DONOR-DERIVED CELL-FREE DNA (DD-CFDNA)

ADVANCES AND FUTURE OUTLOOK FOR NGS-BASED POST-TRANSPLANTATION MONITORING

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INTRODUCTION

Advances in organ transplantation have revolutionized and expanded the capacity to both save lives and improve the quality of recipient lives. Important strategic goals for the transplant community are: increasing the number of patients receiving transplants, improving access to transplantation for all, and improving long-term transplant outcomes. However, despite enormous success in other phases of the transplant process, dramatic improvements in long-term allograft survival have yet to be achieved.

Improved allograft survival may be possible by modernizing laboratory methods used to monitor graft health and viability. Renal allograft function is often monitored by indirect markers of graft health, e.g., serum creatinine, urine protein, and donor-specific antibodies. Despite the common use of these methods, they lack specificity and reliability in predicting and identifying allograft rejection. The emergence of molecular diagnostic techniques has the potential to alter that paradigm, and may enable significant improvements in long-term allograft function. Of particular note is Next-Generation Sequencing (NGS, or "Next-Gen" Sequencing). The clinical utility of NGS in obstetrics and oncology has been validated, and its applications are rapidly expanding, to include utility in post-transplantation surveillance. The introduction of Next-Gen Sequencing represents a valuable tool in the monitoring of allograft rejection and dysfunction, with unprecedented and unparalleled precision, cost, and speed.

THE INTRODUCTION OF NEXT-GEN SEQUENCING AND ITS RECENT TECHNOLOGICAL ADVANCES PRESENT A VALUABLE TOOL IN THE MONITORING OF ALLOGRAFT REJECTION AND DYSFUNCTION, WITH UNPRECEDENTED AND UNPARALLELED PRECISION, COST, AND SPEED.

CLINICAL UTILITY OF NEXT-GENERATION SEQUENCING TECHNOLOGIES

Early technologies differentiating donor genomes from recipient genomes relied on sex- mismatch between donor and recipient(e.g., a female recipient of an organ from a male donor) or prior genotyping of the donor or recipient. These approaches can be costly and sometimes impossible to employ. The development of targeted Next-Gen Sequencing (NGS) assays has enabled cost-efficient, rapid discrimination between donor and recipient genomes. NGS has demonstrated utility in a variety of clinical and life science fields, from reproductive medicine to oncology, obstetrics, and forensics. Studies have been published to demonstrate the validity and utility of NGS-based methods in transplantation medicine of donor-derived genetic material.

Study	Key Findings
Universal noninvasive detection of solid organ transplant rejection, Snyder et al., 2011	Demonstrated that organ-specific donor DNA is detectable in heart transplant recipients, and increases significantly in allograft rejection. Results indicate sufficient sensitivity of dd-cfDNA to measure transplant rejection, and the utility of NGS in post-transplantation surveillance.
Cell-Free DNA and Active Rejection in Kidney Allografts, Bloom et al., 2017 (DART)	Utilized a targeted NGS assay to determine that dd-cfDNA may be used to assess both allograft rejection and injury in renal transplant recipients.
Applying rigor and reproducibility standards to assay dd-cfDNA as a non-invasive method for detection of acute rejection and graft injury after heart transplantation, Agbor-Enoh et al., 2021	Employed NGS technologies to detect allograft acute rejection in cardiac transplant recipients.
Initial Analysis of the dd-cfDNA Outcomes AlloMap Registery (D-OAR) Study, Kobashigawa et al., 2016	Employed NGS to identify dd-cfDNA from surveillance visits in heart transplant recipients. Although patients were clinically well and displayed low levels of dd-cfDNA overall, high levels of dd-cfDNA were correlated with hospitalization for graft dysfunction or infection.
Clinical outcomes from the ADMIRAL Study, Bu et al., 2021	Further validated the ability of NGS to detect cf-DNA in renal transplant recipients, as an indicator of acute and subclinical allograft rejection