

RECOMMENDATIONS

Institute of Medicine

MARCH 2016 • BIOMARKER TESTS FOR MOLECULARLY TARGETED THERAPIES

Given rapid developments in the field of precision medicine, how can health care providers, regulators, payers, and test developers ensure that patients have timely access to tests that can accurately direct targeted treatments, while at the same time protect them from potential harm caused by the use of poorly validated or inappropriate tests?

The Institute of Medicine of the National Academies of Sciences, Engineering, and Medicine appointed a committee of experts to examine this question. In its report, *Biomarker Tests for Molecularly Targeted Therapies: Key to Unlocking Precision Medicine*, the committee recommends an integrated set of actions aimed at addressing clinical practice, regulatory and reimbursement policy, and data challenges through the framework of a rapid learning system.

The committee identified ten goals to further advance the development and appropriate clinical use of biomarker tests for molecularly targeted therapies. The committee's recommended approaches to achieving those ten goals are found below.

Goal 1: Establish common evidentiary standards of clinical utility—using evidence generated both within and outside the context of clinical trials—across all stakeholders.

RECOMMENDATION 1

The Secretary of HHS should facilitate the development of common clinical utility evidentiary standards that are applied for initial and ongoing coordinated regulatory, coverage, and reimbursement decisions for biomarker tests for molecularly targeted therapies. One mechanism for development of these evidentiary standards could be convening one or more independent, public-private, multi-stakeholder bodies.

- Consistent and coordinated evidentiary standards and study design approaches, including rapid learning systems, should be developed that simultaneously accommodate the various types of decisions (including clinical, regulatory, coverage/reimbursement, and guideline recommendations), and facilitate the ongoing development of evidence of clinical utility.
- Involvement of a variety of stakeholders will be critical to ensure that clinical utility studies are designed to reflect a range of decision-making needs and to strike an acceptable balance between ideal utility assessment and study feasibility. Stakeholders participating in these initiatives should include patients, health care providers, clinical practice guideline

developers, public and private payers (including the Centers for Medicare & Medicaid Services), the Food and Drug Administration, test developers, pharmaceutical companies, molecular pathologists, clinical laboratory geneticists, and research funders (e.g., the Patient-Centered Outcomes Research Institute, the National Institutes of Health, and the Agency for Healthcare Research & Quality).

- Recognizing that evidentiary standards for clinical utility may vary across diseases, HHS could determine that more than one advisory body may be necessary to develop such disease-specific standards.
- Standards for ongoing development of clinical utility evidence will be used to guide the creation of new labels for biomarker tests and corresponding therapies (see Recommendation 3), and for guideline development (see Recommendation 10).
- Analytic and clinical validity of biomarker tests should be assured prior to assessing clinical utility.
- HHS should continue to support ongoing refinement of common evidentiary standards as they evolve.

Goal 2: Establish a more coordinated and transparent federal process for regulatory and reimbursement decisions for biomarker tests for molecularly targeted therapies.

RECOMMENDATION 2

The Secretary of HHS should facilitate the development of a new integrated federal review process involving FDA and CMS, as a pathway for coordinated regulatory, coverage, and reimbursement decisions for IVD and LDT biomarker tests for molecularly targeted therapies, including multi-analyte tests performed using current or new technologies, and any corresponding molecularly targeted therapies. This coordinated pathway should accomplish all of the following through application of common evidentiary standards (as described in Recommendation 1):

- Primary (and follow-on) biomarker test review and approval with detailed test labeling requirements (as described in Recommendation 3).

- Drug review and approval with detailed labeling that includes standardized biomarker test information (as described in Recommendation 3), when occurring concurrently with biomarker test review.
- A national uniform coverage decision for a biomarker test and molecularly targeted therapy in specific clinical uses, including financial incentives for data submission on use and outcomes (see Recommendation 7).
- A defined process for coordinated updates of biomarker test and drug labels.
- Public sharing of the summary data upon which the review process based their approval and coverage decisions for a biomarker test and drug combination.

Goal 3: Enhance communication to patients and providers about the performance characteristics and evidence for use of specific biomarker tests for molecularly targeted therapies.

RECOMMENDATION 3

FDA should develop a patient- and provider-friendly standardized label for IVD and LDT biomarker tests to facilitate transparency of test performance characteristics and the level of evidence for the intended use(s) of the test. The FDA or laboratory accrediting bodies should approve the label for each biomarker test, including tests not reviewed through the integrated process specified in Recommendation 2.

- Labels should prominently feature an easily understood ranking system (e.g., 4-star scales) separately for the evidence to

support the clinical validity and clinical utility for each intended clinical use of a test. The evidence ranking standards could be developed by the process described in Recommendation 1.

- Labeling should be subject to expedited revision as further evidence develops, providing an incentive for developers to establish the clinical utility of their products.
- Labels should use standardized terminology and should be clear enough for patients to understand as well as sufficiently useful to inform clinical decision making and to provide a basis for reimbursement.

Goal 4: Update and strengthen the oversight and accreditation of laboratories providing biomarker tests for molecularly targeted therapies.

RECOMMENDATION 4

The Secretary of HHS should establish and enforce up-to-date laboratory accreditation standards for biomarker tests for molecularly targeted therapies, either through CMS' CLIA or in collaboration with an existing up-to-date accreditation organization. Reimbursement for such biomarker testing should be dependent on meeting these standards.

- Current CLIA standards are inadequate for current advanced biomarker tests performed using NGS and other emerging technologies.
- These standards should comply with test labeling requirements (see Recommendation 3).

Goal 5: Ensure ongoing assessment of the clinical utility of biomarker tests for molecularly targeted therapies.

RECOMMENDATION 5A

When existing evidence of clinical utility is sufficient for initial use of a biomarker test for a molecularly targeted therapy, CMS and other payers should develop reimbursement models that support the ongoing collection of data within a rapid learning system. Such data will be used to further assess the evidence of clinical utility.

Potential approaches that payers could use to support this data collection include the following:

- Reimbursement for biomarker tests that meet predefined clinical and evidentiary criteria (see Recommendation 1), with the requirement for ongoing postmarket data collection and assessment (through the national database as proposed in Recommendation 7).
 - These data could support decisions for continued reimbursement or provide the rationale for discontinued reimbursement for a specific biomarker test

and its molecularly targeted therapy for specific patient groups.

- Reimbursement for biomarker tests with data collection for patient populations for which the evidence is less substantial, such as rare diseases or underrepresented populations and less studied groups.
- Consider innovative incentives to promote the submission of data to the national repository for biomarker tests and molecularly targeted therapies that have initial evidence of clinical utility.
- CMS should seek to clarify and expand appropriate implementation of CED, which has potential to be an effective policy lever to generate evidence to support reimbursement decisions for promising technologies, such as biomarker tests for molecularly targeted therapies.

RECOMMENDATION 5B

PCORI and NIH, as well as other funding groups, should develop granting mechanisms that support the assessment of the clinical utility of biomarker tests for molecularly targeted therapies using rapid learning approaches.

Goal 6: Ensure development and use of EHRs and related biomedical informatics tools and assessments that support the effective clinical use of biomarker tests for molecularly targeted therapies.

RECOMMENDATION 6A	RECOMMENDATION 6B	RECOMMENDATION 6C	RECOMMENDATION 6D
<p>EHR and LIS vendors and relevant software developers should enable the capture and linkage of biomarker tests, molecularly targeted therapies, and longitudinal clinical patient data in the EHR to facilitate data transfer into one or more national databases (as described in Recommendation 7).</p> <p>The information to be structured in the EHR should include, at a minimum:</p> <ul style="list-style-type: none"> • Biomarker test specimen requirements (type, amount, handling). • Specific biomarker test results and interpretation (including actionable panel or NGS test results). • Treatments prescribed and diagnostic tests ordered (whether based on the biomarker test result or not). • Longitudinal clinical patient data. <p>The information to be structured in the LIS should include, at a minimum:</p> <ul style="list-style-type: none"> • Biomarker test descriptions (assay method, analytes assessed, test performance characteristics, quality metrics, and bioinformatics tools). 	<p>EHR vendors and relevant software developers should enable EHRs to facilitate point-of-care decision support for biomarker test ordering, reporting, and shared clinical decision making.</p> <ul style="list-style-type: none"> • EHR decision support should be layered: highly focused for within the office visit and more detailed for before or after the visit. • EHRs should allow for incorporation of practice guidelines and pathways as decision support, and also allow tracking compliance. • Patient portals linked to EHRs should provide biomarker test result information in a patient-friendly manner. • To enhance patient understanding, relevant educational materials should be accessible from within the portal. • Portals should include linkage to test labels (see Recommendation 3). 	<p>Health care institutions and physician practices should use EHRs that facilitate point-of-care decision support for biomarker test ordering, reporting, and clinical decision making. This point-of-care decision support should align with available evidence-based clinical practice guidelines.</p>	<p>Licensing and specialty boards should recognize Continuing Medical Education, Continuing Education Units, and Maintenance of Certification achieved through interaction with point-of-care decision support educational materials.</p> <ul style="list-style-type: none"> • Professional schools, post-graduate training programs, specialty boards, and continuing education programs should ensure that providers are skilled in the use of point-of-care decision support tools.

Goal 7: Develop and maintain a sustainable national database for biomarker tests for molecularly targeted therapies through biomedical informatics technology to promote rapid learning for the improvement of patient care.

RECOMMENDATION 7
<p>The Secretary of HHS should charge FDA and NIH to convene a Task Force (comprising FDA, CMS, the Department of Veterans Affairs, NIH, the Department of Defense, PCORI, and other public and private partners) to develop a sustainable national repository of biomarker tests, molecularly targeted therapies, and longitudinal clinical patient data to facilitate rapid learning approaches.</p> <ul style="list-style-type: none"> • This prospective, integrated, and structured database should include: biomarker test description, test results and interpretation, treatment decisions and outcomes, other relevant EHR data generated during clinical practice, clinical trial data, billing/reimbursement data, patient-reported outcomes, and longitudinal clinical patient data. • The national repository should be built and made accessible with appropriate de-identification, data security, and patient consent measures. • HHS should provide incentives to encourage data submission by all health care providers/health systems.

Goal 8: Promote equity in access to biomarker tests for molecularly targeted therapies and the expertise for effective use of the results in clinical decision making.

RECOMMENDATION 8A	RECOMMENDATION 8B	RECOMMENDATION 8C
<p>Agencies that fund the development or evaluation of biomarkers should include funding to identify and overcome barriers to promote equity, access, and public understanding of precision medicine.</p> <ul style="list-style-type: none">• Potential challenges include but are not limited to: economic factors, cultural/ethnic heterogeneity, geographic diversity, and the complexity of precision medicine.	<p>The Secretary of HHS and CMS should conduct demonstration projects to enable and assess the effectiveness of collaboration between community health care providers and larger health care centers and/or academic medical centers to be part of a rapid learning system.</p> <p>The demonstration projects should examine:</p> <ul style="list-style-type: none">• Use of reimbursement incentives by CMS for the multidisciplinary collection and review of patient data with clinical recommendations, using distance technology or telemedicine.• Reimbursement by CMS for genetic counseling services.	<p>Licensing and specialty boards should ensure that health care professionals have and maintain competencies needed for effective use of biomarker tests for molecularly targeted therapies.</p> <ul style="list-style-type: none">• Providers should demonstrate competency in communicating with patients about biomarker tests for molecularly targeted therapies.

Goal 9: Enhance specimen handling and documentation to ensure patient safety and the accuracy of biomarker test results.

RECOMMENDATION 9A	RECOMMENDATION 9B
<p>Professional organizations and accrediting entities should develop, and health care institutions and providers should implement, standards for specimen requirements, handling, and documentation (see Recommendation 6a) through an interdisciplinary effort including pathologists, interventionalists, surgeons, and other relevant experts.</p> <ul style="list-style-type: none">• Health care professionals who collect, process, and	<p>handle (label and ship) patient biomaterials for biomarker testing should ensure that adequate tissue is acquired to perform all necessary testing; that patients are protected from unnecessary/repeated procedures; and that samples are properly handled, with documentation in the EHR and/or the laboratory information system.</p> <p>The National Quality Forum should develop quality measures that assess unnecessary repeat specimen collections.</p>

Goal 10: Improve the processes for developing and updating clinical practice guidelines for the effective use of biomarker tests for molecularly targeted therapies.

RECOMMENDATION 10	
<p>Guideline-developing organizations (e.g., CAP, AMP, ACMG, ACC, NCCN, AHA, ASCO, ACP, and others) should expand interdisciplinary collaborations to develop integrated guidelines on the appropriate use of biomarker tests for molecularly targeted therapies.</p> <ul style="list-style-type: none">• Guidelines should be updated regularly and at intervals appropriate to advances in the field, widely disseminated, user-friendly, and developed with patient participation. They should conform to standards articulated by authoritative groups, including the Institute of Medicine and Guidelines International Network.	<ul style="list-style-type: none">• Guideline developers should consider the evolving clinical utility evidence, relative to the standards discussed in Recommendation 1, and from the proposed rapid learning system for biomarker tests.• The National Guideline Clearinghouse should expand its work in reviewing and rating guidelines.• EHR vendors/EHR purchasers should ensure that recommendations from high-quality guidelines are available within the EHR at the point of care (see Recommendation 6).• Frequently updated guidelines should serve as input to the iterative updating of test and drug labeling by the integrated federal review process (see Recommendation 2).

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