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Review Article



# Emerging Biomarkers for Transplant Diagnostics for Long-Term Graft Survival

**Ritu Pokhrel Dahal[2,3] and Tara K. Sigdel[1,3*]**

[1]University of California San Francisco, USA

[2]St. Joseph's University Medical Center, USA

[3]Nexus Institute of Research and Innovation, Nepal

## Abstract

Organ transplantation remains the definitive therapy for end-stage organ failure, yet long-term graft survival depends on precise and timely detection of injury. Conventional markers such as serum creatinine and histology identify damage only after functional decline. In contrast, emerging molecular and functional biomarkers—spanning mRNA and microRNA signatures, exosomal vesicles, donor-derived cell-free DNA (dd-cfDNA), HLA and non-HLA antibody repertoires, proteomic, and metabolic profiles—are reshaping transplant surveillance through earlier and more specific insights into graft health.

This review integrates data from over 200 recent studies on diagnostic biomarkers across kidney, liver, heart, and lung transplantation. A list of 30 important references is listed in Table 1. The analysis emphasizes cross-organ trends in multi-omics integration, spatial and single-cell profiling, and AI-enabled analytics that collectively predict graft dysfunction with increasing accuracy and reproducibility.

Transplant diagnostics is transitioning from single analyte testing to integrated, predictive, and personalized biomarker ecosystems. The convergence of multi-omics assays, machine-learning algorithms, and regulatory standardization is driving this evolution toward pre-informed long-term graft survival strategies. While broad clinical adoption requires further multicenter validation, the next decade will likely see these molecular diagnostics redefine how transplant injury is detected, interpreted, and prevented.

**Keywords**: Organ transplantation; Biomarkers; Kidney Transplantation; Transplant Diagnostics; Graft Survival; Graft Failure

**Abbreviations**

AR: Acute Rejection; TCMR: T-Cell Mediated Rejection; ABMR: Antibody-Mediated Rejection; EMB: Endomyocardial Biopsy; DSA: Donor-Specific Antibodies; dd-cfDNA: Donor-Specific Cell-Free DNA

**Article Highlights**

- Organ transplant suffers from late graft failure. Identification and clinical application of a marker that could accurately predict, diagnose, and monitor the risk of transplant rejection and dysfunction would be beneficial.
- Despite ongoing efforts with multiple strategies, including cell-free DNA, mRNA transcripts, proteins and metabolites, allo- and auto-antibodies, immune cells, and TCR and BCR repertoires, such an effective and robust diagnostic marker is yet to be discovered.
- The effort must continue until a novel diagnostic is discovered that could help in personalized medicine in the non-invasive diagnosis and management of transplanted organs, including kidney, heart, liver, lung, and pancreas.
- The future of the transplant will be heavily dependent on the use of artificial intelligence-aided machine learning in integrating massive amounts of molecular data at a single cell level with spatial context retained.

## INTRODUCTION

Organ transplantation is the best available treatment option for many organ failures [1]. Since the first successful kidney transplant in 1954, advances in surgery and immunosuppression have transformed survival outcomes [2,3]. On one hand, there is a high demand for organ transplants and a long wait time for prospective transplantation; transplanted organs fail due to immune and non-immune related causes, putting an additional burden on the already existing shortage of donation-eligible organs. Eight decades of clinical progress has not significantly improved in preventing graft loss from immune- and non-immune–mediated injury [4-6]. According to global Observatory on Donation and Transplantation report published in 2023, globally, approximately 172,000 solid organ transplants are performed annually, but up to 30 % of recipients develop subclinical graft injury within the first year [7]. This number of grafts that go through uncaptured injuries in the absence of proper detection tools underscores the urgent need for reliable, early, and non-invasive diagnostic methods [8-11].

Although biopsies remain the diagnostic gold standard, they are invasive, costly, and subject to sampling variability. Moreover, histology often detects late-stage injury and cannot reliably discriminate overlapping processes such as antibody-mediated rejection, infection, and

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***Corresponding author:** Tara Sigdel, Department of Surgery, University of California San Francisco, 513 Parnassus Ave, S-1269 Med Sci Bldg, San Francisco, CA 94143, USA, Tel: (415) 502-3561



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drug toxicity. Over the last decade, the paradigm of transplant diagnostics has shifted from treating visible graft dysfunction toward anticipating molecular injury before clinical manifestations arise [12]. This shift toward precision-based molecular monitoring combining omics, advanced imaging, and AI-driven analytics to detect injury before irreversible histologic damage [12,13]. These integrated diagnostics aim not only to detect early allograft injury but also to contextualize it—distinguishing between alloimmune, metabolic, infectious, or drug-induced causes. This transition defines the emerging discipline of precision transplant diagnostics-an integration of molecular, cellular, imaging, and digital data that collectively forecast graft trajectory [13,14]. More importantly, non-invasive, quantitative, and temporally dynamic tools are now considered essential to both graft survival and individualized immunosuppression [15]. Parallel developments in machine learning enable pattern recognition across thousands of biomarkers, creating predictive models for rejection and tolerance.

A biomarker, defined as "a characteristic objectively measured and evaluated as an indicator of normal biological or pathogenic processes or pharmacologic responses," now encompasses mechanistic, prognostic, and response categories within the FDA–EMA biomarker qualification pathway [16,17]. Within transplantation, this classification has evolved into a structured validation framework emphasizing analytical reliability, clinical relevance, and regulatory acceptance. The FDA-EMA pathway, refined through the BIOMARGIN and CTOT consortia, differentiates between discovery biomarkers, qualified surrogate endpoints, and diagnostic companion tools [18,19]. These guidelines are driving a move toward multiplex assays with standardized reference ranges and inter-laboratory reproducibility.

Non-invasive diagnostic modalities, such as donor-derived cell-free DNA (cfDNA), gene expression signatures, and high-sensitivity protein panels illustrate the translation of discovery-stage biomarkers into routine practice. Multi-assay integration now enables longitudinal graft surveillance: cfDNA reflects donor tissue injury dynamics; mRNA and microRNA signatures mirror immune activation; and plasma proteomic panels report metabolic stress responses. A growing body of multicenter validation trials confirm that combining these readouts yields greater diagnostic precision than any single assay. Integration of cloud-based algorithms further supports real-time decision-making and remote patient monitoring.

Consequently, transplant diagnostics is evolving from static, histology-based assessments toward integrated, predictive, and personalized biomarker ecosystems [5]. The following sections review organ-specific advances and outline how multi-dimensional molecular evidence can shape the next generation of transplant diagnostics. This transformation embodies a fundamental paradigm shift—from reactive detection to proactive health maintenance of the graft. The convergence of molecular assays, digital pathology, and computational modeling signals a new phase in transplant medicine where diagnostics are not merely confirmatory but continuously informative, guiding both clinical and research strategies for the coming. A summary of the current status of transplant diagnostics and its possible evolution into more robust biomarkers and diagnostics in the near future is summarized in Figure Figure 1A and 1B.

## THE ELUSIVE BIOMARKERS IN ORGAN TRANSPLANTATION

The discovery and validation of reliable biomarkers in transplantation have remained an elusive goal despite decades of effort [20,21]. Many candidate molecules have shown initial promise, but few have achieved consistent performance across cohorts or clinical applicability. Several challenges exist including rejection prevention, long-term organ survival, and safety from complications due to drug toxicity, viral infection, non-compliance, etc [22,23]. The complexity of transplant immunopathology, donor heterogeneity, and temporal variation in immune response contribute to this challenge. Although hundreds of biomarker candidates have been proposed, the field continues to have a "validation bottleneck." For instance, early discoveries such as CXCL9 and CXCL10 mRNA in urine and blood—long considered indicators of T-cell mediated rejection—have shown variable predictive accuracy when applied across different organ types and immunosuppressive regimens. Similarly, donor-derived cell-free DNA (dd-cfDNA), now commercialized through AlloSure® and Prospera®, provides high sensitivity for detecting graft injury but still lacks precise specificity to distinguish immune injury from ischemic or drug-induced damage.

Each discovery phase tends to generate enthusiasm, followed by a plateau during clinical translation, highlighting the need for rigorous validation, standardization, and multi-center reproducibility. This limitation is magnified by differences in sampling (blood, urine, tissue), analytic platforms, and statistical models. Efforts like the BIOMARGIN, CTOT, and INTERLIVER consortia have now emphasized tiered validation—defining discovery, qualification, and clinical utility stages under FDA–EMA frameworks. Multi-analyte panels, rather than single markers, are showing greater translational robustness: for instance, combinations of cfDNA + CXCL10, or KIM-1 + NGAL, outperform single-analyte diagnostics in predicting early rejection and delayed graft function.

Moreover, heterogeneity in rejection phenotypes complicates interpretation. Histologically "similar" rejection patterns often arise from distinct molecular signatures—such as endothelial injury driven by donor-specific antibodies versus macrophage-rich inflammation

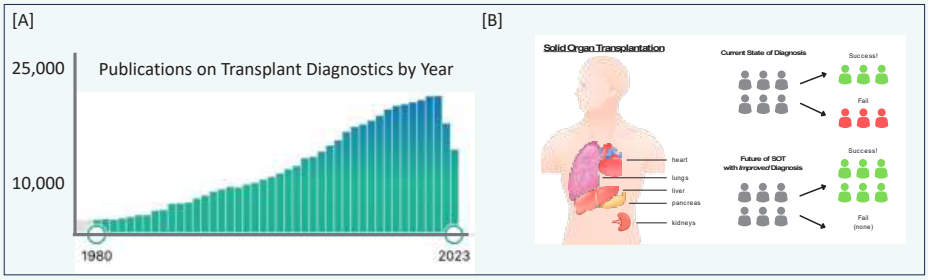


**Figure 1:** Transplant diagnostics over the years and its importance. [A] Increased acknowledgment of the significance of transplant diagnostics in recent decades as reflected by the number of publications related to this topic. [B] The vision of improved transplant diagnostics of solid organ transplantation (SOT).

reflecting innate activation. Novel profiling approaches, including spatial transcriptomics and proteomic tissue imaging, now help parse these micro-niches and could eventually refine how biopsies and molecular readouts are correlated. Biomarker discovery thus remains a moving target influenced by both biological and technical noise. Integration of omics datasets with clinical metadata through AI-driven classifiers has become an emerging solution, allowing feature selection that transcends single biomarker variability. The search for universal biomarkers has therefore given way to organ- and context-specific signatures, recognizing that no single assay can capture the diversity of injury mechanisms in transplantation. A shift is now underway toward "contextual biomarker ecosystems"—modular panels tailored to organ type, donor quality, and time post-transplant. This approach emphasizes practical integration into care algorithms rather than universalization. It mirrors the trend toward precision immune monitoring, where the clinical question—not the technology—defines which biomarker panels are deployed.

The community has felt an increasing need for robust yet non-invasive or minimally invasive diagnostic biomarkers that could be assessed through blood or urine tests that can accurately detect rejection without surgical procedures in the following aspects [24].

- *Early-stage biomarkers:* Detecting transplant injury early for successful intervention and transplant management. Developing sensitive diagnostic tests capable of identifying transplant injury before significant organ damage is a priority [25,26].

- *Personalized biomarkers*- It is well established that transplant recipients' responses to immunosuppressive medications vary. Therefore, tailoring treatment to an individual's specific immune fingerprint will help optimize appropriate drug dosing. Better tools for monitoring and adjusting immunosuppression regimens to balance the prevention of rejection with minimizing side effects and infection risk [27,28].

- *Markers assisting in differentiating types of rejection/infection*- A proper diagnosis of the type of dysfunction, such as the type of rejection or infection type, is necessary to tailor a proper treatment plan [29].

- *Predictive diagnostic markers*- These would help identify transplant recipients at higher risk of rejection or infection after transplantation and will help guide preemptive immunosuppressive drug dosing and interventions whenever necessary.

- *Long-term monitoring*- Many transplant recipients need lifelong monitoring. Developing cost-effective and practical long-term home-based monitoring solutions would be desirable.

It is not easy to integrate initial data generated through different studies and trials across various studies. It will require leveraging data analytics and artificial intelligence to integrate various diagnostic data sources for enhancing diagnostic accuracy and predictive capabilities. As the field moves forward, it is increasingly evident that biomarker discovery must be tightly linked to mechanistic understanding and clinical validation. True progress will hinge on collaborative multi-omics pipelines, harmonized data standards, and prospective interventional studies that test biomarker-guided decision-making. These efforts are beginning to close the gap between discovery and practice, setting the stage for organ-specific diagnostic frameworks explored in the next sections.

## KIDNEY TRANSPLANT DIAGNOSTICS

Kidney transplantation remains the most studied organ system for biomarker discovery, given the relative accessibility of urine and blood samples and the high frequency of allograft monitoring. Early studies focused primarily on serum creatinine and histologic biopsy findings, which, though standard, detect damage only after significant nephron loss [22,30-33].

Modern diagnostics now emphasize molecular and functional precision, using biomarkers that can detect subclinical injury before irreversible fibrosis develops. Donor-derived cell-free deoxyribonucleic acid (dd-cfDNA) is being used as a noninvasive marker for the early detection of rejection before clinical allograft dysfunction [34-38]. dd-cfDNA is reported in percentage and is assessed for its utility in rejection [39-41], ABMR [42,43], viral infection [44]. dd-cfDNA is also assessed in the urine of kidney transplant recipients and found to be helpful in kidney transplant injury [44,49]. Recent reports have reported testing with a tool that uses dd-dfDNA and gene expression profiles [50]. The use of blood and tissue gene transcript markers for rejection and transplant injury has been reported and is currently in the validation phase [51-55]. Several protein markers have been reported [56-60]. studied in the context of kidney transplant injury where proteins such as CCL2, CXCl10 [61-66]. Detection of increased urinary mRNA levels for CD3ε, perforin, granzyme B, proteinase inhibitor 9, CD103, IP-10, and CXCR3 are associated with acute cellular rejection of kidney allografts [67]. Urinary proteins like CXCR3-binding protein CXCL9 in T-cell-mediated rejection and CXCL10 in antibody-mediated rejection [3]. Elevated levels of CXCL9 and CXCL10 in urine may suggest rejection. Even though HLA mismatch and donor-specific antibodies against HLA antigens are used for transplant monitoring, non-HLA antibodies have received attention lately [68-70]. One Lambda, a vendor, has started to make non-HLA assessment kits available for transplant centers. Currently, different biomarkers are at different stages of their application in clinical application in transplant diagnostics.

Despite this development, histologic biopsy continues to be the gold standard for definitive diagnosis. However, its role is being redefined through molecular augmentation. Integration of spatial transcriptomics and proteomic tissue imaging allows correlation between cellular phenotypes and spatial microenvironments within the biopsy. These methods uncover hidden rejection subtypes and reveal metabolic gradients distinguishing adaptive repair from chronic injury. Emerging commercial platforms now quantify rejection-associated gene clusters directly from FFPE biopsy slides, bringing molecular precision to conventional histopathology.

The future of kidney transplant diagnostics will likely involve combined models incorporating both non-invasive and tissue-based molecular data. Multimodal integration frameworks, such as those under the CTOT-30 and iBOX 2.0 initiatives, are actively developing predictive algorithms that merge cfDNA, gene-expression, and digital pathology metrics. These models outperform traditional parameters in predicting graft survival and therapeutic response.

Together, these advances signal a transition from static measurements toward dynamic, data-driven surveillance of kidney allografts. The next frontier lies in personalized immunomonitoring—where patient-specific molecular signatures guide the timing and intensity of immunosuppressive therapy. As computational pathology, longitudinal biomarker analytics, and AI-assisted prediction models mature, the kidney will continue to serve as the blueprint for molecular diagnostics in other solid-organ transplants.

## LIVER TRANSPLANT DIAGNOSTICS

Liver transplantation presents unique diagnostic challenges because of the organ's regenerative capacity, complex metabolic profile, and the multifactorial nature of post-transplant dysfunction [71]. Conventional markers such as AST, ALT, and bilirubin lack specificity for the type or severity of injury and often change only after substantial cellular damage [72]. Acute liver transplant rejection poses a significant problem in liver

transplant survival [73]. Diagnostic biomarkers would provide a tool to improve how the rejection and dysfunction events are detected relative to the invasive biopsy, the current gold standard. Through several studies, several cytokines and inflammatory markers have been suggested as markers of liver transplant rejection, including IL-2, IL-4, IL-6, IL-15, IL-18, IL23, IFN-gamma, TNF-alpha, CD28, CD38, CD25, ICAM-1 IL-6 etc [74]. Felix et al., found that IL-2 receptor expression showed highest diagnostic accuracy among other markers like acid labile nitroso-compounds (NOx), serum amyloid A protein, procalcitonin, peripheral blood eosinophil count, peripheral blood T-cell activation and interleukin 2 (IL-2) receptor, guanylate-binding protein-2 mRNA, graft-derived cell-free DNA, pi-glutathione S-transferase, alpha-glutathione S-transferase, and serum HLA class I soluble antigens. Nevertheless, liver biopsy has been proven superior to the non-invasive test in clinical practice [75]. In addition, total bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, and alkaline phosphatase have been used as markers for liver transplant rejection. As with other organ transplant fields, a widely accepted biomarker with high sensitivity and specificity for liver transplant diagnostic for rejection is yet to be validated and accepted for clinical application [76].

Amid this progress, histologic evaluation remains an essential part of assessing graft quality. However, spatial transcriptomic and single-cell RNA-seq profiling of donor and post-reperfusion biopsies are redefining pathology by revealing zonal vulnerability within the hepatic lobule. Genes regulating oxidative phosphorylation, iron homeostasis (FTH1, SLC40A1, HAMP), and endothelial activation (VCAM1, VWF) delineate early injury gradient [77-81]. These tools permit correlation of molecular injury signatures with perfusate biomarkers, closing the loop between ex vivo and in vivo diagnostics.

The interpretation of these molecular readouts requires integration with clinical and imaging data. AI-enabled analytics now assimilate perfusate flow metrics, histologic scores, and omics profiles to predict graft survival with high percentage accuracy [82]. Algorithms trained on hundreds of NMP runs can stratify grafts as "transplant-ready," "marginal," or "discard," thereby reducing unnecessary organ loss. The same frameworks are being adapted for hypothermic oxygenated perfusion (HOPE) datasets and for cfDNA quantification in the immediate post-reperfusion period [83].

Thus, liver diagnostics are evolving from static enzyme measurements toward integrated molecular evaluation of organ function and injury. This evolution places the liver at the forefront of multi-omics transplant diagnostics, bridging discovery science and clinical decision-making. Insights from liver perfusion—where metabolism, inflammation, and repair coexist in measurable flux—are now informing similar paradigms in heart and lung transplantation, discussed in the following sections.

## HEART AND LUNG TRANSPLANT DIAGNOSTICS

Recent progress has centered on liquid biopsy–based and imaging-integrated molecular assays. In the heart, donor-derived cell-free DNA (AlloSure Heart) and gene-expression profiling (AlloMap®) have transformed rejection surveillance. dd-cfDNA rises within days of immune activation, preceding histologic evidence of cellular or antibody-mediated rejection, while the AlloMap transcriptomic panel quantifies peripheral immune activation using a 20-gene classifier. Conventional serum biomarkers such as troponin and BNP lack the specificity needed for early or subclinical rejection. Proteomic profiling has now expanded the biochemical toolkit increases in FABP3, SERPINA3, and GDF-15 correlate with cardiomyocyte stress and macrophage-driven inflammation. AI-based algorithms using sequential troponin, echocardiographic strain, and cfDNA trends are under prospective evaluation to individualize biopsy intervals and immunosuppressive dosing.

Lung transplantation poses an even greater diagnostic challenge due to continuous environmental exposure and overlapping infectious and alloimmune injury. Bronchoalveolar lavage (BAL) and plasma biomarkers are increasingly leveraged for non-invasive assessment. Up-regulation of CXCL9/10, Periostin, and MMP-7 distinguishes acute cellular rejection from infection, while elevated Tenascin-C and SP-D predict progression toward Chronic Lung Allograft Dysfunction (CLAD) [84-86]. Metabolomic analyses further identify altered lipid and amino-acid signatures that precede spirometric decline by several months.

Histologic confirmation via transbronchial biopsy remains the diagnostic reference but is limited by procedural risk. Molecular augmentation is improving interpretability: spatial transcriptomic maps of explanted CLAD lungs reveal compartmentalized immune niches dominated by cytotoxic $CD8^+$ T cells and fibroblastic remodeling markers. These data are being integrated with cfDNA and proteomic trends through machine-learning classifiers that predict CLAD development with AUC > 0.90 in validation cohorts [87].

The growing convergence of blood-based, imaging, and tissue-derived assays in thoracic transplantation mirrors the evolution seen in renal and hepatic grafts. Future clinical frameworks envision multimodal dashboards combining cfDNA, transcriptomic, proteomic, and radiomic metrics into unified risk scores for each patient. These integrated systems promise dynamic surveillance that can differentiate immune from infectious pathology in real time, minimizing invasive sampling while improving long-term graft preservation.

## HEART TRANSPLANT DIAGNOSTICS

Traditionally, the presence of DSA is taken as an early indicator of rejection [88,89]. Endomyocardial Biopsy (EMB) and its examination reveal signs of rejection, including infiltration of immune cells and tissue damage, but it is invasive and non-specific [90]. Several potential biomarkers have been suggested because of the development in high throughput analysis of gene transcripts and proteins. To detect heart transplant rejection Horwitz et al. [91], found gene expression profiling (GEP) of peripheral blood leukocytes as an essential tool, further confirmed by Cardiac Allograft Rejection Gene Expression Observational (CARGO) study using PCR. The CARGO study led to the development of Allomap, which is used nowadays for gene expression profiles in clinical practice [91-93]. In addition, the FDA has also approved Allomap for heart transplant recipients >15 years of age and >=55 days post-transplant [94]. Kazuhiro et al., demonstrated phosphorus-31 nuclear magnetic resonance spectroscopy (31P NMRS) in mice as a useful marker for detecting chronic graft rejection of heart transplantation [95], donor-derived cell-free DNA [96]. Heart transplant rejection can be diagnosed and monitored using various biomarkers. Biomarkers are measurable substances or indicators that provide information about the physiological or pathological state of the body. In the context of heart transplant rejection, elevated levels of cardiac troponins, particularly troponin I and troponin T, may suggest rejection or cardiac injury [97]. Elevated levels of BNP can indicate cardiac dysfunction, which may be associated with rejection [98]. Higher levels of CRP may suggest ongoing rejection or inflammation in the transplanted heart [99]. IL-2R, a cell surface marker expressed on activated T lymphocytes, is reported to be elevated in the blood to indicate T-cell activation and rejection [99]. An increase of donor-derived cell-free DNA in the blood of heart transplant recipients has been used as a potential biomarker for heart transplant diagnostics [100,101].

It's important to note that the diagnosis of heart transplant rejection is usually a combination of clinical evaluation, imaging tests, biopsy, and biomarker analysis. Different transplant centers use their unique way of heart transplant follow-up care. Most importantly, most of the reported potential markers have yet to be transformed into widely accepted biomarkers for heart transplant rejection.

## LUNG TRANSPLANT DIAGNOSTICS

Lung transplantation is the best treatment option for people with end-stage lung diseases [102-105]. It is reported that the 1-year and 5-year survival rates of transplanted lung have been 85 and 59%, respectively, for adult lung transplants since 2010 [106]. For lung transplantation, rejection remains a significant problem. ACR, lymphocytic bronchiolitis, and AMR are all risk factors for the subsequent development of chronic lung allograft dysfunction (CLAD). Whereas ACR and lymphocytic bronchiolitis are well characterized, diagnosis of AMR is still complex, and CLAD continues to remain a challenge for long-term survival of lung transplants. CLAD, subclassified as bronchiolitis obliterans syndrome (BOS) and restrictive allograft dysfunction (RAS), In between, BOS and RAS is associated with a worse prognosis [107]. Diagnostic markers that better distinguish RAS from BOS are needed [108]. Conventional diagnostics of lung transplant monitoring include transbronchial biopsy [109], and molecular markers in bronchoalveolar lavage [110]. Amit et al., identified transbronchial biopsy showing the presence of perivascular and interstitial mononuclear cell infiltrates in lung tissue to diagnose acute rejection. Similarly, pulmonary function tests have been used to diagnose CLAD [107]. Sarmad et al., used hyperpolarized (HP) [1-13C] pyruvate MRI in a rat model for the detection of acute rejection, showing metabolic assessment in real-time based on changes in cellularity and metabolism of lung tissue and the infiltrating inflammatory cells which predicts rejection earlier than X-ray and CT [111]. Key diagnostic approaches for lung transplant AMR include donor-specific HLA antibodies (DSA) identified through a single antigen assay [112]. However, it's acknowledged that non-DSA HLA antibodies and non-HLA antibodies may also contribute to antibody-mediated rejection (AMR) [113]. Complement activation, particularly through the C1q assay, is considered central in AMR pathogenesis, predicting late graft failure [114]. Recent advances highlight donor-derived cell-free DNA (dd-cfDNA) as a sensitive marker for allograft injury, correlating with AMR severity; elevated dd-cfDNA levels precede AMR diagnosis [115]. Yet, dd-cfDNA elevation is nonspecific and may occur in cellular rejection and infection. Adjusting threshold levels based on transplanted lung mass improves accuracy. Additional diagnostics of lung transplant rejection include interleukin-2 (IL-2), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha) [116], the elevation of CD40 ligand, which is released by activated T cells [117]. Elevated levels of eosinophils and neutrophils in the blood or lung tissue have been associated with acute rejection [118]. Identifying highly specific and sensitive diagnostic lung transplant biomarkers will require more research and integrative analysis of the data generated using machine learning methods, which is also true with other organ transplants.

## PANCREAS TRANSPLANT DIAGNOSTICS

Pancreas transplant outcomes are slowly improving due to improvements in surgical techniques, donor-recipient matching and selection, diagnostic imaging, and improved immunosuppressive medications. Despite this improvement, AR remains a challenge and is the primary cause of death-censored pancreas allograft loss after three months posttransplant. Current statistics estimate that about 87% of pancreas transplants in the US are simultaneous pancreas-kidney (SPK) transplants. Approximately 5% are performed as sequential pancreas after kidney transplant, and 7-10% comprise pancreas transplants alone [119,120]. To detect acute rejection of pancreas transplant, Redfield et al. found elevation of pancreatic enzyme initially (lipase more specific than amylase) followed by CT scan and biopsy in the perioperative period (<45 days) or in the presence of abdominal symptoms, whereas only biopsy for the patients beyond perioperative period and without abdominal symptoms [121]. The eosinophil-to-monocyte ratio has been reported as an excellent predictor of acute cellular rejection in pancreas transplants [122]. As with other organ transplants, the assessment of dd-cfDNA in post-transplant blood is suggested to be useful in transplanted graft monitoring for pancreas transplantation [123,124].

## INTEGRATED MULTI-ORGAN DIAGNOSTICS AND FUTURE OUTLOOK

The search for reliable and timely transplant diagnostics has evolved from organ-specific studies toward a unified systems approach. Advances across kidney, liver, heart, and lung research now converge on the principle that early molecular injury can be measured and interpreted before irreversible dysfunction occurs. The contemporary vision of transplant diagnostics is therefore integrative and cross-platform. Rather than viewing each organ in isolation, multi-omics and AI frameworks now merge biomarkers across tissues, fluids, and imaging modalities to define shared biological axes of injury, such as endothelial activation, metabolic stress, and alloimmune signaling. Comparative analyses from demonstrate that cfDNA, CXCL10, and oxidative-stress proteomic panels capture overlapping pathophysiology across multiple graft types. This cross-organ reproducibility supports the development of universal risk signatures applicable to any solid-organ transplant.

A major challenge remains in translating discovery-stage signatures into regulatory-approved diagnostic tools. Shared informatics platforms enable federated machine-learning models trained on diverse populations without exposing raw patient data, enhancing both reproducibility and privacy. The incorporation of artificial intelligence into transplant medicine is accelerating this convergence. Deep-learning architectures now integrate omics, histology, and imaging data to generate real-time rejection risk scores. Federated learning across global transplant centers has achieved predictive accuracies exceeding 90 % for allograft rejection, while explainable-AI frameworks help clinicians interpret feature importance—bridging the gap between algorithmic prediction and clinical trust. These models are beginning to power decision-support systems that dynamically recommend biopsy timing or drug-level adjustments.

Beyond technology, successful implementation will depend on collaboration and equitable access. The global transplant community is now moving toward open-access biomarker consortia and low-cost assay deployment for emerging economies. Initiatives in South Asia and sub-Saharan Africa are piloting simplified cfDNA and protein-panel tests that retain diagnostic accuracy while reducing per-sample cost by over 60 %. Such efforts ensure that molecular innovation benefits both high- and low-resource settings, fulfilling the ethical imperative of translational equity.

The future of transplant diagnostics will be defined by integration, validation, and personalization. In this future landscape, omics-based diagnostics will no longer operate as isolated tests but as components of a continuously learning ecosystem—linking discovery research, clinical care, and patient outcomes in feedback loops. The merger of digital pathology, cloud-based analytics, and precision immune monitoring will allow clinicians to visualize the graft's molecular state in near real time.

## THE FUTURE STATE OF TRANSPLANT BIOMARKERS AND DIAGNOSTICS

Transplant diagnostics is entering a transformative era driven by integration, precision, and prediction. Multi-omics profiling, advanced imaging, and AI-enabled analytics now allow clinicians to visualize molecular injury long before clinical decline. As discovery science merges with regulatory qualification and equitable implementation, diagnostics will evolve from static measurements into living, adaptive systems that learn from each patient. The convergence of cfDNA, transcriptomic, proteomic, and spatial data across organs is establishing a universal language of graft health—where biology, computation, and clinical intuition meet. The next decade will witness the translation of this

molecular insight into actionable care pathways, reducing unnecessary biopsies, expanding donor utilization, and improving long-term graft survival. Ultimately, the promise of precision diagnostics is not only to detect injury early, but to anticipate and prevent it—transforming transplantation from reactive intervention to proactive preservation of life.

## FIVE YEAR REVIEW

Some long-term goals for transplantation include (1) the development of new drugs targeting immunosuppressive with fewer side effects and (2) the development of robust diagnostic biomarkers [21]. In the next five years, we expect to see further acceleration in identifying relevant transplant diagnostic biomarkers as the cost of assays and knowledge about high throughput molecular assays becomes widespread, along with the availability of more data on potential biomarkers reported by earlier studies. The multi-dimensional "omics" data (transcriptomics, proteomics, metabolomics, epigenomics, lipidomics, glycomics, etc) with spatial interrogation methods and single-cell assays to provide a total molecular picture of cells of different kinds and origins with spatial context is expected to provide a detailed biological state that was not available until now. Integrating and analyzing the massive amount of molecular data combined with clinical and demographic information was not easy until the advent of artificial intelligence in answering lingering biological questions [14,125]. Machine learning and neural networks can be successfully employed to generate trainable algorithms to distinguish between phenotypes and establish thresholds of injury based on the biomarker data [126,127]. This process is demonstrated in **Figure 2** schematically illustrates. Panels of biomarkers will become increasingly important in combination with other patient-specific information. Personalized and precision medicine approaches will be combined with these lower-cost, high-throughput assays to yield patient-specific information on rejection and transplant monitoring. Even though we expect to see new avenues of expansion in xenotransplantation [128,129], to lower the burden on the availability of transplant-eligible organs, the momentum toward identifying effective and personalized diagnostic biomarkers is expected to continue with more urgency because of the underlying issues associated with immune barriers [130] (Table 1).

In conclusion, humans are heterogeneous in how they live and respond to internal and external stimuli. The disease biology of transplanted organs is complicated. We have learned from the history of transplant biomarkers that expecting a magic biomarker is too optimistic; nevertheless, we must acknowledge incremental progress made in monitoring transplanted organs today compared to a decade ago. Because of active, relentless participation from all involved parties, the field of transplant diagnostics is reaching new milestones every day, and its relevance remains more important than ever.

## EXPERT OPINION

Advances in the field of organ transplantation have been revolutionary. The field is paying attention to immunomodulation by understanding various complex mechanisms signaling molecules and cellular and humoral mechanisms [131]. of A fundamental weakness in clinical management is identifying which patients are undergoing rejection. For example, current methods of renal monitoring are reactionary, inaccurate, and use relatively late markers of injury [31,132]. For example, in the case of kidney transplantation, serum creatinine drift does not occur until a significant proportion of the kidney's filtration capacity has been compromised. A similar situation exists in terms of the lack of early biomarkers for the detection of rejection events. At this point, a biopsy is typically performed to confirm the suspicion of rejection. The biopsy procedure is costly, invasive, and has complications potentially leading to morbidity in all solid organ transplants. Therefore, there is a need for a clinically validated panel of biomarkers for each solid organ type that could non-invasively monitor and diagnose transplant rejection. The ultimate goal of this field is to 1) accurately map out a comprehensive molecular profile for each solid organ transplant rejection and 2) identify which biomarkers are elevated (or reduced) in response to various etiologies of rejection. Ideally, this would be a low-cost and noninvasive clinically applicable diagnostic test.

A challenge for transplant diagnostics efforts is obtaining sufficient quality and quantity of clinical specimens to allow for this type of high throughput biomarker discovery. Biospecimen processing and storage must be standardized and performed well to ensure the study results' validity. Cost and clinical benefit conferred from biomarker data must also be considered when designing any biomarker test for clinical application; if the information has minimal clinical impact or is too costly, it is not worthwhile to continue to pursue it. This multidisciplinary approach requires much planning, personnel, resources, and expertise. Interdepartmental collaborations will likely be increasingly advantageous as basic science biomarker data is further developed into clinical tools

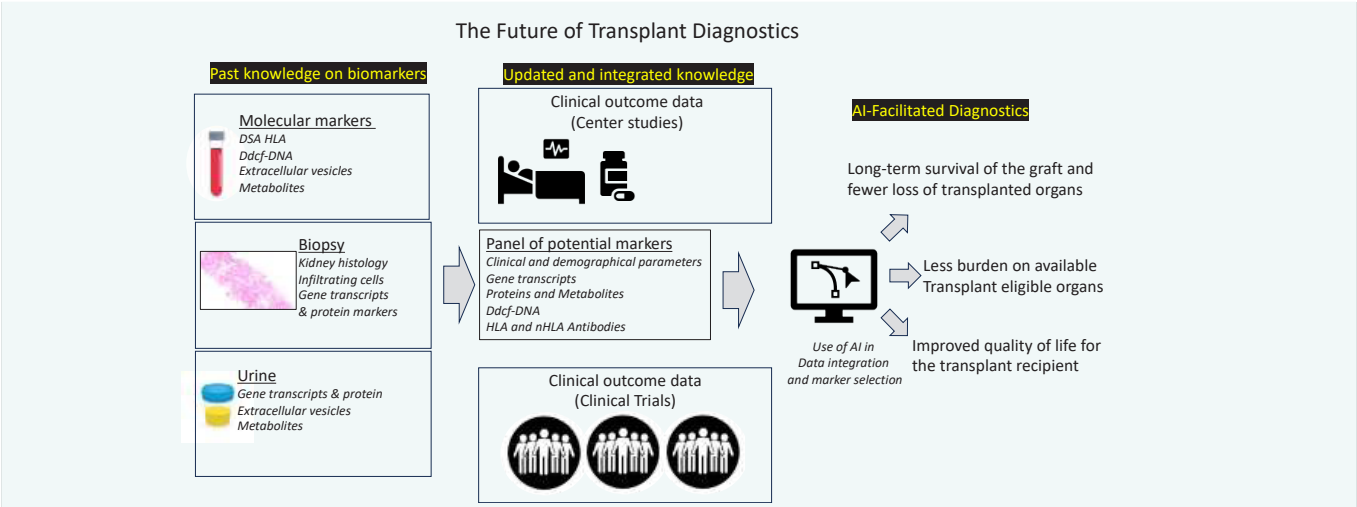


**Figure 2:** The promising future of transplant diagnostics. Using the invaluable information gained combined with newly available data on clinical and demographic parameters with the help of artificial intelligence is expected to deliver elusive diagnostic biomarkers in organ transplantation.

**Table 1:** A list of important papers in transplant diagnostics in the past 5 years.

| S.N0. | Title of the paper | First Author | Year Published | PMID |
|---|---|---|---|---|
| 1 | Impact of Belatacept Conversion on Renal Function, Histology, and Gene Expression in Kidney Transplant Patients With Chronic Active Antibody-mediated Rejection | Dhiren Kumar | 2021 | 32510913 [133] |
| 2 | Gene Expression Profiling in Kidney Transplants with Immune Checkpoint Inhibitor–Associated Adverse Events | Benjamin Adam | 2021 | 34244334 [134] |
| 3 | A Decentralized Kidney Transplant Biopsy Classifier for Transplant Rejection Developed Using Genes of the Banff-Human Organ Transplant Panel | Myrthe Van Baardwijk | 2022 | 35619722 [135] |
| 4 | Kidney Transplant Outcome Is Associated with Regulatory T Cell Population and Gene Expression Early after Transplantation | Magdalena Krajewska | 2019 | 30729139 [136] |
| 5 | Proteomics in Kidney Allograft Transplantation—Application of Molecular Pathway Analysis for Kidney Allograft Disease Phenotypic Biomarker Selection | David Marx | 2019 | 30680934 [137] |
| 6 | Urinary Proteomics in Kidney Transplantation | Goce Spasovski | 2021 | 35032373 [138] |
| 7 | Urinary epidermal growth factor is a novel biomarker for early diagnosis of antibody mediated kidney allograft rejection: A urinary proteomics analysis | Somaye-Sadat Heidari | 2021 | 33785428 [139] |
| 8 | Biomarker discovery in cardiac allograft vasculopathy using targeted aptamer proteomics | Aws Almufleh | 2019 | 31815308 [140] |
| 9 | Noninvasive biomarkers for prediction and diagnosis of heart transplantation rejection | Yeraz Khachatoorian | | 33401139 [141] |
| 10 | Circulating microRNAs in cellular and antibody-mediated heart transplant rejection | Palak Shah | 2022 | 35872109 [142] |
| 11 | Donor-derived Cell-free DNA in Solid-organ Transplant Diagnostics: Indications, Limitations, and Future Directions | Ashish Kataria | 2021 | 33534526 [47] |
| 12 | Banff Schema for Grading Pancreas Allograft Rejection: Working Proposal by a Multi-Disciplinary International Consensus Panel | C.B. Drachenberg | 2008 | 18444939 [143] |
| 13 | non-HLA antibodies against endothelial targets bridging allo- and autoimmunity | Duska Dragun | 2016 | 27188505 [144] |
| 14 | non-HLA Antibodies and Epitope Mismatches in Kidney Transplant Recipients With Histological Antibody-Mediated Rejection | Marta Crespo | 2021 | 34305943 [145] |
| 15 | Antibody-medicated rejection after heart transplantation: diagnosis and clinical implications | Vidang P Nguyen | 2020 | 32304428 [146] |
| 16 | Antigen and Cell-Based Assays for the Detection of non-HLA Antibodies | Rosa G. M. Lammerts | 2022 | 35603145 [147] |
| 17 | Association of vimentin antibody and other non-HLA antibodies with treated antibody mediated rejection in heart transplant recipients | Xiaohai Zhang | 2020 | 33041085 [148] |
| 18 | The impact of non-HLA antibodies on outcomes after lung transplantation and implications for therapeutic approaches | Ramsey R. Hachem | 2019 | 31005400 [113] |
| 19 | Donor-Derived Cell-Free DNA (dd-cfDNA) and Acute Antibody-Mediated Rejection in Kidney Transplantation | Vishal Jaikaransingh | 2021 | 34062714 [149] |
| 20 | Donor-derived cell-free DNA accurately detects acute rejection in lung transplant patients, a multicenter cohort study | Moon Kyoo Jang | 2021 | 34130911 [150] |
| 21 | Cell-Free DNA to Detect Heart Allograft acute rejection | Sean Agbor-Enoh | 2021 | 33435695 [151] |
| 22 | Donor-derived cell-free DNA: An independent biomarker in kidney transplant patients with antibody-mediated rejection | Dongrui Cheng | 2021 | 33971294 [152] |
| 23 | Monitoring of Donor-Derived Cell-Free DNA by Short Tandem Repeats: Concentration of Total Cell-Free DNA and Fragment Size for acute rejection Risk Assessment in Liver Transplantation | Esther Fernández-Galán | 2021 | 34407295 [153] |
| 24 | A Novel High-throughput Droplet Digital PCR-based Indel Quantification Method for the Detection of Circulating Donor-derived Cell-free DNA After Kidney Transplantation | Jeroen Verhoeven | 2022 | 35283452 [154] |
| 25 | Elevated cell-free DNA in respiratory viral infection and associated lung allograft dysfunction | Katrina Bazemore | 2022 | 35729715 [155] |
| 26 | Transcriptome Analysis in Renal Transplant Biopsies Not Fulfilling Rejection Criteria | Francesc Moreso | 2020 | 32213927 [ 156] |
| 27 | Peripheral blood transcriptome analysis and development of classification model for diagnosing antibody-mediated rejection vs accommodation in ABO-incompatible kidney transplant | Hee Jung Jeon | 2020 | 31373158 [157] |

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| 28 | Transcriptome analysis of novel macrophage M1-related biomarkers and potential therapeutic agents in ischemia-reperfusion injury after lung transplantation based on the WGCNA and CIBERSORT algorithms | Zhiyuan Zhang | 2023 | 37230395 [158] |
| 29 | Single-Cell Transcriptome Analysis of Chronic Antibody-Mediated Rejection After Renal Transplantation | Fanhua Kong | 2022 | 35111153 [159] |
| 30 | Whole transcriptome analysis reveals that immune infiltration- lncRNAs are related to cellular apoptosis in liver transplantation | Shile Wu | 2023 | 37081883 [160] |

and assays. The key to this approach is generating large volumes of clinical data that can correlate with biomarker values.

Increasingly, the focus on biomarker identification will be shifted to prospective clinical validation of those biomarkers and to exploring how these values fluctuate throughout a transplanted organ's lifetime. This information can be used to influence clinical trials of novel approaches to immunosuppressive pharmacotherapeutics. Initially, a biopsy would likely still be required to allow for histologic confirmation of transplant rejection. Over time, the biomarker panel will replace invasive biopsy as the ideal monitoring method.

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