

Clarion Healthcare's Highlights from the
Termeer Center Roundtable Panel Discussion
Precision Medicine 2.0: Conquering Heterogeneity and Therapeutic Resistance in Cancer

On January 18, 2017, Clarion attended a roundtable event hosted by **Keith Flaherty**, **Daniel Haber**, and **Henri Termeer** of the Termeer Center for Targeted Therapies at MGH. The panel included distinguished experts, **Priscilla Brastianos** (Director of the Brain Metastasis Program at MGH), **Phil Stephens** (CSO of Foundation Medicine), **Douglas Lauffenburger** (Professor of Biological Engineering at MIT), and **Jonathan Pachter** (CSO of Verastem), and was moderated by **Dejan Juric** (Director of Translational Research at the Termeer Center at MGH). 50+ renowned academic experts, biopharma execs, and other industry professionals came together to discuss how to take precision medicine to the next level in the treatment of cancer.

Precision medicine—the rational selection of specific treatments for specific patient subgroups—has become a cornerstone of oncology. Time and again, drugs acting on specific molecular targets have transformed the treatment of cancers defined by those targets: endocrine therapies for breast cancer defined by hormone receptor expression; Herceptin (trastuzumab) for breast cancer defined by HER2 overexpression; Gleevec (imatinib) for chronic myeloid leukemia defined by the BCR-ABL fusion gene; Xalkori (crizotinib) for lung cancer defined by ALK fusion; and Zelboraf (vemurafenib) for melanoma defined by BRAF activating mutations, are just some of the prominent examples.

These past successes exemplify the “one gene, one drug” model—what the group referred to as “Precision Medicine 1.0.” Although this approach may be powerful in specific circumstances, its limitations are increasingly clear. The January 2017 Termeer Roundtable discussion articulated the key challenges, but also brought forward key steps for moving forward to “Precision Medicine 2.0.”

Heterogeneity and Drug Resistance Are Daunting Challenges for Precision Medicine

“You could not step twice into the same river.” —Heraclitus

The one gene, one drug paradigm ultimately fails because it is too simplistic an approach for a complex and heterogeneous set of diseases. Cancer—like the proverbial river—is never quite the same when you look at any two patients, any two cancer sites in the same patient, or any two points in time.

Patient heterogeneity is inescapable because cancer may involve hundreds of gene alterations, and no two patients have the exact same molecular profile; this results in widely varying responses to targeted therapy. One BRAF-mutant melanoma patient may not experience any clinical benefit from a BRAF inhibitor while another patient may have tumor regression that lasts for years, and others will see a response somewhere in between.

Site-to-site heterogeneity occurs because when metastatic cancer spreads from a primary tumor to other sites around the body, the colonizing cells encounter different microenvironments and undergo evolutionary changes over time. Thus a cancer originally driven by one gene (e.g., HER2 amplification) may evolve a dependency to a different gene alteration (e.g., EGFR mutation) when it colonizes a different tissue. A drug that targets only the original gene alteration (e.g., a HER2 inhibitor) may thus fail to treat all of the cancerous lesions. Brain metastases in particular may evolve distinct molecular profiles given the unique environment of the CNS and the relative isolation offered by the blood-brain barrier.

Acquired treatment resistance occurs when cancer cells, under selective pressure from a drug, evolve mechanisms to overcome or bypass the effects of the drug. This problem is compounded by site-to-site heterogeneity, as different cancer sites will evolve independently. Thus, when a patient is treated with a targeted drug, one tumor site may acquire a mutation that desensitizes the target protein to the drug, while another tumor site may activate a separate signaling pathway that bypasses the original target.

Predictive molecular testing therefore becomes extremely challenging. Given the complexities described above, how do you decide what to test, where to test, and when to test for each patient? And is the technology up to the challenge?

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Precision Medicine 2.0: New Approaches Offer New Hope

Although the challenges are daunting, the panelists remain hopeful, and outlined several approaches to continue to advance precision medicine in oncology.

The “simple things”: Given that Precision Medicine 1.0 does work in some cases, there is the hope that minor tweaks can extend the paradigm to a broader set of patients or for a longer treatment duration.

Dose optimization. For example, Phil Stephens recounted a story of a patient with ALK-rearranged lung cancer who was treated with crizotinib and developed a treatment-resistant brain metastasis; a simple increase in the crizotinib dose overcame the resistance and caused the brain met to shrink.

Rational combinations. In many cases, treatment resistance may be mitigated or delayed by adding another targeted drug to support the first. For example, adding a CDK4/6 inhibitor to an endocrine therapy in hormone receptor-positive breast cancer seems to greatly delay the development of resistance to the endocrine therapy. Biomarkers may be used to guide new combinations.

Multigene sequencing/molecular testing. Tests like Foundation Medicine's sequencing panels that test hundreds of genes at once are already available, and the routine implementation of such tests would provide highly valuable data for gaining insight into new precision medicine strategies.

Liquid biopsies: Tests that characterize circulating tumor cells, cell-free DNA, exosomes, or other factors may enable convenient sampling of all tumors in the body at once. Such tests are already showing the ability to detect more mutations than conventional multi-site tumor biopsies, and thus could help clinicians address site-to-site heterogeneity by giving them a handle on the specific gene alterations involved. The convenience of blood-based testing would also greatly facilitate serial testing over time.

Research, research, research: There is no doubt that continued nonclinical and clinical research is required to open new avenues for precision medicine. The panelists advocated for focused applications of high-throughput molecular profiling—not just “big data” but “intelligent big data”—as well as continued “artisanal” experiments not reliant on massive data sets. More studies of serial tumor biopsies, serial liquid biopsies, and rapid autopsies will continue to provide insight into tumor heterogeneity and evolution of treatment resistance. Greater collaboration and pooling of data was also deemed critical.

Precision Medicine 3.0?

The discussion also extended beyond near-term steps to envision more drastic potential innovations in the future, including:

Quantitative computational models may be developed to fill in the gaps and extrapolate beyond imperfect data sets.

Novel experimental models such as three-dimensional organoids may be developed to test novel combinations preclinically in a faster, higher throughput manner than can be done in animal models, and in a more biologically meaningful manner than can be done in cell culture.

Studies of exceptional responders may yield new insights into drug sensitivity and prevention of resistance.

Blood tests for tumor proteins may be developed to extend the power of liquid biopsies.

New predictive biomarkers for immunotherapy beyond PD-L1, to inform novel immunotherapy combinations.

New ways to combat metastasis itself and thus prevent site-to-site heterogeneity. For example, new therapeutics that target the tumor microenvironment may circumvent the need to target different cancers at different sites—targeting the “soil” rather than the “seed”.

Thus, despite the current challenges, it is clear that best results of precision oncology are yet to come.