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Dear Mr. Wright and Ms Van Brakle:

Subject: Request for information (CMS-03326-NC) related to 42 CFR

Numerous advances have taken place over the last 30 years in the setting of clinical histocompatibility testing and the practice of solid organ transplantation. A majority of donor/recipient compatibility assessments no longer require a pre-transplant physical crossmatch (ie; testing recipient sera against donor lymphocytes). Rather, **due to advances in HLA antibody testing technologies, immunologic compatibility between a given donor and recipient can be assessed "virtually" using HLA antibody profiles and donor HLA genotyping data, without the need for a physical crossmatch**. In November of 2014, CLIAC recommended that CMS "...explore; regulatory changes or guidance that would allow virtual crossmatching to replace physical crossmatching as a pre-requisite for organ transplantation."[1]

On the 9th of January 2018 the Centers for Medicare and Medicaid Services (CMS) issued a Request for information (RFI) on several aspects of 42 CFR §493. Specifically, CMS sought input on *Revisions to Personnel Regulations, Proficiency Testing Referral, Histocompatibility Regulations* and *Fee Regulations* under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (Federal Register Docket CMS-3326–NC). **We, the undersigned organizations and individuals, are contacting CMS to request a revision of a rule addressed in this RFI; specifically, section C, Histocompatibility; sub-section 1, Crossmatching.** This particular section requested comments on the proposed rule related to 42 CFR §493.1278(e-f) and the use of a "virtual crossmatch" in lieu of a physical crossmatch.

The Clinical Laboratory Improvement Act of 1988 (CLIA) has not undergone any updates to histocompatibility-specific regulations since 1992 and therefore certain requirements lag far behind current clinical capabilities. Most notably is 423 CFR §493.1278(f)(2) and its requirement that laboratories;

> "*For renal allo-transplantation and combined organ and tissue transplants in which a kidney is to be transplanted, have available results of final crossmatches before the kidney is transplanted.*"

CMS specifically stated in this RFI that "although not specified in the regulation, the crossmatching procedures in use in 1992 were physical crossmatches", as well as that regulatory changes may be necessary to allow virtual crossmatching to replace physical crossmatching prior to organ transplantation.

For the laboratory, the American Society for Histocompatibility and Immunogenetics (ASHI) has recently developed **regulatory guidelines for "Virtual Crossmatching" that have been approved by CMS** (ASHI-Standards for Accredited Laboratories, 2020 Revised Standards. Approved by CMS: February 16, 2021; available at www.ashi-hla.org). For the transplant center, newer therapeutic options to mitigate recipient/donor HLA incompatibilities at the time of transplantation have meant that a positive physical crossmatch is no longer an absolute contraindication to transplantation. Importantly for some patients a

false-positive physical crossmatch (absence of donor-specific HLA antibodies) can mistakenly prevent safe transplantation and increase the risk of a candidate dying on the transplant waiting list, as false positive reactions can occur up to 20% of the time[2]. Thus, the final decision to transplant a candidate is based on the immunological assessment provided by the histocompatibility laboratory as well as the specific clinical practices of the individual transplant program as they are applied to each individual patient based on the patient's medical urgency and level of immunologic risk.

To date, the delay in a decision by CMS on this specific issue has created significant concerns within the transplant community. Many centers have adopted virtual crossmatching as a "standard of practice" to improve patient outcomes, while others are hesitant due to the regulatory ambiguity. However, there are numerous scientific publications, worldwide, providing evidence for the clinical utility and safety of this practice[2-19]. In fact, many organizations such as ASHI, UNOS, CAP, ACLA (Am Clinical Laboratory Assoc.) and AHA (Am. Hospital Assoc.) submitted letters in response to the RFI supporting the adoption of the virtual crossmatch.

Of importance, recent changes in deceased-donor kidney allocation established wider regional and national sharing of kidney allografts, as the removal of donor service areas (DSAs) as a unit of allocation was required by the Department of Health and Human Services (HHS). Renal allograft distribution over broader distances has increased the need for virtual crossmatching to reduce allograft cold-time ischemic injury and facilitate equitable allocation to immunologically sensitized patients. This need may increase with the proposed "Continuous Distribution" model for organ allocation[20]. Requiring a physical crossmatch specifically disadvantages immunologically sensitized patients who depend on nationally shared allografts and 42 USC §274(2)(A)(ii) requires the national organ allocation system to consider "individuals whose immune system makes it difficult for them to receive organs". We cannot in good faith recommend continuing a practice that is often not needed due to technological advances, and that enforces a systemic inequity towards biologically disadvantaged patients.

Due to advances in clinical capabilities, we feel that it is necessary to codify this aspect of clinical histocompatibility laboratory practice. The virtual crossmatch needs to be deemed equivalent to a physical crossmatch for final immunological evaluation, thereby permitting transplant programs and histocompatibility laboratories to use a safe and established practice without reservation or limitation. **We request a meeting at your earliest convenience to address any questions that you may have regarding our concerns about the current federal regulation and request for an expedient update**.

Sincerely,

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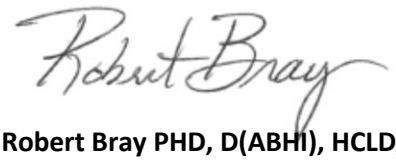

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