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Commentary: The burden of conceptual proof

J. W. Awori Hayanga, MD, MPH, FACS, FRCS, FCCP

In this manuscript, Kanou and colleagues¹ elaborate upon the extraction of cell-free DNA collected from human donor lungs between 2010 and 2015 and sampled at 1 and 4 hours of perfusion. The authors used conventional polymerase chain reaction and correlated the results with clinical outcomes post-lung transplantation, with the intent of deriving a predictive tool through observations of correlation. This is a timely and relevant endeavor performed by a group with a track record and credibility in *ex vivo* techniques. The authors sought to define a mechanism to more accurately predict markers of severe primary graft dysfunction (PGD). Their efforts constitute an exciting contribution to an ongoing body of work. The paper, nevertheless, is somewhat technical and speaks to the more esoteric side of solid-organ transplantation. As such, the nuances and contention of PGD grading may not necessarily directly speak to the broader readership. Nevertheless, it is these nuances upon which the novelty is based in the selection of one category of cell-free DNA over another. The difference between nuclear DNA and mitochondrial DNA (mtDNA) is predicated on a selective relationship with PGD grade 3 and the perceived susceptibility to somatic mutation to which the latter is prone.

The mitochondrial genome encodes proteins required for oxidative phosphorylation-dependent ATP production and oxygen radical-dependent mitochondrial signaling.^{2,3} As such, disruption of mitochondrial transcription results in cytotoxicity and altered cell signaling. Further, oxidative mtDNA damage may lead to molecular fragmentation and

J. W. Awori Hayanga, MD, MPH, FACS, FRCS, FCCP

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Cell-free DNA may be used to predict graft function.

the occurrence of damage-associated molecular patterns.^{2,3} An explicit differentiation of mtDNA as damage-associated molecular patterns, or as responsible for producing them, is thus worthy of mention. Indeed, other unrelated nucleic acid receptors may also potentially activate the innate immune system response and propagate injury themselves.^{2,3} In this vein, cell-free DNA may be used to predict PGD and, when coupled with targeted pharmacologic intervention, may even be used to prevent it from occurring altogether.

Some limitations are worthy of discussion. First, the small sample size attenuates the freedom with which to proffer authoritative conclusions. Furthermore, it precludes the ability to analyze relationships between donation-after-cardiac-death time and nucleic acid levels. Second, the retrospective nature of the study prevented the measurement of wet-to-dry lung weight ratio(s). Third, the perpetual threat of the confounding effect of unrelated nucleic acids. Nevertheless, the paper reflects a credible and plausible “proof of concept” and is celebrated as such. In this capacity, the authors explore the promise and potential for biomarkers to permit greater prognostic accuracy. This has implications for decision-making regarding suitability for transplantation beyond the traditional reliance on arterial oxygen tension/inspired oxygen fraction ratio(s) and chest radiographs by affording greater granularity and, by extension, prognostic accuracy. Admittedly, the association between study variable and outcome implies but does not confirm causality. This remains, nevertheless, a promising step and a thought-provoking, hypothesis-generating thrust that will spur interest in larger, prospective studies in the quest to bring this proof of principle to mainstream clinical practice.

From the Department of Cardiovascular and Thoracic Surgery, West Virginia University, Morgantown, WV.

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Address for reprints: J. W. Awori Hayanga, MD, MPH, FACS, FRCS, FCCP, West Virginia University School of Medicine, 1 Medical Center Dr, Morgantown, WV 26505-8059 (E-mail: jeremiah.hayanga@wvumedicine.org).

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