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Clinical implementation of genetic testing in medicine: a US regulatory science perspective

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Heterogeneity of treatment effects in unselected patient populations has stimulated various strategic approaches to reduce variability and uncertainty and improve individualization of drug selection and dosing. The rapid growth of DNA sequencing and related technologies has ramped up progress in interpreting germline and somatic mutations and has begun to reshape medicine, especially in oncology. Over the past decade, regulatory agencies realized that they needed to be proactive and not reactive if personalized medicine was to become a reality. The US Food and Drug Administration, in particular, took steps to nurture the field through peer-reviewed publications, co-sponsoring public workshops and issuing guidance for industry. The following two major approaches to personalized medicine were taken: (i) encouragement of *de novo* co-development of drug–genetic test combinations by industry; and (ii) retrospective assessment of legacy genetic data for the purpose of updating drug labels. The former strategy has been more successful in getting new targeted therapies to the marketplace with successful adoption, while the latter, as evidenced by the low adoption rate of pharmacogenetic testing, has been less successful. This reflection piece makes clear that several important things need to happen to make personalized medicine diffuse in more geographical areas and among more therapeutic specialties. The debate over clinical utility of genetic tests needs to be resolved with consensus on evidentiary standards. Physicians, as gatekeepers of prescription medicines, need to increase their knowledge of genetics and the application of the information to patient care. An infrastructure needs to be developed to make access to genetic tests and decision-support tools available to primary practitioners and specialists outside major medical centres and metropolitan areas.

Introduction

Individualization of drug therapy has been the 'holy grail' of medicine for hundreds of years [1]. The recent application of genomics to stratifying diseases, targeting drugs and defining optimal dosing has been called 'personalized medicine', a concept that has grown dramatically since the milestone discovery of the *Her-2/neu* gene approximately 30 years ago. However, personalized medicine is not a new concept. For example, in breast cancer, the first molecular target for an oncolytic agent was the cellular receptor for the female sex hormone estrogen that many breast cancers require for growth. Several drugs that interfere with the binding of estrogen to the estrogen receptor, such as tamoxifen, have been recommended for estrogen receptor-positive breast cancer. However, more recently, in 1993, Genentech initiated pivotal clinical trials of a monoclonal antibody that interfered with the HER2/neu receptor and demonstrated improved overall survival in late-state, metastatic HER2-positive breast cancer. Herceptin® (trastuzumab) subsequently became the first widely used targeted anti-HER2/neu monoclonal antibody for treatment of HER2/neu-overexpressing breast cancer to be approved by the US Food and Drug Administration (FDA) in 1998 and by the European Medicine Agency (Committee for Proprietary Medicinal Products for Human Use or CHMP) in 1999. Many follow-on breakthroughs in personalized medicine continued to occur in oncology, and they have markedly changed the landscape of cancer research and therapeutics. Targeted therapies that rely on a test to direct and predict therapeutic response in breast, lung, blood and colon cancer types are now widely available. However, progress in drug development and advances in clinical implementation of targeted therapies

in therapeutic areas other than cancer have been slower and have not reached the pinnacle of personalized medicine. Owing to the slow pace of progress in non-oncology areas, the question has been raised: is personalized medicine an elusive dream or an imminent reality, and what challenges need to be addressed to make this dream a reality [2]?

Herceptin® became the 'poster child' for personalized medicine or so-called 'efficacy genetics'. Other categories of personalized medicine include 'safety genetics' and 'dosing genetics'. Genetic tests can also be categorized as being 'prognostic' or 'predictive'. Clinical implementation – as expressed in the title of this paper – can broadly refer to the complex process of translating genetic/genomic data obtained from gene discovery (the target), murine models of the target, cloning of the target, linking the target to a disease phenotype (the pathophysiology), identifying lead compounds in, for example, cancer cell lines, conducting proof-of-concept and pivotal clinical trials of drug–test pairs in patient populations (i.e. clinical outcomes), transferring critical results into approved product labels and, finally, uptake by clinicians for use in their patients. As was the case in the development of Herceptin®, a prospective research strategy that is robust and informative (e.g. efficient co-development clinical trials of drug and test) provides an example, in that it results in labels with specific recommendations that facilitate clinical implementation of the drug–test pair. In contrast, with warfarin, for example, where clinical outcomes are known to be influenced by genetic variations in *CYP2C9* and *VKORC1* as well as other important nongenetic factors, there is an insufficient amount of evidence of clinical utility that has been prospectively generated, such that the label cannot be written as specifically as possible, which presents a challenge for clinical adoption.

There has been a tremendous effort on the part of regulatory agencies around the world during the past 15 years through the International Conference on Harmonization (ICH), involving the regions of the USA, Europe and Japan, to encourage DNA collection in clinical trials in order to reduce uncertainty in drug response and improve the benefit/risk profiles of medical products. Many believe that DNA biobanking will become routine in drug development in the near future. This is evident from the language in the 2013 FDA Guidance for Industry on Clinical Pharmacogenomics, in which the Agency states: 'Ideally, baseline DNA samples should be collected from all patients in all arms of clinical trials in all phases of drug development' [3]. Clearly, this is a forward-looking statement, hoping to increase the opportunities to link genotype and phenotype and better understand the interpatient variability in pharmacokinetics (PK) and pharmacodynamics (PD). However, routine DNA collection in drug development is not yet the case. Collection of DNA is challenging, and in some cases non-informative, because many early phase clinical trials are exploratory, with no formal genomic hypothesis, and have small sample sizes that would make it difficult to identify important gene variants influencing PK and PD beyond the common cytochrome P450 (CYP450) mutations. A survey by the Pharmaceutical Research and Manufacturers of America (PhRMA) of 16 companies found that while the pharmaceutical industry has made some attempt to incorporate genomic variations in development, the effort has been modest and inconsistent [4]. This is understandable from the intent of developing a drug for as broad an indicated population as possible. But in therapeutic areas such as oncology and rare diseases, genomic variations have become the major drivers of the drug development process intended for narrowly defined populations. An example of applying genomics can be found in the FDA guidance on enrichment strategies for clinical trials that was issued in 2013 [5]. This guidance recommends genomic testing as part of a prognostic or predictive enrichment strategy for clinical trials to identify high-risk patients in cases where there is an *a priori* hypothesis to discern a beneficial treatment effect more readily in a patient subset. Currently, most genomic enrichment strategies involve tumour genomics, and successes in other therapeutic areas have been limited to infectious diseases (e.g. hepatitis C) and rare hereditary diseases (e.g. cystic fibrosis). In contrast, improving drug safety is of primary interest to industry and regulators. Collecting DNA during drug development provides the ability to go back and look at potential genetic causes of drug-induced serious adverse events.

Progress to date

Co-development of drug–diagnostic test pairs

A decade ago the FDA, in partnership with the European and Japanese regulatory agencies and the pharmaceutical industry, decided it was timely to raise the visibility of personalized medicine in terms of using inherited (germline) mutations or acquired (somatic) mutations to guide decision making in new drug development [6]. Regulatory perspectives were presented on the benefits and challenges of making DNA-based decisions for selection of a subpopulation of responders, optimizing doses and identifying patients at high risk for serious adverse events, with the intent of stimulating dialogue between drug developers, regulatory scientists and the clinical community [7]. Initially, pharmaceutical companies were reluctant to collect DNA samples from participants in their clinical trials because they feared what regulatory reviewers would do with information derived from genetic analysis. To help overcome these fears and provide a forum for industry–regulator dialogue, a series of five workshops were convened between 2002 and 2010 and were co-sponsored by the FDA and the PhRMA, with participation by regulators from Europe and Japan. Each workshop was followed by

published reports of key findings, challenges, desired outcomes and next steps [8–11]. These workshops were instrumental in advancing genetics, genomics and personalized medicine.

One of the most groundbreaking ideas to arise from the second workshop was the voluntary genomic data submission process, or the 'safe haven' proposal. When adopted by the FDA, the 'safe haven' facilitated the submission of exploratory genomic data without fear of the FDA taking premature regulatory action except in the case of a major safety concern. Voluntary genomic data submission meetings, often with participation by European and Japanese regulators, became an outstanding success with many companies submitting data. After gaining experience with more than 50 submissions, the FDA issued Guidance for Industry on Pharmacogenomics Data Submissions in 2005 [12].

In contrast to the voluntary genomic data submission success, the third workshop introduced the drug–test co-development concept paper that was intended to be the precursor of anticipated FDA guidance for industry on the topic. Industry's initial reaction was negative. The general consensus was that the scope of the paper was to narrowly focused on a one-test–one-drug paradigm, that the parallel time lines for drug and test co-development were idealistic and that the demonstration of clinical utility of the test was too burdensome. Additional concerns were expressed by industry that label implications of co-development were not discussed in the concept paper and too little attention was paid to the complexities of global drug development. At the fifth workshop, there was continuing discussion of the subsequent regulatory agency thinking and important industry issues around the co-development of drugs and tests, but many issues remained unresolved. To date, there is no regulatory guidance on drug–test co-development in the USA, Europe or Japan that specifically discusses the scientific and regulatory processes and time-line challenges of drug–test co-development.

Some companies have succeeded with co-development and approval of drug–test combinations with relative speed and efficiency in therapeutic areas of unmet medical need. This is true for well-understood disease phenotypes (e.g. pathway-defined cancers) and Mendelian disorders (e.g. cystic fibrosis). Three recent examples of progress with drug–test co-development are as follows. The first example is crizotinib (Xalkori®), which is an anticancer drug acting on the *ALK* fusion gene for treating late-stage nonsmall-cell lung cancers that express the abnormal *ALK* gene. A drug and a test to identify *ALK*-positive tumours in nonsmall-cell lung cancer patients was co-developed and approved by the FDA in 2011. It also received a favourable granting of marketing authorization from the CHMP in 2012. Second, vemurafenib (Zelboraf®) was approved in the USA in 2011 and the European Union (EU) in 2012 for treatment of late-stage melanoma in patients with BRAF V600 mutations. Third, ivacaftor (Kalydeco®) was approved in the USA and EU for cystic fibrosis in patients with the G551D mutation. In 2013, under the Food and Drug Administration Safety and Innovation Act (FDASIA), the FDA was able to grant 'breakthrough' designation to ivacaftor monotherapy and to the combination regimen of VX-809 (an experimental cystic fibrosis transmembrane conductance regulator corrector) with ivacaftor in homozygous ΔF508 cystic fibrosis patients. Breakthrough designation means that a drug (and co-developed test in some cases) is intended to treat a serious condition, and there is preliminary evidence that the medical product demonstrates substantial improvement over existing therapies.

Update of labels of previously approved drugs with genetic information

Starting about 10 years ago, the FDA embarked on a review of the genetic/genomic landscape, with the intent of identifying previously approved drugs for which new genetic data were available and to decide whether or not such information could be used to update the label of 'old drugs' with diagnostic test information [13]. As we have since seen in the case of paediatric acute lymphoblastic leukaemia, optimal use of 'older drugs' (e.g. 6-mercaptopurine) with pharmacogenetic testing can improve the 5 year survival rate to >85% [14]. Beginning in 2003, the labels of numerous drugs, including 6-mercaptopurine, irinotecan, warfarin, carbamazepine, abacavir, panitumamab, cetuximab, clopidogrel, pimozide and cisplatin, were updated with new genetic test information. The rationale for the label updates was based on mechanistic and clinical evidence as defined in the USA regulations, expressed in Section 21 CFR 201.57 of the Code of Federal Regulations, which states that 'if evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, the labeling shall describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug'. Furthermore, under the FDA Amendment Act (FDAAA) of 2007, the FDA was granted the authority to revise drug labels to include warnings on clinically significant safety risks when 'there is reasonable evidence of a causal association with a drug' [15]. Most of the label updates were related directly and mechanistically to a high risk of genetically determined serious drug-induced adverse events (e.g. thiopurine methyltransferase deficiency and the risk of myelosuppression with 6-mercaptopurine) or to the failure of efficacy in a serious disease (e.g. poor response to panitumamab in patients with colon cancer who have a mutated KRAS protein). The absence of efficacy was regarded as a safety issue according to the 2007 FDAAA. Genetic information was also added to labels to determine a patient's optimal starting dose (e.g. warfarin) or to avoid

treatment completely because of safety risks (e.g. carbamazepine and abacavir).

There are several major challenges to updating labels with specific recommendations for using genetic tests. The most important barrier has been the lack of agreement on what constitutes clinical utility of the test [16]. This was because most of the label updates were based on retrospective analysis of clinical studies or observational case–control studies, both of which had limited statistical power and inconsistencies between studies. Subsequently, a general framework for evidence was constructed by FDA reviewers for label updates, based on a modification of the Bradford Hill criteria for causality adopted from epidemiological research [17]. In some cases, such as with warfarin, the debate over clinical utility centred on whether one should accept 'surrogate endpoints' (i.e. international normalized ratio control) or require clinical outcome measures (e.g. reduction in major bleeding event rates) as evidence of clinical utility. The clinical implementation of warfarin genetic testing was also hampered by the fact that genetics explained a relatively small fraction of heterogeneity in clinical response (<50%), with demographic factors (e.g. age and race), concomitant drug use, diet, smoking and intended indication also playing a major role in causing variability. This made it difficult to predict optimal doses even with genetic test results being available. In other cases, such as with carbamazepine, the debate focused on clinical utility in terms of the generalizability of HLA B*1502 testing as a way to identify the risk of Stevens–Johnson Syndrome and toxic epidermal necrosis in Asian patients beyond the subpopulation of Han Chinese in which the association was first confirmed. In Singapore, the regulatory agency has recommended that all patients receiving carbamazepine first be tested for HLA B*1502 to reduce the risk of Stevens–Johnson Syndrome. One of the most important lessons learned regarding clinical implementation of genetic testing was that label changes do not necessarily result in physician adoption and test cost reimbursement by payers. Likewise, there have been instances where tests with robust evidence of clinical utility have been adopted clinically before the FDA took action on a label update (e.g. KRAS testing with panitumamab).

If Herceptin® was the poster child for early co-development of targeted therapies in personalized medicine, abacavir was the poster child for postmarketing safety label updates. The pharmaceutical sponsor conducted a double-blind, prospective, randomized clinical study adequately powered with 1956 patients with HIV-AIDS to compare a cohort of patients who underwent prospective HLA-B*5701 screening, with exclusion of biomarker-positive patients, with another cohort of patients who received standard of care without prospective screening. Screening was shown to reduce the clinical diagnosis of hypersensitivity from 7.8 to 3.4% and the immunologically confirmed hypersensitivity from 3.4 to 0% [18].

The abacavir clinical risk management plan, covering a 7 year time frame from discovery of the HLA-B*5701 risk allele (2001) to an FDA label update (2008) went beyond simply conducting a 'gold standard' randomized controlled trial and demonstrated that there are other important factors enabling clinical adoption. These factors included the following: demonstrating analytical and clinical test validity; providing physician education and access to fully accredited test laboratories; easily interpretable test results; availability of genetic counsellors; inclusion of testing in professional guidelines; endorsements by governmental agencies (e.g. US Department of Health and Human Services); and positive reimbursement decisions by third-party payers. Apart from abacavir, none of the other drugs listed above for which the FDA made label updates was supported by the level of evidence and infrastructure for clinical implementation that was demonstrated with abacavir.

The fifth FDA–PhRMA Pharmacogenomics workshop focused on lessons learned from product labels and label updates that included genetic tests and discussed how to design drug development programmes better in order to avoid the problems of clinical utility delineated above. The consensus was that the easiest case for which to establish clinical utility is during drug–test co-development, when solid evidence can be determined prospectively to show, for example, that biomarker-positive subgroups are more likely to be responders to a drug than biomarker-negative subgroups. More challenging are those instances where pharmacogenetics (e.g. polymorphism in CYP P450 enzymes, such as 2D6) are believed to influence dosing and subsequent clinical response but a pharmaceutical company is reluctant to stratify target populations by phenotype (e.g. for ultra, extensive, intermediate and poor phenotypes of 2D6) unless there is very compelling evidence that stratification will result in significant improvements in the benefit/risk ratio.

It is also challenging to identify genetic tests in advance that predict the likelihood of serious drug-induced adverse events, because these events are seen as idiosyncratic and therefore unpredictable without an *a priori* hypothesis. Phase I–IIA clinical trials are exploratory and they enrol relatively small numbers of subjects, making it difficult to achieve statistical significance in terms of drug–gene effects. Phase IIB–III trials, even with the large number of patients, are not designed to detect drug-induced adverse events as either primary or secondary clinical end-points. This is understandable because of the low frequency of serious adverse drug event rates. For clinical trials, especially those deemed to be pivotal to approval, it has been recommended by regulatory agencies that drug developers should prespecify the collection of DNA samples in all patients, have robust analytically and clinically validated assays available when

needed, and have an *a priori* statistical plan spelled out in the protocols to analyse relationships between DNA analysis and clinical outcomes, both beneficial and harmful.

A critical element of personalized medicine is actionable labels, which means that labels must be specific and unambiguous in what to do with genetic information. In many cases, words used in prescription drug labels, whose labels have been updated with genetic information, have not required or even strongly recommended that genetic testing be done. This has generally been due to the absence of evidence of clinical utility obtained from randomized controlled trials. For example, under the indications and usage sections of the panitumamab label, KRAS testing is not specifically recommended. Rather, under 'limitations of use', the label states that 'patients whose tumors had KRAS mutations have not shown a treatment benefit'. It is assumed that prescribers would not administer panitumamab to their patients with metastatic colon cancer without testing for KRAS mutations. As another example, the updated warfarin label does not recommend genetic testing but states that '2C9 and *VKORC1* genotype information, when available, can assist in the selection of the initial dose of warfarin', without being specific on how to incorporate genetic information and other covariates into dosing decisions. The exceptions to this are for drugs such as carbamazepine and abacavir, where the totality of evidence convincingly points towards a genetic cause of a serious adverse event, and therefore, labels for these medicines are specific in terms of genetic testing.

Summary

Personalized medicine has evolved considerably in the past 15 years and, while there are some great opportunities moving forward, there are also significant challenges that need to be addressed; these are summarized below.

- Co-development of new drug–test combinations will probably be the most successful path to personalized medicine in the future but will require new insights into disease pathophysiology.
- The frequency of label updates of previously approved drugs will probably decline because of the high hurdles for evidence generation expected for clinical utility; the exception to this will be for cases like abacavir, where there is strong evidence of genetic causes of drug-induced adverse events.
- Advances in targeted therapies for cancer will probably continue to lead the way in personalized medicine because of the intense focus on tumour biology and target identification.
- Personalized medicines for rare Mendelian diseases (i.e. rare diseases and orphan drugs) will increase dramatically because of their well-established causal mechanisms, known drug targets and lucrative niche pricing.
- There will be continued debate over clinical utility between healthcare providers and third-party payers that will dampen progress in personalized medicine in the absence of consensus conferences and workshops on what constitutes adequate evidence of clinical utility and cost-effectiveness.
- Successful education of most practising physicians (e.g. those in primary care) in personalized medicine will be problematic, but introducing the concepts and hands-on experience with personalized medicine into the medical school curriculum may pave the way for future physicians to integrate personalized medicine into their practices.
- Personalized medicine will continue to benefit primarily the outliers in pharmacogenetics (e.g. those requiring the highest or lowest doses of a drug), patients deemed eligible or not eligible for targeted therapies, and those instances where a small number of patients are at risk for serious drug-induced adverse events.
- Patients in large metropolitan areas with access to major teaching hospitals or academic clinical research centres with specialties such as oncology will probably continue to be the major beneficiaries of personalized medicine.
- Personal consumer genetic testing will be likely to have increasing impact on healthcare because it provides for greater access to genetic testing, lower costs, online help with interpretation of the clinical significance of DNA analysis and large databases for identifying genotype–phenotype associations.

Competing Interests

The authors have not received any financial support for writing this manuscript. LJL was formerly the Director of the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research at the Food and Drug Administration, and now is Clinical Professor at the University of Florida Center for Pharmacometrics and Systems Pharmacology (CPSP) in Orlando, FL. SS is an Assistant Professor at the University of Florida Center for Pharmacometrics and Systems Pharmacology (CPSP) in Orlando, FL.

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