 Advances in Genomics and Proteomics: Their Role in Future of Molecular Medicine

Harsha Gowda

INTRODUCTION
Before the advent of molecular medicine, physicians relied on macroscopic observations and symptomatic manifestations in a patient to diagnose and treat diseases. Availability of microscopes a century ago somewhat changed this by providing an ability to establish causal relationship of various microbes to several infectious diseases. This resulted in better diagnosis and opened up avenues for specific treatment options for specific infections. Microscopes also revolutionized diagnosis and classification of non-infectious diseases including cancers. Research efforts toward identifying molecular signatures that serve as surrogates for presence of a disease, classification of disease subtypes, determining treatment options and monitoring therapeutic outcomes have all revolutionized the practice of medicine over the years. Today, both physicians as well as diagnostic labs play important roles in diagnosis, treatment and clinical management of a number of diseases. Advances in DNA sequencing and protein monitoring technologies have revolutionized molecular medicine in ways that one could not predict a decade ago.

The first draft of the human genome was released in 2001. This was a multibillion dollar effort where various research laboratories from across the world participated. This catalyzed development of a multitude of DNA sequencing technologies that we now call as next-generation sequencing technologies or massively parallel sequencing technologies. It has revolutionized the field of genomics and holds great promise to change the practice of medicine. Thousands of individual human genomes are now being sequenced across the world to determine genetic variations across population. In addition, there are several efforts where large cohorts of patients with genetic diseases are also being sequenced to identify underlying genetic basis. These studies are providing genetic markers that can identify individuals with genetic predisposition to various diseases. A lot of emphasis is now being put on appropriate utilization of this vast molecular information to improve diagnosis and clinical management of a number of diseases. In addition to genetic testing, molecular tests that rely on transcript or protein measurements are also being investigated in various diseases. For example, one of the most successful examples of a molecular test that relies on protein measurement is pregnancy test where human chorionic gonadotropin (hCG) produced by trophoblast cells of the fertilized ovum is measured in either blood or urine. This particular test is so simplified that women can test their pregnancy by buying the kit at pharmacy and testing themselves at home before deciding on consulting a doctor. Molecular tests are now being routinely used for various purposes including prenatal screening, newborn screening, presymptomatic gene testing, diagnosis and prognosis and also to determine appropriate treatment strategies for patients.

PRENATAL SCREENING
Tests to diagnose molecular defects that cause genetic disorders including Down’s syndrome, neural tube defects, muscular dystrophy, Huntington’s disease, cystic fibrosis, Tay-Sachs disease and fragile X syndrome are being routinely performed to determine these defects in fetus or embryo before the child is born. These tests are often being recommended when one or more affected individuals are there in the family and there are reasons to believe that the genetic anomaly is inherited. This provides an opportunity for the couples to decide early in their pregnancy about either retaining or aborting the fetus or taking any remedial steps for appropriate therapeutic intervention.

NEWBORN SCREENING
There are several molecular tests for screening newborns for suspected congenital birth defects or genetic disorders that could potentially be treated early in life. The most common ones in this category include metabolic disorders like phenylketonuria that are potentially treatable.

PRESYMPTOMATIC GENE TESTING
Several genetic anomalies manifest as a disease in a due course after the birth. In cases where there are affected individuals in the family, there are molecular tests to determine and predict the risk of a disease even when the individuals are asymptomatic. This is especially true in several forms of familial cancers. For example, women with mutation in BRCA1 have 80% chance of developing breast cancer by the age of 65 years. Another example in this category is retinoblastoma where the Rb gene is mutated. Although the manifestation of these diseases need not be absolute in individuals carrying mutant genes, they are at higher risk of getting these diseases than the general population.

DIAGNOSTIC TESTING
A plethora of molecular tests are now available for accurate diagnosis of various diseases. Compared to symptomatic diagnosis which often follows a trial-and-error method, molecular diagnostic tests are definitive. Successful implementation of this can be witnessed particularly in the case of infectious diseases.
Heterogeneity in patient response to drugs is well known. Pharmacogenomics deals with efforts to determine molecular signatures that could facilitate selection of optimal drug therapy and dosage for different patients.

Last 5 years have seen tremendous amount of research efforts toward genomic and proteomic characterization of various types of cancers. These studies have revealed previously unappreciated degree of heterogeneity within each cancer type that has forced us to rethink our strategy on diagnosis and treatment of cancers. These studies have encouraged stratification of patients based on molecular subtypes prior to treatment. This will ensure better efficacy. From nonspecific cytotoxic agents, cancer therapy has now moved toward determining targeted therapeutic agents based on molecular aberrations that drive cancers. Successful examples of this strategy include Imatinib that is used to treat chronic myelogenous leukemia (CML) where BCR-ABL fusion protein drives proliferation, and Erlotinib is used to treat a subset of non-small cell lung carcinomas where a mutant epidermal growth factor receptor (EGFR) tyrosine kinase is known to drive proliferation.

Molecular diagnostic tests now accompany several cancer drugs. These are being called companion diagnostics that are being used to preselect patient populations that are most likely to benefit from a targeted therapy. Pharmaceutical industry has woken up to the change that practice of medicine is undergoing and is changing its historically successful blockbuster model of drug development to novel concept of personalized medicine. Genomic, transcriptomic and proteomic approaches are being extensively used to identify biological markers that could aid in diagnosing a disease, staging a disease, determining appropriate therapeutic options and also to monitor drug response. It will not be long before these molecular tests will be available for clinicians. These developments will change the way medicine is practiced in the future.