

ASHI POSITION ON FDA OVERSIGHT

The American Society for Histocompatibility and Immunogenetics

The American Society for Histocompatibility and Immunogenetics, or ASHI, is a not-for-profit, professional association comprised of immunologists, geneticists, transplant physicians and surgeons. ASHI is dedicated to advancing the science and application of histocompatibility and immunogenetics and promoting the highest standards of laboratory testing in the interest of optimal patient care and, to this end, ASHI applauds the efforts of the Food and Drug Administration to improve health care through thoughtful regulatory oversight. ASHI is concerned, however, that strict and/or premature enforcement of the new FDA guidance on the sale of research use only (RUO) and investigational use only (IUO) IVD products will significantly reduce the availability of laboratory testing needed for the safe practice of transplantation, detrimentally impacting transplant patient care. Many of the laboratory derived tests (LDTs) used in our laboratories are dependent on access to RUO or IUO reagents or devices. **ASHI proposes that the FDA partner with professional groups to permit the continued safe performance of critical LDTs in testing for transplantation and disease analysis, and to permit the use of RUO and IUO IVDs in these LDTs.**

Histocompatibility Testing Must Rely on Laboratory Developed Tests

Clinically, histocompatibility testing is required for transplantation of solid organs and hematopoietic stem cells and is utilized to investigate the underlying basis of certain diseases and, to develop new and improve existing vaccines. Histocompatibility testing utilizes a variety of laboratory developed tests which **do** support optimal care of transplant and transfusion patients because of the way in which the analytes are tested, the requirements for test validation, and the oversight of laboratory performance. Further, a long history of international workshops and scores of peer-reviewed scientific and medical publications on clinical outcomes analyses in transplantation, contribute to both the analytical and clinical validity of the tests. ASHI, the National Marrow Donor Program (NMDP), the American Society of Transplantation, the American Society for Blood and Marrow Transplantation, other professional organizations and sub-specialty societies lead the process of integrating LDTs into routine practice based on this solid peer-reviewed research on clinical outcomes, while maintaining high quality standards for the testing.

Histocompatibility Testing Analytes are Tested by Multiple Assays

In clinical histocompatibility testing analytes are often tested using multiple assays and technologies. This is necessary because of the analyte complexity for which no single assay provides a definitive answer. These tests are of high complexity as defined in the Federal Regulations implementing CLIA, and require careful and expert interpretation. Notably, histocompatibility testing is one of only two clinical laboratory sciences for which not only the director, but also, the technical supervisor must have an appropriate earned doctoral degree. Clinical interpretation and utilization of test results is carried out through close interaction and communication between the laboratory scientists and the clinical team providing direct patient care. Risk to patients is reduced because the clinical care relies on multiple medical criteria and information from other assays and measurements such as biopsies, hematologic and biochemical assays, and radiology.

Use of Any Test Requires an Elaborate Validation Process

Utilization of any assay in an ASHI accredited histocompatibility laboratory requires a rigorous validation process and undergoes careful and regular oversight. Most laboratories performing testing for solid organ and tissue transplantation are approved by the ASHI Accreditation Program. ASHI has an elaborate set of standards and laboratory evaluation program that

exceed the requirements specified in the Federal Regulations and, as such, ASHI is deemed by the Centers for Medicare and Medicaid Services to perform laboratory evaluations for CLIA certification. ASHI requirements for test validation include data showing that the test meets all necessary performance criteria including specificity, sensitivity, accuracy, reproducibility, precision, reportable range of results, normal values, and limitations; the step-by-step procedure; description of personnel training and documentation of their competency; quality control procedures; equipment calibration data; parallel testing with samples tested by an approved method; and, for methodologies new to the laboratory, blinded parallel testing with a laboratory accredited by ASHI to perform that methodology. After careful validation, all newly purchased reagents (RUO, IUO or any other) are parallel tested with previous lots as another quality assurance measure. An internationally respected, curated database of HLA sequence alignments is available to all laboratories performing identification of HLA alleles. This is the only known curated, genomic sequence database for personalized medicine use.

Multiple government agencies and professional societies are involved in the oversight of histocompatibility laboratories. These include, CMS, Joint Commission, the National Organ Procurement and Transplantation Network, the NMDP, the College of American Pathologists, the American Association of Blood Banks, and the Healthcare Facilities Accreditation Program.

Limited Commercial Assays for Histocompatibility Testing are Available.

Finally, we note that there are few commercial entities providing FDA cleared assays for histocompatibility testing. New molecular and cellular testing tools are now a quantum leap in sensitivity and specificity, significantly raising the quality of testing. Laboratory developed testing continues to evolve in response to a need that has not or cannot be met by commercial entities in a timely way.

Each year in the United States, > 28,000 solid organ transplants are performed, with 116,000 patients on waiting lists, including >91,000 needing kidney transplantation and 20,000 needing heart, liver and/or lung transplants. There are also > 8,000 hematopoietic stem cell transplants, with >30,000 stem cell donor searches (overseen and regulated by the NMDP) per year. Most importantly, two critical tests necessary for all solid organ and/or hematopoietic stem cell transplants, are not available commercially. The first of these is the donor-recipient crossmatch, which is performed by testing recipient or donor serum against target cells from the donor or recipient, respectively. This test cannot be produced commercially as it utilizes donor and recipient biologic materials. The second is the identification of HLA alleles performed by DNA sequencing using analyte-specific reagents from commercial suppliers. At present, there are no FDA cleared HLA sequencing kits nor cleared automated sequencers. There are also no flow cytometers cleared for the performance of crossmatch tests. **Disapproval of LDTs, or limiting access to commercially produced reagents required for these laboratory developed tests, for histocompatibility testing would reverse the progress we have made in increasing safety in transplantation and assuring equity of access to transplantation. Stem cell transplantation would be restricted to those recipients with family donors. Organ transplantation would be restricted to recipients with no alloantibodies. Both cases would lead to undue patient harm and extraordinary expense.**

Oversight of much needed laboratory developed tests is a critical, daunting task. Until FDA-cleared testing systems that meet current professional association standards become available, ASHI requests that the agency continue its discretionary enforcement policy for laboratories and vendors utilizing ASR or RUO reagents and RUO instruments for histocompatibility typing. **ASHI proposes that the FDA partner with professional societies that are already providing needed oversight in order to permit the continued safe performance of critical laboratory developed tests.**