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Commentary

Genomics and personalized medicine

A B S T R A C T

The role of genomics in personalized medicine continues to undergo profound changes, in step with dramatic technological advances. Ability to sequence the entire human genome with relative ease raises expectations that we can use an individual's complete genomic blueprint to understand disease risk and predicting therapy outcomes, thereby, optimizing drug therapy. Yet, doubts persist as to what extent genetic/genomic factors influence disease and treatment outcomes or whether robust predictive biomarker tests can be developed. Encompassing more than just DNA sequences, the definition of genomics now often is taken to include transcriptomics, proteomics, metabolomics, and epigenomics, with integration of genomic and environmental factors, in an area referred to systems biology. While we can learn much about a cell's innermost workings, summation of these diverse areas is far from enabling the prediction of therapeutic outcomes. Typically, only a handful of specific biomarkers, genetic or otherwise, are 'actionable', *i.e.*, they can be used to guide therapy. I will focus on pharmacogenetic biomarkers, highlighting current successes but also the main challenges that remain in optimizing individualized therapy.

1. Pharmacogenomics in personalized medicine and health care

Genetic/genomic sciences have accelerated a trend back to personalized medicine (Xu et al., 2008), which for a while has been supplanted by a one-drug-fits-all mentality. Optimizing therapy of the individual patient increasingly relies on diverse sets of biomarkers, including genetic polymorphisms, but clinical applications are still evolving and remain at an early stage. We can agree on the notion that the relative contributions of genetic factors vary greatly between diseases and therapies, and they could play only a subordinate role in determining inter-individual differences in some areas. In most other applications we may have a reasonable estimate as to how much genetic variation causes different treatment outcomes, but the underlying mechanisms and responsible genetic variations remain largely unknown. To take full advantage of pharmacogenomics in drug therapy, we must strive to discover all genetic variants relevant to therapy, namely those with a sufficient effect size and frequency in the target population. Much more work needs to be done before this goal is achieved, enabling the development of robust multi-gene biomarker tests with strong predictive power.

Likely to play a growing role in personalized drug therapy, pharmacogenomics can substantially improve treatment outcomes. On the other hand, our focus should broadly shift towards personalized health care (rather than 'medicine'), with emphasis on maintaining wellness and early treatment if not preventing disease altogether. Our current concepts in the biomedical sciences and clinical applications are still largely driven by a strict focus on illness. Yet much more effective, health care and disease prevention can well benefit from increasing knowledge of the underlying biology, and critical other factors such as environment, culture, lifestyles. By adopting healthy life styles (diet, exercise, no smoking, alcohol restriction), a majority of the most prevalent complex diseases (cardiovascular, diabetes, cancer) can be prevented—to an extent unmatched by drug therapy alone. This does not mean that the environment trumps genetic predisposition; only that unhealthy lifestyles will cause disease, a process that may be exacerbated by genetic factors. Drug therapy therefore represents only a portion of possible interventions. As with lifestyles, drug therapy initiated early may be most effective; hence predictive biomarkers indicating disease risk will become most valuable—but at present little economic incentives are available to promote this most promising approach in drug therapy/prevention. I discuss here the promise and limitations of pharmacogenomics, seen as one part of a multifaceted approach to improving our health care system.

2. Biomarkers as guides in drug therapy

The main goals of pharmacogenomics vary across a broad spectrum, from drug discovery to individualized therapies. A genomics approach to drug target discovery is often the first step towards novel drug design. Specifically, molecularly targeted therapies – guided by biomarkers – have emerged in cancer chemotherapy, with some dramatic success. However, even with initial complete remission, typically the cancer returns, growing more resistant to many types of therapies. As a result, the search for predictive biomarkers has moved center stage in cancer therapy, designed to avoid excessive toxicities while maximizing efficacy. From our current knowledge, we can reasonably expect that optimizing drug therapy for each individual patient could significantly improve treatment outcomes, with new and existing drugs.

Biomarkers as a whole represent a diverse spectrum of measures – now mostly emerging from genomics research (Sadee and Dai, 2005; Sadee, 2008). Different goals are to be achieved whether one employs genetic variants, represented by genomic sequences, or profiles of expressed RNAs, proteins, and metabolites (all representing phenotypes). The former is typically invariant in somatic tissues, except for malignancies and some other conditions, whereas the phenotypic 'genomic' changes respond to environmental conditions, disease state, and drug treatment. Therefore,

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genetic biomarkers typically serve as predictors of disease risk or treatment outcome, whereas phenotypic biomarkers can be both predictive (e.g., cholesterol levels) or serve as surrogate measures for drug response.

The main challenge for all genomic biomarkers is to understand the relationship between biomarker test results and clinical outcomes. For example, statins reliably reduce cholesterol levels in a majority of patients but prevent coronary events in only 30–40% of cases. A biomarker predictive of a positive outcome, namely the absence of coronary events, is urgently needed and would be most valuable clinically. On the other hand, genetic biomarkers have the potential to predict adverse drug effects, for example the much cited role of a *SLC01B1* polymorphism in statin myelotoxicity (The Search Collaborative and Group, 2008).

3. Clinical application of pharmacogenomics in drug therapy

Drug therapy has often followed the principle of one-drug-fits-all, but this approach is changing rapidly. Increasing use of biomarkers to guide therapy is the means by which therapies can be individualized, or response measured. Typical pharmacogenetic biomarkers include genetic variants in CYP enzymes (oxidative metabolism), UTG1A1 (glucuronidation), VKORC1 (warfarin target), EGFR (example of growth factor receptors driving cancers), NAT2 (acetylation), MDR1 and BCRP (efflux transporters), and more. While the clinical utility of these biomarkers remains under debate, an entire industry has emerged within a short time period dedicated to the generation of clinically used biomarkers.

Pharmacogenetics in the strict senses initially focused on drug metabolizing enzymes and then membrane transporters, strong factors in determining whether a drug reaches its target or how long it will remain in the body. As a result, such genetic markers serve mainly for dose optimization, but they also could affect the choice of drug, avoiding toxicity in poor metabolizers for a specific drug, for instance antipsychotics that depend on CYP2D6 for elimination for the body. In distinction, genetic biomarkers related to drug receptors and signaling pathways are expected to guide choice of the type of drug class to be taken. While this latter approach is beginning to take route in cancer therapy, by and large our knowledge is still quite limited in most other clinical areas.

Recently, several new drug therapy related biomarkers have emerged as the lead beacons for pharmacogenomics advances. These include mutations in CYP2C19, required for activation of clopidogrel (Shuldiner et al., 2009), CYP2D6, activating tamoxifen and codeine, and CYP2C9/VKORC1, modulating warfarin dosages and effects (Flockhart et al., 2008). Currently, a genetic biomarker test of CYP2C19 metabolizer status is rapidly gaining acceptance as a useful addition to therapy with the anticoagulant clopidogrel, even while the clinical utility remains to be fully evaluated. Poor metabolizers can be prescribed another drug not dependent upon CYP2C19 for generating the active metabolite in the body. While several genetic variants begin to emerge as valid clinical biomarkers, acknowledged by the FDA through insertion into drug labels and alerts, closer inspection of the underlying genetics and biology, not to mention the process of clinical application, reveals multiple complexities that require reduction to simple recommendations to have practical impact. Such simplifications however also engender the danger of errors or misinterpretation.

Combination of a drug with a biomarker – predicting response rate or risk of toxicity – have already become obligatory in a few cases (see FDA Table of Valid Pharmacogenomic Biomarkers at http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm), possibly heralding a mainstream future trend. This approach to drug therapy has been termed theranostics, defined in Wikipedia as follows: "*Theranostics* is the term used to describe the proposed process of diagnostic therapy for individual patients—to test them for possible reaction to taking a new medication and to tailor a treatment for them based on the test results." It is however also becoming apparent that genetic biomarkers provide information only on a portion of the critical factors determining disease progression and treatment response. To be successful, multiple types of biomarkers and traditional clinical observations need to be combined to achieve optimal health care/therapy for the individual. We have still a long way to go before closing in on this goal.

4. Pharmacogenomics: what are limiting factors and how can we overcome them?

First, genetic biomarkers are often used without proper knowledge of the underlying mechanisms, or the marker polymorphism serves merely as a surrogate for a functional genetic marker that remains unknown. This approach can introduce additional uncertainty and error, for example in different ethnic groups where the marker and functional variants are not linked to each other (lack linkage disequilibrium), as was the case for SNP markers in *VKORC1* (Wang et al., 2008). Therefore, I emphasize the need to unravel the molecular genetics of any clinically used genetic biomarker – knowledge that can be used to predict effects across different populations, and in different diseases/tissues – before countless clinical trials are conducted that often yield inconclusive results (Sadee, 2010).

Second, a biomarker test may utilize a known functional polymorphism, but we have not addressed the question to what extent this single polymorphism accounts for the genetic variability in a given population. As a result, the genetic effect size is underestimated, the test account for only a small portion of variability, and an opportunity for enhanced personalized health care is missed. For example it is likely that we have yet to discover all important mutations in *CYP2D6*, so that its value as a biomarker is diminished. Thus, genetically defined 'intermediate CYP2D6 metabolizers' can have such discrepant actual enzyme activities that prospective genotyping has yet to become standard care practice, even though potential clinical utility is undisputed (Phillips et al., 2001).

Third, many genomic biomarker panels consist of complex profiles, for example 50 mRNAs expressed in breast cancer. While such test can be predictive of outcomes to the extent that they have been accepted into clinical practice, these panels have arisen from heuristic models—countless different panels with varying mRNA profiles could provide similar predictions, and a single strongly penetrant gene/test could match that of the complex mixture. Once the test is used clinically, it is difficult to change the mRNA profile, and our ability to learn the underlying causes is suppressed.

Fourth, we can expect that multiple genes interact and that only their combined influence is sufficiently predictive to reach clinical significance. Certainly, biomarker panels with multiple genes known to interact with each other are on the horizon, but current approaches are still poorly suited for effective development of optimal biomarker panels. Any combination of biomarkers should be based on a firm understanding of the underlying biology. If a biomarker merely serves as a surrogate for the responsible genetic/genomic factors, one runs the risk of compounding uncertainty with adding more and more biomarkers to a clinical test. Such an effort might yield effective predictions under the initial test conditions, but it is likely to fail when applied to diverse populations under varying conditions.

5. Outlook

Recent advances in technologies – for example ultra-rapid sequencing – promise further insights into the biology of health and disease, and treatment modalities and outcomes. We can expect

an increasing diversity of treatment modalities; increased emphasis on early therapy/prevention; marked emphasis on optimization of existing therapies in personalized health care; fewer new single mega-drugs but emergence of combination therapies; molecularly targeted therapies for niche markets (together with cost reduction in drug development to achieve economic sustainability). Biomarkers will play a rapid increasing role, but the guiding principles outlined above for valid biomarkers need careful consideration, lest one drowns in growing databases of unimagined size and complexity. We can anticipate that our insights into the biology of disease, and interactions with the environment and human conditions in our civilization, will mature to a point where health care and treatment of diseases will transform in as yet unexpected ways.

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