The Semantics of Cancer Genome Medicine

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Some of the most exciting recent discoveries in cancer have been made possible by the technological advance known as next-generation sequencing (NGS). NGS is a catch-all term used to describe a number of different modern sequencing technologies. NGS platforms perform massively parallel sequencing, during which millions of fragments of DNA from a single sample are sequenced simultaneously. NGS technologies permit the sequencing of DNA and RNA much more quickly and cheaply than the previously used Sanger sequencing, and have revolutionized the study of genomics and molecular biology. For example, utilizing NGS and other technologies, The Cancer Genome Atlas (TCGA) has cataloged the prevalent genomic aberrations in multiple malignancies (1). NGS continues to be utilized for basic biologic discovery in cancer laboratories across the world and has led to additional discoveries not observed in TCGA that have clear potential to lead to new cancer therapeutics (2).

Typically, NGS interrogates the genome for DNA-based aberrations. However, other complementary assays may probe for other molecular aberrations, including those in the proteome, transcriptome, metabolome, or epigenome, which have been collectively coined “omic” aberrations (Fig. 1; ref. 3). Omics-based assays may identify one or more types of abnormalities in DNA, such as mutations, deletions/amplifications, or translocations. They may also identify overexpression at the RNA or at the protein level, or other transcript abnormalities such as splice variants. Finally, in addition to alterations in protein expression levels, omics-based assays may identify posttranslational modifications, such as glycosylation or lipidation. When an “omics” aberration is known to be a sign of a normal or abnormal process, or a condition of disease, it is called a biomarker.

It is important to distinguish a biomarker in concept from one or more tests that might be used to identify, and quantify, the biomarker for application in the clinic. A cancer “biomarker test” is intended to be indicative of some clinically relevant phenomenon, such as risk categorization, screening, establishment of a diagnosis, indication of prognosis, prediction of response to treatment, or sequential monitoring of a patient’s disease status. We would like to emphasize that NGS is a technology, not a biomarker or diagnostic test. Having said that, specific mutations or combinations of aberrations identified by NGS may be biomarkers, and specific assays to test these biomarkers may be developed into biomarker tests. Biomarker test validation is a process that establishes the link between the diagnostic test and the clinically relevant phenomenon.

The classic cancer biomarker test analyzes a single factor (or “analyte”) known to have diagnostic, prognostic, and/or predictive utility. One example of a single analyte test is the determination of estrogen receptor (ER) protein expression in breast cancer, which is known to be predictive of sensitivity to endocrine therapy. Laboratories may “bundle” several well-established analytes into a single report to the clinician. For example, ER, progesterone receptor, and HER2 protein assay results will often be reported together, which is logical because each is known to have individual prognostic and predictive

Abstract

This is an exciting time to be in cancer medicine. New technologies, such as next-generation sequencing (NGS), have increased our understanding of the molecular aberrations that define cancer. This, in turn, has led to the identification of cancer-specific molecular targets and potential drugs to confront these targets. As these new technologies move toward clinical application, a new vocabulary of “genome medicine” has been introduced to the field of oncology. Unfortunately, unclear or incorrect use of the new terminology has led to semantic misunderstandings that impair communication between the basic research and clinical practice arenas. These

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value and are routinely used in the care of the patient. However, each analyte is interpreted (and reimbursed) separately from the others, and each was individually validated.

More recently, this concept has been expanded by commercial firms to construct, and market, larger panels of omics-based assays that are packaged together. These packages are often termed "genomic risk panels" when they apply to interrogations of germ-line genes, or "tumor profiles" when applied to cancer tissue. Panel assays can be thought of as a collection of single analyte tests performed as a distinct billable unit. Clinicians are very familiar with the concept of panel assays, such as the comprehensive metabolic panel, which includes 24 separate chemical tests of electrolytes and hepatic enzymes. Examples of panel assays in cancer medicine include tests for germline anomalies thought to be associated with cancer risk susceptibility, such as Myriad’s myRisk Hereditary Cancer panel, which tests 25 genes. Other manufacturers, such as FoundationOne (4), have focused on the development of tumor profiling tests that provide information on >300 of somatic cancer gene aberrations. In contrast, Caris Molecular Intelligence advertises that it uses multiple technologies, including IHC, FISH/chromogenic in situ hybridization, NGS, and PCR, to detect and interrogate a variety of analyte types.

A third model of an "omics"-based cancer assay is to combine several analytes into a weighted algorithm that provides a multiparameter signature with a single score, such as the 21-gene recurrence score (OncotypeDx). Finally, one might perform complete DNA sequencing and RNA expression analysis of the patient’s tumor and provide simplified summary describing potential "actionable" findings to the clinician. Currently, no such tests are on the market, but investigations of these methods are ongoing at many academic sites (5).

**Utility of Cancer Genome Assays**

The simple fact that a test is marketed as a “cancer assay” does not indicate that the test is clinically useful. For example, although it is true that a clinician might use some of the tests commonly included in an NGS tumor profile (such as EGFR and ALK mutations in a lung cancer patient), it is unclear that the clinician would want, or know how to use, results of the other tests.
provided in the profile/assay. In addition, although a multiparameter signature with the ability to discern patients with a worse prognosis may be available, if there is no way to use this information to improve the outcome of these patients, then the signature is not clinically useful. Over the last decade, led initially by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative convened by the Centers for Disease Control (6), several authors and guidelines bodies have proposed a set of semantics to help organize the fields of genetic and tumor biomarker tests, which have been rather chaotic in the past. These include three key terms: (i) analytical validity, which implies that the assay for the biomarker is technically accurate and reproducible; (ii) clinical validity, which implies that the assay divides one group of subjects into two or more whose clinical outcomes differ; and (iii) clinical utility, which implies that for a given context, high levels of evidence are available that demonstrate that application of the assay improves clinical outcomes compared with not knowing the results. In the United States, the Clinical Laboratory Improvement Act as overseen by the Centers for Medicare and Medicaid Services addresses the analytic validity of clinical laboratory tests. However, no U.S. regulatory body has specific oversight responsibility for clinical utility. Oddly enough, this inconsistent regulatory environment has led to a situation in which public and private insurance payers are in the position to enforce clinical utility standards, by deciding whether or not to provide coverage (7, 8).

There are many examples of single-factor biomarker tests with widely accepted clinical utility, including tests for Her2 amplification or overexpression to select patients for treatment with trastuzumab in breast or gastric cancers, BRAF V600E mutation to select for treatment with vemurafenib in melanoma, ALK mutation analysis to aid in identifying patients eligible for treatment with crizotinib, and EGFR mutations test to select for the use of erlotinib in lung cancer, to name a few. There are also several examples of multiparameter signatures that provide useful information to help guide the care of cancer patients. For example, the OncotypeDx, PAM50/Prosigna Breast Cancer Index, and EndoPredict assays all appear to identify a population of patients with ER-positive, node-negative breast cancer whose prognosis is so favorable that they can safely avoid adjuvant chemotherapy, which, before availability of these assays, was previously applied to most patients in this category. The success of these particular signatures is likely related to the process of developing them, which depended heavily on correlation with relevant clinical outcomes (good prognosis without chemotherapy), and was specifically geared toward establishing clinical utility by interrogating archived specimens collected during conduct of prospective randomized trials (9).

In contrast, many commercial cancer risk panels were developed based on the knowledge of cancer biology and analytic technology, but not on the ability to affect clinical outcomes. Although they may be performed in quality-certified laboratories with excellent analytical reliability and suggestions of clinical validity, the full set of components is rarely put to the test of clinical utility. For example, the identification of germline mutations in such well-known cancer susceptibility genes as BRCA1 and BRCA2, PTEN, and p53, when rationally applied to families whose medical history suggests a familial cancer syndrome, is useful for the provision of counseling, risk stratification, and application of preventative or prophylactic procedures. However, recently marketed genomic risk panels provide these, plus additional germline genetic analyses to patients without a suspicious family history. In these examples, there are little if any data to support clinical validity, let alone clinical utility. This same concern applies to some commercial tumor profiling products, which venture to extend use of both validated and nonvalidated biomarkers across multiple tumor types with the tacit assumption that if a targeted drug works in one context (such as colon cancer) that contains that aberration, it will work in others (such as breast or lung). At present, although appealing, this assumption is far from proven with any level of evidence.

Despite these concerns, tumor profiling is gaining traction within the oncologic community. Some oncologists’ practices advertise the availability of such testing, to attract patients. Some research-minded cancer centers perform tumor profiling on the majority of their patients to facilitate both investigator-initiated as well as pharmaceutical-sponsored clinical trials. This practice may make the center more attractive as a clinical research site that will provide “free” screening for a clinical trial of a drug targeting a rare aberration. In contrast, other clinical centers have been slow to take up routine tumor profiling, citing lack of demonstrated clinical utility and unclear reimbursement by third-party payers.

**Clinical Studies to Test Genome Medicine Hypotheses**

Scientists and clinicians alike are familiar with the scientific method. We believe that genome medicine should be subjected to hypothesis-driven scientific inquiry, and that the hypotheses tested should emphasize improved patient outcomes. In the past, oncologic drugs were tested in trials in which patients were first selected based on histology (breast, colorectal, and lung) and then, if possible, within subgroups that were enriched by biologic factors that were known or felt to be likely to predict benefit from the specific agent being tested. For example, in the last decade, clinical trials of endocrine therapy in breast cancer have only been performed in patients with ER-positive disease. Genomic medicine trials may or may not be histology based; patients are selected for the trials using tumor profile panels or complete genomic sequencing. Below, we provide some examples of hypotheses and trial designs in genome medicine.

**Hypothesis 1: Drugs “A–Z” will provide clinical benefit to patients with -omic aberrations "a–z," in histologic context *1–10*"**

This basic question embodies the challenge of clinical research in genome medicine. Hundreds of separate clinical trials would be necessary to evaluate all of the potential "omics"/drug matches in all of the different cancer types, and this number will continue to increase. Besides the large number of trials, another challenge is the large number of patients that need to be screened to perform any single “AA” match trial. Furthermore, if single-factor biomarkers are utilized, a patient’s tumor tissue may need to be accessioned multiple times for multiple trial screens. One side benefit of the widespread uptake of tumor profiling may be the more efficient identification of patients to participate in exploratory clinical trials of "omics"-targeted therapy.

Many investigators interested in genome medicine have suggested a move toward “histology-agnostic” trials that allow participation of patients with multiple tumor types in a single trial. Some pharmaceutical companies have adopted this approach and
have begun to take advantage of the tumor profiling being done at some centers, to identify patients to participate in so-called ‘bucket’ or ‘basket’ trials (Fig. 2A). These trial designs draw from a large population of screened patients to identify a few whose tumors have specific "omics" aberrations for treatment with a targeted drug. There have been some notable successes with this experimental approach, even leading to drug approvals with very small patient numbers tested. For example, imatinib is famous for being approved in a histology-specific biomarker-driven way for chronic myelogenous leukemia and gastrointestinal stromal tumor. However, less widely known is the fact that imatinib is also approved by the FDA for a host of other ultra-rare malignancies based on a phase II trial that allowed diverse tumors with associated genomic abnormalities (10, 11). An extension of the bucket/basket trial concept is the simultaneous study of multiple targeted drugs across multiple histologies, such as is proposed in the Molecular Analysis for Therapy Choice (NCI-MATCH; ref. 12) project, which is under development in the National Clinical Trials Network (NCTN). NCI-MATCH will prospectively enroll about 3,000 patients with multiple histologic cancer subtypes, whose disease has progressed on at least one line of standard therapy. Patients will undergo a research-related biopsy for NGS, which will be performed in specified reference laboratories. The trial aims to develop a longitudinal cohort of

![Figure 2](https://example.com/figure2.png)

**Figure 2.** A, illustration of a “bucket” or “basket” trial. This trial design tests a specific “omics”/drug match across multiple histologic subtypes. B, illustration of an “omics master protocol.” A master protocol may include multiple embedded clinical trials, each testing specific “omics”/drug matches, and may also provide uniform “omics” testing for the participants. In this illustration, the embedded trials test targeted therapy against a standard therapy within a specific histologic subtype. C, illustration of an “omics strategy trial.” This trial design tests whether the strategy of assigning patients to a therapy based on their “omics” profile provides better outcomes than existing standard therapy without consideration of “omics” profile. D, observational study. Patients receiving oncology care, which may include routine “omics” testing and off-label use of targeted therapies, agreed to have their “omics,” treatment, and outcomes data submitted for retrospective hypothesis testing.
patients with multiple histologies who can be matched to one or more embedded single-arm drug trials that are biomarker guided.

In recent years, “master protocols” (Fig. 2B) have been developed to allow the exploration of multiple “omics”/drug matches of interest within a single histologic context. Master protocols provide a single molecular screening point to identify “omics” aberrations that could make the patient eligible for one or more targeted therapy trials. New trials can be added within the master protocol after some embedded trials meet their endpoints and are closed, or if new “omics”/drug matches become available. For example, the NCI, the NCTN, patient advocacy groups, and industry have worked together to develop the “S1400 Biomarker-Targeted Second-Line Therapy in Treating Patients With Recurrent Stage IIIB–IV Squamous Cell Lung Cancer” (LUNG-MAP) protocol (13). In LUNG-MAP, tumor genome profiling is provided to a population of squamous cell carcinoma of the lung (SCCL) patients following failure of first-line chemotherapy. The genome profile results are linked to eligibility in a suite of clinical trials; each embedded clinical trial has the potential to lead all the way to regulatory approval of both the drug and the “omics” assay, if efficacy is demonstrated. There is considerable interest in the master protocol approach in other histologies as well, as it is viewed as a way to provide access to uniformly performed tumor profiling as well as to reduce the regulatory burden of maintaining multiple targeted therapy clinical trials within a cancer type.

Hypothesis 2: Off-label use of currently available targeted therapy based on tumor profiling will lead to better patient outcomes compared with standard therapy

Investigators have wrestled with study designs to test Hypothesis 2; in the meantime, some oncologists have moved ahead at the assumption that Hypothesis 2 is correct, and have begun prescribing off-label. Proponents of off-label prescribing cite frustration with the slowness of bringing new treatments to patients in dire need. Conversely, the potential harm of this practice is that, based on their tumor profile, patients may be offered a targeted therapy that may be ineffective, toxic, and costly. Worse, such an approach might be taken with patients for whom standard therapy with demonstrated clinical benefit exists, denying them the proven potential benefit.

Recognizing that this practice is already occurring, some investigators have proposed studying the outcomes of patients treated in this manner. A strategy trial (Fig. 2C) randomizes patients to therapy that is “matched” to a commercially available targeted therapy based on the tumor profile, versus to a treatment that represents the current standard of care. A strategy trial is not powered to test the specific aA-zZ matches, but focuses instead on testing the clinical outcomes of populations of patients that have a treatment assigned based on tumor profiling; thus, no single biomarker is ever evaluated, just the conglomeration of all that were in the panel.

As an example of a strategy trial, the NCI’s intramural program has launched a study entitled “The Molecular Profiling-based Assignment of Cancer Therapeutics,” or M-PACT, trial (14). In this trial, patients with advanced refractory solid tumors will be screened with an assay to sequence 20 genes “known to affect the utility of targeted therapies.” One hundred eighty patients with a biomarker of interest will be randomized either to (i) a drug from the set corresponding to one of the predetermined mutation/amplification categories, or (ii) a drug chosen, by physician choice, from the complementary set (not corresponding to one of the mutation/amplification categories). The primary outcome measure is a comparison of the response rate and/or 4-month progression-free survival between the arms.

The problem with the strategy trial approach is that, although some promising “omics”-directed treatments in specific tumor types might be included within the “profile strategy” arm, the overall strategy will fail to show benefit over standard of care if only a small subset of the “omics”/drug matches yield positive results. In other words, the “profile strategy” arm is only as good as the sum of the individual treatments included. In addition, strategy trials may not be ethical in situations where targeted therapy is already known to be advantageous for patients.

Others have proposed observational studies of the off-label use of targeted therapies, illustrated in Fig. 2D. Recently, led by Richard Schilsky, the American Society of Clinical Oncology has proposed a community-based off-label drug registry, designated the Targeted Agent and Profiling Utilization Registry (TAPUR, ref. 15). Although details about this initiative are still being developed, such an approach is a pragmatic strategy to at least capture data regarding the use of tumor profiling to guide treatment outside of clinical trials. However, there are considerable challenges to collecting such data outside of a clinical trial, especially data on toxicity, response rate, and progression. These challenges will need to be addressed in the design of the registry to make the data useful for testing hypotheses.

Conclusions

In conclusion, we believe that genome medicine is revolutionizing cancer care and has enormous potential to improve patient outcomes. However, there are many opportunities for mistakes to occur in its incorporation into the standard of care, especially if we charge forward assuming clinical utility without taking the time to objectively assess patient outcomes. It is essential for clinicians, clinical trialists, clinician-scientists, and basic scientists to continue hypothesis-directed pursuit of new biomarkers and targeted therapies, but in order to do so we must better understand each other. Unified by a common nomenclature, we will reach our goals more quickly.

NOTE: In this commentary, we have included specific industry-marketed products as examples of different types of genomic tests that are available. Recognizing that we have not made an effort to be all-inclusive, we regret if we have overlooked a specific assay or trial that is available. Further, our comments are provided as examples and do not represent an endorsement of these products for routine care.

Disclosure of Potential Conflicts of Interest

C.M. Perou is in board of directors of, has ownership interest (including patents) in, and is a consultant/advisory board member for Bioclassifier LLC/University Genomics. D.F. Hayes reports receiving commercial research grants from AstraZeneca, Janssen R&D, Pfizer, and Puma; speakers bureau honoraria from Eli Lilly; has ownership interest (including patents) in OncImmune (stock options) and Inbiomotion; is a consultant/advisory board member for Pfizer; and has provided expert testimony on three patents for circulating tumor cells licensed by the University of Michigan Comprehensive Cancer Center to Janssen. No potential conflicts of interest were disclosed by the other author.

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