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Implementing Genomic Profiling: Opportunities and Obstacles for Academic Medicine

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Abstract

The Baylor PGP's design and implementation are guided by the following guiding principles: high quality, robustness, low cost, adaptability, practical clinical utility, and the capacity to facilitate numerous areas of clinical research. The focus on extensive screening for rare disease-causing mutations rather than common risk-increasing polymorphisms is the approach's single most distinctive feature. The ability to screen for these variants at a low cost could have a significant impact on disease diagnosis, carrier detection, early detection of late-onset disease before symptoms appear, and even prenatal diagnosis. This system will not only create a counselling tool for individual "consumers," but it will also fit into the existing medical record and be used by doctors who provide direct patient care.

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Introduction

In order to coordinate these efforts within the institution, BCM joined the Personalized Medicine Coalition as an active member, established an infrastructure for the Personalized Medicine Alliance, and began planning a new graduate training curriculum to educate the next generation of medical leaders [1]. A first-generation Personal Genome Profile assay was developed by BCM faculty members as part of this larger strategy to help physicians in this new era of medicine diagnose and manage patients. High quality, robustness, low cost, flexibility, practical clinical utility, and the capacity to facilitate broad areas of clinical research are the guiding principles of the Baylor PGP's design and implementation. The prototype Personal Genomics' tests were narrowed down to specific Baylor Clinic and affiliated clinical and translational research programs [2]. We include genetic tests that are linked to individual responses to pharmacologic agents and can assist in risk classification, like the majority of other groups developing testing for personalized medicine. Rather than focusing solely on common risk-increasing polymorphisms, our strategy places an emphasis on comprehensive screening for rare disease-causing mutations [3]. We are working on tools that can be used to genotype a large number of rare mutant alleles that are already known to cause genetic diseases. We believe that the ability to screen for these variants at a low cost could have a significant immediate impact on disease diagnosis, carrier detection, presymptomatic detection of late-onset disease, and even prenatal diagnosis. We emphasize that our goal is not just to develop a counselling tool for individual "consumers," but rather to create a system that can be used by doctors who are involved in direct patient care and fits into the established medical record [4].

Material and Methods

Common varieties modifiers of disease risk and effects of Pharmacogenetics

The fact that for the first time epidemiologically robust and statistically sound demonstrations of the effect of these common variants on disease are available thanks to these studies has been a tremendous success. The discovery of previously unknown pathogenic mechanisms, which have the potential to open up new avenues for drug and intervention development, is a remarkable outcome. However, it is unclear how knowing a person's specific variant pattern will affect them [5]. In a recent study, Brautbar. show how incorporating a single genetic variant into a well-established risk prediction model for coronary artery disease could be used to decide whether or not to start statin therapy in people with moderate risks. The general idea that clinical decision algorithms can incorporate genetic tests is very appealing. On the other hand, numerous concerns regarding acceptability, cost, efficacy, and application are raised by ambiguous assertions regarding lifestyle counselling based

on genetic risks [6]. There are currently a few loci and genetic variants that have been shown to have an impact on drug metabolism or the risk of drug-induced toxicity, according to convincing data. Individual differences in pharmacokinetics have been linked to genetic variants that influence the absorption, distribution, metabolism, and elimination (ADME) of various drugs. Additionally, a number of genetic variants have been linked to an increased risk of drug toxicities and side effects. The entire issue of pharmacogenetics goes beyond the scope of this brief commentary, but it is evident that only a small number of such markers have significant effects and that only a few require testing before they can be used in clinical practice. Despite this, we are aware that one of the most significant diagnostic genotyping applications is pharmacogenetics testing [7]. At least one laboratory offered clinical pharmacogenetics testing for distinct genes when our assay was designed. Studies with adequate sample sizes, consistently defined effects on drug metabolism or toxicity, independent repeated replication of the claimed genetic effect, and clearly defined risk alleles or haplotypes only support a subset of these, according to a review of the literature. Even though we have included genetic analysis of all of these potential genes in our version 1.0 assay, we only intend to notify referring physicians about a select few established markers. The CYP2D9 and VKORC loci, which have been shown to have a significant impact on warfarin metabolism, are two prime examples.

The justification for including mutations that cause disorders of only one gene

Despite the fact that these conditions are uncommon on their own, most doctors tend to dismiss them as zebras because of their combined impact. Nearly 3,000 Mendelian disease-causing human genes have been identified in the last two decades [8]. A job for a portion of these transformations is unequivocally thought in more normal problems and demonstrated to be risk factors in numerous illnesses in any case, until this point in time, there has been no orderly examinations that address how much uncommon changes add to normal sicknesses. There are almost no single-gene disorders with a higher prevalence in which the underlying genes have not been identified. There is now population information regarding the mutant alleles that are underlying the most significant of these diseases, either because they are more prevalent or because they have a significant medical impact. Numerous studies have been conducted on autosomal recessive conditions like phenylketonuria and cystic fibrosis. Familial bosom disease, an autosomal prevailing attribute whose hereditary qualities include locus heterogeneity, age-subordinate penetrance, and variable articulation, has been the object of extremely huge scope DNA sequencing [9]. Numerous X-linked recessive disorders, particularly Factor IX deficiency, have been extensively studied and offer a wealth of information regarding human mutation mechanisms. Because most Mendelian diseases are even rarer, these "classic" genetic diseases are unique in some ways. The majority of the several thousand Mendelian diseases have never been seen in more than one thousand people, so there is a short list of mutations for those for which a disease gene has been identified. There are some general lessons that can be gleaned from all of the mutational data that are available, regardless of whether the diseases in question have a high prevalence or are extremely uncommon. Some disease phenotypes are the result of the unique expression of just one or very few alleles. Maybe the most sensational representation of this component is the ways that of people with achrondroplastic dwarfism bears the G380R transformation in the FGFR locus. The structural characteristics of some disease genes make them more susceptible to particular mutational mechanisms. For instance, the dystrophic locus is very big and has intragenic low copy repeat structures. These structures cause common deletions, which together make up 70% of the mutant alleles. The most common form of Charcot-Marie-Tooth disease is caused by the duplication of a short chromosome region. Certain alleles responsible for the most prevalent autosomal recessive diseases have much higher frequencies than the average among all such alleles due to demographic factors like migration, founder effects, and possibly selection [10]. The fact that certain nucleotide positions have intrinsic mutation rates that are higher than those of the surrounding bases is yet another important consideration. The T transition brought about by the deamination of methyl cytosine is the one of these mechanisms that is best understood. Triplet-repeat expansions are another special kind of mutation that only affects certain loci and have a normal repeat structure but a predisposing mutation. At last, changes in some nucleotide positions are bound to prompt malicious amino corrosive replacements in protein coding succession and subsequently are bound to be destinations seen in people with Mendelian sickness.

Conclusions

High quality, robustness, low cost, flexibility, practical clinical utility, and the ability to facilitate broad areas of clinical research are the guiding principles of the first generation Personal Genome Profile Baylor PGP assay. The emphasis placed on extensive screening for rare disease-causing mutations rather than common risk-increasing polymorphisms is the single most distinctive aspect of its development. The ability to screen for these variants at a low cost could have a significant impact on disease diagnosis, carrier detection, early detection of late-onset disease before symptoms appear, and even prenatal diagnosis.

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