Innovation in Oncology Precision Medicine: Diagnostics and Therapeutics

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Precision Medicine in Oncology

Precision medicine is the promise of more effective diagnostics, predictive analytics, and therapeutics, based on personal factors such as genetics, environment, and lifestyle. In 2008, five years after the sequencing of the human genome, precision medicine was defined as:

> *The tailoring of medical treatment to the individual characteristics of each patient … to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not [1].*

According to Renub Research, the global precision medicine market specific to oncology was $33.40 billion in 2021 and is expected to reach $64.66 billion by 2027, with a CAGR of 11.6% [2]. The two primary contributors to the global oncology precision medicine market are diagnostics and therapeutics.

Using a diagnostic to identify the most effective therapeutic relies heavily on patient data derived from the characterization of a patient's tumor via molecular profiling, depending on technologies such as next-generation sequencing (NGS) for identification of mutations, insertions, deletions, or copy-number alterations. Many of these tests rely on tissue biopsy for molecular profiling, such as **Exact Science's Oncotype MAP™ Pan-Cancer Tissue Test** which tests 257 genes (via NGS) and 24 immunohistochemistry stains, the results of which are actionable via NCCN-recommended single agent therapies and combination therapies [3]. However, a rising number of companies are developing tests that use non-invasive liquid biopsies, relying on circulating cell-free DNA (cfDNA), such as **Grail** and **Natera**. Yet other innovative companies are developing novel diagnostic platforms that rely on saliva, stool, and urine biopsies, with novel modalities such as proteomics, metabolomics, and novel nucleic acid methods that do not depend on NGS.

Companion Diagnostics

To accurately identify a patient who will benefit from a precise therapeutic, we need companion diagnostics, which rely on two main factors: (1) the identification of a subset of patients with a specific variable or characteristic that sets them apart (precise diagnostic), and (2) a treatment strategy that targets or leverages said variable or characteristic (precise therapeutic). Whether developed together or paired after individual development, these companion diagnostics and associated therapeutics bring powerful treatment strategies to physicians and patients.

However, if careful attention and collaboration are not taken in the development of precision diagnostics and therapeutics, one of two unproductive scenarios could result: (1) having a diagnostic that accurately identifies a population for which there is no effective therapeutic, or (2) having a therapeutic for a population for which there is no reliable identification method. For example, only 17% of ovarian cancer patients are diagnosed when their cancer is still localized [4]. Developing a therapeutic for this population without a reliable diagnostic would be futile. Understanding the importance of co-developing a diagnostic to identify the correct population is essential in developing a precise therapeutic.

Co-Development

The FDA itself recognized the importance of co-development and issued a guidance in 2014 entitled **"In Vitro Companion Diagnostic Devices,"** wherein the FDA "encourages the joint development of therapeutic products and diagnostic devices that are

essential for the safe and effective use of those therapeutic products" [5]. Further, in a 2016 draft guidance entitled **"Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product,"** the FDA provides a practical guide for the co-development of therapeutic products with companion diagnostics, offering contemporaneous review of a diagnostic assay along with its corresponding therapeutic product [6].

This concept of co-development of a diagnostic and therapeutic was first applied when **Agilent's HercepTest™** was paired with their own therapeutic product Herceptin® (trastuzumab), identifying patients more likely to have a therapeutic response [7]. Herceptin was approved in 1998 and was the first targeted oncology therapeutic guided by molecular alterations [8]. HercepTest is an immunohistochemical companion diagnostic that measures expression levels of human epidermal growth factor receptor 2 (HER-2) in breast cancer tissue [9].

A more recent example is that of **FoundationOne CDx**, an NGS-based method which offers biomarker tests that are paired with targeted, FDA-approved therapies [10]. One particular companion diagnostic for lung cancer can identify mutations that lead to MET exon 14 skipping in advanced non-small cell lung cancer, a test that was developed in parallel with Novartis' Tabrecta® (capmatinib). Tabrecta is a targeted therapy for the 2-3% of lung cancer patients with the METex14 cancer driver. Partnering with biopharma was essential for Foundation Medicine to develop their companion diagnostic.

So, what about programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1), which has received much publicity in the last five years? Indeed, the FDA has approved seven anti-PD-1 or PD-L1 therapies for use across 19 malignancies and with 77 different indications [7]. However, the expression of PD-L1 has not proven to be a reliable biomarker for predicting response to targeted therapy. Even so, companion diagnostics have been developed to determine PD-1 status, which are then combined with measurement of tumor mutational burden, frequency of driver gene alterations, etc., to determine appropriate use of PD-1/PD-L1 inhibitors [11]. Most often, PD-1/PD-L1 inhibitors are used to treat those cancers that are microsatellite instable high (MSI-h) or mismatch repair deficient (dMMR), rather than based on the expression of PD-1 itself.

ADAPTABILITY – A WINNING BUSINESS STRATEGY

The beauty of the relationship between the diagnostic and therapeutic realms of precision medicine lies in its specificity to an (often small) population of patients. The goal is the be *precise*, after all. While small populations may have great impact, that small number for that one application may not be largely profitable or sustainable. In precision medicine, diagnostic companies must be accurate and precise, but they must also rise to the challenge of adaptability.

Thankfully, there are at least two modes of adaptation for consideration once a specific diagnostic has been developed (or even better, in parallel to development): (1) Find additional target populations – Perhaps there is another disease or population that the diagnostic can identify (Foundation Medicine did just that with their BRAF biomarker in both non-small cell lung cancer and melanoma). and (2) Diagnostic method – Instead of thinking about the test itself, think about the method by which the test was developed. Is that method reusable? In a multi-step process of finding the biomarker or signature, are their shared steps that can be used to find a new biomarker or signature? That is as adaptation that has the possibility to create a platform technology and a pipeline of potential products.

While creating precision medicine tools in oncology is an arduous task, the promise of more effective diagnostics, predictive analytics and therapeutics, based on personal data, depends on the most careful coordination.

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Dr. Cramer earned her PhD from the University of Pittsburgh in Pathology, with a focus on intestinal stem cells and their link to intestinal cancer. When the opportunity came to join a local life sciences startup that had licensed a technology from the University of Pittsburgh, she embraced the challenge and quickly came to understand how it takes careful management of a cross-disciplinary team to navigate the often turbulent entrepreneurial waters.

Dr. Cramer then returned to her alma mater to work in commercial translation at the University of Pittsburgh's Innovation Institute. Acting as liaison to the University's close clinical partner, UPMC, Dr. Cramer managed diverse programs, including digital health and immunotherapy, to enable nascent technologies to mature into valuable intellectual property ready for licensing.

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