ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

October 14, 2020

The Honorable Richard Burr
United States Senate
217 Russell Senate Office Building
Washington, DC 20510

The Honorable Diana DeGette
United States House of Representative
2111 Rayburn House Office Building
Washington, DC 20515

The Honorable Michael Bennet
United States Senate
261 Russell Senate Office Building
Washington, DC 20510

The Honorable Larry Bucshon
United States House of Representatives
2313 Rayburn House Office Building
Washington, DC 20515

RE: Verifying Accurate Leading-edge IVCT Development Act of 2020 (S 3404/HR 6102)

Dear Senators Burr and Bennet and Representatives DeGette and Bucshon:

The American College of Medical Genetics and Genomics (ACMG) appreciates the opportunity to provide feedback on the Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2020 (S 3404/HR 6102). ACMG is the only nationally recognized medical professional organization solely dedicated to improving health through the practice of medical genetics and genomics, and the only medical specialty society in the US that represents the full spectrum of medical genetics disciplines in a single organization. ACMG is the largest membership organization specifically for medical geneticists, providing education, resources, and a voice for more than 2,400 clinical and laboratory geneticists, genetic counselors, and other healthcare professionals, nearly 80% of whom are board-certified in the medical genetics specialties. ACMG's mission is to improve health through the clinical and laboratory practice of medical genetics as well as through advocacy, education, and clinical research, and to guide the safe and effective integration of genetics and genomics into all of medicine and healthcare, resulting in improved personal and public health.

The ACMG appreciates your interest in ensuring that *in vitro* diagnostics (IVDs) and laboratory-developed tests (LDTs) are accurate and of high quality. ACMG has long been committed to supporting the development of high-quality genetic and genomic tests that are both analytically and clinically valid, as demonstrated by our development and ongoing maintenance of expert-reviewed technical standards and guidelines, disease-specific standards and guidelines, clinical practice resources,

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and supporting policy statements. We are deeply concerned that the VALID Act ignores the notable differences between the manufacture and distribution of test kits and clinical testing performed by laboratory healthcare professionals. Further, we are concerned that implementation of the VALID Act would result in unintended consequences that would ultimately impede innovation and reduce access to clinical tests. When considering regulatory reform for clinical tests, we urge Congress to consider additional avenues to modernize clinical testing oversight that will not negatively impact testing laboratories, especially academic, nonprofit, and specialty laboratories. When applying least burdensome principles, the stark differences between manufacturers and laboratory professionals must be considered.

The VALID Act merges IVDs and LDTs into a single definition for *in vitro* clinical tests (IVCTs) as if they are the same. However, IVDs are manufactured products, currently regulated by the Food and Drug Administration (FDA) as medical devices, which are packaged and distributed throughout the country. The manufacture of the product is disconnected from how it is actually performed in a clinical laboratory, and the manufacturer is disconnected from the clinical evaluation of the patient being tested. LDTs, on the other hand, are developed and performed by board-certified laboratory professionals who engage with the ordering healthcare providers to deliver clinical testing services. Further, LDTs are not distributed. These laboratory professionals operate at the interface of new test development, research, clinical investigations, and clinical patient management which is the center of diagnostic innovation. In fact, even when testing laboratories use manufactured IVDs that have been approved by the FDA, they often still have to make adjustments to account for variations that may occur outside of the limited laboratory environments involved in the manufacturer's validation studies (e.g., temperature, humidity, length of exposure to various reagents). Such variations are to be expected since the tests are being performed in different laboratories than those used by the manufacturer for their validations, and such minor adjustments are necessary to ensure that tests perform as stated. In some cases, these adjustments may improve the tests and their performance. In other cases, as more scientific information surfaces, adjustments may be made to better serve a specific patient population's testing needs.

As another example, laboratories may receive specimen types from healthcare providers that differ from those used to validate the manufacturer's test kit. It is not reasonable for a manufacture to try to validate their tests and sample processing methods for every type of specimen that could be sent to a laboratory. Instead, the laboratory professionals must have the expertise and training to be able to adjust protocols as necessary to ensure the test is accurate for the specimen types they receive. Manufacturers often depend on this model in which laboratories expand the use of a test kit by validating on different specimen types under the Clinical Laboratory Improvement Amendments (CLIA). There may also be variances in the way that specimens are processed, including the storage and handling that occurs in the clinical setting before the specimen ever reaches the laboratory, which may require that the laboratory professional adjust their protocols. Laboratories are required by federal regulations under CLIA to ensure that LDT's perform as stated, and such adjustments are often necessary to ensure that those requirements are met. This also highlights the importance of CMS's enforcement of

regulations under CLIA to ensure that laboratory professionals are adequately trained and that tests perform appropriately in each individual laboratory setting.

Reliance on LDTs performed by highly trained, board-certified laboratory professionals also allows for a rapid response to emerging conditions and new scientific evidence about a given condition or technology. This was particularly evident with the COVID-19 pandemic response. The need for SARS-CoV-2 testing emerged rapidly and at a rate that could not be handled by the Centers for Disease Control and Prevention (CDC) and public health laboratories alone. Moreover, testing was needed even though we were still learning and trying to understand the disease. This is the precise type of situation in which we must rely on experienced laboratory professionals who can rapidly develop a testing procedure and continually improve that procedure as more information is learned. Offering services to their local medical center/hospital system should be considered the first line of testing.

Clinical testing laboratories were ready to use their wealth of knowledge and test-development experience to address the testing need, but this was delayed by FDA's decision to require that LDTs go through their emergency use authorization (EUA) process, even though they typically do not regulate such tests. This meant that laboratories had to navigate an agency that they are largely unfamiliar with, they had to wait on FDA to develop guidance on what type of studies and supporting information they wanted to accompany an EUA, and they also had to wait to acquire the reference specimens that FDA wanted them to use. FDA's lack of flexibility in validation designs was discordant with CLIA regulations and resulted in delay of EUA approvals for factors that do not affect test performance. LDTs are developed by experienced laboratory professionals and, in accordance with CLIA requirements, are continually adjusted based on available scientific information. Such laboratories could have had their tests ready by developing them in accordance with CLIA requirements then continuing to adjust them as additional positive patient specimens or other reference panels became available. This would have led to earlier access to testing in areas most affected which, as we have seen firsthand, is critical for controlling a pandemic such as the one we are currently facing.

As the SARS-CoV-2 testing needs surged, the FDA even realized that more flexibility with LDTs was needed. Therefore, they changed their guidance to allow CLIA-certified laboratories to offer their LDTs as soon as they were available then submit an EUA application to FDA at a later date. Thus, FDA agreed to let LDTs be made available without any sort of premarket review by FDA. The Department of Health and Human Services (HHS) also subsequently realized the issues created by FDA's fluctuating requirements for LDTs and issued a statement rescinding all FDA guidances and statements that required premarket review of any LDTs, not just those related to SARS-CoV-2 testing. This action meant that LDTs were no longer required to submit an EUA application at any point, or go through any other sort of premarket review/approval, which is consistent with how LDTs have been regulated for decades. On October 7th, FDA took this a step further and announced that they were now declining to review EUA requests for LDTs altogether so that they can focus their resources on EUAs for manufactured IVDs.

With regard to genetic and genomic tests, many are highly complex and based on recently acquired and rapidly evolving knowledge. Diagnosis is often not determined by the test result alone but requires consideration of the result within the context of medical and family histories and currently available clinical data. Such tests sometimes also require complex expert interpretation in which laboratory professionals provide individualized clinical reports in the context of a patient's medical and family history following a bidirectional communication with the ordering healthcare provider. Individualized professional interpretations such as these are a resource used by the physician to diagnose or make medical management decisions for the patient. These physician resources cross into the practice of medicine and are appropriately regulated by the federal government through enforcement of the Clinical Laboratory Improvement Amendments (CLIA) of 1988. The Verified Innovative Testing in American Laboratories (VITAL) Act of 2020 more accurately reflects the differences between IVDs and LDTs, and we encourage the VALID Act sponsors to incorporate the concepts of the VITAL Act. **The definition of IVCT in the VALID Act should be modified to exclude LDTs such that the VALID Act remains focused on manufactured IVD products and resulting legislation appropriately acknowledges the distinct differences between IVDs and LDTs.** Separate legislation, or a separate section of the VALID Act, could be created to address any components of existing LDT regulation under CLIA that need to be modernized. Further, the definition of an LDT needs to be clearly defined in federal legislation.

As requested, our top three areas of concern with the VALID Act include 1) unmanageable burden on academic and other laboratories; 2) risk categorization and the corresponding regulatory framework; and 3) modification of grandfathered tests.

1) Burden on Laboratories

By including LDTs in the definition of IVCT, the VALID Act would subject clinical testing laboratories, including hospital and academic laboratories, to unnecessarily burdensome regulations by two separate federal agencies. We are deeply concerned that this would result in unintended consequences such as delays in patient access to specialized and innovative tests, weakened test performance, and excessive burdens on laboratories resulting in reduced test offerings and even laboratory closures. While the VALID Act attempts to minimize specific regulatory duplications, the general burden of submitting information about their tests for review to both agencies, reporting to both agencies, and facilitating inspections from both agencies would be very burdensome and unnecessary. Much of the information that the FDA would require is already reviewed by CMS (e.g., analytical validity, test components, etc.), and any additional oversight needed could be addressed through modernization of CLIA. The burden of regulation by two agencies would only impact clinical testing laboratories as test manufacturers are not regulated by CMS.

Additionally, FDA's regulatory process is costly due to user fees, registration fees, and the cost of hiring regulatory staff. While manufacturers rely on profits from selling their

products and can easily manage these costs, clinical testing laboratories such as those in the academic or hospital setting do not sell products. They offer clinical services and rely on tenuous coverage and reimbursement policies. Laboratories already face notable financial constraints due to the reimbursement environment, and cuts to Medicare payment for clinical testing services due to the Protecting Access to Medicare Act (PAMA) of 2014 are increasingly threatening their ability to provide patient access to clinical testing services. Further, manufacturers often depend on a model in which they validate their test kits on a common specimen type knowing that laboratories will have to expand the use of that test kit by validating it on different specimen types under CLIA. Under the VALID act, clinical laboratories would have to absorb the financial burden of FDA submission for additional specimen types that are needed for patient care.

If the VALID Act were implemented as currently written, user fees would need to be waived for laboratories, especially academic, nonprofit, and other small or specialty laboratories. Clinical testing laboratories do not market commercial products, and we are unaware of any precedent in which such an establishment is required to pay user fees. Even with the waiving of user fees, many of these laboratories would still struggle to manage the costs of hiring the additional regulatory staff needed to navigate FDA's regulatory process and manage premarket submissions, notifications, and listings. Smaller laboratories and specialty laboratories may not be able to afford to customize tests and innovation would be impeded. To offset the costs, laboratories could be forced to reduce their test offerings or possibly close altogether, resulting in reduced offerings and access for patients. This would be especially concerning for laboratories that develop specialty tests for rare diseases that may not be widely available elsewhere. Such tests may not be developed by manufacturers relying on profits because the number of tests used throughout the year would be too low.

Another potential concern is that clinical testing could be pushed into more of a pharmaceutical company model with only several very large clinical laboratories developing tests because it's too much of a financial risk for smaller laboratories with lower test volumes. In addition to reducing market competition, fewer laboratories also mean greater impact when/if unexpected circumstances arise such as disruptions caused by supply issues, natural disasters, and other events that can significantly disrupt a large laboratory's ability to offer testing services. Closing of academic and clinical laboratories would also be concerning as this is where certified training programs for new medical genetics laboratory professionals are offered. The medical genetics field is already challenged by limited medical genetics training program openings, and the burdens imposed by the VALID Act could result in even fewer training programs.

2) Risk Categorization and Corresponding Regulatory Framework

ACMG continues to support a three-tiered framework for risk categorization in which the majority of tests would be considered low or moderate risk. Most, if not all, genetic tests cannot be interpreted in a vacuum and must be interpreted with knowledge of the

patient's medical and family history to inform diagnosis. While the VALID Act attempts to classify tests as either high- or low-risk, it also creates a third unofficial category of high-risk with mitigating measures. This further supports the need to use a three-tiered risk classification approach to address the gap that exists between high- and low-risk tests.

ACMG has published our recommendations for categorization of LDTs which takes into consideration two key elements: 1) risk with medical decision-making based on test results and the clinical significance of an erroneous result, and 2) factors that impact analytical performance and the likelihood of an erroneous result based on methodology. In addition, our recommendations describe the corresponding regulatory oversight structure that would be appropriate for each level of risk. While our statement does not get into which agency should be responsible for this framework, we note that much of the oversight is already being provided by CMS through CLIA, and modernization of CLIA would be the least burdensome and least disruptive way of enacting this regulatory approach. We also want to emphasize that this framework only works for LDTs because both development and performance of the tests as well as personnel educational and training requirements are regulated. This framework is not applicable to manufactured tests since the manufacturer is not involved in running and continually improving each of the tests it manufactures nor is it subject to the additional regulations provided under CLIA.

Please see the table below for our description of risk categories and oversight recommendations. We note that this table focuses specifically on LDTs for inherited diseases, but we believe the framework can be applied for all LDTs. For additional information, please see our complete statement.[1]

[1] South, S.T., McClure, M., Astbury, C. et al. Risk categorization for oversight of laboratory-developed tests for inherited conditions: an updated position statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*: 22, 983–985 (2020). https://doi.org/10.1038/s41436-020-0765-x

Table 1. ACMG's proposed approach to risk classification and oversight of laboratory-developed tests for inherited conditions.

Classification	Determining factors	Oversight recommendations	Potential mitigating factors
Low risk	The consequence of an incorrect result is unlikely to lead to serious morbidity or mortality for patients or their blood relatives. The test result is typically used in conjunction with other clinical findings to establish or confirm a diagnosis; no claim that the test result alone determines prognosis or direction of therapy. AND All aspects of the test methodology are well-established, commonly performed, and commonly applied to the clinical indication.	The laboratory internally performs analytical validation and determines adequacy of clinical validation before offering for clinical testing; the accreditor will verify that the laboratory performed appropriate validation studies during routinely scheduled inspections. The lab is overseen, and the test is developed and validated by a board-certified MD (ABPath/ABMGG), PhD (ABMGG), or equivalently trained and certified professional.	N/A
Moderate risk	The consequence of an incorrect result may lead to serious morbidity or mortality for patients or their blood relatives. The test result may be used for predicting disease progression or identifying whether a patient is eligible for a specific therapy. AND Test methodology is well understood and independently verifiable; interlaboratory comparisons can be performed or external proficiency testing is available.	The laboratory internally performs analytical validation and determines adequacy of clinical validation. Laboratory notifies third-party accreditor and provides validation summary prior to offering for clinical testing. Third-party review and approval not required prior to launch. Accreditor has option to request additional documents for review and/or may delay or suspend clinical testing. The lab is overseen, the test is developed and validated, and the test results are interpreted by a board-certified MD (ABPath/ABMGG), PhD (ABMGG), or equivalently trained and certified professional.	N/A
High risk	The consequence of an incorrect result could lead to serious morbidity or mortality for patients or their blood relatives. The test is used to predict risk of a disease associated with, progression of a disease associated with, or patient eligibility for a specific therapy associated with significant morbidity or mortality. AND Test methodology is based on a unique algorithm or proprietary method and result is not independently verifiable (interlaboratory comparisons cannot be performed).	The laboratory must submit comprehensive validation documentation to the third-party accreditor for review and receive approval before offering the test clinically. The accreditor determines compliance. Because of constantly expanding knowledge and technology, a rapid turnaround time for the accreditor review is necessary. The lab is overseen, the test is developed and validated, and the test results are interpreted by a board-certified MD (ABPath/ABMGG), PhD (ABMGG), or equivalently trained and certified professional.	External, regulated proficiency testing is available in which the lab actively participates. Established clinical protocol for use of test, including provider and patient education components. May include user comprehension verification. Extensive peer-reviewed literature establishing the analytical parameters and clinical utility of the test. Appropriate labeling, advertising, and information on laboratory website and provided when requested.

ABMGG American Board of Medical Genetics and Genomics, *ABPath* American Board of Pathology, *ACMG* American College of Medical Genetics and Genomics.

3) Modification of Grandfathered Tests

We appreciate that the VALID Act includes provisions to allow tests already being used in laboratories to be exempted from premarket review requirements, although they would still be subject to requirements for registration and listing (587I) and adverse reporting requirements (587L). The VALID Act lists the following as key components necessary to be considered a grandfather test:

- the test was enacted before date of enactment of the VALID Act;
- the test is developed in a laboratory that is CLIA-certified for high complexity tests;
- the test is performed in same laboratory it was developed in or another laboratory for which a CLIA certificate is in effect within the same corporate organization and having common ownership by the same parent corporation; and
- the test is not modified after the date of enactment of the VALID Act in a manner such that the test is a new IVCT as described in 587A(l).

While we agree that a test should not be covered under the grandfathered provision if it is modified to the extent that it becomes a new test, we are concerned about the definition in 587A(l) and what the VALID Act considers to be a new test. The VALID Act explains that an IVCT would be considered a new test if the modification affects the analytical or clinical validity of the test or the modification causes the test to no longer comply with applicable mitigating measures (587E) or restrictions (587N). However, a modification that positively affects the analytical or clinical validity should not necessarily be considered a new test. To be sure that available tests remain current with new scientific evidence, laboratories modify and improve their tests on a regular basis. This continual improvement may also help improve efficiency and decrease the cost of testing, and it is important that Congress not place regulatory burden on well-validated tests currently performed in laboratories that might discourage a laboratory from pursuing continual improvement.

Modifications to clinical tests are common. As of 2018 it was estimated that almost 75,000 genetic tests were being offered by CLIA-certified laboratories.[2] This number only reflects genetic tests and does not include other diagnostics such as those for infectious diseases or common clinical chemistry tests. While some tests may be straightforward and unlikely to need modification, adjustments may be common for a good portion of these tests. It would be unrealistic to expect FDA to review every test each time it is modified to improve performance. Premarket review of these continual modifications would overwhelm the FDA and impede their ability to complete reviews in a timely manner. Such reviews would also delay patient access, increase costs to the clinical laboratory, and discourage continual improvement.

[2] The Current Landscape of Genetic Testing, 2018 Edition. White Paper, Concert Genetics (April 2018).

For example, we are continually learning more about genes that contribute to the risk of developing hereditary breast or ovarian cancer. A laboratory may add or remove a gene from a testing panel as more clinical evidence and standards become available. While adding or removing a gene requires new analytical and clinical validations, it does not change the overall chemistry of the test and should not require a new review. Records for the new analytical and clinical validations would be retained though and could be made available for review as needed, such as during inspection. As another example, as technology advances we are able to replace manual procedures with automated or semi-automated methods. This improves efficiency and often reduces costs but does not change the overall chemistry of the test and should not require a new premarket review.

We are most concerned about the three issues described above which point to problems with the overarching framework of the VALID Act. However, we also provide additional comments about specific parts of the VALID Act that would create other problems if enacted.

Definitions (Section 587)

Cross-Referenced Tests (Section 587(5)) – The VALID Act defines a cross-referenced test as an IVCT that references in its labeling the name or intended use of another medical product that is not an IVCT. We seek clarification regarding whether this would also include a test that references a specific group of therapeutic products or general type of product used to treat a given condition.

Developer (Section 587(7)) – The VALID Act defines a developer as a person who engages in an activity described in the definition of develop (587(6)) which includes A) designing, validating, producing, manufacturing, remanufacturing, propagating, or assembling an IVCT; B) importing an IVCT; and C) modifying an IVCT. By referring to the developer as a person rather than an establishment or facility, it is unclear whether a person can be the developer for multiple establishments. For example, is a technology certification, which is given to the person, applicable to any other establishment for which that person serves as a developer? We would like additional clarification on the relationship between the developer (person) and establishment. Also, if a laboratory purchases a manufactured IVD, they still must validate that test for use within their institution regardless of whether any modifications are made to the test. A person should not be considered a developer for performing such standard validations, and we recommend that the definition of developer be adjusted accordingly. This distinction may also be important for issues related to product liability.

Low-Risk Test Exemption (587A(e))

Under the VALID Act, low-risk tests would be exempt from premarket review requirements but still subject to registration and listing requirements, adverse event reporting, quality system requirements, and labeling requirements. Further, the Secretary has the discretion to determine which tests are low-risk, and a list of low-risk tests would be maintained on FDA's website. Based on the current wording in the VALID Act, it appears that the Secretary can move tests on

or off of the low-risk list without requesting feedback from public stakeholders. Although we expect this to be a rare scenario, we recommend that public notice in the Federal Register, comment period, and review of stakeholder comments be required if the Secretary intends to reclassify a low-risk test as high-risk.

As noted earlier in this letter, ACMG proposes a three-tiered risk framework in which both low- and moderate-risk categories would not require premarket review prior to launch when that test is developed and performed within a single laboratory (i.e., an LDT). For moderate-risk tests, analytical and clinical validations would be submitted to a third-party reviewer prior to launch, but premarket review would not be required. This model works for LDTs since the laboratory is overseen, the test is developed and validated, and the test results are interpreted by a board-certified doctoral-level laboratory professional. The resulting laboratory report is reviewed, approved, and signed by the laboratory professional before becoming part of the medical record. The third-party reviewer is able to intervene at any point and even delay or suspend that clinical testing. This model does not work for manufacturers in which tests are developed in mass quantities and distributed throughout the US, and the manufacturer is not involved in performing each of those tests. This is an example that highlights the unique differences between LDTs and manufactured tests and why they cannot be appropriately regulated using a single regulatory framework.

Custom and Low-Volume Tests (Section 587A(h))

The VALID Act would exempt custom and low-volume tests from pre-market approval requirements, quality system requirements, and notification requirements, although they would still be subject to adverse event reporting and labeling requirements. A low-volume tests is defined as a test that is offered as an LDT and administered to no more than 5 patients a year. It is unclear where the 5-patient limit came from, and we request additional information regarding the rationale for this limit. If a condition is that rare, then it is likely that there may only be a single academic laboratory offering that testing, meaning that any patient suspected of having that condition would be tested by that same laboratory. Also, for genetic conditions, the biological parents of an affected individual often need to be tested to understand the familial or de novo contributions. Therefore, limits should be based on disease incidence rather than the number of people tested. We agree that there should be exemptions made for low-volume tests, however the 5-patient limit is too low. Tests such as these would only be developed and offered by laboratories that traditionally develop LDTs because there would be no monetary benefit for a manufacturer. Further, such tests would be subject to generic billing codes with poor reimbursement rates or not be reimbursed at all, even if there were 20 tests performed in that year. For certain rare conditions in which only a single laboratory in the US would provide testing for all patients in the US with that condition, these same challenges may be encountered even if 100 tests were performed. We recommend that the low-volume limit be reconsidered following discussion with clinical testing laboratories and development of a clear rationale to support that limit.

Under the VALID Act, a custom test is one that is developed or modified to diagnose a unique pathology or physical condition of a specific patient for which no other test is commercially available in the US and is not intended for use with respect with other patients. With regard to tests for suspected heritable conditions, we recommend that this definition be expanded to include the specific affected patient as well as the biological parents and family members for whom testing is needed to better understand the genetic contribution to disease in the affected individual. Such testing is common for genetic conditions, especially when a novel variant is suspected of causing or contributing to the disease. Further, we emphasize the point that such tests would still be subject to regulation, including validation and quality system requirements, under CLIA.

Humanitarian Test Exemption (Section 587A(g))

The VALID Act would allow tests to be exempt from premarket approval if the test is intended for use for a disease or condition for which no more than 10,000 (or such other number determined by the Secretary) individuals would be subject to negative or positive diagnosis by such test in the United States per year, and the test is not intended to diagnose a contagious disease or condition that is highly likely to result in fatal or irreversibly debilitating outcome and for which prompt and accurate diagnosis offers the opportunity to mitigate a public health impact of the condition. These tests would still be subject to other provisions of the VALID Act such as registration and listing requirements, adverse event reporting, quality system requirements, and labeling requirements.

It appears that this exemption is intended as an equivalent to a rare disease exception, however this description is based on a positive or negative diagnosis. Many genetic tests do not result in a direct diagnosis but rather are used to inform medical decision making or better understand the hereditary nature and familial risks of a disease. For example, a patient diagnosed with breast cancer may undergo genetic testing to better estimate the risk of recurrence before deciding whether to undergo a lumpectomy or mastectomy.

As many tests associated with rare conditions are not necessarily diagnostic, and it may be challenging to predict the number of tests that might be offered by other laboratories in a year, we recommend revising the exception so that it includes tests that are intended for use for a disease or condition for which the incidence of the disease or condition is no more than 10,000 (or such other number determined by the Secretary) in the US per year. We note that this approach is consistent with that already in use for humanitarian use device designations.

The humanitarian test exemption also needs to address how it would be applied to tests that can detect multiple conditions at once, such as gene panel tests. A genetic test that targets just a single condition may be under the humanitarian threshold, but a more efficient panel that includes targets for numerous conditions that have similar clinical presentations may be over the humanitarian threshold. In this case, the increased regulatory burden may be incentive to offer multiple individual tests rather than the more efficient panel testing. Performing multiple individual tests may increase the number of clinical visits required, increase the number or

amount of patient specimens that must be collected, prolong the testing or diagnostic process, and it would increase the overall cost of testing. Regulatory requirements must be developed in such a way that they do not discourage innovation or impose increased regulatory burdens for development of tests that are more cost effective for patients and payers or that more efficiently lead to a diagnosis.

Technology Certification (Section 587D)

Tests covered under a technology certification would be exempt from premarket review but still subject to inspections and other provisions of the VALID Act such as registration and listing requirements, adverse event reporting, quality system requirements, and labeling requirements. We agree with the idea of a technology certification pathway as a method for easing the burden of premarket review on laboratories, and we appreciate inclusion of the requirement for FDA hold a public meeting open to stakeholders. However, we urge Congress to ensure that this pathway is highly accessible to laboratories providing clinical testing services under CLIA, especially academic and nonprofit laboratories, where additional regulation and oversight exists.

Postmarket Surveillance (Section 587X)

Under the current version of the VALID Act, tests that are exempt from premarket review requirements could still be subject to postmarket surveillance as determined by the Secretary. However, we are concerned that this could become unreasonably burdensome for academic and other laboratories. We urge Congress to ensure that limits are placed on FDA's use of postmarket surveillance requirements for tests that are exempt from premarket review and regulated under CLIA.

User Fees (Section 9)

The financial impact of requiring clinical laboratories to comply with the provisions of the VALID Act could be devastating, resulting in reduced test offerings, laboratory closures, diminished innovation, and more. The impact to laboratories could be especially problematic for individuals with inherited conditions which are often rare, require highly specialized testing and interpretation, and require consideration of rapidly evolving scientific knowledge to better understand the genetic contribution to disease. A decrease in test offerings and the number of laboratories performing a test could have a negative impact on our efforts to improve equitable access to healthcare, including testing, for all communities within the US. While the financial impact extends well beyond that of user fees, we urge Congress to lessen the burden by exempting CLIA-certified clinical testing laboratories from the user fee requirements. At minimum, academic laboratories, nonprofit laboratories, and other small or specialty laboratories should be exempt from all user fee requirements. While this will not eliminate the negative impact to clinical testing, it will help minimize the impact. Additionally, a thorough financial impact analysis should be required before requiring user fees from any other type of clinical testing laboratory.

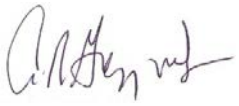
Conclusions

In recent years we have seen a significant increase in the demand for genetic testing services. Maintaining proper oversight and regulation of the development, performance, and ordering of these tests is crucial, and it is also imperative that federal regulations do not impede innovation, reduce patient access to tests, or increase costs to clinical laboratories. Flexible regulations must be appropriately consistent with the goals of the precision medicine initiative and accommodate the rapid pace at which our understanding of the genetic contributions to disease is expanding. Further, we must acknowledge the vital role of board-certified laboratory professionals and recognize their evolving contributions as healthcare professionals.

As such, we encourage Congress to revisit the overarching framework of the VALID Act. The definition of IVCT should be modified to exclude LDTs such that the VALID Act remains focused on manufactured IVD products and resulting legislation appropriately acknowledges the distinct differences between IVDs and LDTs. Separate legislation, or a separate section of the VALID Act, could be created to address any components of existing LDT regulation under CLIA that need to be modernized. Further, the definition of an LDT needs to be clearly defined in federal legislation.

We appreciate the opportunity to provide these comments and look forward to continuing to engage with Congress to identify the most appropriate and efficient way to ensure that clinical tests are highly accurate, readily accessible to all patients, and remain aligned with the most currently available clinical evidence. For additional questions or discussion, please contact Dr. Michelle McClure at mmcclure@acmg.net.

Sincerely,



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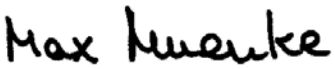

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