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The FDA and genetic testing: improper tools for a difficult problem

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ABSTRACT

The US Food and Drug Administration (FDA) has recently issued draft guidance on how it intends to regulate laboratory-developed tests, including genetic tests. This article argues that genetic tests differ from traditional targets of FDA regulation in both product as well as industry landscape, and that the FDA's traditional tools are ill-suited for regulating this space. While existing regulatory gaps do create risks in genetic testing, the regulatory burden of the FDA's proposal introduces new risks for both test providers and patients that may offset the benefits. Incremental expansion of current oversight outside of the FDA can mitigate many of the risks necessitating increased oversight while avoiding the creation of new ones that could undermine this industry.

KEYWORDS: genetic testing, FDA, laboratory-developed tests, LDTs

PART I. INTRODUCTION TO THE CURRENT STATE OF GENETIC TESTING

Background of genetic testing

Variations in DNA between individuals may cause or increase the likelihood of disease. Genetic testing is a tool that reads the DNA sequence of genes to identify variations. Not all variations have a noticeable effect on health or other traits, and a great deal of research is devoted towards identifying those that do. Over the last decade, the price of sequencing has dramatically decreased while the number of known genetic variants

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with human health associations has grown. As a result, genetic testing is increasingly being incorporated into clinical practice. Today, genetic tests can be used to screen a patient's risk of developing cancer or genetic diseases, for non-invasive early prenatal testing or to identify the likelihood of rare genetic diseases. At the time of writing, ClinVar, a user-generated database of genetic variations hosted by the National Institutes of Health, contains over 100,000 variations in more than 6000 genes.[1]

As genetic testing becomes more integrated into everyday clinical practice, more attention has been placed on the regulatory structure overseeing this field. The FDA has traditionally regulated clinical genetic testing in a patchwork approach depending on the type of test offered. Tests in which a physician sends a sample to a laboratory for analysis by scientists are classified as laboratory-developed tests (LDTs). The FDA claims jurisdiction over LDTs, but historically has exercised enforcement discretion, choosing not to regulate them. However, if a non-physician orders an equivalent test, the FDA classifies it as a direct to consumer test and as such is subject to pre-market review, even if the test is otherwise identical to an LDT. Finally, the FDA considers kits that enable testing to be done by non-experts *in vitro* diagnostics (IVDs), subject to pre-market review and approval. These classifications have created an inconsistent regulatory landscape where oversight of genetic testing is determined not by the risk of the test, but by the customer and method of testing.

Proposed FDA guidelines for LDT oversight

The FDA has recently issued draft guidance on new regulations for LDTs, intending to subject them to pre-market review and approval.[2] These guidelines call for measures including but not limited to pre-market approval, test registration, adverse event reporting, and establishment of quality control systems. LDTs will be stratified into three tiers based on risk, with the level of pre-market review varying by tier. Risk will not be based on the complexity of the test, but on its use and thus the harm to the patient if the test should give either a false positive or negative result.[3] This pre-market review is intended to evaluate the analytical and clinical validity of LDTs, which are not assured by current oversight. A test is analytically valid if it correctly identifies the sequence, copy number, or other marker being examined. Clinical validity describes the ability of that marker to correctly predict or detect the clinical condition for which the test is intended to screen.

In some sense, these proposed regulations bring regulatory coherence to genetic testing: all forms of genetic tests will be subject to pre-market approval by the FDA. This harmony is part of the motivation behind these regulations, as the FDA has expressed concern that manufacturers of IVDs will attempt to classify themselves as LDTs to avoid FDA regulatory oversight.[4] However, whether the FDA even has the

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1 National Center for Biotechnology Information, ClinVar submissions, http://www.ncbi.nlm.nih.gov/clinvar/submitters/ (accessed Dec. 23, 2014).

2 Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs), 79 FR 59776 (2014) [hereinafter *Guidance*] (proposed Oct. 3, 2014).

3 Molika Ashford, *AMP Members Reiterate Position on LDT Regulation; Questions to FDA Suggest Confusion Remains*, https://www.genomeweb.com/clinical-genomics/amp-members-reiterate-position-ldt-regulation-questions-fda-suggest-confusion-re (accessed Dec. 26, 2014).

4 *Id.*

regulatory authority to regulate LDTs has stirred controversy. Since LDTs are not physical items for sale but a process performed by researchers in a laboratory, proponents claim that LDT testing methods should qualify as a practice of medicine not subject to FDA authority; this interpretation may also have support in legislative intent.[5] Despite these claims, this analysis will assume FDA authority over LDTs and focus on the degree to which the FDA *should* regulate them. This will involve examining existing oversight of these tests, their risks, and the extent to which the FDA's guidelines address these risks. The consequences of regulation on the genetic testing industry will also be discussed. This paper will close by examining alternatives that may be more suitable for regulating this industry.

Existing oversight

Currently, the primary regulatory body for laboratories that perform genetic testing is the Center for Medicare and Medicaid Services (CMS). CMS certifies laboratories performing testing under Clinical Laboratory Improvement Amendment (CLIA) guidelines. These guidelines certify the accuracy and reliability of a laboratory to conduct the test.[6] However, CMS does not examine the safety of the test nor does it require demonstration of the clinical validity of the test. In other words, CMS certifies the qualifications of the laboratory and the testing methods, but it does not make assurances about its applications to the clinical setting.

CLIA certification then can be seen as an indication of laboratory quality. Certifying the methods in a laboratory means a lab does not have to seek approval each time it develops a new test or improves existing methods. So long as these changes are validated and properly documented, CLIA standards are satisfied.[7] This regulatory focus on a laboratory's analytical methods instead of specific review of each test is an approach to managing risk that eliminates a layer of oversight between innovation and the patient.

The LDT landscape also self-regulates with support from various associations and institutions. The National Institute of Standards and Technology, the CDC, and commercial vendors have developed quality control standards that laboratories may use to validate the accuracy of their methods.[8] Additionally professional societies, such as the American College of Medical Genetics and the Clinical Laboratory Standards Institute play an important role in drafting guidelines for clinical use of genetic tests.[9] Finally, the College of American Pathologists runs a Laboratory Accreditation Program, which requires member laboratories to undergo proficiency testing to certify their performance.[10] One of the downsides of self-regulation is enforcement. While these

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5 See *21st Century Cures: Examining the Regulation of Laboratory Developed Tests: Hearings Before the Subcomm. On Health of the House Comm. On Energy and Commerce*, 113th Cong., 2d. Sess. (2014) (statement of Alan Mertz, President, ACLA).

6 Centers for Medicare & Medicaid Services, *LDT and CLIA FAQs*, http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf (accessed Dec. 22, 2014) (CMS explanation of CMS and FDA authority on LDTs).

7 Guidance, *supra* note 2, at 7.

8 Staff of Secretary's Advisory Comm. on Genetics, Report on U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services at 116 (2008) [hereafter *SACGHS Report*].

9 *Id.* at 120.

10 *Id.* at 120. It also bears mentioning that there are other associations and institutes, including various state and local regulatory bodies, that have similar contributions but spelling these in detail is not pertinent here.

guidelines and standards are beneficial for participating laboratories in verifying their quality and methods above CLIA standards, there is no requirement to follow them or receive accreditation before listing a test.

Beyond the voluntary nature of accreditation and self-regulation, there are several oversight deficiencies. In addition to safety and efficacy concerns, CMS does not require (1) registration of available LDTs, (2) demonstration of clinical validity, (3) adverse event reporting, (4) any mechanism or quality system assurance to demonstrate safe manufacture of tests, or (5) post-market tracking of LDTs. The FDA believes that these problems—lack of assurance around safety and clinical validity plus the lack of adverse event reporting—create a regulatory gap that necessitates FDA intervention.[11]

PART II. EVALUATION OF PROPOSED OVERSIGHT

Risks of genetic tests

As a rationale for increasing regulatory scrutiny of LDTs, the FDA cites the changing market landscape for these tests. The FDA argues that enforcement discretion was a viable model when the tests were simple and more locally applied, but the growth in scale, complexity, and importance of these tests necessitate increased oversight. To continue with minimal FDA oversight, the FDA argument goes, would leave regulatory gaps that could lead to patient harm. An inaccurate result could very well shape a physician's diagnosis and treatment recommendations, and so the FDA is rightfully concerned that these results should be analytically accurate.

Beyond just ensuring that tests can report variants accurately, the FDA also wants to ensure the clinical validity of its tests. These tests can shape medical, personal, and lifestyle decisions due to their ability to screen for or predict genetic diseases. Genetic tests currently inform decisions such as whether to terminate a pregnancy, undergo a preventative mastectomy, or adjust drug dosages based on genetic sensitivity. It is important to make sure the implications of a genetic variant are known and understood to avoid misapplication or misinterpretation of a finding.

There is an additional risk from uncertainty. The impact of a genetic variant on a condition (its 'effect size') can often be quite small because of interactions with other genes and the environment. The probabilistic nature of some genetic tests can make demonstrating the utility of these tests difficult. It may be difficult for physicians to make diagnoses or inform clinical decisions based on measures with small predictive value. The potential for mitigating effects of genetic background, gender, or lifestyle make it difficult to know how the effects of genetic variants reported in the literature apply to other patient groups. These are risks of clinical utility, or how useful the results of genetic tests will be to physicians. While the FDA is not addressing clinical utility in its guidance, it is an important consideration. Because most of these risks deal with the inherent uncertainty of genetic testing, they also carry an additional risk of potentially unnecessary economic costs to the healthcare system.

FDA approach to managing risk and applicability to genetic testing

Traditionally, the FDA's regulatory philosophy is to operate under the Precautionary Principle, which mandates the provider of a product to first prove that the product is not

[11] Guidance, *supra* note 2, at 8.

harmful before being marketed and sold. In most cases, this requires that manufacturers demonstrate both the safety and efficacy of drug and device products before they can be used in patients. This perspective errs on the side of rejection or delay of beneficial treatments in order to prevent approval of an unsafe or ineffective treatment.[12] In other words, there may be delays in new treatments or fewer treatments overall, but we can be confident that the treatments that do exist are safe and efficacious.

The Precautionary Principle is highly appropriate for traditional drugs and devices for several reasons: (1) there are large potential risks to patients from untested products, (2) the products are usually for general application and so the risks can be examined in a small number of targeted studies, (3) the market delay imposed by regulation is proportional to the lengthy time a product is in development, (4) the path towards demonstrating safety and effectiveness is achievable and often clear, and (5) the product is not expected to change once it is in the market. Each of these qualities contributes to a large but knowable risk to patient safety that merits caution. Overall, this approach works well in fields like small molecule therapies or implantable devices where moderate innovation disruption is offset by prevention of large and real risks.

Genetic testing differs from products regulated using the Precautionary Principle. Differences include: (1) high analytical accuracy of genetic tests used to inform/screen rather than provide diagnosis; (2) clinical findings are often probabilistic and interpretation is individualized; (3) effect sizes from tests are often extremely low and interpretation is subject to change over time; (4) genetic testing is more rapidly changing with short development times—new variants are continuously discovered and testing methods can be quickly improved; and (5) genetic tests involve manual procedures and thus methods will vary across each laboratory. Each of these differences either lowers the risk of a genetic test or makes proof of efficacy more difficult and burdensome relative to development time.

In a patent-protected industry that rewards compliance with a legal monopoly and pricing power, the FDA approach is an appropriate fit. Existing players have sufficient resources to meet FDA criteria or find investors who can expect high margins if a product is approved. Genetic testing by contrast is marked by competition and in most cases tests are performed in in-house laboratories with limited ability to scale. Overall, the FDA's approach is mismatched with the current state of genetic testing, and it risks undermining the entire LDT industry.

Costs of increased FDA oversight

The FDA's proposed LDT regulations could have myriad effects on the genetic testing industry. Currently, labs across the country can be extremely reactive to new science. Thousands of laboratories compete to develop new tests or apply new techniques allowing for rapid innovation. For example, clinical laboratories developed an HIV screening test two years before an FDA-approved kit became available.[13] As mentioned above, our knowledge of clinically relevant genetic variants and methods for testing is continuously expanding. Patients directly benefit from this rapid transition from discovery to

[12] See Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1798 (1996).

[13] Edward R. Ashwood, *Letter to OMB from Lab Leaders* (2014), http://www.acla.com/wp-content/uploads/2014/07/Letter-to-OMB-from-Lab-Leaders.pdf (accessed Nov. 1, 2014).

the clinic. By compelling a pre-market review, the FDA will slow down laboratories' ability to provide physicians with tests based on genetic research. While true of any form of pre-market regulation, the effects are amplified with genetic testing due to the pace of discovery and improvement in the field.

Unique features of genetic testing would make these requirements particularly burdensome. The human genome has tens of thousands of tests that can potentially be offered, if one were to develop one sequencing test for each gene. Rather than requiring a general ability to sequence genes correctly, the FDA's draft regulations ask for validation of individual tests. By current estimates, there are more than 11,000 laboratories authorized to perform LDTs, and genetic tests for more than 1200 conditions are available today.[14] Some genetic tests examine multiple loci at once, and a requirement to validate each site increases the regulatory burden commensurately; this will discourage the use of new, powerful parallel sequencing technologies that allow for multisite testing. If every modification of a testing method or substitution of a gene panel requires a new submission, patients and physicians may have to wait months or longer for new tests.[15] In a field where science updates continuously, there is a risk of a widening lag between the latest science and latest medicine.[16] Worse still, this regulation could create disincentives for laboratories to improve or update their methods because scarce resources will only allow submission and resubmission for a limited number of tests. As an example of this, the FDA-approved HIV test mentioned above has changed little since initial approval because of regulatory cost of updating the test.[17] Ultimately, such a system could reshape the industry into one more closely resembling pharma with fewer players and high costs, thus negating much of the upside of the LDT model.

Further adding to the worry about disruption, the FDA has not yet declared whether it will expand its staff to accommodate the more than 11,000 genetic tests that will need to be reviewed and approved (to say nothing for the other forms of LDTs). The FDA will have a herculean task once it assumes this responsibility, increasing its workload significantly. This expansion would come when other efforts at the FDA are underway to expand its reach into mobile health applications and clinical decision software. It is difficult to see how the FDA can ensure speedy review of LDT tests while not extending the time frame of other 510(k) reviews.[18] The length of 510(k) reviews has already

[14] Kelly Servick, *FDA Defends Plan to Regulate Lab-Developed Tests*, Science Insider (2014), http://news.sciencemag.org/health/2014/09/fda-defends-plan-regulate-lab-developed-tests (accessed Sept. 10, 2014) (number of certified laboratories); Audrey Huang, Genetics & Public Policy Center, *FDA Regulation of Genetic Tests* (2008), http://www.dnapolicy.org/images/issuebriefpdfs/FDA_Regulation_of_Genetic_Test_Issue_Brief.pdf (accessed Nov. 1, 2014) (number of genetic conditions with tests offered).

[15] The FDA plans to require resubmission after altering a test or testing method. See Guidance, *supra* note 2, at 17 ('it should be noted that when a laboratory makes a significant change… the LDT will be considered by the FDA to be a new LDT.')

[16] This is independent of another problem with the FDA's approach: How to conduct pre-market approvals in a field where the interpretation about a variant may change in the time frame of FDA review. See Brian H. Shirts & Lisa S. Parker, *Changing Interpretations, Stable Genes: Responsibilities of Patients, Professionals, and Policy Makers in the Clinical Interpretation of Complex Genetic Information*, 10 Genet. Med. 778 (2008) ('information about complex genetic risk as assessed by genetic panels and whole genome scans is constantly changing; the interpretation might change substantially over months and is likely to be very different in two to five years').

[17] Ashwood, *supra* note 13, at 3.

[18] 510(k) describes pre-market notification process for devices that are the same or similar to an already approved device. Around 75% of new devices are reviewed by the FDA via the 510(k) process; genetic tests would also presumably be reviewed in this manner.

increased by 25% from 2008 to 2012, and review times for pathology IVDs, a division that may be the best fit for absorbing LDT review, took an average of 324 days to review in 2012, more than twice the length of the average device.[19] Altogether, it is difficult to believe that the FDA will be able to review these tests in a timely manner.

An additional risk of increased FDA regulation is the effect it will have on the genetic testing industry as a whole. Currently, many genetic tests are provided by institutional laboratories charging for testing as a service. Because of the uncertain clinical utility of many tests, it is currently difficult for many genetic tests to be reimbursed by payers, further eroding margins.[20] It is likely that the financial burden imposed by submitting these tests for approval will cause many of these tests to be pulled from the market and may even force some labs to be shut down.[21] These regulations may have the unintended consequence of reducing competition that drives the market, further slowing innovation and raising prices for patients.

Unaddressed risks

Genetic testing informs serious medical decisions and this has prompted the FDA to act in an attempt to guarantee their analytical and clinical efficacy. However, reports about harms from genetic testing often do not focus on the accuracy or marketing of a test, but the misuse or misinterpretation of these tests by physicians and patients.[22] Many genetic tests may invariably produce ambiguous or uncertain results, which may have serious consequences for the patient. The FDA hopes to protect the patient by assuring the analytical and clinical efficacy of genetic testing, but this focuses attention on the wrong part of problem. Not all physicians are equipped with the tools to accurately understand these tests correctly. Genetic counselors from ARUP Laboratories reviewed physician-ordered genetic tests and found that around 30% of these were incorrectly ordered.[23]

Inappropriate clinical application is one of the biggest risks of genetic testing, and it cannot be solved by FDA action. This is a problem with the practice of medicine, and can only be addressed through better education and guidelines for physicians on how to apply these tests to clinical care. Attention to the validity of the tests, typically quite high, is a distraction and will divert attention and resources away from the larger issue of better incorporating these tests into care. Not only will the FDA's actions reduce the number of overall tests and providers and slow the pace of innovation, but it may also

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[19] Jeffery N. Gibbs, Allyson B. Mullen & Melissa Walker, *510(k) Statistical Patterns*, Medical Device and Diagnostic Industry News (2014), http://www.mddionline.com/article/510k-statistical-patterns-12-02-2014 (accessed Dec. 26, 2014).

[20] See SACGHS Report, *supra* note 9, at 41–43, for more on difficulty in demonstrating medical necessity of genetic tests to payers. For example, Medicare will not cover screening tests and so will only cover genetic tests on patients who are already symptomatic or to predict responsiveness to treatment.

[21] Sarah C.P. Williams, *Clinical Labs Worry Proposed FDA Rules May Force Tough Choices*, 20 Nat. Med. 973 (2014).

[22] Eg Beth Daley, *Oversold and Misunderstood*, New England Center for Investigative Reporting (2014), http://features.necir.org/prenatal-testing (accessed Dec. 26, 2014) discusses the misinterpretation of the reliability of tests and their use for screening and not diagnostic purposes, and Denise Grady & Andrew Pollack, *Finding Risks, Not Answers, in Gene Tests*, The New York Times, Sept. 23, 2014, discuss the uncertain clinical utility for many genetic tests.

[23] ARUP Laboratories, *Value of Genetic Counselors in the Laboratory* (2011), http://www.aruplab.com/files/resources/genetics/White-paper-1-value-of-GCs-in-lab.pdf (accessed Dec. 26, 2014).

shift the focus of regulators and professional associations towards compliance and away from solving this larger problem.

PART III. HOW BEST TO ADDRESS THE RISKS OF GENETIC TESTING?

An unregulated genetic testing industry carries risks for patients and physicians. Even with CLIA oversight and self-regulation, it is clear that regulatory gaps remain, and the FDA should be commended for attempting to fill these gaps using the tools it has available. However, the FDA must acknowledge that regulation itself also carries risks. Weighing the clinical risks from untested analytical and clinical validity and the practical risks from the proposed regulations, a strong argument can be made that the proposed LDT regulations will do more harm than good. These regulations also fail to address some of the larger problems in genetic testing around improving clinical utility, physician education, and how to most appropriately incorporate these tests into the practice of medicine. Regulation itself imposes systemic risks and consideration of its use should attempt to strike a balance between options. As a regulatory body, the FDA's actions directly shape patient and physician options, and so the FDA's regulations should be tailored to ensure safe and effective products without overly burdening test providers.

A more appropriate regulatory structure for genetic testing would address the larger risks of inappropriate testing or interpretation while preserving the nimbleness and competition that make it a beneficial market for consumers. The FDA should leave in place its proposal to register and list all genetic tests, an effort that was already underway, led by the National Institutes of Health. An alternative to requiring pre-market approval for each genetic test would be to implement a genetics licensing program that qualifies laboratories offering genetic tests generally. The FDA should work with CMS to expand laboratory CLIA certification beyond analytical methods to include regular analytical validity audits of a representative sample of tests, and require laboratories to enroll in a proficiency-testing program to retain their license. This alone should do much to ensure analytical validity while imposing a lesser burden; a CDC study found validity of tests highly correlated with whether a lab participated in proficiency testing.[24] CMS can incentivize participation by making Medicare and Medicaid reimbursement for tests contingent on whether it was performed in a licensed lab. Under this model, once a lab is cleared to offer genetic tests, they only need to register a new or updated test when it is offered. Overall this would ensure analytical quality from laboratories without spreading their resources too thin, protecting smaller providers and thereby maintaining the competitive nature of the industry.

Several things must happen to adopt a licensure model. Further proficiency testing standards must be developed, but regulators could leverage existing tests and partner with NIST and professional organizations to expand existing programs rather than creating new ones *de novo*. Without pre-market approval for each individual test, clinical concerns would need to be addressed in some other manner. Scientific literature is currently one source for demonstrating clinical validity, and the FDA has indicated receptiveness to using it in lieu of trials for pre-market review. Thus, the only new data in an FDA submission may be proof analytical validity. If clinical validity can be demonstrated with existing data, and a licensing model is enough to ensure high analytical

[24] SACGHS Report, *supra* note 9, at 81.

validity with lower burdens, why is pre-market approval necessary in the first place? Licensed laboratories could continue to market products much as they are today and test registration can publicly reference scientific literature to demonstrate clinical validity. The FDA can review these claims at its leisure in collaboration with the FTC and monitor for fraudulent marketing. Regulators would not be alone; the current competitive environment of LDTs creates incentives for the industry to monitor itself and report its bad actors. Overall, addressing regulatory gaps through registration, laboratory licensing, and expansion of CLIA harnesses existing industry dynamics to reinforce regulations with a small regulatory burden. In contrast, the FDA's proposal ignores the dynamics of the LDT industry. Proposed guidelines drastically alter the industry landscape to achieve compliance, which risks undermining many of the industry's benefits.

The final problem that still remains unaddressed is that of clinical utility. In many cases, the clinical utility of a test is questionable or unclear. Many tests are incorrectly ordered by physicians and not properly integrated into standards of care. However, these are problems with the practice of medicine and will not be solved by increased regulatory oversight. LDT providers must work with professional societies and payers to address this problem. In fact, the FDA's increased oversight may only distract from improvement in this area by forcing resources to be allocated towards FDA compliance.

Genetic testing is in an area with substantial knowledge gaps; both regulators and providers have acknowledged this issue. While CMS is in the best position to address these gaps using the existing CLIA framework, it has shown a reluctance to do so and the FDA has stepped in.[25] Nonetheless, it is hard to believe that the tools available to the FDA are a better fit for the task. While the FDA's goals are admirable in trying to bring regulatory coherence to the genetic testing industry, the FDA is imposing an undue regulatory burden that will change the industry in a way that harms providers and patients while not addressing the greatest problems. These problems are best solved by better clinical guidelines from medical associations, increased proficiency testing from laboratories (through CMS and self-regulation), and reliance on the latest peer-reviewed research which will allow this industry to stay innovative, agile, and open.

[25] See SACGHS Report, *supra* note 9, at 30. A commission called for CMS to create a genetics testing specialty to CLIA as early as 1997. CMS indicated that it would do so, then in 2006 reversed course. One reason stated was that 'the field is so dynamic, prescriptive standards for genetic testing would be outdated before they were published'. It is easy to believe that the FDA's approach is even more poorly suited to this problem.