Precision Medicine: Implications for Science and Practice

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As aptly stated by President John F Kennedy, "Change is the law of life. And those who look only to the past or the present are certain to miss the future."[1] This quote is a reminder that although proven scientific findings provide a firm foundation for standard practices, the key is to also position ourselves to both prepare for and drive future research studies, including the use of targeted approaches to cancer diagnosis and treatment. Recent advancements in molecular diagnostic capabilities have put us in a strong position for future studies and efforts to enhance the effectiveness of patient care based on individual patient and disease characteristics. Precision medicine encompasses this diagnostic and therapeutic paradigm, with important implications for clinical care and research. This review is focused on therapeutic efforts in oncology, although the discussion and general concepts are applicable to many other clinical and therapeutic areas of medicine and intervention. Additionally, although most of the diagnostic efforts discussed herein relate more to the assessment of DNA or genomics, additional diagnostic markers are available and emerging, including the transcriptome, proteomics, metabolomics, and imaging analysis.

Technologic advances have led to the development of massively parallel sequencing strategies, also known as next-generation sequencing (NGS).[2] Next-generation sequencing enables analysis of multiple target regions of the genome in parallel, with high depth, including assessment in clinically relevant, formalin-fixed, paraffin-embedded tumor specimens that are readily available. This capability to assess for multiple genomic alterations is important because cancer growth is usually dependent on more than 1 genomic alteration, and different individual cancers of similar histology may have different underlying mutations. The cost and time for assessment of genomic information obtained using this advanced technology has decreased dramatically over the last decade, enabling results of this testing to influence point-of-care decisions. Although whole genome sequencing is now a reality, enrichment strategies have also made it possible to focus on specific genes, further improving the cost and timeliness of assessments. Many of these strategies have increased the ability to rapidly detect multiple types of molecular alterations in smaller tumor specimens.[3] With such opportunity for efficient analysis in real time, many Clinical Laboratory Improvement Amendments (CLIA)-certified commercial and academic laboratories have used NGS platforms to develop analytically validated tumor-sequencing panels for use in clinical decision-making.[4]

A vision for personalized or precision cancer medicine based on genomic profiling will involve a paradigm shift in both diagnosis and treatment. Traditionally, tumors are classified by site of origin and histologic appearance, possibly supplemented by expression of a few protein markers assessable by immunohistochemistry. In the future paradigm, cancer classification may depend as much, or more, on the specific set of genomic alterations present in the tumor as on disease histology and organ of origin. Such classification may allow for informed treatment strategies that target the genomic alterations driving tumor growth. For example, lung cancer, which has long been classified primarily by histology, is really many different diseases defined by a wide spectrum of underlying genomic alterations.[2] The *KRAS*-mutant lung cancers are likely a completely separate set of diseases compared with *EGFR*-mutant lung cancers, with different natural histories and responses to treatments (see eDocument 1, available online, for a complete list of gene abbreviations and expansions used throughout this article). At present, the number of gene alterations in lung cancer responding to specific targeted therapies is steadily growing, and currently includes alterations in *EGFR*, *BRAF*, *HER2*, and *ALK*, as examples. Most of these alterations are present only in a small minority of lung cancer cases, but in sum, they represent a significant

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Abbreviations and Acronyms
CLIA = Clinical Laboratory Improvement Amendments
ER = estrogen receptor
NCI = National Cancer Institute
NGS = next-generation sequencing

fraction. In such situations, broad up-front tumor genomic testing may be more informative and cost-effective than serial analysis of individual biomarkers in tumor specimens. On the other hand, although a set of "actionable" gene alterations has been identified, which are known to drive cancer growth and for which targeted therapy is available, numerous other genomic alterations are being identified, and their clinical impact is unknown. As molecular diagnostic technology increasingly outpaces current evidence related to biomarker-based targeted therapy, the implementation and growth of precision medicine approaches currently in use, and the development of future approaches to study and understand biomarker alterations, represent an extraordinary opportunity as well as an evolving challenge.

CURRENT APPROACHES

Multiple examples of US Federal Drug Administration (FDA)-approved therapies based on a biomarker indication exist in various areas of medicine. These include nongenomic biomarkers, involving the expression of certain proteins. Examples include CD20, a marker for treatment with rituximab in non-Hodgkin's lymphoma, and the estrogen receptor (ER), a marker for treatment with hormonal therapy in breast cancer. In these cases, the biomarker is not associated with an underlying genomic alteration, or even differential expression from normal tissue, but marks classes of cancer that are more likely sensitive to a specific intervention. The discovery and clinical utility of gene expression-based biomarkers are more advanced in breast cancer, where gene expression panels are in clinical use to help determine which patients with ER-positive breast cancers will benefit from addition of chemotherapy to hormonal therapy.[5] Patient selection for targeted therapy is now being increasingly guided by genomic biomarkers in many cancer types, such as crizotinib or ceritinib for *ALK* gene rearrangement-positive lung cancer; dabrafenib, trametinib or vemurafenib for *BRAF*-mutant melanoma; and trastuzumab for breast cancer characterized by *HER2* amplification or HER2 protein overexpression (Table 1).[6] Although most FDA-approved agents with biomarker-based indication and usage fall under the category of oncology, the use of a biomarker-based drug approval approach in other therapeutic areas, including endocrinology, cardiology, gastroenterology, and inborn errors of metabolism, is growing.

With regard to oncology, most anticancer agents approved by the FDA in 2014 have associated drug targets.[7] In most of these cases, single biomarkers direct therapy with single agents, and the biomarker tests are FDA-approved to have analytic validity, clinical validity (ie how accurately and reliably the biomarker analyzed in a test accurately and reliably predicts 1 or more clinical

Table 1. Examples of Biomarkers Incorporated into Labels of FDA-Approved Drugs

Gene/biomarker	Drug	Indication	Medical area
LDLR mutation	Lomitapide, Mipomersen, Pravastatin	Familial hypercholesterolemia	Endocrinology
CYP2D6	Eliglustat	CYP2D6 ultra-rapid, intermediate or poor metabolizers	Inborn errors of metabolism
EGFR exon 19 deletion or L858R mutation	Afatinib, Erlotinib	Non-small cell lung cancer characterized by activation *EGFR* mutation	Oncology
ER, PgR	Anastrozole, Tamoxifen	Receptor-positive breast cancer	Oncology
ALK gene rearrangement	Ceritinib, Crizotinib	ALK-positive lung cancer	Oncology
BRAF V600E/K mutation	Dabrafenib (E/K), Trametinib (E/K), Vemurafenib (E)	BRAF mutation-positive melanoma	Oncology
ERBB2 (or ERBB2 protein)	Trastuzumab, Pertuzumab, Lapatinib, TDM-1	*ERBB2* (HER2) amplification/HER2 protein overexpression in advanced breast cancer	Oncology

Adapted from the U.S. Food and Drug Administration.[6]
ALK, anaplastic lymphoma receptor tyrosine kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CD20, cluster of differentiation 20; CYP2D6, cytochrome P450 family 2 subfamily D member 6; *EGFR*, epidermal growth factor receptor gene; ER, estrogen receptor; *ERBB2*, v-erb-b2 erythroblastic leukemia viral oncogene homolog 2; HER2, human epidermal growth factor receptor 2; LDLR, low-density lipoprotein receptor gene mutation; PgR, progesterone receptor; TDM-1, ado-trastuzumab emtansine.