**Donor-Specific Digital Twin for Living Donor Liver Transplant Recovery**

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**Background & Purpose**

Living donor liver transplantation (LDLT) is a life-saving procedure for recipients, but its long-term success relies on the donor liver's ability to regenerate after surgery. This regeneration is a highly coordinated and complex process, essential for the complete restoration of liver mass and function. Normally, hepatocytes remain in a quiescent (G0) state, but after partial hepatectomy, they transition into the cell cycle, responding to various stresses such as physical injury, altered blood flow, and metabolic demands. These changes activate key gene expression programs that govern liver regeneration. However, donor heterogeneity significantly influences recovery trajectories, making individualized monitoring crucial. With the increasing global incidence of liver diseases, ensuring safer transplant procedures and optimizing donor outcomes is more important than ever. Existing clinical markers provide only limited snapshots of recovery, lacking predictive power for personalized post-surgical management. To address this gap, we developed the Personalized Progressive Mechanistic Digital Twin (PePMDT)—a deep learning-based framework that integrates mechanistic mathematical modeling with gene expression analysis to predict donor-specific recovery. This method enables precise monitoring of the liver recovery phase, essential for optimizing transplant success.

**Methodology & Design**

We analyzed whole transcriptome RNA sequencing data from 12 healthy LDLT donors, collected over 14 time points throughout one year. Using Weighted Gene Co-expression Network Analysis (WGCNA), we identified liver resection-specific gene expression patterns and categorized them into distinct transcriptional clusters with unique dynamics. These gene expression patterns were then mapped to a previously developed mechanistic model of liver regeneration using deep learning techniques, enabling the development of PePMDT - a virtual representation of patient-specific liver recovery.

**Results & Conclusions**

The PePMDT successfully predicted individual recovery trajectories, demonstrating the ability to translate gene expression data into dynamic regenerative responses. By linking blood-derived gene expression profiles to computational liver models, PePMDT provides a quantitative framework for tracking and forecasting patient-specific post-surgical outcomes. While digital twins have gained recognition in various medical applications, their role in regenerative medicine remains limited. Our study demonstrates how PePMDT functions as a disease-specific digital twin for LDLT, offering a continuous, mechanistic, and predictive approach to precision medicine. Given the complexity of donor heterogeneity, PePMDT helps clinicians anticipate variations in recovery, allowing for tailored post-surgical care and enhanced long-term transplant success. This work represents a critical step forward in integrating computational modeling with clinical genomics to improve the safety and efficacy of liver transplantation.