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Using Cancer Genomics to Guide Clinical Decisions

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Detailed portraits of thousands of cancer genomes are now available, and they illustrate the variety of genomic changes that drive cancer; they are termed landscapes.¹ Cancer landscapes include alterations such as point mutations, indels, rearrangements, amplifications, and deletions (see Table 1). Moreover, the landscapes reveal that genetic alterations common to one cancer are found at low frequencies in other cancer types. Two factors have heightened the clinical relevance of this discovery. First, it is now possible to identify patients who have these rare alterations via clinical DNA sequencing. Second, targeted therapies approved for one cancer type are often effective in other types with the same genetic driver. Thus, the clinical testing of a tumor occasionally provides a remarkable benefit to a patient. Yet, interpreting tests and selecting appropriate therapy remain a challenge. Molecular tumor boards can help to interpret genomic results, provide uniform guidelines, and track patient outcomes, but they remain inaccessible to most oncologists. Here, we provide insights into the challenges and opportunities related to using genomic tests to make clinical decisions.

Genomic Testing

Available assays for genome sequencing include panel, whole exome, and whole genome assays (see Table 1). These assays offer distinct compromises between the breadth of the genome encompassed and the sequencing depth. Panel sequencing offers the greatest depth and is the most sensitive for alterations in samples with admixed stromal tissue or subclonal cell populations. By contrast, genome and exome sequencing finds genomic alterations more broadly and allows the discovery of uncommon driver alterations at the cost of lower depth. Recently, cell-free DNA tests have become available, and they allow the testing of circulating tumor DNA in blood. We generally recommend panel sequencing for routine use,

CONFLICT OF INTEREST DISCLOSURES

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whole exome sequencing for research (eg, when panel alterations are not found), and cell-free DNA for monitoring resistance mutations or when biopsy is not possible.

Two challenges arise in interpreting results: distinguishing somatic alterations from germline alterations and distinguishing drivers from passengers (see Table 1). Some assays perform simultaneous sequencing for the blood and the tumor and then filter out germline variants found in the blood. Other tests focus solely on the tumor sample and computationally filter alterations found in databases of known human genomes (which are incomplete). Thus, it is important to understand the nature of the test, especially when hereditary germline cancer syndromes are possible.

To distinguish driver mutations from passenger mutations, the known genetic landscape of cancers is an important guide. Drivers are commonly mutated in tumors, and the function of some specific mutations has been demonstrated in cancer models. Annotated databases of common cancer drivers provide confidence that some alterations are drivers.^{2,3} Passenger mutations can occur in oncogenes, so each particular alteration within a gene should be assessed for function. In particular, missense mutations that appear rarely in the cancer landscape are likely passengers unless they are functionally characterized or the position is known to alter protein function. Conversely, clinicians should be aware that potentially actionable driver alterations may be unfamiliar. These include, for example, ERBB2/HER2 missense mutations, MET exon 14 skipping mutations, and BRAF mutations outside of V600. Importantly, some driver mutations can be germline and indicate inherited cancer syndromes.

Not all apparent drivers are relevant. First, when multiple drivers are found, it is difficult to understand their relative importance; this is a particular concern with amplifications and deletions encompassing large chromosome regions. For example, apparent co-amplification of CDK4, MDM2, and GLI1, all on chromosome 12, might mean that one, all, or none are actual drivers. Drivers are occasionally found in rare cell populations such as subclones or infiltrating noncancer cells. Some tests will report the variant allele frequency, which, if low, could indicate alterations that are subclonal or occur in rare cell populations, such as infiltrating blood.⁴ Thus, optimal interpretation requires consideration of the test type, gene function, chromosomal location, effect of the particular alteration, and frequency of alterations in the cancer landscape and in inherited cancer syndromes.

Therapeutic Decisions

Genetics-driven clinical trials such as the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) and the Targeted Agent and Profiling Utilization Registry (TAPUR) are ideal when genomic tests are being used.^{5,6} However, trials are inaccessible for many patients because of location or restrictive eligibility criteria. Thus, the off-label use of targeted drugs outside a trial is reasonable. However, there is a risk of using genomic data inappropriately to rationalize nonstandard therapies when the likelihood of benefit is low. In addition, cancer signaling pathways are complex and interdependent, so targeting activated pathways several steps removed from the driver mutation is rarely successful.

Thus, we propose 3 rules for off-label therapy:

1. Do not use off-label precision approaches for potentially curable cancer.
2. Genomics-driven clinical trials, if available, are preferred to off-label drug use.
3. Genomics-driven treatment should be restricted to targeted drugs on the basis of validated principles establishing a biologic rationale, safety, and efficacy for patients with the genetic marker, regardless of the tumor type.

Today, a number of drugs potentially meet these principles (Table 2), although alterations are rare in some tumor types (Fig. 1). The approach that we consider generally valid as a biologic rationale is oncogene addiction, in which the inactivation of an oncogene with a direct chemical inhibitor is sometimes effective. This concept has been validated mechanistically in diverse preclinical oncogene models⁷ and in human tumors, with tumors driven such as EGFR, ALK, ROS, RET, and BRAF able to be reversed by direct inactivation.⁸ However, there are exceptions such as single-agent BRAF inhibitors, which are ineffective against colorectal cancer.⁹ Thus, direct inhibition of activated oncogenes is reasonable, regardless of the histopathology, unless a specific exception is known. Validated drug-biomarker pairs outside oncogene addiction are scarce. Poly(adenosine diphosphate ribose) polymerase inhibitors, which are synthetically lethal with deficient homologous recombination due to a BRCA1/2 mutation, are one example.¹⁰ Emerging biomarkers predict a benefit from immunotherapy. For example, mutations causing microsatellite instability predict sensitivity to immune checkpoint therapy,¹¹ and the mutational load is proposed as a biomarker.¹²

In conclusion, the genomic analysis of tumors is a powerful tool for identifying the fundamental drivers of each patient's cancer. Emerging data support the use of genomic-targeted therapy to improve patient outcomes and even to decrease medical costs.^{13–15} In precision oncology, improved data sharing among oncologists and molecular tumor boards is critical for replicating success and curtailing failures. Oncologists should seek to share successes and failures through reporting systems or case reports to optimize community knowledge.

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Figure 1.

Frequency of mutations in the genes listed in Table 2 in different solid tumor types. We have limited this figure to analyses published by The Cancer Genome Atlas with at least 200 samples. Note that this is likely an overestimate of the frequency of actionable mutations because databases do not fully distinguish between driver and passenger mutations in these genes. GBM indicates glioblastoma multiforme; H&N, squamous cell carcinoma of the head and neck; NSCLCa, non-small cell lung cancer.

TABLE 1

Definitions

Alteration or variant. A generic term for a genetic change from a reference genome occurring in cancer cells. It encompasses point mutations, indels, amplifications, deletions, and rearrangements. Alterations are classified as drivers or passengers.
Amplification. A genomic region that exists in many copies within the cancer cell. By next-generation sequencing, this is identified when the sequence from a particular genomic region is read more often than other portions of the genome. <i>MYC</i> is an example of a gene that is commonly amplified in cancer.
cfDNA or ctDNA sequencing. cfDNA and ctDNA assays are performed via the sampling of DNA circulating freely in plasma. These assays have the advantage of analyzing the current tumor genome without a new biopsy. These tests are usually performed as panels to find only cancer-specific mutations, and they are less useful for amplifications and other alterations.
Driver. An alteration that promotes cancer development or progression. Drivers are typically classified as oncogenes or tumor suppressors. Not all driver alterations can be targeted for therapy with currently available drugs.
Filtering. A way of distinguishing germline and somatic alterations. In some assays, this is partly accomplished through simultaneous sequencing of blood or other tissue with germline DNA. In other assays, this is accomplished computationally by the removal of known alterations found in databases of germline sequences of many individuals.
Frameshift. An indel within an exon that adds or subtracts a number of nucleotides not divisible by 3. This results in an out-of-frame protein code. Typically, a small number of abnormal nucleotides are translated, and this is followed by a stop codon. This is reported as fs*X, where X is the number of abnormal amino acids encoded before the stop. These alterations commonly inactivate gene function and are found in tumor-suppressor genes.
Gene deletion. A genomic region, spanning a gene, that is deleted from the genome. By next-generation sequencing, this is detected by the relative absence of sequences read from this region. <i>CDKN2A</i> is an example of a gene that is commonly deleted in cancer.
Germline. The genome of most normal cells in an individual. It is expected to match what is transmitted to progeny.
Indel. A small genomic alteration within a gene in which nucleotides are either <i>inserted</i> or <i>deleted</i> .
Missense. A point mutation in which a single amino acid is changed with respect to the expected sequence. These mutations often do not alter gene function, and many missense variants identified in tumor-only sequencing reports may represent unusual polymorphisms in the germline. However, some are well known to alter gene function, such as <i>KRAS</i> G12V and <i>BRAF</i> V600E.
Mutational burden. The frequency of somatic mutations in a tumor, including drivers and passengers. It is usually expressed as mutations per kilobase.
Nonsense. A point mutation that inserts a premature stop codon, which leads to a truncated protein. This is common with tumor suppressors such as <i>BRCA1</i> . These alterations commonly inactivate gene function.
Off-label therapy. Use of an approved drug outside the approved cancer type.
Oncogene. A driver alteration in which gene function is activated (eg, <i>PIK3CA</i>).
Oncogene addiction. The well-validated concept that cancers originating from an oncogene alteration continually depend on the activated oncogene. This supports the use of drugs that directly inhibit an oncogene.
Panel sequencing. Next-generation sequencing of a set of target genes or regions of the genome to identify the most common mutations, rearrangements, amplifications, or deletions with high coverage depth. This typically is accomplished through DNA-amplification steps specific for the desired regions. Most panels cover approximately 50 to 500 genes or genomic regions.
Passenger. A somatic alteration that does not contribute to cancer development or progression.
Point mutation. A mutation of a single base pair. It is classified as nonsense, missense, or silent according to how it affects the protein sequence.
Read depth or coverage. In sequencing, this refers to the number of times a given region of the genome is identified. This is typically expressed as a mean across the desired regions of the genome. When a sequencing platform is being selected, there is a tradeoff between the depth and breadth of the genome read (see the entries for panel sequencing, whole genome sequencing, and whole exome sequencing). High read-depth sequencing is sometimes called deep sequencing, and it has enhanced sensitivity for alterations in cell subpopulations.
Rearrangement. A genomic break and fusion that leads to the abnormal juxtaposition of 2 genes. The product is a fusion protein that is activated because of either abnormally high expression or activated gene function. Examples include <i>BCR-ABL</i> and <i>ALK</i> rearrangements.
Somatic. This refers to the genome of cells expected to differ from the germline, such as cancer cells.
Synthetic lethality. The concept that the simultaneous inactivation of 2 genes is lethal, whereas the inactivation of each gene individually is not. This supports the use of drugs that inactivate a gene that has a synthetic lethal relation with a tumor suppressor.
Tumor complexity or heterogeneity. This refers to the number of different DNA sequences that may be found in a tumor sample because of an admixture with nontumor cells and subclonal cell populations within a tumor.

Tumor suppressor. A driver alteration in which gene function is inactivated (eg, *TP53*).

Variant allele frequency. The fraction of reads of a particular genomic region that detect the genetic variant. For tumors with oncogenes present in all cells, this is expected to reach as high as 0.5 (because of the existing wild-type copy) but can be lower according to the purity of the cancer cells within the tumor sample.

Whole exome sequencing. Next-generation sequencing of the protein-coding regions of the genome (exome). This is made possible by DNA-capture technology, in which the desired regions of the genome are captured with surfaces coated with partly complementary DNA sequences. It covers approximately 1% of the genome.

Whole genome sequencing. Next-generation sequencing of the entire set of DNA extracted from the genome. It typically covers part or most of the approximately 3 billion base pairs of the genome at a low sequencing depth. No processing is used to preselect genomic regions of interest.

Abbreviations: cfDNA, cell-free DNA; ctDNA, circulating tumor DNA.

TABLE 2

Drug-Gene Matches

Gene With Activating Mutation	FDA-Approved Agent
Oncogene addiction	
<i>ABL1</i>	Imatinib, nilotinib, dasatinib, bosutinib, ponatinib
<i>ALK</i>	Crizotinib, ceritinib, alectinib
<i>BRAF</i> V600E ^a	Vemurafenib, ^b dabrafenib ^b
<i>EGFR</i>	Erlotinib, gefitinib, afatinib, osimertinib
<i>ERBB2/HER2</i>	Trastuzumab, ^c pertuzumab, ^c T-DM1, ^c lapatinib, afatinib
<i>KIT</i>	Imatinib, sunitinib, regorafenib
<i>MEK1, MEK2</i>	Trametinib
<i>MET</i>	Crizotinib, cabozantinib
<i>mTOR</i>	Everolimus, temsirolimus, sirolimus
<i>PDGFRA</i>	Imatinib
<i>RAF1</i>	Vemurafenib, dabrafenib
<i>RET</i>	Cabozantinib, vandetanib
<i>ROS1</i>	Crizotinib
<i>PTCH1, SMO</i>	Vismodegib, sonidegib
Synthetic lethality	
<i>BRCA1, BRCA2</i>	Olaparib, rucaparib

Abbreviation: FDA, Food and Drug Administration; T-DM1, ado-trastuzumab emtansine.

^aExisting drugs are specific for this mutation.

^bOften used in combination with an MEK inhibitor because of the known safety and enhanced efficacy.

^cEspecially for amplification rather than mutation.