Clinical Molecular Genetic Laboratory Practice, Where We Stand in 2018

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Heath system has been gradually evolving from patient-care to prevention-oriented medicine. He breakthroughs in the genomic technologies and database curation contribute significantly to the transformation. We enter the "genomic era" as we step on the blueprint of the first human genome sequence. He growing role of genomics in healthcare for patient diagnoses, treatment, and disease prevention thrives with the global effort of personalized medicine; also called precision medicine. Meanwhile, we are facing challenges of the new model of health systems, insurance policies, and bioinformatics (Figure 1).

We have gradually learned that nearly all conditions and disorders have a genetic component. The technology has advanced from single gene Sanger sequencing to microarray, next generation sequencing (NGS) panel, exome sequencing, and most recently to whole genome sequencing. The development of genetic technology has facilitated a rapid implementation of these newer generation technologies into clinical medicine, which significantly increases diagnostic rate in symptomatic individuals [1]. Genomic sequencing (GS) is now an essential tool for evaluating rare disorders with estimated detection rate to be 20% to 45% depending on the clinical presentation, age of onset, and population [2,3].

Meanwhile, the Affordable Care Act promotes re-focusing on the health of both individuals and communities to decrease the overall cost on medical care. Newborn screening (NBS) was the first step toward preventive medicine at the population level and started in the 1960s by testing newborns for phenylketonuria (PKU). In the United States, a uniform newborn screening panel was recommended by the American College of Medical Genetics and Genomics (ACMG) in 2006 [4]. The most successful example of NBS in the USA is cystic fibrosis (CF) which has increased the lives of many due to high frequency; however, the clinical utility in some disorders such as Krabbe disease is still controversial [5]. More recently, noninvasive prenatal testing (NIPT)/circulating free DNA (cfDNA; also called liquid biopsy) testing revolutionized prenatal and oncological screening tests. These tests have made the diagnosis less invasive.

Carrier-screening (CS) has extended efforts to the preconception level in high risk populations. He most widely used and mature CS in the USA is for CF in Caucasian and a multiple gene hotspot panel for Ashkenazi Jewish. Nowadays the expanded CS includes other less common disorders that are prevalent in minorities and is considered part of precision medicine. For this reason, the expanded carrier screening (ECS) was accepted by the American College of Obstetricians and Gynecologists (ACOG) [6].

Another major achievement in clinical molecular genetics was the expansion of diagnostic and prognostic tests to therapy-related screening for drug selection, pharmacogenomics (PGx), which is a key component of personalized therapy. Statistics show that 1 of 5 injuries or deaths per year to hospitalized patients may be as a result of adverse drug reactions [7]. A wide range of gene variants are related to drug selection, such as single nucleotide variants (SNVs; such as CYP2B6, CYP2C9, HLA-B57:01), deletions (CCRS-Δ32 allele), amplifications (HER2), and gene rearrangements (BCR-ABL1, ALK). Therapeutic targets (such as cetuximab/panitumumab and KRAS; vemurafenib and BRAF) and predisposition to certain drug side effects (abacavir and HLA-B57:01; carbamazepine and HLA-B1502; thiopurines and TPMT) are both considered parts of PGx in this communication [8].

Figure 1: This figure illustrates the shift of health care from patient care oriented to preventive case oriented. And this shift fundamentally affects the clinical laboratory genetic practice, which is abled by advanced medical technologies, and bioinformatics. Meanwhile, it is also complicated by existing medical practices, insurance policies, et al.
The increased frequency and complexity of clinical molecular genetic tests across the nation make regulation challenging especially since a majority are laboratory developed tests (LDTs). In 2010, the FDA announced its intent to reconsider its policy of enforcement discretion for LDTs and held a workshop to obtain input from stakeholders on such policy. The FDA used this feedback to develop an initial draft approach for LDT oversight and published draft guidance in 2014. Existing nondiscrimination provisions such as the Health Insurance Portability and Accountability Act (HIPAA) generally prohibits health insurers or health plan administrators from requesting or requiring genetic information of an individual or the individual's family members. In 2008, a federal law, GINA (Genetic Information Nondiscrimination Act), was implemented to further protect individuals from genetic discrimination in health insurance and employment. In the past 10 years, public awareness of GINA has increased in response to the dramatically growing genetic testing [9,10]. However, we are facing tremendous challenges in the preliminary period of the “genomic era”. Awareness of a standardization of NGS tests such as validation and quality control are emerging, but not yet fully developed [11-14]. Furthermore, underdeveloped public databases limit the clinical interpretation of patient's results. A cost-effective follow-up testing strategy for cancer surveillance still falls into the blind site if the variant is not common. Collaborative oversight of LDTs between, FDA, ACMGG, CAP (College of American Pathology), and CLIA’88 (Clinical Laboratory Improvement Amendments of 1988) is still under discussion and developing. While we work together to navigate in the genomic era, one thing is certain: personalized medicine will continue to positively impact patient care and health system.

References