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American Society for Histocompatibility and Immunogenetics (ASHI) follow-up to 09/06/2023 E.O. 12866 Meeting (RIN 0910-AI85)

September 7, 2023

The American Society for Histocompatibility and Immunogenetics (ASHI) appreciated the opportunity to meet on September 6th, 2023, to provide considerations with respect to the Food and Drug Administration's (FDA) proposed rule under consideration entitled "Medical Devices; Laboratory Developed Tests". ASHI stands in support of appropriate federal regulation and oversight to ensure accuracy and validity of laboratory developed tests (LDTs) and guarantee patient safety. However, **ASHI does not support promulgation of the proposed rule providing for FDA regulation of LDTs. In the event this proposed rule is promulgated, ASHI requests that FDA continue to exercise enforcement discretion for Histocompatibility testing remaining consistent with 1) FDA's 2014 draft guidance concerning a risk-based framework for FDA regulation of LDTs and 2) the 2011 recommendation from the HHS Secretary's Advisory Committee on Organ Transplantation for LDTs used in CLIA-certified, high-complexity Histocompatibility laboratories, when used in connection with organ, stem cell, and tissue transplantation.** The Secretary's Advisory Committee recognized that Histocompatibility LDTs were rapidly evolving and often individualized within each transplant center to reflect local HLA diversity and patient demographics. These attributes raise significant concern that enforcement of FDA regulatory requirements for these devices could lead to the unavailability of testing for immunologically high-risk transplant candidates and minority populations. ASHI believes that the addition of FDA oversight is unwarranted and does not support promulgation of the proposed rule under consideration, particularly to the extent it fails to maintain continued enforcement discretion with respect to Histocompatibility testing. ASHI strongly maintains FDA regulation of Histocompatibility testing is unwarranted in light of the current, extensive system of regulatory oversight that has ensured analytical and clinical validity and patient safety in our field.

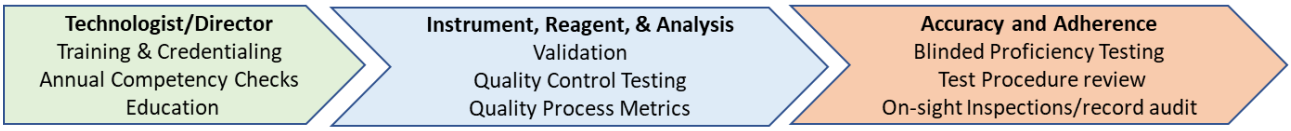
Transplantation is the treatment of choice for patients with end-stage-organ failure of kidneys, heart, lung, liver, pancreas, intestine and for patients in need of hematopoietic stem cell transplants, including those suffering blood malignancies (e.g., leukemias) and many other life-threatening diseases. The exemption of Histocompatibility testing from FDA regulation in the DAIA recognizes, in part, the use of the lymphocyte crossmatch test as a primary "gate keeper" to determine transplant compatibility; the crossmatch is mandated by CLIA standard §493.1281, which specifies quality metrics and parallel proficiency testing. To date, no FDA cleared crossmatch tests exist because the primary test components consist of patient sera and donor lymphocytes.

As a threshold matter, we agree with the FDA's categorization of Histocompatibility testing as "high risk" given the complexity of our testing and the direct involvement in clinical decision-making surrounding lifesaving transplants. This reality has necessitated the development of the current, multilayer processes that exist to ensure quality testing and successful outcomes for both solid organ and stem cell transplantation. ASHI is pleased to provide the following overview of the unique, existing layers of mandatory regulations ensuring the validity and safety of Histocompatibility testing and demonstrating that continued exemption is warranted and a sound policy.

In addition, we present concerns that FDA oversight risks disrupting Histocompatibility testing necessary for the safe performance of solid organ and hematopoietic stem cell transplants and consequently limiting access to these lifesaving treatment options.

1. Sufficient regulatory oversight currently exists.

Analytical Validity: CLIA, ASHI



In accordance with the final rule implementing the accreditation provisions of the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (57 FR 33992), the Centers for Medicare & Medicaid Services (CMS) may grant deeming authority to an accreditation organization if its requirements are equal to or more stringent than the applicable CLIA program laboratory requirements in 42 CFR part 493. ASHI was granted deemed status by CLIA in 1994 to provide regulatory oversight for the mandatory accreditation required for all clinical human leukocyte antigen (HLA) laboratories. This accreditation process ensures adherence to specific histocompatibility and immunogenetics regulatory standards that go beyond the mandates of CLIA.

This strict oversight ensures the analytical validity (accuracy and precision) of tests to identify the presence or absence of particular analytes (HLA gene or HLA antibody). ASHI accreditation involves robust education and training requirements, annual review of policies and procedures, review of blinded proficiency testing results, and onsite audits of records. ASHI also performs an external review for all test validations, whether that test is FDA approved or is a laboratory developed test.

Analytical and Clinical Validity: OPTN/UNOS, NMDP, FACT

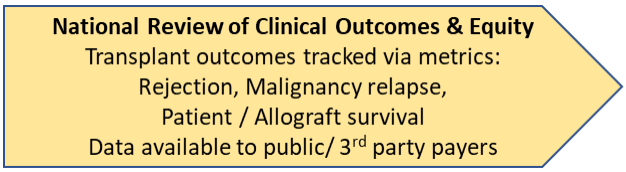
Unlike any other diagnostic testing field, the accuracy and clinical validity of Histocompatibility testing in support of solid organ and hematopoietic stem cell transplantation is subjected to a mandatory review process by the United Network for Organ Sharing (UNOS)/ the Organ Procurement and Transplantation Network (OPTN)[1] and the National Marrow Donor Program (NMDP)[2]; additional voluntary oversight for hematopoietic stem transplantation is provided by the Foundation for the Accreditation of Cellular Therapy (FACT)[3].

Mandatory oversight by UNOS/OPTN and NMDP involves a complex network of parallel

[1] https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf
[2] https://network.bethematchclinical.org/transplant-centers/nmdp-standards/?_ga=2.234888513.1194833903.1626781322-9854937.1624043165
[3] http://www.factwebsite.org/Inner.aspx?id=486&blogid=106&terms=hla+standards

testing, which is performed as multiple organs from each deceased donor transit through the transplant process of crossmatching and verification HLA typing at different recipient transplant centers. This parallel testing occurs 1) across different laboratories; 2) using unique and separate patient samples; and 3) using different test methods and reagent sets. The cumulative testing results are uploaded and reviewed for accuracy. ALL discrepancies are investigated within a proscribed timeline by the regulatory agencies; the transplant program and the HLA laboratory.

Clinical Validity and Utility: SRTR and CIBMTR



Clinical validity refers to how well a positive/negative test result correlates with clinical outcomes. Each transplant program must participate in clinical outcome monitoring through The Scientific Registry of Transplant Recipients (SRTR) and the Center for International Blood and Marrow Transplant Research (CIBMTR), in solid organ and hematopoietic cell transplants, respectively. Clinical endpoints to assess the clinical validity of Histocompatibility testing include rejection rates, transplant rates, waiting times, stem cell engraftment, malignancy relapse, and quality/success of transplantation using patient and allograft survival outcome metrics.

Regulatory Agencies specific to Histocompatibility Testing and Transplantation

The following provides a brief summary of organizations involved in ensuring the analytical and clinical validity of Histocompatibility testing and patient safety in the transplant discipline:

ASHI: The American Society of Histocompatibility and Immunogenetics was established in 1972 to provide oversight specific to HLA high complexity testing and ensure accuracy and validity of HLA laboratory testing (https://www.ashi-hla.org/). ASHI was granted deemed status by the Centers for Medicare & Medicaid Services (CMS) in 1994 as a mandatory accrediting organization for clinical HLA laboratories utilizing a robust process outlined in Analytical Validity section.

OPTN/UNOS: The Organ Procurement and Transplantation Network/United Network for Organ Sharing (https://unos.org) plays a critical oversight role in the operation and accuracy monitoring of Histocompatibility laboratories supporting solid organ transplant programs. OPTN/UNOS bylaws specify mandatory criteria for facilities, personnel and clinical testing. Beyond CLIA requirements that accredited labs must meet, OPTN/UNOS also defines more detailed clinical testing guidelines (see Histocompatibility in Section 4) specific for solid organ transplant that laboratories must follow.

SRTR: The Scientific Registry of Transplant Recipients provides advanced statistical and epidemiological analyses related to solid organ allocation and transplantation in support of the Department of Health and Human Services and its agents in their oversight of the national organ transplantation system. SRTR is a trusted resource for epidemiological data and statistical analyses regarding the status of solid organ transplantation and the transplantation system in the United States (https://srtr.transplant.hrsa.gov).

NMDP: The National Marrow Donor Program is an organization that coordinates the identification and procurement of peripheral blood or bone marrow from unrelated donors (https://bethematch.org). The NMDP mandates specific criteria for HLA typing in support of these transplants and oversees the accuracy of HLA laboratory typing. NMDP has mandatory processes in place to review HLA typing data and address discrepancies to ensure the accuracy of testing

CIBMTR: The Center for International Blood and Marrow Transplant Research is a research collaboration between the National Marrow Donor Program (NMDP)/Be the Match and the Medical College of Wisconsin. The CIBMTR collaborates with the global scientific community to advance hematopoietic stem cell transplantation and other cellular therapy worldwide to increase survival and enrich quality of life for patients. The CIBMTR is a robust, collaborative affiliation and outcomes-focused research endeavor (https://www.cibmtr.org/Pages/index.aspx). Outcomes reporting to the CIBMTR by hematopoietic stem cell transplantation (HSCT) programs is mandatory in the US.

FACT: The Foundation for Accreditation of Cellular Therapy provides voluntary accreditation for hematopoietic cell transplant programs (http://www.factwebsite.org). FACT is, in essence, an international counterpart to OPTN/UNOS, but with respect to HCT. As part of the process, FACT standards define HLA typing requirements for HSCT and require that affiliated laboratories be accredited by national agencies. As a result, FACT provides an additional level of oversight of clinical application of HLA laboratory testing

2. Negative impact on patient morbidity and mortality

Histocompatibility testing is performed by relatively few, geographically dispersed HLA laboratories that are staffed by a small number of highly trained technologists with required oversight from a board-certified HLA Laboratory Director. We feel strongly that FDA oversight of Histocompatibility testing would have unintended negative consequences. Specifically, ASHI is concerned this added administrative hurtle will negatively impact access to life saving solid organ and hematopoietic stem cell transplants through the disruption of accurate testing and potential closure of small Histocompatibility laboratories due to the inability to support this additional regulatory burden given the continued discovery of HLA variants/diversity within the HLA genetic system. It is recognized scientifically that the HLA system exhibits variability unlike any other system in nature, requiring ASHI mandated annual updates of HLA gene variant databases (https://www.ebi.ac.uk/ipd/imgt/hla/docs/release.html) and validation of corresponding analysis software. This diversity also requires the need for flexibility to optimize testing and provide accurate Histocompatibility testing results for specific patient demographics. This flexibility exists under the current regulatory regime, while also ensuring appropriate oversight and assurance of validity and patient outcomes.

Importantly, the closure of smaller HLA laboratories would disproportionally impact minority groups (unique HLA gene variants) and more socioeconomically burdened areas of our country[4]. The unintended consequence of impeding innovation would impact the hard to

[4] JAMA Surg. 2020;155(8):679-681. doi:10.1001/jamasurg.2020.1455

transplant patients, such as immunologically complex patients, who are predominantly female and non-white[567], and patients living in rural areas with limited access to healthcare.

Laboratory Developed Tests are essential for accurate Histocompatibility testing and successful patient outcomes, as well as ensuring equitable access to transplantation. The expertise providing the optimal regulatory oversight for these tests lie within the current transplant regulatory network outlined in this document. ASHI is grateful for the opportunity to provide this overview and sincerely appreciates consideration of our position and request. We welcome the opportunity to answer any questions or provide any additional follow-up materials that would be helpful.

[5] https://onlinelibraryOPTN/SRTR 2019 Annual Data Report:.wiley.com/toc/16006143/2021/21/S2
[6] Ann Transplant. 2019 Jun 28;24:383-392. doi: 10.12659/AOT.915769.
[7] Clin J Am Soc Nephrol. 2016 Mar 7;11(3):505-11. doi: 10.2215/CJN.07720715.