# PRECISION MEDICINE A NEW ERA

*A scientific and clinical evolution*

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The Cancer Moonshot program has elevated the importance of Precision Medicine. It has wide reaching implications for changing standards of care and the underpinnings of how the Life Science industry develops therapeutics and targets patients.

**Precision Medicine (PM) is a scientific and clinical evolution, not a revolution.**

An indicator of this evolution is reflected in the National Cancer Institute's Precision Medicine Initiative (PMI) transition between their first and second trials. The first NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) clinical trial assigned adult patients to 10 targeted treatment arms and delivered less-than-expected results. The assignment of patients to clinical trial arms based on therapeutic inhibition of driver genetic alterations was advanced through the MATCH Trial-1. MATCH Trial-2 is now underway, with 24 treatment arms selected from over 4,000 variants previously identified across 143 genes. This Trial-2 is expected to demonstrate benefits by:

- Recognizing importance of identifying the evolution of sub-clonal cancer populations
- Applying for deep sequencing to identify rare driver mutations associated with therapeutic resistance
- Expanding development of liquid biopsy technologies to non-invasively, serially monitor development of additional genetic alterations.

The scope of PM has broadened as we understand more about cancer pathobiology. The MATCH Trial-2 plays a vital role in demonstrating how pathobiologic and technological advances can improve patient outcomes through targeted monitoring and treatments.

The insights gained from understanding the evolution of driver genetic alterations, improves predictability and impact on patient and therapy selection. One example of PM's potential to shift the current paradigm is in the approach to single-agent cancer treatment. The cost of multiple novel oncology agents is not economically scalable, and therefore a growing need exists to improve the selection of responders, and allow appropriate combination-therapy earlier in treatment. Such PM

advances can also help payers understand which patients will actually benefit from these expensive oncology therapies.

Researcher Dr. Pia Kvistborg, at Netherlands Cancer Institute, observes that *"In the future, cancer treatment is likely to be a combination of traditional treatments, such as chemotherapy, and new immunotherapies. For that reason it's important for scientists to know how immunotherapy treatment forms function at the molecular level so that we can combine treatments to achieve the most effective result."* This cannot be accomplished without PM insights.

**Precision medicine is impacting the Life Sciences industry across discovery, development, and commercialization.**

The effects of PM have already begun to refresh various life science sectors by offering the opportunity to develop new products and technologies. To drive significant improvement in cancer patient outcomes, it becomes scientifically critical to understand the tumor specific target and how it evolves. Tumors are not static as they spread and become resistant to therapy, and this knowledge influences how cancer researchers design and conduct smarter, focused trials. Clinicians increasingly utilize PM 'Omics' capabilities to select, monitor, and reassign patients — thanks to improved discovery and development advances. For example:

- Novel therapies, designed against multiple biomarker targets which identify specific carcinogenesis mechanisms, can determine efficaciousness earlier. With these tools, the biopharma sector can test earlier and more frequently, accelerating the assessment of target directed therapies in development. An example is the growing RNA therapeutics, including microRNA (miRNA), small interfering RNA (siRNA) and mRNA vaccines. There are 700 DNA and RNA therapeutics in drug development pipelines, 35% of which target oncology with RNAi and RNA antisense technologies dominating the market.
- Liquid biopsy analysis will monitor the cancer to detect loss of early efficaciousness or initial refractoriness with identification of sub-clonal resistance development. Many liquid biopsy approaches include analysis of an increasing number of biomarker classes (i.e. exosomes, miRNA, and others) and have enabled multiple start-up companies.
- Data structure and data management will significantly advance development of software applications and analytic strategies, e.g. virtual representation of cancer biology and therapeutic intervention. Precision medicine management companies will look to grow substantially by serving private practice oncologists as well as non-academic affiliated hospital systems.

**Patients will increasingly benefit from precision medicine advances and applications.**

PM's original premise was to match an individual's tumor DNA to a specific therapy. PM is transitioning to benefit patients in three major areas:

1) Access to early clinical trials - Where validated effective therapy options are not available, new hope of efficacious therapy in development is possible through access to first-in-man and Phase I Clinical Trials. PM enables clinical studies, sufficient in size, for Clinical Trial advancement due to establishment of patient cohorts, built across multiple cooperative institutions and based on innovative drugs matched to tumor genotype/phenotype. With the advent of basket studies, patients gain broader access to the most promising treatment in clinical development.

2) Immunotherapy clinical applications - The growing field of immunotherapy shows extraordinary promise in assisting or replacing standard chemotherapy. The early success of checkpoint inhibitors has brought greater attention and investment to other areas as well, including advances beyond checkpoint inhibitors:
   - Activation of T-cell receptors by various approaches (e.g. bi-specific antibodies) to overcome the suppression of the cytotoxic T-cell response allowing tumor proliferation.
   - Targeting of inducible T cell co-stimulator (ICOS) to promote T-cell function and antitumor response.
   - Control of the immune response against cancer by the tumor microenvironment.

3. Predictive response - Newly diagnosed patients will be treated by combination of drugs designed for both a specific driver mutation and to generate significant and specific immune responses. Patients will further benefit from the increased understanding of mechanisms associated with resistance, sub-clonal proliferation and/or morbidity associated with current multiple drug combination therapy. These developments reflect a second generation in PM, beyond first generation PM driver mutation/drug matching.

   The confluence of big data and cognitive machine learning are playing a crucial role, as we improve our understanding and integration of data fields associated with patients, their medical history, treatment and outcomes. Next-Generation Precision Medicine will use combined data from multiple technologies (i.e. NGS, proteomics, metabolomics) and biomarker classes to stratify patients more appropriately.

Many factions across the industry are exploring how to continually improve and apply the fundamentals of precision medicine to benefit patients. Over the next 10 years the utility will not be limited to the few, but will be integral to defining value across the care spectrum from preventive to end-of-life care.