to the matched heart recipient only control group;
- Mean length of hospital stay was longer in multi-organ vs. single organ recipients (20 days vs. 9 days, $p = 0.029$);
- When matched with the heart only group, there was no difference in 1 year survival, incidence of CMV or incidence of rejection.

3. Higher Rate of Hospitalizations for Infection and Cancer Than Rejection in Low Risk Heart Transplant Patients Followed by Gene Expression Profiling

J. Teuteberg, MD¹, M. Shullo¹, P. Berman², N. Haglund MD³, M.A. Wigger³, G.A Ewald⁴

Presentation at the 37th Annual ISHLT Meeting, April 27th 6:00 – 7:00PM

¹ University Of Pittsburgh, Pittsburgh, PA

² Tampa General Hospital. Tampa FL

³ Vanderbilt University Medical Center, Nashville, TN

⁴ Washington University School of Medicine, St. Louis, MO

3. Higher Rate of Hospitalizations for Infection and Cancer Than Rejection in Low Risk Heart Transplant Patients Followed by GEP: OAR Hospitalization Results

Background:

- OAR is the first heart transplant registry to focus on GEP with a target of ≥ 2000 patients;
- The study was to hypothesize that active infection or serious cancer following transplantation may be a sign of over immunosuppression.

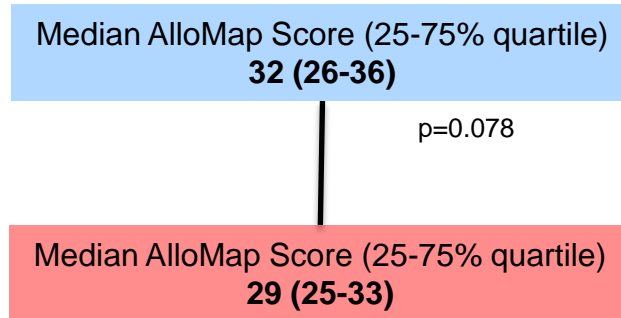
Data:

- Enrollment at time of analysis was 720 patients from 24 transplant programs;
- 32 patients have recorded diagnosis of cancer;
- Pre-transplant CMV serology available for 95% of patients.

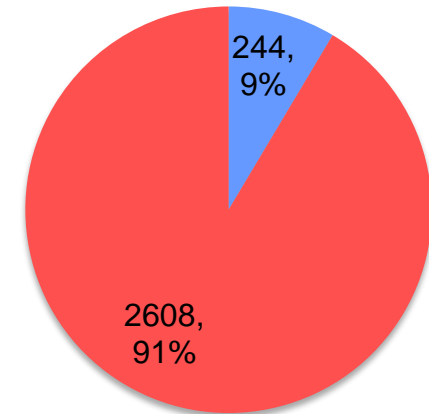
Results:

- OAR have a higher incidence of hospitalization for new infections and new diagnosis of cancer than ACR;
- Considering the very low incidence of ACR, there may be opportunity to reduce interval hospitalization and incidence of cancers by selective immunosuppressive minimization, perhaps in part guided by AlloMap GEP patterns in the individual.

3. (cont.) Higher Rate of Hospitalizations for Infection and Cancer Than Rejection in Low Risk Heart Transplant Patients Followed by GEP: OAR Hospitalization Results

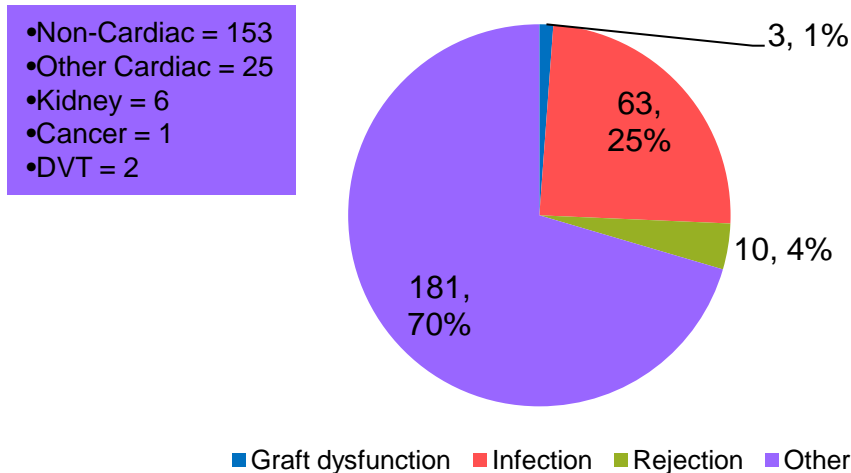


Interval Hospitalization



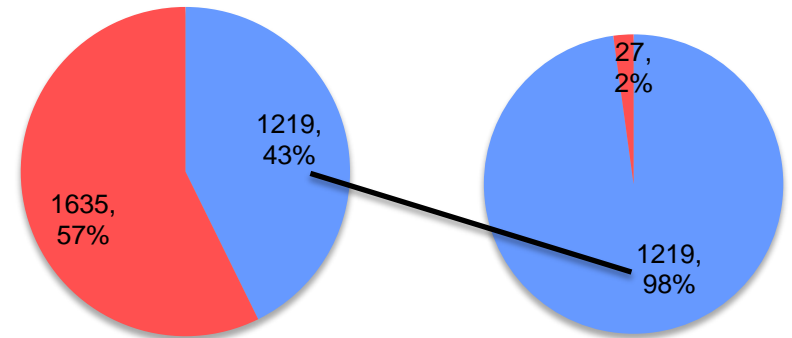
■ Interval Hospitalization ■ No Hospitalization

Reasons for Hospitalization

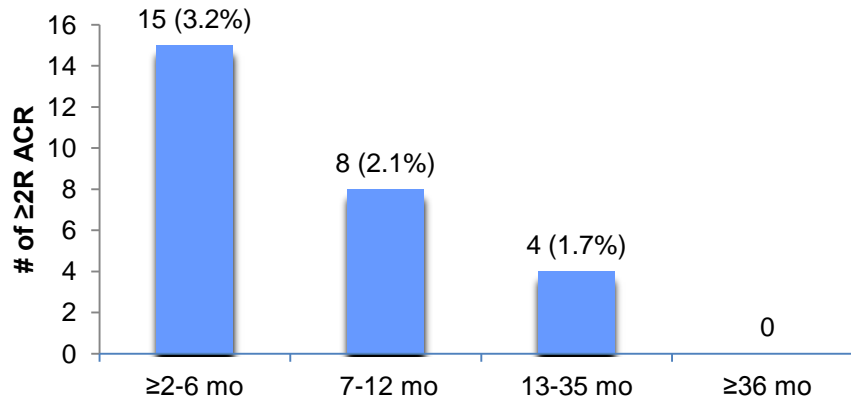


3.(cont.) Higher Rate of Hospitalizations for Infection and Cancer Than Rejection in Low Risk Heart Transplant Patients Followed by GEP: OAR EMB and GEP Results

Endomyocardial Biopsies (EMB)



Time post transplant of 27 grade ≥2R ACR



■ EMB Done ■ EMB Not Done

■ Grade <2R ■ Grade ≥2R

(ISHLT 2004) Rejection grades provided by local pathologists

Median AlloMap Score (25-75% quartile)

At the time of ≥2R rejection

32 (29-37)

Without rejection

29 (25-33)

Teuteberg J et al "Higher Rate of Hospitalizations for Infection and Cancer Than Rejection in Low Risk Heart Transplant Patients Followed by GEP" ISHLT 2016

4. Initial Analysis of the Donor-Derived Cell-Free DNA Outcomes AlloMap Registry (D-OAR) Study in Heart Transplant Recipients Undergoing Surveillance for Rejection

J.A Kobashigawa¹, K. Khush², J.Teuteberg³, M. Song⁴, M. Grskovic⁴, D. Hiller⁴, R. Woodward⁴, E. Deljkich⁴, J. Yee⁴, F. Latif⁵, N. Sulemanjee⁶, S. Murali⁷

Presentation at the 37th Annual ISHLT Meeting, April 28th 3:00 -3:15 PM

¹ Cedars-Sinai Heart Institute, Los Angeles, CA

² Stanford University , Palo Alto, CA

³ University of Pittsburgh Medical Center, Pittsburgh PA

⁴ CareDx, Brisbane, CA

⁵ Columbia University Medical Center, New York, NY

⁶ Aurora St. Luke's Medical Center, Milwaukee, WI

⁷ Allegheny General Hospital, Pittsburgh, PA

4. Analysis of the Donor-Derived Cell-Free DNA Outcomes AlloMap Registry (D-OAR) Study in Heart Transplant Recipients Undergoing Surveillance for Rejection

Background:

- D-OAR characterizes a new biomarker of allograft rejection in heart transplant recipients who are receiving rejection surveillance with gene-expression profiling (AlloMap) as part of their standard of care;
- Patients typically are asymptomatic and clinically stable at the time of routine surveillance visits.

Data:

- dd-cfDNA (plasma) and AlloMap (peripheral blood mononuclear cells) were obtained at surveillance visits (90% < 12 m post OHT; range 2 to >36 m);
- Interim analysis on 111 patients and 190 patient visits.

Results:

- AlloMap scores were not correlated with dd-cfDNA;
- Clinical factors most correlated with either high AlloMap scores or a rise in dd-cf DNA was hospitalization for infection (n=3) or graft dysfunction (n=2);
- dd-cfDNA and GEP may offer complementary information;
- Larger numbers of patients (> 400) and samples (>1,000) are being accumulated in the D-OAR study for correlation with clinical events to further delineate the utility of dd-cfDNA in heart transplant recipients

4. (cont.) Analysis of the Donor-Derived Cell-Free DNA Outcomes AlloMap Registry (D-OAR) Study in Heart Transplant Recipients Undergoing Surveillance for Rejection

N = 190 visits	111 patients
Male	76%
Caucasian	72%
ACR	1.4% 2R
AMR	1.4%
CAV	2.9%
AlloMap Score (m)	27
dd-cfDNA %	75% < 0.4%*

- AlloMap scores were not correlated with dd-cfDNA;
- Clinical factors most correlated with either high AlloMap score or dd-cfDNA was hospitalization for: infection (n =3) or graft dysfunction (n =2).

*0.4% is the limit of detection of dd-cfDNA assay

5. Utility of Gene Expression (AlloMap Score) in Antibody Mediated Rejection Detection

S. Adatya¹, E. Delijkich², D. Hiller², J. Yee², G. Sayer¹, J. Yee², N. Uriel¹

The 37th Annual ISHLT Meeting, April 28th 3:15 PM- 3:30 PM

¹ University of Chicago, IL

² CareDx, Brisbane, CA

5. Utility of Gene Expression (AlloMap Score) in Antibody Mediated Rejection Detection

Background:

- Antibody mediated rejection (AMR) occurs in approximately 10 – 20% of heart transplant patients, and is associated with hemodynamic compromise, increased cardiac allograft vasculopathy (CAV), and increased mortality.

Data:

- Retrospective analysis from the OAR database was performed, including the AlloMap score along with the 11 component gene subsets were correlated with the pathologic diagnosis of AMR;
- Dataset includes 596 patients with 27 cases of AMR reported.

Results:

- No statistically meaningful difference of mean AlloMap scores between the AMR Group vs. No AMR 27.8 vs. 29.2;
- Future studies using total AlloMap score and gene subsets to risk stratify patients with asymptomatic AMR vs AMR associated with either hemodynamic compromise or progressive CAV are needed.

5. (cont.) Utility of Gene Expression (AlloMap Score) in Antibody Mediated Rejection Detection: Results

Demographics

N = visits	No AMR (n=636)	AMR \geq 1 (n=27)	P- value
Age	54.7	51.1	0.3
Sex (M)	442 (70%)	18 (67%)	0.8
Ischemic etiology	280 (44%)	8 (30%)	0.2
Post MCS	326 (51.3%)	16 (59.3%)	0.4
Mean GEP	29.2	27.8	0.4

Results by Gene Subset

Gene Subsets	AMR \geq 1	AMR = 0	P
MARCH8	714	802	0.291
SEMA7A	35.5	38.6	0.332
IL1R2	19.7	23.8	0.402
RHOU	672	722	0.106
WDR40A	1291	1630	0.081
FLT3	122	137	0.485
C6orf25	6893	6437	0.658
ITGA4	2713	2894	0.212
ITGAM	4729	4771	0.888
PDCD1	115	131	0.296
PF4	18756	17211	0.495

There were no statistically significant differences in the gene subsets for each group

6. Outcomes with Gene Expression Profiling for Cardiac Transplant Recipients within North America

P. Shah¹, D. Hiller², M. Maydosz¹, E. Deljkich² J. Yee² , A. Cochrane¹

The 37th Annual ISHLT Meeting, Washington DC, April 2016

¹ Heart Failure and Transplantation, Inova Heart and Vascular Institute, Falls Church, VA

² CareDx, Brisbane CA

6. Outcomes with Gene Expression Profiling for Cardiac Transplant Recipients within North America

Background:

- Gene expression profiling (GEP) is a biomarker of immune system activity in cardiac transplant recipients;
- Study is to assess if GEP is a reliable biomarker of immune system activity and has the ability to predict the complications of immunosuppression;
- Immunosuppression Complication Event (ICE) is defined as: new infection, new malignancy or infection requiring hospitalization.

Data:

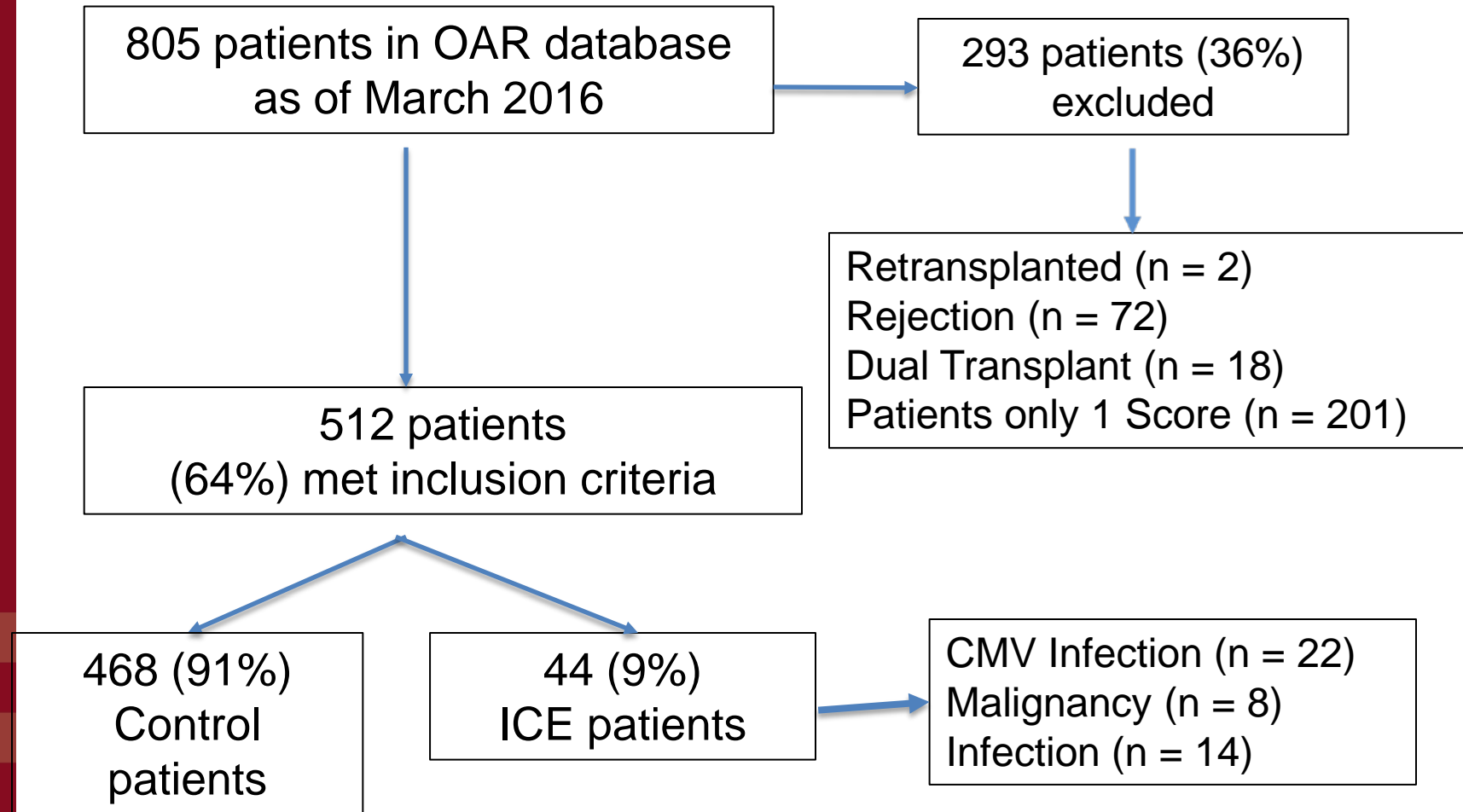
- Retrospective analysis from OAR database; 44 patients in ICE group and 468 in control group;
- Data controlled for age, race, cardiomyopathy type, BMI and PRA.

Results:

- Median time after transplant for an ICE varied: 299 days for CMV (IQR 265-349) and 647 days for new malignancy (IQR 428-866);
- GEP scores are lower before the event in patients who develop CMV infection;
- Differences in gene expression levels of the 11 genes in GEP are not significant *except* for ITGA4;
- The adverse effects of immunosuppression are seen in a significant portion of post-transplant recipients.

6. (cont.) Outcomes with Gene Expression Profiling for Cardiac Transplant Recipients within North America: Results

Patient Population



6. (cont.) Outcomes with Gene Expression Profiling for Cardiac Transplant Recipients within North America: Gene Expression Levels

Gene Name	ICE Group Med [IQR]	Control Group Med [IQR]	P-value
MARCH8	667 [526, 820]	646 [547, 831]	0.944
SEMA7A	34 [29, 39]	36 [30, 43]	0.209
IL1R2	20 [11, 41]	18 [12, 27]	0.556
RHOU	664 [584, 798]	630 [538, 746]	0.075
WDR40A	1285 [1003, 1516]	1131 [923, 1507]	0.351
FLT3	104 [74, 212]	122 [92, 169]	0.526
C6orf25	8060 [5693, 11080]	6625 [4487, 9337]	0.043
ITGA4	2693 [2332, 3024]	3084 [2678, 3557]	< 0.001
ITGAM	4830 [3974, 7132]	4595 [3809, 5360]	0.053
PDCD1	119 [72, 160]	113 [85, 155]	0.891
PF4	21589 [13896, 29913]	19331 [13727, 26174]	0.141

7. Monocyte Gene Expression before and after LVAD Implantation

N. Uriel¹, D.E. Rodgers¹, G. Sayer¹, N. Sarawat¹, G.H. Kim¹, V. Jeevanandam¹, J. Yee², S. Adatya¹

The 37th Annual ISHLT Meeting, Washington DC, April 2016

¹ Cardiology, University of Chicago, IL

² CareDx, Brisbane, CA

7. Monocyte Gene Expression before and after LVAD Implementation

Background:

- Patients supported with a left ventricular assist device (LVAD) are at high risk for both bleeding and thrombotic events;
- This study aims to report changes in the GEP of patients supported by LVADs before and after device implantation.

Data:

- Prospective study data from consecutive patients undergoing LVAD implantation
- Blood collected 1 week prior to LVAD and 1, 3 and 6 months post LVAD included GEP (AlloMap and gene subset) and Von Willebrand factor.

Results:

- No significant change in gene expression was found 1 month following LVAD implementation;
- Longer follow-up is needed to assess whether any changes occur with prolonged support post device.

7. (cont.) Monocyte Gene Expression before and after LVAD Implantation: Results

N = 21		Pre-LVAD	Post-LVAD (1 month)	P value
Age (mean)	54.2			
Male	72.7%			
GEP (total)		31.7	32.8	p = 0.63
PF4		24.9	25.2	p = 0.40
C6orf25		26.2	25.9	p = 0.84
WDR40		27.6	27.4	p = 0.75
MARCH8		28.6	28.5	p = 0.88
Von Willebrand			90% type 2A	

ISHLT 2016: Key Takeaways for CareDx

- OAR remains a unique and useful tool to review clinical issues across transplantation centers;
- The role of CMV and an increase of longitudinal GEP scores over time is of clinical interest;
- The role of dd-cfDNA testing in transplant patients may be complementary to GEP.

Please contact CareDx for additional information or copies of presentations: [info@caredx.com](mailto:info@ caredx.com) / 1 888 ALLOMAP.