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From Research to Clinical Application: Challenges in Regulating Companion Biomarker Tests for "Personalized" Drugs

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Pharmacogenomics (PGx) provides information on inter-individual genetic variability that can be used to "personalize" therapeutic regimes by predicting drug efficacy, patient clinical response, and adverse drug reactions. As the genomics of pharmacology became a reality with the inception of high-throughput DNA sequencing technologies and the subsequent mapping of the human genome, the expectation was for "true individualization of therapy" and a shift away from the current population-based drug development paradigm to a pharmacogenomic-guided one that would "maximize benefit and minimize toxicity" [1]. After more than a decade since the completion of the Human Genome Project, however, the initial vision that PGx would rapidly lead to the development of new "personalized medicines" [2] for customized patient care has not been fully realized. This note summarizes some of the regulatory challenges confronting pharmacogenomics and the path to personalized medicine, specifically as they relate to biomarkers and diagnostic testing.

Currently, the U.S. Food and Drug Administration (FDA) has approved less than 150 distinct drugs that have pharmacogenomic information in their labels [3]. This statistic does not necessarily mean that these drugs are "personalized" [4], but that pharmacogenomic biomarkers for these drugs have been identified, and these genetic identifiers can play critical roles in the prescribing process, including identifying responders and non-responders (patient differentiation), optimizing therapeutic dosage, and reducing the incidence of adverse events (risk identification). Most pharmacogenomic biomarkers are developed as companion diagnostic tests post hoc as a means of personalizing drugs [4]. One example of this post hoc development is the pre-therapy HLA-B*5701 allele screening test designed to predict and prevent severe hypersensitivity reactions to the HIV/AIDS drug abacavir [5]. By contrast, one of several FDA-approved drugs that was developed in tandem with companion diagnostics is the breast cancer biologic trastuzumab [6]. The FDA requires the administration of the human epidermal growth factor receptor (HER-2) test before prescribing the drug in order to identify responsive HER-2 positive breast cancer patients who are likely to benefit from the drug. In this case, valuable time and money are saved by stratifying the potential patient population for the purpose of improving therapeutic response rate. More recently, the FDA simultaneously approved the personalized drug vemurafenib (Zelboraf) in conjunction with its companion diagnostic (Cobas 4800 BRAF V600E mutation test) for use in treating metastatic or unresectable melanoma [7]. Clinical validity of the diagnostic was established based on data from the same clinical study that evaluated the efficacy and safety of vemurafenib [7], thus illustrating the regulatory efficiency of having the diagnostic and therapeutic tied together from the outset of the clinical trial period. Vemurafenib is indicated only for those patients who are $BRAF^{V600E}$ positive based on the Cobas mutation test. The FDA approval of crizotinib for treatment of patients with metastatic non-small cell lung cancer is another example of the benefit and regulatory efficiency of biomarker-driven clinical trials. By linking the therapeutic and diagnostic early enough in the investigational new drug (IND) process, pharmaceutical stakeholders can avoid lengthy and costly additional clinical trials required for demonstrating that stratification of the patient population results in improved drug response rates [4].

As the aforementioned examples demonstrate, the success of personalized medicines requires valid pharmacogenomic biomarkers that can be "translated into precise diagnostic tests" to identify specific patients who can benefit from targeted therapies [4,8]. Furthermore, parallel development of therapeutics and companion diagnostics is considered ideal [4] because it increases the probability of an improved therapeutic profile (e.g., as exemplified in the cases of the FDA-approved drugs vemurafenib and crizotinib).A regulatory challenge that continues to limit the possibilities of PGx-directed personalized healthcare is a lack of clarity and precise, cohesive guidance by the FDA on the "regulatory pathways for coordinated approval of co-developed diagnostics and therapeutics" [8]. Implicit in this challenge is whether the existing structure of the U.S. regulatory frame work can adequately accommodate the high-throughput, transformative methodologies and technologies of genomics, as well as the complexity of the information involved in PGx-based genetic tests. Some drugs for example, particularly in the area of oncology (e.g., cetuximab and imatinib), are associated with multiple genomic biomarkers [3], making an understanding of their clinical utility critically important if the FDA mandates a gate keeping diagnostic test(s) as a condition of prescription. The Agency has attempted to explain how pharmacogenomic data will be used within the context of the current regulatory scheme by issuing a number of guidance documents, including the publication of FDA Guidance for Pharmacogenomic Data Submission, Guidance on Pharmacogenomic Tests and Genetic Tests for Heritable Markers, and draft guidance for "In Vitro Diagnostic Multivariate Index Assays" (IVDMIAs) [9,10]. Thus far, however, the FDA's approach has not been to proactively revise any regulations, but, instead, to suggest how pharmacogenomics data, such as biomarkers, may be addressed by the federal government's existing laws and regulations [9]. Therefore, the question of the adequacy of the Agency's current model for regulating personalized medicine remains a possible obstacle to realizing the full potential of PGx-guided healthcare.

In addition to the paucity of clear regulatory guidance, the review and approval process for companion diagnostic tests is complicated by separate regulatory oversights, depending on whether the pharmacogenomic biomarker is developed as an in-house test by a clinical laboratory or developed as an in vitro diagnostic device by a medical device

manufacturer [10]. The Center for Medicare and Medicaid Services (CMS) is authorized to regulate quality standards for clinical laboratory tests through the Clinical Laboratory Improvement Amendments (CLIA). The FDA enforces Good Laboratory Practice (GLP) regulations, which govern the testing of in vitro medical diagnostic devices. This divided oversight can confuse stakeholders with regard to the regulatory decision-making process. New advancements in genetic testing technologies have created multiple types of diagnostic tests which may be regulated under different authorities, depending for example on whether patients are profiled using single-gene sequencing analysis or microarray-based genomic analysis [11]. To date, the FDA has assumed a predominant role in regulating PGx-based diagnostic tests, as evident from the Agency's fast-track approval of companion diagnostic tests for trastuzumab, vemurafenib, and crizotinib. Manufacturers of PGx tests, nonetheless, need to receive clear regulatory guidance on how PGx-based diagnostic tests will be reviewed because "no regulatory category called 'personalized medicine'" exists [12].

Another major regulatory issue specifically relevant to PGx therapeutics is the lack of adequate oversight to evaluate the clinical utility of pharmacogenomic biomarkers for regulatory purposes. Clinical utility is defined as a measurement of the effectiveness of a diagnostic test in predicting clinical outcomes [10]. An accurate assessment of clinical utility is critical in the approval of a companion diagnostic test for a personalized drug because genomic/genetic testing may define who receives certain drug treatments. As some experts have astutely noted, "if there is uncertain clinical utility for testing, there is the potential that some patients who will benefit could be denied access or that the drug therapies will be ineffective or unsafe" [11]. However, a current regulatory gap lies in the fact that neither the FDA nor the CMS is charged with evaluating the clinical utility of companion diagnostic tests [11]. In sum, the regulatory gaps and challenges extant in the co-development of PGx-based drugs and diagnostics will need to be resolved before the full benefit of PGx-directed personalized medicines on actual clinical practice can be realized.

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