Precision Medicine: Progress, Pitfalls, and Promises
Patrick G. Pilié1, Patricia M. LoRusso2, and Timothy A. Yap3

See related article by Chae et al., p. 2645

Cancer initiation and progression are driven by the accumulation of deleterious aberrations in key tumor suppressor genes and oncogenes. These are anomalies that give way to a network of interconnected, highly regulated pathways and biochemical processes that all serve to prevent cancer cell death, mitigate cellular stress, and promote tumor growth. Precision oncology has rapidly moved to the forefront of cancer management as a rational strategy encompassing cancer diagnostics and therapeutics, which necessitates the understanding of errant cancer pathways through in-depth molecular analyses of individual patient tumor tissue, followed by the pharmaceutical targeting of those abnormality pathways in a cancer tissue-specific manner. Although a personalized approach to cancer therapy that minimizes toxicities while maximizing benefit by using an individual’s molecular data to guide treatment has long been promised, it has been challenging to accomplish.

The definition of precision medicine is fluid and what it truly encompasses is constantly expanding. The explosion of precision medicine initiatives, trials, advertising, and fundraising is directly tied to the revolution of genomic, next-generation sequencing technologies, which over the past decade have gone from cumbersome, costly endeavors found only in major academic research laboratories, now to a low-cost, relatively efficient process that is available to physicians in community practice and even to private consumers (1–3). The Cancer Genome Project in conjunction with transcriptomic and proteomic profiling of human cancers across anatomic lineages has moved our understanding of cancer biology and drug design forward leaps and bounds, but the interpretation and implementation of the vast data generated by these -omic technologies in a broad, clinically meaningful manner has unfortunately not kept pace (4–6).

In this issue of Molecular Cancer Therapeutics, Chae and colleagues provide a review summarizing past precision oncology successes, current precision oncology trial design, and some of the pitfalls of precision oncology in practice in its current form. These pitfalls of precision medicine are multifactorial, ranging from biologic to economic and psychosocial, and highlight that precision medicine moving forward necessitates cooperative, multidisciplinary, global efforts of biomedical researchers, biostatisticians, community and academic clinicians, governments, and private industry. The application of imatinib in patients with chronic-phase BCR-ABL–mutated chronic myelogenous leukemia (CML) was a watershed in the history of precision clinical oncology. However, subsequent studies of targeted therapies matched to patients with specific genomic aberrations have unfortunately not had similar dramatic response rates or long-term durations of response as imatinib in CML. Trial results comparing an overarching precision medicine algorithmic approach with therapy selection versus physician’s choice of therapy have not shown benefit to the allocation of therapies based on genetic analysis (7). However, there are examples of clinically successful targeted therapies in biomarker-selected populations of cancer patients, including trastuzumab for HER2-overexpressing breast cancers, vemurafenib for BRAF mutant melanomas, and erlotinib for EGFR (epidermal growth factor receptor) mutant non–small cell lung cancer (NSCLC).

These therapies have some common features, such as the development of targeted agents that center mostly on the inhibition of a single driving oncogenic pathway paired with relatively simple, clinically feasible biomarkers for rational patient selection. Nevertheless, with these therapies, most, if not all, tumors eventually become resistant to treatment approaches. In addition, antitumor responses are not uniform even in selected biomarker subgroups, with context dependency also observed between different cancers. Intra and intertumor heterogeneity and a lack of functional biomarkers that define true genotype–phenotype correlations are some of the major biologic shortcomings of how we match the right drug to the right patient in current clinical practice. Large-scale sequencing projects have shown that there are relatively few driver mutations across different cancer types; and, some of the most common mutations seen in cancer, such as in the tumor protein p53 (TP53) gene, are not currently pharmaceutically “druggable.”

For genes in which mutations are potentially “actionable” or druggable, the majority of variants found from whole-exome sequencing of that gene will be of unknown functional significance, whereas pathogenic, deleterious variants may occur at very low allele frequencies within the tumor. Next-generation sequencing provides a historical, static record of mutations in that tumor up to the time of biopsy or resection, but lacks the capacity to inform dynamic active signaling. Also, there are multiple examples of patients in studies who lack identifiable, actionable mutations in a gene of interest, yet respond to the drug targeting that gene pathway. Sequencing studies of multiple metastatic tumors from the same individual show significant inter- and intratumor heterogeneity. It is therefore clear that all mutations are not created equally and that the tumor microenvironment can significantly impact the mutational landscape and therapeutic response. Finally, current clinical tumor sequencing relies on comparing tumor to “normal” tissue or blood from the patient to delineate somatic from germline variants, and thus could be excluding novel, pathogenic hereditary mutations in cancer-related genes.

These biologic shortcomings of current clinical tumor sequencing highlight the need for an integrated, holistic molecular analysis of the patient and their tumor that incorporates genomic and functional data to identify the dynamic, targetable pathways that the cancer cell is relying on for survival at that point in oncogenesis.
There are numerous computational approaches to help delineate actionable versus passenger gene mutations that take into account gene size, functional domains, protein structure and conformation, drug binding sites, and published literature (10). In addition, there have been multiple gene expression signatures and proteomic scores that have come out of discovery studies and clinical trials as putative functional biomarkers of drug sensitivity or resistance (11, 12). Nevertheless, computational approaches still require validation steps, and RNA or protein expression-level signatures are highly variable and dependent on the quality of starting material. This makes the use of many biomarkers problematic outside of large quaternary care centers, which have robust bioinformatics support, core facilities, and molecular tumor boards - a problem that cannot be overstated given that the large majority of patients receive their cancer diagnosis and care in the community setting.

Many of these challenges in precision medicine can be overcome by improvements in biologically driven clinical trial designs, national and international standardization of biomarkers, liquid biopsies for solid tumors, and, most importantly, increased efforts towards cooperative rather than competitive research projects, data sharing, peer-reviewed publishing, and dissemination of information. Large-scale randomized control trials based on histology alone are not well suited for precision medicine, thus adaptive yet rigorous clinical study designs are being used with more relevant endpoints (13). Following the success of the Cancer Genome Project, there are now many multicenter and multinational cooperative precision medicine trials and big data initiatives that seek to evaluate the efficacy and safety of targeted therapies while also undertaking biological deep dives into the molecular underpinnings of cancer progression and underly ing mechanisms of drug resistance using data from sequential tumor biopsies, paired clinical outcomes, and machine learning (14–17). The success of these studies requires a significant commitment from our patients who have to undergo multiple tumor biopsies and additional tests for scientific discovery. A recent study of 46 clinical trials requiring research biopsies showed that only 39% of those trials reported results related to the biopsies (18). Thus, there needs to be a stronger commitment from the medical community to report and share the molecular data from patient tissue studies, regardless of the outcomes of the trial. Circulating tumor cell (CTC) and circulating-tumor DNA (ctDNA) technologies that require a minimally invasive blood draw from patients can potentially alleviate some of the burden of multiple tissue biopsies, but it is still not clear whether CTCs or ctDNA are representative of the entire tumor process.

Another major hurdle to precision oncology in everyday clinical practice is the significant fiscal burden of new targeted therapies that often provide only marginal clinical benefit at best. The annual cost of a new cancer therapy in the United States can easily exceed $100,000, and the cost to benefit ratio of cancer drugs is particularly poor compared to drugs used to treat other medical diseases. Thus, governmental and national oncology organizations, such as the American Society of Clinical Oncology (ASCO) have already implemented value frameworks that compare novel therapies with standard of care treatment options (19, 20).

Immunotherapy (IO) is now dominating the treatment landscape in hematologic and solid tumors, with the advent of novel classes of drugs, such as immune checkpoint inhibitors and designer, engineered autologous T-cell therapies. Precision medicine remains relevant in this new era of oncology therapy as we define sensitivity and resistance patterns to IO in a mutation-specific manner (21). An early success for tumor profiling in IO is the approval of pembrolizumab (Merck) for tumors that display microsatellite instability as a result of deficient mismatch repair regardless of anatomic origin (22). In addition, there are now multiple early-phase clinical trials across cancer subtypes, which include IO and targeted therapies administered either sequentially or in combination. These immunotherapy-based treatments require another biomarker layer with immune profiling of the tumor and immune cell populations, and studies have already confirmed that tumor genomic heterogeneity engenders heterogeneous immune cell density and clonality (23).

With standard of care approaches, most patients do not see immune therapies or targeted therapies until they have metastatic disease, and even then not until after they have been heavily pretreated with chemotherapy. Trials of targeted therapies that enroll only heavily pretreated patients with metastatic cancers may be setting up for failure or minimal benefit given the genomic and immune pressures applied from prior therapy. Studying whether targeted and/or immune therapies may be effective as prevention or early intervention strategies in certain high-risk patient populations is also warranted (24).

The timing and sequence of molecularly targeted therapies in relation to immune therapy or chemotherapy is an active and important area of research that requires integrated genomic and immune analyses of pre-treatment, on-treatment, and post-treatment biopsies. Although initial responses were promising, the true paradigm with CML was when imatinib was applied to earlier stage disease, shifting patient benefit from mere tumor response to long-term patient survival (25). This paradigm is also reflective of select neoadjuvant therapies in the treatment of breast cancer; except in rare circumstances (e.g., bevacuzimab), induction of a pathologic complete response (pCR) with neoadjuvant breast therapy has translated into an overall survival advantage for patients (26). As an example, the I-SPY-2 trial, a unique personalized clinical trial design treating breast cancer patients who have stage II/III disease, assesses novel treatment interventions in combination with standard neoadjuvant chemotherapy. Exciting data from I-SPY-2 have demonstrated an improved pCR of several targeted agents over standard-of-care treatment in select patient subsets (27). These examples question whether we are introducing many of our targeted agents too late in our treatment armamentarium, and should be focusing more on the earlier, neoadjuvant setting in our personalized medicine treatments.

There have been many successes both in basic research and clinical medicine due to the marriage of molecular biology, pharmacology and patient care. However, most precision medicine studies have led to more questions than answers. We must recognize that a cancer is never the result of a single mutational event, nor is it a foreign antigen that can be easily targeted while sparing normal tissue. Rather, a cancer is a dynamic and complex ecosystem, which requires sophisticated and modern technologies and expertise to enable the accurate interpretation of multiple genetic and epigenetic aberrations, as well as the...
rational matching of patients with appropriate antitumor agents. The challenges of initiating precision medicine therapies in advanced-stage patients, often with complex molecular signatures, include difficulties experienced when combining therapies. Overall, the cancer community has been challenged with the inability to successfully obtain drugs for many promising targets. The predictive value of preclinical model systems, especially those in rodent systems is poor, with the success rate of novel drugs passing from animal models through phase I clinical trials only reaching 8% (28–30). Aside from financial and drug availability factors of combination therapies, there are significant limitations to current in vivo model systems in defining drug-toxicity overlap as well as both inter- and intrapatient tumor heterogeneity, limiting the success of many combination strategies (31). With so many unknowns still in place, it is important for the academic, healthcare, biotechnology, and pharmaceutical industries to increase collaborations and pursue a thoughtful path toward fully unleashing the true potential of precision medicine.

Disclosure of Potential Conflicts of Interest

P.M. LoRusso is a consultant/advisory board member for Agios, Alexion, Cytoxa, Ontrix, Ignyta, FivePrime, Takeda, Ariad, GenMIb, Glenmark, Halozyne, Menarini, Novartis, Roche-Genentech, and Genentech. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: P.G. Pilié, T.A. Yap

Writing, review, and/or revision of the manuscript: P.G. Pilié, P.M. LoRusso, T.A. Yap

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