



AdvaMed**Dx**

Vital Insights | Transforming Care

DIAGNOSTIC EVIDENCE: Relevant Terms and Definitions

**Prepared For:
ADVAMEDDX**

**BY:
QUINTILES GLOBAL MARKET
ACCESS CONSULTING**



June 2012

Developing a Common Language for Diagnostics

Existing and emerging diagnostics are poised to play a key role in facilitating increasingly personalized health care, more efficient and cost-effective health delivery approaches, and improved health outcomes. A 2005 report by the Lewin Group (*The Value of Diagnostics: Innovation, Adoption and Diffusion into Healthcare*) noted that over 70% of patient treatment decisions are influenced by diagnostics.¹ Targeted application of health technologies is also increasingly in alignment with regulatory, payer and provider decision maker objectives as health care budgets tighten and the effectiveness and efficiency of care options and processes come under greater focus. As our knowledge of the role of biomarkers (that can be detected by diagnostics) increases, the potential for diagnostics to further shape and improve healthcare decision making is also increasing.

Despite the promise of diagnostics, the language of diagnostics can be unfamiliar or confusing for those not heavily involved in the industry. One key challenge in the diagnostic's area is that there needs to be a common and consistent terminology that decision makers and influencers can use when discussing issues relevant to diagnostics. A recent study of US payers and other health stakeholders conducted by Faulkner (2009)² indicated that payers variably define even common terminology associated with diagnostics. There are also a number of terms associated with the expanding area of personalized medicine that are also variably defined by multiple stakeholders, including those intimately involved in diagnostics and personalized medicine. When extrapolated out to the multiple stakeholders involved in policy making relevant to diagnostics, this inconsistent use and understanding of terms can result in unclear expectations and potentially misaligned or uninformed policy development.

Developing a more consistent terminology to support discussion of diagnostics, particularly in the context of evidence development and value assessment, would create a more consistent foundation for deliberation and appropriate policy making. The purpose of this diagnostic definitions document is to provide a common language in understandable terms that stakeholders can use in discussions regarding diagnostics policy development.

¹ The value of diagnostics: innovation, adoption and diffusion into health care. Prepared by the Lewin Group for the Advanced Medical Technology Association. Jul 2005

² Faulkner E. Clinical utility or impossibility? addressing the molecular diagnostics health technology assessment and reimbursement conundrum. J Managed Care Med. 2009; 4:42-55.

Table of Contents

Methods & Test Applications.....	5
Test use terminology.....	5
<i>Personalized Medicine, Diagnostics, Biomarker, Reagent, Analyte, In vitro Diagnostic (IVD) Test, Test Kit, Stand Alone Diagnostic, Companion Diagnostic, Point of Care (POC) Testing</i>	
Standard testing approaches.....	10
<i>Clinical Chemistry, Genetic Testing, Molecular Testing, Immunohistochemistry (IHC), In Situ Hybridization (ISH), Probe, Polymerase Chain Reaction (PCR), Pharmacogenetic</i>	
Common complex testing approaches.....	12
<i>Algorithm, Gene Sequencing, Multiplex Testing, Array Test, Circulating Biomarker, Proteomic Test</i>	
Test Performance & Value.....	15
Common test rationale / objectives.....	16
<i>Predictive Test, Screening Test, Prognostic Test, Test for Treatment Selection and Use, Monitoring Test</i>	
Test Performance.....	19
<i>Clinical Sensitivity, Clinical Specificity, Analytical Sensitivity, Analytical Specificity, Accuracy, Precision, Positive Predictive Value, Negative Predictive Value, False Positive, False Negative</i>	
Test validation and related terminology.....	22
<i>Analytical Validity, Clinical Validity, Clinical Utility</i>	
Diagnostic Assessors/Schemes.....	22
US FDA.....	22
<i>Humanitarian Use Device (HUD), Research Use Only (RUO), Analyte Specific Reagent (ASR), Investigational Use Only (IUO), Laboratory Developed Tests (LDT)</i>	

Note: This definitions document has been developed in a clear format that defines terms in simple language that does not require the reader to be expert in diagnostics and to ensure a common language is being used in policy-making or other discussions applicable to diagnostics. Some definitions have been reframed from more complex technical definitions to help the reader better understand the relevance of the terms in the context of clinical practice. The definitions included in this document are drawn from a variety of sources that are commonly accepted in the industry and are intended for use by a wide range of audiences. For some terms, multiple acceptable definitions and sources may exist. Therefore, while we have cited the sources used for the terms included herein, these sources and definitions should not be construed as the only available or acceptable definitions.

AdvaMedDx wishes to thank Eric Faulkner, Joshua Ransom and Arshi Gupta of Quintiles Global Consulting for their assistance in preparing this document.

Term	Definition	Source	Relevance and Context
<i>Methods & Test Applications</i>			
<i>Test use terminology</i>			
Personalized Medicine	The use of an individual's genetic or related molecular information to improve the safety, effectiveness, and health outcomes of that patient via more efficiently tailored prevention, diagnosis, and treatment decisions.	<p>National Institute of Health (NIH) http://ghr.nlm.nih.gov/glossary=personalizedmedicine</p> <p>International Society for Pharmacoeconomic and Outcomes Research (ISPOR) http://www.ispor.org/sigs/PM/ISPOR-Personalized-Medicine-SIG-DR_Wrkng-Grp_Manuscript.pdf</p>	<p>Personalized medicine primarily involves testing for genetic or other factors that reflect risk for disease / disease characteristics specific to that patient. Testing may involve information from one or more diagnostic tests to characterize the - appropriateness of a specific treatment for a specific patient.</p> <p>The adoption of personalized medicine has led to increases efforts to identify new biomarkers across tumor types. For example, measurement of well-established biomarkers such as, the epidermal growth factor receptor (EGFR) and the human epidermal growth factor receptor 2 (HER2) in breast, lung and colorectal cancer patients are taken to help identify appropriate treatments based on the presence or absence of these disease biomarkers.</p>
Diagnostics	The use of clinical tests to inform clinical decision making. The area includes both tests conducted on specimens from the body (i.e., in vitro diagnostics) and imaging tests (e.g., in vivo diagnostics), for the purpose of disease prediction, screening, diagnosis, treatment selection, prognosis and monitoring.	Harvard University http://www.health.harvard.edu/diagnostic-tests/	Diagnostics serve as a key input to routine clinical decision making.

Term	Definition	Source	Relevance and Context
<i>Test use terminology (continued)</i>			
Biomarker	<p>A biological property or substance(s) that is:</p> <ul style="list-style-type: none"> • a sign of a normal or abnormal process, or of a condition or disease • used to determine how patients respond to treatments 	<p>National Cancer Institute http://www.cancer.gov/dictionary?cdrid=45618</p>	<p>Knowledge of the association between biomarker status and disease risk or state can inform more focused treatment or patient management decisions. The diagnostic test detects the biomarker of interest.</p> <p>Biomarkers may cover various properties and be identified using a variety of testing approaches, including physical properties (e.g., eye color and cataract risk), imaging techniques (e.g., MRI, X-ray and cancer diagnosis), chemistry (e.g., cholesterol level and heart attack risk, blood gas composition and lung function), as well as tests for genes, proteins, and/or their biochemical by-products (e.g., BRAF gene mutations and likely response to Zelboraf).</p>
Reagent	<p>A chemical substance (other than the specimen) used in conducting a diagnostic test/assay.</p>	<p>IUPAC http://goldbook.iupac.org/R05163.html</p>	<p>As part of a diagnostic test, reagents are necessary to complete and collect test results (e.g., to determine the absence or presence of a certain disease.). Often multiple reagents are used to make a diagnostic test.</p>
Analyte	<p>A substance measured by a diagnostic test, for instance, a specific mutation or blood chemistry component.</p>	<p>National Human Genome Research Institute http://www.genome.gov/10002399</p>	<p>Biomarkers may include one or more analytes that are being detected and measured during the diagnostic test</p>
In Vitro Diagnostic (IVD) Test	<p>A diagnostic test that is conducted outside of the body on specimens such as blood or tissue.</p>	<p>US Food & Drug Administration (FDA) http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/default.htm</p>	<p>IVD is also a regulatory designation of tests that include a broad array of laboratory tests. These are distinct from imaging tests that look at or into a patient's body.</p> <p>IVDs may be used in hospital laboratories, doctor's offices, pharmacies, in the field, or in some cases (such as store-bought ovulation tests) in the patient's home.</p>

Term	Definition	Source	Relevance and Context
<i>Test use terminology (continued)</i>			
Test Kit	An FDA cleared or approved IVD test package that includes all of the reagents necessary to obtain test results (excluding the patient specimen/sample) and a protocol with instructions for using the test kit.	US Food & Drug Administration (FDA) http://www.fda.gov/biologicsbloodvaccines/safetyavailability/ucm105888.htm	<p>A test kit has been reviewed by the FDA and cleared as a 510(k) or approved as a PMA product. The test can be marketed in the US as a clinical diagnostic for specified indications. This is in contrast to laboratory developed tests (LDTs) which are assays developed by the laboratory, which are for internal use and are not sold to outside entities. Although laboratory-developed genetic tests are regulated by CMS under CLIA'88, and are part of the accreditation inspection processes, the majority are not subject to FDA 510(k) or PMA requirements. The FDA currently regulates genetic tests sold as kits and the analyte specific reagents (ASRs) used to 'make' genetic LDTs.</p> <p>Test kits do not necessarily include the instrumentation that is used to run the test, such as in the case of HIV home test kits which require that an individual send a self-collected blood sample to a lab for testing.</p>

Term	Definition	Source	Relevance and Context
<i>Test use terminology (continued)</i>			
Stand-Alone Diagnostic	A test that is developed and/or used separately from a drug.	Chicoye A, Faulkner E, Housman L, Garfield S. Developing evidence to support reimbursement and value-based pricing: issues and challenges for stand-alone versus companion diagnostics. International Society for Pharmacoeconomics and Outcomes Research, 16th Annual International Meeting, Baltimore, MD, May 2011.	<p>This term is important from a policy perspective because stand-alone tests have different practical factors that affect their development compared to companion diagnostics developed in the context of a Phase II or III drug trial.</p> <p>One of the key differences is in terms of trial design constraints where manufacturers of stand-alone diagnostics may be more limited in terms of supporting a study design that facilitates direct connections between test use and health outcomes. For most stand-alone diagnostics, study designs are more focused on test performance vs. characterizing direct influence on improving health outcomes.</p> <p>Tests may begin as stand-alone diagnostics but become companion diagnostics if and when a drug is developed that leverages the diagnostic test (but at that time the clinical trial study design will require collection of health outcomes data).</p> <p>Stand-alone does not in this context refer to absence of adjunct use with another test.</p>

Term	Definition	Source	Relevance and Context
<i>Test use terminology (continued)</i>			
Companion Diagnostic	A test that provides information that is essential for the safe and effective use of a corresponding therapeutic product.	US Food & Drug Administration (FDA) http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf	<p>A test that is used as a “companion” to inform prescription or dosing of the drug based on test results (i.e., the patient would receive the test prior to a treatment decision to ensure that is appropriate for that particular patient, or the test could be used to monitor drug response and alter dose).</p> <p>A companion diagnostic may be developed in conjunction with a particular drug (often referred to as codevelopment) or after a drug has entered a market. Drug labels may reference using a companion diagnostic.</p> <p>Targeted therapies and companion diagnostics are two pillars of personalized medicine. Integration of companion diagnostics into clinical practice requires several parties to work collaboratively, including test and treatment manufacturers, regulators, payers, clinicians and patients. Genetic markers are already integral standard of care for their respective targeted cancer therapies. More and more drugs are becoming subjects for companion diagnostic test development as understanding of their clinical relevance expands.</p>

Term	Definition	Source	Relevance and Context
<i>Test use terminology (continued)</i>			
Point of Care Testing (POCT)	Testing that occurs at the point of treatment or patient interaction with a healthcare provider (e.g., the bedside, home, or physician office).	<p>Kost, Gerald J. (2002). "1. Goals, guidelines and principles for point-of-care testing". Principles & practice of point-of-care testing. Hagerstwon, MD: Lippincott Williams & Wilkins pp. 3–12.</p> <p>Columbia University http://bme.columbia.edu/~sia/Sam_LO_C_b817915h.pdf</p>	<p>In addition to improving the convenience of testing, point of care tests enable the person performing the test to obtain rapid results (versus sending off a sample to a laboratory for testing). This is particularly important when immediate diagnostic information is needed or desired (e.g., in the emergency room or when it is important to use the test information to render immediate guidance on patient care).</p> <p>POC testing conducted at a hospital bedside (e.g., non-waived near patient testing) requires a different level of regulatory review compared to tests conducted in a physician's office, which require a CLIA-waiver from the FDA.</p> <p>Examples of POC tests include: blood glucose testing, blood gas and electrolytes analysis, rapid coagulation testing, rapid cardiac markers diagnostics, drugs of abuse screening, urine strips testing, pregnancy testing, fecal occult blood analysis, food pathogens screening, hemoglobin diagnostics, infectious disease testing, cholesterol screening, and protein expression testing.</p>

Term	Definition	Source	Relevance and Context
<i>Standard testing approaches</i>			
Clinical Chemistry	A test that uses biochemical products or chemicals from the body as the target for the test. Also known as chemical biochemistry.	Royal College of Pathologists http://www.rcpath.org/index.asp?PageID=411 JS Madsen, M Nybo, E Magid, et al. (2008) More Studies on Outcomes Using Biochemical Diagnostic Tests are Needed: Findings from the Danish Society of Clinical Biochemistry. <i>Clin Chem.</i> 54(7):1254-6. PMID: 18593971.	A broad variety of chemical tests are commonly used in clinical practice. These tests measure levels of biochemical products from samples like blood or urine. For example, chemical tests include commonly used tests like, potassium, triglycerides, cholesterol, and glucose.
Genetic Testing	A direct analysis of genetic information (DNA, RNA, genes, chromosomes) to determine the presence or risk of developing a particular disease(s) or condition.	Secretary's Advisory Committee on Genetics, Health and Society http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf	There are an expanding variety of genetic / molecular diagnostic tests that are being used to segment potential treatment responder populations. For example, gene sequencing of the BRCA1/2 gene in breast cancer or EGFR mutations in lung cancer may have different outcomes / responses for different mutations compared to tests that evaluate gene expression levels.
Molecular Testing	Direct analysis of molecular information that may include genetic materials (DNA, RNA, genes, chromosomes) but also proteins and other molecular biomarkers.	National Human Genome Research Institute http://ghr.nlm.nih.gov/glossary=genetic_testing	
Immunohistochemistry (IHC)	The process of detecting antigens in cells and/or tissue sections by binding antibodies specifically to antigens in biological tissues.	National Cancer Institute http://www.cancer.gov/dictionary?cdrid=653117	IHC is one of the oldest molecular diagnostic testing methods, but remains commonly used in clinical practice today.
In Situ Hybridization (ISH)	A testing technique for binding of a labeled probe to the DNA by complementary base pairing. The probe label can be made from a fluorescent dye (FISH) or other radioactive/chemical dye (ISH).	An Introduction to Human Molecular Genetics, Jack J. Pasternak, P465	By looking for presence and level or pattern of fluorescence or other DNA binding signal, the test can determine whether the number or structure of genes/chromosomes is normal or variant. When used on RNA, (F)ISH can determine if a patient has a gene expression profile consistent with disease.

Term	Definition	Source	Relevance and Context
<i>Standard testing approaches (continued)</i>			
Probe	General term for a diagnostic test reagent made from a piece of DNA or RNA that binds and marks a gene of interest.	A Molecular Biology Glossary by Dr. Robert H. Lyons, Director, University of Michigan DNA Sequencing Core http://seqcore.brcf.med.umich.edu/doc/educ/dnapr/mbglossary/mbgloss.html	Probes can bind to any complementary DNA or RNA sequence of humans, animals, or infectious disease organisms, etc. Probes can be labeled in a variety of ways, including radioactivity, fluorescent chemicals, or with some other detectable protein, such as biotin, digoxigenin or fluorescein.
Polymerase Chain Reaction (PCR)	A testing technique where small segments of DNA or RNA are copied exponentially by a biochemical reaction to detectable levels.	National Human Genome Research Institute http://www.genome.gov/10000207	Because the amount of nucleic acid in a sample or specimen may be too low for direct detection, PCR is used to create more copies of the DNA target of interest up to detectable levels. Because some diseases result in increases or decreases in gene copy number and/or expression compared to the normal healthy state, PCR is often used to detect abnormal levels of gene expression that can be associated with disease. PCR amplification simply means to increase the number of specific DNA segments through repetitive copying, which lead to increases by tens of millions to a billion fold. Other techniques for amplifying DNA include strand displacement amplification (SDA) and Ligase chain reaction (LCR).
Pharmacogenetics	The study of the effects of genetic variation on differential efficacy and side effects of drugs.	The Lewin Group http://www.advamed.org/NR/ronlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf	Knowledge of patient drug metabolizing gene variants, found in more than half of patients, can help determine the appropriateness and dosage of many of the most commonly prescribed drugs. 'Pharmacogenomics' on the other hand begins with looking for genetic differences within a population that explain certain observed responses to a drug or susceptibility to a health

Term	Definition	Source	Relevance and Context
			problem. These two terms are often used interchangeably.
<i>Common complex testing approaches</i>			
Algorithm	A mathematical and/or statistical tool used for medical diagnoses. These tools can range from simple calculations (e.g., Body Mass Index) to complex outcome predictions that involve multiple analytes/biomarkers (eg, oncotype Dx score).	Medinfo 2001: Proceedings of the 10th World Congress, Volume 10, Part 2, Vimla L. Patel, Ray Rogers, Reinhold Haux, P298	Algorithms are often important in scenarios where the result of one or more tests requires a means to synthesize the test results in an interpretable manner that informs patient care decisions. For example, some tests for breast cancer involves over 20 unique biomarkers and the algorithm associated with the test helps practitioners by providing a single interpretable test result versus requiring the physician to understand the relevance and interplay among results from each individual biomarker test.
Gene Sequencing	Determining the order of DNA nucleotides or bases in a gene.	National Institute of Health (NIH) http://publications.nigms.nih.gov/thene/wgenetics/glossary.html#R	Gene sequencing tests are typically used to identify genetic changes or mutations in DNA that can influence or cause disease. In whole genome sequencing, the entire genome of a patient has the potential to identify a broad array of genetic risks for future disease development and/or correlate multiple genetic changes with risk of disease development. While the technology to enable whole genome sequencing exists, sequencing of the entire genome has not yet entered routine clinical practice.

Term	Definition	Source	Relevance and Context
<i>Common complex testing approaches (continued)</i>			
Multiplex Testing	A testing technique whereby more than one analyte/biomarker is tested for in a single tube or biochemical reaction at the same time.	The Lewin Group http://www.advamed.org/NR/ronlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf	<p>Multiplex tests aim at introducing efficiency to the testing process by enabling multiple analytes to be tested for simultaneously. This is particularly important where a high volume of testing is required and/or scenarios where availability of source material (e.g., tissue) to test for the analyte is limited.</p> <p>Multiplex molecular testing can be used to ascertain presence or absence of a target sequence simultaneously instead of sequentially for making differential diagnoses between diseases or conditions that may have similar symptoms, but different causes (e.g., respiratory viral panel).</p>
Array Test	A testing technique involving a collection of multiple unique tests for different biomarkers on the same testing medium (e.g., plate, glass slide, microfluid chip).	The Lewin Group http://www.advamed.org/NR/ronlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf	<p>As our knowledge of the relationship of multiple biomarkers to specific diseases has increased, the need for testing for multiple biomarkers that can contribute to disease has also increased.</p> <p>Array-based tests may require use of complex bioinformatic systems that help the test interpreter evaluate the test results in a meaningful manner that goes beyond interpretation of multiple test results to inform a single conclusion or decision about patient health or clinical actions that may be warranted.</p>

Term	Definition	Source	Relevance and Context
<i>Common complex testing approaches (continued)</i>			
Circulating Biomarker	Biomarker that is shed or separated from a primary disease site, which then travels in the blood stream and thus can be measured in the blood.	<p>Schwarzenbach, H et al. Cell-free nucleic acids as biomarkers in cancer patients. <i>Nat Rev Cancer</i>. (2011) 11(6): 426-37. PMID 21562580</p> <p>Stefan Sleijfer et al, Circulating tumour cell detection on its way to routine diagnostic implementation? <i>European Journal of Cancer</i> (2007) www.ejccancer.info/article/S0959-8049(07)00746-0/abstract</p>	<p>For sufficiently sensitive tests, analysis of circulating biomarkers offers a potential alternative to more invasive test sample acquisition techniques such as biopsy.</p> <p>Circulating cells, circulating tumor cells (CTCs), circulating rare cells (CRCs) and disseminated tumor cells (DTCs) are versions of a similar type of principle for detecting cell-based circulating biomarkers.</p> <p>Similar to circulating cells, physicians may be able to use circulating free-DNA to diagnose some diseases and select treatment without the need for tissue biopsies</p>
Proteomic Test (Protein testing)	The large-scale study of proteins, particularly their structures and functions.	National Cancer Institute http://proteomics.cancer.gov/whatisproteomics	Proteomics analyzes the structure and function of biological systems that may not be clear by sequencing of genomic nucleic acid (DNA and/or RNA). For example, the protein content of a cancerous cell is often different from that of a healthy cell. Certain proteins in the cancerous cell may not be present in the healthy cell, making these unique proteins potential targets for anti-cancer drugs. Understanding the proteome, the structure and function of each protein and the complexities of protein–protein interactions will be critical for developing the most effective diagnostic techniques and disease treatments in the future.

Term	Definition	Source	Relevance and Context
<i>Test Performance & Value</i>			
<i>Common test rationale / objectives</i>			
Predictive Test	A test that ascertains an individual patient's level of risk or probability of particular outcomes at some point in the future such as developing disease or response to therapy.	The Lewin Group http://www.advamed.org/NR/ronlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf	Prediction is an overarching objective of multiple types of testing which includes testing types such as, screening test (primary risk prediction), prognostic test (secondary risk prediction) and treatment selection testing to predict outcomes associated with treatments. Predictive tests enable providers and patients to be informed about potential future disease risks and make treatment or lifestyle changes that can help to mitigate that risk. In some cases, predictive tests can result in a clear treatment action and in other cases no specific treatment action aside from watchful waiting is possible. One critical aspect underlying such testing is that early identification of individuals at risk of a specific condition will lead to better disease management, especially prior to disease onset.
Screening Test	A test used to determine whether an <i>asymptomatic</i> patient has a particular disease.	Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008. Quality Issues in Clinical Genetic Services; By U. Kristoffersson, P148	While screening tests are used on patients that do not exhibit signs or symptoms of disease, they may be recommended for patients with certain risk factors (e.g., family history, exposure to infectious agents). This use of a screening test is sometimes referred to as 'population screening'. The primary goal of population screening is to predict with high accuracy which individual in a group is at significant risk of developing or transmitting a disease. Once individuals at high risk for a

Term	Definition	Source	Relevance and Context
<i>Common test rationale / objectives (continued)</i>			
Prognostic Test	A test that identifies the likelihood of a disease course in the absence of treatment (e.g., breast cancer recurrence).	<p>Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008.</p> <p>Workman SR (2010) Prediction versus prognosis. CMAJ. 182(2):176. PMID: 20142392.</p>	While patient history and physician experience are important in estimating prognosis, modern diagnostics can offer more accurate characterization of patient status and/or likelihood for a particular treatment response.
Test for Treatment Selection and Use (also refer to Companion Diagnostic)	A test used to inform the use of a specific drug or treatment combination.	<p>The Lewin Group http://www.advamed.org/NR/rdonlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf</p> <p>Paul NW, Roses AD. Pharmacogenetics and pharmacogenomics: recent developments, their clinical relevance and some ethical, social and legal implications. J Mol Med 2003;81:135-40</p>	<p>Treatment selection tests often fall into three categories: (1) tests that can identify responders who will benefit from treatment prior to or just after initiation of treatment, (2) tests that can inform patient dosing, and (3) tests that identify patients with a differential risk for having an adverse reaction to a particular drug.</p> <p>Tests may be used to distinguish those patients likely to respond to the drug (i.e., responders) from those unlikely to respond, based on the patients' genetic makeup, the drug's mechanism of action, or other factors. The percentage of potential responders can be important in value assessment of the test, particularly in circumstances where the responder population is particularly low or high.</p> <p>In other circumstances, tests may be used to identify whether the patient should be on a higher or lower dose of a particular drug.</p> <p>In rarer circumstances, the test may help identify patients that face potential severe safety risks, such as significant morbidity or mortality from use of a specific drug. Such tests can be difficult to develop, particularly if the safety event is rare</p>

			(e.g., <1 in 100 patients) due to requirements for statistically powering associated clinical studies to demonstrate test performance and value.
Term	Definition	Source	Relevance and Context
<i>Common test rationale / objectives (continued)</i>			
Monitoring Test	A test used to evaluate patient health status or disease state or to determine whether or to what extent disease has progressed.	Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008. US Congress Office of Technology Assessment. (2011) "Genetic monitoring and screening in the workplace."	Monitoring tests are conducted periodically over time to evaluate patient health or disease status. They can be performed by continuously measuring certain parameters, including drug resistance, drug appropriateness, disease progression, patient adherence, safety, etc., (e.g., blood glucose in people with diabetes mellitus) or at discrete time intervals (e.g., every 3-6 months for assessing BCR-ABL in chronic myelogenous leukemia).

Term	Definition	Source	Relevance and Context
<i>Test Performance</i>			
Clinical Sensitivity	Probability that the test gives a positive result among individuals that have the disease or condition of interest. Specifically, the ratio of true positives to the sum of true positives and false negatives.	Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008. AIDS epidemiology: a quantitative approach, Ron Brookmeyer, Mitchell H. Gail, P148	The higher the sensitivity of the test, the less likely the test will result in false negative results (i.e., misdiagnosing a patient that actually has the disease or condition).
Clinical Specificity	Probability that the test will give a negative result among individuals who do not have the disease or condition of interest. Specifically, the ratio of true negatives to the sum of true negatives and false positives.	Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008. AIDS epidemiology: a quantitative approach, Ron Brookmeyer, Mitchell H. Gail, P148	Tests with high specificity can reliably detect the target analyte/biomarker and will not be influenced by other biomarkers or physiological factors in a way that produces false positive results (e.g., a person with a condition that may have similar symptoms (emphysema) will not test positive for the disease of interest (lung cancer).
Analytical Sensitivity	The smallest quantity of substance in a sample that can accurately be measured by an assay.	Alfred J. Saah and Donald R. Hoover “Sensitivity” and “Specificity” Reconsidered: The Meaning of These Terms in Analytical and Diagnostic Settings. <i>Annals of Internal Medicine</i> January 1, 1997 vol. 126 no. 1 91-94	Tests with high sensitivity can reliably detect the target analyte/biomarker, even if it occurs at very low levels. Tests with low analytical are unlikely to have high clinical sensitivity.

Term	Definition	Source	Relevance and Context
<i>Test Performance (continued)</i>			
Analytical Specificity	The ability of an assay to measure one particular organism or analyte, rather than others.	Alfred J. Saah and Donald R. Hoover "Sensitivity" and "Specificity" Reconsidered: The Meaning of These Terms in Analytical and Diagnostic Settings. <i>Annals of Internal Medicine</i> January 1, 1997 vol. 126 no. 1 91-94	Tests with high analytical specificity reduce possible false positive or false negative results that are generated by cross-reactants or interferents present in the sample instead of the true analyte.
Accuracy	A measure of deviation of test results from the true value.	Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008.	Accurate test methods have high sensitivity and high specificity. When comparing multiple accurate test methods, the test will deliver the same results from the same patient sample and not require statistical correction.
Precision	A measure of how close test results are when repeated multiple times on the same sample.	Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008.	Tests with high precision will not be as influenced by user variability or the environment. High precision contributes to lab-to-lab standardization Tests can be very precise, but not accurate, and vice versa. Together, precision and accuracy determine a test's reliability.
Positive Predictive Value	The probability that a patient with a positive (abnormal) test result actually has the disease.	Department of Health, NY http://www.health.ny.gov/diseases/chronic/discreen.htm	The higher the test specificity, the more likely an individual with a positive test will be have the disease and the greater the positive predictive value.
Negative Predictive Value	The probability that a person with a negative (normal) test result is truly free of disease.	Department of Health, NY http://www.health.ny.gov/diseases/chronic/discreen.htm	The higher the test sensitivity, the more likely an individual with a negative test will not have the disease and thus the greater the negative predictive value.
False Positive	A test result that indicates that an individual does have a specific disease when the individual actually does not have the disease.	National Cancer Institute http://www.cancer.gov/dictionary?expand=F	A false positive test means that an individual may be given a treatment or subject to additional procedures when they don't have the disease. High specificity therefore is a requirement for tests where there is a significant risk associated with the downstream clinical consequences of treatment. False positives can be analytical (i.e.,

Term	Definition	Source	Relevance and Context
<i>Test Performance (continued)</i>			
False Negative	A test result that indicates that an individual does not have a specific disease when the individual actually does have the disease.	National Cancer Institute http://www.cancer.gov/dictionary?expand=F	A false negative test means that an individual may not be given a treatment or undergo a procedure when they need it. Therefore, high sensitivity is necessary when there is a significant risk of morbidity or mortality if the disease is missed. False negatives may be analytical (e.g., if there are interfering substances or concentration issues that prevent detection of the analyte) or clinical (if the biomarker can be present when disease is absent).

Term	Definition	Source	Relevance and Context
<i>Test validation and related terminology</i>			
Analytical Validity	The ability of a test to measure accurately and reliably the analyte/biomarker of interest in a sample or specimen.	Centers for Disease Control & Prevention (ACCE Framework) http://www.cdc.gov/genomics/gtesting/ACCE/	Analytic validity encompasses basic aspects of test performance, such as analytical sensitivity, and specificity, precision, and reproducibility.
Clinical Validity	The ability to check how consistently and accurately a test detects or predicts the outcomes of interest in a patient population.	Centers for Disease Control & Prevention (ACCE Framework) http://www.cdc.gov/genomics/gtesting/ACCE/	. Clinical validity links test performance to the ability to identify a specific disease or condition, and encompasses aspects of test performance such as clinical sensitivity and specificity and predictive value.
Clinical Utility	The ability of a test to inform an appropriate clinical treatment decision to improve patient outcomes.	Centers for Disease Control & Prevention (ACCE Framework) http://www.cdc.gov/genomics/gtesting/ACCE/	In addition to determining the degree to which a test informs an appropriate treatment decision, clinical utility implies that the test is relevant for use in clinical decision making and that action based on test results has the potential to <i>improve patient outcomes</i> . Tests that are clinically valid, however, may not be clinically useful (e.g., a gene mutation may be associated with a clinical condition; however, knowledge of a mutation may not change patient management in a way that can chance health outcomes).

Term	Definition	Source	Relevance and Context
<i>Diagnostic Assessors/Schemes</i>			
<i>US FDA</i>			
Humanitarian Use Device (HUD)	Devices that are used in small patient populations (i.e., affecting fewer than 4,000 individuals in the US per year).	US Food & Drug Administration (FDA) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm	HUD is a regulatory category designated by FDA to promote development of medical devices and laboratory tests for rare diseases and conditions. To obtain approval for a HUD, a sponsor must submit a humanitarian device exemption (HDE) application to the FDA. An HDE is similar in both form and content to a premarket approval (PMA) application but is exempt from the effectiveness requirements of a PMA (i.e., must show safety, with plausible evidence of effectiveness through post market study annual reports and/or clinical literature).
Research Use Only (RUO)	Tests (or other products) primarily for research/laboratory use only that have not been approved or cleared for clinical use as a marketed product by FDA. A research device cannot be intended for human clinical diagnostic or prognostic use.	US Food & Drug Administration (FDA) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm253307.htm http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=809.10	RUO products are differentiated from clinical products in that, since results are not intended to be returned to the patient or used in patient care, the tests are not required to be manufactured under the Quality Systems Regulations requirements for good manufacturing practices.

Term	Definition	Source	Relevance and Context
<i>US FDA (continued)</i>			
Analyte-Specific reagent (ASR)	ASRs may include a variety of test components required to make the test work, including antibodies, receptor/ligand proteins, and nucleic acid sequences, primers or probes. These test components enable the test to work via specific binding or chemical reaction with a specimen.	US Food & Drug Administration (FDA) http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?FR=864.4020	Most ASR's are exempt from pre-market approval or notification requirements that apply to IVDs but must adhere to current Good Manufacturing Practices (cGMP) under the quality systems regulations and medical device reporting / labeling requirements. Some ASRs, such as those used in bloodbanking, donor screening, or to detect infectious agents of high public health significance (e.g., HIV or tuberculosis) require FDA review prior to marketing. ASRs are differentiated from General Purpose reagents, which do not have specific binding reactivity with any particular analyte (eg, general purpose buffers, enzymes, etc.).
Investigational Use Only (IUO)	A term used to describe tests (or other products) that may be used in clinical studies that may lead to their clearance or approval for use in clinical practice.	US Food & Drug Administration (FDA) http://www.personalizedmedicinecoalition.org/sites/default/files/files/FDA_Guidance_IVD_IUO_RUO.pdf	IUO tests are not intended to be used in clinical practice outside of the clinical research setting, but may be marketed and used in research and investigation of other FDA-regulated products.

Term	Definition	Source	Relevance and Context
<i>Methods & Test Applications</i>			
<i>Test use terminology</i>			
Personalized Medicine	The use of an individual's genetic or related molecular information to improve the safety, effectiveness, and health outcomes of that patient via more efficiently tailored prevention, diagnosis, and treatment decisions.	National Institute of Health (NIH) http://ghr.nlm.nih.gov/glossary=personalizedmedicine International Society for Pharmacoeconomic and Outcomes Research (ISPOR) http://www.ispor.org/sigs/PM/ISPOR-Personalized-Medicine-SIG-DR_Wrkng-Grp_Manuscript.pdf	Personalized medicine primarily involves testing for genetic or other factors that reflect risk for disease / disease characteristics specific to that patient. Testing may involve information from one or more diagnostic tests to characterize the - appropriateness of a specific treatment for a specific patient. The adoption of personalized medicine has led to increases efforts to identify new biomarkers across tumor types. For example, measurement of well-established biomarkers such as, the epidermal growth factor receptor (EGFR) and the human epidermal growth factor receptor 2 (HER2) in breast, lung and colorectal cancer patients are taken to help identify appropriate treatments based on the presence or absence of these disease biomarkers.
Diagnostics	The use of clinical tests to inform clinical decision making. The area includes both tests conducted on specimens from the body (i.e., in vitro diagnostics) and imaging tests (e.g., in vivo diagnostics), for the purpose of disease prediction, screening, diagnosis, treatment selection, prognosis and monitoring.	Harvard University http://www.health.harvard.edu/diagnostic-tests/	Diagnostics serve as a key input to routine clinical decision making.

Term	Definition	Source	Relevance and Context
<i>Test use terminology (continued)</i>			
Biomarker	<p>A biological property or substance(s) that is:</p> <ul style="list-style-type: none"> • a sign of a normal or abnormal process, or of a condition or disease • used to determine how patients respond to treatments 	<p>National Cancer Institute http://www.cancer.gov/dictionary?cdrid=45618</p>	<p>Knowledge of the association between biomarker status and disease risk or state can inform more focused treatment or patient management decisions. The diagnostic test detects the biomarker of interest.</p> <p>Biomarkers may cover various properties and be identified using a variety of testing approaches, including physical properties (e.g., eye color and cataract risk), imaging techniques (e.g., MRI, X-ray and cancer diagnosis), chemistry (e.g., cholesterol level and heart attack risk, blood gas composition and lung function), as well as tests for genes, proteins, and/or their biochemical by-products (e.g., BRAF gene mutations and likely response to Zelboraf).</p>
Reagent	<p>A chemical substance (other than the specimen) used in conducting a diagnostic test/assay.</p>	<p>IUPAC. http://goldbook.iupac.org/R05163.html</p>	<p>As part of a diagnostic test, reagents are necessary to complete and collect test results (e.g., to determine the absence or presence of a certain disease.). Often multiple reagents are used to make a diagnostic test.</p>
Analyte	<p>A substance measured by a diagnostic test, for instance, a specific mutation or blood chemistry component.</p>	<p>National Human Genome Research Institute http://www.genome.gov/10002399</p>	<p>Biomarkers may include one or more analytes that are being detected and measured during the diagnostic test</p>
In Vitro Diagnostic (IVD) Test	<p>A diagnostic test that is conducted outside of the body on specimens such as blood or tissue.</p>	<p>US Food & Drug Administration (FDA) http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/default.htm</p>	<p>IVD is also a regulatory designation of tests that include a broad array of laboratory tests. These are distinct from imaging tests that look at or into a patient's body.</p> <p>IVDs may be used in hospital laboratories, doctor's offices, pharmacies, in the field, or in some cases (such as store-bought ovulation tests) in the patient's home.</p>

Term	Definition	Source	Relevance and Context
<i>Test use terminology (continued)</i>			
Test Kit	An FDA cleared or approved IVD test package that includes all of the reagents necessary to obtain test results (excluding the patient specimen/sample) and a protocol with instructions for using the test kit.	US Food & Drug Administration (FDA) http://www.fda.gov/biologicsbloodvaccines/safetyavailability/ucm105888.htm	<p>A test kit has been reviewed by the FDA and cleared as a 510(k) or approved as a PMA product. The test can be marketed in the US as a clinical diagnostic for specified indications. This is in contrast to laboratory developed tests (LDTs) which are assays developed by the laboratory, which are for internal use and are not sold to outside entities. Although laboratory-developed genetic tests are regulated by CMS under CLIA'88, and are part of the accreditation inspection processes, the majority are not subject to FDA 510(k) or PMA requirements. The FDA currently regulates genetic tests sold as kits and the analyte specific reagents (ASRs) used to 'make' genetic LDTs.</p> <p>Test kits do not necessarily include the instrumentation that is used to run the test, such as in the case of HIV home test kits which require that an individual send a self-collected blood sample to a lab for testing.</p>

Term	Definition	Source	Relevance and Context
<i>Test use terminology (continued)</i>			
Stand-Alone Diagnostic	A test that is developed and/or used separately from a drug.	Chicoye A, Faulkner E, Housman L, Garfield S. Developing evidence to support reimbursement and value-based pricing: issues and challenges for stand-alone versus companion diagnostics. International Society for Pharmacoeconomics and Outcomes Research, 16th Annual International Meeting, Baltimore, MD, May 2011.	<p>This term is important from a policy perspective because stand-alone tests have different practical factors that affect their development compared to companion diagnostics developed in the context of a Phase II or III drug trial.</p> <p>One of the key differences is in terms of trial design constraints where manufacturers of stand-alone diagnostics may be more limited in terms of supporting a study design that facilitates direct connections between test use and health outcomes. For most stand-alone diagnostics, study designs are more focused on test performance vs. characterizing direct influence on improving health outcomes.</p> <p>Tests may begin as stand-alone diagnostics but become companion diagnostics if and when a drug is developed that leverages the diagnostic test (but at that time the clinical trial study design will require collection of health outcomes data).</p> <p>Stand-alone does not in this context refer to absence of adjunct use with another test.</p>

Term	Definition	Source	Relevance and Context
<i>Test use terminology (continued)</i>			
Companion Diagnostic	A test that provides information that is essential for the safe and effective use of a corresponding therapeutic product.	US Food & Drug Administration (FDA) http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf	<p>A test that is used as a “companion” to inform prescription or dosing of the drug based on test results (i.e., the patient would receive the test prior to a treatment decision to ensure that is appropriate for that particular patient, or the test could be used to monitor drug response and alter dose).</p> <p>A companion diagnostic may be developed in conjunction with a particular drug (often referred to as codevelopment) or after a drug has entered a market. Drug labels may reference using a companion diagnostic.</p> <p>Targeted therapies and companion diagnostics are two pillars of personalized medicine. Integration of companion diagnostics into clinical practice requires several parties to work collaboratively, including test and treatment manufacturers, regulators, payers, clinicians and patients. Genetic markers are already integral standard of care for their respective targeted cancer therapies. More and more drugs are becoming subjects for companion diagnostic test development as understanding of their clinical relevance expands.</p>

Term	Definition	Source	Relevance and Context
<i>Test use terminology (continued)</i>			
Point of Care Testing (POCT)	Testing that occurs at the point of treatment or patient interaction with a healthcare provider (e.g., the bedside, home, or physician office).	<p>Kost, Gerald J. (2002). "1. Goals, guidelines and principles for point-of-care testing". Principles & practice of point-of-care testing. Hagerstwon, MD: Lippincott Williams & Wilkins pp. 3–12.</p> <p>Columbia University http://bme.columbia.edu/~sia/Sam_LO_C_b817915h.pdf</p>	<p>In addition to improving the convenience of testing, point of care tests enable the person performing the test to obtain rapid results (versus sending off a sample to a laboratory for testing). This is particularly important when immediate diagnostic information is needed or desired (e.g., in the emergency room or when it is important to use the test information to render immediate guidance on patient care).</p> <p>POC testing conducted at a hospital bedside (e.g., non-waived near patient testing) requires a different level of regulatory review compared to tests conducted in a physician's office, which require a CLIA-waiver from the FDA.</p> <p>Examples of POC tests include: blood glucose testing, blood gas and electrolytes analysis, rapid coagulation testing, rapid cardiac markers diagnostics, drugs of abuse screening, urine strips testing, pregnancy testing, fecal occult blood analysis, food pathogens screening, hemoglobin diagnostics, infectious disease testing, cholesterol screening, and protein expression testing.</p>

Term	Definition	Source	Relevance and Context
<i>Standard testing approaches</i>			
Clinical Chemistry	A test that uses biochemical products or chemicals from the body as the target for the test. Also known as chemical biochemistry.	Royal College of Pathologists http://www.rcpath.org/index.asp?PageID=411 JS Madsen, M Nybo, E Magid, et al. (2008) More Studies on Outcomes Using Biochemical Diagnostic Tests are Needed: Findings from the Danish Society of Clinical Biochemistry. <i>Clin Chem.</i> 54(7):1254-6. PMID: 18593971.	A broad variety of chemical tests are commonly used in clinical practice. These tests measure levels of biochemical products from samples like blood or urine. For example, chemical tests include commonly used tests like, potassium, triglycerides, cholesterol, and glucose.
Genetic Testing	A direct analysis of genetic information (DNA, RNA, genes, chromosomes) to determine the presence or risk of developing a particular disease(s) or condition.	Secretary's Advisory Committee on Genetics, Health and Society http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf	There are an expanding variety of genetic / molecular diagnostic tests that are being used to segment potential treatment responder populations. For example, gene sequencing of the BRCA1/2 gene in breast cancer or EGFR mutations in lung cancer may have different outcomes / responses for different mutations compared to tests that evaluate gene expression levels.
Molecular Testing	Direct analysis of molecular information that may include genetic materials (DNA, RNA, genes, chromosomes) but also proteins and other molecular biomarkers.	National Human Genome Research Institute http://ghr.nlm.nih.gov/glossary=genetic_testing	
Immunohistochemistry (IHC)	The process of detecting antigens in cells and/or tissue sections by binding antibodies specifically to antigens in biological tissues.	National Cancer Institute http://www.cancer.gov/dictionary?cdrid=653117	IHC is one of the oldest molecular diagnostic testing methods, but remains commonly used in clinical practice today.
In Situ Hybridization (ISH)	A testing technique for binding of a labeled probe to the DNA by complementary base pairing. The probe label can be made from a fluorescent dye (FISH) or other radioactive/chemical dye (ISH).	An Introduction to Human Molecular Genetics, Jack J. Pasternak, P465	By looking for presence and level or pattern of fluorescence or other DNA binding signal, the test can determine whether the number or structure of genes/chromosomes is normal or variant. When used on RNA, (F)ISH can determine if a patient has a gene expression profile consistent with disease.

Term	Definition	Source	Relevance and Context
<i>Standard testing approaches (continued)</i>			
Probe	General term for a diagnostic test reagent made from a piece of DNA or RNA that binds and marks a gene of interest.	A Molecular Biology Glossary by Dr. Robert H. Lyons, Director, University of Michigan DNA Sequencing Core http://seqcore.brcf.med.umich.edu/doc/educ/dnapr/mbglossary/mbgloss.html	Probes can bind to any complementary DNA or RNA sequence of humans, animals, or infectious disease organisms, etc. Probes can be labeled in a variety of ways, including radioactivity, fluorescent chemicals, or with some other detectable protein, such as biotin, digoxigenin or fluorescein.
Polymerase Chain Reaction (PCR)	A testing technique where small segments of DNA or RNA are copied exponentially by a biochemical reaction to detectable levels.	National Human Genome Research Institute http://www.genome.gov/10000207	Because the amount of nucleic acid in a sample or specimen may be too low for direct detection, PCR is used to create more copies of the DNA target of interest up to detectable levels. Because some diseases result in increases or decreases in gene copy number and/or expression compared to the normal healthy state, PCR is often used to detect abnormal levels of gene expression that can be associated with disease. PCR amplification simply means to increase the number of specific DNA segments through repetitive copying, which lead to increases by tens of millions to a billion fold. Other techniques for amplifying DNA include strand displacement amplification (SDA) and Ligase chain reaction (LCR).
Pharmacogenetics	The study of the effects of genetic variation on differential efficacy and side effects of drugs.	The Lewin Group http://www.advamed.org/NR/rdonlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf	Knowledge of patient drug metabolizing gene variants, found in more than half of patients, can help determine the appropriateness and dosage of many of the most commonly prescribed drugs. 'Pharmacogenomics' on the other hand begins with looking for genetic differences within a population that explain certain observed responses to a drug or susceptibility to a health

Term	Definition	Source	Relevance and Context
			problem. These two terms are often used interchangeably.
<i>Common complex testing approaches</i>			
Algorithm	A mathematical and/or statistical tool used for medical diagnoses. These tools can range from simple calculations (e.g., Body Mass Index) to complex outcome predictions that involve multiple analytes/biomarkers (eg, oncotype Dx score).	Medinfo 2001: Proceedings of the 10th World Congress, Volume 10, Part 2, Vimla L. Patel, Ray Rogers, Reinhold Haux, P298	Algorithms are often important in scenarios where the result of one or more tests requires a means to synthesize the test results in an interpretable manner that informs patient care decisions. For example, some tests for breast cancer involves over 20 unique biomarkers and the algorithm associated with the test helps practitioners by providing a single interpretable test result versus requiring the physician to understand the relevance and interplay among results from each individual biomarker test.
Gene Sequencing	Determining the order of DNA nucleotides or bases in a gene.	National Institute of Health (NIH) http://publications.nigms.nih.gov/thene/wgenetics/glossary.html#R	Gene sequencing tests are typically used to identify genetic changes or mutations in DNA that can influence or cause disease. In whole genome sequencing, the entire genome of a patient has the potential to identify a broad array of genetic risks for future disease development and/or correlate multiple genetic changes with risk of disease development. While the technology to enable whole genome sequencing exists, sequencing of the entire genome has not yet entered routine clinical practice.

Term	Definition	Source	Relevance and Context
<i>Common complex testing approaches (continued)</i>			
Multiplex Testing	A testing technique whereby more than one analyte/biomarker is tested for in a single tube or biochemical reaction at the same time.	The Lewin Group http://www.advamed.org/NR/ronlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf	<p>Multiplex tests aim at introducing efficiency to the testing process by enabling multiple analytes to be tested for simultaneously. This is particularly important where a high volume of testing is required and/or scenarios where availability of source material (e.g., tissue) to test for the analyte is limited.</p> <p>Multiplex molecular testing can be used to ascertain presence or absence of a target sequence simultaneously instead of sequentially for making differential diagnoses between diseases or conditions that may have similar symptoms, but different causes (e.g., respiratory viral panel).</p>
Array Test	A testing technique involving a collection of multiple unique tests for different biomarkers on the same testing medium (e.g., plate, glass slide, microfluid chip).	The Lewin Group http://www.advamed.org/NR/ronlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf	<p>As our knowledge of the relationship of multiple biomarkers to specific diseases has increased, the need for testing for multiple biomarkers that can contribute to disease has also increased.</p> <p>Array-based tests may require use of complex bioinformatic systems that help the test interpreter evaluate the test results in a meaningful manner that goes beyond interpretation of multiple test results to inform a single conclusion or decision about patient health or clinical actions that may be warranted.</p>

Term	Definition	Source	Relevance and Context
<i>Common complex testing approaches (continued)</i>			
Circulating Biomarker	Biomarker that is shed or separated from a primary disease site, which then travels in the blood stream and thus can be measured in the blood.	<p>Schwarzenbach, H et al. Cell-free nucleic acids as biomarkers in cancer patients. <i>Nat Rev Cancer</i>. (2011) 11(6): 426-37. PMID 21562580</p> <p>Stefan Sleijfer et al, Circulating tumour cell detection on its way to routine diagnostic implementation? <i>European Journal of Cancer</i> (2007) www.ejccancer.info/article/S0959=8049(07)00746-0/abstract</p>	<p>For sufficiently sensitive tests, analysis of circulating biomarkers offers a potential alternative to more invasive test sample acquisition techniques such as biopsy.</p> <p>Circulating cells, circulating tumor cells (CTCs), circulating rare cells (CRCs) and disseminated tumor cells (DTCs) are versions of a similar type of principle for detecting cell-based circulating biomarkers.</p> <p>Similar to circulating cells, physicians may be able to use circulating free-DNA to diagnose some diseases and select treatment without the need for tissue biopsies</p>
Proteomic Test (Protein Testing)	The large-scale study of proteins, particularly their structures and functions.	National Cancer Institute http://proteomics.cancer.gov/whatisproteomics	Proteomics analyzes the structure and function of biological systems that may not be clear by sequencing of genomic nucleic acid (DNA and/or RNA). For example, the protein content of a cancerous cell is often different from that of a healthy cell. Certain proteins in the cancerous cell may not be present in the healthy cell, making these unique proteins potential targets for anti-cancer drugs. Understanding the proteome, the structure and function of each protein and the complexities of protein–protein interactions will be critical for developing the most effective diagnostic techniques and disease treatments in the future.

Term	Definition	Source	Relevance and Context
<i>Test Performance & Value</i>			
<i>Common test rationale / objectives</i>			
Predictive Test	A test that ascertains an individual patient's level of risk or probability of particular outcomes at some point in the future such as developing disease or response to therapy.	The Lewin Group http://www.advamed.org/NR/ronlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf	<p>Prediction is an overarching objective of multiple types of testing which includes testing types such as, screening test (primary risk prediction), prognostic test (secondary risk prediction) and treatment selection testing to predict outcomes associated with treatments.</p> <p>Predictive tests enable providers and patients to be informed about potential future disease risks and make treatment or lifestyle changes that can help to mitigate that risk. In some cases, predictive tests can result in a clear treatment action and in other cases no specific treatment action aside from watchful waiting is possible. One critical aspect underlying such testing is that early identification of individuals at risk of a specific condition will lead to better disease management, especially prior to disease onset.</p>
Screening Test	A test used to determine whether an <i>asymptomatic</i> patient has a particular disease.	Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008. Quality Issues in Clinical Genetic Services; By U. Kristoffersson, P148	<p>While screening tests are used on patients that do not exhibit signs or symptoms of disease, they may be recommended for patients with certain risk factors (e.g., family history, exposure to infectious agents).</p> <p>This use of a screening test is sometimes referred to as 'population screening'. The primary goal of population screening is to predict with high accuracy which individual in a group is at significant risk of developing or transmitting a disease. Once individuals at high risk for a</p>

Term	Definition	Source	Relevance and Context
<i>Common test rationale / objectives (continued)</i>			
Prognostic Test	A test that identifies the likelihood of a disease course in the absence of treatment (e.g., breast cancer recurrence).	<p>Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008.</p> <p>Workman SR (2010) Prediction versus prognosis. CMAJ. 182(2):176. PMID: 20142392.</p>	While patient history and physician experience are important in estimating prognosis, modern diagnostics can offer more accurate characterization of patient status and/or likelihood for a particular treatment response.
Test for Treatment Selection and Use (also refer to Companion Diagnostic)	A test used to inform the use of a specific drug or treatment combination.	<p>The Lewin Group http://www.advamed.org/NR/rdonlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf</p> <p>Paul NW, Roses AD. Pharmacogenetics and pharmacogenomics: recent developments, their clinical relevance and some ethical, social and legal implications. J Mol Med 2003;81:135-40</p>	<p>Treatment selection tests often fall into three categories: (1) tests that can identify responders who will benefit from treatment prior to or just after initiation of treatment, (2) tests that can inform patient dosing, and (3) tests that identify patients with a differential risk for having an adverse reaction to a particular drug.</p> <p>Tests may be used to distinguish those patients likely to respond to the drug (i.e., responders) from those unlikely to respond, based on the patients' genetic makeup, the drug's mechanism of action, or other factors. The percentage of potential responders can be important in value assessment of the test, particularly in circumstances where the responder population is particularly low or high.</p> <p>In other circumstances, tests may be used to identify whether the patient should be on a higher or lower dose of a particular drug.</p> <p>In rarer circumstances, the test may help identify patients that face potential severe safety risks, such as significant morbidity or mortality from use of a specific drug. Such tests can be difficult to develop, particularly if the safety event is rare</p>

			(e.g., <1 in 100 patients) due to requirements for statistically powering associated clinical studies to demonstrate test performance and value.
Term	Definition	Source	Relevance and Context
<i>Common test rationale / objectives (continued)</i>			
Monitoring Test	A test used to evaluate patient health status or disease state or to determine whether or to what extent disease has progressed.	Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008. US Congress Office of Technology Assessment. (2011) "Genetic monitoring and screening in the workplace."	Monitoring tests are conducted periodically over time to evaluate patient health or disease status. They can be performed by continuously measuring certain parameters, including drug resistance, drug appropriateness, disease progression, patient adherence, safety, etc., (e.g., blood glucose in people with diabetes mellitus) or at discrete time intervals (e.g., every 3-6 months for assessing BCR-ABL in chronic myelogenous leukemia).

Term	Definition	Source	Relevance and Context
<i>Test Performance</i>			
Clinical Sensitivity	Probability that the test gives a positive result among individuals that have the disease or condition of interest. Specifically, the ratio of true positives to the sum of true positives and false negatives.	Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008. AIDS epidemiology: a quantitative approach, Ron Brookmeyer, Mitchell H. Gail, P148	The higher the sensitivity of the test, the less likely the test will result in false negative results (i.e., misdiagnosing a patient that actually has the disease or condition).
Clinical Specificity	Probability that the test will give a negative result among individuals who do not have the disease or condition of interest. Specifically, the ratio of true negatives to the sum of true negatives and false positives.	Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008. AIDS epidemiology: a quantitative approach, Ron Brookmeyer, Mitchell H. Gail, P148	Tests with high specificity can reliably detect the target analyte/biomarker and will not be influenced by other biomarkers or physiological factors in a way that produces false positive results (e.g., a person with a condition that may have similar symptoms (emphysema) will not test positive for the disease of interest (lung cancer).
Analytical Sensitivity	The smallest quantity of substance in a sample that can accurately be measured by an assay.	Alfred J. Saah and Donald R. Hoover “Sensitivity” and “Specificity” Reconsidered: The Meaning of These Terms in Analytical and Diagnostic Settings. <i>Annals of Internal Medicine</i> January 1, 1997 vol. 126 no. 1 91-94	Tests with high sensitivity can reliably detect the target analyte/biomarker, even if it occurs at very low levels. Tests with low analytical are unlikely to have high clinical sensitivity.

Term	Definition	Source	Relevance and Context
<i>Test Performance (continued)</i>			
Analytical Specificity	The ability of an assay to measure one particular organism or analyte, rather than others.	Alfred J. Saah and Donald R. Hoover "Sensitivity" and "Specificity" Reconsidered: The Meaning of These Terms in Analytical and Diagnostic Settings. <i>Annals of Internal Medicine</i> January 1, 1997 vol. 126 no. 1 91-94	Tests with high analytical specificity reduce possible false positive or false negative results that are generated by cross-reactants or interferents present in the sample instead of the true analyte.
Accuracy	A measure of deviation of test results from the true value.	Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008.	Accurate test methods have high sensitivity and high specificity. When comparing multiple accurate test methods, the test will deliver the same results from the same patient sample and not require statistical correction.
Precision	A measure of how close test results are when repeated multiple times on the same sample.	Marshall, WJ and Bangbert SK. Clinical Chemistry. Mosby Elsevier. 2008.	Tests with high precision will not be as influenced by user variability or the environment. High precision contributes to lab-to-lab standardization Tests can be very precise, but not accurate, and vice versa. Together, precision and accuracy determine a test's reliability.
Positive Predictive Value	The probability that a patient with a positive (abnormal) test result actually has the disease.	Department of Health, NY http://www.health.ny.gov/diseases/chronic/discreen.htm	The higher the test specificity, the more likely an individual with a positive test will be have the disease and the greater the positive predictive value.
Negative Predictive Value	The probability that a person with a negative (normal) test result is truly free of disease.	Department of Health, NY http://www.health.ny.gov/diseases/chronic/discreen.htm	The higher the test sensitivity, the more likely an individual with a negative test will not have the disease and thus the greater the negative predictive value.
False Positive	A test result that indicates that an individual does have a specific disease when the individual actually does not have the disease.	National Cancer Institute http://www.cancer.gov/dictionary?expand=F	A false positive test means that an individual may be given a treatment or subject to additional procedures when they don't have the disease. High specificity therefore is a requirement for tests where there is a significant risk associated with the downstream clinical consequences of treatment. False positives can be analytical (i.e.,

Term	Definition	Source	Relevance and Context
<i>Test Performance (continued)</i>			
False Negative	A test result that indicates that an individual does not have a specific disease when the individual actually does have the disease.	National Cancer Institute http://www.cancer.gov/dictionary?expand=F	A false negative test means that an individual may not be given a treatment or undergo a procedure when they need it. Therefore, high sensitivity is necessary when there is a significant risk of morbidity or mortality if the disease is missed. False negatives may be analytical (e.g., if there are interfering substances or concentration issues that prevent detection of the analyte) or clinical (if the biomarker can be present when disease is absent).

Term	Definition	Source	Relevance and Context
<i>Test validation and related terminology</i>			
Analytical Validity	The ability of a test to measure accurately and reliably the analyte/biomarker of interest in a sample or specimen.	Centers for Disease Control & Prevention (ACCE Framework) http://www.cdc.gov/genomics/gtesting/ACCE/	Analytic validity encompasses basic aspects of test performance, such as analytical sensitivity, and specificity, precision, and reproducibility.
Clinical Validity	The ability to check how consistently and accurately a test detects or predicts the outcomes of interest in a patient population.	Centers for Disease Control & Prevention (ACCE Framework) http://www.cdc.gov/genomics/gtesting/ACCE/	. Clinical validity links test performance to the ability to identify a specific disease or condition, and encompasses aspects of test performance such as clinical sensitivity and specificity and predictive value.
Clinical Utility	The ability of a test to inform an appropriate clinical treatment decision to improve patient outcomes.	Centers for Disease Control & Prevention (ACCE Framework) http://www.cdc.gov/genomics/gtesting/ACCE/	In addition to determining the degree to which a test informs an appropriate treatment decision, clinical utility implies that the test is relevant for use in clinical decision making and that action based on test results has the potential to <i>improve patient outcomes</i> . Tests that are clinically valid, however, may not be clinically useful (e.g., a gene mutation may be associated with a clinical condition; however, knowledge of a mutation may not change patient management in a way that can chance health outcomes).

Term	Definition	Source	Relevance and Context
<i>Diagnostic Assessors/Schemes</i>			
<i>US FDA</i>			
Humanitarian Use Device (HUD)	Devices that are used in small patient populations (i.e., affecting fewer than 4,000 individuals in the US per year).	US Food & Drug Administration (FDA) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm	HUD is a regulatory category designated by FDA to promote development of medical devices and laboratory tests for rare diseases and conditions. To obtain approval for a HUD, a sponsor must submit a humanitarian device exemption (HDE) application to the FDA. An HDE is similar in both form and content to a premarket approval (PMA) application but is exempt from the effectiveness requirements of a PMA (i.e., must show safety, with plausible evidence of effectiveness through post market study annual reports and/or clinical literature).
Research Use Only (RUO)	Tests (or other products) primarily for research/laboratory use only that have not been approved or cleared for clinical use as a marketed product by FDA. A research device cannot be intended for human clinical diagnostic or prognostic use.	US Food & Drug Administration (FDA) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm253307.htm http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=809.10	RUO products are differentiated from clinical products in that, since results are not intended to be returned to the patient or used in patient care, the tests are not required to be manufactured under the Quality Systems Regulations requirements for good manufacturing practices.

Term	Definition	Source	Relevance and Context
<i>US FDA (continued)</i>			
Analyte-Specific reagent (ASR)	ASRs may include a variety of test components required to make the test work, including antibodies, receptor/ligand proteins, and nucleic acid sequences, primers or probes. These test components enable the test to work via specific binding or chemical reaction with a specimen.	US Food & Drug Administration (FDA) http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?FR=864.4020	Most ASR's are exempt from pre-market approval or notification requirements that apply to IVDs but must adhere to current Good Manufacturing Practices (cGMP) under the quality systems regulations and medical device reporting / labeling requirements. Some ASRs, such as those used in bloodbanking, donor screening, or to detect infectious agents of high public health significance (e.g., HIV or tuberculosis) require FDA review prior to marketing. ASRs are differentiated from General Purpose reagents, which do not have specific binding reactivity with any particular analyte (eg, general purpose buffers, enzymes, etc.).
Investigational Use Only (IUO)	A term used to describe tests (or other products) that may be used in clinical studies that may lead to their clearance or approval for use in clinical practice.	US Food & Drug Administration (FDA) http://www.personalizedmedicinecoalition.org/sites/default/files/files/FDA_Guidance_IVD_IUO_RUO.pdf	IUO tests are not intended to be used in clinical practice outside of the clinical research setting, but may be marketed and used in research and investigation of other FDA-regulated products.

Term	Definition	Source	Relevance and Context
<i>US FDA (continued)</i>			
Laboratory Developed Tests (LDTs)	Tests that are developed in and for use specifically by a particular laboratory. These were referred to in the past as “home brew” tests.	National Human Genome Research Institute http://www.genome.gov/10002399	<p>FDA has asserted having the legal authority but historically has not exercised its oversight enforcement with respect to LDTs. Generally LDTs are subject to the test performance standards of CLIA. CLIA performance standards do not cover safety and efficacy of the test (which is an element of FDA clearance or approval) but focus of demonstration that the test is replicable in a quality-controlled environment. CLIA requires quality of all LDTs to be established and verified in the laboratory, with approval by the laboratory director.</p> <p>As of July 2010, FDA has begun signaling they plan to exercise their regulatory authority over some LDTs as medical devices.</p>