# Complexity of Delivering Precision Medicine: Opportunities and Challenges

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## OVERVIEW

**Precision medicine has emerged as a tool to match patients with the appropriate treatment based on the precise molecular features of an individual patient's tumor. Although examples of targeted therapies exist resulting in dramatic improvements in patient outcomes, comprehensive genomic profiling of tumors has also demonstrated the incredible complexity of molecular alterations in tissue and blood. These sequencing methods provide opportunities to study the landscape of tumors at baseline and serially in response to treatment. These tools also serve as important biomarkers to detect resistance to treatment and determine higher likelihood of responding to particular treatments, such as immune checkpoint blockade. Federally funded and publicly available data repositories have emerged as mechanisms for data sharing. In addition, novel clinical trials are emerging to develop new ways of incorporating molecular matched therapy into clinical trials. Various challenges to delivery of precision oncology include understanding the complexity of advanced tumors based on evolving "omics" and treatment resistance. For physicians, determining when and how to incorporate genetic and molecular tools into clinic in a cost-effective manner is critical. Finally, we discuss the importance of well-designed prospective clinical trials, biomarkers such as liquid biopsies, the use of multidisciplinary tumor boards, and data sharing as evidence-based medicine tools to optimally study and deliver precision oncology to our patients.**

Precision medicine in oncology aims to match individual patients with the right treatment at the right time based on the patient's biologic and molecular characteristics. Early successes with molecularly targeted agents included the approval of the tyrosine kinase inhibitor imatinib (Gleevec; Novartis), directed at *BCR-ABL* in chronic myeloid leukemia, and trastuzumab, a monoclonal antibody that targets HER2 amplification in breast cancer.[1,2] These agents demonstrated great promise in transforming disease outcomes and improving patient survival. Currently, precision medicine approaches are being applied with molecularly targeted and immune-based therapeutics across multiple histologies, most notably advanced melanoma and non–small cell lung cancer (NSCLC), among many others. Now, with the advancement and availability of genomic, transcriptomic, proteomic, and metabolomic data, the field is approaching a tipping point. These tools have opened a window through which we can view the incredible complexity and dynamic nature of an individual tumor and begin to assess tumor heterogeneity and predict treatment resistance. When assessing "-omics" data from single patients, there are many challenges that complicate therapeutic decision-making. These include relatively simple challenges, such as distinguishing driver and passenger mutations in a given patient, to complex problems, such as accurately assessing and predicting the safety and efficacy of combination therapies based on clinical, pathology, and molecular profiles. Furthermore, across larger cohorts, novel strategies for biomarker-driven therapies, clinical trial design, and meaningful data sharing are necessary to move the field forward. In this article, we review opportunities and challenges in delivering precision medicine to individual patients and explore effective tools under development that will inevitably change the way oncology is practiced.

## TARGETED THERAPY

Through the years, there have been a number of success stories demonstrating the promise of targeted therapy in precision oncology. In several instances, particular drug regimens have demonstrated promise based on molecular targets across multiple tumor histologies. For example, the tyrosine kinase inhibitor imatinib has demonstrated efficacy in both chronic myeloid leukemia with BCR-ABL fusion gene and tumors expressing *c-kit* in gastrointestinal stromal tumors based on blocking activated receptor tyrosine kinase activity, but no efficacy was reported in adenoid cystic carcinomas

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of the salivary gland expressing c-kit.[1,3,4] As another example, the combination of trastuzumab with chemotherapy in patients with breast cancer, metastatic gastric adenocarcinoma, and salivary ductal adenocarcinoma with HER2 amplification improves clinical outcomes.[2,5,6]

In other histologies, targeted therapies against precise molecular aberrations have produced differing outcomes, suggesting a tissue- or microenvironment-dependent response or perhaps another factor that is either driving the malignancy or causing resistance to the treatment. For example, in melanoma, about 50% of patients have mutations in the *BRAF* gene, with the majority of these mutations occurring in the V600E domain. Vemurafenib and dabrafenib have demonstrated prolonged progression-free survival and overall survival in patients with *BRAF V600E* mutations in melanoma, leading to the approval of these drugs based on the phase III studies BRIM-3 and BREAK-3.[7,8] However, the example of BRAF-mutated cancers has illustrated several other important points in precision oncology. First, molecular aberrations are often shared across multiple histologies, with *BRAF*-mutated tumors in nearly 15% of all cancers, including hairy cell leukemia, colorectal cancer, and lung cancers. Based on the results from basket trials, different histologies have vastly different response rates, complicating treatment assignment. For instance, in colorectal cancer harboring *BRAF V600E*, treatment with single-agent vemurafenib produced response rates of less than 10%, compared with the 57% objective response rate with melanoma.[7,9] The mechanism for this difference in response is hypothesized to be mediated by EGFR signaling with patients with colorectal cancer having much higher level of EGFR expression relative to patients with melanoma. In a vemurafenib basket trial with an extension arm for previously treated patients with colorectal cancer, the safety and efficacy of vemurafenib combined with cetuximab, an anti-EGFR antibody, was assessed.[10] Further data indicate vemurafenib may sensitize these tumors to cetuximab and produce responses in some patients with chemotherapy refractory disease. Therefore, *BRAF* was determined to be a relevant target, but only in the context of appropriate dual targeting after elucidation of the molecular pathway. The study by Hyman et al[10] was also important in identifying NSCLC as a target for *BRAF* and later *BRAF* and mitogen-activated protein/extracellular signal–related kinase dual inhibition.

NSCLC is an example in which the presence of specific driver mutations is important for selecting targeted agents. Somatic mutations in EGFR, ALK, and ROS1 are often oncogenic and promote proliferation and survival in the absence of ligand binding. These mutations primarily occur in patients with adenocarcinoma, with a different frequency of mutations depending on geography (e.g., approximately 15% of white vs. approximately 50% in East Asian patients).[11,12] Mutations in EGFR typically occur in exons 19 to 21, leading to a constitutively active kinase domain. The most common mutations include EGFR *L858R* in exon 21 and in-frame deletions in exon 19.[13,14] EGFR-targeted therapies include erlotinib, gefitinib, afatinib, and osimertinib. The ALK inhibitors crizotinib, ceritinib, alectinib, and brigatinib have all been approved by the U.S. Food and Drug Administration (FDA) between 2011 and 2017. First- (crizotinib) and second-generation (ceritinib, alectinib, and brigatinib) ROS1 inhibitors (crizotinib) also are in clinical use. The success of EGFR-targeted therapies, in addition to ALK inhibitors and ROS1 inhibitors, has led to the recommendation of using genomic profiling for all patients with advanced NSCLC.[15]

**PRACTICAL APPLICATIONS**

- **Precision medicine aims to match patients with appropriate molecularly matched treatments.**
- **Several examples of targeted therapies have demonstrated considerable success, but this varies by molecular target and histology.**
- **Biomarkers are emerging to predict response to therapy, detect resistance, and select patients for molecularly driven or immune-checkpoint blockade as opposed to conventional chemotherapies or best supportive care. Additionally, some biomarkers may be beneficial to monitoring response, although this application still needs more data.**
- **Data sharing and regulatory science are critical components of precision medicine.**
- **Analysis of tissue and liquid biopsies, molecular tumor boards, and well-designed prospective trials are needed to move the field forward.**

## BIOMARKERS TO PREDICT RESPONSE TO THERAPY

### Tools to Monitor Resistance

Reliable biomarkers are a critical component of precision medicine to match the right patient with the right treatment at the right time. Clinically relevant biomarkers include genomic alterations in tissue or blood, circulating tumor cells (CTCs), gene expression assays, protein assays, and tools to predict response to immune checkpoint blockade, chemotherapy, targeted therapy, or radiation therapy. These tools are still being explored in their clinical potential.

In advanced malignancies, resistance to treatment is common after frontline therapy. For example, in *EGFR*-mutated NSCLC, resistance mechanisms to first-line EGFR-targeted therapies, with a mutation of a threonine 790 to methionine (*T790M*) in exon 20 being the most common. This resistance mutation restores the tyrosine kinase affinity to adenosine triphosphate and is one of several resistance mechanisms, including *MET* gene amplification, *PIK3CA*, and transformation into small-cell lung cancer.[16] These targets are a very active area for drug development.

The question remains how best to identify mutations in patients with advanced malignancies. Traditionally, tissue biopsies have been used to establish the histology and tumor architecture at baseline. With improvement in sequencing technologies, comprehensive genomic profiling (CGP) of tissue has become the standard of care for sequencing across multiple tumor histologies. However, the practicality

of using tissue biopsies to monitor for mutations serially is limited due to patient discomfort and risk associated with repeat tissue biopsy and difficulty in capturing spatial tumor heterogeneity. Therefore, emerging data have demonstrated the feasibility of cell-free circulating tumor DNA (ctDNA) to detect amplifications, fusions, insertions, deletions, and point mutations with noninvasive blood draws. ctDNA has a relatively short half-life, ranging from approximately 16 minutes to 2.5 hours, and is detected in blood after it has been actively secreted or shed into the blood supply after a localized region of the tumor has become hypoxic, leading to apoptosis or necrosis.[17]

Multiple sequencing technologies have been used to detect genomic alterations or mutations, such as next-generation sequencing and digital-droplet polymerase chain reaction.[18,19] The sensitivity and specificity depends on the technology and individual sequencing platform, and specificity, particularly at higher mutant allele frequencies, is quite high. The ongoing hypothesis is if mutations are detected in blood, treatment could be changed reliably based on the detection of known resistance mutations with potential for improvement in patient outcomes.[20] Ongoing research is establishing optimal intervals and time frame of detection in relation to treatment, but lower sensitivity of particular assays may require confirmatory tissue biopsy, in some suspected cases, if no resistance mutations are detected in blood. Further research is needed to assess whether changing treatment based on alterations in blood prior to radiographic disease progression improves outcomes and the potential role and cost of incorporating ctDNA biopsies in the metastatic setting as a surrogate for tumor burden on imaging.

In breast cancer, approximately 70% of tumors express estrogen receptors. ESR1 is an example of an acquired mutation to endocrine therapy.[21,22] This mutation results in estrogen-independent constitutive activation of the estrogen receptor, which results in acquired resistance to therapy by aromatase inhibitors. *ESR1* mutations can be detected on CTCs and using ctDNA in approximately 25% to 39% of patients with acquired endocrine resistance. These mutations may predict response to other therapies. Potential exists to perform ex vivo testing of therapeutics based on isolation of CTCs, cells lines, establishment of patient-derived xenografts, or other models to explore next-line therapies. Future therapies and trials for targeting mutations with *ESR1* mutations are in laboratory and clinical development. Beyond mutations, a growing body of literature has demonstrated the use of CTCs and ctDNA as prognostic and often predictive biomarkers for progression-free survival and overall survival, as well as a tool to identify disease recurrence and to monitor dynamic changes in real time.[23]

### Biomarkers for Immune Checkpoint Blockade

Beyond targeted therapy, the field of immunotherapy has transformed over the last decade. Responses to immunotherapy have been observed across multiple tumor types, most notably melanoma, NSCLC, renal cell carcinoma, and bladder carcinoma. Early on, it was noted that tumors with a high mutagenic load had a higher proportion of patients who responded to immune checkpoint blockade. This led to the emergence of tumor mutational burden (TMB) as a biomarker for response to immune checkpoint blockade.[24-26] TMB likely serves as a probabilistic indicator of neoantigens and potential immunogenicity. Importantly, this biomarker has been shown as an independent predictor across diverse cancers, suggesting that the marker may be tissue agnostic. Still, research is ongoing to identify whether particular histologies may have different TMB cut points and what algorithm is best used to quantify TMB as a predictor of neoantigen burden for cytotoxic T cells.

Mismatch repair (MMR) deficiency has emerged as another clinically meaningful biomarker. Based on a landmark phase II trial, PD-1 blockade with pembrolizumab demonstrated high immune-related objective response rates (ORRs) in patients with MMR-deficient colorectal cancer and noncolorectal cancers.[27] In a more recent study, PD-1 MMR deficiency predicted response across 12 different tumor types of MMR deficiency with an ORR of 53% and complete responses in 21% of patients. This led to the approval of pembrolizumab as the first tissue-agnostic indication for MMR-deficient or microsatellite instability-high tumors in May 2017.[28] Prior research has also demonstrated the association of microsatellite instability high predicting high TMB.[29]

## NEXT-GENERATION SEQUENCING AND LANDMARK TRIALS

Improvements in sequencing technologies have revolutionized the accessibility of tissue CGP in clinical use. For example, current National Comprehensive Cancer Network guidelines recommend CGP in patients with advanced NSCLC adenocarcinoma.[15] Across other histologies, clinical use of tissue CGP is more variable and controversial, depending on the particular tumor histology. With decreasing costs, there has been a shift in academic centers away from smaller, targeted panels with limited exon coverage toward in-house or commercial use of CGP, depending on the particular institution. The number of genes included in these panels continues to increase, and the use of RNA-sequencing and germline testing is expanding. Although there are clear success stories with known resistance mutations, general applicability of molecularly targeted therapy is more difficult.

The first randomized precision medicine trial, SHIVA, failed to demonstrate an improvement in progression-free survival using molecularly targeted therapies in heavily pretreated patients (2.3 months in the experimental group and 2.0 months in the control group).[30] This trial has generated polarized viewpoints, with many suggesting that weaknesses in trial design may have masked potential benefits of a molecularly guided approach based on lack of combination therapy and some questionable molecularly targeted matches. In particular, monotherapy targeting mutations in the PI3K/Akt/mTOR pathway has been shown to have

**TABLE 1. Representative Precision Medicine Trials**

| Trial Name | Trial Abbreviation/Company | Distinctive Features |
|---|---|---|
| Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials | ALCHEMIST | Aims to improve outcomes using molecularly targeted or immune-based therapy in early-stage NSCLC |
| Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer | AURORA | Compares targeted gene sequencing and RNA sequencing on matched primary and metastatic samples |
| A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients with Advanced Non-Small Cell Lung Cancer | BATTLE-2 | Uses biomarker-based tissue enrollment with adaptive randomization |
| Dual Anti–CTLA-4 and Anti–PD-1 Blockade in Rare Tumors | DART | Demonstrates feasibility to enroll patients with rare tumors quickly onto clinical trials |
| Identification of Men With a Genetic Predisposition to Prostate Cancer: Targeted screening in men at higher genetic risk and controls | IMPACT | Aims to screen a high-risk genetic group with known germline *BRCA1* and *BRCA2* mutations using an international cohort |
| Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer | I-SPY2 | Uses an adaptive clinical trial design with novel design features aiming to decrease time, cost, and number of patients in phase II trials |
| A Study Evaluating Herceptin/Perjeta, Tarceva, Zelboraf/Cotellic, Erivedge, Alecensa, and Tecentriq Treatment Targeted Against Certain Molecular Alterations in Participants With Advanced Solid Tumors | MyPathway/Genentech | Reported high objective response rates in particular subgroups, including HER-2–amplified colorectal cancer and v-raf murine sarcoma viral oncogene homolog B1 *V600*-mutated NSCLC |
| National Cancer Institute-Molecular Analysis for Therapy Choice | NCI-MATCH | Uses a large-scale design with many treatment arms based on tissue tumor NGS sequencing |
| Molecular Targeted Therapy based on Tumor Molecular Profiling Versus Conventional Therapy for Advanced Cancer | SHIVA | Demonstrated a prospective randomized controlled trial design in precision oncology |
| Signature | Novartis | Incorporates large community enrollment with no limit to the number of enrollment sites |
| Targeted Agent and Profiling Utilization Registry Study | TAPUR | Uses FDA-approved agents off label to examine efficacy of these drugs in clinical practice |

Abbreviation: NGS, next-generation sequencing.

limited efficacy, and patients with mutations in this pathway accounted for a considerable proportion of the cohort.

More recently, MyPathway and Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT) were published.[28,31] The MyPathway study was an open-label (nonrandomized), phase IIa basket study that matched patients based on genomic alterations with targeted drugs for off-label use. Treatment arms included pertuzumab plus trastuzumab (HER2 overexpression/amplification), erlotinib (EGFR-activating mutations), vemurafenib (BRAF-activating mutations), or vismodegib (hedgehog pathway). Objective responses were observed in 23% of patients (52 of 230), which included 48 partial responses and four complete responses in a heavily pretreated cohort. The key benefit of this basket design was to identify subgroups with notable responses, which in this cohort were metastatic HER2-overexpressing colorectal cancer (ORR 38%), salivary gland (80% ORR), and BRAF-mutated NSCLC (ORR 43%). At The University of Texas MD Anderson Cancer Center, the IMPACT trial reported over 1,000 patients with CGP, of which approximately 82% had detectable mutations. A total of 637 patients had at least one actionable alteration, with 390 (61%) treated with matched therapy and 247 (39%) with unmatched therapy. In the subset of patients treated with molecularly targeted therapy, response rate, progression-free survival, and overall survival were longer as compared with unmatched patients, with relative failure-free survival of 0.5 months and overall survival benefit of 1.1 months. There were some exceptional responders in the matched cohort. Multiple other trials are ongoing, with a representative sample of trials included in Table 1.

The promise of liquid biopsies to identify metastatic disease and best reflect spatial tumor heterogeneity has been an area of excitement for many years. In 2004, immunomagnetic sorting and detection of CTCs was established as having both prognostic and predictive roles in metastatic breast cancer using the FDA-approved CellSearch method (Menarini Silicon Biosystems, LLC).[32] The finding now has been validated across other tumor types, including lung, prostate, colorectal, bladder, and kidney cancers. More recently, early evidence indicates the potential for CTCs to predict late relapse in hormone receptor–positive, HER2-negative stage II to III tumors prior to radiographic evidence of disease 5 years after diagnosis.[33] Early work exploring the "-omics" of single-cell CTCs has been published, with further work ongoing.

ctDNA has emerged as another component of liquid biopsies as a quantitative marker of tumor DNA to reflect genomic alterations in blood. ctDNA detection varies by clinical stage and tumor type with greater than 75% of patients with

advanced colorectal, pancreatic, breast, bladder, and melanoma compared with less than half of patients with brain and renal cancers.[34] Potential clinical applications include detection of early disease relapse after surgery, monitoring response to therapy prior to radiographic progression of disease, and detection of resistance mutations.[17,35] With the emergence of multiple commercial companies, turnaround time for sequencing has decreased, and costs likely will decrease to make serial sampling more accessible in clinical practice.

## ROLE OF DATA SCIENCE IN PRECISION MEDICINE

Computing, data management, analytics, and associated disciplines have been transforming many industries and created a whole new economy. In 2017, the top five companies measured with cash on hand were all new economy companies—Apple, Microsoft, Alphabet (holding company for Google), Cisco, and Oracle.[36,37] Thanks in part to these companies and the constant pace of innovation coming from the computing sector, we now have ubiquitous computing at our fingertips, and through pervasive connections to the internet, we have the "internet of things" that brings information to us and make sensor data available about us through many sources, including social media. Health care has been slow to adopt and slow to innovate to make effective use of these technologies. National challenges, like the presidential Precision Medicine Initiative, the National Strategic Computing Initiative, and the Beau Biden Cancer Moonshot have helped define a narrow, but informative path toward using data science, sensors, and devices to improve the health of the nation.[38-42] This path highlights the importance of data sharing, the continued support of public data sets through open interfaces, resources that provide powerful but intuitive analytics, create a cancer research data ecosystem, encourage data reuse and software reuse, enhance validation and reproducibility, and lay the foundation for a cancer learning health system, in which the experience of every patient provides the evidence necessary for making data-driven health care decisions in oncology.

### Data Sharing and Repositories

During the buildup to the signing of the 21st Century Cures Act that funded the Beau Biden Cancer Moonshot, then-Vice President Biden extolled the cancer community to share information more broadly and break down the existing silos that surround projects, organizations, and even consortia, as exemplified by his address at ASCO's annual meeting in 2016.[43-45] As cancer care and cancer research organizations, our ability to share clinical, genomic, imaging, and laboratory data are crucial to our ability to maximize our understanding of cancer and minimize the impact of cancer on tomorrow's patients. Federally funded repositories, such as The Cancer Genome Atlas (TCGA), Therapeutically Applicable Research to Generate Effective Treatments, the data coming from CTD,[2] ENCyclopedia of DNA Elements, Model Organism ENCyclopedia of DNA Elements, and Genotype-Tissue Expression all contribute to the public cancer landscape.[46-51] The International Cancer Genome Consortium has been an important international initiative that has engaged cancer researchers across the world in generating publicly available cancer genomic data.[52] More recently, the American Association for Cancer Research project Genomics Evidence Neoplasia Information Exchange has brought many cancer organizations together to release clinical and genomic information publicly, through a collaboration with Sage Bionetworks and also through the National Cancer Institute–supported Genomic Data Commons (GDC).[53,54] Other projects, such as the Department of Veteran Affairs' Million Veteran Program and the National Institutes of Health "All of Us" Precision Medicine Initiative project, are contributing data about health and disease in the population.[55,56] Together, these many projects are providing us with public data that opens a window into the intersection of genomics, population health, prevention, surveillance, treatment, and outcomes.

### Insights From Public Repositories

TCGA has become the standard reference for variant frequencies in human tumors.[57-60] In 2017, more than 1000 publications cited TCGA as a data source, and this number has been steadily increasing each year.[61] As Genomics Evidence Neoplasia Information Exchange and other well-curated data sets such as the Multiple Myeloma Research Foundation COMMpass study become available publicly through the GDC, the ability to associate a given constellation of tumor mutations, clinical presentation, therapy, and patient outcomes becomes possible.[62] Currently, much of the use of TCGA is to estimate variant frequency in a given tumor type and occurrence by race and ethnicity and examining variant co-occurrence. Other uses of TCGA, Therapeutically Applicable Research to Generate Effective Treatments, and many other data sets available either in Database of Genotypes and Phenotypes or the GDC include pathway analysis, correlation between imaging features (both pathology and radiology images available from The Cancer Imaging Archive), clinical phenotype, and proteomics (available from the Clinical Proteomic Tumor Analysis Consortium).[63-65]

Additional information on the prevalence of variants and classification of variants is available from cBioPortal, which has multiple current versions, including a version used to visualize data in the GDC.[66] Likewise, ClinGen and ClinVar have been assembling information on variants present in both germline (inherited) and somatic tissues, including tumors.[67,68] COSMIC provides an extensive, curated view of cancer somatic mutations, with COSMIC identification numbers used by many projects and clinical annotation pipelines to refer to a given somatic variant.[69] MyCancerGenome, a resource developed at Vanderbilt University, provides both clinical synopses and lists potential targeted agents for mutations present in a given gene as well as available clinical trials relevant for the mutation.[70]

### Reuse and Reproducibility

Both reuse and reproducibility have gotten a lot of attention. Reuse, simply put, is the use of data, code, tools, or other research artifacts by groups other than those involved in generating, writing, documenting, and releasing those artifacts. For instance, protected data in TCGA have been accessed by thousands of investigators, and the openly accessible data have been accessed by many, many more. Release of data, code, and tools through standard resources, such as the GDC or Database of Genotypes and Phenotypes for data, Bioconductor and Galaxy for analysis packages, and GitHub for source code, promote data sharing and reuse. Adhering to good documentation standards, using tools like Jupyter Notebooks and Docker, and using well-defined Application Programming Interfaces, all contribute to lowering the barriers to reuse and collectively accelerate the pace of research. Reproducible science requires meticulous attention to all aspects of experimental design, experimental methods, reagents and protocols, and careful documentation and archival of experimental conditions, with care taken to document sources of variability to document systematic error, measurement error, biologic heterogeneity and variability, and analysis and interpretation bias.[71]

## REGULATORY SCIENCE: THE ROLE/ CHALLENGES OF "SMALL DATA"

As precision medicine has segmented disease definitions into smaller populations, so have clinical trials enrolled smaller numbers of patients. For molecularly targeted agents that have a profound effect on a disease, this has not presented difficulties for marketing approval of new drugs and biologics. Trial designs that have supported marketing approval include both single-arm and randomized trials, and the FDA may use either accelerated approval, in which additional clinical trials may be required to verify and/or describe the clinical benefit, or regular approval, in which no further trials are required. Examples of products that were approved based on single-arm trials include: tisagenlecleucel, the CD19-directed autologous chimeric antigen receptor T cell, which was approved for the treatment of B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse based on a response rate of 83% complete responses/complete remission with incomplete blood count recovery in 63 patients; crizotinib, approved for ROS1-positive NSCLC based on a 66% ORR in 50 patients; and pembrolizumab, which was approved for the treatment of microsatellite instability-high or MMR-deficient solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options based on a 40% ORR in 149 patients across tumor types.[72-74]

After a targeted therapy has gained marketing approval, any physician in the United States may prescribe it for any use. The FDA has no regulatory authority over whether a physician is prescribing a drug for an off-label use, which is considered the practice of medicine. However, prescribing a molecularly targeted agent for a tumor in which the target has not been clinically validated as an oncogenic driver or to have single-agent activity may lead to a patient deriving all of the risk of product side effects and no benefit. There are clinical trials to address this issue, the most relevant of which to address off-label use of approved targeted agents is ASCO's Targeted Agent and Profiling Utilization (TAPUR) Study. This trial aims to evaluate molecularly targeted agents, which have received FDA approval in at least one indication and collect data on clinical outcomes, to inform potential additional uses of these drugs in indications not already approved by the FDA. As TAPUR uses only agents that already have FDA approval in at least one oncologic indication, this somewhat mimics what an oncologist may recommend for an individual patient whose tumor expresses a druggable target.

Single-patient Investigational New Drug applications allow access to therapies that are not yet approved for individual patients. A physician must apply to both the pharmaceutical company and the FDA for permission to use a product in a patient as well as obtain Institutional Review Board approval, under the assumption that the patient cannot be enrolled in any of the ongoing clinical trials for that product. Since 2009, the FDA has approved more than 99% of the requests for single-patient Investigational New Drug applications submitted to the FDA.[75,76] Similar to off-label use of approved targeted agents, use of a single-patient Investigational New Drug application to gain access to a targeted therapy for a patient whose tumor harbors a druggable biomarker offers an unknown benefit/risk profile.

## CHALLENGES IN PRECISION MEDICINE AND WHAT IT MEANS TO THE SINGLE PATIENT

After the successes of imatinib, trastuzumab, and other targeted agents, the age of precision medicine was proclaimed. Over the last decade, although continued progress has been made across multiple tumor histologies and biomarker-based trials, important challenges remain. We outline several aspects of precision medicine that must be addressed to move the field forward.

First and foremost, tumor heterogeneity has presented a considerable challenge to matching patients with the right treatment at the right time. Numerous studies have demonstrated that the molecular features of tumors differ based on the location of tissue biopsies and between primary and metastatic sites.[77,78] Therefore, with tissue biopsies, there are inherent limitations of a single biopsy reflecting the genetic complexity of an advanced tumor and heterogeneity of the tumor microenvironment. To complicate matters further, expression of genomic alterations, such as EGFR in NSCLC, may differ across geographic populations, suggesting an additional level of genotype/phenotype/environment interactions.

Liquid biopsies have emerged as a theoretical tool to overcome spatial heterogeneity. Many concordance studies have been published in the literature with high specificity, but variable sensitivity when comparing tissue and blood biopsies.[79-82] Methodologic challenges exist when comparing across platforms containing different exon coverage with

different depth of sequencing. In addition, the time frame of collection in relation to therapy or progression may affect concordance results, particularly to detect low mutant allele frequency variants. More precise study designs and transparency in data sharing are necessary to move the field forward.[83]

Furthermore, the more we sequence, the more genomic alterations we detect. Basket trials have demonstrated that drugs for patients with particular mutations vary across histology, indicating that tissue microenvironment that may mediate response and resistance. Beyond known driver mutations, many passenger mutations are detected, and strategies for optimal combination therapies are unknown. Because of the rapid evolution of both evidence and the presentation of CGP reports, it is difficult for physicians to keep up with the current genomically informed treatment guidelines and practices. Standardization of suggested treatments based on the latest level of evidence is very difficult to keep current. To compound this, patient understanding is often limited. Physician or midlevel provider time is necessary to explain the difference between germline and somatic alterations and explain how and which molecular alterations may be appropriate for treatment and to what extent changes in ctDNA warrant clinical progression or actionability. Molecular tumor boards to discuss genomic alterations in the context of prior treatment and current performance status have become more common, particularly at academic institutions. For these practices to become more uniform, there is a need to standardize and formalize the recommendations of molecular tumors boards, along with education and accessibility of tumor boards in the community.

Choosing an appropriate platform (tissue vs. blood) with an appropriate sequencing depth depends on clinical context. Many institutions are beginning to develop in-house panels, but a considerable proportion of CGP is performed by commercial next-generation sequencing platforms. With outsourcing of tissue and blood specimens, data sharing and transparency are critical. Many questions arise, such as defining the appropriate thresholds for calling particular genomic alterations or amplifications. How is TMB calculated by different commercial platforms? How should RNA-sequencing data be incorporated into research or clinical practice? How can institutions and practices best collaborate with industry to improve outcomes for our patients?

Ultimately, we must better define which patients should be tested or when the testing is most appropriate. In treating patients with advanced malignancies, there is an important balance between maintaining quality of life, while also matching patients with palliative treatments that optimally control disease progression, while also monitoring for therapy resistance. We hope that as further competition enters the marketplace, cost will continue to decrease, making serial sampling more accessible for our patients. Further evaluation is necessary to validate that targeting circulating biomarkers in the blood in advanced disease improves clinical outcomes.

From an individual patient perspective, the tendency is often "more is better" and "what else can be done" to help the patient feel better or live longer. Precision medicine has generated considerable and, at times, unreasonable, expectations in the popular press. With the expansion of clinically available genetic and molecular testing, along with direct-to-consumer marketing, patients often present to clinic with questions regarding utility of these tests and treatments. Each individual patient wants the best possible treatment and, in many cases, requests these tests to help guide treatment. Ultimately, it is the responsibility of the medical professional to stay well informed regarding appropriate circumstances to order precision medicine tests and recommend molecularly matched therapy. Furthermore, physicians must be prepared to discuss risks, benefits, alternatives, and implications of these results and treatments.

## NEXT STEPS

Prominent opinion pieces in journals have questioned recent advancement of precision oncology in medicine. In some respects, these pieces paint a grim picture of the challenges of precision medicine.[84,85] However, we see precision medicine as a step further down the road of progress, and, much like other areas of science, we must apply sound scientific methods to further advance the field.[86]

First, we need well-designed, prospective, biomarker-based clinical trials. Novel clinical trial designs are underway or are completing. TAPUR, I-SPY2, NCI-MATCH, and DART are examples of collaborative efforts to design trials and accrue patients in new ways. Second, multidisciplinary molecular tumor board implementation is critical. As medical professionals, we are responsible for interpreting the tests that we order, and with rapid changes, collaborative teams are necessary to match patients with the optimal therapy. Third, formal educational programs reaching both academic and community physicians are necessary. In addition, educational tools for patients to understand these complex genetic data and to maintain the patient-physician relationship within the context of complicated, inference-based medical decisions are necessary. Fourth, a culture of data sharing and resources and repositories capable of supporting data sharing are needed to reduce the time from discovery to practice.

Precision oncology is not simply about matching patients with the appropriate targeted or immune-based therapy. Broadly speaking, it is about matching patients with the right therapy or withholding unnecessarily toxic therapy based on precise knowledge of the clinical and molecular features of the tumor. Therefore, this may encompass targeted therapy, immune-based therapy, or hospice if the tumor features and potential treatment side effects are not beneficial in the context of patient performance status. In summary, the field of precision oncology is continuing to evolve, much like the tumors in which we are applying these tools. We as a medical and scientific community must work together to best understand, study, and implement these tools for our patients.

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