Scripps Health/Scripps Clinic Biorepository and Bioinformatics Core Monthly Report

4/2025

Specimen Collection

Total Aliquots: **61,559 (in physical inventory)**
Aliquots added in April: **743**

Total Samples: **25,622 (in physical inventory)**
Samples added in April: **153**

Specimens (aliquots) Released for Research in April: **131**
Total Specimens Released for Research: **12,109**

New Contributing Sources: **0**
Total Contributing MD Sources/locations: **25**

Participants

BR Consented: **3,261**
New Consents in April: **18**
Non-Consented Contributors (inherited studies/remnant specimens): **11,667**

Remnant Samples

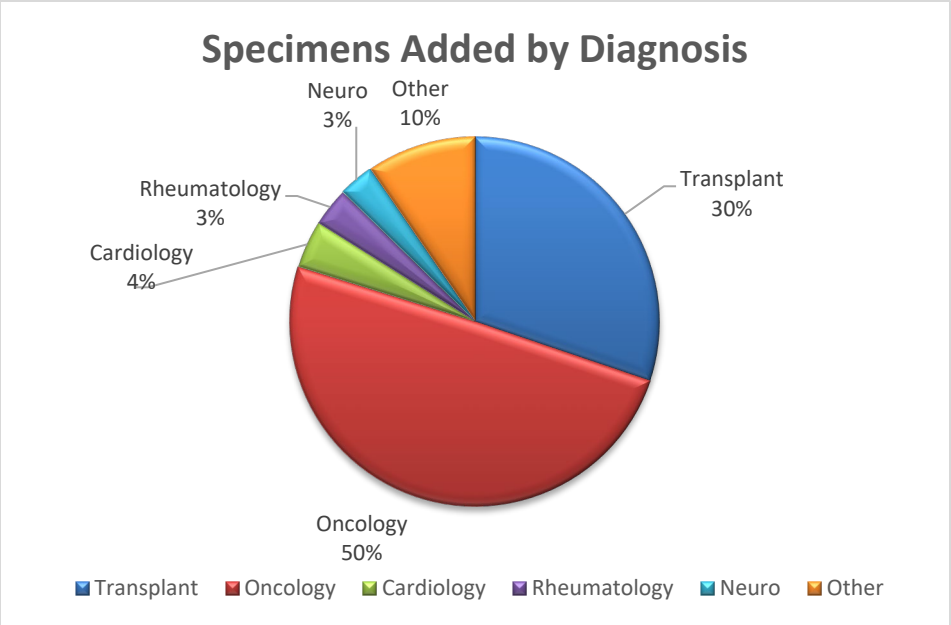
COVID-19: **2,065**
FLU A: **1,227**
FLU B: **22**
RSV: **19**
Normal: **463**
Others: **1,392**

Normal Samples

Apparently Healthy Donors (Consented): **167**
Participants added in April: **0**

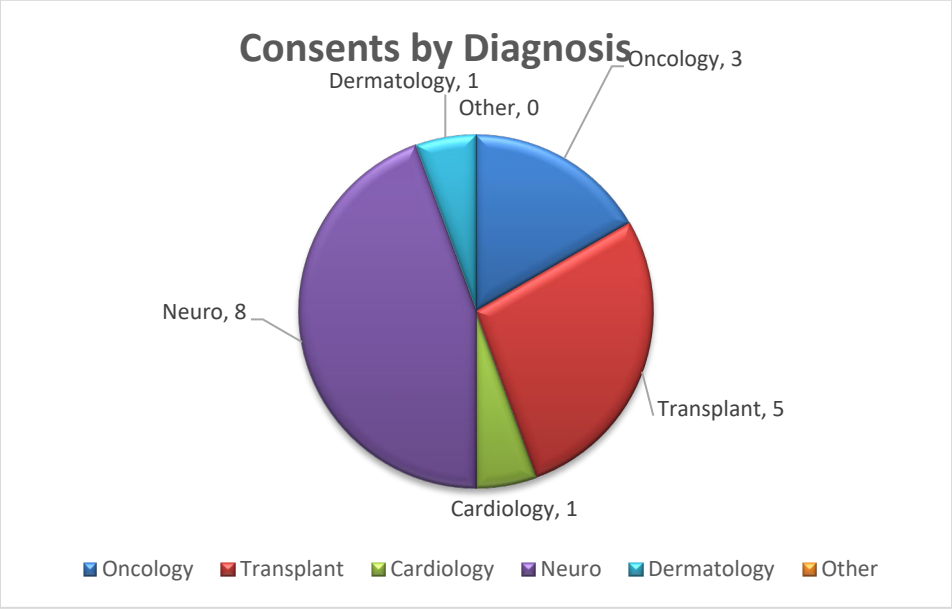
Primary Diagnosis Breakdown

Specimens added to Inventory
Transplant: **224**
Hematology/Oncology: **368**
Cardiology: **31**
Rheumatology: **25**
Neuro: **23**
Other: **71**



New Consents:
By Diagnosis

Oncology: **3**
Transplant: **5**
Cardiology: **1**
Neuro: **8**
Dermatology: **1**
Other: **0**



Bio-Specimen Requests

Pending Requests: 0
Requests Approved by the Oversight Committee in April: 1

Andre Basbaum (Resolute Science) Local biotech company based in San Diego. They are requesting sections from FFPE blocks from various cancer types to perform immunohistochemistry for evaluating the expression levels of targeted receptors in specific cancer types.

Recent Publications from SCBBC Staff & Investigators Utilizing the SCBBC (2023-2024 FY)

1. Bhagar R, Gill SS, Le-Niculescu H, Yin C, Roseberry K, Mullen J, Schmitz M, Paul E, Cooke J, Tracy C, Tracy Z, Gettelfinger AS, Battles D, Yard M, Sandusky G, Shekhar A, **Kurian SM**, Bogdan P, Niculescu AB. Next-generation precision medicine for suicidality prevention. Transl Psychiatry. 2024 Sep 6;14(1):362. doi: 10.1038/s41398-024-03071-y.
2. Stephanie Almeida, William Snyder, Mita Shah, **Jonathan Fisher**, **Christopher Marsh**, Alana Hawkes, Diana Gorial, Sean DeWolf, **Dianne B. McKay**. Revolutionizing Deceased Donor Transplantation: How New Approaches to Machine Perfusion Broadens the Horizon for Organ Donation. Transplantation Reports. 2024.100160. ISSN2451-9596.https://doi.org/10.1016/j.tpr.2024.10016.
3. DeWolf SE, Hawkes AA, **Kurian SM**, Gorial DE, Hepokoski ML, Almeida SS, Posner IR, McKay DB. Human pulmonary microvascular endothelial cells respond to DAMPs from injured renal tubular cells. Pulm Circ. 2024 Jul;14(3):e12379. doi: 10.1002/pul2.12379. eCollection 2024 Jul. PubMed PMID: 38962184; PubMed Central PMCID: PMC11220341.
4. **S. Kurian**, J. Fleming, B. Barrick**, A. Martin, C. M. Marsh.** Diagnostic Performance of Peripheral Blood Gene Expression At 2 Months Post-transplant And Interim Correlation of Tests with Renal Function Over 2 Years. Abstract accepted as late breaking poster at the American Transplant Congress, Philadelphia, USA: June 1 – 5 2024.
5. **S. Kurian, A. Martin, E. Burgess, C. Marsh**. Serial Metagenomic Profiling Reveals Temporal Shifts in Microbial Composition in Kidney and Liver Transplant Recipients. Abstract accepted a poster at the American Transplant Congress, Philadelphia, USA: June 1 – 5 2024.
6. Hill MD, Gill SS, Le-Niculescu H, MacKie O, Bhagar R, Roseberry K, Murray OK, Dainton HD, Wolf SK, Shekhar A, **Kurian SM**, Niculescu AB. Precision medicine for psychotic disorders: objective assessment, risk prediction, and pharmacogenomics. **Mol Psychiatry.** 2024 Feb 8. doi: 10.1038/s41380-024-02433-8. Epub ahead of print. PMID: 38326562.
7. New J, Cham J, Smith L, Puglisi L, Huynh T, **Kurian S**, Bagsic S, Fielding R, Hong L, Reddy P, Eum KS, **Martin A, Barrick B, Marsh C**, Quigley M, Nicholson LJ, Pandey AC. Effects of antineoplastic and immunomodulating agents on postvaccination SARS-CoV-2 breakthrough infections, antibody response, and serological cytokine profile. **J Immunother Cancer.** 2024 Jan 31;12(1): e008233. doi: 10.1136/jitc-2023-008233. PMID: 38296596; PMCID: PMC10831464.
8. Long JJ, Motter JD, Jackson KR, Chen J, Orandi BJ, Montgomery RA, Stegall MD, Jordan SC, Benedetti E, Dunn TB, Ratner LE, Kapur S, Pelletier RP, Roberts JP, Melcher ML, Singh P, Sudan DL, Posner MP, El-Amm JM, Shapiro R, Cooper M, Verbesey JE, Lipkowitz GS, Rees MA, **Marsh CL**, Sankari BR, Gerber DA, Wellen JR, Bozorgzadeh A, Gaber AO, Heher EC, Weng FL, Djamali A, Helderman JH, Concepcion BP, Brayman KL, Oberholzer J, Kozlowski T, Covarrubias K, Massie AB, McAdams-DeMarco MA, Segev DL, Garonzik-Wang JM. Characterizing the risk of human leukocyte antigen-incompatible living donor kidney transplantation in older recipients. **Am J Transplant.** 2023 Sep 23: S1600-6135(23)00698-6. doi: 10.1016/j.ajt.2023.09.010. Epub ahead of print. PMID: 37748554.
9. Long JJ, Nijhar K, Jenkins RT, Yassine A, Motter JD, Jackson KR, Jerman S, Besharati S, Anders RA, Dunn TB, **Marsh CL**,

Rayapati D, Lee DD, Barth RN, Woodside KJ, Philosophe B. Digital imaging software versus the "eyeball" method in quantifying steatosis in a liver biopsy. **Liver Transpl.** 2023 Mar 1;29(3):268-278. doi: 10.1097/LVT.0000000000000064. Epub 2023 Jan 19. PMID: 36651194.

10. Towards precision medicine for anxiety disorders: objective assessment, risk prediction, pharmacogenomics, and repurposed drugs. Roseberry K, Le-Niculescu H, Levey DF, Bhagar R, Soe K, Rogers J, Palkowitz S, Pina N, Anastasiadis WA, Gill SS, **Kurian SM**, Shekhar A, Niculescu AB. **Mol Psychiatry**. 2023 Mar 7. doi: 10.1038/s41380-023-01998-0.

Active/in Startup Studies currently supported by the Biorepository.

	Research Projects - Ongoing	Lead/BR Staff	Project Type	Mechanism	Funding	Study Description
1	Genzyme Proteomics Study	Kurian, Marsh	Study	Pilot Award	Scripps RIC	Proteomic profiling of post-transplant kidney patients to look at inflammatory responses
3	ARIMA Genomics cfDNA	Kurian, Marsh	Study	Pilot Award	SCMG	Profiling the promoter landscape of the genome in kidney transplant patients
4	LOMR Molecular Studies	Marsh, Deising, Kurian	Study	Pilot Award	Scripps RIC	Developing a clinical and molecular predictor of liver transplant outcomes
5	Metagenomic early post-transplant clinical outcomes in kidney transplant recipients	Kurian, Martin, Burgess	Study/Research Coordinator	Pilot Award	Scripps RIC	Looking at the responses in post-transplant microbiome profiles in the tissue urine and stool
6	KW Biomarker Project	Kurian, Marsh	Study	KW Award Subcontract	Kruger-Wyeth Settlement	Creating new molecular predictors of breast cancer using genomic and proteomic profiling
7	KW REFRESH Study	Kurian, Martin	Study	KW Award Subcontract	Kruger-Wyeth Settlement	Evaluate cognitive decline and dementia indicators in women
8	KW AM-WELL Project	Kurian, Martin	Study, Phlebotomy, Processing, Storage	KW Award Subcontract	Kruger-Wyeth Settlement	Creating care across the continuum of a patient's cancer journey by implementing a Breast Cancer Survivorship Program
9	ALTA TIPS	Deising, Martin	Research Coordinator	Academic Study	Univ of Michigan	Assess contemporary patterns of use of TIPS stents and associated patient related outcomes
10	Cardiac Amyloidosis Cohort	Mohan, BR Staff	Sample Collection	_	_	Cardiac Amyloid disease study of risk factors and molecular correlates
11	ClearNote (previously	Martin	Phlebotomy,	Sponsored	ClearNote	Liquid Biopsy colorectal

	Bluestar Genomics)		Processing, Storage	Study		cancer detection
12	aiGENE	Kurian, Martin, Burgess	Study,Research Coordinator	Sponsor	aiGene - Industry	Measure the effectiveness of any cancer therapy. The technology is based on cfDNA and ctDNA binding poperties.
13	DREAM BMT	Martin, Kurian	Study	Pilot Award	SCMG	Enhance the diagnosis, management, and overall care of patients undergoing allogenic hematopoietic stem cell transplant (alloHSCT) who are at risk of developing Graft-versus-Host Disease (GVHD).
14	Retro-ART	Martin, Kurian, Burgess	Study, Pathology Requests	Sponsor	Castle Biosciences, Inc. - Industry	To determine the efficacy of adjuvant radiation therapy (ART) in a population of subjects tested with the DecisionDx-SCC test
15	OCS Liver Perfusion Registry (OLP-II)	Martin, Kurian	Study, Research Coordinator	Sponsor	Transmedics - Industry	collect short and long-term post-transplant clinical outcomes data of donor livers preserved and assessed on OCS Liver system and to document performance of the OCS Liver device in the real-world setting
16	FETOLY Heart Study	Kurian	IRB Support	Sponsor	Diagnoly Inc	To evaluate the performance of Fetoly-Heart in automatically detecting and localizing standard fetal heart quality criteria.
17	PrRLS	Martin, Kurian	Phlebotomy, Processing, Storage		Dr. Karen Lei	

Notes:

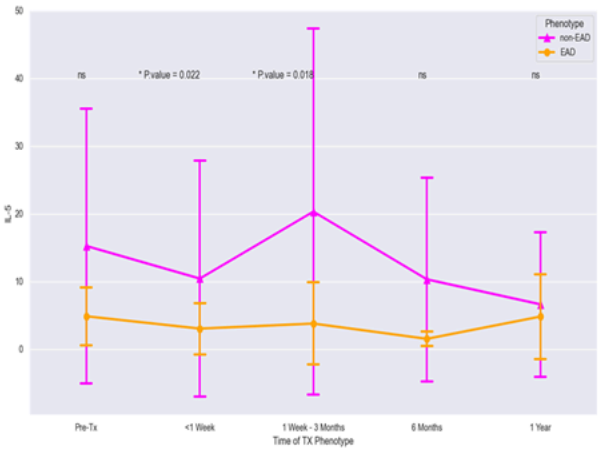
- Three of our presentations have been accepted for the upcoming annual transplant meeting. Two will be presented as posters, and one has been selected for an oral presentation by Dr. Marsh. The accepted abstracts are attached to this report.
- The updated biorepository charter has been shared with all committee members, and we are currently awaiting their feedback.
- We now have a clear process in place to request remnant tissue blocks from the pathology archives that would otherwise be discarded. Working closely with the pathology team, we've established a protocol to obtain and store these tissues at the biorepository. The first set of blocks will be accessioned and transferred to the biorepository by the end of the month. Our goal is to make this a recurring process to ensure that valuable tissue blocks are preserved and not discarded.

Control/Tracking Number: 25-A-2742-WTC
Activity: Abstracts
Current Date/Time: 2/19/2025 5:31:44 PM

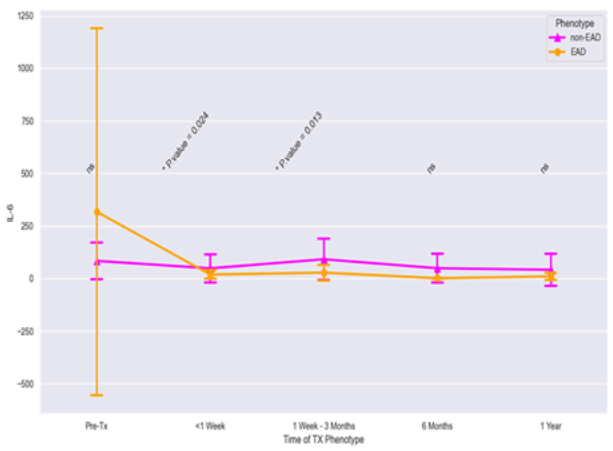
Machine Learning-Based Cytokine Profiling for Predicting Early Allograft Dysfunction in Transplant Patients

Author Block: S. Kurian[1], A. Chinni Krishnan[2], A. Martin[1], E. Burgess[1], Y. Subburaj[2], C. Marsh[1], *[1]Scripps Clinic, La Jolla, CA, [2]Agilisium Consulting, Thousand Oaks, CA*

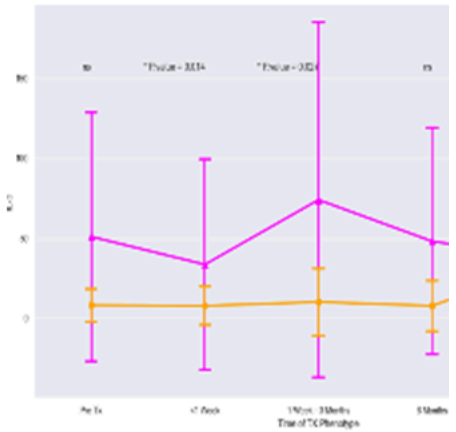
Abstract:
***Purpose:** Early allograft dysfunction (EAD) is a major complication after liver transplantation with an incidence rangingfrom 5-40%. Cytokine profiling may provide insights into its prediction and prevention. We aimed to build a classifier to identify cytokine profiles associated with EAD using machine learning techniques applied to cytokine data collected from 71 transplant patients over multiple timepoints (up to 1 year).
***Methods:** The dataset underwent data cleaning, including timepoint standardization and feature engineering. Thirty-eight cytokines in plasma from 71 liver transplant patients (EAD- 23 and Non-EAD -48) were measured using a Luminex assay at various time points up to a year post-transplant. A total of 381 total measurements were analyzed using univariate and correlation analysis. Three feature selection algorithms were applied to generate optimized feature sets. Naïve Bayes, Random Forest, eXtreme Gradient Boosting and K-Nearest Neighbors algorithms were trained and evaluated for predictive performance using standard Train-Test Split Methods.
***Results:** Significant cytokines associated with EAD included IL-5, IL-6, IL-9, IL-13, MCP-3, TNFb, and VEGF, with varying significance across timepoints. Highly correlated cytokines (e.g., IL-9 and IL-13) were identified. Feature selection highlighted IL-3, G-CSF, TNFβ, and VEGF as critical predictors. The Naïve Bayes classifier outperformed other models, achieving a Positive Predictive Value (PPV) of 0.36, a Negative Predictive Value (NPV) of 1.00, and a Precision Class Recall of 0.89, indicating strong predictive ability for the non-EAD group while highlighting challenges in accurately identifying EAD cases which is the minority class.
***Conclusions:** Machine learning approaches successfully identified key cytokine profiles associated with EAD, with Naïve Bayes performing best for predicting non-EAD cases. However, additional model optimization on a second cohort of 53 patients are being analyzed. Additional cohorts and the inclusion of clinical data may be needed to improve the final prediction accuracy for EAD. These findings highlight the potential of cytokine-based predictive learning modeling for transplant outcomes and warrant further validation in larger cohorts.



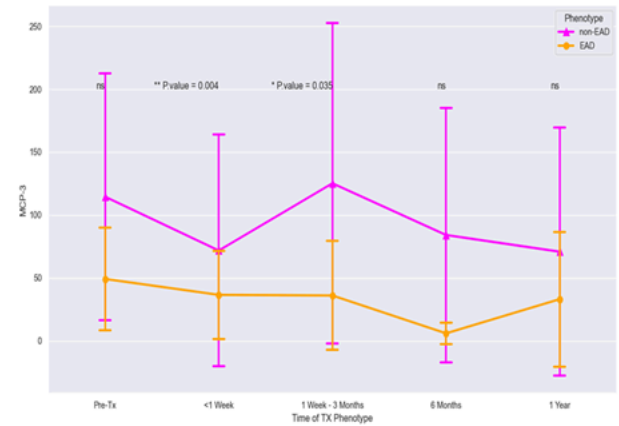
IL-5
<1 Week: P.Value - 0.022 *
1 Week – 3 Months: P.Value - 0.018 *



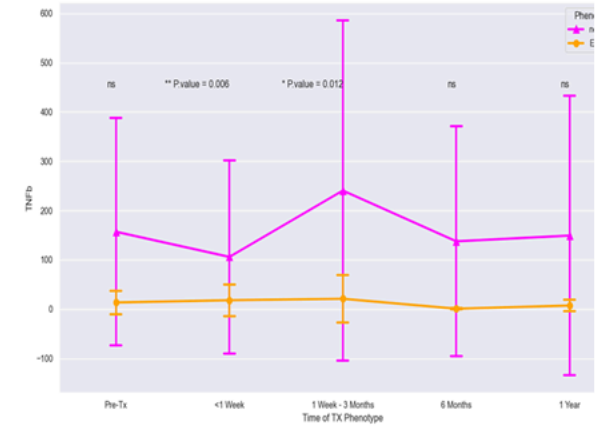
IL-6
<1 Week: P.Value - 0.024 *
1 Week – 3 Months: P.Value - 0.013 *



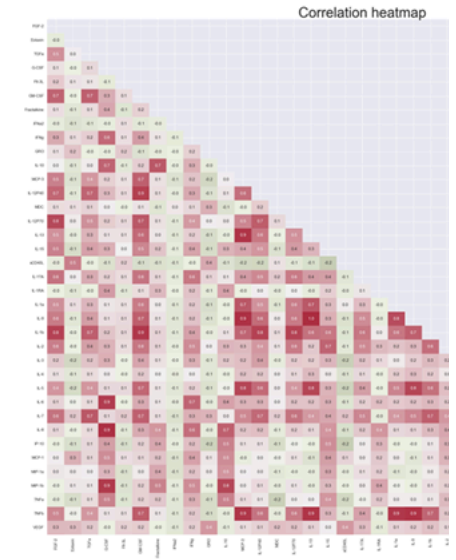
IL-9
<1 Week: P.Value - 0.014
1 Week – 3 Months: P.Value -



MCP-3
<1 Week: P.Value - 0.004 **
1 Week – 3 Months: P.Value - 0.035 *



TNFb
<1 Week: P.Value - 0.006 **
1 Week – 3 Months: P.Value - 0.012 *



Category (Complete): 73 - Liver: Large Data and Artificial Intelligence
Keyword (Complete): Liver transplantation ; Graft failure ; Diagnostics
Questionnaire (Complete):
Please indicate if you would like to considered for an award: No, do not consider for the award
Please indicate your presentation preference: Either Poster or Oral

Please state learning objective for your presentation: : To develop and evaluate machine learning-based cytokine profiling models for predicting early allograft dysfunction (EAD) in liver transplant patients, identifying key biomarkers and improving predictive accuracy.

Please indicate your slide release authorization: I give permission to AST/ASTS/TTC/WTC to use one or more of my actual oral presentation slides and/or audio for educational purposes following the WTC.

Does your study abide by the principles listed above?: Yes, my study abides by the principles listed above

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If this information has been previously presented, please indicate the venue and date: : Preliminary results were in a poster frpm AASLD 2022

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Activity: Abstracts
Current Date/Time: 2/10/2025 4:06:47 PM

Association of Gene Expression Profile with 10-year All Cause Graft Loss in a Multicenter Prospective Cohort

Author Block: C. Marsh[1], S. Kurian[2], J. Fleming[3], L. Zhao[4], C. Rebello[4], J. Friedewald[4], *[1]Scripps Clinic, La Jolla, CA, [2]Scripps, La Jolla, CA, [3]Eurofins Transplant Genomics, SC, [4]Northwestern University, IL*

Abstract:
***Purpose:** KTx is the treatment of choice for ESKD, but long-term outcomes remain suboptimal. A previous multicenter analysis identified multiple positive GEP tests as associated with graft loss up to 4 years post-transplant, but the sample size was too small for adjustment of confounding variables.
***Methods:** The CTOT-08 was a multicenter, 24-month observational study that was designed to develop noninvasive biomarkers predictive of subclinical rejection and 2-year allograft outcomes. Subjects were then matched with the SRTR database to collect 10-year graft and patient survival. The aim of this analysis is to evaluate the relationship between TruGraf GEP results over time and 10-year all-cause graft loss (ACGL)). A Kaplan Meier Curve evaluated event-free survival between amongst the population based on the number of positive TruGraf GEP over the 24-month prospective follow-up (Quartile 1: 0 positive tests, Quartile 2: 1-2 positive tests, Quartile 3: 2-4 positive tests, Quartile 4: 5 or more positive tests). A Cox Regression time-to-event analysis was planned using baseline covariates (Black race, diabetes as cause of ESKD, living donor, recipient age, donor age) as well as clinical acute rejection events and positive GEP as time-varying covariates. Stepwise selection was used to determine the final model.
***Results:** Anonymized data with 10-year graft outcomes and dd-cfDNA results was available for 285 of the original 307 subjects in CTOT-08. Subjects had an average of 10 visits during the 24 months of CTOT follow-up, corresponding to an average of 10 GEP results per subject. The Kaplan Meier curve demonstrates a significant difference in 10-year ACGL between quartiles ($p<0.0001$) (Figure 1). The final Cox Regression model after stepwise selection can be seen in Table 1. The final model included diabetes, GEP, and clinical acute rejection as independently associated with ACGL, while living donor was protective.
***Conclusions:** In the longest prospectively collected multicenter analysis of the association of GEP as a repeated measure with patient and allograft outcomes, GEP was independently associated with a 2-fold greater hazard of ACGL over the 10-year follow-up. This association was found after correcting for well-established risk factors for graft loss, including the impact of clinical acute rejection.

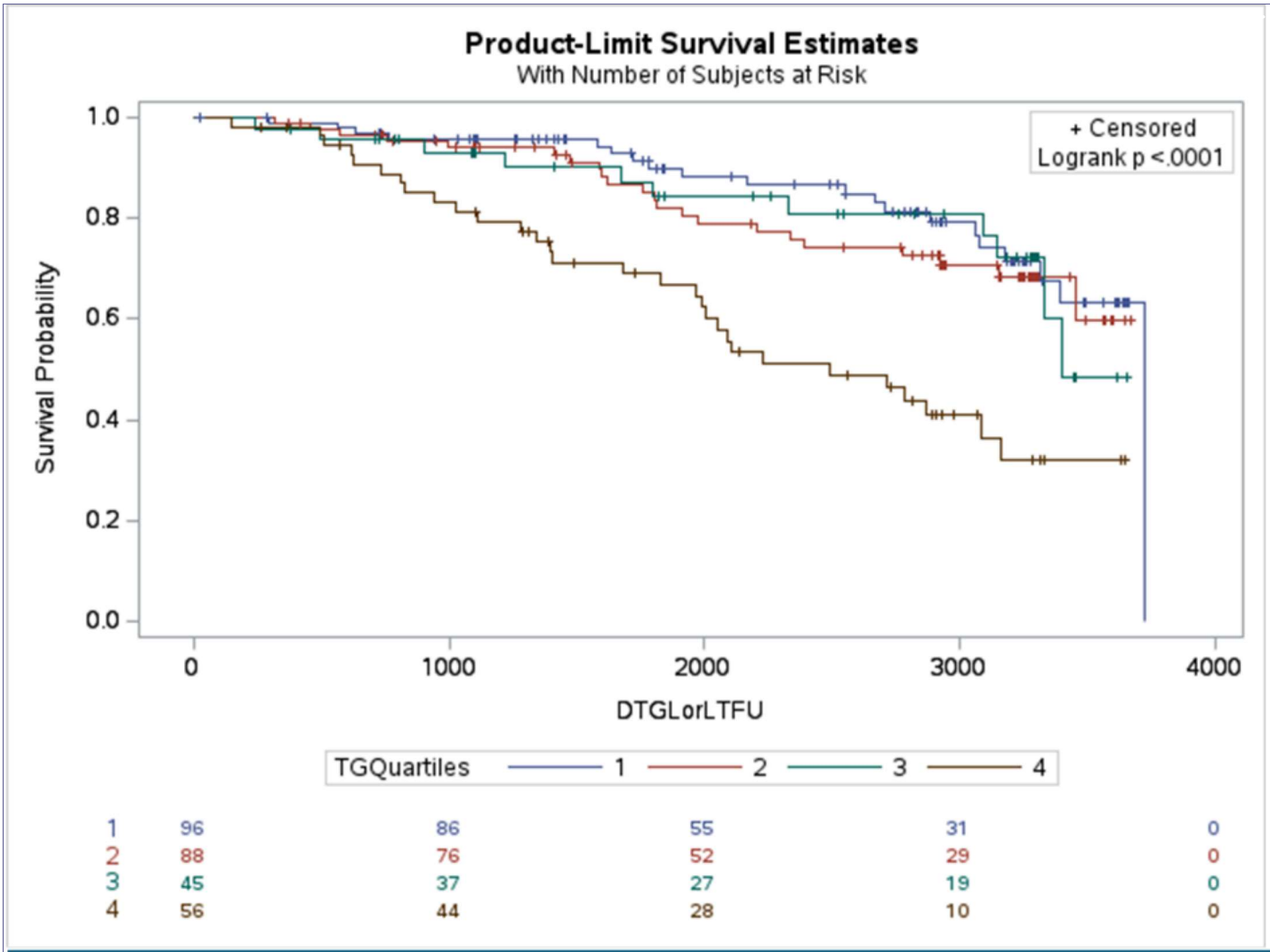

Table 1. Cox Regression Model

Variable	Hazard Ratio	95% Confidence Interval	P-value
Living Donor	0.52	0.32, 0.84	<0.01
Diabetes	1.68	1.03, 2.73	0.04
Gene Expression Profile	1.98	1.24, 3.17	<0.01
Clinical Acute Rejection	2.79	1.08, 7.21	0.03

Category (Complete): 60 - Kidney: Biomarkers
Keyword (Complete): Gene expression ; Graft failure
Questionnaire (Complete):
Please indicate if you would like to considered for an award: No, do not consider for the award
Member Type: N/A
Please indicate your presentation preference: Either Poster or Oral
Please state learning objective for your presentation: : Positive gene expression profile tests are indepentdently associated with all cause graft loss at 10 years of follow-up
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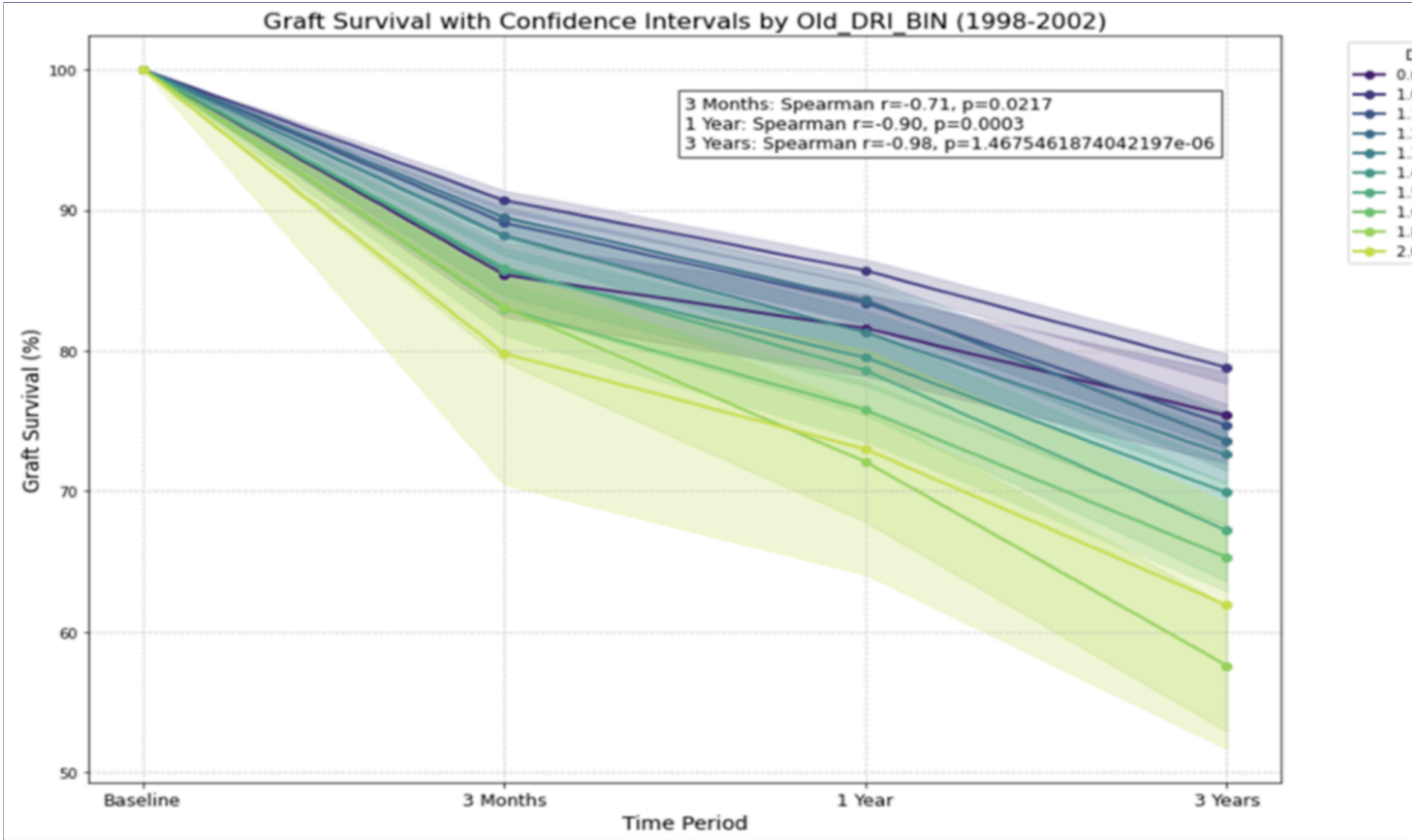
Control/Tracking Number: 25-A-2759-WTC
Activity: Abstracts
Current Date/Time: 2/19/2025 5:33:11 PM

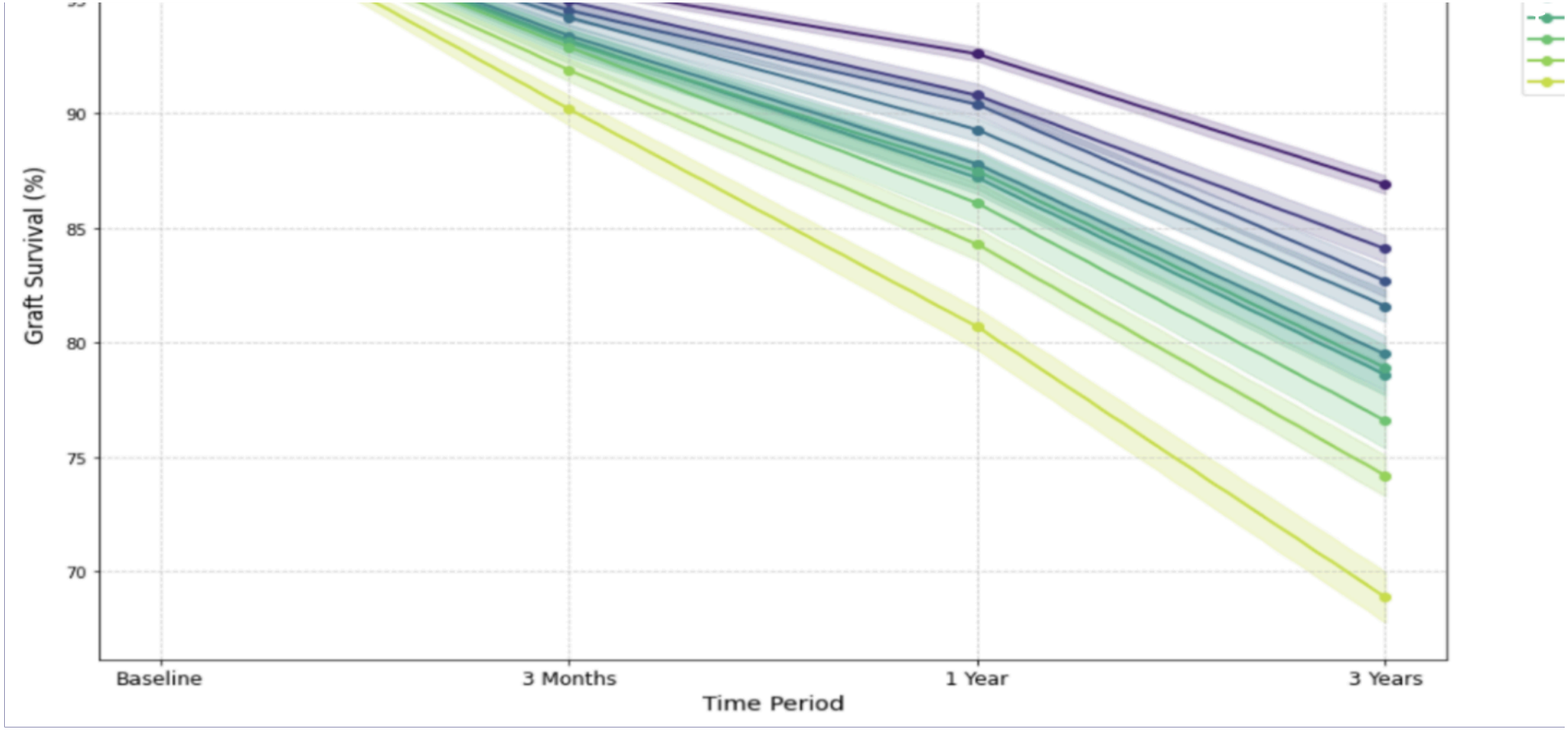
Development and Evaluation of a New Liver Donor Risk Index

Author Block: S. Kurian[1], D. Janarthanan[2], A. Chinni Krishnan[2], P. Balasubramanian[2], Y. Subburaj[2], C. Marsh[1], *[1]Scripps Clinic, La Jolla, CA, [2]Agilisium Consulting, Thousand Oaks, CA*

Abstract:
***Purpose:** The Liver Donor Risk Index (LDRI) from 2006, is outdated, as it does not account for modern donor and recipient characteristics and other critical transplant factors. It also lacks key predictors like liver steatosis, fibrosis, and machine perfusion advances, which impact graft survival. Also, improvements in immunosuppression, and hepatitis C treatments have altered survival outcomes, rendering the original LDRI obsolete. While newer models (D-MELD, BAR Score, Donor Risk Score) exist, further refinement is needed.
***Methods:** The original LDRI was recreated from OPTN data (1998-2002) with the same equation. The new LDRI analyzed cross-sectional data from the United Network for Organ Sharing (2002-2023), including 90.3% adult recipients, 29.2% racial and ethnic minorities, and 34.1% female recipients. Kaplan-Meier survival analysis assessed graft survival at 3 months and 1 and 3 years, and Spearman correlation evaluated the association between DRI scores and survival outcomes. Log-rank tests determined statistical significance between risk groups, and χ^2 values and p-values were compared to assess model performance.
***Results:** The new LDRI data from 126,572 adults, showed African American race (aHR = 1.15, 95%CI: 1.11, 1.18), males (aHR = 1.12, 95%CI: 1.09, 1.14), older adult patients (aHR = 1.68, 95% CI: 1.58, 1.78), patients with Type I or II diabetes (aHR = 1.50, 95%CI: 1.41, 1.60 and aHR = 1.23, 95%CI: 1.20, 1.26 respectively), had a higher graft loss. Differences in graft survival between higher and lower index grafts were observed at three months and became more pronounced with time. Comparison between the old and new models demonstrated that the new LDRI showed stronger correlations with post-transplant outcomes, with improved predictive accuracy at 3 months, 1 and 3 years compared to the original model.
***Conclusions:** The updated LDRI model provides a more accurate, clinically relevant assessment of graft survival risk by incorporating a larger, more diverse dataset that reflects recent transplant outcomes and improves donor risk stratification. These findings support the need for ongoing model refinement to enhance predictive performance and optimize liver allocation. We are now developing predictive models using machine learning, including ensemble and Bayesian approaches, to further improve accuracy. Additional validation will be conducted using a dataset of over 2,000 patients from Region 5 of UNOS, collected under the Liver Outcomes Monitoring Registry, which comprehensively captures both donor and recipient characteristics.


Graft Survival with Confidence Intervals by Old_DRI_BIN (1998-2002)
3 Months: Spearman r=-0.71, p=0.0217
1 Year: Spearman r=-0.90, p=0.0003
3 Years: Spearman r=-0.98, p=1.4675461874042197e-06
Graft Survival (%)
100
90
80
70
60
50
Baseline
3 Months
1 Year
3 Years
Time Period


Graft Survival with Confidence Intervals by New_DRI_BIN (2002-2023)
3 Months: Spearman r=-1.00, p=6.646897422032013e-64
1 Year: Spearman r=-0.99, p=9.307459988955517e-08
3 Years: Spearman r=-0.99, p=9.307459988955517e-08
100



Category (Complete): 70 - Liver: Expanding the Donor Pool (Liver: MELD Allocation / Donor Issues)
Keyword (Complete): Liver ; Prediction Models
Questionnaire (Complete):
Please indicate if you would like to considered for an award: No, do not consider for the award
Please indicate your presentation preference: Either Poster or Oral
Please state learning objective for your presentation: : To refine and validate an updated Liver Donor Risk Index (LDRI) using modern transplant data and machine learning techniques to improve graft survival prediction and donor risk stratification.
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