Personalized Genomic Medicine in Current Clinical Practice

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Medical science has tremendously evolved over the past decade, particularly in the field of genetics. Our society is currently experiencing an explosion of information and the challenge, especially for us in the medical profession, is to identify which ones are appropriate and useful in managing our patients. The process of sifting through every new information and knowledge could be daunting but the risk of immediately adopting any new molecular diagnostic test or technique into clinical practice is certainly not to be overlooked. Patients can be subjected to unnecessary intervention and treatment not to mention the added stress and anxiety to the patient and to the immediate family as well.

The Human Genome Project begun formally in 1990 by the coordinated effort of the United States National Institutes of Health and the Department of Energy. Its primary goal is to identify the approximately 25,000 genes and sequence the 3 billion chemical base pairs that make up the human genome, the entire human genetic information.[1,2] The completion of the project in 2006 paved the way to the most promising field in modern medicine and research – genomics, the structural and functional studies of the genome. Genomics through genome-wide disease association studies and whole genome sequencing will eventually facilitate the practice of personalized genomic medicine.

Personalized genomic screening or profiling makes use of data derived from genome-wide association studies to predict a person's risk of developing certain conditions throughout his lifetime.[3] These information are usually derived from case-control studies of people to identify genetic markers that are found to be more common in diseased individuals in comparison to the control group. These markers are called single nucleotide polymorphisms (SNPs)-variations in deoxyribonucleic acid (DNA) sequences in the general population involving single nucleotide replacements which may or may not have a known clinical significance. Results are typically reported as likelihood of a person to develop a certain disease. In contrast, Mendelian genetic testing makes use of validated laboratory methods that focuses on one gene or a group of genes that are previously proven to cause that particular disease or predict an outcome. Such is the case in the inborn errors of metabolism or in familial breast cancer. These so-called Mendelian disorders are caused by specific genetic mutations that are strongly-associated with the disease and exhibit clear familial inheritance patterns.

The increasing cost of medical care and intervention has gradually shifted the focus of clinical care towards prevention and screening. The idea of genetic testing and being able to determine one's odds of developing a particular disease in the future has spawned several biotechnology companies to offer direct to consumer personalized genome screening. One can just look up in the web and pay online for sampling kits to be delivered at home. To the uninformed and those unfamiliar with the test, it is fairly easy to accept the results generated as valid and true and thus allow these results to dictate an action or a specific clinical management. It is important to stress that very few of those SNPs being tested in personalized genome screening have full clinical validation. Identifying the risks based on SNP data from retrospective studies may not correlate with planned prospective studies. Also, the test result interpretations based on SNP data derived from a particular ethnic group may not necessarily be applicable to another. Even in the ongoing 1000 Genomes Project where a thousand genomes are being sequenced "to provide a comprehensive resource on human genetic variation", it is not clear if Asians are well represented.[4]

In a more accurate sense, most personalized genomic sequencing tests are not true genome-wide sequences. Most often, laboratories sequence and detect only the predetermined most common disease-associated SNPs or variations. True whole genome sequences are still labor-intensive and time-consuming, not to mention quite expensive even with the most recent and advanced laboratory methods. Whole genome sequencing has its issues as well. Interpretation of data from full sequencing of

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the genome can be difficult. It may also identify some rare polymorphisms and variations in genes that assessing their clinical significance can be quite challenging.[5] However, this is not to say that in the future the interpretation can be streamlined.

The primary care physician will most likely encounter patients inquiring about personalized genome screening more and more often in clinical practice. The challenge is to convey to the patient the applicability and validity of such tests. It is therefore important that the doctor be updated and aware of the current evidence available and to know the limitations of these tests. Moreover, the question now is - should the doctor recommend personal genomic screening as a routine preventive diagnostic test? At present, there is still no clear evidence that such screening tools are medically indicated. Large, prospective cohort studies of specific SNPs and their associations with cardiovascular disease and type-2 diabetes still has not significantly improved the ability to predict development of these diseases compared to the usual clinical and family history.[6,7]

Currently, nucleic acid-based molecular tests are used in diagnosis, prognosis, prevention, and prediction. Test menu in clinical laboratories are growing exponentially as mutations in more genes are identified for many Mendelian disorders and nucleic acid base changes are utilized in stratifying patients who will respond to particular therapeutic agents. There is no doubt that molecular diagnostics will flourish and become an inherent tool in everyday clinical practice with the steady advances in biotechnology and bioinformatics. However, for this to be fully realized, the gaps in physician education in genetics and genomics need to be addressed appropriately.[8] Such efforts are underway in some institutions[9,10,11,12] and for certain, there will be important lessons to be learned. There are also available materials that can be perused by clinicians online and in print.[10,13]

As an attempt to clarify how to best harness all the advances in genetic medicine, clinicians need to understand the specific indications, limitations, and proper interpretations of molecular genetic tests as well as their ethical, legal and social implications. The counseling issues are as important as ordering the appropriate test for a particular patient condition. As some tests are too complicated, the expertise of a geneticist or a genetic counselor can be sought. The clinician must be cognizant on when a referral to a genetic expert is called for. Proper genetic counseling prior, during, and after genetic testing for constitutional or germline genetic changes cannot be overemphasized. Involvement of a molecular genetics pathologist or a molecular geneticist, knowledgeable of the technology being employed and its limitations, in ordering tests will prevent unnecessary and wasteful testing. The use of appropriate test and testing algorithm definitely will improve test yield so that cost-benefit can be optimized.

Five years after the completion of the Human Genome Project and we are entering the era of personalized genomic medicine but much is still to be learned about how we can incorporate it in clinical practice. The amount of information that is constantly churned out everyday by various research groups is staggering and we are still barely able to scratch the surface. Genomic information will shape the future of medicine with continuous research done on specific genotype-phenotype correlations as well as gene-gene and gene-environment interactions and clinical outcomes, so we have to prepare for it.

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