Introduction: Molecular Medicine in the Common Era

Applications and Impact of Molecular Pathology in Health and Disease

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KEYWORDS

• Molecular pathology • Methods • Genomics • Omics • High throughput • Quality • Polymorphisms

KEY POINTS

- Molecular pathology has profoundly influenced general pathology practice and the understanding of pathobiology and its techniques have provided medicine with accurate, sensitive, and rapid opportunities to diagnose and prognosticate disease in an unprecedented manner.
- Detection of abnormal genes and differences in patterns of gene expression can influence disease diagnosis and guide specific therapy in many disease settings.
- In addition to the clinical setting, molecular pathology has expanded to the direct-to-consumer market for general commercial use.
- Application of molecular pathology to high-throughput automation and multiplex analysis has provided unprecedented support for evolving omics platforms toward personalized medicine.

The history of medicine aligns with the history of humanity. The Bible recounts Rachel's request of *da'aduim* (mandrakes) from her sister as putative means of promoting fertility[1] and the prophet Isaiah states to "bring a cake of figs, and let them take and lay it on the boil, that he may recover"[2] as a remedy for king Hezekiah's ailment. The maturation of medicine, disease diagnosis, and patient treatment has progressed over millennia, transcended religion and gender and developed in various spheres of people, culture, class, and geography. The Israelite priest diagnosed leprosy and cured it.[3] Egyptian doctors used powdered charcoal as a medicine to

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absorb poisons and cure food poisoning, and women physicians including Merit Ptah (c. 2700 BCE) and Peseshet (c. 2500 BCE) served as the common day Chief of Service.[4,5] Hippocrates (c. 400 BCE) described the four humors as representing ones personality, and Galen (c. 130 BCE) further applied this concept to body fluids defining mood and temperament ("sanguine," "choleric," "melancholy," and "phlegmatic"), which related to disease when out of balance.[6] Saint Basil of Caesarea (CE 369) founded the first 300-bed large-scale hospital for the seriously ill and disabled,[7] and Maimonides and Ibn al-Nafis (circa CE 1100 and 1200, respectively), deduced that the heart sends blood to the lungs to get air.[5]

Innovation is often slow to gain acceptance. The germ theory of disease confirmed and proven by Pasteur and Lister was previously proposed by Ignaz Semmelweis years earlier. However, his suggestion to wash one's hands in clinical practice and before a procedure was met with ridicule and mockery.[8] Kary Mullis, who received the Nobel Prize in chemistry for polymerase chain reaction technology, initiated a technology that was time consuming and laborious. Fortuitously, the alignment of thermostable *Taq* polymerase enzyme with automation yielded the prototype of the polymerase chain reaction technology, which gave rise to molecular pathology used today.

To this end, the success of the Human Genome Project has expanded molecular biology in an exponential manner.[9] It has facilitated the identification of numerous novel genes whose functions can now be determined and whose expressions can be monitored in different disease states. Whereas the discipline of pathology often refers to the rubric of the study of disease in general, molecular pathology refers to the submicroscopic analysis of nucleic acids and proteins to diagnose disease, predict the occurrence of disease, predict the prognosis of diagnosed disease, and guide therapy.

Furthermore, recent advances in molecular pathology have positively affected the practice of medicine, especially diagnostic medicine. These changes result from abilities to clone disease-causing genes and the proteins that they encode and to detect the presence of these genes and proteins in the serum and other body fluids and tissues of patients, even though they may be present in minute quantities. This detection has been made possible by a veritable explosion of new, highly sensitive techniques involving amplification methods, such as polymerase chain reaction, branched DNA, fluorescence in situ hybridization, next-generation sequencing, and mass spectroscopy, among others.[10] The ability to streamline testing in a high-throughput manner, many of which have been automated, enables a single patient sample to be analyzed for multiple genes or proteins.

Molecular pathology has afforded physicians the ability to drill down and interrogate disease states for causes related to chromosomal abnormalities, point mutations, polymorphisms, and the like, which can provide a personalized medicine approach to diagnose a wide spectrum of diseases. To this end, genes that encode drug-metabolizing enzymes, activating and inactivating, and genes that encode ligands and receptors may show polymorphisms that either decrease or increase the therapeutic effectiveness or toxicity of drugs already in clinical use, thus accounting for some idiosyncratic responses previously not understood or predictable.[11] As such, there have been major advances in testing patients for genetic expression of selective enzyme isoforms, allowing prediction of which drugs would be the most effective ones for use in a personalized manner.[12]

As more polymorphisms are identified and correlated with individual patient response to treatment, pathologists will be called on increasingly to profile