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Letters to the Editor

Proposed Regulatory Framework for Direct-to-Consumer Genetic Testing: Diagnostics vs. Genetic Screening

To the Editor:

On December 6, 2013, 23andMe stopped marketing direct-to-consumer (DTC)[1] disease-predictive genetic testing to comply with the FDA's directive *(1)*. Although the FDA's action was intended to protect the American public from questionable disease risk predictions, we believe the agency failed to assess all the benefits of DTC testing. Despite assurances asserting support for consumer genetic testing *(2)*, the FDA's action strongly discourages DTC providers from offering the tests to consumers, undermining the investments the US government has made in the genome project. We list examples where, in our opinion, the FDA's regulatory requirements for the DTC industry are excessive.

Is there too much emphasis on the analytical specificity rather than the diagnostic sensitivity of a test? The performance of a genetic test depends on both sensitivity and specificity. Yet the FDA's focus on reproducibility overemphasizes analytical specificity while diminishing the role of diagnostic sensitivity, resulting in a bias toward simplified single-nucleotide polymorphism (SNP) panels. Luminex and Autogenomics have received FDA approval for smaller genotyping panels for cytochrome P450 genes with 4 alleles, and extended panels with 19 alleles have secured European Union In Vitro Diagnostic Directive certification and are marketed in Europe. Reducing the number of markers improves technical replication but reduces the tests' sensitivity and clinical relevance for the ethnically diverse US population.

Is the FDA excessively protective? The FDA expressed concern at 23andMe disclosing genotype data on the 3 SNPs mentioned on Warfarin drug labels directly to consumers. Is it really dangerous, and can this knowledge cause more harm than an accidental skipping of a pill or accidental drug overdose? Also, the FDA's concern of "risk of prophylactic mastectomy as a result of [breast cancer gene] BRCA-related risk" is overstated; this form of intervention is unlikely to be done without an expert medical professional who should be able to consult with the patient.

The FDA recently allowed the marketing of one manufacturer's next generation sequencing (NGS) device as a clinical diagnostic tool for a gene-specific panel [CFTR, cystic fibrosis transmembrane conductance regulator (ATP binding cassette subfamily C, member 7)] and granted de novo petitions for its use with the manufacturer's universal kit reagents as an FDA-regulated test system that allow laboratories to develop and validate sequencing of any part of a patient's genome. NGS will inevitably capture novel and potentially disease-causing variations. As the 1000 Genomes Project has demonstrated, approximately 40% of potentially disease-causing variations are novel, thus posing a challenge in data interpretation and reporting. CLIA certification and technical FDA approval of integrated platforms *(3)* does not validate the interpretation of genetic data, which is the most critical part of clinical genetics.

Professional standards and guidelines for reporting known variants in established and disease-causing genes such as *BRCA1* (breast cancer 1, early onset)[2] or *MLH1* (mutL homolog 1) are clear, but how will novel and rare mutations be reported? With hundreds of such mutations being identified, current regulatory frameworks cannot ensure standardization of interpretation and reporting.

It is impossible for the FDA to "hit pause" until the pathogenicity of all rare variants are established in mendelian and complex disorders; it took 20 years to implement genetic screening and collect enough clinical data to classify the majority of cystic fibrosis (*CFTR*) mutations, one of best annotated genes among inherited disorders.

Genome sequencing is not yet a clinical diagnostic tool, but the results of a genetic test have practically never been used as the sole diagnostic tool *(4)*. Even for cystic fibrosis, where genetic variants have been clinically validated, genetic testing is only one of the clinical diagnostic tools used, along with sweat chloride test and nasal potential difference, to establish clinical diagnosis. Therefore, genome sequencing should be mainly considered a screening/discovery tool.

An emphasis on genome screening rather than diagnostics may enable direct marketing of genetic tests while adhering to FDA's guidelines on "research only use" *(5)*. According to section 812.2(c) *(3)*, DTC genetic test providers can be exempt from regulations applied to diagnostic devices by following three critical steps: (*a*) noninvasive nature of testing, (*b*) not used as sole or primary disease diagnostic tool, and (*b*) traditional methods used to confirm the diagnosis.

The FDA should consider an interim solution if the DTC providers adhere to the following:

[1] Nonstandard abbreviations: DTC, direct-to-consumer; SNP, single nucleotide polymorphism; NGS, next-generation sequencing.

[2] Human genes: *CFTR*, cystic fibrosis transmembrane conductance regulator (ATP binding cassette subfamily C, member 7); *BRCA1*, breast cancer 1, early onset; *MLH1*, mutL homolog 1.

1. Emphasizing benefits and limitations of a genetic testing in marketing materials;
2. Informing clients about potential implications of testing for individuals and family members;
3. Facilitating discussion between client and genetic consultant or healthcare provider before and after the test purchase;
4. Explaining that test results are a screening procedure that tags potential health risk that may or may not materialize;
5. Ensuring robustness of the genetic testing process according to CLIA guidelines; and
6. Independently replicating variations with potentially strong clinical impact, such as *BRCA1* and *BRCA2* mutations, using established technology.

We urge the FDA to work with service providers to ensure that the interpretation of genetic data is conscientious and that companies promote their services responsibly. The agency could take a leadership role in establishing guidelines by continuing the dialogue initiated in 2011 with the DTC industry and overseeing a program for educating doctors on the interpretation of genomic data.

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References

1. 23andMe. About the 23andMe personal genome service. https://customercare.23andme.com/entries/22591668-About-the-23andMe-Personal-Genome-Service (Accessed September 2014).
2. Hollmer M. FDA asserts support for consumer genetic tests despite 23andMe crackdown. http://www.fiercemedicaldevices.com/story/fda-asserts-support-consumer-genetic-tests-despite-23andme-crackdown/2013-12-06 (Accessed September 2014).
3. Luminex. xTAG® CYP2C19 kit v3. http://www.luminexcorp.com/Products/Assays/ClinicalDiagnostics/xTAG2C19 (Accessed September 2014).
4. Biesecker LG. Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: lessons from the ClinSeq™ project. Genet Med 2012;14:393–8.
5. FDA. Distribution of in vitro diagnostic products labeled for research use only or investigational use only: guidance for industry and Food and Drug Administration staff. http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253307.htm (Accessed September 2014).

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