Commentary

Toward Best Practice in Using Molecular Diagnosis to Guide Medical Management, Are We There Yet?

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Molecular genetics testing has made several huge breakthroughs in the past two decades and many molecular technologies have been applied to our daily medical progress. However, the clinical utility has not reach a consensus by the medical and genetic peers as well as third party payers. The predictive value and clinical applications are variable from one condition to the other. Numerous questions remain including technology deficits, data interpretation and unpredicted phenotypes in complex disorders. In this commentary, the authors reviewed the historical perspective of genetic testing and summarized the current technical deficit, clinical dilemma and suggested a few critical threshold to overcome before the implementation of useful genetic information in standard health care can become a reality.

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The medical specialty of clinical genetics was accredited in 1982 in the USA.[1] The practice of medical genetics started with dysmorphology and syndromic diagnosis mainly by clinical impression followed by very limited cytogenetic and biochemical/enzyme analysis in the 1960's, and with restriction enzyme based molecular analysis beginning in the late 1970's. Before the turn of the millennium, most scientific and medical efforts for studying and diagnosing genetic conditions were focused on rare single gene disorders such as Huntington's disease, Duchenne muscular dystrophy, cystic fibrosis, and metabolic disorders, as well as identifying chromosomal abnormalities. Initially, genetic testing was exclusive to clinical geneticists with limited options including high resolution karyotyping, single to multiple colored FISH analysis and Sanger sequencing for limited conditions. Beginning around 2005, array comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) arrays were employed. In addition, next generation sequencing, and deep re-sequencing became readily available for clinical application around 2010. Presently, every discipline in medicine has its own special interest in molecular genetics and the focus of the genomics and genetics research community has shifted toward understanding the basis of common complex disorders and cancers.[2,3]

Common complex diseases are by definition common and comprise the bulk of genetic diseases encountered by most physicians. The genetic variants contributing to these disorders may be highly penetrant with a high predictive value or may have such a low penetrance to be of virtually no predictive value. In addition, most common diseases involve the interaction of several genes and environmental factors, as well as stochastic events. Cancer is typically a multi-step process involving multiple genes, pathways and environmental factors. Certain germ line mutations in cell cycle regulators, tumor suppressor or oncogenes can predispose one to have cancer but the prediction value is inconsistent. The common traits or diseases under study include coronary artery disease, CVA, obesity, hypertension, type 2 diabetes, breast cancer, cervical cancer, colorectal cancer, prostate cancer, celiac disease, Crohn's disease, bipolar disorder, and many more. Should incorporation of these research results into current clinical and public health practice become possible allowing the practice of personalized or genomic medicine, physicians will need to be prepared for the changes and challenges!

Genetic tests, for diagnosis or screening, are required to detect a genetic alteration in an affected or at risk person. The ability to detect a genetic alteration depends on many factors, including the location of the gene, the nature of the mutation and the sensitivity and specificity of the test. From the allelic drop out, intronic mutations to promoter changes to new pitfalls result from next gen sequencer, many clinical obstacles remain. A single disorder can result from different aetiologies; for example, more than 400 genes can cause retinal degeneration and more than 100 genes can cause hearing loss. Therefore, for some disorders, panel analysis has replaced single gene assay. At this point, most panel assay either by next generation sequencing or focused exome sequencing continues to miss 50% of the gene changes from the capturing process of the coding regions. In addition, exon

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1 mutations, GC rich genes and psuedogenes continue to confound mutation analysis. Numerous questions still abound regarding bioinformatics analysis of sequence data, including what is the threshold for calling variants, what script is used to record a mutation, and what method(s) should be employed for predicting the consequences of the variant. In the author's experience, it is not uncommon to encounter an obvious mutation being missed by one reputable reference lab and while being detected by another laboratory using a different platform/methodology. Therefore, appreciation of the limitations of molecular testing is critical.

The predictive power of genetic testing is influenced by the complex interaction between genetic predisposition and environmental influences. Further, there are unique social, ethical and legal issues related to genetic testing. These all come together in the molecular diagnosis of cancer. The author has the experience of performing tumor line analysis on a breast cancer with bone metastasis hoping to identify specific somatic and germ line pathway changes to guide the management. A germ line mutation in the ATM gene was identified; mutations in this gene are known to cause ataxia-telangiectasia and increase the risk for breast and other cancers. The patient had one sibling with breast cancer and the patient's grandson developed a rare follicular hyperplasia of parotid lymph nodes from multiple oral x-rays. While all the clinical constellations and history of these two other individuals fit the ATM carrier manifestation, a subsequent study of the sibling did not identify the said mutation, nor was it present in the grandson. This case highlights the complexity of genetic counseling of cancer syndrome. The overall effectiveness of genetic testing for predicting the likelihood of cancer and for guiding treatment remain to be determined, as the complexity of genes and environmental factors are difficult to quantitize or delineate. The ascertainment of tumor lines (mosaic and contamination) and multiple secondary effect of a disturbed cell cycle can mask or dilute the "molar ratio" of a crucial molecular changes and miss the diagnosis.

Translation of research findings to useful health-care applications appears to be always behind as implementation of useful research findings may take years or decades. As discussed above, many applications remain of very limited clinical utility as neither the technology is perfect nor the disease spectrum is straight forward to be diagnosed to a professional personnel. However, all the testing may have become available directly to the consumers, which complicated the situation. Many "nontraditional genetic lab" also offer inexpensive testing without proper validation or counseling, which result in many misunderstandings and inappropriate treatment, e.g. MTHFR. While as a community we are careful and strict about our practicing guideline at a professional level, information can be used inappropriately, intentionally or not, by others.

In summary, difficulties with the translation of research findings need to be understood and addressed if genetics and genomics research is to fulfill its promises towards improving diagnosis, treatment, and prevention.[2-4] At this point, although millions of research dollars continue to be devoted into genetic and genomic research, except a few well-documented and non-equivocal testing, the genetics research community is skeptical that the application of genetic susceptibility testing and screening would contribute significantly to the improvement of the quality of health care. In 2014, we are not there yet. The implementation in health care of useful genetic information still needs to overcome several hurdles.

CONFLICT OF INTEREST

None.

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REFERENCES

1. Epstein CJ. Medical genetics in the genomic medicine of the 21st century. Am J Hum Genet. 2006;79(3):434-438.
2. McCarthy JJ, McLeod HL, Ginsburg GS. Genomic medicine: a decade of successes, challenges and opportunities. Sci Transl Med. 2013; 5(189):289sr4.
3. Manolio TA, Chisholm RL, Ozenberger B, et al. Implementing genomic medicine in the clinic: the future is here. Genet Med. 2013; 15(4):258-267.
4. Gilissen C. Hehir-Kwa JY, Thung DT et al. Genome sequencing identifies major causes of severe intellectual disability. Nature. 2014 511(7509):344-347.