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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)

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This document represents an update to the proposed approach of the American College of Medical Genetics and Genomics (ACMG) to categorize laboratory-developed tests (LDTs) for inherited conditions according to risk.[1] Risk classification has historically been a determinant of whether, and to what extent, the US Food and Drug Administration (FDA) has overseen and regulated clinical tests. LDTs for constitutional variants continue to proliferate without a comprehensive federal regulatory framework in place. Therefore, an ACMG-appointed workgroup of laboratory and clinical geneticists considered the analytical and health care–related risks and implications resulting from laboratory testing of constitutional genetic information in a variety of contexts to develop a proposed approach. This document is provided as a proposed framework to guide federal agencies, policymakers, and other stakeholders.

The ACMG, through this document, has categorized testing for inherited conditions by utilizing a three-tiered risk-based system (Table 1) incorporating two elements. The first element is consistent with the usual FDA determination of testing-associated risk, whereby the FDA aligns risk with medical decision making based on the test results and the clinical significance of an erroneous result. The second element considers factors that impact analytical performance and the likelihood of an erroneous result based on methodology. It is recognized that novel technologies for an otherwise lower risk clinical application could temporarily place that test in a higher risk category until additional experience with the methodology is gained. The risk model specifies criteria that define each level of risk and identifies mitigating factors that could potentially lower the chance of inappropriate or harmful clinical action based on the test

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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.

result. It should be recognized that genetic testing is a process including not only the analytical phase addressed in this document, but also preanalytical and postanalytical components, which are beyond the scope of this document. Patient harm can occur in the preanalytical phase (e.g., lack of education/counseling, disregard for the informed consent process, incorrect test ordered) as well as postanalytically in the delivery of results and subsequent clinical follow-up.

Although the ACMG agrees that the elements recommended by the College of American Pathologists be included in the oversight framework for LDTs,[2] we recommend additional considerations for clinical constitutional genetic

testing. When initially considering risk level, there are elements that can reduce overall risk of a test, irrespective of the indication for testing (e.g., diagnostic, presymptomatic, predisposition, and pharmacogenomic genetic testing; carrier detection; preimplantation genetic diagnosis; and prenatal testing). These elements include factors such as (1) using nonproprietary methods or algorithms, (2) being amenable to interlaboratory comparisons, and (3) being evaluated by external proficiency testing. We are also proposing recommendations for laboratory director oversight of testing based upon risk (Table 1). Published data are available demonstrating that LDTs developed, validated, and performed within an experienced laboratory supervised by appropriately credentialed individuals are generally accurate.[3] Finally, as risk also exists in the pre- and postanalytical phases, we recommend pre- and post-test educational content/counseling developed and/or delivered by an appropriately trained professional, particularly for higher complexity tests.

DISCLOSURE

E.D.E. wishes to disclose stock ownership in Invitae and S.T.S. wishes to disclose stock ownership in 23andMe, Ancestry, and Peel Therapeutics. The other authors declare no conflicts of interest. All authors (except S.T.S., M.M., J.B., and M.S.W.) direct clinical testing laboratories that use laboratory-developed tests.

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