Precision Oncology: Who, How, What, When, and When Not?

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OVERVIEW

Precision oncology, defined as molecular profiling of tumors to identify targetable alterations, is rapidly developing and has entered the mainstream of clinical practice. Genomic testing involves many stakeholders working in a coordinated fashion to deliver high-quality tissue samples to high-quality laboratories, where appropriate next-generation sequencing (NGS) molecular analysis leads to actionable results. Clinicians should be familiar with the types of genomic variants reported by the laboratory and the technology used to determine the results, including limitations of current testing methodologies and reports. Interpretation of genomic results is best undertaken with multidisciplinary input to reduce uncertainty in clinical recommendations relating to a documented variant. Non–small cell lung cancer has emerged as a prototype disease where genomic data from at least several well-documented alterations with approved targeted agents are essential for optimal treatment from diagnosis of advanced disease. Due to the development of resistance to targeted therapies, resampling and retesting of tumors, including using liquid biopsy technology after clinical progression, may be important in making treatment decisions. The value of molecular profiling depends on avoiding both underutilization for well-documented variant target-drug pairs and overutilization of variant-drug therapy without proven benefit. As techniques evolve and become more cost effective, the use of molecular testing may prove to add more specificity and improve outcomes for a larger number of patients.

The goal of precision medicine is simply to deliver the right cancer treatment to the right patient at the right dose and the right time. Several lines of investigation came together nearly simultaneously to usher in the beginning of the precision oncology era. In 1998, the *BCR-ABL* rearrangement in chronic myeloid leukemia was successfully targeted by the small molecule imatinib, leading to dramatic clinical remissions and U.S. Food and Drug Administration approval in 2001. The first draft sequence of the human genome was accomplished the same year,[1] followed by the first cancer genome.[2] Rapid discovery of multiple, nonoverlapping driver mutations and tyrosine kinase inhibitors with clinically effective inhibitory properties in non–small cell lung cancer and melanoma led to assays of alterations performed by polymerase chain reaction (PCR) quickly and inexpensively. Use of these biomarkers to drive treatment decisions in solid tumors raised expectations and interest in molecular profiling. Sequencing technology and costs improved rapidly during the early 2000s, particularly with the advent of NGS on formalin-fixed, paraffin-embedded tissue whereby massive parallel sequencing allows determination of alterations in a large number of genes through a timely, cost-effective process.

Underpinning precision oncology is the concept of somatic mutations as the foundation of cancer development.[3] Mutations in oncogenes rendering them constitutively active are considered driver mutations and are central control points for progression of malignancies. Conversely, tumor suppressor genes, involved naturally in controlling tumor pathogenesis, can cause cancer progression when inactivated through mutation or allele loss. Multiple processes result in dysregulation of the genetic machinery in DNA RNA or protein, leading to altered expression of the protein coded for by the gene. To capture the entire spectrum of potential alterations, multiple technologies, termed a multi- or pan-omic approach, are best considered. The vast number of choices of technologies, commercial entities offering testing, and sometimes conflicting results have overwhelmed clinicians looking to obtain molecular information that will result in clinical utility for their patients. Even in academic centers, oncologists report varying confidence in their ability to use the genomic findings appropriately.[4]

At its most fundamental level, a genomic test with clinical utility should be predictive of a treatment response from a targeted agent. An early example in solid tumor oncology was the ability to test for *HER2* positivity as defined as fluorescent in situ hybridization–based gene amplification or immunohistochemistry to demonstrate overexpression of the protein. Positive results predicted response to

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Disclosures of potential conflicts of interest provided by the authors are available with the online article at asco.org/edbook.

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trastuzumab-based therapies, whereas *HER2*-negative tumors did not derive benefit from this approach. As we have moved into multiplex testing of many genes or other biologic species, including messenger RNA and proteins, the same criteria should apply—is the variant alteration sufficiently predictive of response to a paired agent?

To date, success in using precision approaches to treatment have been mixed. A prospective phase II study of molecular profiling to assign matched therapy did not show superior outcomes for the matched group but suffered from serious methodologic design issues.[5] Large retrospective series have documented that 80%–90% of patients tested will have potentially actionable genomic alterations, although the definition of actionable can vary substantially.[6-9] However, only a minority of patients to date actually receive genomically directed therapy, usually on a clinical trial.

TECHNICAL ASPECTS OF NGS TESTING FOR THE CLINICIAN

Types of Alterations Detected

A range of genomic somatic variants can be ascertained with NGS, including single nucleotide variants (SNVs), also known as point mutations, and small insertions or deletions of bases (indels), which can lead to a nonfunctional or absent protein. Additionally, copy number variants, which reflect amplifications and deletions of genes and/or larger portions of a chromosome, gene rearrangements and fusion genes can be detected.

Read Depth and Coverage

This criterion refers to the number of times a particular base position in the DNA is read during the NGS analysis. The greater the coverage of a particular alteration, the more likely it is to be detected, which is especially important in tumor samples with low tumor content. By covering the same area of the gene fragment multiple times, the likelihood of picking up a variation of low allelic frequency is enhanced.

KEY POINTS

- **The goal of precision oncology has begun to be realized through multiplex molecular testing including NGS.**
- **Oncologists should be familiar with technical aspects of NGS to facilitate selecting the most appropriate and cost-effective testing platform.**
- **Considerations for molecular testing include which tissue type to utilize, timing of profiling in the disease course, extent of panel to order, and degree of clinical annotation reported.**
- **Actionable biomarkers of non–small cell lung cancer make this disease a paradigm for precision oncology at diagnosis of advanced disease, during therapy, and at time of progression.**
- **Interpretation of molecular data to facilitate best practice remains a challenge; clinical trial participation and sharing of linked molecular/clinical data sets are strongly encouraged.**

For hot spot testing, coverage of at least 100–300X is recommended.

Breadth and Scope of Testing

How many genes are included and what areas of the gene are analyzed. The most frequent NGS offerings today are hot spot testing, where alterations in exons or intron/exon junction areas of a preselected panel of cancer genes, including known activating oncogenes and tumor suppressor genes, are analyzed. Targeted hot spot panels focus on the best-annotated cancer genes, typically 35 to 350 genes, and provide high depth of coverage. The greater depth allows for assessing lower allele frequency and can account for intratumoral heterogeneity and low allele frequency of the alteration. NGS panels are not ideal for large-scale rearrangements and/or deletions and certain fusion genes. Addition of RNA sequencing can help identify these alterations.

Recently, whole-exome sequencing and whole-transcriptome sequencing have become available at academic and some commercial laboratories. At the moment, the value of whole-exome sequencing information is largely confined to the translational research space, where it offers enormous potential to produce novel variant-pathogenic associations leading to clinical trials investigating new agents. Lengthy turnaround time and lack of clinical associations for the large majority of genomic alterations preclude current effective clinical use.

Variant Calling

The bioinformatics approach to lining up the vast amount of information obtained in an NGS sequence, and accurately calling variants, is important to achieve quality results. Variant quality scores are generated for each test within a laboratory. Technical validity results can be provided to the practitioner upon request and may be useful in determining which assay to use due to interlaboratory differences. Federal guidelines for technical validity do not currently exist for NGS tests, which are classified as laboratory developed tests.

Variant Allele Frequency

This reflects the percentage of reads identifying a variant divided by the overall coverage of that locus. If tumor cells represent 100% of the sample DNA analyzed, heterozygous loci such as seen in germline mutations should be near 50% variant allele frequency, homozygous loci should be near 100% and reference loci should be near zero. In actual practice, the contamination from normal cells, local copy number alterations and tumor heterogeneity often yield unpredictable variant allele frequency.

Variant Meaning

Particularly for single nucleotide variants, it is not always easy to determine if a mutation is pathogenic or not. Publicly available databases, such as the Catalogue of Somatic Mutations in Cancer (COSMIC),[10] and the laboratory's internal databases, are reviewed by the evaluating pathologist, and a

determination is made whether the alteration is pathogenic, probably pathogenic, probably benign (meaning that it is likely a single nucleotide polymorphism without functional significance), benign representing a known single nucleotide polymorphism or a variant of unknown significance. As panel testing grows larger, the reporting of a variant of unknown significance has grown dramatically. It is hoped that in the future, sharing of genomic data will settle the issue for the growing number of alterations without a clinical correlate to call pathogenic or not. At the moment, utilizing a laboratory with deep molecular expertise, including molecular pathologists and geneticists on staff to help make the call, is extremely important. Alternatively, third-party organizations like N-of-1 use extensive resource capabilities to perform this function for laboratories or health care systems. Their role is to generate content relevant to the spectrum of variants so that clinically appropriate decisions can be made.

Tumor Only Versus Tumor Normal

When a tumor alone is tested, variants are compared with databases such as COSMIC and ClinVar[11] to determine whether the variant is a known pathogenic variant or a known single nucleotide polymorphism. Simultaneously sequencing tumor and normal tissue allows more precise calling of somatic mutations. Moreover, germline cancer predisposition genes can be clearly distinguished from somatic mutations in the same genes. As bioinformatics improves, value from the additional cost and complexity of sequencing both tumor and normal tissue routinely appears to be diminishing.[12] Though advances in bioinformatic techniques and reference germline databases are improving the accuracy of tumor-only sequencing, matched-tumor and normal-tissue sequencing is still the gold standard for somatic mutation detection.

IMPLEMENTING PRECISION ONCOLOGY TESTING AND INTERPRETATION IN PRACTICE

Doing precision oncology optimally depends on getting operational issues of testing right. Many considerations factor into selecting the right molecular test (Sidebar 1). Communication between medical oncologists and local pathologists becomes more critical than ever, particularly when the material will be sent to an outside facility. Local pathologists control the tissue, and the rationale for testing and the technical needs of the outside laboratory must be clearly stated. Standard operating procedures for molecular testing are useful to facilitate the process and improve the likelihood of timely, successful and accurate molecular result reporting. Importantly, tissue blocks must be assessed for adequate tumor tissue so that the results are interpretable and infrequent mutations can be characterized. Formalin-fixed, paraffin-embedded samples, including fine-needle aspirates and cytology samples with sufficient cellularity, can be used for NGS. The amount of DNA needed, expressed either in nanograms or the number of slides necessary to do testing, should be considered upfront to avoid a quantity-not-sufficient result. NGS technology requires at least 10 to 20 slides for a complete analysis, so the pathologist may have to evaluate multiple blocks to pick the sample with the most tumor tissue likely to yield an interpretable result.

SIDEBAR 1. Diagnostic Considerations in Molecular Testing

- Choice of assay and design
- Cost
- Tissue quality
- Turnaround time
- Clinical Laboratory Improvement Amendments and/or College of American Pathologists certification
- Bioinformatics analysis
- Clinical interpretation

Many patients undergo fine-needle aspiration or core biopsies for histologic diagnosis of malignancy, so remnant tissue may be sparse and careful decision making weighing the risks and benefits of biopsy for the express purpose of genomic testing is essential. For patients likely to require molecular testing at some point in their course, it is helpful to plan the initial biopsy of metastatic disease with this need in mind, so that tissue will be available later. Decisions to rebiopsy are complex and include morbidity and cost associated with the procedure versus the value of assessing the current tumor biology, particularly after exposure to genomic-altering agents.

Typically, specific informed consent for testing in the context of clinical decision making is not required for molecular profiling. An oncology clinic's general consent form for testing and treatment should cover molecular testing under the scope of medical practice. If patient results will be used in a prospective registry maintained by the practice, the institution, the testing laboratory or an academic consortium, informed consent based on a collection and analysis protocol is advisable. Should molecular alterations render a patient eligible for a clinical trial, the patient will be required to provide consent again to use this information for the study.

Who and When?

Many patients with metastatic disease may be good candidates for genomic testing at varying times in their clinical course. Patients with disease with fewer or no standard treatment options are candidates for early molecular profiling in the hope that they will be a candidate for a clinical trial evaluating a particular alteration. Such trials are called basket studies and typically are agnostic to the tissue of origin as long as specific variants are identified. When no trial is available or the patient is not eligible, using an approved agent for a specific alteration in another disease state (e.g., BRAF V600E mutation) might be appropriate after failure of standard therapy. Often there is no definitive trial data to base decisions on appropriateness of molecular targeted therapy in noninvestigational settings, and a balance of risks and benefits of an unknown approach should be carefully

TABLE 1. Online Knowledge Bases to Aid Clinical Decision Making

Resource	Website
My Cancer Genome	www.mycancergenome.org
JAX Clinical Knowledgebase	https://ckb.jax.org
Clinical Interpretation of Variants in Cancer	https://civic.genome.wustl.edu
Oncology Knowledge Base	https://oncokb.org
Clinical Genome	https://clinicalgenome.org

weighted. One potential hierarchy for decision making is presented in Table 1. Emerging evidence suggests overall tumor mutational load, analyzed in either large target gene panels of 300 to 600 genes or utilizing whole-exome sequencing, can be predictive of response to immune checkpoint inhibitors.[13,14] Additionally, mismatch repair deficiency assessment through genomic analysis is another valuable molecular assay with applicability to immune-oncology therapies.[15]

In general, early-stage patients undergoing definitive treatment do not typically require somatic gene panels. They will not have actionable alterations provided by NGS beyond what can be ascertained from standard histologic evaluation (e.g., estrogen receptor, progesterone receptor, and HER2 in the case of early-stage breast cancer). Broader molecular information will be of research use only.

For certain diseases where a first-line decision depends on multiple molecular markers, such as advanced non–small cell lung cancer, the use of a multiplex NGS panel at diagnosis becomes increasingly attractive given the growing number of targetable genes, the ability to simultaneously obtain the information from one sample and the ever lower cost of multiplex testing. Conversely, when other disease states exhaust evidence-based lines of standard therapy, panel testing is often appropriate if the patient remains a good candidate for further treatment.

A decision must be made whether to send a new biopsy or use archival tissue. Discordant genomic results may be seen between primary tumors and metastases, although this is highly disease site specific. For instance, *RAS* mutations in colorectal cancer are an early event in tumorigenesis, and reliable actionable information regarding use of anti-EGFR antibodies in the metastatic setting can obtained from the primary tumor.[16] Conversely, estrogen receptor 1 mutations conferring resistance to aromatase inhibitors in breast cancer appear to occur as a consequence of exposure to aromatase inhibitors and are unlikely to be present in the primary tumor.[17]

Molecular evolution of the tumor has been documented in many cancers under the selective pressure of prior therapy. This is most apparent in patients receiving targeted therapy whereby one of the mechanisms of resistance is secondary mutations in the gene of interest or along the relevant pathway.[18] In these circumstances, repeat biopsies may be very informative. Currently, the degree of heterogeneity exhibited by metastatic lesions in various sites is unclear. When heterogeneity is suspected, liquid biopsies for circulating tumor DNA or circulating tumor cells may reflect the clinical situation better, presumably integrating tumor status from a variety of sites and reflecting a composite mutational landscape.[19] This concept is attractive but far from established and requires further study. However, minimal invasive tissue sampling using blood samples to yield components such as circulating tumor DNA and circulating tumor cells is likely to become standard as an alternative to biopsy in clinically risky situations and in monitoring progressive alterations over tumor during exposure to targeted agents.

Molecular Tumor Board

As precision oncology expands, there is an increased need to include multiple domain experts in decision making to best harness the massive amount of information wisely. In the community setting where generalist oncologists now have to add management of genomic data to the clinical information, having access to additional expertise is enormously valuable. Either virtual or real-time molecular tumor boards can be accomplished in a practice setting. Ideally, members would include medical, surgical, and radiation oncologists as would be found in any conventional tumor board complimented by pathologists, genetic counselors, and research staff. Additional expertise is often available from commercial laboratories in the form of molecular pathologists and molecular geneticists. In more robust practice settings, access to biostatisticians, bioinformaticists, epidemiologists, and translational scientists may be available to participate. Multiple databases are publicly available for searching during molecular tumor boards to help in making variant-therapy associations. A number of free, frequently updated, and deeply curated websites offer information on a large number of variants and can be very useful to the practicing clinician in helping ascertain whether a particular therapy is right for a patient (Table 2). Archived, online molecular tumor boards such as those provided by ASCO are a good reference source.[20]

Data Integration

Integration of molecular data into electronic health records remains in the infancy of development. Typically, genomic results are sent to the oncologist in Portable Document Format and are therefore not available in structured fields that are searchable, filterable, and linked to clinical data. Integration of clinical and genomic data are a necessary goal to aid electronic matching of patients to molecular-based trials and to aggregate multiple N-of-1 experiments on individual patients to develop real-world evidence of benefit. Custom interfaces can be developed through relationships with third-party genomic laboratories and information technology companies or as a standalone in larger institutions that possess deep bioinformatics and information technology resources. Several laboratories now offer resources, such as the Caris Life Sciences Molecular Intelligence portal[21] and the Foundation Medicine Interactive Cancer Explorer

TABLE 2. U.S. Food and Drug Administration–Approved Drugs and Companion or Complementary Diagnostics for Non–Small Cell Lung Cancer

Targeted Agents	Tumor	Blood
EGFR		
Erlotinib	cobas EGFR Mutation Test v2	cobas EGFR Mutation Test v2
Gefitinib	Therascreen EGFR RGQ PCR Kit	
Afatinib	Therascreen EGFR RGQ PCR Kit	
Osimertinib	cobas EGFR Mutation Test v2	cobas EGFR Mutation Test v2
ALK/ROS1		
Crizotinib	ALK IHC (D5F3, Ventana)	
	ALK Break Apart FISH Probe Kit (Vysis)	
Ceritinib		
Alectinib		
PD-L1		
Pembrolizumab	PD-L1 IHC (22c3, Dako)	
Nivolumab	PD-L1 IHC (28-8, Dako)	
Atezolizumab	PD-L1 IHC (SP142, Ventana)	

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; PCR, polymerase chain reaction, RGQ, Rotor-Gene Q.

portal,[22] which allow result searches with some data-basing capability, and provide documentation of available preclinical and clinical research pertaining to observed variants and therapies. The clinical interpretation of molecular alterations is at the heart of providing the value of precision oncology.

NON–SMALL CELL LUNG CANCER AS THE PARADIGM OF PRECISION ONCOLOGY

Recently, lung cancer, after several decades of choosing platinum-based doublets for every patient, has undergone a transformation integrating precision medicine. There are now numerous biomarkers needed for treatment assessment in patients with lung cancer (Table 3), and this number will continue to increase as new molecularly defined subsets are identified. When diagnosing a patient, measuring *EGFR* mutation, and *ALK* or *ROS1* fusions, will help determine whether a tyrosine kinase inhibitor (TKI) should be used in lieu of cytotoxic chemotherapy.[23] Recently, PD-L1 expression (tumor proportion score ≥ 50%) has proven to be effective in enriching patients with lung cancer who may benefit from immunotherapy (pembrolizumab) instead of chemotherapy.[24] When considering patients who are diagnosed with non–small cell lung cancer, these biomarkers may alter treatment decisions in approximately 50% of patients to biologic agents instead of cytotoxic chemotherapy.

Increasing utilization of targeted therapies also brings to the forefront the growing clinical challenge of acquired drug resistance, currently a very active area of research. This is best exemplified by the emergence of the EGFR T790M mutation, which occurs in 50% of patients previously treated with an EGFR-TKI.[25] These gatekeeper mutations, which directly interfere with drug-target interactions, are a recurring theme across many kinase-driven tumors treated with kinase inhibitors.[26] Propelling their significance is the accompanying development of (1) therapies designed to target these mutations and overcome resistance (e.g., T790M/osimertinib), and (2) noninvasive assays that can monitor status of the resistance mutations (e.g., cobas EGFR Mutation Test v2), sequentially and in real time.

The complexity associated with acquired resistance is compounded by intra- and intertumor heterogeneity[27] and adaptive tumor biology that is facilitated by genetic instability.[25] The selective pressure of kinase inhibition can lead to the disappearance of drug resistance mutations,[28] emergence of varying resistance mechanisms at different metastatic sites,[29] histology transformation to small cell lung cancer,[30] or emergence of new resistant clones (e.g., C797S, Leu792).[31] Each of these situations presents unique treatment approaches. For example, there are reported responses to specific small cell lung cancer treatments for tumors that have transformed into small cell lung cancer.[30] Rechallenge with first-generation EGFR TKIs in patients where the T790M clone disappearshas also been successful.[32]

The utilization of the evolving genetic landscape of tumors to inform treatment decisions will be made possible through sequential and real-time monitoring of the patient. Rebiopsy with traditional biopsy techniques at time of progression, which may occur at multiple time points through the treatment course, is not safe for the patient, nor feasible from a practical perspective. Furthermore, patients may have multiple tumors. Therefore, the challenge is also identifying the tumor that would yield the best-quality biopsy; however, that approach still does not address the potential for intertumor heterogeneity.

Much progress has been made to address these complex and evolving issues through the development of noninvasive plasma-based assays for the detection of emerging

resistance mutations. The U.S. Food and Drug Administration approved the first liquid biopsy–based companion diagnostic to detect the T790M resistance mutation in patients whose disease is progressing on erlotinib, gefitinib or afatinib, for consideration of osimertinib. Furthermore, the search for assays, utilizing PCR- or NGS-based detection methods, that have high sensitivity and specificity, are cost-effective, and have high concordance with tumor biopsies is intensifying.[33-35] Some studies note, however, that liquid biopsy is still not ready for replacement of tumor biopsies but, in some instances, such as monitoring response or progression, may be prioritized.[36,37] Therefore, in cases in which a liquid biopsy test is negative for a resistance mutation, guidelines recommend a tissue biopsy.[23]

Collectively, these research efforts are converging to create a new paradigm in precision medicine in oncology. The discovery of resistance mutations, designing new drugs that target these resistance mechanisms, and development of noninvasive techniques to monitor emergence of resistance are all integral components advancing the field forward. The following case highlights the precision medicine revolution occurring in lung cancer.

Case Example

Mr. G, a 55-year-old man, has felt fatigued during the last couple months. A persistent cough led to a doctor's appointment. He did not have a history of smoking, although his parents did smoke cigarettes. His performance status was good, and he did not have any other chronic medical conditions. Radiographic imaging with CT identified several lesions in the lungs bilaterally. A CT–guided biopsy revealed a well-differentiated adenocarcinoma. The rest of the staging scans revealed stage IV disease in the bilateral lungs. Molecular testing was performed and revealed an exon 19 deletion. The patient started treatment with afatinib 40 mg daily. He had grade 1 acne and grade 1 diarrhea. Follow-up CT after 2 months of treatment revealed significant response of the tumors. He continued treatment, eventually dose reducing to 30 mg after several months of treatment. The patient continued taking afatinib for 20 months when a restaging scan revealed new disease bilaterally. The disease was peripherally located, with the largest lesion approximately 1 cm. Performing a tissue biopsy would be challenging but feasible. A serum circulating tumor DNA test revealed a T790M mutation. The patient then started treatment with osimertinib 80 mg daily. Restaging after 2 months revealed shrinkage of the tumors. He is tolerating the therapy well and continues at this time.

PRECISION ONCOLOGY IN THE ERA OF VALUE-BASED MEDICINE

The goal of precision testing is to identify the optimal therapy for the patient that will maximize their survival and quality of life. In some cases, there are well-validated biomarkers in a specific tumor context with high-quality clinical evidence (often approved by the U.S. Food and Drug Administration) of improved efficacy using a specific targeted agent or class of agents vis-à-vis an unselective therapy. For example, every new diagnosis of metastatic non–small cell lung cancer should undergo molecular testing for *EGFR* mutation, *ALK* rearrangement, *ROS1* rearrangement and *PD-L1* expression, all of which have demonstrated improved benefit with targeted agents for tumors positive for these biomarkers compared with chemotherapy in the first-line setting. In contrast, mutated *RAS* is a contraindication for the addition of anti-EGFR therapy for metastatic colorectal cancer due to well-demonstrated lack of efficacy in this setting. Testing for these biomarkers in the appropriate clinical context is the standard of care and is covered by insurance. With proven benefits, clear indications and financial coverage, the major challenge in this subset is underutilization of testing and dissemination and implementation of timely adoption to maximize benefits for all patients. The National Comprehensive Cancer Network, ASCO, and other tumor-specific societies provide regularly updated guidelines and are good references for evidence-based testing. Examples of these validated context-biomarker-drug combinations are listed in Table 3.

However, there is a much longer list of context-biomarker-drug combinations without sufficient evidence to make standard of care (Table 4). The cost of NGS has decreased by orders of magnitude in recent years. Cancer centers and other academic medical centers often have their own "home-grown" panels of cancer genes, anda number of companies offer gene panel sequencing for several thousand dollars within a few weeks. Given the reasonable cost, rapid turnaround time, and the potential for discovery of

TABLE 3. Examples of U.S Food and Drug Administration–Approved Biomarkers/Drug Pairs for Specific Tumors

Biomarker	Drug	Tumor Context
HER2/neu (ERBB2) expression	Trastuzumab, pertuzumab	Metastatic breast cancer
EGFR L858R	Erlotinib	Metastatic NSCLC
*BCR-ABL*1 fusion	Imatinib	Chronic myeloid leukemia
17p deletion	Venetoclax	Chronic lymphocytic leukemia
KIT expression	Imatinib	Gastrointestinal stromal tumor
BRAF V600E	BRAF and MEK inhibitors	Metastatic melanoma

Abbreviation: NSCLC, non–small cell lung cancer.

TABLE 4. Examples of Precision Tests Without Established Clinical Utility

Biomarker	Drug	Tumor Context
EGFR L858R	EGFR TKI	Non-NSCLC tumor
BRAF V600E mutation	BRAF and MEK inhibitors	Nonmelanoma
BRAF L597 mutations	BRAF and MEK inhibitors	Any tumor
ATM mutation	PARP inhibitor + alkylator	Any tumor

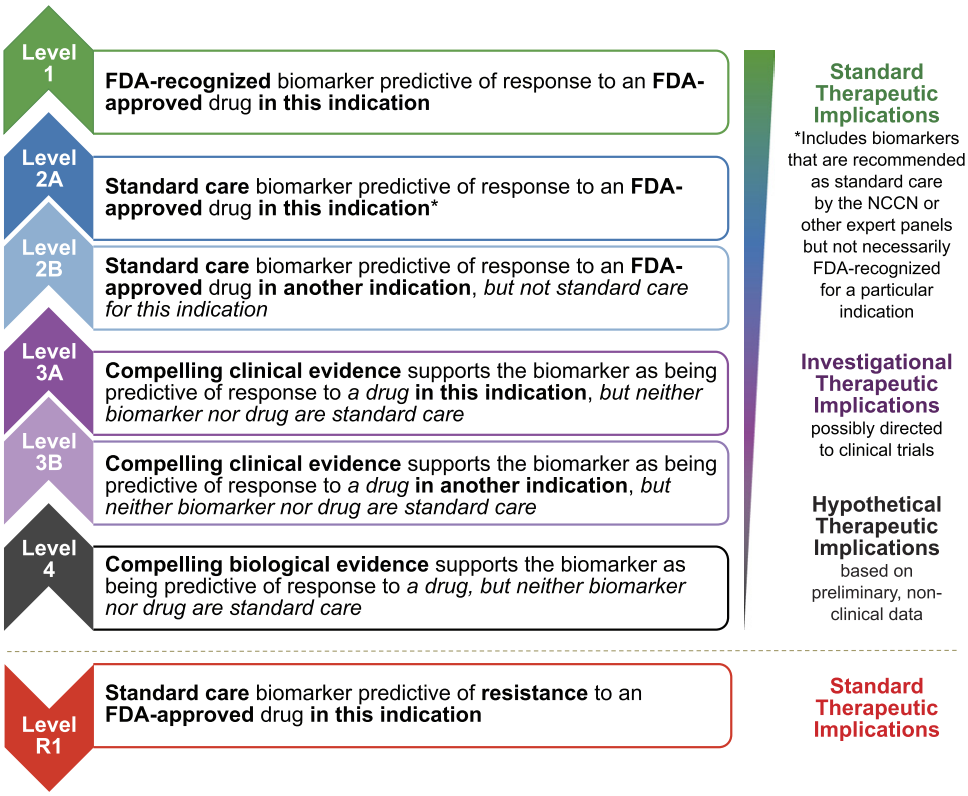
Abbreviations: NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.

new biomarkers that are targetable, the use of panel testing has proliferated in academic medical centers and the community. Standard biomarkers are tested in these gene panels, but in addition, alterations in genes without sufficient evidence of corresponding efficacious therapy are also routinely presented.

Interpretation and communication of this data to patients and translation into therapeutic interventions is a daunting challenge for clinicians. For example, *BRAF* V600E–mutated melanomas respond exceptionally well to *BRAF* and *MEK* inhibitors, but the response in colorectal cancers to these drugs as monotherapies has been disappointing.[38,39] Closely curated databases of genomic alterations such as OncoKB[40] and MyCancerGenome[41] have developed frameworks to assist prioritization of therapies for genomic alterations (Fig. 1). However, use of these biomarkers to select therapy is still largely experimental and should be done in the setting of a clinical study at an experienced center, where structured support is available for the patient and data can be appropriately collected and aggregated to answer clinical and research questions. It should be emphasized that in communication with patients, clinicians should make clear that beyond the limited set of validated tests with corresponding validated therapies, selection of therapy based on tumor genomic profiles is experimental and with no clearly established benefit.

Whenever possible, patients should be encouraged to participate in clinical studies. Molecular stratification of patient tumors increases the challenge of accruing sufficient patients to power detection of benefit (or lack thereof) in these tumor subsets. A variety of clinical trial designs have been developed to validate predictive biomarkers, including random assignment of patients stratified by biomarkers (IPASS,[42] MARVEL[43]), enrichment studies with assignment to study arms by biomarker status (BATTLE,[44] I-SPY 2[45]) and adaptive trial designs.[46] NCI-MATCH (NCT02465060) is a National Cancer Institute–sponsored clinical trial designed to

FIGURE 1. Example of Hierarchy of Evidence of Genomic Alterations



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handle the problem of low accrual by combining multiple tumor types as a basket trial based on molecular alteration rather than tumor type, as well as to maximize the number of participating sites to optimize enrollment.[47] ASCO has initiated the Targeted Agent and Profiling Utilization Registry Study (TAPUR), which will collect real-world data on use of approved agents to treat molecular targeted variants across disease types.[48] Umbrella trials, such as the National Cancer Institute–sponsored Lung MAP trial (NCT02154490), recruit patients of a given tumor type (recurrent metastatic squamous cell carcinoma) and place them into arms based on biomarkers (e.g., *PI3KCA* mutation) with targeted therapies (e.g., taselisib).[49]

The vast majority of patients do not participate in biomarker-driven clinical studies, and their genomic and clinical data would be a huge boon for research if able to be collected, aggregated and structured appropriately. This has prompted initiatives to share and pool data between multiple institutions, such as the American Association for Cancer Research–sponsored GENIE project[50] and ORIEN.[51] Further, direct patient collaborations such as the Metastatic Breast Cancer Project,[52] in which individual patients directly give permission for clinical data and tumor tissue to be collected from disparate medical centers and centrally analyzed, could provide important data in low-frequency disease. ASCO is further developing the CancerLinQ[53] program to create a data platform in which clinical (and genomic, where available) data from the much larger group of patients treated in a broader range of settings can be collected and analyzed both for clinical and research benefit. The Cancer Moonshot Initiative[54] identified data aggregation and a common data ecosystem as key components of accelerating the pace of cancer research.

Beyond the current set of existing tests, new promising technologies are being developed. Cell-free tumor DNA found in blood plasma has been detected in multiple metastatic tumor settings[19]; a liquid biopsy avoids the morbidity of traditional biopsies and allows more frequent monitoring, enabling earlier detection of response or development of resistance. Further, tumor genomic heterogeneity has been demonstrated between primary and metastatic lesions and [55] different metastatic lesions[56,57] and even in different regions[58] of the same lesion. A liquid biopsy may thus present an integrated profile of the tumor. Further, novel techniques using bio-informatic approaches to infer deficiencies in DNA repair pathways from genomic data[59] may predict response to DNA-damaging therapies. Single-cell RNA sequencing,[60] or deconvolution of bulk RNA sequencing[61] to identify specific immune cell subsets in the tumor microenvironment,[62] may assist in predicting which tumors are likely to respond to immune therapy. It is likely that in the future mulitple omic approaches including genomic DNA alterations, epigenetic modifications, transcriptome-based expression of mRNA, proteomic expression, and alterations in regulatory molecules such as microRNA and immune factors will provide a more integrated portrait of the tumor and microenvironment.

In a value-based reimbursement world, where quality is defined by outcome/cost, it is essential for oncology practices to maintain up-to-date lists of biomarker/target–driven pairs for which there is compelling evidence that biomarker testing identifies an important therapeutic opportunity (e.g., crizotinib for *ALK*-rearranged lung cancer) or allows for avoidance of a toxic therapy (e.g., cetuximab in *KRAS* mutant colorectal cancer). Quality metrics will increasingly focus on avoiding underutilization of these established tests, as clinical evidence has already established biomarker selected therapy as a superior strategy.

In contrast, use of broad panel tests is more complex. Payers may have prior authorizations built in to limit use of panel testing in certain clinical circumstances. Panel tests may be valuable if they are used to identify a batch of validated biomarker/target–driven pairs as well as to support investigation. However, overuse of panel tests should also be avoided. It is critical that when these tests are obtained, oncologists have access to the necessary support for interpretation. Finally, it is anticipated that linking these genomic reports with detailed treatment histories and clinical outcomes such as response, duration of response and survival will accelerate discovery of efficacious therapeutic strategies.

CONCLUSION

Precision oncology has clinical utility in the here and now, but the promise for the future is much greater. With rapid improvements in technology, enhanced ability to probe beyond single DNA alterations to other molecular components that influence tumor behavior and represent targets for new therapeutics is clearly in sight. Responsible use of this remarkable technology will depend on generating evidence through new clinical trial designs, aggregation of molecular and clinical data in real-world databases and careful analysis to determine relevant target-agent associations. Ultimately, the approach must prove value across specific patient populations. The practicing oncologist should make an effort to understand the power and limitations of the current testing and treatment landscape to help patients make the best informed decisions.

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