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Recognizing the Value of Precision Medicine: Oncology and Beyond

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A NEW ERA OF HEALTH CARE delivery and treatment is emerging. The focus is changing from a one-size-fits-all model to tailored care that accounts for each patient's clinical situation and targets the precise molecular alterations involved in disease processes. Known as precision medicine, this fresh perspective on care involves understanding the underlying mechanisms of disease, specifically targeting molecular abnormalities and stratifying patients' responses to specific drugs.[1,2]

Considering individual variability when addressing healthcare strategies is not a novel idea. For instance, blood typing has been used for more than a century to guide blood transfusions; however, informatics and information breakthroughs, such as full-genome sequencing, next-generation sequencing (NGS) technologies, and the ability to stratify patients based on proteomic, genomic, and metabolomic signatures has expanded the application of personalized medicine to a wider range of possibilities, from initial diagnosis to treatment selection to dosing.[2,3]

Two components that are crucial in the implementation of precision medicine (PM) are targeted therapies and companion diagnostics. Targeted therapies are specifically designed to treat a subpopulation of patients within a given disease, typically based on genetic markers (or immunologic markers). For these patients, companion diagnostics are used to identify the genes, proteins, and other signatures needed to implement use of the targeted therapies. Through the disease course, companion diagnostics also may help provide additional information on the effectiveness of treatment or the progression of disease.[3]

Precision Medicine Today

Cancer is among the leading causes of death, both nationally and worldwide. Today, PM is particularly important in oncology, as it requires an in-depth understanding of the tumor biology of each patient. Over the past several decades, researchers have identified molecular patterns and targets that are useful in defining the prognosis of a given cancer, determining the appropriate treatments to administer, and designing targeted treatments to address specific molecular alterations. By concentrating on certain molecular features and characteristics that are present only in cancer tissues or predominantly in cancer tissues, PM therapeutics minimize the effects of treatment on healthy cells and improve the diagnosis and use of targeted treatments.[1,4] »

Precision Medicine Milestones in Cancer Therapy

Chronic Myeloid Leukemia

The PM era is characterized by certain milestones. One such milestone was identification of a contributor mutation in chronic myeloid leukemia (CML) that involves the fusion of 2 genes: *BCR* and *ABL1*. This fusion results in a mutated tyrosine kinase domain known as the ABL1 tyrosine kinase domain. In the 1990s, this molecular alteration was recognized as a potential treatment target. Tyrosine kinase inhibitors (TKIs) have changed not only the treatment of CML, but also the treatment of many other cancers. The first-generation TKI, imatinib, transformed the end result for many patients. Further refinement of TKIs led to the development of others, such as dasatinib and nilotinib, which improved on the characteristics of the originator agent.[5]

Breast Cancer: Specific Subtypes

Breast cancer is noted as a leading cause of morbidity and mortality worldwide. The complexity of biomarkers involved in human breast cancer reveals multiple mechanisms, diverse tumors, and numerous categories the disease. Two of the most important predictive markers in breast cancer are the human epidermal growth factor (HER2) and the estrogen receptor (ER). If either of these is present in a primary or metastatic tumor, endocrine or HER2 targeted therapy may be used, respectively. For example, one therapy, Tamoxifen, an ER antagonist originally developed to create new contraceptives and cholesterol-lowering drugs, was approved in 1972 for the treatment of ER-positive breast cancer.[1,6,7]

> **“Prognostic biomarkers are useful in many conditions for predicting recurrence rates and optimizing treatment regimens for patients.”**

A major challenge of metastatic breast cancer (MBC) is its resistance to systemic therapy, which is attributed to the evolutionary changes of the initial tumor during therapy and tumor progression. Moreover, several biopsies from the same patient from various metastatic sites have shown high genetic heterogenicity. When assessing the prognosis and progression of MBC, a liquid biopsy can detect circulating tumor cells (CTCs), which reflect the tumor heterogenicity of multiple metastatic sites. Therefore, they are used for determining gene expression, protein expression, and the malignant nature of a tumor. The detection of CTCs provides an opportunity to study the resistant characteristics of MBC, the evolutionary changes in HER2 and ESR1 (estrogen receptor 1), and the treatment response, all on a molecular level.[6]

Molecular Monitoring and More

With advancements of technology and the increasing focus on individualized therapy, especially with respect to genetics, various laboratory tests are being developed to identify genetic and molecular markers in oncology and, increasingly, in other domains of medicine. Examples include:

- **Quantitative reverse transcription polymerase chain reaction**: a technology used to detect gene expression, found an early application in detection of molecular alterations in CML and monitoring of disease progression[5]
- **NGS:** a technology capable of rapidly sequencing an entire genome, including the changed genome of a cancer cell[8]
- **Liquid biopsies:** a noninvasive test that detects circulating DNA to identify changes in disease processes. This technology was first used in pregnant women to test for Down syndrome.[9]

The National Institutes of Health defines PM as an “emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.” This personalized approach to medicine will continue to influence the provision of health care for the forseeable future.[10] Because cancer comprises a heterogenous set of diseases, each type of cancer must be approached through a highly individualized approach. As cancers evolve resistance to treatments, novel combinations of treat-

ments and approaches may be necessary, based on specific genetic, epigenetic, and molecular tests, to optimize patient response.[1,11]

Liquid biopsies, NGS technologies, and biomarker detection tests are vital to current treatment and prevention strategies, as well as to the development of new risk-assessment techniques and approaches toward diagnosis and treatment. Already, prognostic biomarkers are useful in many conditions for predicting recurrence rates and optimizing treatment regimens for patients.[12]

To enable the further growth and adoption of PM, pharmaceutical companies must invest in new technologies and demonstrate readiness to collaborate with medical professionals, academic research teams, and managed care professionals to encourage the best possible use of technologies for delivery of efficient care. PM has made enormous strides in oncology, and its use will continue to grow both in oncology and other areas of medicine, optimizing patient assessment and care across the spectrum of care.[4,9] ■

REFERENCES

1. Coyle KM, Boudreau JE, Marcato P. Genetic mutations and epigenetic modifications: driving cancer and informing precision medicine. *Biomed Res Int.* 2017;2017:9620870. doi: 10.1155/2017/9620870.

2. Dzau VJ, Ginsburg GS, Chopra A, et al. Realizing the full potential of precision medicine in health and health care: a vital direction for health and health care. National Academy of Medicine website. nam.edu/wp-content/uploads/2016/09/Realizing-the-Full-Potential-of-Precision-Medicine-in-Health-and-Health-Care.pdf. Published September 19, 2016. Accessed July 18, 2017.

3. Personalized Medicine Coalition. Personalized medicine regulation: pathways for oversight of diagnostics. PMC website. personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_pathways_for_oversight_diagnostics.pdf. Accessed September 13, 2016.

4. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med.* 2015;372(9):793-795. doi: 10.1056/NEJMp1500523.

5. Alikian M, Gale RP, Apperley JF, Foroni L. Molecular techniques for the personalised management of patients with chronic myeloid leukaemia. *Biomol Detect Quantif.* 2017;11:4-20. doi: 10.1016/j.bdq.2017.01.001.

6. Aaltonen KE, Novosadová V, Bendahl PO, Graffman C, Larsson AM3, Rydén L. Molecular characterization of circulating tumor cells from patients with metastatic breast cancer reflects evolutionary changes in gene expression under the pressure of systemic therapy. *Oncotarget.* 2017;8(28):45544-45565. doi: 10.18632/oncotarget.17271.

7.Mannello F. New horizon for breast cancer biomarkers discoveries: what might the liquid biopsy of nipple aspirate fluid hold [ePub ahead of Print]? *Proteomics Clin Appl.* 2017. doi: 10.1002/prca.201700060.

8. Behjati S, Tarpey PS. What is next generation sequencing? *Arch Dis Child Educ Pract Ed.* 2013;98(6):236-238. doi: 10.1136/archdischild-2013-304340.

9. Mathur S, Sutton J. Personalized medicine could transform healthcare. *Biomed Rep.* 2017;7(1):3-5. doi: 10.3892/br.2017.922.

10. U.S. National Library of Medicine. What is precision medicine? Genetics Home Reference website. ghr.nlm.nih.gov/primer/precisionmedicine/definition. Published July 25, 2017. Accessed July 18, 2017.

11. Boland CR, Yurgelun MB. Mutational cascades in cancer. *Oncotarget.* 2017;8(26):41784-41785. doi: 10.18632/oncotarget.18481.

12. Ong FS, Das K, Wang J, et al. Personalized medicine and pharmacogenetic biomarkers: progress in molecular oncology testing. *Expert Rev Mol Diagn.* 2012;12(6):593-602. doi: 10.1586/erm.12.59.