Biomarker Validation

Research Advocacy Network
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Introduction

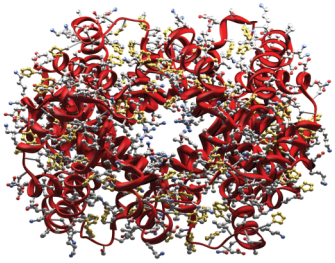
Biomarkers are increasingly used in all areas of medicine to help better predict, characterize, and treat disease. In cancer, biomarkers are often used to help us make medical decisions such as whether or not to undergo chemotherapy, or whether a given medication is likely to be effective for us. Given this important role, it is critical that biomarkers be as accurate as possible.

Biomarker validation refers to the process by which biomarkers are tested for their accuracy and consistency, as well as their ability to tell us something important about our health or disease. Although there is no one single measure that can be used to determine the validity of all biomarkers, there are general criteria that all biomarkers must meet in order to be useful. In the following text, we review the definition of biomarkers and discuss the components of validity. We then examine the methods by which biomarkers are validated and consider some examples of cancer biomarkers in use today. We conclude with information about situations where advocates might find this information useful.

What are Biomarkers?

Before delving into biomarker validation, it may be useful to review exactly what biomarkers are. Definitions abound, and even different groups within the National Institutes of Health do not always agree on what constitutes a biomarker. Given the evolution of technologies that allow us to view the body and its workings ever more precisely, it is probably best to consider a broad definition of biomarkers instead of a narrow one. One good definition comes from the Biomarker Consortium, a Foundation that operates under the rubric of the National Institutes of Health:

> **Biomarkers** are characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic interventions.



Protein Structure

Under this definition, biological molecules such as proteins can be biomarkers, as can physiological processes such as blood flow. Findings from imaging technologies—essentially pictures of the body—also qualify as biomarkers as long as they are objectively measured and used for one of the purposes stated above.

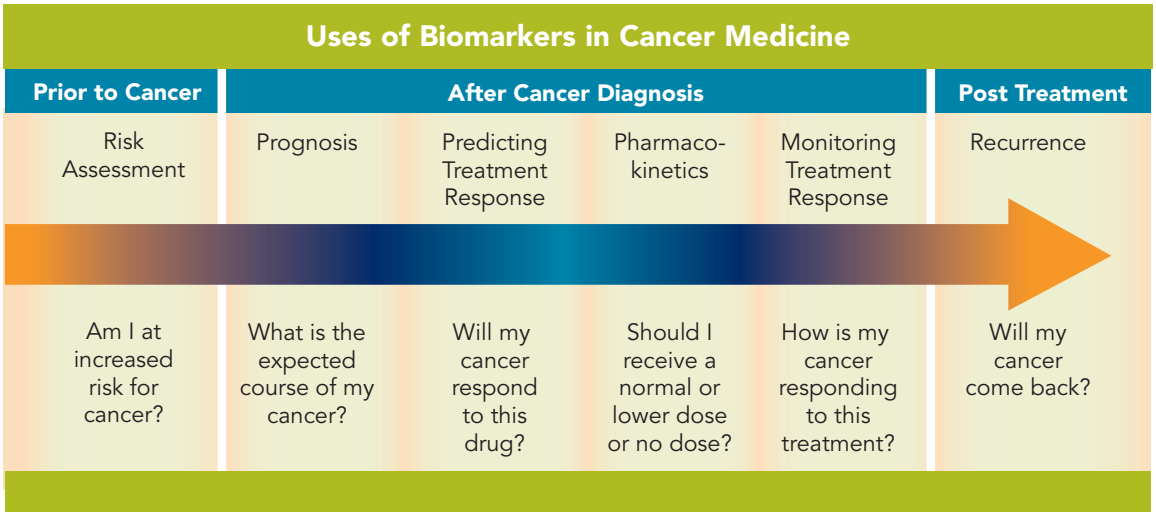
In cancer medicine today, biomarkers are often proteins. Examples include CA 125, which may be used as a biomarker for ovarian cancer, and prostate specific antigen levels, which may be used as a biomarker for prostate cancer. The following table lists examples of biomarkers that represent different types of biological compounds or processes.

Examples of Some Biomarkers

Biomarker	Type	Condition
C reactive protein	Molecular/biochemical	Inflammation
High cholesterol	Molecular/biochemical	Cardiovascular disease
S100 protein	Molecular/biochemical	Melanoma
HER2/neu gene	Molecular/biochemical	Breast cancer
BRCA genes	Molecular/biochemical	Breast and ovarian cancers
Prostate Specific Antigen (PSA)	Molecular/biochemical	Prostate cancer
CA-125	Molecular/biochemical	Ovarian cancer
Cerebral blood flow	Physiologic	Alzheimer disease, stroke, schizophrenia
High body temperature	Physiologic	Infection
Size of brain structures	Anatomic	Huntington disease

What Are Biomarkers Used For?

Biomarkers have many different uses in cancer medicine, as shown in the graphic below. They may be used to help determine a person's risk of getting cancer, determine the expected course of cancer (eg, its aggressiveness), determine response to certain drugs, determine the risk of side effects to certain drugs, monitor treatment response, or predict risk of cancer recurrence. Some biomarkers have more than one use.



What is Validation?

Validation is the process of determining how well a test or process measures, represents, and/or predicts something else. Validation is not specific to biomarkers, but instead applies to all types of tests and measures. For example, in order to get our driver's license, we are required to pass a test. In order to be valid, the driver's test must accurately determine whether we know how to drive and follow the rules of the road. If we went into the licensing bureau and were given an arithmetic test, it would not be a valid measure of our driving skills—it would not measure what it is supposed to measure. It would also not be a good measure of the intended outcome: whether or not we know how to drive and follow the rules of the road.

Validation:
The process of determining how well a test or process measures, represents, and/or predicts something else.

Specificity:
The ability of a test to give a negative result when the thing we are looking for is not present. Said another way, a specific test only gives a positive result when the person has a given biomarker.

Sensitivity:
The ability of a test to detect the something when it is actually present.

Validity has a number of different components. Here we focus on four components that are particularly applicable to tests that measure cancer biomarkers: sensitivity, specificity, analytical validity, and clinical validity.

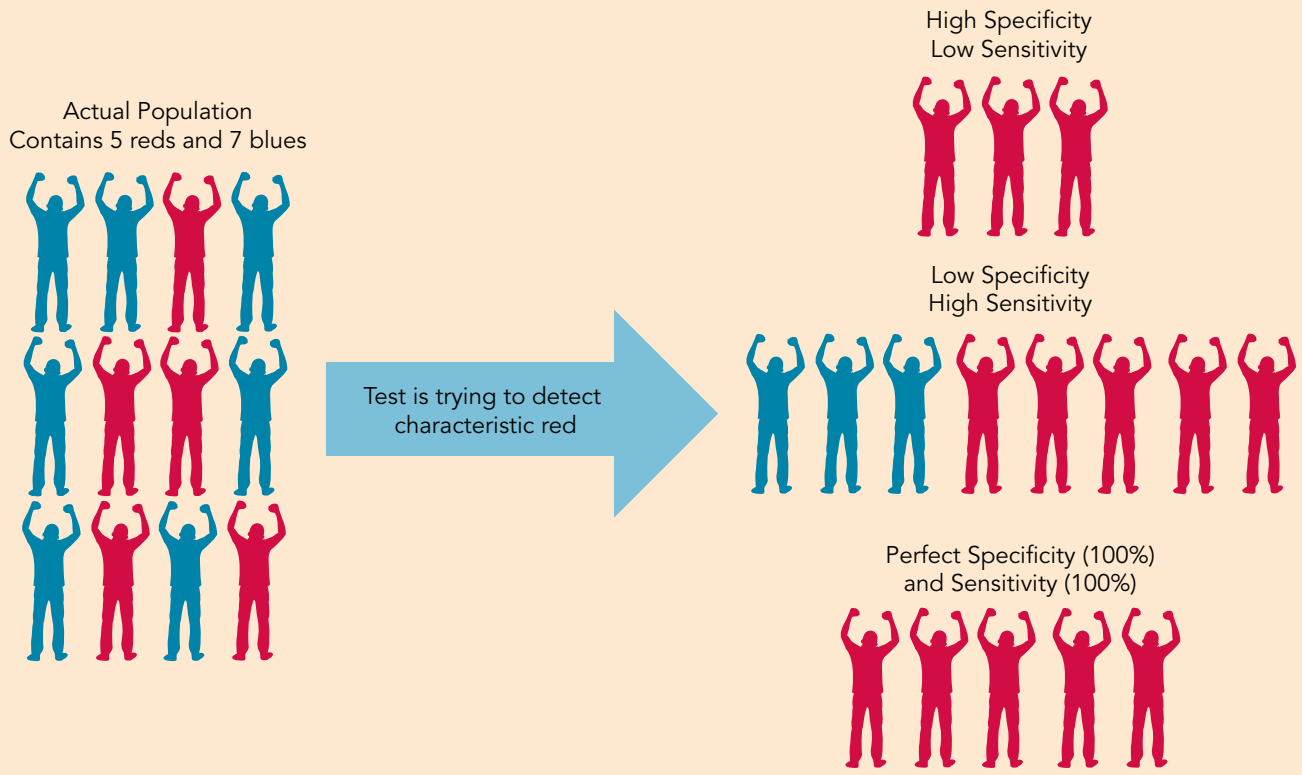
Test sensitivity and specificity

Test sensitivity and specificity are usually considered together because they are essentially two sides of the same coin. A test is specific if it gives a positive result only if the biomarker is present and gives a negative result when the biomarker is not present. A test is sensitive if it gives a positive result every time the biomarker is present.

For diseases such as cancer, it is often difficult to identify biomarkers that are both specific and sensitive. We may find that a candidate biomarker is associated not only with cancer, but also with other diseases or conditions. In this case, the presence of the biomarker would not necessarily tell us if a person has cancer; he or she may have some other condition that causes the same biomarker to be

present. In this case, the biomarker does not have good specificity. On the other hand, a biomarker test may accurately detect some of the people who have the biomarker, but may miss others who also have the biomarker. In this case, the test lacks sensitivity. Ideally, we would like biomarker tests that are 100% specific (only detects people with the biomarker) and sensitive (detects all people with the biomarker).

Example of Test Specificity and Sensitivity



In this example population, some of the people have the characteristic red, whereas others have the characteristic blue. Let's assume that we are trying to detect the characteristic red because it is a biomarker for response to a cancer drug. In the actual population, 5 people have the characteristic red and 7 have the characteristic blue. A test with high specificity would give a positive result only for the red characteristic; it would not give a positive result for any blues. However, in the top example, the test has low sensitivity because it misses two of the reds. The middle example shows a test with high specificity and low sensitivity. This test would detect all of the reds (high sensitivity) but would also include some blues (low specificity). The bottom example shows the results of an ideal test. This test would have perfect sensitivity and perfect specificity: It would detect all of the reds and none of the blues. In the real world, few tests ever achieve perfect sensitivity and specificity.

Analytical validity:
How well the test measures what it is supposed to measure.

Clinical validity:
How well the test predicts a clinically important outcome.

Analytical validity

Analytical validity refers to how well the test measures what it is supposed to measure. Test sensitivity and specificity are essential components of analytic validity. Any test, whether it be for a cancer biomarker, driving ability, assessing intelligence, or determining pregnancy, must show analytical validity in order to be useful. The analytical validity of a newly developed test is often judged by comparing the results to those obtained from the best available test, sometimes referred to as the "gold standard."

Clinical validity

Clinical validity is another important aspect of biomarker validation. Clinical validity refers to the ability of the test to accurately predict a clinically important outcome. Often, a clinically valid test will correlate with improvement in patient care.

A good biomarker test must have both analytical and clinical validity. A biomarker test that has high analytic specificity and sensitivity is no good if the result doesn't tell us something important about our health status. For instance, a test may be very good at detecting whether we have a certain protein in our blood—let's say an antibody against the flu virus. It has good analytical validity. That test may be good at predicting whether or not we will get the flu (clinically valid for the flu), but may not tell us anything about whether we are likely to get cancer (not clinically valid for cancer).

As with analytical validity, sensitivity and specificity are also important measures of clinical validity. A biomarker with ideal clinical validity would detect 100% of the people who would eventually have a certain outcome such as response to treatment or cancer recurrence within 5 years, and 0% of the people who would not. As noted previously, in real life, biomarkers are not this accurate, and it is typically a judgment call of whether the analytical and clinical validity make the use of a biomarker worthwhile in routine medical use.

Test Reliability

Test reliability is a concept that is often discussed along with test validity. Test reliability means that the results of the test are repeatable. A tire pressure gauge that shows your tire pressure to be 32 pounds per square inch one minute and 14 pounds per square inch the next is not reliable. Because biomarker tests often require precise measurements, complicated equipment, and/or different mixtures of chemicals, reliability can be difficult to achieve. Ideally, tests would be standardized, meaning that they would be performed exactly the same way on the same equipment with the same chemicals each time. However, this is often not the case for biomarker tests. In order to get around this problem, some companies that have designed biomarker tests require that samples for testing be sent to the company's own laboratory. In this case, the biomarker testing can be standardized – performed the same way each time – and the company has control over the reliability of their test results.

Reliability:
The ability of a test to give the same answer every time.

Clinical utility:
The benefits versus drawbacks of a test in the context of clinical use.

Clinical Utility

Another important concept in the area of biomarker development has to do with the benefits and drawbacks of a test in the context of clinical use. This is known as clinical utility. Biomarker tests should provide some sort of benefit to patients in order to have clinical utility. For example, they must aid in diagnosis, treatment selection, outcome prediction, or another medically important variable. However, in order for a biomarker test to show clinical utility, demonstration of benefit is not enough—the benefits of the test must also outweigh its drawbacks. In some cases, biomarker tests that require multiple samples of tumor cells (eg, from a brain or pancreatic tumor) may be too invasive and therefore may lack clinical utility.

Additionally, the test must be feasible for use in clinical practice. If a reliable and valid test is developed but samples must be sent from the United States to India for analysis, it may not have clinical utility. Similarly, if the test requires 2 years to get the results or is prohibitively expensive, it may lack clinical utility.

Biomarker Development

The process of biomarker development can be divided into 6 steps: discovery of a candidate biomarker(s), qualification, verification, research assay optimization, biomarker validation, and commercialization. This process, as outlined by Dr. Rifai and his colleagues from Boston, refers specifically to protein biomarkers because these are currently the most promising class. However, it may be possible to adapt this general process to other types of biomarkers as they become more widespread.

Candidate discovery

The discovery of candidate or putative biomarkers is the unbiased process by which different levels of certain proteins are found to occur in disease or health. For instance, we may find that healthy people have low levels or one or more proteins in their blood, whereas people with cervical cancer have high levels. Alternatively, differential levels of proteins may signal a more or less aggressive cancer, or one that is responsive to certain types of treatment. Such candidates are usually found by comparing healthy and diseased tissue.

Qualification
This phase of biomarker development is concerned with the consistency of the biomarker. First, the biomarker must be consistently found to differentiate tissues (eg, healthy vs. cancerous) using different methods. Second, it must show differential levels of the biomarker in blood if the discovery was not initially performed in blood. For example, if the discovery was initially found in tumor tissue vs. normal tissue, it must be confirmed in blood—specifically, the liquid portion of the blood called plasma. In the qualification phase, biomarker sensitivity (the likelihood that a tissue affected with the condition you are studying will test positive) is of greater importance than specificity (the likelihood that an unaffected tissue will test negative).

Verification
The verification phase is a testing of the biomarker in a larger number of human blood samples—at least hundreds. This phase further confirms biomarker candidate sensitivity, but also begins to consider biomarker specificity (ability to correctly identify a tissue sample as negative).

Research assay optimization
In this stage, alterations are made to the biomarker test in order to make it better. These changes may improve the sensitivity of the test and enhance its ability to assess numerous samples quickly. Few candidate biomarkers make it to the test optimization stage.

Validation
In the validation stage, a form of the biomarker test designed for research (research grade) is used to evaluate thousands of samples from individuals representing the full population for which the test is ultimately intended (eg, women with stage 2 breast cancer). The validation stage takes the form of a clinical study or studies in which the ability of the biomarker to predict some important clinical outcome is evaluated.

Validation studies must be conducted for each potential use of a biomarker. The level of evidence needed in the validation stage varies depending on the intended use of the biomarker. If a biomarker is being used as supporting clinical evidence, the level of validation required is lower than if the biomarker is being used as a complete substitute for a clinical endpoint (called surrogate endpoint).

Surrogate endpoint: use of an endpoint to substitute for a historically established clinical endpoint; for example, use of a biomarker to substitute for progression free survival in cancer.

Candidate biomarkers can be validated by looking at the tissues and outcomes of a study that has already been conducted or by conducting a new study. If the study has already been conducted or the data has already been collected outside the context of a study (eg, patient records), it is called retrospective. If the study is conducted going forward, it is called prospective.

For instance, validation can be done retrospectively by looking at blood or tumor tissue from individuals for whom the disease outcome is already known, Alternatively, a study may be conducted in which participants provide their blood or tumor tissue as part of the study and their outcomes are followed into the future. Although prospective studies are considered the gold standard in biomedical research, they are expensive and time consuming. For biomarker validation, retrospective studies provide an important alternative that helps speed biomarker development while preserving the validation requirement.

An additional important point of validation is that the ability of the biomarker to predict the clinically relevant outcome must be tested in a population of patients that is different from the population in which the biomarker was originally identified.

Commercialization and regulatory pathway

Biomarkers that have been validated in the laboratory may be commercialized, or made available for clinical use. Prior to commercialization, the research assay (test that measures the biomarker) must be further optimized so that it meets the strict requirements needed for clinical tests.

The regulatory pathway for biomarkers and the tests that measure them are complex and differ from the process for approval of drugs and therapeutics. The pathway to FDA clearance or approval is dependent on the intended use of the test. These types of tests are often considered in vitro diagnostics (IVDs). The FDA Office of In Vitro Diagnostics (OIVD) usually handles the regulatory process for these types of tests. IVDs are considered medical devices as by the FDA and may also be biological products which make them subject to other regulations (section 351 of the Public Health Service Act). Like other medical devices, IVDs are subject to premarket and postmarket controls.

The FDA defines in vitro diagnostics as "tests that can detect diseases, conditions, or infections. Some tests are used in laboratory or other health professional settings and other tests are for consumers to use at home." The FDA classifies these IVD products into "classes" according to the level of regulatory control that is necessary to assure safety and effectiveness. For an overview of the IVD Process at FDA go to: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm123682.htm#4

Biomarker tests may be available through physicians or as commercial products without a healthcare intermediary. The way that the test is packaged and sold is one factor that determines whether it is available through physicians or is sold directly to the consumer.

Biomarker tests are usually classified as kits (also referred to as products or devices) or as services. If the physical materials to conduct the biomarker test are provided to physicians so that they can perform the tests in their offices or affiliated laboratories, the test is considered a kit. This is also true for biomarker tests sold directly to the public for home use, such as pregnancy tests. If the tissue sample must be sent to a company's laboratory for analysis, it is considered a service.

Whether a biomarker test is sold as a kit or service determines the type of regulation to which it is subject. Tests sold as kits must be approved by the US Food and Drug Administration (FDA). The level of scrutiny to which the test is subjected depends on its use. For example, pregnancy tests are associated with minimal potential harm to the consumer, so they are scrutinized at a minimal level. Cancer diagnostic tests have high potential for harm so they are highly scrutinized. This is an area in which advocates may be helpful in working to streamline the regulatory process while still ensuring adequate biomarker validation. This can be done by commenting on guidance documents or participating in the FDA Office of Special Health Initiative programs or similar committees.

Biomarker tests sold as services and IVDs are also subject to the Clinical Laboratory Improvement Amendments (CLIA). CLIA regulations specify the conditions that all laboratories must meet in order to be certified to perform testing on human specimens, and were developed to ensure quality laboratory testing. The CLIA requirements vary according to the technical complexity in the testing process and risk of harm in reporting erroneous results. CLIA labs performing moderate or high complexity tests are subject to specific laboratory standards governing certification, personnel, proficiency testing, patient test management, quality assurance, quality control, and inspections. CLIA certification applies to the performance of the test and does not indicate the clinical performance or safety and effectiveness of the biomarker. Manufacturers apply for CLIA certification during the pre-market process. It is important for advocates to understand what CLIA approval does and does not mean when discussing the development and use of biomarker tests.

Some biomarkers are used to identify who would respond to a certain drug or therapy (example, HER2 in breast cancer and recently ALK in lung cancer and BRAF in melanoma). These types of biomarker tests are called "companion diagnostics." In July 2011 the FDA issued a draft guidance concerning the development of companion diagnostics (to see the guidance document go to: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262292.htm. The guidance intends to assist sponsors who are developing a therapeutic product that depends on the use of an in vitro companion diagnostic device (or test) for its safe and effective use and is intended to be used with a corresponding therapeutic product.

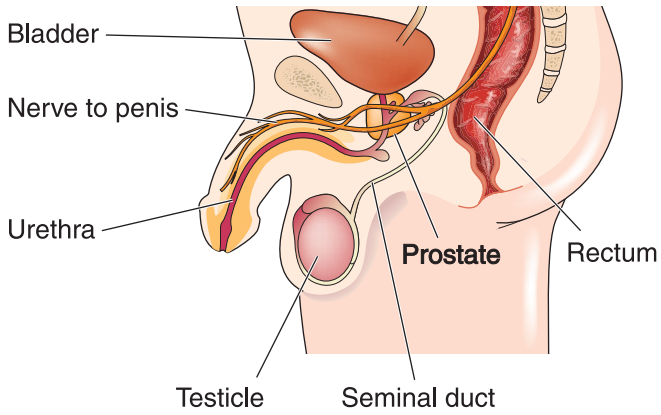
Also, some genomic tests such as Onco*type* DX or Mammaprint are offered to help determine the risk of recurrence and to aid in the treatment decision making process. The tests are based on a panel of genes (multi gene signatures). The validation process of the gene panels that comprise the respective tests was done through a retrospective analysis and verified in prospective clinical trials. In the past there has not been a clear regulatory pathway for these multi gene signature tests. The FDA is working to clarify this process. In addition, recent events have led to an Institute of Medicine report that will make further recommendations about "omics-based" tests. Advocates should watch for the publication of the IOM report and other draft guidance and regulatory announcements from FDA that are open for public comment.

Examples of Cancer Biomarker Reliability and Validity Issues

Let's turn to a few examples of cancer biomarkers that illustrate some of the difficulties with reliability and validity issues that we've been discussing.

Example #1: Prostate Specific Antigen
The prostate is a gland that makes up part of the male reproductive system. Cells of the prostate produce prostate specific antigen (PSA), a protein that can be detected at a low level in the blood of all adult men.

Anatomy of the Prostate and Nearby Structures



Several medical conditions can increase the levels of PSA in the blood. These conditions include inflammation of the prostate, benign prostatic hyperplasia (enlargement of the prostate), and prostate cancer. The link between high levels of PSA in the blood and prostate cancer led to the use of this biomarker for prostate cancer screening and the monitoring of recurrence. The United States Food and Drug Administration has approved the PSA test to be used along with a digital rectal exam to help detect prostate cancer in men 50 years of age and older. The goal of these screening tests is to help identify prostate cancer before symptoms appear.

Although the PSA test has been used as a biomarker for prostate cancer since 1986, its value as a screening tool is controversial for several reasons. The first concern is that high levels of PSA are not specific to prostate cancer, but rather can be due to a number of different conditions. That is, the specificity of PSA as a biomarker is not very high. This was illustrated in a study conducted by researchers at Washington University in St. Louis. Researchers tested the PSA levels of 30,000 men in the community. Results showed that 25% to 33% of the men who had high PSA levels in their blood had prostate cancer. This means that 67% to 75% of the men in this study with high PSA levels did not have prostate cancer.

The problem with low specificity is that it can lead people to undergo additional medical procedures unnecessarily. For instance, men with high PSA levels and/or abnormal findings on a digital rectal exam may elect to undergo a needle biopsy. Such biopsies can cause stress and anxiety and are associated with financial costs. Although prostate needle biopsies are relatively safe, they can cause severe bleeding or infection of the prostate gland or urinary tract in 1% of patients. Thus, these tests are not without drawbacks and risks and, as with all tests, it is best to minimize the number of patients who undergo them unnecessarily.

It should be noted that there is less controversy in the use of PSA levels for monitoring cancer recurrence, with most experts agreeing that the test is useful for this purpose. However, the use of PSA testing as a screening tool illustrates the challenges with biomarkers that have low specificity.

Example #2: HER2

Approximately one quarter of breast cancers are characterized by overexpression of a gene called HER2. This overexpression leads cells to produce too much HER2 protein. Breast cancers that overexpress HER2 often respond to trastuzumab, a drug that inhibits the activity of the HER2 protein. However, this drug does not work on breast cancers that do not overexpress HER2. As a result, HER2 may be used as a biomarker for response to a specific treatment – trastuzumab.

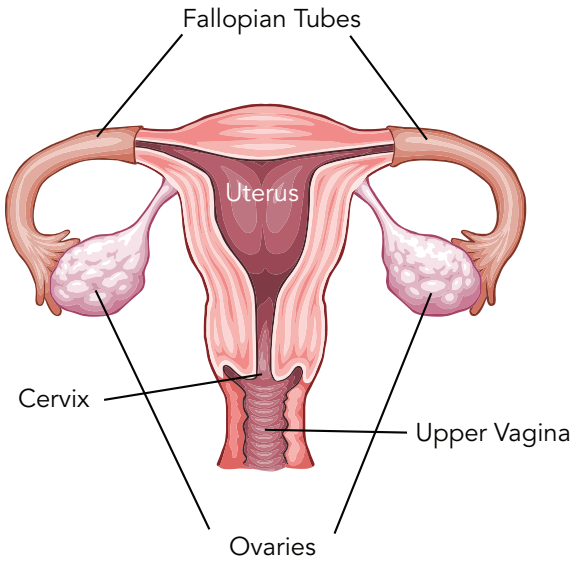
Two different types of tests may be used to detect HER2 overexpression. One test uses a method called immunohistochemistry (IHC), which measures the level of HER2 protein on the outside of tumor cells. The other method used to detect HER2 is called FISH (fluorescence in situ hybridization). This method measures the underlying gene alteration in the tumor cells instead of the protein.

Whereas the problem with PSA was that the actual biomarker was not specific for the prostate cancer, the problems with HER2 appear to be related to the tests for the biomarker rather than the biomarker itself. One problem with the HER2 tests is that they do not always give the same result for the same specimen—a problem with reliability. Guidelines from the American Society for Clinical Oncology (ASCO) and College of American Pathologists (CAP) state that 20% of current HER2 testing may be inaccurate. This means that some women who initially test negative for HER2 overexpression may actually overexpress HER2 and vice-versa.

Many variables can affect the outcomes of HER2 tests. One variable is the collection of the tissue sample – it is important that the sample contain only cancerous cells and not normal cells that may surround the borders of the tumor. Additionally, many laboratory- and technique-related variables can affect the two different methods. The National Comprehensive Cancer Network (NCCN) indicates that both tests can be performed successfully if adequate controls and verifications are in place. They indicate that strict quality control and assurance measures must be conducted by each laboratory performing these tests for clinical purposes, including formal test validation and concordance studies. ASCO and The College of American Pathologists also recommend formal validation of laboratory assays for HER2 testing, in addition to the use of standardized operating procedures and compliance with defined testing criteria. According to published guidelines, compliance with these procedures should be monitored via the implementation of strict laboratory accreditation standards and ongoing proficiency testing.

Example #3: CA125
A third example of a biomarker in clinical use today is CA-125 or cancer antigen-125. This biomarker is a protein that may be found in high amounts in the blood of patients with certain types of cancer, including ovarian cancer.

Anatomy of the Ovaries and Nearby Structures



Unfortunately, the use of CA-125 as a biomarker for ovarian cancer is not specific – the same problem we saw with the use of PSA. Elevated levels of CA-125 can be associated with many other conditions, including diverticulitis, endometriosis, liver cirrhosis, normal menstruation, pregnancy, uterine fibroids, and non-ovarian cancers. In fact, an expert panel concluded that 98% of women in the general population who show abnormal CA-125 levels in their blood do not have ovarian cancer. Because of this extremely high false positive rate, CA-125 is not currently recommended as a general screening test for individuals without a history of ovarian cancer.

Another problem with the use of CA-125 is that there is very little evidence to suggest that earlier detection of ovarian cancer will delay death. Thus, its clinical validity as a biomarker to help prolong a patient's life is not established.
The current recommendations for CA-125 are that the test should not be used to screen for ovarian cancer because of the low prevalence of this cancer and the invasive nature of diagnostic testing that would likely follow a positive test. The government's expert panel concluded that the potential harms of CA-125 testing for ovarian cancer screening outweigh its benefits.

Similarly, study results that became available in 2009 called into question the clinical validity of using CA-125 levels to monitor recurrence. In this study, women were treated for recurrent ovarian cancer either when their CA-125 levels became high or when they exhibited clinical symptoms or signs of ovarian cancer. Results showed no difference between groups in the duration of survival. That is, the earlier treatment given to women when their CA-125 levels increased did not increase the length of life compared with women who were given treatment later when they began to show symptoms. Thus, knowing one's CA-125 levels may not be clinically useful.

Institute of Medicine Reports on Biomarkers

In recognition of the importance of biomarker development to healthcare advances, the US Food and Drug Administration asked the Institute of Medicine to develop a consensus statement on biomarker evaluation. This resulted in recommendations for biomarker evaluation that were published on the Web and can be accessed at the following link: http://iom.edu/Reports/2010/Evaluation-of-Biomarkers-and-Surrogate-Endpoints-in-Chronic-Disease.aspx. The report recommended that biomarker evaluation consist of the following steps:

- Analytical validation: analyses of available evidence on the analytical performance of an assay;
- Qualification: assessment of available evidence on associations between the biomarker and disease states, including data showing effects of interventions on both the biomarker and clinical outcomes; and
- Utilization: contextual analysis based on the specific use proposed and the applicability of available evidence to this use. This includes a determination of whether the validation and qualification conducted provide sufficient support for the use proposed.

A more recent Institute of Medicine report is now available on omics-based tests for predicting patient outcomes in clinical trials. Omics tests refer to tests based on the so-called omics sciences such as genomics, proteomics, and metabolomics. The report was released March, 2012 and is available on the Web at the following link: http://iom.edu/Activities/Research/OmicsBasedTests.aspx.

The Center for Medical Technology is also working on guidance document that will provide recommendations for methods used to conduct comparative effectiveness research studies of molecular diagnostics in oncology. This guidance document, which is not yet available, is intended to focus on features that are important to clinical and health policy decision making. According to the Center for Medical Technology's Web site, "The overarching goal of the guidance document is to provide these decision makers with a reasonable level of confidence that the intervention improves net health outcomes." Advocates who are interested in working with this organization may want to consider joining on the working groups. You can learn more about these groups by clicking on the "Get Involved" tab on the organization's Web site: http://cmtpnet.org/.

Status of Biomarkers

Although biomarkers have the potential to be extremely useful indicators of health and disease, their development is not proceeding as rapidly as we would like. For more than 10 years, new protein biomarkers approved by the US Food and Drug Administration have averaged only one per year. This slow progress contrasts with the huge advances in genomics that have occurred during this time, including the sequencing of the entire human genome.

The lack of useful new biomarker is most likely due to the arduous processes involved from biomarker discovery to a useful biomarker test, and the lack of a well-defined process for the entire sequence of biomarker development. Another important factor may be that blood—the preferred tissue for biomarker tests—contains proteins that occur in vastly different levels. For example, some proteins occur at levels that are a billion times higher than other proteins. It can be difficult to design tests that are able to screen out proteins at the higher levels while still being sensitive enough to detect proteins that are present at exceedingly low levels.

How Advocates Can Get Involved

As advocates, we want to improve the information available about a person's health status that can be used for making treatment decisions. We want to advance the development and approval of biomarkers, while making sure they are reliable and valid. The advocate's voice is important in deliberations regarding biomarkers because we remind people of the critical needs of patients and provide needed perspective about what patients want, how to involve patients in research, and patient quality of life issues.

Advocates can help by participating in a variety of different ways. In addition to suggestions for involvement mentioned in the text about commenting on guidance documents and participating in FDA Committees through the Office of Special Health Initiatives, advocates can be aware of efforts such as the Early Detection Research Network (http://edrn.nci.nih.gov/), Women's Oncology Research and Dialog (WORDs of Wisdom; http://wordoncancer.org/cms/word-site/multimedia/words-of-wisdom), the Center for Medical Policy Technology (http://cmtpnet.org/), or by participating in clinical studies. Advocates can also join Institutional Review Boards, Protocol Review Committees, Data Safety and Monitoring Boards, Study Sections at the National Institutes of Health, the Patient Representative Program at the US Food and Drug Administration, and many other organizations. For more information, you can contact Research Advocacy Network (www.researchadvocacy.org).

Summary

As our knowledge of genes and proteins has increased over the years, the identification of biomarkers has expanded, particularly in cancer medicine. In order to ensure that these biomarkers are useful for patients, they must be validated. That is, the results of biomarker tests must be valid and reliable. Does the biomarker test measure what it is supposed to measure? Does the test give the same result each time? Does the biomarker predict an outcome that is clinically important such as cancer recurrence, response to a cancer drug, or the aggressiveness of the cancer? Affirmative answers to these questions are critical in establishing the utility of biomarkers in cancer medicine and can only be given once adequate validation testing has been conducted.

Despite the immense clinical need for reliable and valid biomarkers, their rate of approval has been low over the past decade. The process spanning from discovery of candidate biomarkers to commercialization has been divided into 6 steps, each of which is critical in moving biomarkers toward availability for clinical use. In reality, few biomarkers pass beyond the verification stage and strategies are needed to overcome the current barriers.

Advocates can make a difference in biomarker development by participating on committees or in organizations that are generating guidelines for biomarker validation and commercialization. Ideas on how to participate are summarized in the preceding section and in the *Genomics in Cancer Training Manual* available from Research Advocacy Network (www.researchadvocacy.org). As advocates, we can speak to the urgent need for development of reliable and valid biomarkers in cancer and can provide the patient perspective to complement the concerns of other stakeholders such as the government, researchers, and medical professionals.

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