



**ASSOCIATION FOR MOLECULAR PATHOLOGY**  
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**Association for Molecular Pathology**  
**Comments on the draft discussion of the Diagnostic Accuracy and Innovation Act (DAIA)**

Thank you for the opportunity to provide these supplemental comments on the draft legislation “Diagnostic Accuracy and Innovation Act” (DAIA). The Association for Molecular Pathology (AMP) truly appreciates your willingness to engage a broad range of stakeholders and for the time and effort that you have devoted to this important issue. These comments should be taken into consideration along with AMP’s [general position](#) on the discussion draft that was submitted on April 7, 2017. While we have long believed that the regulation of manufactured diagnostic test kits and systems (IVDs) needs to be less onerous, we maintain that the Food and Drug Administration (FDA) is not the appropriate agency to regulate laboratory developed testing procedures (LDPs). We hope that these supplemental comments highlight where FDA regulation of LDPs will drastically hinder the advancement of precision medicine and interfere with the practice of medicine.

**Pages 2-13**

- **Page 2, beginning line 10:** The draft legislation attempts to create one term, in vitro clinical test (IVCT), for both laboratory developed procedures (LDPs) and in vitro diagnostic kits (IVDs), setting the stage to establishing a common regulatory pathway for both. IVDs are distributed in interstate commerce to laboratory customers of varying skill levels and over whom the manufacturer has no control. LDPs are not designed and developed by manufacturers but by board-certified professionals who perform these procedures as a part of their professional practice. The central role of the medical professional throughout the entire test process minimizes the risks of LDPs and ensures their safe and effective use. It is the laboratory director’s legal and professional responsibility to assure the safety, accuracy and appropriateness of all laboratory tests. Thus, due to the inherent differences in IVD kits and LDPs, a common regulatory pathway is inappropriate and unattainable.
- **Page 3, beginning line 13:** The definition of ‘laboratory test protocol’ in the draft segregates the various activities required for high quality testing, where the design of a testing procedure is excluded from laboratory operations. This proposed definition is not only in opposition to CMS’s current definition of examination and procedures, it also conflicts with the clarifying definition of laboratory developed testing procedures (LDPs) in AMP’s CLIA modernization proposal. AMP suggests that the draft legislation use the phrase laboratory developed testing procedures, not laboratory test protocol, and that you utilize AMP’s suggested definition which is “a testing procedure or service that encompasses and integrates, in a single CLIA-certified laboratory, the design, development, validation, verification, and quality systems used in laboratory testing and interpretative reporting in the context of clinical care or public health services.” Unlike manufactured, packaged, and distributed IVD test kits, LDPs are a medical service, which encompass the design, validation, performance, ongoing monitoring, and interpretation of test results. These activities are intrinsically linked during the normal operations of a laboratory and should not be separate.

Furthermore, the draft’s definition of ‘laboratory test protocol’ inappropriately infers that these testing procedures are unfinished products and of lower quality as compared to IVDs. This is incorrect and in many

cases, LDPs fill a key clinical need not provided by IVDs. There are numerous examples of LDPs that provide faster diagnosis or a better understanding of the patient's disease than the available IVD and led to demonstrated improvements in care management.<sup>1</sup> Additionally, LDPs are integral to patient care because, unlike IVDs, a board-certified professional is involved in the whole testing procedures and thus is able to incorporate context and patient specific information. As an example, a published case study of a 44-year-old man with non-small-cell lung cancer worsened after a single cycle of chemotherapy.<sup>2</sup> As a result, additional testing was done to determine his tumors' positivity for the *ALK* mutation. The dominant method for determining *ALK* mutation positivity uses an IVD kit by Abbott called the *ALK* break-apart fluorescent in situ hybridization (FISH) assay. The assay performs well with clearly defined positivity criteria, but borderline or atypical negative cases occur. The use of the IVD indicated that the patient was not positive for an *ALK* mutation. However, a professional's use of an LDP revealed otherwise which further indicated that patient might benefit from the use of a treatment called crizotinib. The cancer patient was given the treatment and showed significant improvement. If the healthcare providers had only relied upon the IVD results, the patient outcome would have been very different.

The quality of LDPs is very high, as indicated by Proficiency Assessments conducted by the College of American Pathologists (CAP). For example, a recent assessment of over 1,000 gene mutations from cancer panel testing in 111 laboratories showed 98.3% concordance.<sup>1</sup>

- **Page 5, beginning line 17:** AMP opposes that the draft legislation seeks to widely expand FDA's jurisdiction to encompass regulation of LDPs, which is a medical service and emphasizes the ongoing involvement of appropriately trained and qualified professionals in every aspect of the procedure, in addition to the interpretation of results. As such, LDPs represent the practice of medicine and the FDA has consistently asserted that it does not regulate the practice of medicine.
- **Page 6, beginning line 14:** The draft discussion attempts to include language that limits FDA from interfering with the practice of medicine for treating physicians, but does not appropriately limit FDA regulation of the medical practice conducted by molecular pathologists, which already includes the legal responsibility of the testing performed in their laboratories.
- **Page 6, beginning line 22:** We do not believe that the resources required to create a new center at FDA is warranted or feasible. Instead, we urge you to focus this legislation on streamlining the regulation of IVDs and making it much easier for manufacturers to improve and update their products, e.g., add specimen types or indications for use. We likewise urge you to consider an improved approach to addressing safety concerns and enhancing transparency while maintaining patient access to innovative testing by updating the existing CLIA program to accommodate the current state of and future updates to the field of molecular pathology.
- **Page 7, beginning line 24:** We agree that it is necessary to include language that says that clinical validity excludes clinical utility. This definition should also be used by the CLIA program in their activities associated with the regulation LDPs as outlined in our CLIA modernization proposal.

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<sup>1</sup> Kaul, KL et al., The Case for Laboratory Developed Procedures: Quality and Positive Impact on Patient Care. *Academic Pathology*. 2017; 4: 1-21 <http://journals.sagepub.com/doi/full/10.1177/2374289517708309>

<sup>2</sup> Ren S, Hirsch FR, Varella-Garcia M, et al. Atypical Negative *ALK* Break-Apart FISH Harboring a Crizotinib-Responsive *ALK* Rearrangement in Non-Small-Cell Lung Cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2014;9(3):e21-e23. doi:10.1097/JTO.000000000000013.

- **Page 9, beginning line 12:** Again, it is inappropriate for FDA to have jurisdiction over LDPs, even those that are modified.
- **Page 10, beginning line 5:** AMP urges you to expand the definition of ‘rare disease in vitro clinical test’ to reflect the current definition of rare disease which is a disease or disorder with a prevalence of fewer than 200,000 newly diagnosed individuals per year in the United States.<sup>3</sup>

**Pages 13-81**

In general, AMP does not support FDA regulation of LDPs and thus, does not believe that these sections should apply to LDPs. In addition:

- **Page 13, beginning line 18:** In our CLIA modernization proposal, AMP provides a definition of the highest risk LDP. In summary, it is an LDP used to predict risk or risk of progression of a life-threatening disease ***and*** uses methodologies that involve proprietary algorithms or computations. AMP believes that transparency is a critical component of how much risk a test presents to a patient. When a test uses proprietary methodology, the test cannot be easily evaluated by the broader community of appropriately trained professionals. AMP believes that third party review is warranted for such tests. Proprietary methodology is not addressed in the draft legislation’s risk classification system.
- **Page 15, beginning line 22:** We urge you to consider the expertise of laboratory professionals as a risk reducing factor. With every LDP exists inherent connectedness and interdependence amongst the components of the test, the results, and the role of these specialty-trained and certified health care professionals.
- **Page 64, beginning line 13:** The necessary requirements associated with custom in vitro clinical tests (IVCT) in the draft discussion may be useful in a discussion exclusively devoted to IVD kits, but are overly restrictive for LDPs. The narrow definition will severely impede the development of new testing services that uniquely serve a patient’s need. A nimble environment that promotes innovation and allows testing services to be quickly adapted and improved by appropriately qualified professionals is central to the continued advancement of personalized, or precision, medicine. One example of an improvement to this section includes removing lines 20-23 on page 65 which would result in greater flexibility for health care professionals to develop patient-specific tests in instances where currently available options are not appropriate. The criteria of genetic test designed for certain “unique pathology or physiological condition” is too restrictive because often currently available tests for a particular condition may fail to include all relevant analytes or biomarkers that may be associated with a set of symptoms for a unique clinical situation. Beyond the association with a condition, other factors such as technology and platform capabilities, clinical presentation, unknown variants, sample quality, etc. may indicate the need for a custom IVCT. Moreover, tests are not designed to “treat” a condition, but are intended to provide information about the analytes and biomarkers of interest to help a health care professional in making diagnostic and treatment decisions. As you may be aware, FDA recently approved Merck’s pembrolizumab (Keytruda) for the treatment of tumors that express one of two biomarkers regardless of where in the body the tumors are located showing that the government is taking steps towards the adoption of precision medicine where molecular profiles are used to inform medical decisions when appropriate. We urge you to remove language that would deter these advancements and tie FDA to old and outdated ways of thinking about molecular testing.

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<sup>3</sup> [21 CFR §316.21](#)

Thank you again for working with AMP on this difficult and complex issue. We look forward to continued discussions on this topic. We continue our commitment to the advancement of molecular diagnostics to inform medical care by holding ourselves to high standards and working with Congress and the Administration in that pursuit. If you have any questions or if AMP can be of further assistance, please contact Tara Burke at [TBurke@amp.org](mailto:TBurke@amp.org).

Sincerely,

Federico A. Monzon, MD  
President, Association for Molecular Pathology