Biomarker Tests for Molecularly Targeted Therapies

Key to Unlocking Precision Medicine
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The IOM Committee will:

• Examine policy issues related to the clinical development and use of biomarker tests (including genomics-based tests) for targeting therapies to patients

• Review opportunities for and challenges to the use of biomarker tests to select optimal therapy

• Formulate recommendations to accelerate progress in the field

Areas of focus:

- **Regulation**: variability in the regulation of tests and combination products and the role of various oversight bodies

- **Reimbursement**: standards of evidence used by payers to make coverage decisions, and how to generate evidence of clinical utility

- **Clinical practice**: interpretation of molecular tests, clinical decision-making, dissemination of new technologies, and implications for clinical practice
Study Context

• Precision Medicine Initiative
• National Cancer Moonshot
• Evolving regulatory environment for Laboratory-Developed Tests (LDTs)
Study Context (con’t)

• 21st Century Cures
  – Removing barriers to data sharing/telehealth
  – Modern trial design and evidence development
  – Medical device regulation improvements

• Senate HELP Committee bills
  – Improving EHRs
  – FDA Device Accountability
  – Advancing Targeted Therapies for Rare Diseases
  – Combination Products Innovation
  – Advancing Breakthrough Medical Devices for Patients
Key Report Themes

- Accurate, reliable, clinically useful, and appropriately implemented biomarker tests for molecularly targeted therapies are key to realizing the full potential of precision medicine.

- Substantial variation in the evidence used to inform regulatory, reimbursement and treatment decisions ultimately limits the broader adoption of potentially useful biomarker tests for molecularly targeted therapies into clinical practice.

- In this rapidly changing field, regulation, coverage, reimbursement and practice guidelines will continue to evolve as evidence is generated and new information becomes available. A rapid learning system represents a framework for collecting and analyzing data and information and enables continuous learning from research and clinical practice.
Supportive Policy Environment

- Common evidentiary standards of clinical utility for biomarker tests for molecularly targeted therapies
- Integrated regulatory and reimbursement decision-making process
- Enhanced communication about test information
- Strengthened laboratory accreditation standards
- Ongoing assessment of clinical utility through research and clinical use of biomarker tests for molecularly targeted therapies

Processes to Improve Patient Care

- Equitable access to biomarker tests for molecularly targeted therapies
- Improved specimen handling and documentation standards
- Enhanced clinical practice guidelines development

Supporting Data Infrastructure

- Structured EHR data
- Capture of test information in a national database
RECOMMENDATION 1

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.
RECOMMENDATION 1 (con’t)

Involvement of a variety of stakeholders is critical to ensure that clinical utility studies reflect a range of decision-making needs and strike a balance between ideal clinical utility assessment and study feasibility:

- Patients
- Health care providers
- Clinical practice guideline developers
- Private and public payers
- Food and Drug Administration
- Test developers
- Pharmaceutical companies
- Molecular pathologists
- Clinical laboratory geneticists
- Research funders (e.g., PCORI, NIH, AHRQ)
RECOMMENDATION 2

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.

- This process will serve as a pathway for coordinated regulatory, coverage, and reimbursement decisions for IVD, LDT, and/or NGS biomarker tests and corresponding molecularly targeted therapies.
Biomarker Tests Submitted for Integrated FDA-CMS Review

Tests/Therapies

In Vitro Diagnostic (IVD)  Laboratory Developed Test (LDT)

Other tests/panels using Next Generation Sequencing (NGS) or other technology

Evidence

Application of Common Evidentiary Standards

Biomarker Test and Targeted Therapy Reviewed Together  Biomarker Test Reviewed Separately

Results

✓ Regulatory decision and national uniform coverage decision for biomarker test and molecularly targeted therapy for specific clinical uses

✓ Incentives for data submission to national repository

✓ Patient- and provider-friendly labels
RECOMMENDATION 3

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 review process (Recommendation 2).
## TEST FACTS

<table>
<thead>
<tr>
<th>CFTR G551D Mutation</th>
<th>Laboratory: Ajax Clinical Laboratory</th>
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<tbody>
<tr>
<td><strong>Test Purpose</strong></td>
<td>Detect a germline variant p.G551D in the CFTR gene associated with cystic fibrosis (CF) disease or carrier status.</td>
</tr>
<tr>
<td><strong>FDA Approved or Cleared</strong></td>
<td>☐ Yes ☑ No</td>
</tr>
</tbody>
</table>
| **Test Accuracy**    | **Analytic sensitivity:** 99% (95% CI 90%-100% when compared against referent method).  
**Analytic specificity:** 99% (95% CI 94%-100% when compared against referent method) |
| **Limitations**      | Only the targeted variant will be detected. Mutations or variants in other genes will not be detected. Although rare, false positive or false negative results may occur. All results should be interpreted in context of clinical findings, relevant history, and other laboratory data. |
| **Method Used**      | Allele-specific PCR (polymerase chain reaction) |
| **Sample Type**      | Peripheral blood |
| **Intended Use**     | Predict response of CF patients to treatment with ivacaftor. |
| **Clinical Relevance** | **** Does this improve health outcomes? **** |
| **Intended Use**     | Predict response of CF patients to treatment with lumacaftor. |
| **Clinical Relevance** | **** Does this improve health outcomes? **** |
RECOMMENDATION 4

Goal 4: Update and strengthen 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 should be dependent on meeting these standards.

- Current CLIA standards are inadequate for advanced biomarker tests performed using NGS and other emerging technologies.

*CMS regulates clinical laboratories through the Clinical Laboratory Improvement Amendments (CLIA)
RECOMMENDATION 5

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.
Reimbursement Policy Mechanism to Support Ongoing Assessment of Biomarker Tests for Molecularly Targeted Therapies

Investigational Experimental
Adequate evidence for initial clinical utility
Continued coverage
No longer covered

Ongoing data collection

Assessing Clinical Utility

Strength of Evidence
Low
High

Analytic Validity
Clinical Validity
RECOMMENDATION 5 (con’t)

• CMS should seek to **clarify and expand appropriate implementation of coverage with evidence development (CED)**, which has potential to be an effective policy lever to generate evidence to support reimbursement decisions for 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.
RECOMMENDATION 6

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: 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 (Recommendation 7).

Information to be structured in the EHR should include:
- Biomarker test specimen requirements (type, amount, handling)
- Test result and interpretation
- Treatment prescribed and test ordered
- Longitudinal clinical patient data
Recommendation 6b: 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.

- 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
  - Accessible patient educational materials
  - Linkage to test labels
RECOMMENDATION 6 (con’t)

Recommendation 6c: 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.

Point-of-care decision support should align with available evidence-based clinical practice guidelines.

Recommendation 6d: Licensing and specialty boards should recognize CME, CEU and MOC achieved through interaction with point-of-care decision support educational materials.

• 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.
RECOMMENDATION 7

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: The Secretary of HHS should charge FDA and NIH to convene a Task Force to develop a sustainable national repository of biomarker tests, molecularly targeted therapies, and longitudinal clinical patient data to facilitate rapid learning approaches.

Task Force members to include:
- FDA
- CMS
- NIH
- PCORI
- Department of Veteran’s Affairs
- Department of Defense
- Other public and private partners
National prospective, integrated, structured database to include:

- Biomarker test description
- Test results and interpretation
- Treatment decisions and outcomes
- Clinical trial data
- Longitudinal clinical patient data
- Patient-reported outcomes
- Billing/reimbursement data

Database to be made accessible with appropriate de-identification, data security and patient consent measures
RECOMMENDATION 8

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: 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.

• Potential challenges include but are not limited to: economic factors, cultural/ethnic heterogeneity, geographic diversity, and the complexity of precision medicine.
**RECOMMENDATION 8 (con’t)**

**Recommendation 8b:** 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.

The demonstration projects should examine:
- 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.

**Recommendation 8c:** 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.
RECOMMENDATION 9

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

Recommendation 9a: Professional organizations and accrediting entities should develop, and health care institutions and providers should implement, standards for specimen requirements, handling, and documentation through an interdisciplinary effort.

• Health care professionals 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.

Recommendation 9b: The National Quality Forum should develop quality measures that assess unnecessary repeat specimen collections.
RECOMMENDATION 10

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: Guideline-developing organizations should expand interdisciplinary collaborations to develop integrated guidelines on the appropriate use of biomarker tests for molecularly targeted therapies.

Guidelines should be:
- Updated regularly and at intervals appropriate to advances in the field
- Widely disseminated
- User-friendly
- Developed with patient participation
- Conform to standards articulated by authoritative groups, including the Institute of Medicine and Guidelines International Network
Rapid Learning System for Biomarker Tests for Molecularly Targeted Therapies

Ongoing Assessment of Clinical Utility of Biomarker Tests

- Integrated Regulatory and Reimbursement Review
- Improved Communication regarding Test Performance and Use through Standardized Labels
- Strengthened Laboratory Accreditation

Key:
- Policy Environment Recommendations 1-5
- Data Infrastructure Recommendations 6-7
- Patient Care Processes Recommendations 8-10

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