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BLUEPRINT FOR BREAKTHROUGH FORUM

RESEARCH AND REIMBURSEMENT IN THE AGE OF PRECISION MEDICINE

GOAL

This whitepaper addresses the need to establish minimum analytical and clinical data elements to improve transparency in test performance and expand sources of evidence collection that could ensure patient and provider confidence. This whitepaper focuses specifically on next generation sequencing-based tests intended to detect somatic mutations in clinically actionable genes in solid tumors.

INTRODUCTION

Next-generation sequencing (NGS) is becoming a commonly used tool in cancer treatment to provide essential information about a patient's diagnosis and treatment options. These tests are widely available as laboratory developed tests (LDT) and, in recent months, the Food & Drug Administration (FDA) approved several new diagnostic tools that utilize NGS technologies as well. Further, the Center for Medicare & Medicaid Services (CMS) issued a national coverage decision to support coverage for certain NGS-based tests.

These advancements in diagnostic technology and regulatory and coverage policy present new opportunities to gain information about hundreds of genomic alterations at once. Providing adequate information about tests to patients and physicians is critical to ensuring the appropriate clinical use and interpretation of test results. Transparency regarding the clinical performance and utility of different NGS-based tests available will aid in

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clinical decision-making and facilitate improvements in patient care. Furthermore, this information could help inform reimbursement decisions by private and public payors. However, the types of evidence and mechanisms to communicate this information are an area of continual debate. Demonstrating analytical and clinical validity and clinical utility of diagnostic tests requires time and money. Innovative reimbursement mechanisms can help facilitate and encourage the development of evidence over time with the ultimate goal of ensuring maximum benefit to patients and the healthcare system overall.

This whitepaper will address three key questions regarding reimbursement mechanisms designed to facilitate more transparency and robust evidence development for diagnostic tests with the intent of establishing consensus on best practices and next steps.

1. What is the minimum core dataset that should be made publicly available for NGS-based diagnostic tests? What information is important to patients, providers, and payors? How can this be updated over time based upon changes to the test or clinical knowledge?

2. What mechanisms exist to support the collection of this data in a real-world setting? What are the standards needed to ensure collection of high-quality data?

3. How should the reporting of this data be formatted to make it readily informative to patients and providers in diagnostic and treatment decision-making?

Establishing a core dataset for informing patients, providers, and payors of optimal use of NGS-based diagnostic tests.

The technology upon which diagnostic tests are based is becoming increasingly sophisticated, making it more difficult, and simultaneously more imperative, to validate them and accurately and transparently communicate their performance specifications. Patients, providers, and payors require greater transparency regarding the analytical and clinical validity and clinical utility of diagnostic tests to ensure public confidence and support their use. However, appropriate levels of transparency are difficult to achieve for these complex tests as the type and depth of information that should be shared varies according to the specific consumer of that information. Certainly, while payors require a wide range of detailed analytical and clinical data to support reimbursement decisions, patients and providers may desire access to more clinically relevant information conveyed in a meaningful manner to ensure that patients receive the most appropriate diagnostic test for them.

One approach to addressing transparency could be for laboratories to provide test performance characteristics in a standardized format available in a public database, on company websites, or

on third party sites (e.g., NIH, ASCO, AMP, CAP, etc.). This transparency would allow physicians and patients the opportunity to assess the potential advantages and disadvantages of individual tests. A second approach would be to provide a publicly available list of individual tests that meet certain analytical, and possibly clinical, performance characteristics using properly qualified reference samples and/or materials. This would provide patients and their physicians with assurance that the test being used to guide their care is accurate and reliable, without placing the potential burden of test evaluation on the patient or treating physician. Processes for certifying the test performance and updating the list of tests would require additional discussion. Ultimately, the goals are to ensure maximum benefit for patients and to incentivize clinically beneficial innovation by providing reimbursement commensurate with the quality and transparency of data provided.

In addition, one must also balance between the availability of such information and the administrative burdens of reporting it. Communicating adequate information in an appropriate format for each of the various stakeholders (patient, provider, and payor) will necessitate agreement upon a minimum set of validation elements that should be made public concerning each test and a standardized template for communicating these specifications in the least burdensome manner. For example, a standardized questionnaire could be adopted for reporting test validation elements to payors and a similar but simplified questionnaire could be adopted for making data publicly available for providers. Reports containing the data elements outlined in Table 1 could be generated and provided to patients, either as part of patient education materials concerning their specific test or as part of their laboratory test report.

Table 1: Data elements for public availability*

Validation Element	Validation Element Detail
Accuracy	
Method Comparison(s)[1, 2]	Compare new test to "standard of care" reference method
Specimen Types[1]	List all specimen types and how they were validated
Matrix Comparison(s)[1]	Indicate all validated sample matrices and how they were validated
Analytical Sensitivity	
Limit of Blank (LOB)	If applicable
Limit of Detection (LOD)	
Limits of Quantitation[1]	Include descriptions of analytically measurable range and clinically reportable range, if applicable
Linearity and Reportable Range[1]	If applicable
Minimum Input Quantity and Quality[1]	
Minimum Tumor Content[1]	
Precision	
Repeatability	Single operator, instrument, lot, day, and run
Intermediate Precision[1, 2]	Multiple operators, instruments, days, and runs within a lab
Reproducibility	Multiple labs/sites, if applicable
Lot-to-lot Reproducibility	Multiple reagent, calibrator, and control lots, as applicable
Reference Intervals	If applicable
Sample Stability	
Primary Sample	
Clinical Performance Characteristics	
Positive Percent Agreement (PPA)	Reported with respect to each variant type and LOD for that variant
Negative Percent Agreement (NPA)	
Overall Percent Agreement (OPA)[1, 2]	
Clinical Utility[1, 2]	
Intended Use Population(s)[1, 2]	
Clinical Outcomes Data[1, 2]	Summaries of studies supporting clinical outcomes of the specific test

*All validation elements should be reported with confidence intervals.
Note: All information above should be provided to payors, while only certain subsets may be appropriate and relevant for providers(1) and patients(2).

Furthermore, particularly for NGS-based gene panels, it may not be necessary to provide this information for all genes and variants on a panel but only for "clinically actionable" genes to reduce the administrative burden associated with reporting and provide predictability as to when reporting is appropriate. While the definition of "clinically actionable" can be controversial, one approach is to make publicly available a test's performance on FDA-approved biomarkers linked to the prescribing of an FDA-approved drug (Table 2).

Table 2: Representative clinically actionable gene targets relevant to oncology*

Gene	Disease	Indicated Drug(s)
BRAF	Non-Langerhans Cell Histiocytosis/Erdheim-Chester Disease, Anaplastic Thyroid Cancer, Melanoma, Non-Small Cell Lung Cancer	Vemurafenib, Dabrafenib + Trametinib, Dabrafenib, Vemurafenib, Binimetinib + Encorafenib, Cobimetinib + Vemurafenib, Trametinib
BRCA1	Ovarian Cancer	Niraparib, Rucaparib
BRCA2	Ovarian Cancer	Niraparib, Rucaparib
EGFR	Non-Small Cell Lung Cancer	Afitinib, Erlotinib, Gefitinib, Osimertinib
ERBB2	Breast Cancer, Esophagogastric Cancer	Ado-Trastuzumab Emtansine, Lapatinib, Lapatinib + Trastuzumab, Neratinib, Pertuzumab + Trastuzumab, Trastuzumab
KIT	Gastrointestinal Stromal Tumor	Regorafenib, Imatinib, Sunitinib
KRAS	Colorectal Cancer	Cetuximab, Panitumumab, Regorafenib
PDGFRA	Gastrointestinal Stromal Tumor	Imatinib
TSC1	CNS Cancer	Everolimus
TSC2	CNS Cancer	Everolimus

*This is not a comprehensive list. This list was limited to include single nucleotide variants and insertion/deletion events, initially, and could eventually be expanded to include other events relevant to oncology, including rearrangements with companion diagnostic claims such as ALK and ROS1 in non-small cell lung cancer or PDGFRB in dermatofibrosarcoma protuberans.

Many laboratories have also begun reporting gene signatures relevant to oncology, such as microsatellite instability and tumor mutational burden, which add further complexity to validation and should also be considered for NGS-based test reporting.

Further refinement of reporting could be achieved if different validation elements could be identified for public availability based upon different uses of a test. For example, limited public information, such as summary analytical validity, may be desired for lower tier tests since they are likely to be largely utilized for research purposes and the evidence base is still being established. However, it should be made clear to patients what is known and not known about the test being performed on them. For clinical uses to make treatment decisions, it may be desired to have components of analytical and clinical validity data available, and ultimately for the highest tiered tests that are used as companion diagnostics, clinical outcomes data would be important to be made readily available for different stakeholders.

Equally as critical as determining the appropriate metrics by which to assess a test's performance, is the source of data and the entity that validates the data. Evaluation of analytical and clinical performance may require access to appropriate clinical samples and/or reference materials. The availability of clinical samples, especially with clinical outcomes, is limited, so other sources and types of evidence should be explored, and the limitations understood. Specifically, the below sources of evidence would not be used to support clinical utility, see section "*Identifying innovative methods and standards for data collection on evolving uses in the real-world setting*" for exploration of the use of real-world data to support evidence of clinical utility.

Table 3: Sources of evidence to assess test performance

Sources of Evidence	**Evidence Supporting**
Clinical samples (with outcomes)	Analytical and clinical validity
Clinical samples (with known biomarker status but no clinical outcomes)	Analytical validity only
Reference materials (RMs)	Analytical validity only
Reference samples (as distinct from RMs)	Analytical validity only
Published literature	Clinical validity only

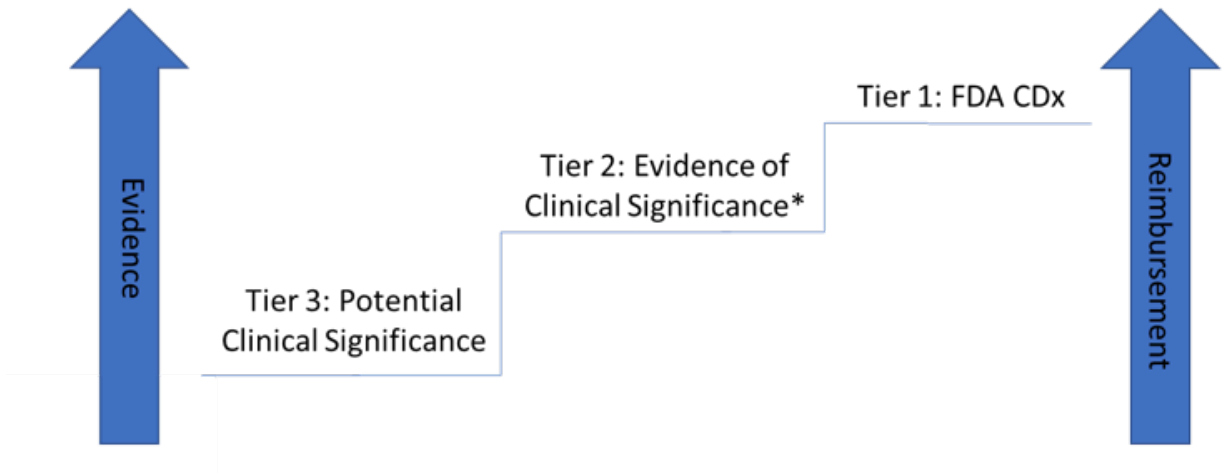
Appropriate third-party reviewers and frameworks for reporting validated data will be discussed in "*Identifying mechanisms to readily communicate data to patients and providers for diagnostic and treatment decision-making.*"

Identifying innovative methods and standards for data collection on evolving uses in the real-world setting.

The extensive efforts of test developers that have demonstrated analytical and clinical validity and clinical utility of their diagnostic tests should be recognized in some way such that it provides an incentive for test developers to pursue evidence generation (e.g., differential reimbursement, Figure 1). Mechanisms to establish clinical utility without a randomized clinical trial and assess changes in patient outcomes to justify payment and the role of evidence from the real-world setting were explored. Vehicles and standards for data collection in the real-world should be explored, including identifying real-world endpoints that can establish the clinical utility of molecular tests; defining a pathway to validate real-world endpoints; and a framework for the potential use of real-world evidence to support reimbursement of molecular tests.

Figure 1. Tiered reimbursement scheme. A potential model to incentivize test developers to pursue additional evidence generation.

Figure 1: Tiered reimbursement scheme



*with reporting of analytical and clinical validity

Table 4 lists possible real-world evidence that can be collected in order to support the use of a diagnostic test based upon the clinical outcome data elements and clinically actionable genes identified in Tables 1 and 2.

Table 4. Types of evidence to collect through real-world sources

	Component	**Description**	**Purpose and Utilization for Decision-making**
What is the context of use of the molecular test?	Disease Characteristics	Primary Cancer Type Stage at Diagnosis Current Clinical Stage/ Metastatic Disease Status Prior Line of Therapy	Clinical characteristics of patient population and impact on clinical endpoints
	Diagnostic Test	Test Vendor Test Type Genes and Variant Types Tested Genomic Results Quality Measures (as defined in Table 1)	Understand the testing performed
Does the molecular test impact clinical care decisions?	Change in Care	*Following physician receiving molecular test results…* Intent to Change Treatment (including stop and start of treatment; inclusive of targeted therapies, immunotherapies, and clinical trials) Change in Treatment (as measured by successful fill/ administration) Difference between Intent and Change (assess whether obstacles in therapy procurement or trials enrollment effected molecular test impact)	Understand whether testing led to change in care decisions
Does the molecular test improve outcomes?	Clinical Outcomes	Overall Survival Progression Free Survival Proxies (e.g. Time on Treatment, Time to Treatment Discontinuation, Time to Next Treatment) Tolerability / Toxicity (Time to First Hospitalization, Adverse Event Frequency) Objective Response Rate Proxies	Assess impact of testing-driven decisions on clinical outcomes
	Non-Clinical Outcomes	Patient Reported Outcomes (including Quality of Life, symptoms, physical function, impact on social roles)	Assess impact of testing-driven decisions on patient experience

Identifying mechanisms to readily communicate data to patients and providers for diagnostic and treatment decision-making.

While access to adequate and high-quality information regarding diagnostic tests for providers, patients, and payors is imperative, it is equally important that this information is made available in a format that is tailored to meet the needs of the intended audience.

PROVIDERS

A mechanism that identifies the appropriate information to convey expectations and capabilities of each test to providers is needed to support decision making. The CMS Appropriate Use Criteria (AUC) Program for advanced diagnostic imaging tests could be adapted for communicating information concerning quality and appropriateness of prescribing specific diagnostic tests. As with the existing AUC Program, entities with expertise in diagnostic assessments could be identified for certification as provider led entities (PLE). These PLEs would be qualified to develop, modify, and endorse AUC based on the submissions of a minimum set of validation elements (Table 1) by diagnostic test manufacturers or clinical labs. AUC would then be incorporated into a qualified electronic clinical decision support mechanism (CDSM) to be referenced by providers. This process would enable physicians to order diagnostic tests on a patient-specific basis according to the test analytical and clinical validity and clinical outcomes information provided through the mechanism in a user-friendly format.

PATIENTS

Patients may not be aware of concerns with the specifics of a test's analytical validation, such as comparisons of minimum input quality or limits of detection, but an overall assurance that the test has been adequately validated is necessary to ensure confidence. A general grading scale of A, B, or C administered through the Appropriate Use Criteria program and reported to patients by providers could be used to convey the level and quality of data reported for tests to enable patients to become more informed and increase patient confidence in test outcomes. Overall performance results from organizations administering proficiency testing could also be provided for inclusion as a metric in the AUC grading scheme to provide a better understanding of the comparability of analytical performance across platforms and laboratories (Table 5). This grading scheme and reporting will be essential for standardizing the information reported to patients and physicians and ensuring the interpretability of lab report information. However, appropriate confidentiality mechanisms would be needed when implementing such a framework to avoid use of the framework as a marketing tool, which could undermine the true intent of the grading system. Further, patient and provider groups could make available a standardized questionnaire (Supplemental Table 1) to guide patient discussions with their healthcare team concerning their diagnostic tests to enable more informed patients and providers.

Table 5. Elements for consideration in a diagnostic test grading check-list

	Grade		
Validation or Proficiency Element	A	B	C
Accuracy			
Analytical Sensitivity			
Precision			
Sample Stability			
Gene Coverage			
Clinical Performance Characteristics (PPA, NPA, OPA)			
Clinical Validity (Quality and quantity of data)			
Clinical Utility (Impact on clinical care and outcomes)			

PAYORS

Consistent with the existing Appropriate Use Criteria program, Medicare reimbursement decisions could be tied to provider consultation of AUC through qualified CDSMs during their diagnostic test decision making process. As the AUC program currently specifies, ordering providers would be required to consult CDSMs and report this consultation information to furnishing providers. Furnishing providers would then be responsible for including on the Medicare claim information about the ordering professional's consultation with a CDSM.

Questions for consideration

1. For a clinically well characterized biomarker with an existing companion diagnostic test, what is required to establish confidence in that test by physicians? Patients? For reimbursement? Is a clinical trial always necessary?

2. Could data collected from clinical experience with an NGS test be used to identify a targeted population? If so, what would the desired data elements be?

3. Are there scenarios in which an NGS test could be eligible for reimbursement without being contemporaneously developed with a drug (if so, when is a prospective demonstration of clinical outcomes the only acceptable approach)?

4. When a new companion diagnostic/drug pair becomes approved for a "new" variant or for a "new" indication, what evidence should existing tests provide in order to qualify for regulatory approval? For reimbursement?

5. Should "higher" levels of evidence support higher levels of reimbursement from payors? What are the "tiers" of evidence that warrant higher levels of reimbursement? Is this feasible given the existing billing codes?

6. What incentives or legal protections would need to be in place to promote data sharing and development of an evidence base (either for reimbursement purposes or regulatory decisions?

7. Is it possible to promote sharing into research-grade databases, using the established metrics, such that these could be elevated to regulatory-grade with improved evidence base?

SUPPLEMENTAL TABLE 1

Patient Questionnaire
Important Questions to Ask My Healthcare Team Before My Procedure

PATIENT NEEDS	BASIC QUESTIONS	YES	NO	NOTES FOR HEALTHCARE TEAM
Transparency	Has it been explained to me why I need this test?			
	Have the benefits of the test been explained to me?			
	Have the risks associated with the test been explained to me?			
	Has the accuracy of this test been explained to me, as compared to other, similar tests?			
	Who will be performing the diagnostic test? (Doctor, Technician, Nurse, Clinician, etc.?)			
Ongoing Communication with my Healthcare Team	Have the diagnostic test, procedure, and expected outcomes been explained to me in a way I understand?			
	Are other similar diagnostic tests available and have they been explained to me? (Why do I need this test; could another test help me more?)			
	Has the intent of the test been explained to me (what will it confirm or rule out)?			
	Has my informed consent been explained to me and do I understand what I am signing?			
	Have I been told what the test involves?			
Cost, Co-Pays, Financial Responsibilities	Has the actual cost of the test, co-pays, and other out-of-pocket expenses been explained to me?			
	Will my private insurance pay for this test?			
	Will Medicare or Medicaid pay for this test?			
	Do I need prior authorization for this test?			

This questionnaire was developed as a guideline to assist patients and caregivers with specific questions to ask their healthcare team in the event of the necessity of a diagnostic test. It is not all inclusive. Each patient has a different story with different treatments and care plans for their disease, as well as other concerns. This is meant to initiate a good foundation and obtain information that is very basic to the needs and questions of a patient undergoing diagnostic procedures.

PATIENT NEED	BASIC QUESTIONS	YES	NO	NOTES FOR HEALTHCARE TEAM
Procedure / Test Description	Do I understand the actual procedure (has it been explained to me in a way I understand)?			
	Will I have pain? (Will I be anesthetized?)			
	Has the length of the procedure been explained?			
	Has the prep (if any) for the procedure been explained?			
	Have I been told how soon the procedure will be scheduled?			
	Is there a video / handout / or other resource available that I can research the procedure to be better prepared?			
	Have medications used in the procedure been explained to me?			
	Have they explained to me how long it will take to receive the results?			
	Have possible medications been explained to me due to the results of the procedure?			
	Have any potential interactions with my current treatment plan been explained to me?			
Understanding Terminology	Have medical terms, abbreviations, or acronyms been explained to me?			
	Do I understand them fully?			
	Do I have further questions on anything relative to the procedure?			
Resources, Research & Other Questions	What genes does this test identify and are they relevant for my cancer and possible treatment decisions?			
	Where can I obtain more information on my specific test (FDA approved? Lab Developed Test?, etc.)			
	What information is available regarding the clinical outcomes of the test that was ordered for me?			
	If I have other specific questions, who do I ask?			
	Can I change my mind about receiving the test?			

Patient Date