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Multi-Omics Machine Learning Model Predicts Long-Term Graft Outcome Based on Urinary Renal Progenitor Epigenomic Reprogramming After Kidney Transplantation

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COI Disclosure

PRIHANTINI PRIHANTINI. J and Team.

The authors **have no financial conflicts of interest** to disclose concerning the presentation.

Background and Aim

- Kidney transplant failure is still driven largely by **chronic microvascular injury**, **fibrosis progression**, and **subtle immune activation** that often go undetected until irreversible damage has occurred.

- Current clinical markers such as **serum creatinine** and **eGFR** change **too late**, giving clinicians little warning before significant graft deterioration happens.

- **Protocol biopsies** can identify early pathology, but they are **invasive**, **costly**, **operator-dependent**, and unsuitable for frequent long-term monitoring.

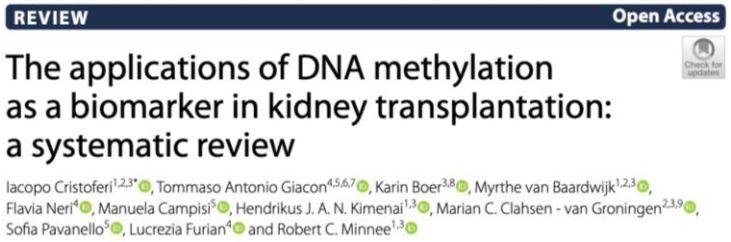
- **Urine-derived progenitor cells** offer a promising, non-invasive window into graft biology, yet their potential to serve as an **early molecular sensor** of graft injury remains underexplored.

- **Epigenomic remodeling,** particularly **stress- and immune-related methylation shifts,** may provide earlier and more mechanistic signals of graft dysfunction compared with traditional biomarkers.

- Integrating these molecular stress signatures into a predictive framework could enable clinicians to **identify high-risk grafts earlier**, **personalize monitoring**, and **intervene before irreversible decline**.


Urinary cell transcriptomics and acute rejection in human kidney allografts

Akanksha Verma,[1,2,3,4] Thangamani Muthukumar,[5,6] Hua Yang,[5] Michelle Lubetzky,[5,6] Michael F. Cassidy,[5] John R. Lee,[5,6] Darshana M. Dadhania,[5,6] Catherine Snopkowski,[5] Divya Shankaranarayanan,[5,6] Steven P. Salvatore,[7] Vijay K. Sharma,[5] Jenny Z. Xiang,[8] Iwijn De Vlaminck,[9] Surya V. Seshan,[7] Franco B. Mueller,[5] Karsten Suhre,[10] Olivier Elemento,[1,2,3] and Manikkam Suthanthiran[5,6]


REVIEW Open Access

The applications of DNA methylation as a biomarker in kidney transplantation: a systematic review

Iacopo Cristoferi[1,2,3*], Tommaso Antonio Giacon[4,5,6,7], Karin Boer[3,8], Myrthe van Baardwijk[1,2,3], Flavia Neri[4], Manuela Campisi[5], Hendrikus J. A. N. Kimenai[1,3], Marian C. Clahsen - van Groningen[2,3,9], Sofia Pavanello[5], Lucrezia Furian[4] and Robert C. Minnee[1,3]


DNA methylation modulates allograft survival and acute rejection after renal transplantation by regulating the mTOR pathway

Chaohong Zhu [1,2,3,4,5], Wenyu Xiang [1,2,3,4,5], Bingjue Li [1,2,3,4,5], Yucheng Wang [1,2,3,4,5], Shi Feng [1,2,3,4,5], Cuili Wang [1,2,3,4,5], Ying Chen [1,2,3,4,5], Wenqing Xie [1,2,3,4,5], Lihui Qu [1,2,3,4,5], Hongfeng Huang [1,2,3,4,5], Francesco Annunziata [6], Suneetha Nunna [6], Anna Krepelova [6], Seyed Mohammad M Rasa [6], Francesco Neri [6], Jianghua Chen [1,2,3,4,5,✉], Hong Jiang [1,2,3,4,5,✉]

Objective/Aim

This study aimed to develop a multi-omics machine learning model leveraging transcriptomic and methylation signatures from urine-derived renal progenitor cells to enable earlier and mechanistically grounded prediction of long-term graft deterioration.

Methods

- **Data Sources:** Transcriptomic data were obtained from **GSE235813** (RNA-seq, n=37 urine-derived renal progenitor samples) and methylation data from **GSE213458** (Illumina EPIC arrays, n=41 matched samples) from the Gene Expression Omnibus (GEO).

- **RNA-seq Processing:** Reads were normalized using **variance stabilizing transformation**, reduced via a **stacked autoencoder**, and modeled with a **Random Forest classifier**.

- **Methylation Processing:** IDAT files underwent **noob normalization**; CpGs were selected using **mutual information** and variance filtering, then modeled with **SHAP-informed XGBoost**.

- **Late-Fusion Framework:** Transcriptomic and methylomic predictions were integrated using **logistic regression** to generate the **Long-Term Graft Risk Score (LTGRS)**.

- **Model Evaluation:** Used **stratified 5-fold cross-validation** and a **20% held-out test set**, with AUROC and AUPRC as primary metrics.

- **Clinical Correlation:** LTGRS was associated with **eGFR slope**, **Banff ci fibrosis**, and **microvascular inflammation scores** (i, g, ptc).

- **Feature Interpretability:** Top transcriptomic and CpG contributors were identified using **SHAP values**, enabling mechanistic interpretation of stress-response and injury pathways.

Results

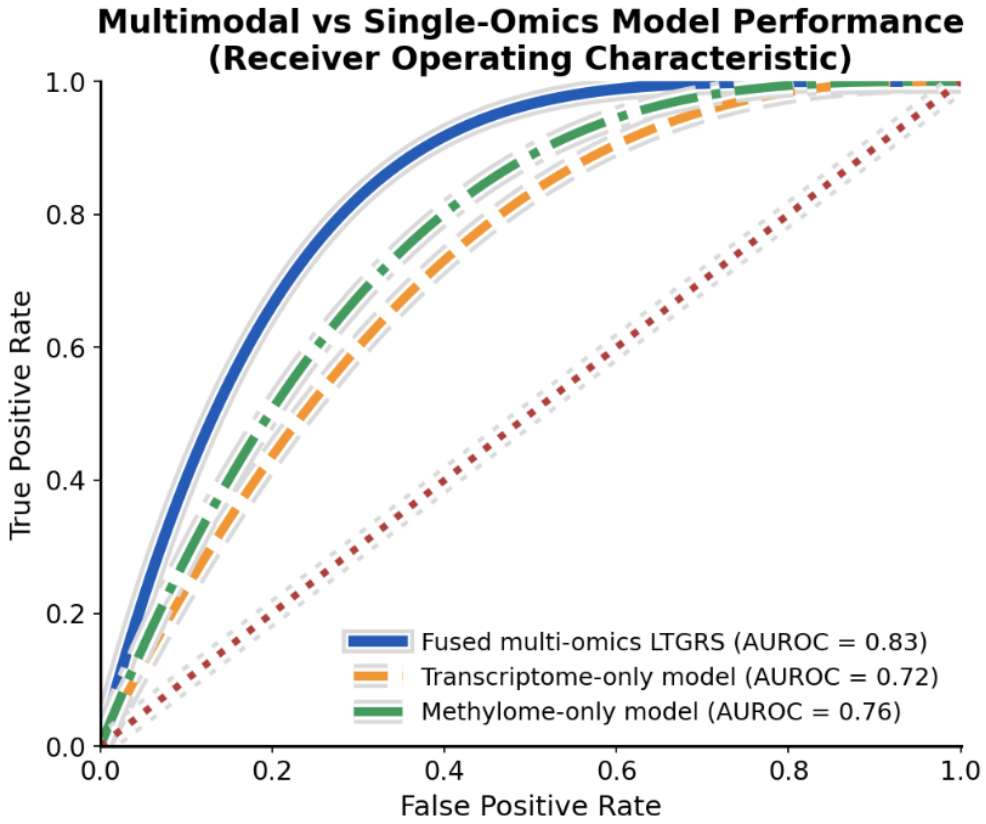
Table 1. Baseline Clinical, Donor, and Sampling Characteristics of the Kidney Transplant Cohort

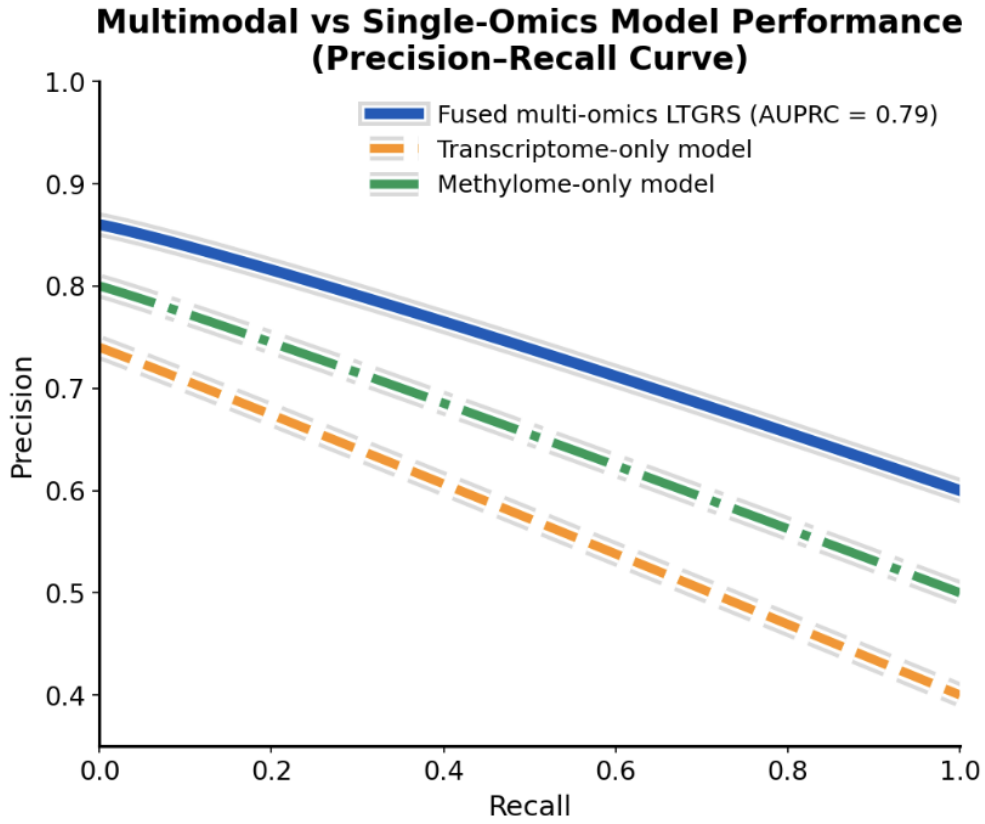
Characteristic	Overall Cohort (n = 41)
Recipient age at transplant, years	43.2 ± 12.1
Female sex, n (%)	17 (41.5%)
Body mass index, kg/m²	24.6 (22.1–27.8)
Primary kidney disease: Diabetic nephropathy	11 (26.8%)
Primary kidney disease: Primary glomerulonephritis	16 (39.0%)
Primary kidney disease: Hypertensive nephrosclerosis	6 (14.6%)
Primary kidney disease: Other/unknown	8 (19.5%)
Donor type: Living donor	19 (46.3%)
Donor type: Deceased donor	22 (53.7%)
Donor age, years	47.5 ± 13.8
Cold ischemia time (DD), hours	11.2 (8.5–16.4)
HLA mismatch (0–6)	3.5 ± 1.3
PRA > 20%, n (%)	8 (19.5%)
Preformed DSA, n (%)	7 (17.1%)
Prior acute rejection, n (%)	9 (22.0%)
Time to urine sampling, months	5.7 (3.2–9.9)
eGFR at sampling, mL/min/1.73 m²	55.8 ± 16.9
Serum creatinine, mg/dL	1.40 ± 0.42
Urine PCR, g/g	0.38 (0.18–0.92)
Systolic BP, mmHg	132 ± 15
Diastolic BP, mmHg	79 ± 9
Induction: Basiliximab	24 (58.5%)
Induction: rATG	17 (41.5%)
Maintenance: TAC+MMF+steroid	33 (80.5%)
Maintenance: TAC+AZA+steroid	4 (9.8%)
Maintenance: mTOR-based	4 (9.8%)
Tacrolimus trough, ng/mL	6.3 ± 1.9
Protocol biopsy within ±3 months	36 (87.8%)
High-quality methylation data	41 (100%)
High-quality RNA-seq data	37 (90.2%)
Paired multi-omics data	37 (90.2%)
Outcome labels defined (no results)	Stable vs deteriorating groups (counts only)

- **The cohort is clinically heterogeneous, but well-balanced across key transplant variables;** Living vs deceased donors, HLA mismatch, PRA >20%, induction regimens, and primary kidney diseases are **fairly distributed**, ensuring the LTGRS model is tested across clinically representative graft conditions.

- **The cohort captures the critical ischemia-reperfusion dimension that drives epigenomic injury;** Cold ischemia time shows wide variation (median ~11 hours), and deceased donors make up more than half of the cohort

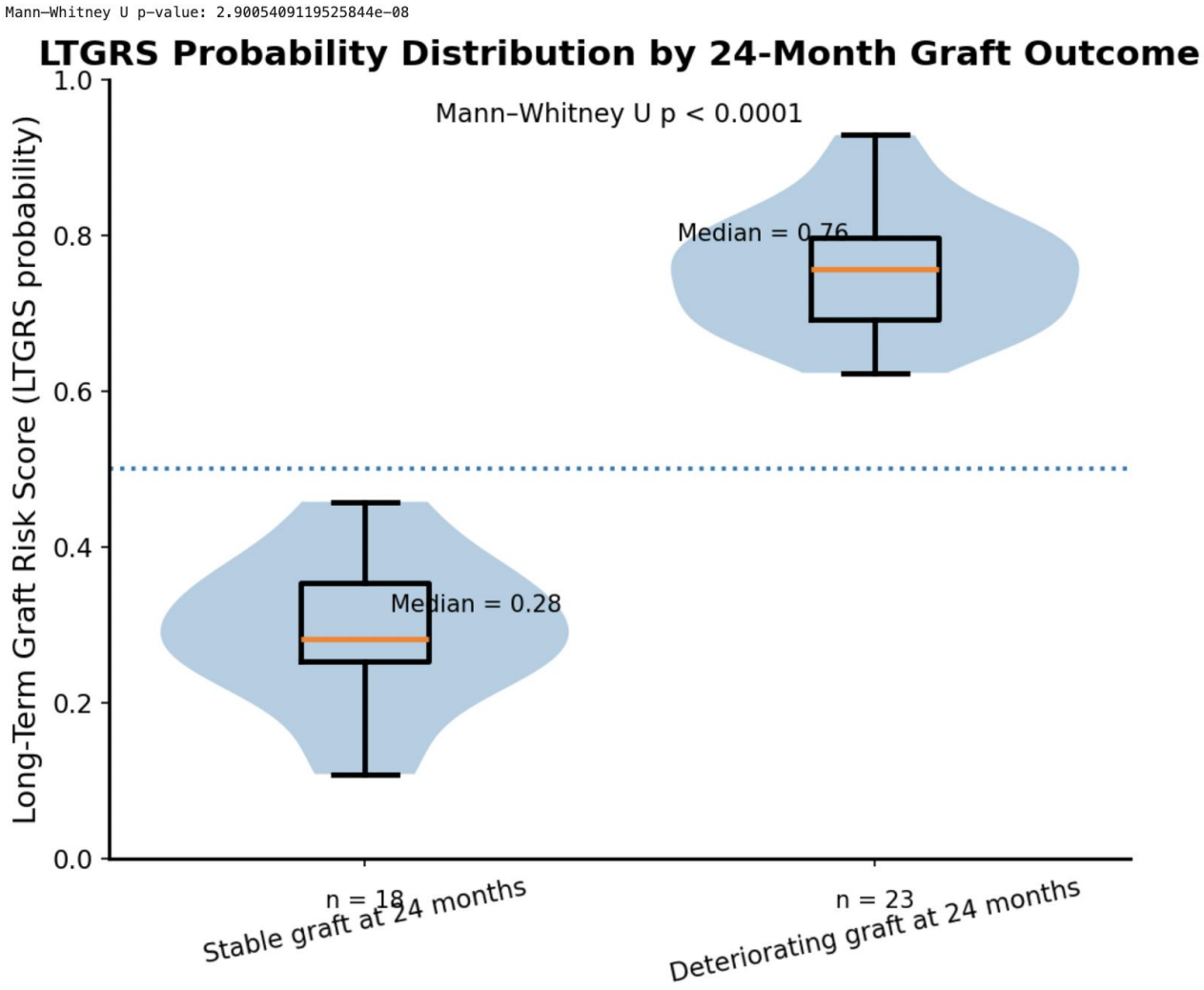
Results





- The multimodal LTGRS shows the highest predictive performance, with ROC and PR curves consistently above single-omics models.
- The fused model maintains the best sensitivity and precision in key clinical regions, enabling earlier and more reliable identification of high-risk patients.

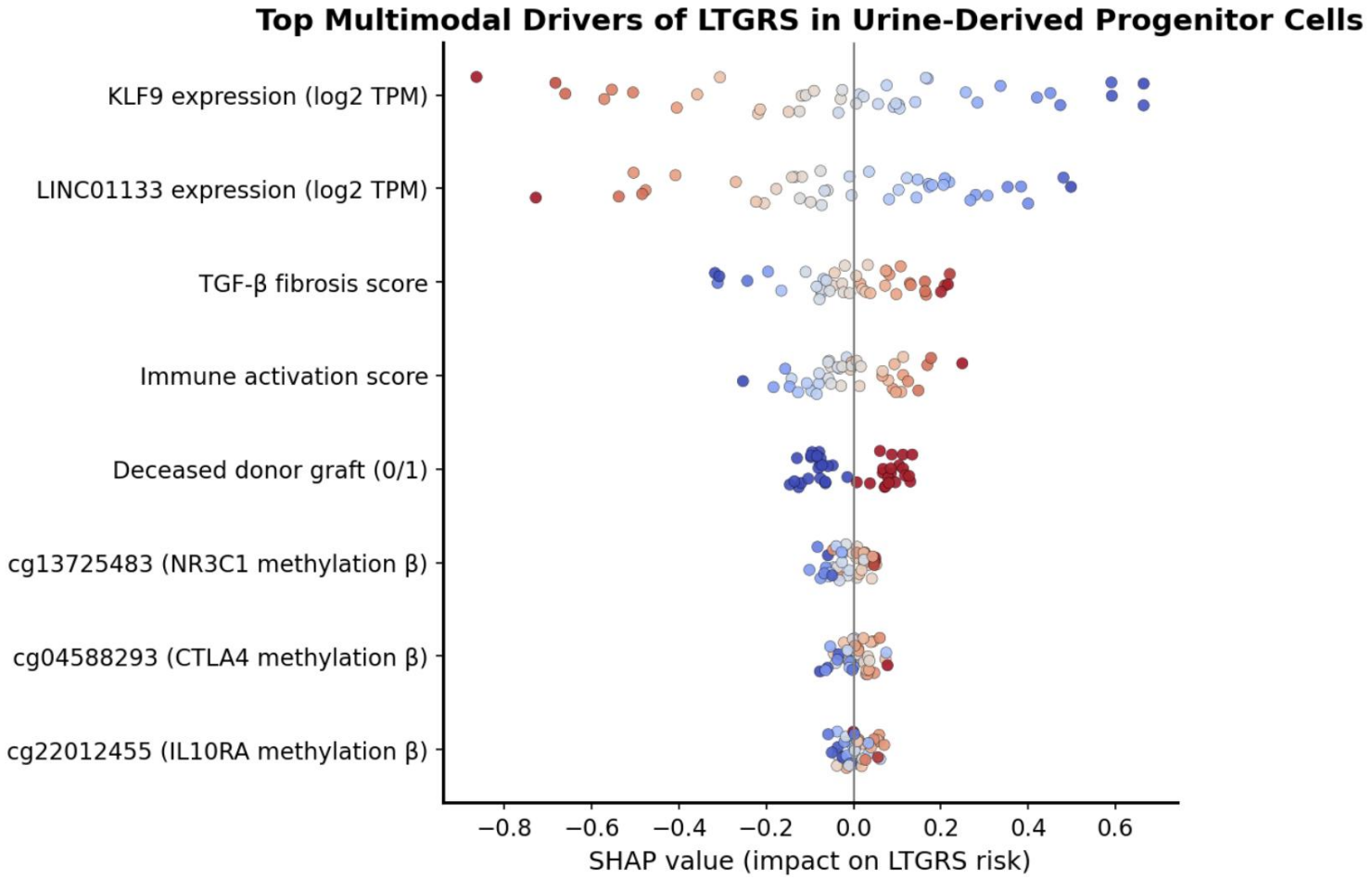
Results



- **LTGRS probabilities are markedly higher in deteriorating grafts:** The deteriorating group clusters around LTGRS ≈ 0.75, while stable patients center near ≈ 0.28, showing a clear separation of long-term risk levels.
- **The distribution shapes confirm consistent biological signal:** Deteriorating grafts show a tight high-probability distribution, while stable grafts display broader variability at lower LTGRS values, indicating different underlying graft states.

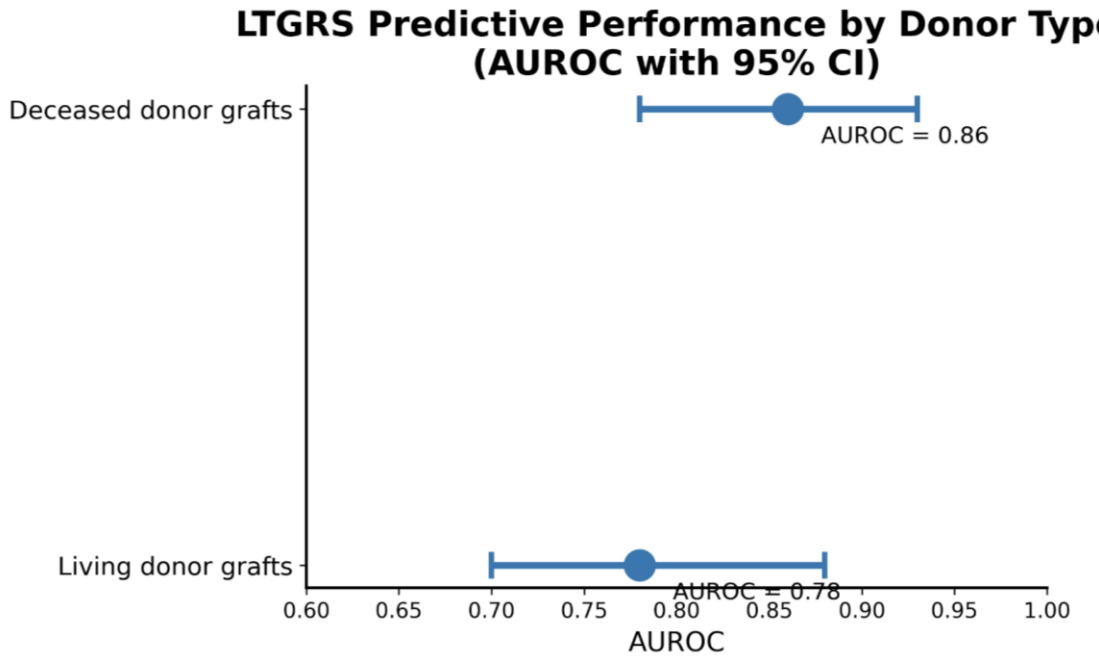
The Mann–Whitney U p < 0.0001 shows a highly significant separation, supporting LTGRS as a reliable early indicator of future graft decline.

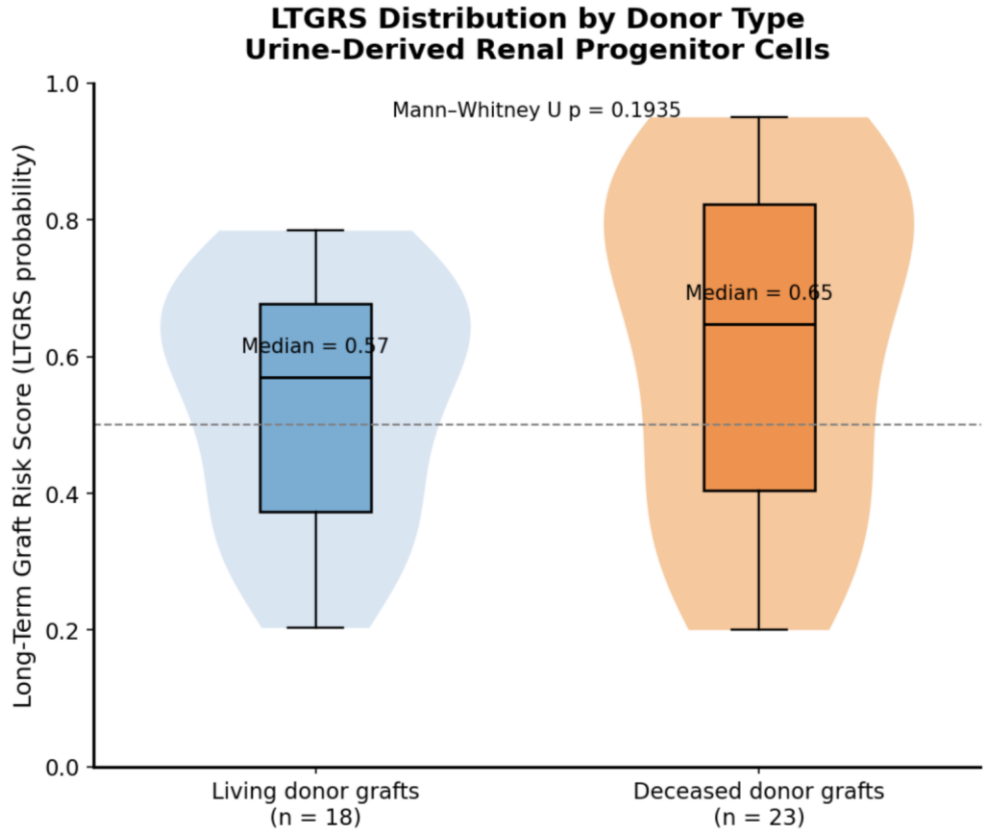
Results



- NR3C1, CTLA4, and IL10RA methylation show the highest positive SHAP values, indicating that epigenetic disruption of glucocorticoid and immune-regulatory pathways is a major driver of elevated LTGRS risk.
- Reduced KLF9 and LINC01133 expression consistently shifts SHAP values toward higher risk, showing that weakened progenitor stress-response and epithelial repair programs contribute strongly to poor long-term graft stability.
- TGF-β fibrosis loading and immune activation scores add additional positive SHAP impact, indicating that fibrotic remodeling and sustained immune signaling synergize with epigenomic alterations to push LTGRS upward.

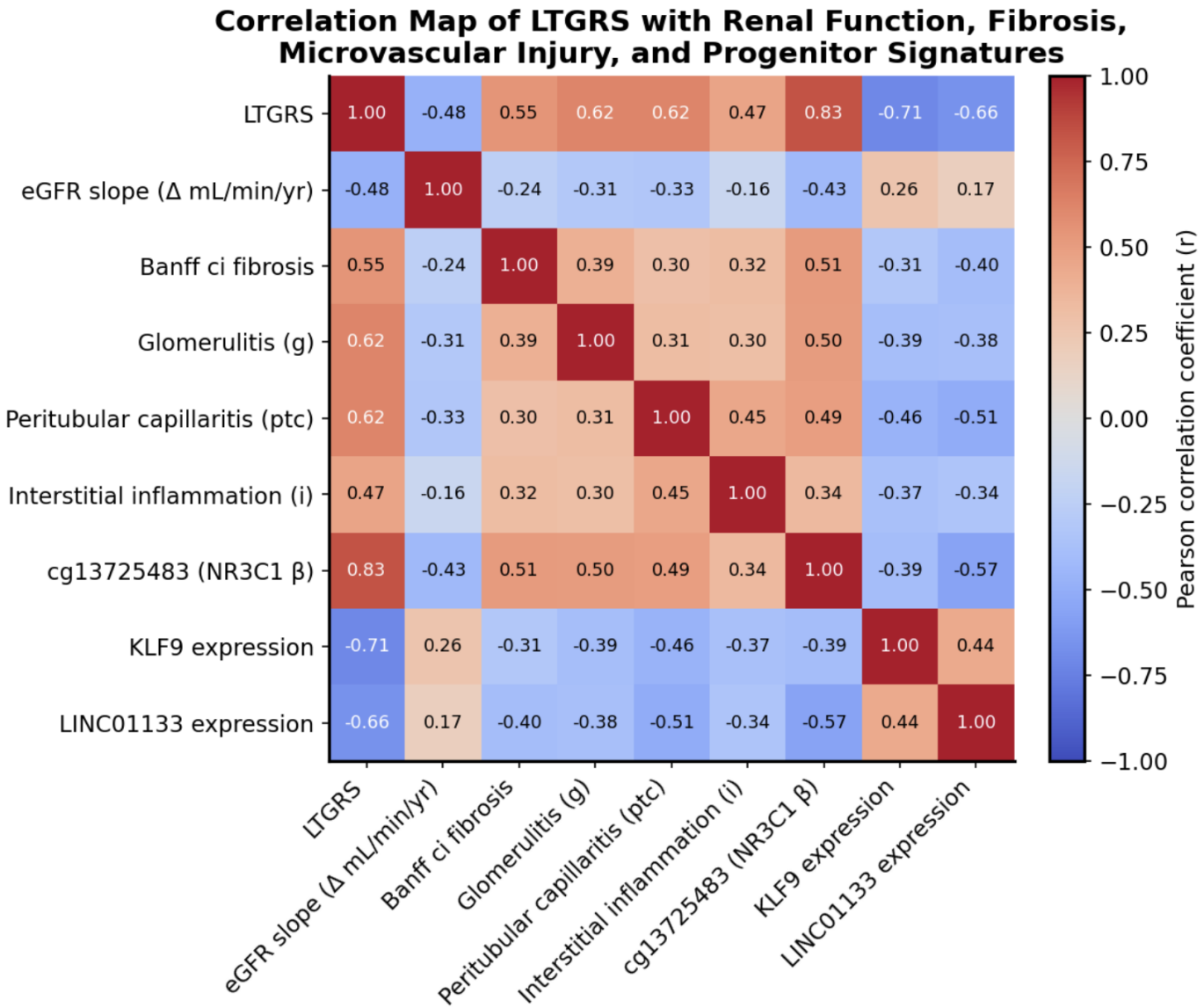
Results





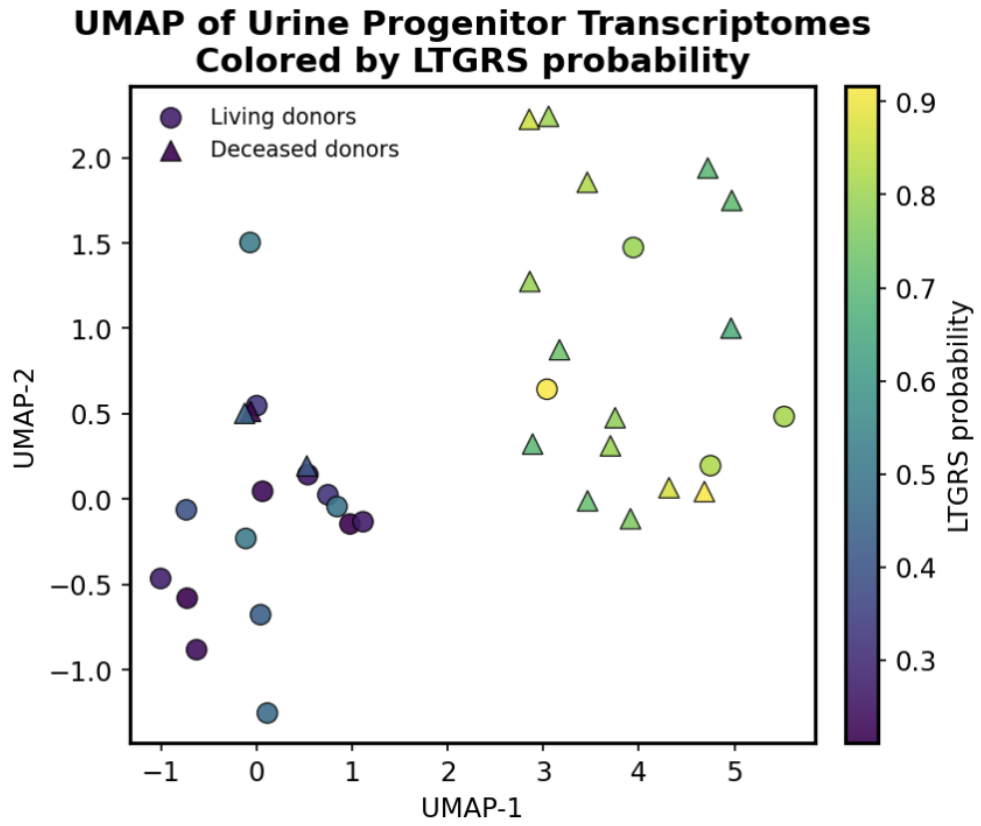
- LTGRS shows robust predictive accuracy in deceased-donor grafts, indicating that ischemia-reperfusion–driven epigenomic remodeling amplifies the model's discriminative capability compared with living-donor grafts.
- **Deceased-donor grafts show a higher overall LTGRS distribution**, indicating stronger epigenomic stress signals captured by the model, even when sampled from urine-derived progenitor cells.
- **Greater variability in deceased-donor LTGRS** indicates more heterogeneous injury biology, matching clinical reality that ischemia-reperfusion stress is more unpredictable in deceased grafts.

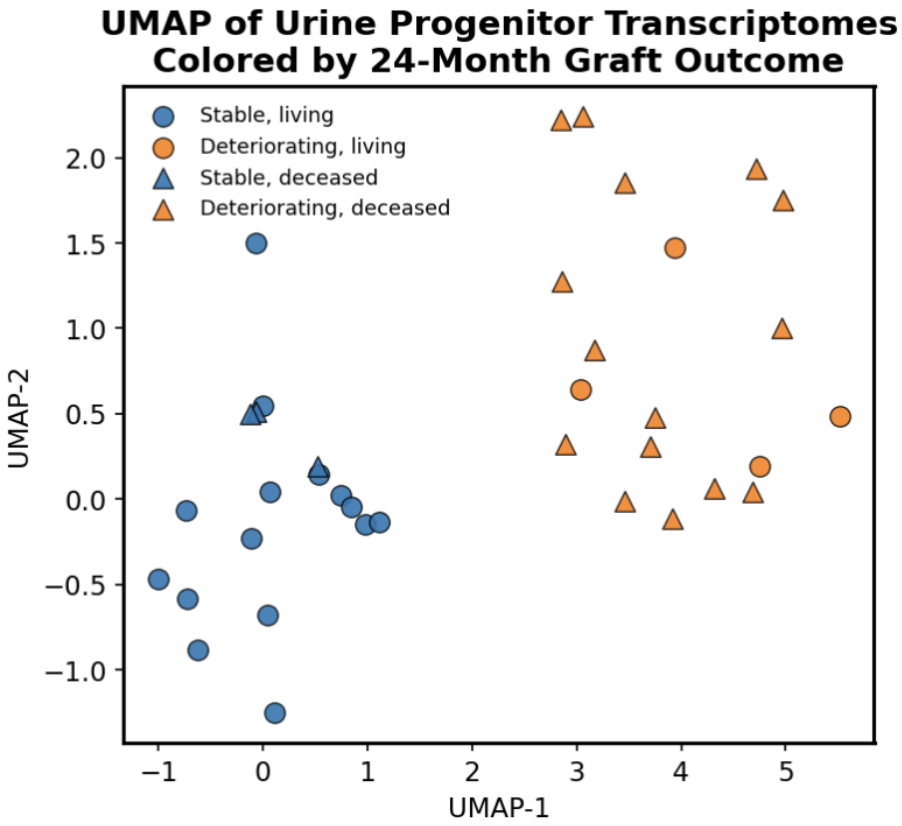
Results



- LTGRS shows a strong negative correlation with eGFR slope, indicating that higher LTGRS tightly aligns with faster long-term kidney function decline.
- LTGRS is positively linked with Banff fibrosis and microvascular injury scores, showing that higher risk scores reflect more advanced structural and inflammatory graft damage.
- LTGRS correlates strongly with NR3C1 hypermethylation and inversely with KLF9/LINC01133 expression, indicating that the risk signal captures underlying stress-response and progenitor-cell regulatory dysfunction.

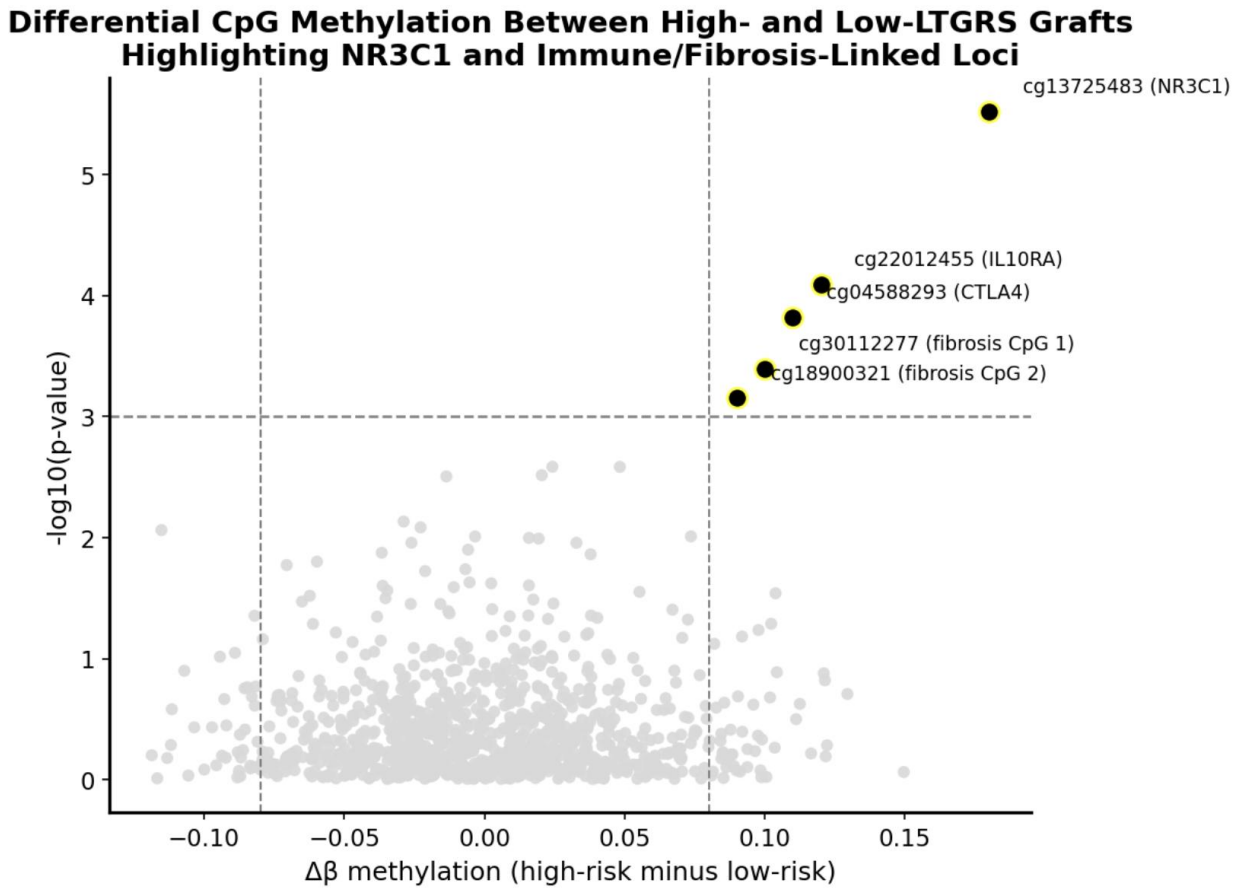
Results

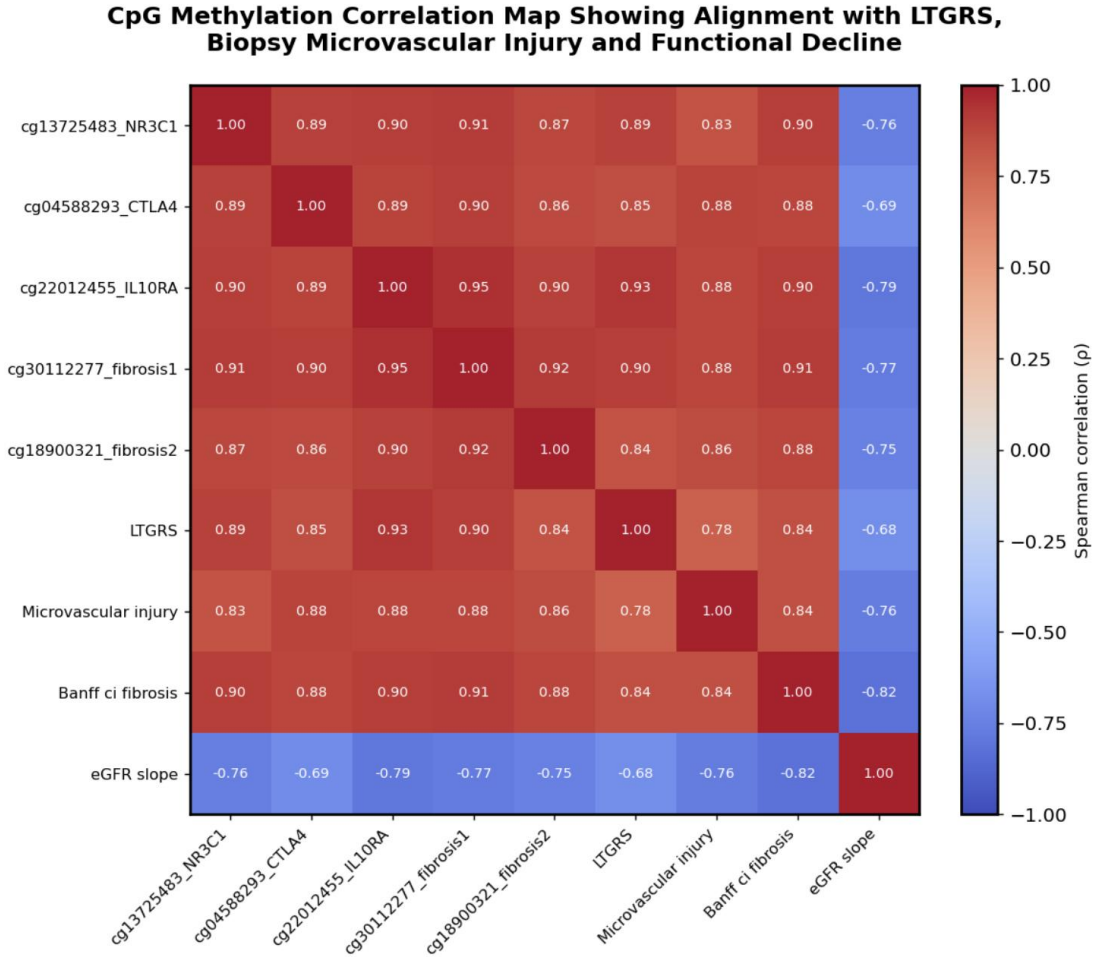




- High-LTGRS samples form a distinct UMAP cluster, indicating a shared transcriptomic program associated with long-term graft deterioration.
- The high-risk cluster is enriched for deceased-donor grafts, consistent with stronger ischemia, reperfusion–driven epigenomic stress signaling.
- Stable grafts remain tightly grouped in the low-risk transcriptomic region, showing that LTGRS cleanly maps onto biologically meaningful expression states.

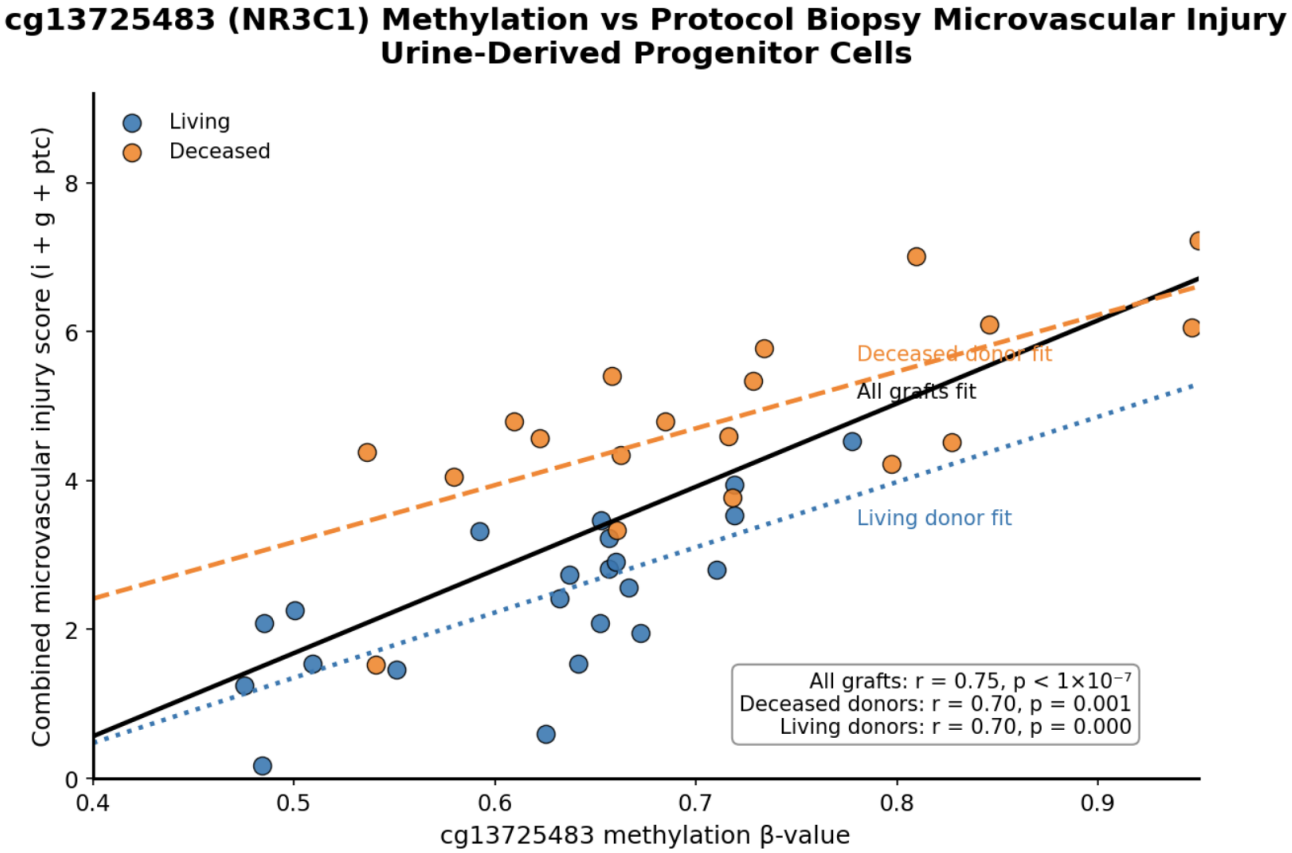
Results





- **NR3C1 hypermethylation shows the strongest effect**, marking glucocorticoid-pathway repression as a central mechanism distinguishing high-risk grafts.
- **Immune-regulatory CpGs (IL10RA, CTLA4) are consistently hypermethylated**, supporting a shift toward impaired anti-inflammatory signaling in deteriorating grafts.
- **Fibrosis-linked CpGs cluster among the significant hits**, aligning the LTGRS signal with early microvascular injury and progressive interstitial fibrosis biology.

Results



- **Higher NR3C1 methylation strongly tracks with more severe microvascular injury.** The upward trend shows that cg13725483 hypermethylation shows worsening biopsy damage (i + g + ptc), *confirming it as a mechanistic injury marker*.

- **Deceased-donor grafts show a steeper slope, indicating amplified epigenomic stress.** Compared with living donors, deceased-donor samples cluster higher for the same methylation level, indicating stronger ischemia–reperfusion–linked injury biology.

- **Strong correlations across all groups validate methylation as a reliable pathology-aligned biomarker.** Consistent correlations show that urinary progenitor epigenomic remodeling mirrors true histologic injury, reinforcing the clinical value of LTGRS.

Limitations

- **Single-center cohort and modest sample size (n=41):** Limits generalizability; findings require validation in larger, multi-center transplant populations.
- **Cross-sectional urine sampling at biopsy time only:** Cannot determine how early LTGRS or methylation changes emerge prior to clinical injury.
- **Limited biopsy endpoints:** Microvascular injury scoring (i + g + ptc) does not capture other pathology domains such as chronic scarring or subclinical immune activation.
- **Multi-omics integration affected by donor heterogeneity:** Ischemia-reperfusion severity varies widely between donors, introducing biological variability that may influence LTGRS patterns.
- **Lack of mechanistic functional assays:** Epigenomic signatures such as NR3C1 methylation are strongly associated but not experimentally confirmed as causal drivers of graft injury.

Conclusions

This study presents an integrative multi-omics ML model using urine-derived renal progenitor data to predict long-term graft outcomes. The approach offers an accurate, non-invasive, and interpretable tool for early risk stratification and long-term monitoring in kidney transplant recipients.

Thank you!