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References

Matthew B. Greenblatt1
Matthew Torre1,2
Janet Means3
Milenko Tanasijevic1,2
Lillian Vitale Pedulla3
Craig A. Bunnell2
Michael J. Conrad4
Petr Jarolim1,2,3

1 Department of Pathology, Brigham and Women’s Hospital, Boston, MA;
2 Harvard Medical School, Cambridge, MA;
3 Dana Farber Cancer Institute, Boston, MA

* Address correspondence to this author at:
Department of Pathology Brigham and Women’s Hospital,
75 Francis St,
Boston, MA 02115.
E-mail: pjarolim@partners.org

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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 genotyping 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 or 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,2 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) 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 such mutations being identified, current regulatory frameworks cannot ensure standardization of interpretation and reporting.

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


Ruslan Dorfman3*$
Rabia Khan3
Gouri Mukerjee3

3 GeneYouIn Inc.
Toronto, ON, Canada

* Address correspondence to this author at: GeneYouIn Inc.
250 Yonge St., Suite 2201
Toronto, ON, Canada, M5B 2L7
E-mail ruslan@geneyouin.ca

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