Determining If a Somatic Tumor Mutation Is Targetable and Options for Accessing Targeted Therapies

Suanna Steeby Bruinooge, MPH1; Shimere Sherwood, PhD1; Stephen Grubbs, MD1; and Richard L. Schilsky, MD1

Abstract

Targeted cancer therapies are drugs and biologics designed to affect cancer cell growth by blocking or interfering with specific molecular pathways in the cancer cell. Use of targeted agents usually requires verification through molecular testing that the patient’s tumor harbors the molecular biomarker that is the target of the drug or is predictive of treatment benefit. Genomic mutations may be clinically actionable if they are associated with response or resistance to a potential therapy. If a genomic test reveals an actionable alteration, there are several options for accessing the targeted therapy. This article is intended to help clinicians determine if a tumor mutation is potentially treatable with a marketed or investigational drug or biologic product and to offer guidance on how to access the product of interest.

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Introduction

Targeted cancer therapies are drugs and biologics designed to affect cancer cell growth by blocking or interfering with specific molecular pathways in the cancer cell. ASCO’s January 2018 State of Cancer Care in America inaugural event titled Precision Medicine: Expanding Opportunities and a companion article by Levit et al published earlier this year illustrate the complexities associated with implementing cancer precision medicine in community-based settings.

Use of targeted agents usually requires verification through molecular testing that the patient’s tumor harbors the molecular biomarker that is the target of the drug or biologic product or is predictive of treatment benefit. For some targeted treatments, the approved indication is based solely on detection of a molecular biomarker rather than on the tissue type from which the cancer originated, so-called “tissue-agnostic” or “site-agnostic treatment.” Although the US Food and Drug Administration (FDA) has approved more than 80 targeted therapy agents (many of which have multiple indications across cancer types), these agents are still directed against a limited number of genomic or other molecular targets, many of which occur at a low frequency in solid tumors of adults. Indeed, many common genomic alterations remain undruggable, such as the Ras signaling protein, which is frequently mutated in some cancer types and across one quarter of all patients with cancer. This article is intended to help clinicians determine whether a tumor mutation is potentially treatable with a marketed or investigational drug or biologic product and, if so, to offer guidance on how to access the product of interest.

The genomic test laboratory will likely provide a report that includes some interpretation of the significance of the genomic alterations detected. Most reports will focus on molecular markers found in the tumor tissue (somatic mutations) rather than germline mutations that are directly inherited and may signal a familial predisposition to cancer. Distinguishing somatic mutations from germline mutations requires “parallel analysis of paired germline DNA” to isolate mutations that arise in the cancer cell. Many types of somatic mutations can occur, including point mutations in a gene, insertions, deletions, duplications, and frame shifts. The nomenclature used in genomic test reports can be quite difficult to understand and is unfamiliar to many oncologists. Whether a particular alteration is an oncogenic driver rather than an inconsequential (passenger) mutation of little biologic relevance requires that a molecular pathologist interpret the genomic test results, often by consulting one or more genomic knowledge bases that describe the characteristics of the mutation and its potential impact on cellular function.

Genomic mutations may be clinically actionable if they are associated with response or resistance to a potential...
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<tr>
<td>ASCO University Molecular Oncology Tumor Boards</td>
<td>American Society of Clinical Oncology</td>
<td>The Molecular Oncology Tumor Boards are a series of bi-monthly, user-driven discussions designed to help cancer care providers with the interpretation and understanding of tumor molecular profiling tests and studies. Moderated by an expert pathologist and medical oncologist, each case will be updated with new information over a two week period as user comments are added. After two weeks, the discussion forum will be locked to further commentary and users will be able to claim CME credit for their participation.</td>
<td>elearning.asco.org/catalog?text=Tumor%20Boards</td>
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<tr>
<td>Association for Molecular Pathology</td>
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<td>College of American Pathologists</td>
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<td>Cancer Genome Interpreter</td>
<td>Barcelona Biomedical Genomics Laboratory</td>
<td>Flags validated oncogenic alterations, and predicts cancer drivers among mutations of unknown significance. Flags genomic biomarkers of drug response with different levels of clinical relevance.</td>
<td><a href="http://www.cancergenomeinterpreter.org/about">www.cancergenomeinterpreter.org/about</a></td>
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<td>Cancer Biomarkers Database</td>
<td>Several clinical and scientific experts and organized by the Cancer Genome Interpreter</td>
<td>The Cancer Biomarkers Database is curated and maintained by several clinical and scientific experts in the field of precision oncology supported by the European Union’s Horizon 2020 funded project. This database is currently being integrated with knowledge databases of other institutions in a collaborative effort of the Global Alliance for Genomics and Health.</td>
<td><a href="http://www.cancergenomeinterpreter.org/biomarkers">www.cancergenomeinterpreter.org/biomarkers</a></td>
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<tr>
<td>ClinGen (Clinical Genome Resource)</td>
<td>National Institutes of Health</td>
<td>ClinGen is a National Institutes of Health (NIH)-funded resource dedicated to building a central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.</td>
<td><a href="http://www.clinicalgenome.org">www.clinicalgenome.org</a></td>
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<tr>
<td>CIVIC</td>
<td>The McDonnell Genome Institute at Washington University School of Medicine</td>
<td>CIVIC is an open access, open source, community-driven Web resource for Clinical Interpretation of Variants in Cancer. The goal is to enable precision medicine by providing an educational forum for dissemination of knowledge and active discussion of the clinical significance of cancer genome alterations. [The Web site offers information by variant, gene, disease, drugs, evidence, assertions, and sources.]</td>
<td>civicdb.org/home</td>
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<td>ClinVar</td>
<td>National Center for Biotechnology Information</td>
<td>ClinVar is a freely accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence. ClinVar thus facilitates access to and communication about the relationships asserted between human variation and observed health status, and the history of that interpretation. <a href="http://www.ncbi.nlm.nih.gov/clinvar">www.ncbi.nlm.nih.gov/clinvar</a></td>
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<td>COSMIC</td>
<td>Wellcome Sanger Institute</td>
<td>COSMIC – the Catalogue of Somatic Mutations in Cancer – is the world’s largest source of expert manually curated somatic mutation information relating to human cancers. cancer.sanger.ac.uk/cosmic</td>
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<td>cBioPortal for Cancer Genomics</td>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>The cBioPortal for Cancer Genomics is an open-access, open-source resource for interactive exploration of multidimensional cancer genomics data sets. [The Web site provides tutorial slides and a tutorial paper13 to guide the user’s initial navigation of the Web site.] <a href="http://www.cbioportal.org">www.cbioportal.org</a></td>
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<td>GDC Data Portal</td>
<td>National Cancer Institute</td>
<td>The NCI’s Genomic Data Commons (GDC) provides the cancer research community with a unified data repository that enables data sharing across cancer genomic studies in support of precision medicine. [Catalogues data according to major cancer primary site, genes, mutations, and cases.] portal.gdc.cancer.gov</td>
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<tr>
<td>Genomics of Drug Sensitivity in Cancer</td>
<td>Wellcome Sanger Institute</td>
<td>We are performing a large-scale drug screen incorporating detailed genomic analyses to systematically identify drug response biomarkers. This information can be used to inform the optimal clinical application of cancer drugs, as well as having significant effects on the design, cost and ultimate success of new cancer drug development. <a href="http://www.cancerrxgene.org">www.cancerrxgene.org</a></td>
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<td>IntOGen (Integrative Oncogenomics)</td>
<td>Barcelona Biomedical Genomics Laboratory</td>
<td>IntOGen collects and analyses somatic mutations in thousands of tumor genomes to identify cancer driver genes. [Information in the database is organized by cancer type, project, samples, somatic mutations, coding sequence mutations in driver genes and all genes, and proteins affecting mutations in driver genes and all genes.] <a href="http://www.intogen.org">www.intogen.org</a></td>
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<td>ICGC Data Portal (International Cancer Genome Consortium)</td>
<td>Ontario Institute for Cancer Research</td>
<td>The ICGC Data Portal provides many tools for visualizing, querying, and downloading cancer data, which is released on a quarterly schedule. One of the most popular features of the portal is Advanced Search which may be found at <a href="https://dcc.icgc.org/search">https://dcc.icgc.org/search</a>. This is a great place to begin exploring the ICGC data set. (The portal offers the following resources: Compounds Explorer for searching by cancer-targeting therapeutics; Beacon for exploring observations of specific mutated alleles; pathways to examine data according to the molecular pathway that is involved; and Gene Ontology for searching by using standardized gene terms.)</td>
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<td>Personalized Cancer Therapy Knowledge Base for Precision Oncology</td>
<td>MD Anderson Cancer Center, Khalifa Institute for Personalized Cancer Therapy</td>
<td>This Personalized Cancer Therapy website was specifically developed as a tool for physicians and patients to assess potential therapy options on the basis of specific tumor biomarkers. Users can search in the knowledge base by gene. The knowledge base returns information on alterations, frequencies and outcomes, therapeutic implications, drugs, and clinical trials.</td>
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<td>My Cancer Genome</td>
<td>Vanderbilt-Ingram Cancer Center</td>
<td>My Cancer Genome is a precision cancer medicine knowledge resource for physicians, patients, caregivers and researchers. My Cancer Genome gives up-to-date information on what mutations make cancers grow and related therapeutic implications, including available clinical trials. My Cancer Genome is a one-stop tool that matches tumor mutations to therapies, making information accessible and convenient for busy clinicians.</td>
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<tr>
<td>St. Jude Cloud, PeCan</td>
<td>St. Jude Children's Research Hospital</td>
<td>The St. Jude-Washington University Pediatric Cancer Genome Project is the world's most ambitious effort to discover the origins of childhood cancer and seek new cures. By comparing the complete genomes from cancerous and normal cells for more than 800 patients, we have successfully pinpointed the genetic factors behind some of the toughest pediatric cancers.</td>
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<tr>
<td>Washington University in St. Louis School of Medicine</td>
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<td>Raw sequence data for all published results, as well as data analysis and visualization tools, are freely available.</td>
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therapy.8 The Association for Molecular Pathology, ASCO, and the College of American Pathologists released joint consensus recommendations in 2017 to guide clinicians in interpreting genomic test reports.8 The recommendations include a four-tiered system for categorizing genomic data from somatic testing. Tier 1 includes variants with strong clinical significance, Tier 2 denotes variants with potential clinical significance, Tier 3 is reserved for variants with unknown clinical significance, and Tier 4 includes variants likely or known to be benign. There are many online databases and other types of educational resources to provide guidance on determining the actionability of genomic variants (Table 1).10-16

If a genomic test reveals an actionable alteration, there are several options for accessing the targeted therapy (Fig 1). If the actionable target has an existing FDA-approved targeted drug or biologic and an indication for the patient’s cancer type included in the product label, then insurance will typically provide coverage for the drug or biologic as prescribed according to the FDA-approved label. Even if the patient has insurance, the high cost of some drug and biologic products and/or the amount of cost-sharing required may make treatment unaffordable for some patients.17,18 If this is the case, a patient may benefit from financial assistance programs. The Partnership for Prescription Assistance (a collaboration of biopharmaceutical companies, patient advocacy organizations, and professional societies) provides a single Web-based point of access to more than 475 programs that offer assistance to patients and caregivers.19

If the FDA-approved drug or biologic does not have an indication for the cancer type or molecular alteration (which serves as the basis for tissue-agnostic approvals), use of the drug or biologic would then be considered off-label. In these cases, the clinician should determine whether there is sufficient evidence to support the off-label use. Clinical practice guidelines generated by ASCO and the National Comprehensive Cancer Network (NCCN) provide a summary of the literature available when the guidelines were published.20,21 A payer may reimburse for an off-label use if there is support in established compendia, clinical practice guidelines, or the literature.22 To address potential costs to the patient, the clinician can appeal directly to the patient’s health plan to request reimbursement and/or look into whether the manufacturer or another entity offers patient assistance with the cost of the medication. If these options fail, then the only recourse for the patient is to pay out-of-pocket for the therapy, if possible.

If there is not sufficient evidence to support off-label prescribing, ASCO and NCCN guidelines support clinical trial participation. If a trial exists and the patient is eligible, the physician and research staff should engage the patient in an informed consent discussion to address the risks, benefits, and alternatives to the investigational treatment. The discussion should determine the patient’s willingness

### TABLE 1. Resources for Interpreting Genomic Test Results (continued)

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<tr>
<td>AACR Project GENIE</td>
<td>American Association for Cancer Research</td>
<td>AACR Project Genomics Evidence Neoplasia Information Exchange (GENIE) is a multiphase, multiyear, national and international project that catalyzes precision oncology through the development of a regulatory-grade registry aggregating and linking clinical-grade cancer genomic data with clinical outcomes from tens of thousands of patients with cancer treated at participating institutions.</td>
<td><a href="http://www.aacr.org/research/research/pages/aacr-project-genie.aspx">www.aacr.org/research/research/pages/aacr-project-genie.aspx</a></td>
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<tr>
<td>TP53 Database15</td>
<td>World Health Organization, International Agency for Research on Cancer (IARC)</td>
<td>The IARC TP53 Database compiles various types of data and information on human TP53 gene variations related to cancer. Data are compiled from the peer-reviewed literature and from generalist databases. (Quick links allow users to search by mutations/single nucleotide polymorphisms (SNPs), cell lines, and TP53 reference sequences. The Web site also provides a users’ manual, as well as protocols and tools.)</td>
<td>p53.iarc.fr</td>
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NOTE. This table does not provide a comprehensive list of resources. It was assembled on the basis of a review of several publications in the reference list, especially in Van Allen et al6 and Li et al.9 Inclusion of a Web site does not represent an endorsement by the authors or by ASCO of any individual database or product. Many of these Web sites have language indicating that they are intended for research use only. All of the Web sites make information available free of charge without a paywall. All Web sites were last accessed May 1, 2019.
Precision medicine treatments (also known as targeted therapies) have the potential to improve outcomes for patients with advanced cancer. However, it can be challenging for oncologists to navigate the options available for each patient. This illustration provides a guide that clinicians can use to determine whether a targeted therapy is a viable treatment option. The first step is ordering and evaluating a genomic test.

FIG 1. This illustration provides a series of questions and decision points through which clinicians can guide their patients in determining whether a targeted therapy is a viable treatment option. The first step is ordering and evaluating a genomic test. (*) The extent to which a clinician can take clinical action on the basis of the genomic findings will depend on the available evidence related to the role of the genomic biomarker in the patient’s cancer and the ability of a therapy to target the genomic alteration. (†) Dependent on whether trial is locally available or patient is willing and able to travel. For nonlocal trial, if possible, determine in advance whether patient is likely to meet eligibility requirements. (‡) FDA approves 99% of the requests it receives for Expanded Access.
and ability to participate in the trial, including discussion of extra financial considerations, if any.23

If the patient does not qualify for the trial or it is closed to accrual, the drug or biologic manufacturer may choose to provide access to the investigational agent outside clinical trials at the request of the clinician or patient. FDA regulations enable patients with life-threatening or serious disease to access, with the company’s approval, investigational agents through three types of expanded access or compassionate use programs: single-patient use, intermediate-sized groups, and widespread treatment use.24 FDA’s review of requests for expanded access provides a third-party independent assessment of the potential for benefit and risk. FDA responds to requests quickly and grants virtually all (99%) of the requests it receives.25 Companies are now required by law to publicly disclose their policies with respect to expanded access programs, and these can be found using the Expanded Access Navigator provided by the Reagan-Udall Foundation for the FDA.26

The FDA Oncology Center of Excellence (OCE) held a public workshop in May 2019 to announce a pilot program (Project Facilitate) to provide a concierge-type service for patients and clinicians.27 The program focuses on single-patient requests for use of investigational therapies. If an intermediate or widespread program is available, OCE will direct patients and clinicians to resources for these programs. Expert clinicians at OCE can also provide guidance to physicians on appropriate dosing and dose modifications for toxicity. In addition, OCE can document multiple inquiries for single-patient use and discuss with the drug or biologic manufacturer the possibility for opening an intermediate-sized group to help facilitate data collection and other efficiencies.

As of May 2018, the federal government enables patients and clinicians to pursue access directly from manufacturers, bypassing the FDA safeguards and assistance. The Right To Try Act (Public Law 115-176)28,29 was signed into law creating another pathway for terminally ill patients who have exhausted FDA-approved options and are not eligible for a clinical trial to access investigational treatments. If the manufacturer does not offer either expanded access or right-to-try programs, there are no further options for accessing the investigational therapy outside a clinical trial.

ASCO is helping to build the evidence base for use of targeted agents through its Targeted Agent and Profiling Utilization Registry (TAPUR) Study (ClinicalTrials.gov identifier: NCT02693535; TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer).30 ASCO launched the TAPUR Study to capture data in a pragmatic clinical trial to document real-world use of FDA-approved targeted therapies outside their approved indications. The study aim is to help identify safety and efficacy signals in biomarker-driven, off-label use of genomically targeted agents. The study uses a two-stage design to expand or close cohorts once response has been observed in the first 10 participants. Nearly thirty cohorts with eight drug therapies have expanded into phase II (which enrolls a total of 28 participants). A signal of activity at completion of phase II requires seven study participants to have objective tumor response or stable disease of at least 16 weeks duration. The study also closed eight cohorts with five drug therapies because of the absence of a signal. ASCO, in collaboration with 120 participating sites across the United States and seven pharmaceutical companies, is committed to peer-reviewed release of all study results in a timely manner. The initial negative findings from the study were presented as an abstract31 and poster32 at the 2018 ASCO Annual Meeting and have been submitted for publication. The initial positive signals of activity were presented at the 2019 ASCO Annual Meeting. Palbociclib demonstrated evidence of antitumor activity in patients with non–small-cell lung cancer with a CDKN2A gene loss or mutation.33 In addition, pembrolizumab demonstrated antitumor activity in patients who had metastatic breast cancer with high tumor mutational burden.34 Up-to-date information on the status of study cohorts is available through the news link on www.TAPUR.org.

Other ongoing genomics matching trials that provide access to targeted agents include the MATCH (ClinicalTrials.gov identifier: NCT02465060; Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma [The MATCH Screening Trial]) and pediatric MATCH (ClinicalTrials.gov identifier: NCT03155620; Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphomas, or Histiocytic Disorders [The Pediatric MATCH Screening Trial]) trials and the Lung-MAP (ClinicalTrials.gov identifier: NCT03851445; Lung-MAP: A Master Screening Protocol for Previously-Treated Non-Small Cell Lung Cancer) trial, which is enrolling patients with advanced non–small-cell lung cancer. These trials are funded by the National Cancer Institute. Several not-for-profit organizations have also organized disease-specific genomic matching trials such as the BeatAML (ClinicalTrials.gov identifier: NCT03013998; Study of Biomarker-Based Treatment of Acute Myeloid Leukemia) trial organized by the Leukemia and Lymphoma Society.

Practical understanding of these clinical challenges is important to implementing precision medicine. Knowledge regarding precision medicine continues to expand and is especially needed where the majority of patients with cancer are treated: at community-based practices.35 With the increasing development of molecularly targeted therapies and technological advances in genomic testing, precision medicine has become a reality in clinical practice. Despite the challenges, many clinicians and patients have invested in precision medicine programs in an ongoing search for safe and effective therapies to deliver improved patient outcomes.
REFERENCES


Authors’ Disclosures of Potential Conflicts of Interest

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