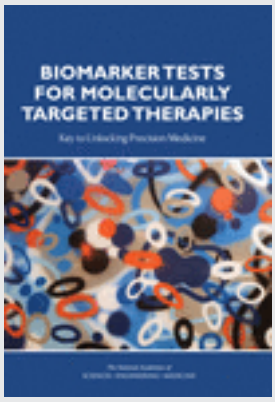

Biomarker Tests for Molecularly Targeted Therapies: Key to Unlocking Precision Medicine

DETAILS

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BIOMARKER TESTS FOR MOLECULARLY TARGETED THERAPIES

Key to Unlocking Precision Medicine

Committee on Policy Issues in the Clinical Development and Use of Biomarkers for Molecularly Targeted Therapies

Laurene A. Graig, Jonathan K. Phillips, and Harold L. Moses, *Editors*

Board on Health Care Services

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Contents

Boxes, Figures, and Tables

BOXES

FIGURES

TABLES

Acronyms

AABB	American Association of Blood Banks
AACR	American Association for Cancer Research
AAFP	American Academy of Family Physicians
ABL1	Abelson murine leukemia viral oncogene homolog 1
ABMS	American Board of Medical Specialties
ACC	American College of Cardiology
ACCE	analytic validity, clinical validity, clinical utility, and ethical/legal/social implications
ACGME	Accreditation Council for Graduate Medical Education
ACLA	American Clinical Laboratory Association
ACMG	American College of Medical Genetics and Genomics
ACP	American College of Physicians
ADLT	advanced diagnostic laboratory test
AHA	American Hospital Association; American Heart Association
AHLA	American Health Lawyers Association
AHRQ	Agency for Healthcare Research & Quality
ALK	anaplastic lymphoma kinase
AMA	American Medical Association
AMIA	American Medical Informatics Association
AMP	Association for Molecular Pathology
ASCO	American Society of Clinical Oncology
ASCP	American Society for Clinical Pathology
ASTRO	American Society for Radiation Oncology

ATA	American Telemedicine Association
AV	analytic validity
BCBSA	Blue Cross and Blue Shield Association
BCR	breakpoint cluster region
BRAF	B-RAF proto-oncogene, serine/threonine kinase
BRCA	breast cancer susceptibility gene
CancerLinQ	Cancer Learning Intelligence Network for Quality
CAP	College of American Pathologists
CCHPCA	Center for Connected Health Policy
CDC	Centers for Disease Control and Prevention
CDD	coverage with data development
CDE	common data element
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDSS	clinical decision support system
CE	continuing education
CED	coverage with evidence development
CER	comparative effectiveness research
CEU	Continuing Education Unit
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CLEP	Clinical Laboratory Evaluation Program
CLFS	Clinical Laboratory Fee Schedule
CLIA	Clinical Laboratory Improvement Amendments of 1988
CLIAC	Clinical Laboratory Improvement Advisory Committee
CME	Continuing Medical Education
CMS	Centers for Medicare & Medicaid Services
CMTP	Center for Medical Technology Policy
COI	conflict of interest
COLA	Commission on Office Laboratory Accreditation
COSMIC	Catalogue of Somatic Mutations in Cancer
CPG	clinical practice guideline
CPT®	Current Procedural Terminology
CU	clinical utility
CV	clinical validity
DNA	deoxyribonucleic acid
DoD	Department of Defense
DTWG	Diagnostic Test Working Group

EGAPP	Evaluation of Genomic Applications in Practice and Prevention
EGFR	epidermal growth factor receptor
EHR	electronic health record
eMERGE	Electronic Medical Records and Genomics
ER	estrogen receptor
FACT	Foundation for the Accreditation of Cellular Therapy
FAERS	FDA's Adverse Event Reporting System
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
FISH	fluorescence in situ hybridization
FTC	Federal Trade Commission
GA4GH	Global Alliance for Genomics and Health
GAO	Government Accountability Office
GDG	guideline developing group
GENIE	Genomics Evidence Neoplasia Information Exchange
GINA	Genetic Information Nondiscrimination Act of 2008
GPC	Green Park Collaborative
GTR	Genetic Testing Registry
GWAS	genome-wide association study
HCPCS	Healthcare Common Procedure Coding System
HELP	Senate Committee on Health, Education, Labor & Pensions
HER2	human epidermal growth factor receptor 2
HGVS	Human Genome Variation Society
HHS	Department of Health and Human Services
HIV/AIDS	human immunodeficiency virus/acquired immune deficiency syndrome
HLA	human leukocyte antigen
HMO	health maintenance organization
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
ICD	*International Classification of Diseases*
IHC	immunohistochemistry
IOM	Institute of Medicine
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IT	information technology

IVCT	in vitro clinical test
IVD	in vitro diagnostic
KRAS	kirsten rat sarcoma viral oncogene homolog
LCD	local coverage determination
LDP	laboratory-developed procedure
LDT	laboratory-developed test
LDTS	laboratory-developed testing service
LIS	laboratory information system
MAC	Medicare Administrative Contractor
MED-C	Molecular Evidence Development Consortium
MedPAC	Medicare Payment Advisory Commissions
MMWR	*Morbidity and Mortality Weekly Report*
MOC	Maintenance of Certification
MoPath	Molecular Pathology
MVP	Million Veterans Program
NASEM	The National Academies of Sciences, Engineering, and Medicine
NCCN	National Comprehensive Cancer Network
NCD	national coverage determination
NCI	National Cancer Institute
NCPF	National Cancer Policy Forum
NGS	next-generation sequencing
NGTS	next-generation tumor sequencing
NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health
NLM	National Library of Medicine
NLP	natural language processing
NQF	National Quality Forum
NRC	National Research Council
NSCLC	non-small-cell lung carcinoma
NYSDOH	New York State Department of Health
OIG	Office of the Inspector General
ONC	Office of the National Coordinator for Health Information Technology
OSTP	Office of Science and Technology Policy
PAMA	Protecting Access to Medicare Act of 2014
PBRSA	performance-based risk-sharing arrangement

PCAST	President's Council of Advisors on Science and Technology
PCORI	Patient-Centered Outcomes Research Institute
PCORNet	National Patient-Centered Clinical Research Network
PCTF	Payer Communication Task Force
PD-1	programmed cell death protein 1
PET	positron emission tomography
PFS	physician fee schedule
PGR	progesterone receptor
PGRN	Pharmacogenomics Research Network
PheWAS	phenome-wide association study
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PMA	premarket approval
PMC	Personalized Medicine Coalition
PMI	Precision Medicine Initiative
PROMIS	Patient Reported Outcomes Measurement Information System
PT	proficiency testing
PTEN	phosphatase and tensin homolog
RCT	randomized controlled trial
RNA	ribonucleic acid
RUSP	Recommended Uniform Screening Panel
SACGHS	Secretary's Advisory Committee on Genetics, Health, and Society
SACHDNC	Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
SNOMED CT	Systematized Nomenclature of Medicine's Clinical Terms
SNP	single-nucleotide polymorphism
TAPUR	Targeted Agents and Profiling Utilization Registry
TCGA	The Cancer Genome Atlas
VA	Department of Veterans Affairs

Summary[1]

Every patient is unique, and the evolving field of precision medicine aims to ensure the delivery of the right treatment to the right patient at the right time. In an era of rapid advances in biomedicine and enhanced understanding of the genetic basis of disease, health care providers increasingly have access to advanced technologies that may identify molecular variations specific to an individual patient, which subsequently can be targeted for treatment. Known as biomarker tests for molecularly targeted therapies, these complex tests have the potential to enable the selection of the most beneficial treatment (and also to identify treatments that may be harmful or ineffective) for the molecular underpinnings of an individual patient's disease. Such tests are key to unlocking the promise of precision medicine.

Biomarker tests for molecularly targeted therapies represent a crucial area of focus for developing methods that could later be applicable to other areas of precision medicine. The appropriate regulatory oversight of these tests is required to ensure that they are accurate, reliable, properly validated, and appropriately implemented in clinical practice. Moreover, common evidentiary standards for assessing the beneficial impact of biomarker-guided therapy selection on patient outcomes, as well as the effective collection and sharing of information related to those outcomes, are urgently needed to better inform clinical decision making. Getting

[1] This summary does not include references. Citations for the findings presented in the summary appear in subsequent chapters of the report.

biomarker tests right is imperative because a bad biomarker test is as problematic and potentially harmful as a bad drug.

Therein is the complicated issue addressed by this study: How do we ensure patients have timely access to appropriate tests that may accurately direct targeted therapies, while at the same time protect them from potential harm due to the adoption of poorly validated tests or inappropriately used tests? Patients with life-threatening diseases, in particular, cannot afford to wait for the answer to this question. The Institute of Medicine appointed an independent committee of experts to examine regulatory, reimbursement, and clinical practice policy issues that currently influence the adoption of biomarker tests for molecularly targeted therapies into routine clinical practice.

Biomarker test development and use are accelerating at a rapid rate, propelled by new research discoveries enabling even deeper understanding of the genetic basis of disease. However, the appropriate adoption and broader implementation into routine clinical use of such tests is held back by several interrelated factors: (1) lack of consensus over common evidentiary standards; (2) inefficient and inconsistent regulatory and reimbursement approaches; (3) the need for an effective framework for collecting patient data on tests, treatments, and outcomes; and (4) the need to translate such data into new knowledge to improve patient care and outcomes. Addressing these challenges will enable biomarker tests for molecularly targeted therapies to realize their potential to advance the clinical practice of precision medicine.

CONCLUSIONS

The first conclusion from the committee's deliberations is that the full potential of precision medicine will not be realized without accurate, reliable, clinically useful, and appropriately implemented biomarker tests for molecularly targeted therapies. Second, an integrated approach is necessary to effectively address the diverse challenges in clinical practice, regulation, reimbursement, and other interrelated issues associated with this highly complex area of health care. The committee proposes a rapid learning system as a framework for its recommendations because the evolving field of precision medicine requires an approach for accelerated learning that integrates research and clinical practice to enhance patient care and improve clinical outcomes.

Third, substantial variation in the evidence used to inform regulatory, reimbursement, and treatment decisions ultimately limits the adoption of potentially useful biomarker tests and targeted therapies into clinical practice. Innovative, customized policy approaches that reflect a clear

understanding of the unique evidentiary issues related to these complex and rapidly evolving tests are needed.

Fourth, the ability to implement a rapid learning system for biomarker tests for molecularly targeted therapies is currently limited, in part, because complete results of complex biomarker tests (including tests performed using next-generation sequencing, or NGS, technologies) are not widely available in the electronic health record (EHR), nor are these data structured for integration into clinical practice and research. The ability to track long-term outcomes for patients treated with molecularly targeted therapies is essential to understanding the potential benefits as well as risks of these complex tests and associated therapies. The development of one or more large, integrated, interoperable, and accessible clinical database(s) on patient outcomes related to use of biomarker tests for molecularly targeted therapies is critical to accelerate progress in precision medicine and to improve patient care.

Finally, the committee concludes that precision medicine may have the unintended consequence of intensifying disparities in access to advanced health care services such as biomarker testing for molecularly targeted therapies. Improved patient and provider education about precision medicine as well as improved collaboration across health care settings may help to reduce disparities.

RECOMMENDATIONS

The committee's recommendations focus on achieving 10 goals to further advance the development and appropriate use of biomarker tests for molecularly targeted therapies (see Box S-1). The recommended approaches to achieving these goals are designed to address a range of policy challenges; some of the committee's recommendations are intentionally broad, while others are more focused. Though the recommendations focus on diverse areas for improvement, they are linked together by a common understanding: properly validated, appropriately implemented biomarker tests hold the potential to enhance patient care and improve outcomes, and therefore addressing the challenges facing such tests is critical.

The committee's 10 recommendations are presented as interrelated components of a rapid learning system for biomarker tests for molecularly targeted therapies (see Figure S-1). Rapid learning systems serve as useful approaches to facilitate knowledge generation, and continuous learning, and accelerate the translation of lessons learned into better patient care and improved clinical outcomes. Thus, the committee's vision identifies opportunities to improve the policy environment, data infrastructure, and

BOX S-1
Goals for Advancing Appropriate Use of Biomarker Tests for Molecularly Targeted Therapies

1. Establish common evidentiary standards of clinical utility—using evidence generated both within and outside the context of clinical trials—across all stakeholders.
2. Establish a more coordinated and transparent federal process for regulatory and reimbursement decisions for biomarker tests for molecularly targeted therapies.
3. Enhance communication to patients and providers about the performance characteristics and evidence for use of specific biomarker tests for molecularly targeted therapies.
4. Update and strengthen oversight and accreditation of laboratories providing biomarker tests for molecularly targeted therapies.
5. Ensure ongoing assessment of the clinical utility of biomarker tests for molecularly targeted therapies.
6. Ensure development and use of electronic health records (EHRs) and related biomedical informatics tools and assessment that support the effective clinical use of biomarker tests for molecularly targeted therapies.
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.
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.
9. Enhance specimen handling and documentation to ensure patient safety and the accuracy of biomarker test results.
10. Improve the processes for developing and updating clinical practice guidelines for the effective use of biomarker tests for molecularly targeted therapies.

patient care processes that influence biomarker tests, while maintaining patients as the focal point.

Integrated Approach to Implementing the Committee's Recommendations

The committee recognizes that the creation of its proposed rapid learning system will require a significant amount of time, planning, resources, and collaboration among a range of stakeholders. Though ideally implemented as a unified set, some of the committee's recommendations, such as those related to EHRs and processes to improve patient care, can be implemented as stand-alone measures. By contrast, the policy recommendations are clearly interrelated and would be most effective if implemented together.

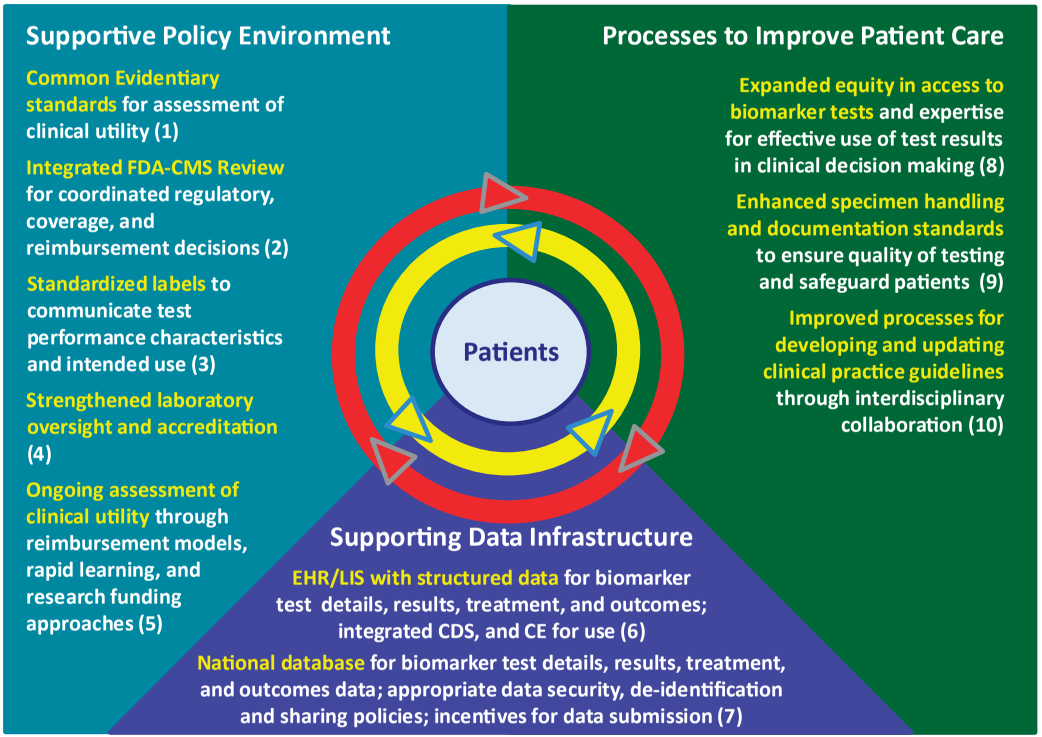

FIGURE S-1 Rapid learning system for biomarker tests for molecularly targeted therapies.
NOTES: Numbers in parentheses refer to committee's recommendations. CDS = clinical decision support; CE = continuing education; CMS = Centers for Medicare & Medicaid Services; EHR/LIS = electronic health record/laboratory information system; FDA = Food and Drug Administration.

The committee recommends that initial implementation efforts focus on the foundational recommendations, as shown in Figure S-2. This approach takes into account the need for and feasibility of achieving each component of the proposed rapid learning system. For instance, the committee recommends that the Department of Health and Human Services (HHS) should immediately begin to facilitate a process for development of common evidentiary standards of clinical utility for biomarker tests for molecularly targeted therapies. One mechanism for the development of such standards could be convening one or more independent, public–private multistakeholder bodies.

Other initial steps include HHS convening a task force to plan and execute the development of a national data repository to ensure that database development efforts proceed apace. At the same time, developers of EHRs and laboratory information systems (LISs) should make products available that can properly manage the data requirements of a rapid learning system for biomarker tests for molecularly targeted therapies.

The process for developing evidentiary standards would inform other aspects of the committee's integrated framework. For example, common evidentiary standards would facilitate the ongoing assessment of biomarker tests' clinical utility (whether use of the test leads to improved patient outcomes), which also would involve the flow of patient biomarker test data and information into a national data repository. The committee's recommended integrated review process for coordinated regulatory, coverage, and reimbursement decisions for biomarker tests for molecularly targeted therapies also would be aligned with common evidentiary standards.

Other interrelated actions recommended by the committee include the development of standardized test labels to communicate test performance characteristics and intended use(s) and rating of the evidence of a test's clinical validity (accuracy of a test for a specific purpose) and clinical utility; such standards would also evolve out of the standards development process. The committee's recommendations regarding updating and strengthening laboratory oversight and accreditation would improve the quality of biomarker testing and would enhance the implementation of the recommendations described above. Ultimately, the combined impact of the committee's recommended changes would translate into more efficient and effective processes to improve patient care, which would be further enhanced through implementation of the committee's specific recommendations relating to equity in access to biomarker tests, improved specimen standards, and coordinated development of clinical practice guidelines.

Health care providers, patients and patient advocates, researchers, test and drug developers and manufacturers, and policy makers all have

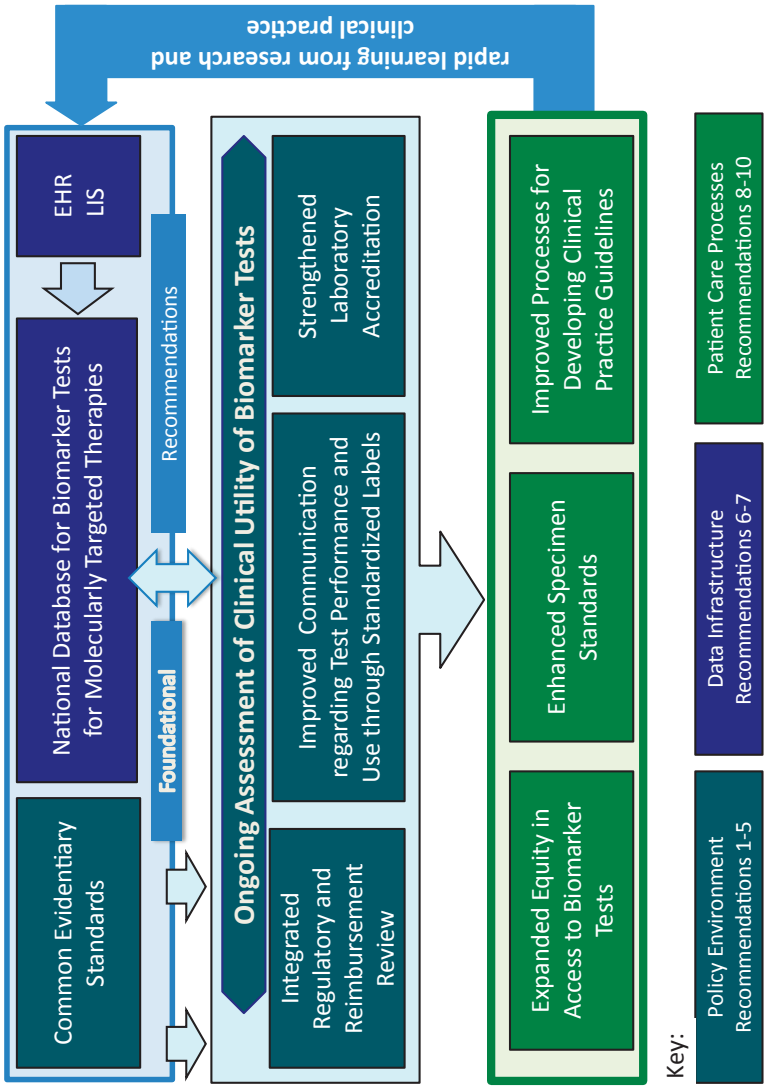

FIGURE S-2 Interrelationship of components of rapid learning system for biomarker tests.
NOTE: EHR = electronic health record; LIS = laboratory information system.

important insights to offer on the most effective way to implement the committee's recommendations. Leveraging the expertise and influence of this diverse stakeholder community will be critical to enhance the appropriate adoption of biomarker tests for molecularly targeted therapies into routine clinical practice. Although some recommendations provide specific direction to individual stakeholders, the full realization of the committee's vision of a rapid learning system requires collaboration among multiple stakeholders (see Figure S-3).

Common Evidentiary Standards

Uncertainty resulting from a lack of common evidentiary standards for clinical utility is a significant limiting factor for patients, health care providers, payers, and test developers. The committee's recommendation that HHS should facilitate the development of such standards recognizes the need for national leadership to bring all relevant stakeholders together. Doing so could provide a forum for sharing stakeholders' diverse perspectives and support the collaboration needed to forge agreement on the critical issue of establishing common evidentiary standards for biomarker tests for molecularly targeted therapies. Such standards will be integral to consistent regulatory, coverage, and reimbursement decisions.

The committee emphasizes that evidentiary standards evolve over time in this rapidly changing and highly complex field. Thus, HHS should ensure ongoing support to continually refine common evidentiary standards. As these standards are developed and modified, they will inform the development of clinical guidelines and be reflected in clinical standards of care.

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 the Department of Health and Human Services (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, multistakeholder bodies.

- **Consistent and coordinated evidentiary standards and study design approaches, including rapid learning systems, should**

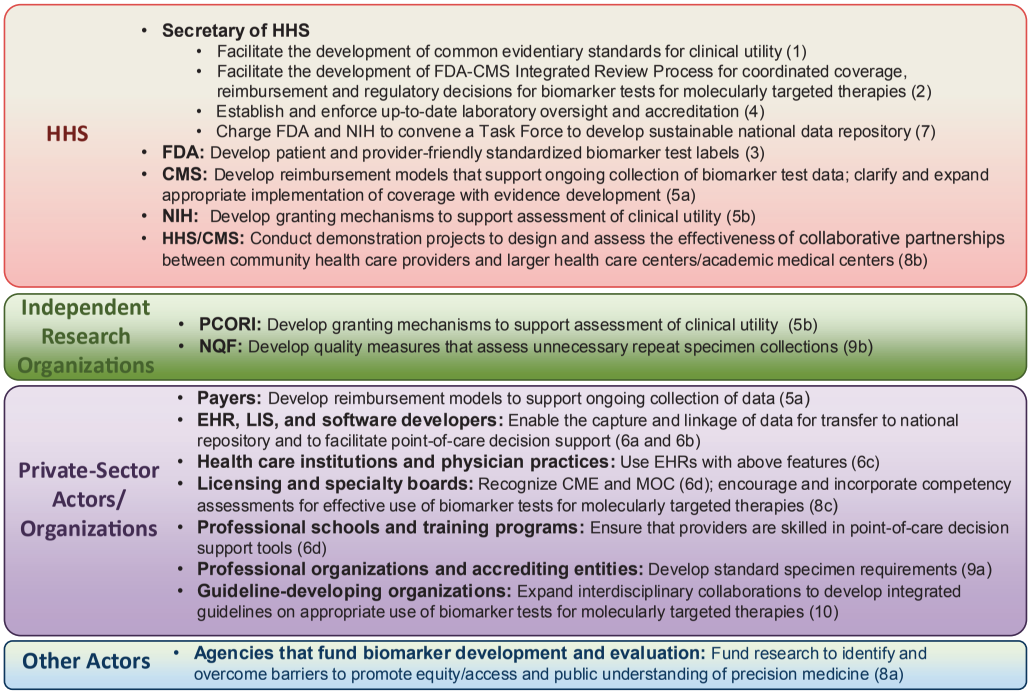

FIGURE S-3 Overview of responsibility for implementation of committee recommendations.
NOTES: Recommendation number in parentheses. CME = continuing medical education; CMS = Centers for Medicare & Medicaid Services; EHR = electronic health record; FDA = Food and Drug Administration; HHS = Department of Health and Human Services; LIS = laboratory information system; MOC = maintenance of certification; NIH = National Institutes of Health; NQF = National Quality Forum; PCORI = Patient-Centered Outcomes Research Institute.

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 and 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.**

Integrated Regulatory and Reimbursement Review

The inefficiencies created by the misalignment of the regulatory and reimbursement decision processes represent a significant challenge to the effective and timely implementation of appropriate biomarker tests for molecularly targeted therapies into clinical practice. The committee emphasizes the need for a coordinated Food and Drug Administration (FDA) and Centers for Medicare & Medicaid Services (CMS) process that enables an integrated concurrent review for regulatory, coverage, and reimbursement decisions for biomarker tests, including in vitro diagnostics (IVDs), laboratory-developed tests (LDTs), multianalyte tests such as NGS, and any associated molecular therapies (see Figure S-4). The committee recognizes the different statutory authority of the two agencies and

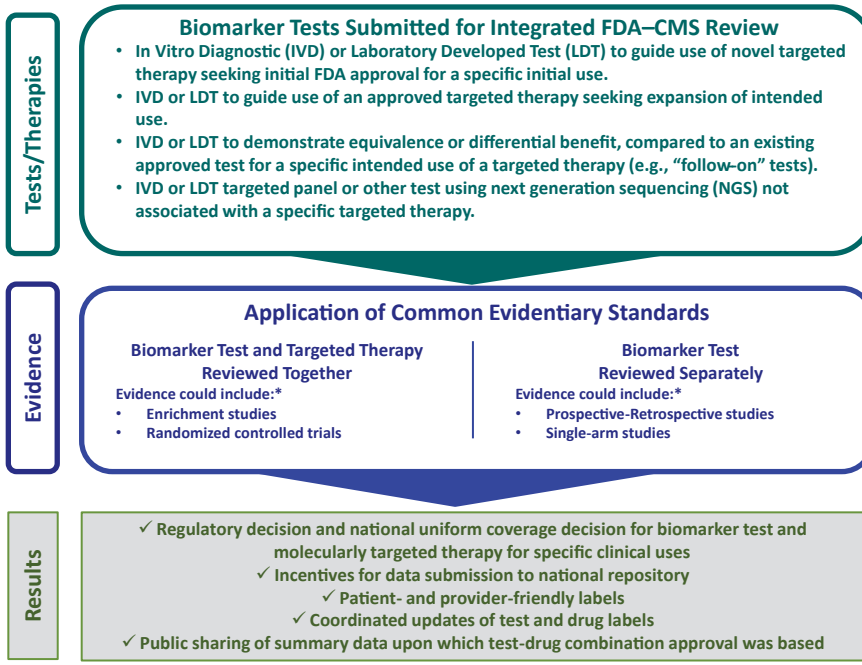

FIGURE S-4 FDA–CMS Integrated Review Process.
NOTE: CMS = Centers for Medicare & Medicaid Services; FDA = Food and Drug Administration.
* See Table 3-1 for descriptions of various approaches to evidence generation.

their distinct evidentiary requirements. The committee is not calling for statutory reconciliation of the two agencies; rather it emphasizes the need for the two agencies to work closely together to coordinate more effectively the decision-making process for regulatory, coverage, and reimbursement decisions related to a small subset of clinical tests: biomarker tests for molecularly targeted therapies.

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 the Department of Health and Human Services should facilitate the development of a new integrated federal review process involving the Food and Drug Administration and the Centers for Medicare & Medicaid Services, as a pathway for coordinated regulatory, coverage, and reimburse-

ment decisions for biomarker tests for molecularly targeted therapies (including in vitro diagnostics, laboratory developed tests, and multianalyte tests performed using current or new technologies, and any corresponding molecularly targeted therapies).[2] 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 the approval and coverage decisions for a biomarker test and drug combination.**

Test Performance and Intended Use Information

New patient- and health care provider-friendly labeling information, including a rating system that ranks the evidence to support the clinical validity and clinical utility of any biomarker test for molecularly targeted therapy, would increase the transparency of test performance and intended use. This would enable health care providers to clearly identify which test to order, while supporting patient engagement. Labeling information would be revised as further evidence develops through clinical use of the test.

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

[2] This coordinated pathway is designed to reflect the current predominant fee-for-service reimbursement system for clinical tests.

Recommendation 3: The Food and Drug Administration (FDA) should develop a patient- and provider-friendly standardized label for biomarker tests (including in vitro diagnostics and laboratory developed tests) to facilitate transparency of test performance characteristics and the level of evidence for the intended use(s) of the test. 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.**

Enhanced Laboratory Oversight

CMS regulates all clinical laboratories through the Clinical Laboratory Improvement Amendments (CLIA). Regulatory oversight under CLIA is widely viewed as insufficient for increasingly complex biomarker tests for molecularly targeted therapies.

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

Recommendation 4: The Secretary of the Department of Health and Human Services should establish and enforce up-to-date laboratory accreditation standards for biomarker tests for molecularly targeted therapies, either through the Centers for Medicare & Medicaid Services' Clinical Laboratory Improvement Amendments (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 next-generation sequencing and other emerging technologies.**

- **These standards should comply with test labeling requirements (see Recommendation 3).**

Ongoing Assessment of Clinical Utility

It is important to view the generation of evidence of the clinical utility of any biomarker test for molecularly targeted therapies as a continuous process; for a biomarker test that is ultimately demonstrated to have clinical utility, the quality of evidence improves over time, progressing along a continuum from investigational/experimental to adequate for initial clinical use, eventually attaining stronger evidence of clinical utility for various intended uses (see Figure S-5).

In many cases, new, promising biomarker tests may be implemented in clinical practice without sufficient data to support definitive reimbursement decisions using current coverage decision approaches. It is important that CMS and other payers develop payment models to support ongoing data collection required to establish sufficiently robust evidence to confirm the clinical utility of promising biomarker tests. These data would be instrumental for evolving payment determinations, includ-

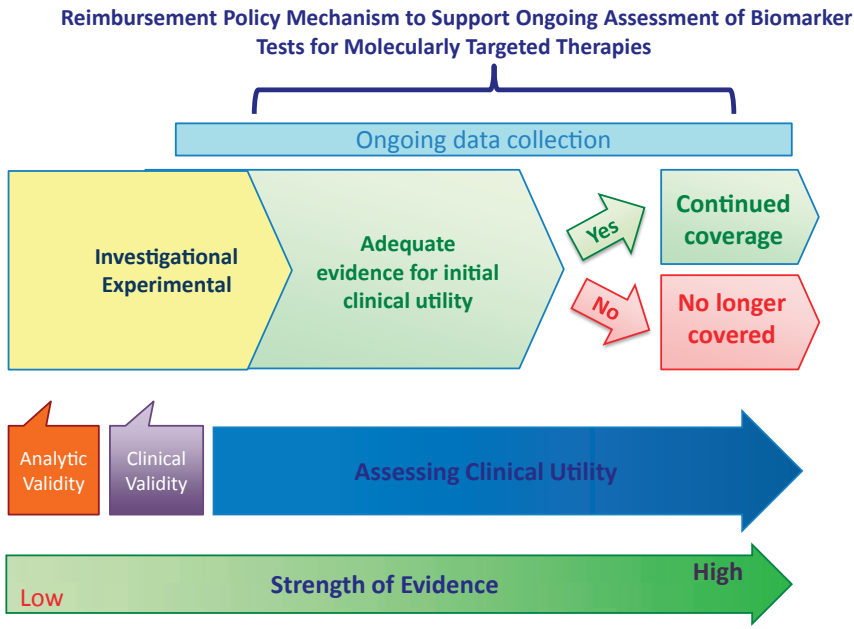

FIGURE S-5 Evidence continuum.

ing whether to discontinue payment for a specific biomarker test for which the clinical utility is not confirmed through additional evidence development.

Consistent with the committee's vision of a rapid learning system, and the central role of data in learning and knowledge generation, the committee recommends that 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 promising technologies such as biomarker tests for molecularly targeted therapies.

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, the Centers for Medicare & Medicaid Services (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 further to 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 coverage with evidence development, 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: The Patient-Centered Outcomes Research Institute and the National Institutes of Health, 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.

Development and Use of Effective EHRs

The committee highlights the critical role of EHRs and LISs in data collection and clinical decision support and underscores the importance of ensuring that EHRs are appropriately developed to facilitate the collection of real-time patient test, treatment, and outcomes data in a structured format. Moreover, EHR patient portals should be designed to provide relevant educational information for patients as well as links to detailed test label information. It is critical not only that vendors and software developers generate effective tools, but that health care providers take advantage of those tools to facilitate point-of-care decision support for biomarker test ordering, reporting, and clinical decision making. Appropriately structured EHR and LIS data will facilitate data transfer to a national data repository recommended by the committee.

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: Electronic health record (EHR) and laboratory information system (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).

The information to be structured in the EHR should include, at a minimum:

- **Biomarker test specimen requirements (type, amount, handling).**
- **Specific biomarker test results and interpretation (including actionable panel or next-generation sequencing test results).**
- **Treatments prescribed and diagnostic tests ordered (whether based on the biomarker test result or not).**
- **Longitudinal clinical patient data.**

The information to be structured in the LIS should include, at a minimum:

- **Biomarker test descriptions (assay method, analytes assessed, test performance characteristics, quality metrics, and bioinformatics tools).**

Recommendation 6b: Electronic health record (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.**
- **To enhance patient understanding, relevant educational materials should be accessible from within the portal.**
- **Portals should include linkages to test labels (see Recommendation 3).**

Recommendation 6c: Health care institutions and physician practices should use electronic health records (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.

Recommendation 6d: 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.

- **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.**

National Data Repository

The committee recognizes that much biomarker test data are not available publicly; rather, they are maintained in separate siloes at individual

institutions—a seemingly incongruous situation of a tremendous volume of genomic and genetic data combined with inability to access the data for broader learning purposes. In an effort to promote the public sharing of critical biomarker test data, the committee calls on HHS to facilitate collaboration between FDA and the National Institutes of Health (NIH) to convene a task force to develop a national repository of data related to biomarker tests and corresponding molecularly targeted therapies. HHS should provide incentive payments to encourage all health systems and providers to submit their data to the national repository, which will be built and made accessible with appropriate de-identification and data security measures.

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 the Department of Health and Human Services (HHS) should charge the Food and Drug Administration (FDA) and National Institutes of Health (NIH) to convene a task force (comprising FDA, the Centers for Medicare & Medicaid Services, the Department of Veterans Affairs, NIH, the Department of Defense, the Patient-Centered Outcomes Research Institute, 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.

- **This prospective, integrated, and structured database should include biomarker test description, test results and interpretation, treatment decisions and outcomes, other relevant electronic health record 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.**

Equitable Access

Patients of particular economic, ethnic, and cultural backgrounds and geographic locations may face challenges in obtaining access to precision

medicine's complex tools such as biomarker tests for molecularly targeted therapies. Dedicated research resources should support a comprehensive investigation to identify existing barriers to equitable access, and subsequently develop approaches to address them. Moreover, collaboration between community health care providers and larger health care centers or academic medical centers should be examined to determine potential impact on access for patients in remote and/or underserved areas.

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 8b: The Secretary of the Department of Health and Human Services and the Centers for Medicare & Medicaid Services (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.

- **Providers should demonstrate competency in communicating with patients about biomarker tests for molecularly targeted therapies.**

Enhanced Specimen Standards

The reliability of biomarker test results depends on the quality of the patient specimens. If the specimen is inadequate for tests that need to be conducted, repeat biopsy procedures may be required to obtain samples sufficient for testing, exposing the patient to unnecessary risk. Professional organizations and health care institutions should develop and implement standards for specimen adequacy and handling, as well as relevant documentation in the EHR and/or LIS.

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 (see Recommendation 6a) through an interdisciplinary effort, including pathologists, interventionalists, surgeons, and other relevant experts.

- **Health care professionals who collect, process, and 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 electronic health record and/or the laboratory information system.**

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

Improved Clinical Practice Guideline (CPG) Development Processes

Increasingly, a broader base of interdisciplinary expertise is needed to generate trustworthy CPGs related to complex biomarker tests. Consistent with the committee's vision of a rapid learning system, CPGs serve an important educational purpose—both for clinical decision making as well as for test and drug labeling—and should consider the evolving nature of evidence of clinical utility for biomarker tests for molecularly targeted therapies.

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 (e.g., the College of American Pathologists, Association for Molecular Pathology, American College of Medical Genetics and Genomics, American College of Cardiology, National Comprehensive Cancer Network, American Heart Association, American Society of Clinical Oncology, American College of Physicians, and others) 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, and developed with patient participation. They should conform to standards articulated by authoritative groups, including the Institute of Medicine and Guidelines International Network.**
- **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.**
- **Electronic health records (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).**

The committee's proposed rapid learning system is expressly designed to promote the proper development, effective and ongoing assessment, and appropriate use of biomarker tests for molecularly targeted therapies. Such a supportive framework would enable precision medicine's promising treatment-tailoring technologies to realize their full potential to improve patient outcomes.

1

Introduction

Every patient is unique, and the evolving field of precision medicine aims to ensure the delivery of the right treatment to the right patient at the right time. In an era of rapid advances in biomedicine and enhanced understanding of the genetic basis of disease, health care providers increasingly have access to advanced technologies that may identify molecular aberrations specific to an individual patient that subsequently can be targeted for treatment. Known as biomarker tests for molecularly targeted therapies, these complex tests have the potential to enable selection of the most beneficial treatment for the molecular underpinnings of an individual patient's disease. Such tests are key to unlocking the promise of precision medicine (see Box 1-1).

Further advances in precision medicine, however, require tests that are accurate, reliable, properly validated, and appropriately implemented in clinical practice, as well as the collection and sharing of information on the outcomes of patients whose treatment is guided by these biomarker tests. In other words, precision medicine requires getting the biomarker tests right to optimize the treatment of each patient and improve patient outcomes, while at the same time advancing our understanding of the role of genetics in disease. Getting the biomarker test right is crucial because a bad biomarker test is as problematic as a bad drug (Hayes, 2013).

Patients recognize the promise of molecularly targeted therapies and are looking to the scientific and biomedical communities to provide validated, reliable biomarker tests that accurately direct treatment at an individual level that has the potential to lead to better outcomes with fewer

BOX 1-1
Precision Medicine Defined

This study uses the definition of precision medicine adopted for use by the National Research Council in *Toward Precision Medicine* (NRC, 2011). The definition, which was developed by the President's Council of Advisors on Science and Technology, specifies precision medicine as:

> The tailoring of medical treatment to the individual characteristics of each patient . . . to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. (PCAST, 2008, p. 1)

side effects (IOM, 2012a). Research discoveries have enabled hundreds of investigational targeted agents to enter the cancer drug development pipeline, and several targeted cancer drugs have been approved for clinical use over the past several years. Progress has been uneven, however, because advances have not been consistent across all types of cancers, and meaningful improvements have been slow to materialize in many other disease domains (IOM, 2015c). Timely access to reliable tests that enable health care providers to accurately match therapies to individual patients is critical for patients with cancer and other diseases.

BIOMARKER TESTS

Remarkable scientific and technical advances have occurred over the past decade and a half, including breakthroughs that emerged from the first draft sequence of the human genome in 2001. That landmark achievement, and subsequent discoveries, served to propel biomedical research in genomics and other omics-based fields,[1] as well as bioinformatics

[1] "Omics" is a term encompassing multiple molecular disciplines that involve the characterization of global sets of biological molecules such as DNAs, RNAs, proteins, and metabolites. For example, genomics investigates thousands of DNA sequences, transcriptomics investigates all or many gene transcripts, proteomics investigates large numbers of proteins, and metabolomics investigates large sets of metabolites. Omics-based tests can be considered a complex form of a biomarker test. An omics-based test is derived from complex high-dimensional data; these data are often generated through measurement of many more variables per sample than the total number of biological samples used to generate the dataset. These data are used to produce a computational model that can be used to analyze samples from individual patients (IOM, 2012a).

and computational biology. This research has afforded a more profound understanding of the molecular and genetic basis of disease (IOM, 2012a). These biomedical advances have converged in the rapidly evolving field of precision medicine with a proliferation of complex tests identifying biological indicators, or biomarkers. Definitions and terminology are critical to a complex, rapidly evolving field such as biomarker tests for molecularly targeted therapies (see Box 1-2). The committee also provides additional scientific and technical definitions in the Glossary of the report.

Biomarkers are defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Biomarkers Definitions Working Group, 2001, p. 91). These can be measurements of macromolecules (DNA, RNA, proteins, lipids), cells, or processes that describe a normal or abnormal biological state in an organism (IOM, 2010a).

Biomarker tests have many different uses in clinical practice (see Table 1-1), including disease screening tests (e.g., prostate-specific antigen), diagnostic tests (e.g., pathologic or histologic assessment of a tissue biopsy), treatment and posttreatment monitoring tests (detection of treatment complications or subsequent disease advancement), and prognostic tests for estimating risk or time to clinical outcomes (e.g., aggressive cancers have a poorer prognosis than more indolent cancers). In addition, biomarker tests are used to predict patient response to specific treatments (IOM, 2007, 2010a).

Such predictive biomarker tests are used by health care providers to tailor treatment to an individual patient's clinical condition and treatment goals. A subset of these tests examines an individual's ability to metabolize a drug, primarily in the context of treatment-related toxicity. Another subset includes biomarker tests for specific aberrations in biological mechanisms of action that are associated with response or resistance to a specific targeted therapy. The clinical use of these predictive tests, referred to in this report as biomarker tests for molecularly targeted therapies, is the focus of this study.

A number of types of biomarker tests for molecularly targeted therapies are in clinical use (see Figure 1-1), ranging from single-analyte tests to guide the use of a single class of therapy (e.g., human epidermal growth factor receptor 2 [*HER2*] amplification and trastuzumab) to a suite of multiple, but separate, tests for single analytes to guide the use of multiple therapy options in a specific clinical context (e.g., estrogen receptor/progesterone receptor [ER/PGR] expression and *HER2* amplification for guiding treatment for breast cancer). Multiple-analyte panels include additional analytes for other clinical or research purposes, including assessing secondary response or resistance to targeted therapies or

BOX 1-2
Key Terms

Analyte: A substance that is the subject of analysis.[a]

Analytic Validity: The accuracy of a test to detect the specific entity that it was designed to detect. This accuracy does not imply any clinical significance, such as diagnosis.[b]

Biomarker: "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a[n] . . . intervention."[c]

Biomarker Test: A biochemical or other measurement developed to quantitate a biomarker.[d] These tests can evaluate biomarkers for the detection and treatment of asymptomatic individuals (screening), establishing the presence and precise description of disease (diagnosis), estimating the risk or time to clinical outcomes (prognosis), identifying patient likelihood to benefit from certain therapies (predictive) or to experience therapy-related risks (pharmacogenomics), or treatment and post-treatment monitoring purposes (e.g., early detection and treatment of advancing disease or complications).

Clinical Utility: "Evidence of improved measurable clinical outcomes, and [a test's] usefulness and added value to patient management decision making compared with current management without testing."[e]

Clinical Validity: The accuracy of a test for a specific clinical purpose, such as diagnosing or predicting risk for a disorder.[b]

Companion Diagnostic: Food and Drug Administration designation for a biomarker test "that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of [a] … companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product."[f]

eligibility for enrollment in clinical trials. Finally, the entire genome may be analyzed using next-generation sequencing (NGS) technology (IOM, 2015c; Meric-Bernstam et al., 2015; Yu et al., 2015). Rapid technological advances have decreased the per-analyte cost of testing (Hayden, 2014; Trosman et al., 2015).

However, the unprecedented amount of data available from a single NGS test, resulting from what is essentially a parallel series of hundreds, thousands, or even millions of single-analyte tests performed on a patient specimen, are blurring the line between clinical research and clinical care.

Germline Mutation: "Any heritable change in DNA sequence."[g]

Molecularly Targeted Therapy: In contrast with cytotoxic therapy, molecularly targeted therapies exploit known "driver" molecular biomarkers as therapeutic targets in diseases such as oncology.

Next-Generation Sequencing: "Also referred to as 'massively parallel sequencing' or 'high-throughput sequencing,' refers to technologies that perform DNA sequencing in parallel, allowing for the production of thousands or millions of sequences concurrently."[f]

Omics: Scientific disciplines comprising the study of related sets of biological molecules. Examples of omics disciplines include genomics, transcriptomics, proteomics, metabolomics, microbiomics, and epigenomics.[a]

Omics-Based Test: An assay composed of or derived from many molecular measurements and interpreted by a fully specified computational model to produce a clinically actionable result.[a]

Predictive Factor: A measure that identifies patients most likely to be sensitive or resistant to a specific treatment regimen or agent. [A predictive factor] is particularly useful when that measure can be used to identify the subgroup of patients for whom treatment will have a clinically meaningfully favorable benefit-to-risk profile.[a]

Prognostic Factor: A measure correlated with a clinical outcome in the setting of natural history or a standard of care regimen; it is a variable used to estimate the risk of or time to clinical outcomes.[a]

Somatic Mutation: "A change in the genetic structure that is neither inherited nor passed to offspring. Also called acquired mutations."[g]

SOURCE: [a] IOM, 2012a; [b] IOM, 2007; [c] Biomarkers Definitions Working Group, 2001; [d] IOM, 2010a; [e] Teutsch et al., 2009; [f] FDA, 2014; [g] HGP, 2012.

In oncology, for example, such a test result could suggest treatment with a variety of drugs, each with varying levels of evidence supporting their efficacy. The implications of this transition, specifically related to tests guiding the use of molecularly targeted therapies, are one of the central topics addressed throughout the subsequent chapters of this report.

Regardless of the type of biomarker test for molecularly targeted therapy being performed, the test results that ultimately inform treatment decisions rely on the performance and interpretation of these biomarker tests by anatomic and clinical pathologists (hereafter referred to collec-

TABLE 1-1 Clinical Uses of Biomarkers

Clinical Biomarker Use	Clinical Objective
Screening	Detect and treat early stage disease in the asymptomatic population.
Diagnosis/differential diagnosis	Definitively establish the presence and precise description of disease.
Classification	Classify patients by disease subset.
Prognosis	Estimate the risk of or the time to clinical outcomes.
Prediction/treatment stratification	Predict response to particular therapies and choose the drug that is most likely to yield a favorable response in a given patient.
Therapy-related risk management	Identify patients with a high probability of adverse effects of a treatment.
Therapy monitoring	Determine whether a therapy is having the intended effect on a disease and whether adverse effects arise.
Posttreatment monitoring	Provide early detection and treatment of advancing disease or complications.

SOURCES: Adapted from IOM, 2007, 2010a.

tively as pathologists), clinical laboratory geneticists, and other laboratory health care professionals. These professionals must be aware of existing and emerging uses and limitations of the testing methodologies and the interpretation of test results in order to reliably report the clinical significance of biomarker test results to other health care providers.

PRECISION MEDICINE

Biomarker tests for molecularly targeted therapies are used to select the therapy most likely to result in a favorable response in a given patient (IOM, 2012a). These tests are key to the clinical implementation of precision medicine, which depends on the application of information about molecular mutations or aberrations in an individual patient's genome or tumor to classify patients into subgroups based on their potential response to a specific treatment. The goal of this stratification is to ensure that patients receive the most beneficial therapies. Accurately matching therapy to the individual patient optimizes treatment selection by focusing specific therapies on those most likely to benefit and decreases treatment harms by avoiding treatment in those unlikely to respond

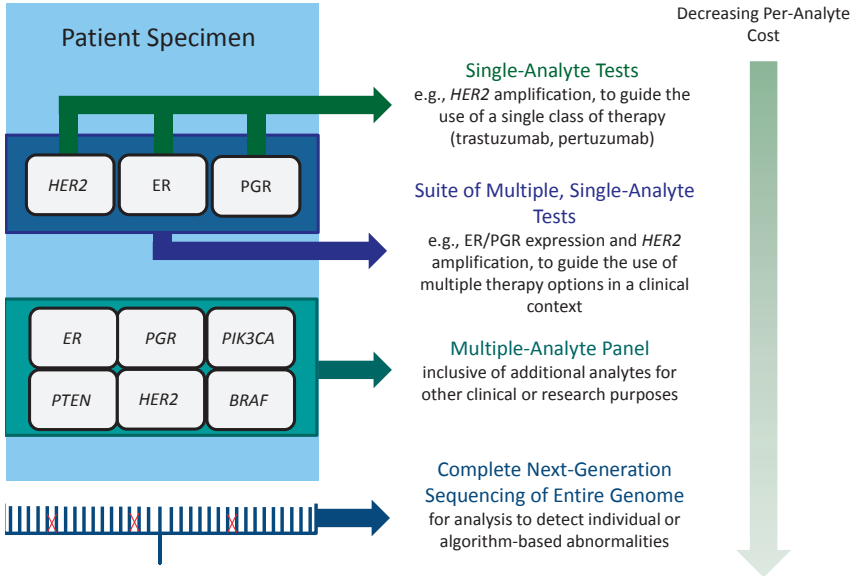

FIGURE 1-1 Types of biomarker tests.
NOTE: BRAF = B-RAF proto-oncogene, serine/threonine kinase, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, PGR = progesterone receptor, PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha, PTEN = phosphatase and tensin homolog; all are analytes potentially detected by biomarker tests in oncology.
SOURCE: Adapted from Yu et al., 2015.

or predicted to have an adverse reaction to treatment. Moreover, biomarker tests for molecularly targeted therapies may have the potential to "bend the health care cost curve" (Armstrong, 2012) through cost savings achieved by avoiding use of nonbeneficial treatments in specific patients (Armstrong, 2012; de Gramont et al., 2015; Jameson and Longo, 2015; NRC, 2011; Schott et al., 2015).

Certain biomarker tests have demonstrated cost-effectiveness, including some gene expression tests to predict risk of cancer recurrence for patients with early-stage breast cancer (Harris et al., 2007). These test results indicate that many women can safely avoid toxic and costly chemotherapy regimens (Jain and Gradishar, 2014; Lyman et al., 2007; Sparano et al., 2015). Studies also have shown that multiplexed testing of tumors for epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) gene rearrangements, followed by biomarker-guided molecularly targeted therapy is cost-effective compared to standard che-

motherapy without any testing in patients with metastatic non-small cell lung cancer (Romanus et al., 2015).

The underlying concept of precision medicine, namely using information about an individual patient's characteristics to direct treatment, is not a recent innovation. For example, "blood typing has been used to guide transfusions for more than a century" (Collins and Varmus, 2015, p. 793). However, the tremendous scientific advances over the past decade and a half are what have led to a deeper understanding of the molecular underpinnings of complex diseases, enabling researchers to identify the genetic alterations in tumors in great detail—including the specific genetic alterations that drive the growth of individual tumors. Much optimism exists that this newfound ability will lead to more effective treatments and improved outcomes for patients (IOM, 2015c). The recently launched Precision Medicine Initiative calls for significant financial investment in this evolving field in an effort to improve health and disease treatment outcomes (see Box 1-3).

Oncology has been at the forefront of advances in precision medicine, primarily due to the genomic nature of cancer: "Most cancers harbor a cocktail of mutated (or otherwise altered) oncogenes and tumor suppressors that work in concert to specify the molecular pathways that lead to their genesis, maintenance, and progression" (Garraway et al., 2013, p. 1). Treatment previously based on the anatomic origin of cancer (e.g., lung, breast, colon, prostate) is being expanded to include the use of genomic

BOX 1-3
Precision Medicine Initiative

This study was launched against the backdrop of the Precision Medicine Initiative, the White House announcement of which coincided with the first meeting of the Committee on Policy Issues in the Clinical Development and Use of Biomarkers for Molecularly Targeted Therapies on January 30, 2015.

Characterized as "a bold new research effort to revolutionize how we improve health and treat disease," the Precision Medicine Initiative calls for significant investments (totaling $215 million in fiscal year 2016) for the National Cancer Institute, National Institutes of Health, Food and Drug Administration (FDA), and Office of the National Coordinator (ONC) to improve treatment for cancer; create a national research cohort; assist FDA in developing a new approach to evaluate next-generation sequencing; and bolster ONC's efforts to support the development of interoperability standards and requirements. Although the proposed initiative has a near-term focus on treatment for cancers, its longer-term focus is on a wide range of health and disease areas (OPS, 2015).

tests to stratify patients into subsets based on the specific molecular drivers of their individual tumors. The tailoring of treatment to specific molecular targets is being applied to other diseases and conditions, including cystic fibrosis and Duchenne muscular dystrophy (Fairclough et al., 2013; Garraway et al., 2013; Mendelsohn, 2013; Rubin, 2015; Schott et al., 2015; Towse et al., 2013; Trosman et al., 2013).

The evolving field of precision medicine has significant potential to improve health care and patient outcomes, but science- and policy-related challenges may constrain further progress. Although significant advances have been made in terms of understanding the biological basis of diseases such as cancer, continued research is required in domains such as molecular biology, cell biology, and biochemistry to further researchers' and health care providers' understanding of the biology behind the alterations that drive the progression of cancer and other "omics-based" conditions (Marcus, 2015; Parkinson et al., 2014; Poste, 2011; Sawyers, 2008).

In oncology, such deeper knowledge of the biology of driver mutations must be combined with the ever-increasing volume of genomic data available to expand the range of targeted treatments. It is important to acknowledge significant sentinel treatment successes, such as imatinib (Gleevec®) in the treatment of patients with chronic myeloid leukemia and erlotinib for non-small cell lung cancers with *EGFR*-activating mutations. However, despite the discovery of *RAS* mutations in many different tumor types, no successful targeted treatment has yet been developed and implemented in clinical practice, leading one expert to observe: "We are still dealing with a large gap between discoveries at the lab bench and treatments at the bedside" (Marcus, 2015, p. 31). Another daunting challenge to the development of targeted cancer treatments is the variability between cancers that were previously considered to have a more uniform biology, such that a patient with one type of cancer likely has subsets of tumor cells that differ genetically (IOM, 2013c). Such tumor heterogeneity has a critical impact on treatment strategies, as a therapy designed to target a driver mutation in one cell subset may not have an impact on another subset within the same tumor (Marcus, 2015). Moreover, evidence reveals that some targeted therapies can be context specific: colon cancers with *BRAF* mutations, for example, are largely unresponsive to BRAF inhibition despite therapeutic effectiveness in *BRAF*-mutant melanoma (Hyman et al., 2015; Prahallad et al., 2012).

The evidence for the clinical use of biomarker tests to direct treatment is constantly evolving; research into therapies thought to target only one variant of a biomarker, for example, may in fact have a more complex mechanism of action and may be found to be effective against other molecular targets (see Box 1-4). Advanced biomarker tests to direct molecularly targeted therapy can be used to characterize a patient's dis-

BOX 1-4
Evolving Evidence for Biomarker Tests for Molecularly Targeted Therapies

The adoption of targeted therapeutics into clinical practice is facilitated by evolving research that clarifies the relationships among biomarker tests, corresponding treatments, clinical events, and health outcomes. An illustrative example is the evolution of non-small cell lung cancer (NSCLC) therapies that target epidermal growth factor receptor (*EGFR*), a gene currently understood to play a crucial role in NSCLC, as well as other cancers.

The drug gefitinib was conditionally approved by the Food and Drug Administration in 2003 to treat NSCLC, based on response to the drug in a small proportion of patients, none of whom had been selected based on a biomarker test. This conditional approval for response in such a small proportion of patients reflected the clinical reality of NSCLC treatment at the time; few effective treatments existed for patients with recurrent or metastatic NSCLC. Research subsequently uncovered specific *EGFR* mutations in patients who responded to gefitinib and erlotinib (a related drug approved based on a study that had the good fortune of including sufficient numbers of such patients). Treatment of NSCLC patients became predicated on the presence of these *EGFR*-activating mutations, identified by various biomarker tests. As a result, the previously small proportion of patients who responded to therapy increased significantly once the association with the biomarker was clarified.

Further research expanded the list of *EGFR*-activating mutations that would predict response to targeted therapy, and importantly also revealed an *EGFR* mutation (T790M) that was associated with a lack of response to targeted therapy (though drugs specifically designed to overcome this resistance are currently in development, and one has recently been approved). NSCLC patients seeking targeted therapy are now required to receive comprehensive testing in order to ensure effective treatment based on the most recent scientific evidence of response or resistance to therapy.

Thus, the clinical development of therapies targeting *EGFR* in lung cancer spans a continuum. An initial unmet need for effective therapy led to a better understanding of the complex biological processes and pathways involved in cancer progression that can be identified and targeted for appropriate treatment. Perhaps most importantly, this evolution is a continuous process: current NSCLC treatments targeting *EGFR* are not effective for every patient whose cancer has an *EGFR*-activating mutation. Future research will continue to characterize response and resistance to treatment, and this will further contribute to the evolving understanding of molecular profiles of disease and the impact of molecularly targeted therapies.

SOURCES: Chong and Janne, 2013; Kuykendall and Chiappori, 2014.

ease, and suggest the use of treatments beyond a drug's FDA-approved intended use (i.e., off-label use). For example, evolving evidence could indicate that a drug originally developed and approved to target one type of tumor may be effective against different types of tumors. For patients faced with few FDA-approved treatment choices, particularly those with rare cancers or other diseases, this off-label use of molecularly targeted therapies has become an important treatment option.

To develop a deeper understanding of the potential benefits and risks of such molecularly targeted therapies, it will be critical to track their impact on patient outcomes, whether the treatment is on- or off-label. These data on biomarker test use and treatment selection, as well as patient outcomes, need to be systematically captured, analyzed, and shared for continuous learning. In this respect the use of molecularly targeted therapies, particularly in patients with an unmet need for effective treatment, represents a blurring of the line between clinical research and clinical care. Traditional clinical trials only enroll a small proportion of patients, and these are often drawn from those patients who are treated at larger medical centers (Murthy et al., 2004; NCI, 2010). The majority of patients with diseases such as cancer, for example, are still treated in smaller community hospital settings (The Moran Company, 2013). Indeed, the process of ongoing evidence development requires effective approaches to handling the large amounts of complex omics-based patient information across various clinical settings, which need to be developed and implemented. Electronic health records (EHRs) must be configured that are capable not only of capturing individuals' genomic and other omics-based information, but also providing support tools to aid clinical decisions based on that information (Kohane, 2015; Mirnezami et al., 2012).

The focus on a deeper understanding of disease based on molecular phenotyping may lead to reclassification of disease states to incorporate molecular data, potentially through modernization of the World Health Organization's *International Classification of Diseases*. The National Research Council proposed a "new taxonomy of disease" and highlighted the need for new disease classifications to reflect both fundamental biology as well as traditional signs and symptoms (Mirnezami et al., 2012; NRC, 2011).

These significant challenges notwithstanding, precision medicine is advancing our understanding of the molecular basis of diseases and leading to new treatment strategies. The advancement of precision medicine needs to balance optimism and enthusiasm about the promising impact of new emerging technologies and targeted treatments with pragmatic approaches to overcoming current challenges (Joyner and Paneth, 2015; Rubin, 2015).

STUDY SCOPE

The advancement of precision medicine depends not only on progress in science and technology, but on the creation of a supportive policy infrastructure to promote and facilitate the adoption of appropriate biomarker tests for molecularly targeted therapies into routine clinical practice. The policy infrastructure encompasses regulatory issues, including the type and level of oversight needed for test development, validation, and use in clinical practice; the type, amount, and quality of evidence required for health plans, health insurers, and other payers to make coverage and payment decisions; and the best methods of disseminating knowledge of new tests and targeted therapies across a range of clinical practice settings to meet the informational needs of patients, families, the public, and health care professionals (Frueh, 2013; Ramsey and Sullivan, 2014; Simonds et al., 2013).

One of the more significant obstacles to creation of a supportive policy infrastructure is the lack of agreement among stakeholders regarding the evidentiary standards for the clinical utility of a biomarker test that directs molecularly targeted therapy. Such a test is deemed to have clinical utility if evidence demonstrates that the test will result in improvement in patient outcomes (IOM, 2012b). Indeed, the increased complexity of biomarker tests and precision medicine more broadly has led many observers to assert that new standards and methods are needed to assess clinical utility as well as to inform regulatory and reimbursement decisions (IOM, 2015c). Moreover, there is concern that payer decisions about coverage and reimbursement for biomarker tests for molecularly targeted therapies are not reflective of their clinical value, leading to reluctance on the part of test developers to invest resources to demonstrate clinical utility to support reimbursement decisions—what Hayes and colleagues characterize as "a vicious cycle" (Hayes et al., 2013).

In an effort to explore these opportunities and challenges, the Institute of Medicine (IOM) appointed an independent committee that was charged with examining policy issues related to the clinical development and use of biomarker tests for molecularly targeted therapies. The committee views this study report as building on the 2012 IOM consensus report *Evolution of Translational Omics: Lessons Learned and the Path Forward* (IOM, 2012a). The *Omics* report examined key issues in the proper development and validation of complex omics-based biomarker tests and recommended a three-step framework for evaluation that includes the discovery phase, the test validation phase, and the evaluation for clinical utility and use stage. The first stage of omics-based test development, as shown in Figure 1-2, includes two phases: discovery and test validation.

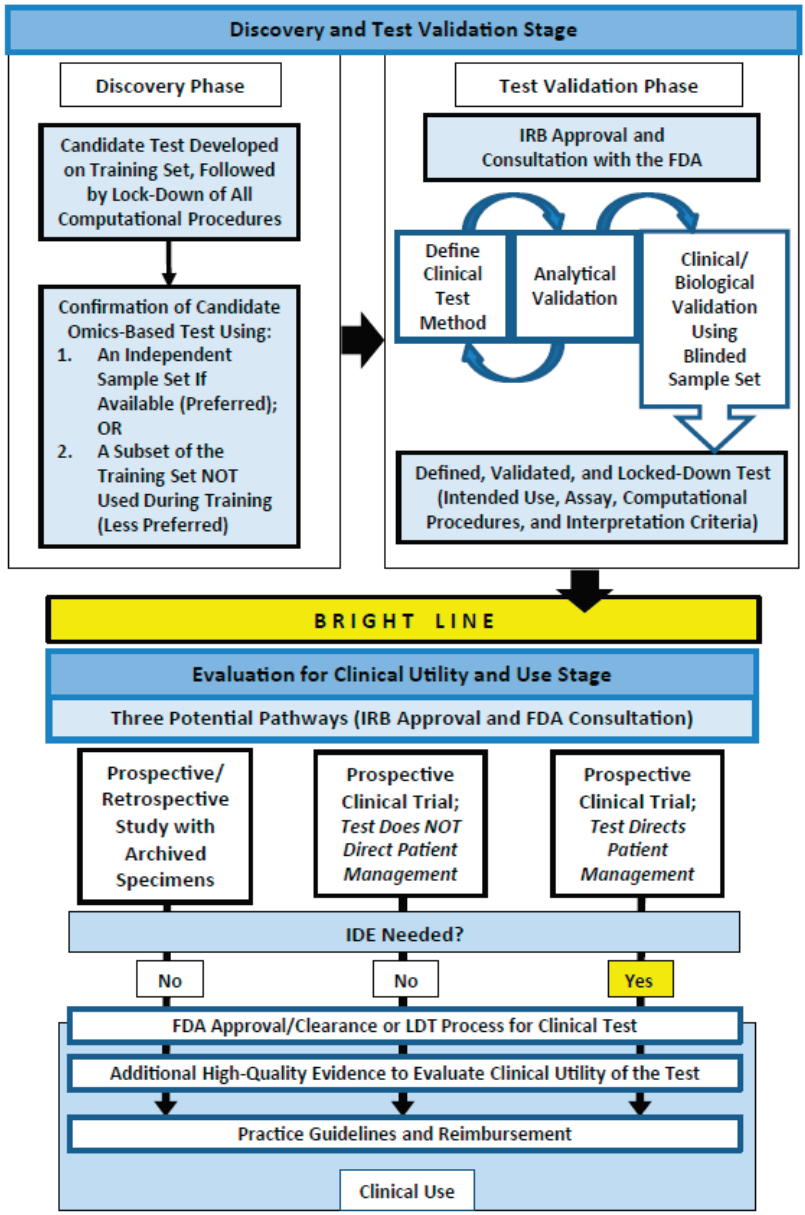

FIGURE 1-2 Recommended development and evaluation process for omics-based tests.
NOTE: FDA = Food and Drug Administration; IDE = investigational device exemption; IRB = institutional review board; LDT = laboratory-developed test.
SOURCE: IOM, 2012a.

> In the discovery phase, a candidate test is developed and confirmed. The fully specified computational procedures are locked down in the discovery phase and should remain unchanged in all subsequent development steps. . . . In the test validation phase, the omics-based test undergoes analytical and clinical/biological validation. The bright line signifies the point in test development where a fully defined, validated, and locked-down clinical test (analytical and clinical/biological validation) is necessary. . . . In the second stage of test development, the fully defined, validated, and locked-down omics-based test undergoes evaluation for its intended clinical use. . . . Statistics and bioinformatics validation occurs throughout the discovery and test validation stage as well as the stage of evaluation for clinical utility and use. (IOM, 2012a, p. 7)

A National Cancer Institute (NCI) working group of scientists and other stakeholders was formed to operationalize the principles set forth in the *Omics* report. The group created a checklist of 30 points to determine whether an omics test is ready for use in a prospective clinical trial involving patient-care decisions, such as the selection of therapy. The checklist will be used to evaluate NCI-sponsored clinical trials in which selection of patient therapy will be based upon the results of omics tests (McShane et al., 2013).

This committee viewed the 2012 report as foundational to its work and reasoned that this current study begins where the *Omics* study ended: at clinical use of biomarker tests for guiding molecularly targeted therapy. In light of the 2012 report's thorough treatment of the clinical development of complex omics-based biomarker tests, the committee did not believe it could improve upon or expand on the report's comprehensive treatment of the topic.

This committee's statement of task was to examine the interconnected regulatory, reimbursement, and clinical practice policy issues related to the use of biomarker tests for molecularly targeted therapies (see Box 1-5). Given this committee's charge was to examine biomarkers for molecularly targeted therapies, this report is focused exclusively on predictive biomarker tests to direct molecularly targeted therapy and the content of this report and the committee's recommendations reflect that focus. Thus, prognostic, screening, monitoring, and drug metabolism pharmacogenomic biomarker tests are outside the scope of this study. The committee took a broad view of molecularly targeted therapies, but many examples in the report pertain to oncology given its position at the leading edge of available targeted therapies.

Support for this study was provided by a broad coalition of public and private sponsors, including the American Society for Radiation Oncology, American Society of Clinical Oncology, Breast Cancer Research Foundation, Centers for Disease Control and Prevention, College of American

BOX 1-5
Charge to the Committee

An ad hoc committee will examine policy issues related to the clinical development and use of biomarker tests (including genomics-based tests) for targeting therapies to patients, including

- Regulatory issues, such as the variability in the regulation of diagnostic tests and combination products and the role of various oversight bodies, such as the Food and Drug Administration and the Centers for Medicare & Medicaid Services (CMS) (under the Clinical Laboratory Improvement Amendments);
- Reimbursement issues, such as the effects of laboratory reimbursement schedules and coding systems, the standards of evidence used by CMS and other payers to make coverage decisions, and how to generate evidence of clinical utility; and
- Clinical practice issues, such as interpretation of molecular tests, clinical decision making, dissemination of new technologies across the spectrum of clinical practice settings, and implications for clinical practice guidelines.

Using previously published Institute of Medicine reports as a starting point, the committee is charged with examining opportunities for and challenges to the use of biomarker tests to select optimal therapy, and will formulate recommendations to accelerate progress in this field.

Pathologists, Gilead Sciences, Janssen Diagnostics, National Cancer Institute, Novartis, Pfizer Inc., Quest Diagnostics, and Susan G. Komen.

The committee membership reflects a broad range of expertise, including genomic medicine, biostatistics, bioinformatics, test development and translational research, outcomes research and health economics, academic clinical laboratories, pharmaceutical, molecular diagnostics and clinical laboratory industries, test coverage and reimbursement, bioethics, medical education, community practice, and patient advocacy. Brief biographies of the 15 committee members are available in Appendix A.

CONTEXT OF THE STUDY

Biomarker tests for molecularly targeted therapies do not exist in a vacuum, and must be viewed within the context of the broader health care system. The U.S. health care system is undergoing rapid and far-reaching changes, from the proliferation of cutting-edge technological advances and the growing influence of precision medicine to innovative care delivery and payment reforms. The accelerating pace and significant scope of change raises considerable challenges for all health care stakeholders—

patients, health care professionals, health plans and insurers, regulatory agencies, researchers, pathologists, geneticists, and in vitro diagnostic and pharmaceutical manufacturers—while also offering new opportunities to improve patient outcomes and cost-effectiveness of care. The ongoing transformation of health care includes the increased use of EHRs, linking data on health care quality and outcomes; growing consolidation and coordination among care providers, including hospital systems and physician practice groups; and intensified focus on clinical outcomes as risk is shifted from payers to health care providers, with payment more closely tied to the value of health care rather than the volume of services. Defining value in health care is challenging as is evidenced by multiple definitions, and varying perspectives on value that exist. Essentially, health care value is premised upon an assessment of the quality of care relative to its cost. Value is seen to be created when health care outcomes improve while costs remain stable, or when costs decrease without an adverse impact on health outcomes (IOM, 2013a).

One important factor influencing the changing health care landscape is the implementation of the Affordable Care Act of 2010, which continues to affect the nearly $3 trillion U.S. health care system through expanded insurance coverage, reform of health care delivery and payment systems, and new measures that transfer more responsibility for cost and quality from payers to health care providers, with a renewed focus on value (Blumenthal et al., 2015). Given that overall health care expenditures represent 17 percent of the nation's gross domestic product, and that government pays for 43 percent of U.S. health care costs, efforts to control costs and improve quality, thereby enhancing the value of health care, are critical (Blumenthal et al., 2015; CMS, 2014).

Proof that health care reform efforts are ongoing is evidenced by two significant pieces of draft legislation currently in discussion in Congress. In July 2015, the House Energy and Commerce Subcommittee voted in a bipartisan fashion to move HR 6, known as the 21st Century Cures Act,[2] out of committee. The bill aims to accelerate the availability of safe and effective treatments and contains a number of provisions related to biomedical research generally and precision medicine and biomarkers in particular. Although the bill has bipartisan support, and has been praised by many stakeholders in health research and care, concerns have been raised regarding some of the draft provisions, particularly those that may affect FDA's ability to regulate medical devices (Redberg and Dhruva, 2015).

In contrast to the comprehensive approach taken in the House of Representatives, the Senate Health Education, Labor and Pensions (HELP)

[2] See http://energycommerce.house.gov/cures (accessed June 6, 2016) for extensive background information.

Committee is drafting a series of bills focused on a number of issues related to electronic health records, medical device regulation, targeted therapies and elements of the president's Precision Medicine Initiative (Alexander, 2016). At the time of this writing, the Senate bills are entering into the mark-up phase and it is not clear what shape the legislation ultimately will take.

Previous IOM Work

In addition to *Evolution of Translational Omics* (IOM, 2012a) noted earlier, previous related IOM work includes *Toward Precision Medicine* (NRC, 2011), *Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease* (IOM, 2010a), and *Cancer Biomarkers* (IOM, 2007). The *Surrogate Endpoints* and *Cancer Biomarkers* reports examined the processes for validation, development, and use of biomarkers, in general, and provided an additional basis from which the committee could explore the policy issues related to the clinical use of biomarker tests to guide molecularly targeted therapy. Other related consensus reports provided important background and context to the committee's work, including *Delivering High-Quality Cancer Care* (IOM, 2013c) as well as *Best Care at Lower Cost* (IOM, 2013a). In addition, the National Academies of Sciences, Engineering, and Medicine's National Cancer Policy Forum and the Roundtable on Translating Genomics-Based Research for Health have produced an extensive number of workshop summaries on a broad range of topics in the fields of cancer and genomics, respectively, which served as a springboard for this committee's examination of policy issues related to biomarkers for molecularly targeted therapies (IOM, 2009, 2010b, 2012b,c, 2013b,d,e, 2014a,b, 2015a,b).[3]

METHODS OF THE STUDY

The committee sought to expand its understanding of the full range of challenges and opportunities facing biomarker tests for molecularly targeted therapies. A diverse range of sources informed the committee's work, including published literature and expert testimony. The committee deliberated during four in-person meetings, as well as numerous conference calls and email exchanges, between January and September 2015.

The committee invited a number of external experts to inform its deliberations during its first three committee meetings (January, April,

[3] See https://www.nationalacademies.org/hmd/Activities/Disease/NCPF.aspx for a complete list of National Cancer Policy Forum Workshop Summaries. See https://www.nationalacademies.org/hmd/Activities/Research/GenomicBasedResearch.aspx for a complete list of Genomics Roundtable Workshop Summaries.

and June 2015). These speakers provided valuable input to the committee on a broad range of issues, including biomarker development, evaluation, and implementation; applications of biomarkers and molecularly targeted therapies in clinical practice; and payment and regulatory issues affecting biomarker tests for molecularly targeted therapies. In addition to in-person testimony, the committee heard from experts in reimbursement, payment, and coverage policy related to biomarker tests for molecularly targeted therapies via webinar (see Appendix C). Moreover, a number of experts provided written input to the committee in areas related to ethics, genomic literacy, and genomic data collection and analysis. Finally, in addition to benefiting from a range of expert oral and written input, the committee reviewed an extensive body of literature on biomarker tests for molecularly targeted therapies to inform its deliberations.

Framework for the Study

The successful adoption of biomarker tests for molecularly targeted therapies into routine clinical practice to improve patient outcomes depends on a number of interrelated factors: ongoing research and development of targeted therapies and associated biomarker tests with a changing body of evidence over time, a responsive regulatory and reimbursement process capable of keeping pace with rapid technological developments, health care providers trained in and knowledgeable about which test(s) to order and how to act on the test results, insurers and other payers who recognize the value of biomarker tests and targeted therapies by coverage and reimbursement (Agarwal et al., 2015), and patients who understand both the potential and current limitations of precision medicine. These complex and interrelated factors are currently affecting the potential of biomarker tests for targeted therapies to improve patient outcomes. The committee emphasizes the interconnected nature of these challenges and the need for an integrated approach to address them—that is, an interdisciplinary perspective that considers all the components in the process and their interactions (IOM, 2012d). An engaged collaboration across stakeholders—including patients, health care providers, payers, health insurers, federal agencies, professional organizations, researchers, and academic as well as community-based health centers—is required for biomarker tests and molecularly targeted therapies to transform promise into the reality of improved patient care and greater cost-effectiveness.

The committee recognizes that a systems approach is required to allow the most effective use of biomarker tests to fully realize the promise of molecularly targeted therapies. For this reason, the committee envisions the creation of a rapid learning system for biomarker tests for molecularly targeted therapies. Such a system has as its core the use

of various types of clinical care data to generate knowledge to improve patient health care and outcomes. Currently, the opportunity for learning about the "real-world" clinical use and treatment outcomes of biomarker tests for molecularly targeted therapies is not being realized, and there is an urgent need for a framework to capture this critical information. The learning health care system concept, and the committee's adaptation of the approach to create a rapid learning system to improve the development and use of biomarker tests for molecularly targeted therapies, is described further in Chapter 2 of this report.

ORGANIZATION OF THE REPORT

This report reviews the literature on biomarker tests for molecularly targeted therapies, presents the committee's findings, and offers recommendations to federal agencies and private organizations, health care providers, EHR developers and vendors, and professional societies. The rapid learning system framework emphasizes the interrelated nature of the policy issues affecting the clinical development and use of biomarkers for molecularly targeted therapies. This study report is organized around the committee's rapid learning system framework and contains five chapters.

This introductory chapter describes the context of the study and discusses the committee's charge and the scope, definition of terms, conceptual framework, and methods of the study. Chapter 2 provides an overview of the concept of a learning health care system and offers illustrative examples of such systems that inform the committee's vision of a rapid learning system for biomarker tests for molecularly targeted therapies. The three components of this rapid learning system are policy environment, data infrastructure, and processes to improve patient care, and are discussed in the Chapters 3, 4, and 5, respectively. Chapter 3 explores the regulatory and reimbursement policy environment influencing the use of biomarker tests for molecularly targeted therapies. Chapter 4 discusses the challenges involved in the development and implementation of a supportive data infrastructure. Chapter 5 focuses on the final component of the committee's vision of a rapid learning health system for biomarker tests for molecularly targeted therapies: processes to improve patient care. Chapters 3 through 5 of the report contain discussion of the challenges facing the effective clinical use of biomarker tests for molecularly targeted therapies, as well as the committee's recommended approach to those challenges.

This report includes three appendixes. Appendix A contains biographical sketches of the committee members and the IOM project staff. Appendix B contains an overview of coding issues related to biomarker

tests for molecularly targeted therapies. Appendix C contains a list of speakers at the committee's public information-gathering sessions.

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2

Envisioning a Rapid Learning System for Biomarker Tests for Molecularly Targeted Therapies

The charge to the Committee on Policy Issues in the Clinical Development and Use of Biomarkers for Molecularly Targeted Therapies, as noted in Chapter 1 of this report, was to examine the regulatory, reimbursement, and clinical practice policy issues that currently influence the adoption of biomarker tests for molecularly targeted therapies into routine clinical practice. Biomarker tests do not exist in a vacuum; rather, they are part of a complex health care system. The active, broad-based participation of, and collaboration among, multiple stakeholders—including patients, health care providers, payers, health care organizations, regulatory agencies, test developers and therapy manufacturers, professional organizations, and researchers—is required to transform the significant potential of biomarker tests for molecularly targeted therapies into the reality of improved patient care through precision medicine. In an effort to address the interrelated regulatory, reimbursement, and clinical practice challenges, the committee calls for the development of a rapid learning system approach that supports the most effective and appropriate use of biomarker tests and their associated molecularly targeted therapies, with continuous evidence development and ongoing assessment of their value.

This chapter provides an overview of the concept of a learning health care system, and describes a number of efforts to establish such systems. It lays the foundation for the committee's vision of an integrated, systematic approach to accelerating the appropriate use of biomarker tests for molecularly targeted therapies to improve patient outcomes and enhance the cost-effective use of relatively expensive targeted therapies. This chap-

ter serves as a preview for the three chapters that follow. They discuss the three interrelated components (supportive policy environment, supporting data infrastructure, and processes to improve patient care) of the rapid learning system envisioned by the committee.

LEARNING HEALTH CARE SYSTEM

The notion of a learning organization was developed by organizational strategist Peter Senge, who advanced the concept in his book *The Fifth Discipline* (Senge, 1990). The idea was subsequently applied in the context of health care. A learning health care system is viewed as an approach to generating evidence about the quality, safety, and value of health care, using electronic health records (EHRs), large complex health care datasets known as "big data,"[1] and learning networks to support and accelerate the practice of evidence-based medicine. Such a system is envisioned as a way to bridge knowledge gaps, promote the adoption of best practices, facilitate learning from the outcomes of patient care, and expedite translation of lessons learned into improvements in patient care (Etheredge, 2007).

The Institute of Medicine (IOM) led some of the recent foundational work on the learning health care system concept, starting with the initial workshop, *The Learning Healthcare System* (IOM, 2007), followed by numerous other workshops—convened first by the Roundtable on Evidence-Based Medicine, and later by the Roundtable on Value & Science-Driven Health Care;[2] altogether the IOM produced a series of 11 workshop summaries on various facets of the learning health care system.[3] In addition, the National Academies of Sciences, Engineering, and Medicine's National Cancer Policy Forum explored a learning health care system for cancer (IOM, 2010). The concept of a learning health care system became the focus of increasing research efforts to refine and apply the concept (Abernethy et al., 2010; Etheredge, 2007, 2014; Ginsburg and Kuderer, 2012; Ginsburg et al., 2011; Schilsky et al., 2014; Sledge et al., 2013; Slutsky, 2007; Tunis et al., 2007; Wallace et al., 2014; Yu, 2015). In parallel, the National Research Council's (NRC's) report *Toward Precision*

[1] "Big data has been described as the rapidly increasing size of available data, the speed with which those data are produced, and the ways in which data are represented. It also can refer not only to the data, but to the possibilities of discovering new knowledge by leveraging massive data collections in novel ways" (Krumholz, 2014, p. 1163).

[2] For a complete list of the work of the Roundtable on Value & Science-Driven Health Care see https://www.nationalacademies.org/hmd/Activities/Quality/VSRT.aspx. The Roundtable's name was changed to the Leadership Consortium for Value & Science-Driven Health Care. See http://nam.edu/programs/value-science-driven-health-care.

[3] See http://www.nap.edu/catalog/13301 (accessed August 4, 2015).

Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease called for a new national research and database system to revolutionize research, clinical care, and public health (NRC, 2011).

The IOM's work culminated in a 2013 consensus report *Best Care at Lower Cost: The Path to Continuously Learning Health Care in America*, which concluded that "achieving a learning health care system—one in which science and informatics, patient-clinician partnerships, incentives, and culture are aligned to promote and enable continuous and real-time improvement in both the effectiveness and efficiency of care—is both necessary and possible for the nation" (IOM, 2013a, p. 17). The potential beneficial impact of implementing such a system was highlighted in the *Health Affairs* July 2014 issue, which focused on the role of "big data," and an examination of a new rapid-learning agenda (Etheredge, 2014). The IOM continues work in this area, most recently with the publication of the workshop summary *Genomics-Enabled Learning Health Care Systems* (IOM, 2015). Additionally, the Leadership Consortium for Value & Science-Driven Health Care, now under the auspices of the National Academy of Medicine, continues to examine this multifaceted issue.[4]

The concept of a learning health care system has been articulated in various ways, including a rapid learning health care system (Abernethy et al., 2010; Etheredge, 2007, 2014; Ginsburg et al., 2011), a continuously learning health care system (IOM, 2013a), and a knowledge-generating health care system (IOM, 2015). Etheredge's working definition of a rapid learning health care system is elegant in its simplicity: "a health system that learns as quickly as possible about the best treatments for each patient—and delivers it" (Etheredge, 2014, p. 1156). In a learning health care system, closed feedback loops between clinical practice and research enable one to inform the other as both work to improve the efficiency and effectiveness of the health care system (Ginsburg, 2014; IOM, 2015). Regardless of the terminology, learning health systems share the common goal of drawing on clinical data to "learn from every patient, and feed the knowledge of 'what works best' back to clinicians, public health professionals, patients and other stakeholders to create cycles of continuous improvement" (Friedman et al., 2015, p. 44).

The creation of such a system of continuous improvement would enable the health care system to "routinely study its own behavior" (Friedman et al., 2015, p. 44) and gain important insight on ways to address issues related to health care quality, cost, and safety, and to improve patient care. The collection, analysis, and shared use of clinical data form the

[4] The Leadership Consortium for Value & Science-Driven Health Care manages five Innovation Collaboratives focusing on a range of issues. See http://nam.edu/programs/value-science-driven-health-care.

cornerstone of a learning health system. Indeed, through the analysis of data—from clinical trials, translational science, patient treatments and outcomes, and other data sources—the learning process occurs as data are shared, transformed into knowledge, and subsequently applied to patient care. As Yu succinctly points out: "Knowledge achieves clinical utility only when it becomes actionable to improve patient health" (Yu, 2015, p. 206). Data have the ability not only to improve clinical decision making for better patient outcomes, but also to transform clinical research, as large databases "enable observational studies on a scale and at a speed randomized controlled trials cannot approach" (Weil, 2014, p. 1110).

The successful development of a rapid learning system for biomarker tests for molecularly targeted therapies depends on the ability of health care organizations to collect and handle large quantities of data; this presents a particular challenge in the age of precision medicine and its complex biomarker tests and molecularly targeted therapies. Biomarker data and outcomes data are distinct, and both are necessary as are patient-level data (Abernethy, 2015). Thus, an effective rapid learning system requires appropriate data collection. In addition, all stakeholders, including health care providers, researchers, and payers, must be able to access, analyze, and use the data effectively, requiring a supportive health information technology infrastructure (IOM, 2013c).

Other data challenges include a lack of uniformity of data; data are often collected in free-text format rather than structured format, rendering analysis difficult (Kean et al., 2012). Moreover, sharing of data across health care organizations and settings may be difficult due to lack of standardized data definitions. Finally, data captured in a rapid learning system may be more biased or inaccurate than data collected in clinical trials (IOM, 2013c). An IOM workshop sponsored by the Patient-Centered Outcomes Research Institute (PCORI)[5] focused on conducting analytical studies in a learning health care system, and examined analytic methods for improving the reliability and validity of results from such studies (IOM, 2013b).

These challenges notwithstanding, the rationale for a learning health care system is simple and clear: health care providers need better, more complete information and knowledge about what works best for individual patients, and they need it as fast as possible. Given the complexity of advanced technologies such as biomarker tests for molecularly targeted therapies, and the high cost of new therapies, accurate information on

[5] Congress authorized the creation of PCORI as part of the Affordable Care Act of 2010. PCORI is a nonprofit, nongovernmental organization, whose mission is to fund comparative effectiveness research with the goal of helping patients, health care providers, payers, and policy makers make informed health care decisions.

what works and what does not work for each patient is critical to improving patient outcomes well as the cost-effectiveness of health care. The transition to a learning health care system would be advantageous for all health care stakeholders, with benefits shared by patients and health care providers, researchers, and payers and the health care system as a whole.

EXAMPLES OF LEARNING HEALTH CARE SYSTEMS

Many of the foundational elements necessary for the creation of a learning health care system are already in place, including widespread use of EHRs, registries (for many conditions, including cancers), a robust clinical trial infrastructure, and biorepositories linked to clinical data (IOM, 2013c). A number of organizations have adapted and applied concepts of the learning health system. These initiatives and other programs that generate data and foster collaboration in clinically relevant research serve as a rich base of experience from which to draw insights for the establishment of a rapid learning system for the most effective use of biomarker tests for molecularly targeted therapies. Selected initiatives are discussed below, and additional examples are found in Box 2-1.

Federal Agencies

The National Institutes of Health (NIH) is involved in a number of collaborative research initiatives that could serve as models for a learning health system. NIH launched the Electronic Medical Records and Genomics (eMERGE) Network through the National Human Genome Research Institute in 2007. The goal of this network is to "develop, disseminate, and apply approaches to research that combine DNA repositories with EHRs for large-scale, high-throughput genetic research." The first phase of the initiative (2007-2011) used genome-wide association analysis to examine the relationship between genetic variation and at least two human traits. A key goal of the second phase (2011-2015) is to examine the best approaches to incorporate genetic variants into EHRs for use in clinical care.[6]

The Department of Veterans Affairs' (VA's) Office of Research & Development is funding the Million Veterans Program (MVP), a national, voluntary research program to study how genes affect health. The MVP program will build one of the world's largest databases on genetic, military exposure, lifestyle, and health information.[7] The VA also plans to use a learning health care system approach with veterans who are diagnosed with non-small-cell lung cancer. Test results from gene sequencing

[6] See http://www.genome.gov/27540473 (accessed September 3, 2015).
[7] See http://www.research.va.gov/mvp (accessed August 14, 2015).

BOX 2-1
At a Glance: Selected Examples of Learning Health Care Systems

Federal Agencies

Food and Drug Administration (FDA)[a]

A major focus of FDA's mission is to monitor the safety and effectiveness of drugs, biologics, and medical device products. FDA launched the *Sentinel Initiative* in 2008 in response to the Food and Drug Administration Amendment Acts of 2007,[b] which required FDA to create a postmarket surveillance system to assess the safety of approved medical products. The Sentinel System aims to enable FDA to actively query diverse automated health care data holders, such as electronic health record (EHR) systems, administrative and insurance claims databases, and registries, to evaluate possible medical product safety issues in a rapid and secure manner.[c]

The initiative began with the Mini-Sentinel pilot program,[d] which drew on EHR and administrative data from medical practices, hospitals, health plans, health care delivery systems, and insurers to monitor product safety. The pilot program included data from nearly 100 million persons. Organizations participating in the program use a distributed data network that allows retention of their data and provides the centralized network with a standardized data summary. The pilot program ended in September 2014, and FDA announced the formal launch of a full-scale system led by Harvard Pilgrim Health Care. The system is now accruing data from disease registries, vital statistics registries, and genomics data repositories, and has more than 350 million patient-years of data in its database.

However, critics contend that FDA has overstated the usefulness of Sentinel, noting that most of the data in the system are from medical claims—considered to be poor indicators of patient outcomes. The most significant charge is that Sentinel has not achieved the initial vision for the system, namely to enable the rapid assessment of potential drug safety problems. In addition, critics also point to the limited number of regulatory actions FDA has taken based on input from the program. Observers point out that the system has been plagued by technical and methodological problems that have limited its effectiveness (*Health Affairs*, 2015).

National Institutes of Health (NIH)

NIH's Health Care Systems Research Collaboratory[e] was launched in 2013 to improve the way clinical trials are conducted by creating a new infrastructure for collaborative research. The ultimate goal is to ensure that health care providers and patients can make decisions based on the best available clinical evidence. The Collaboratory also supports the design and execution of several pragmatic clinical trial demonstration projects and includes a Coordinating Center that provides technical expertise in all aspects of health care systems research. The NIH Collaboratory Distributed Research Network is being developed to facilitate collaborative research using large shared datasets.

NIH also is involved in an initiative called The Commons,[f] which is a cloud-

based platform that will enable biomedical researchers to share databases from publicly supported studies. The development of such a computing infrastructure will support knowledge generation while avoiding duplication of research efforts.

Another NIH initiative is the Big Data to Knowledge (BD2K)[g] project, whose focus is to support the research and development of innovative and transforming approaches and tools to maximize and accelerate the integration of Big Data and data science into biomedical research.

Other Federal Agencies

The *Department of Health and Human Services' Office of the National Coordinator for Health Information Technology*, which directs the federal government's efforts to adopt health information technology and promote health information exchange nationally, identified the national-scale learning health system as its 10-year strategic goal, noting that such a system "would enable lower health care costs, improved population health, truly empower consumers, and drive innovation" (Etheredge, 2014).

The *Agency for Healthcare Research and Quality*–sponsored Electronic Data Methods Forum is another national effort to implement a learning health system integrating research into clinical practice (EDM Forum, 2015; Etheredge, 2014).

Health Care Organizations

Geisinger Health System has developed a framework for translating a learning health care system into practice in the context of an integrated health system (Psek et al., 2015). Consistent with the goals of a learning health care system, Geisinger also is involved in a 5-year study with the goal of sequencing the exomes of 250,000 patients—for research purposes as well as to improve patient care. As part of this effort, Geisinger is currently returning results from 76 genes and putting that information into patients' EHRs (Heger, 2015).

Kaiser Permanente's Research Program on Genes, Environment and Health[h] examines genetic and environmental factors that influence a broad range of diseases, including diabetes, asthma, and cancer. The program intends to advance research by creating a large databank of genetic and medical information along with lifestyle, demographic, and environmental data to identify the genetic and environmental basis for disease, as well as factors that influence healthy aging. For example, the program aims to conduct genotyping of more than 675,000 markers in 100,000 participants. Genome-wide association studies have led to the identification of more than 600 variants that are potentially associated with a variety of traits and diseases.

Optum (a commercial data, infrastructure, and care services subsidiary of UnitedHealth Group) in collaboration with the Mayo Clinic launched an effort to create a learning health care system. The new entity, known as *Optum Labs*, includes 11 collaborators and a Health Insurance Portability and Accountability Act–compliant database with information on more than 150 million persons. The collaborators work to improve patient care by focusing on using patient data to translate new evidence into routine clinical practice (Wallace et al., 2014).

continued

BOX 2-1 Continued

Group Health Cooperative, a nonprofit, integrated health care system in Washington State, built on its experience with a patient-centered medical home pilot project to establish a rapid-learning culture within the organization. This in turn enabled Group Health to undertake new initiatives that developed partnerships between research and clinical operations to improve care in a number of areas, ranging from opioid prescribing to high-end imaging and value-based benefit design (Greene et al., 2012).

Flatiron Health has developed an innovative data platform that features a large sample size (nearly 20 percent of all U.S. cancer patients) (Abernethy, 2015) and includes a cloud-based EHR for oncology, advanced analytics, patient portal, and integrated billing management. Flatiron collaborated with the National Comprehensive Cancer Network (NCCN) to integrate NCCN templates into Flatiron's EHR to improve point-of-care decision making.[i]

The HMO Research Network established one of the earlier versions of a learning health care system in the early 1990s. The network, now known as the *Health Care Systems Research Network*, continues to foster collaboration between public domain research departments of nonprofit learning systems and includes large health systems such as Kaiser Permanente's Division of Research and Institute for Health Research, Geisinger Health System's Center for Health Research, and Harvard Pilgrim Health Care Institute. The network's mission is the improvement of "individual and population health through research that connects the resources and capabilities of learning health care systems." Network partners are involved in a number of collaborative learning system-style projects, including the FDA Mini-Sentinel Initiative, the Cancer Research Network, and the NIH Collaboratory.[j]

SOURCES (accessed May 12, 2016): [a] http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm; [b] Public Law 110-85. See http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/html/PLAW-110publ85.htm; [c] http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm149340.htm; [d] http://mini-sentinel.org/about_us; [e] https://www.nihcollaboratory.org/about-us/Pages/default.aspx; [f] https://datascience.nih.gov/commons; [g] https://datascience.nih.gov/bd2k/about; [h] http://www.dor.kaiser.org/external/DORExternal/rpgeh/index.aspx; [i] http://www.nccn.org/about/news/newsinfo.aspx?NewsID=487; [j] http://www.hcsrn.org/en.

panels will be used to direct therapy, and the information will be used for research purposes (IOM, 2015).

The learning health care system may be facilitated through collaboration among federal agencies. The Centers for Medicare & Medicaid Services (CMS), for example, could support a genetics-enabled learning health care system through its Innovation Center, which could test and advance best practices in genomics-enabled cancer care, using pay-for-performance approaches to improve quality (Etheredge, 2014; IOM, 2015).

Research Collaborations

Another example of a learning health system approach is the American Association for Cancer Research (AACR)–sponsored project called Genomics, Evidence, Neoplasia, Information, Exchange (GENIE). GENIE is a multi-phase, multi-year, data-sharing initiative to develop a regulatory-grade registry that captures and links clinical-grade cancer genomic data with clinical outcomes from thousands of patients sequenced at cancer centers in the United States, Canada, France, and the Netherlands. The registry will provide the statistical analysis to improve clinical decision making, which is a key unmet need particularly for rare cancers and rare variants in common cancers. The project also will aggregate, harmonize and share clinical-grade next-generation sequencing data from routine clinical practice. AACR will work closely with the Food and Drug Administration (FDA) to ensure data could be accepted as evidence necessary for regulatory approval.[8]

Another relevant initiative is the Global Alliance for Genomics and Health (GA4GH). This international coalition of 360 organizational members from 35 countries includes agencies, universities and biomedical research institutions, health care providers, information technology and life-sciences companies, research funders, and patient advocacy organizations. The goal of the alliance is to "establish a common framework of harmonized approaches to enable effective and responsible sharing of genomic and clinical data" (Lawler et al., 2015, p. 1133). The alliance's first cancer-specific demonstration project, the BRCA Challenge, brings together leaders in research and clinical care to develop a catalog of breast cancer susceptibility gene (BRCA) variants according to their phenotypic effects. Another GA4GH effort, the Actionable Cancer Genome Initiative, focuses on harmonizing the data from different clinical sequencing efforts to implement a data-sharing approach to facilitate the use of datasets to guide patient care (Lawler, 2015).

PCORI has developed a national research network, the National Patient-Centered Clinical Research Network (PCORNet), designed to support comparative effectiveness research and clinical trials that take place in clinical care settings. PCORNet provides funding to health system–based networks whose members include hospitals, health information exchanges, and federally qualified health centers that collect electronic health information in the process of providing clinical care. PCORNet also funds patient-powered research networks focused on specific medi-

[8] See http://www.aacr.org/Research/Research/Pages/aacr-project-genie.aspx (accessed January 15, 2016).

cal conditions, such as muscular dystrophy, Crohn's disease, and arthritis, with the research controlled by patients.[9]

The first phase of PCORNet focused on creating infrastructure to support observational and interventional studies across multiple networks. Subsequent work will focus on conducting research using the integrated datasets (Curtis et al., 2014; Fleurence et al., 2014). One such example is ImproveCareNow, which has evolved into PEDSnet, a network of eight of the largest pediatric academic health centers in the United States. Together they provide care for more than 2 million children annually. With PCORI funding, PEDSnet aims to create a national pediatric distributed learning health system linked to three disease-specific networks, focused on complex congenital heart disease, childhood obesity, and pediatric inflammatory bowel disease (Forrest et al., 2014).

PEDSnet has formed partnerships with two national data systems and will link administrative data with clinical data from the member hospitals. Once the system is complete, it will represent the broadest pediatric big data project in the nation, and will be instrumental in ensuring effective large-scale observational research and clinical trials. Such collaboration and data-sharing efforts are critical because pediatric disorders are typically rare diseases; consequently no single health care institution has sufficiently large patient groups to produce broadly generalizable knowledge (Forrest et al., 2014).

Professional Societies

The American Society of Clinical Oncology's (ASCO's) Cancer Learning Intelligence Network for Quality (CancerLinQ) embraces the vision of a rapid learning system described in the IOM workshop summary report *A Foundation for Evidence-Driven Practice: A Rapid Learning System for Cancer Care* (IOM, 2010). ASCO also drew on the IOM's consensus reports such as *Best Care at Lower Cost* (IOM, 2013a) and *Delivering High-Quality Cancer Care* (IOM, 2013c) for guidance in creating CancerLinQ (Schilsky et al., 2014).

Launched in 2015, CancerLinQ is a physician-led data informatics system that draws comprehensive data from EHRs and practice management systems from participating oncology practices. The system captures patient data from EHRs at the point of care, both process (what was done) as well as outcomes data. The system is designed to provide real-time clinical decision support to assist physicians in treatment planning, as well as point-of-care assessments to physicians regarding the quality of

[9] See a list of patient-powered networks at http://www.pcornet.org/patient-powered-research-networks (accessed October 22, 2015).

their work. The data will be used to revise ASCO Clinical Practice Guidelines and clinical decision support tools that will provide physicians with the latest developments in a complex and rapidly changing environment (Schilsky et al., 2014; Sledge et al., 2013).

Other rapid learning system approaches focused on biomarker tests for choosing or optimizing therapy are beginning to demonstrate, on a small scale, their potential to improve patient care. For example, Vanderbilt University Medical Center continuously develops and refines clinical management algorithms to define biomarker testing protocols, in order to lower unnecessary testing or improve rates of testing when clinically indicated (Stead, 2015). Similarly, Geisinger Health System has deployed clinical decision support that queries EHRs for genetic test results indicating hypersensitivity to the HIV drug abacavir, and alerts clinicians to perform testing if results are unavailable (Williams, 2015). Both of these examples of integrating EHRs and clinical decision support are tied into feedback systems measuring outcomes, utilization, efficiency, cost, and other metrics, in order to improve health care delivery and patient care (Stead, 2015; Williams, 2015).

However, as knowledge of the implications of some biomarker tests (for example, those predicting risk of cardiac events) increases, it is becoming clear that institutions and clinical laboratories operating on their own may be unable to fully characterize those relationships (Van Driest et al., 2016). Forming broad networks with a shared commitment to continuous learning may offer a potential approach to this challenge.

The examples discussed above support the feasibility of, and demonstrate the need for, an interconnected system focused on rapid learning for biomarker tests for molecularly targeted therapies. A rapid learning system for biomarker tests for molecularly targeted therapies such as that envisioned by the committee could leverage the existing digital infrastructure and analytics capabilities and catalyze efforts to forge linkages between existing databases and learning systems. Ongoing focus would be on further strengthening cooperation and collaboration and creating solid partnerships among related systems to ensure that a critical learning opportunity is not wasted.

A RAPID LEARNING SYSTEM FOR BIOMARKER TESTS FOR MOLECULARLY TARGETED THERAPIES

The IOM's *Best Care* report identifies three imperatives for achieving a continuously learning health system: managing rapidly increasing complexity; achieving greater value in health care; and capturing opportunities from technology, industry, and policy (IOM, 2013a, p. 8). These three imperatives also provide the rationale for the development of the

rapid learning system envisioned by the committee. Further justification for the development of such a system is the central role of biomarker tests in the evolving field of precision medicine; the need to capture large amounts of genomic information being generated, understand the uses for the data, and translate it into clinically useful knowledge; the necessity to accelerate learning in the field and disseminate knowledge across different clinical practice settings, patient populations, and geographic regions; and the urgency of reaching consensus on common evidentiary standards of clinical utility for biomarker tests for molecularly targeted therapies. Finally, the overarching rationale for such an approach lies in the potential to significantly improve patient care, management, and treatment outcomes.

The heightened awareness of the importance of the genetic basis of disease and the ways in which genetic factors influence patients' varying responses to treatment is of particular relevance for the development of a rapid learning system for biomarker tests for molecularly targeted therapies. The NRC's *Toward Precision Medicine* report called for an update to the *International Classification of Diseases* codes to incorporate the impact of genetic factors on disease (IOM, 2011). A rapid learning system would facilitate and accelerate the analysis of genetic data to guide treatment decisions (Etheredge, 2014).

In crafting the framework for a rapid learning system for biomarker tests for molecularly targeted therapies, the committee drew on two sets of guiding principles. First, the committee took into account the six aims of high-quality care conceptualized in the IOM's landmark 2001 report *Crossing the Quality Chasm*—namely that care should be safe, effective, patient-centered, timely, efficient, and equitable (IOM, 2001). Second, the IOM's *Best Care* report articulated key characteristics of a learning health care system (IOM, 2013a), which served to inform the committee's vision of a rapid learning system for biomarker tests for molecularly targeted therapies (see Box 2-2).

Consistent with the characterization of a learning health care system as the framework to enable the melding of policy, process, and technology (Friedman et al., 2015), the committee's vision of a rapid learning system for biomarker tests for molecularly targeted therapies encompasses three key components: supportive policy environment, supporting data infrastructure, and processes to improve patient care. An illustrative representation of such a rapid learning system is shown in Figure 2-1. The set of double arrows serves to highlight the process through which capturing and translating information generated by clinical research and patient care can create closed feedback loops among data, research, policy, and clinical practice to facilitate continuous learning. In this way, the process of developing new knowledge would be hard wired into the health care

BOX 2-2
Characteristics of a Learning Health Care System

Science and Informatics

- *Real-time access to knowledge*—A learning health care system continuously and reliably captures, curates, and delivers the best available evidence to guide, support, tailor, and improve clinical decision making and care safety and quality.
- *Digital capture of the care experience*—A learning health care system captures the care experience on digital platforms for real-time generation and application of knowledge for care improvement.

Patient–Clinician Partnerships

- *Engaged, empowered patients*—A learning health care system is anchored on patient needs and perspectives and promotes the inclusion of patients, families, and other caregivers as vital members of the continuously learning care team.

Incentives

- *Incentives aligned for value*—A learning health care system has incentives actively aligned to encourage continuous improvement, identify and reduce waste, and reward high-value care.
- *Full transparency*—A learning health care system systematically monitors the safety, quality, processes, prices, costs, and outcomes of care and makes information available for care improvement and informed choices and decision making by clinicians and patients and their families.

Continuous Learning Culture

- *Leadership-instilled culture of learning*—A learning health care system is stewarded by leadership committed to a culture of teamwork, collaboration, and adaptability in support of continuous learning as a core aim.
- *Supportive system competencies*—A learning health care system constantly refines complex care operations and processes through ongoing training and skill building, systems analysis and information development, and creation of feedback loops for continuous learning and system improvement.

SOURCE: IOM, 2013a, p. 18.

delivery system, with the ability and expectations for continuous learning and updating of best evidence and clinical practices (IOM, 2013c), creating what may be characterized as "swift bidirectional learning" in which practice is informed by evidence and vice versa (Greene et al., 2012). A rapid learning system as envisioned by the committee aims to transcend

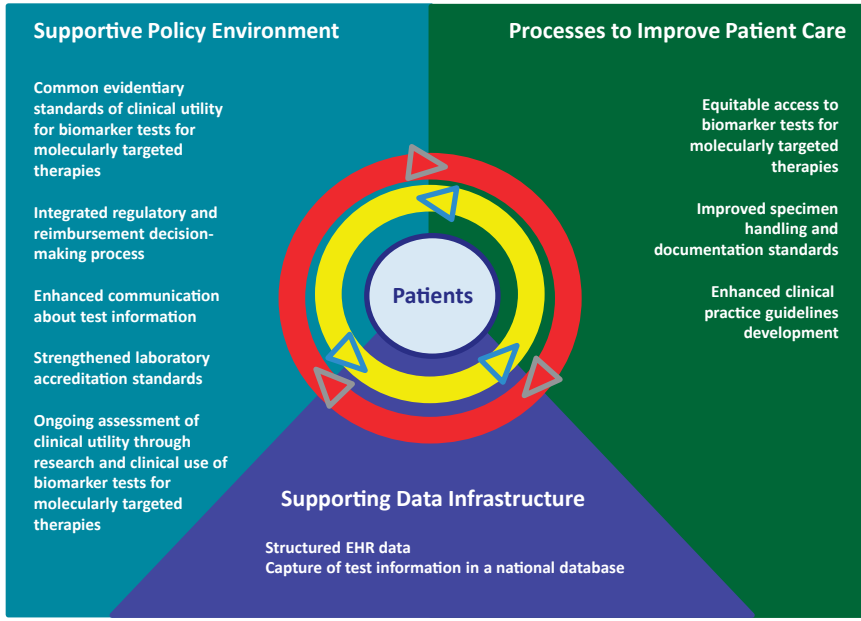

FIGURE 2-1 Rapid learning system for biomarker tests for molecularly targeted therapies.
NOTE: EHR = electronic health record.

traditional barriers between research and clinical practice to support the generation of new knowledge to improve patient management and outcomes. The rapid learning system serves as the conceptual framework for the committee's recommended approaches to addressing key clinical, regulatory and reimbursement issues facing biomarker tests for molecularly targeted therapies. The issue areas targeted by the committee are shown within each of the respective components of the committee's envisioned rapid learning system in Figure 2-1.

Supportive Policy Environment

The committee examined a number of key regulatory and reimbursement policy challenges that influence the development and use of biomarker tests for molecularly targeted therapies. These challenges, highlighted briefly below, are discussed further in Chapter 3.

First, the lack of common evidentiary standards of clinical utility for biomarker tests is a significant challenge to the adoption of effective biomarker tests for molecularly targeted therapies into mainstream clinical practice. The lack of consensus on evidentiary standards influences health care providers' use of tests as well as payers' willingness to pay for the tests; both of these clearly affect patient access to tests. At the same time, some biomarker tests with limited evidence of clinical utility may be used to direct patient treatment, raising concerns about potential patient harm. The concept of the gradual evolution of evidence of clinical utility of a biomarker test for molecularly targeted therapies through clinical use over time is critical, but is not always considered. The committee's envisioned rapid learning system represents one approach to generating evidence of clinical utility of biomarker tests for molecularly targeted therapies, and would systematically collect and analyze data on biomarker tests, molecularly targeted therapies, and patient management and outcomes. The system would support continuous learning about biomarker tests for molecularly targeted therapies by integrating data from both retrospective and prospective studies as well as incorporating "real-world" clinical data captured in EHRs, generating new evidence, and subsequently applying the knowledge gained to improve patient care.

Second, the processes for making regulatory and payment decisions for biomarker tests for molecularly targeted therapies currently are not in alignment. FDA and CMS have distinct statutory mandates. Moreover, the types of evidence required for regulatory and reimbursement decisions are inconsistent. Reimbursement decisions typically require evidence of clinical utility, which is more difficult to demonstrate than the analytic and clinical validity evidence required for regulatory approval of a biomarker test; thus, tests may be clinically available without reimbursement by CMS and other payers. To advance the adoption of appropriate, accurate, and reliable biomarker tests for molecularly targeted therapies more broadly into clinical use, the processes for regulatory and reimbursement decisions should be more closely coordinated to create a more streamlined process, discussed further in Chapter 3.

Third, the proliferation of biomarker tests for molecularly targeted therapies in the absence of transparent communication about the tests' performance characteristics and intended uses creates uncertainty for health care professionals regarding the appropriate selection and use of tests. Clear, consistent, easy-to-understand information is needed for all biomarker tests used to direct molecularly targeted therapy, to enable health care providers to determine which test to order and to support patient engagement in the decision-making process.

Fourth, CMS regulates all clinical laboratories through the Clinical Laboratory Improvement Amendments (CLIA). CLIA oversight of labo-

ratories is not up to date and is widely viewed as insufficient for the oversight of increasingly complex biomarker tests for molecularly targeted therapies. Changes are needed to strengthen the oversight and accreditation of laboratories providing biomarker tests for molecularly targeted therapies.

Finally, it can be quite difficult to generate strong evidence of biomarker test clinical utility prior to clinical use, so in many cases, promising biomarker tests for molecularly targeted therapies may be implemented in clinical practice without sufficient data to support coverage and reimbursement decisions. As noted above, evidence evolves over time, thus continuous data collection is needed to confirm the impact of the test on longer-term patient outcomes and clinical management, or its clinical utility. Innovative reimbursement policy is needed to promote and support the ongoing assessment of clinical utility of biomarker tests. A rapid learning system as envisioned by the committee would facilitate the generation of clinical utility through collection and analysis of data on biomarker tests for molecularly targeted therapies.

The committee's recommended policy measures to address these challenges are presented in Chapter 3. Implementation of these measures will create a supportive policy environment for the assessment and clinical implementation of biomarker tests for molecularly targeted therapies, one of the three components of the committee's vision of a rapid learning system.

Supporting Data Infrastructure

Ideally, a learning health system uses data and technology to "learn" from clinical experience. This would be accomplished by systematically collecting various types of patient data, including laboratory test results, genomic information, treatments, and clinical outcomes; analyzing the captured data; and subsequently translating the knowledge gained from these analyses into clinical practice. To ensure continuous learning and improve the effectiveness of care, treatments, and patient outcomes need to be included in the rapid learning system database and evaluated over time, generating new hypotheses to implement and assess in clinical care (Abernethy et al., 2010; IOM, 2013b, 2015; Krumholz, 2014).

Though such cycles of continuous learning are ideal, in many cases, the opportunity to learn from clinical patient data is unrealized (Krumholz, 2014). EHRs are an important source of information to improve quality of care and generate real-world evidence, but the challenge is to ensure that patient data are structured appropriately so that information on biomarker test-directed treatment and patient outcomes can be linked. An effective learning health system should include the development and use

of EHRs and related tools that support the clinical use of biomarker tests for molecularly targeted therapies by facilitating the capture of structured data on biomarker test use, therapeutic decisions, and patient outcomes for continuous learning, research, and the development of clinical decision support tools.

A second data-related challenge is that while much genetic/genomic, treatment, and outcomes patient data are available, such data remain siloed in separate institutions and organizations and thus are not available to all for continuous learning. Data sharing is critical in order to accrue the large sample sizes needed to study increasingly subdivided, biomarker-defined patient populations. Aggregating shared data across clinical practices into a single national repository will enable research using real-world patient data to support the use of biomarker tests for molecularly targeted therapies.

Addressing these two data-related challenges is critical as "the promise of massive data assets lies not merely in their size, but the way they are used. . . . Adequately utilized, these reservoirs of data can be a practically inexhaustible source of knowledge to fuel a learning health care system" (Krumholz, 2014, p. 1169), though much remains to be learned about the uses of many types of genomic data. Thus, the committee proposes a series of measures related to data use for biomarker tests for molecularly targeted therapies, discussed further in Chapter 4. Implementing these measures will result in the creation of a supporting data infrastructure, the second key component of the committee's vision for a rapid learning system.

Processes to Improve Patient Care

The third and final element of the committee's vision of a rapid learning system involves processes to improve patient care related to the effective use of biomarker tests for molecularly targeted therapies. In considering approaches to implement the process component of the rapid learning system for biomarker tests for molecularly targeted therapies, the committee identified challenges in three key areas.

First, in the context of precision medicine, patients of particular economic, ethnic, cultural, and geographic backgrounds may face challenges in accessing care. These challenges may include the lack of awareness about advances in precision medicine on the part of patients and/or health care providers, as well as the ability of patients to access biomarker testing and to receive treatment with targeted therapies if appropriate. Equitable access to testing for all patients requires that health care professionals possess the expertise to properly order tests, interpret test results, and determine optimal therapy selection, in spite of the challenges posed

by the rapid pace of biomedical advances. A rapid learning system could facilitate research into potential barriers to equity and access.

Second, the reliability of biomarker test results depends on the adequacy and quality of the specimen collected. If the amount of specimen from a patient is inadequate for the tests that need to be conducted, repeat biopsy procedures may be required, exposing the patient to unnecessary risk. Uniform standards are needed regarding the handling and subsequent documentation in the EHR and/or laboratory information system of specimens for biomarker tests for molecularly targeted therapies.

Finally, consistent with the committee's vision of a rapid learning system, clinical practice guidelines (CPGs) serve an important role in the practice of medicine and a critical educational purpose—in terms of clinical decision making as well as input for biomarker test and associated drug labeling. The IOM has recommended that for CPGs to be considered trustworthy, they should be based on a systematic review of the evidence; be transparently developed by a knowledgeable and multidisciplinary panel in conjunction with patients and reflect patient preferences; provide ratings of evidence and strength of recommendations; and be updated regularly (IOM, 2011). Although some CPGs focus on biomarker tests for molecularly targeted therapies, they may not be updated frequently, may not be user-friendly, or may conflict with other guidelines on similar topics. Increasingly, a broader base of interdisciplinary expertise is needed to generate trustworthy and consistent guidelines related to biomarker tests for molecularly targeted therapies.

A detailed examination of these challenges related to processes of patient care is presented in Chapter 5 of this report. The committee's proposed approach to these challenges represents the third component of the committee's vision of a rapid learning system for biomarker tests for molecularly targeted therapies.

Implementation Challenges

The committee recognizes the complexity and challenging nature of implementing such a rapid learning health system, which will require first and foremost collaboration among multiple public and private agencies, health care providers, patients, insurers, researchers, members of the health information community, health policy makers, and test and drug developers and manufacturers (IOM, 2013b). For such a system to operate effectively, all stakeholders need to value and support continuous learning.

The development of a rapid learning system will require investments of time, funding, and expertise. The federal government, particularly HHS, would be expected to play a key role in supporting a rapid learning

system for biomarker tests for molecularly targeted therapies. NIH and the National Cancer Institute (NCI) with their existing efforts detailed above, as well as FDA would be closely involved in the development of a rapid learning system for biomarker tests for molecularly targeted therapies. Moreover, CMS and other payers would be expected to provide incentives for health care researchers, providers, and manufacturers to participate in a rapid learning system.

While HHS would be expected to take a central role, many other stakeholders such as researchers, health care delivery organizations and institutions, health care providers, payers, manufacturers, and health information technology vendors would all need to contribute to—and be active participants in—the rapid learning system through openly sharing data and information for continuous learning and knowledge generation. Just as the establishment of the learning health care system requires broad-based participation, the system, if properly designed and implemented, will yield benefits that will extend across diverse groups of stakeholders: health care researchers, providers, manufacturers, and most critically, to patients who could ultimately benefit from improved patient care and outcomes.

As noted earlier, a rapid learning system represents one approach to generating evidence of clinical utility for biomarker tests for molecularly targeted therapies. Improved data collection and tracking will enable health care providers to focus on the clinical use of the most effective biomarker tests for molecularly targeted therapies. Currently health care resources are spent on some ineffective tests that carry the potential harm to patients of under- or overtreatment (FDA, 2015). The investments required for the system's development and maintenance of a rapid learning system for biomarker tests for molecularly targeted therapies should be viewed within the context of the potential for broader health system and societal benefits to accrue from its implementation.

Other implementation challenges include the difficulties of EHRs to transmit and receive structured data successfully. The lack of such interoperability represents a significant, but not insurmountable obstacle to broad-based data-sharing initiatives as do privacy concerns as discussed further in Chapter 4 of this report. Addressing such challenges is critical for the effective operation of a rapid learning system for biomarker tests for molecularly targeted therapies as envisioned by the committee.

Many foundational elements and models exist to guide the development of such a rapid learning system, which is required to harness the new knowledge from gene-based discoveries in biology and translate it into clinical practice at a rate commensurate with its potential to direct therapy. The imperative of improved patient care underlies the necessity and urgency of building on these models to develop a rapid learning sys-

tem for biomarker tests for molecularly targeted therapies. Such a system offers profound opportunities to improve patient care and outcomes.

The three components of the committee's vision of a rapid learning system—policy environment, data infrastructure, and processes of care—are explored in greater detail in the three subsequent chapters of this report. The rapid learning system serves as the framework for the committee's 10 recommendations, presented in the chapters that follow.

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3

Supportive Policy Environment for Biomarker Tests for Molecularly Targeted Therapies

The committee's vision of a rapid learning system encompasses three key components—supportive policy environment, supporting data infrastructure, and processes to improve patient care—as discussed in the previous chapter. This chapter explores the first of the three components by examining the key policy challenges that influence the integration of biomarker tests for molecularly targeted therapies into routine clinical practice. These challenges—including issues related to standards of evidence for the clinical utility of biomarker tests, alignment of regulatory and reimbursement decision processes, and test coverage and reimbursement[1]—are located at the intersection of interests of an array of stakeholders, including patients, health care providers, payers, regulators, test developers, device manufacturers, and pharmaceutical companies (see Figure 3-1).

These policy challenges must be viewed within the larger context

[1] This report uses the term "reimbursement" as an umbrella term encompassing coverage and payment. Coverage refers to the ways in which public and private plans outline the services and products they will cover and under what circumstances they will reimburse for certain services and products. A coverage decision may be favorable, unfavorable, or limited; coverage decisions typically are based on clinical evidence. Reimbursement is the payment given to a provider or facility for a covered service or product. Coding is often included under reimbursement, as it refers to the systems that detail information about the nature of health care services provided, the technologies used, and the patient's illness. Payment for medical services is based on the code(s) associated with a particular service and the dollar amount(s) assigned to the code (SACGHS, 2006). Coding related to biomarker tests for molecularly targeted therapies is discussed further in Appendix B of this report.

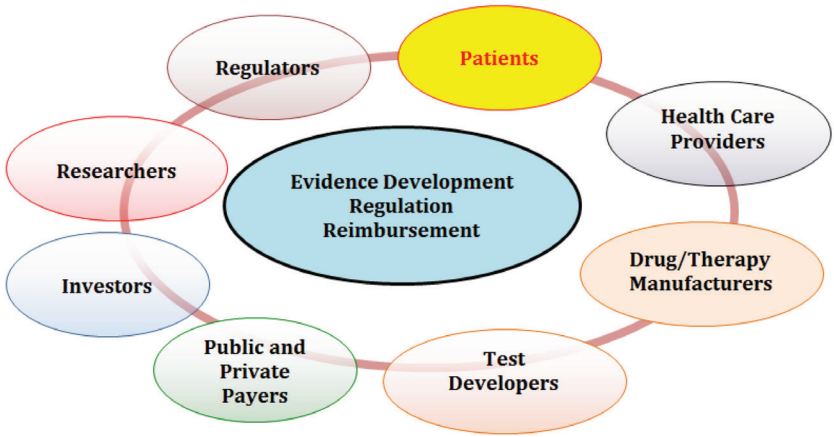

FIGURE 3-1 Policy issues at the intersection of multiple health care stakeholders' interests.

of the current system for biomarker test regulation as well as the U.S. health care reimbursement system, which while still predominantly fee-for-service, is in flux as alternative payment models are introduced that shift risk to health care providers and are aligned more closely with health care value (Anderson et al., 2015; Bipartisan Policy Center, 2015; Burwell, 2015).[2]

Developing appropriate and effective regulatory and reimbursement frameworks responsive to rapidly evolving technologies is critical to ensuring that health care providers and their patients have access to—and the ability to benefit from—the potential of biomarker tests for molecularly targeted therapies to optimize care. At the same time, it is important that regulatory and reimbursement pathways support an environment in which manufacturers and investors continue to see potential economic value in developing such tests and treatments (IOM, 2013b, 2015; PMC, 2015). Indeed, regulatory and reimbursement policy affects all new medical technologies, and has a direct impact on how medical product industries evolve and grow (Deverka and Dreyfus, 2014). To make evidence-based decisions on whether to cover and reimburse the cost of biomarker tests, payers require clarity about the types of information required to establish clinical utility, or the test's usefulness in terms of its impact on clinical outcomes. Thus, policy challenges involve balancing the competing demands of the patient's need and desire for access to tests

[2] Alternative payment models include accountable care organizations, bundled or episode-based payments, capitated payments, and patient-centered medical homes (NASEM, 2015).

to direct novel therapies against the need for sufficient evidence to assess the potential risks and benefits of the tests (IOM, 2013d).

The discussion in this chapter is divided into four parts. The first part explores the issue of evidentiary standards for clinical utility, which is a cross-cutting issue that influences regulatory, reimbursement, and clinical practice areas. The discussion then shifts to an overview of the current regulatory structure for biomarker tests for molecularly targeted therapies and discusses communication and information related to test performance and intended use. The third part of the chapter explores the key reimbursement-related challenges facing clinical implementation of biomarker tests for molecularly targeted therapies. Regulatory and reimbursement challenges are interrelated, and the committee's integrated approach to addressing those challenges forms the fourth and final part of the chapter.

EVIDENTIARY STANDARDS OF CLINICAL UTILITY

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS),[3] which produced a number of detailed reports and recommendations related to the integration of genetic and genomic technologies into health care, specified that information on clinical utility is critical on several levels: for managing the treatment of patients, for developing clinical guidelines to assist health care providers in providing the best available treatment, and for coverage determinations by payers. SACGHS also specified that the lack of evidence of clinical utility is a significant challenge for developing clinical guidelines and ensuring access to tests through coverage and reimbursement decisions (SACGHS, 2008). Achieving consensus on the evidentiary standards for clinical utility has proven to be an elusive goal, however, with the earliest efforts dating back 20 years to the development of a grading system to define levels of evidence for tumor markers (CMTP, 2013; Hayes et al., 1996; IOM, 2012b; Parkinson et al., 2014). Health care providers, payers, and test developers widely perceive the lack of a common evidentiary framework to assess clinical utility to be a limiting factor in the development and use of biomarker tests. Payers increasingly expect evidence of clinical utility of new tests

[3] SACGHS, which was in operation for nearly 10 years until its charter expired in 2011, examined a wide range of topics, including the integration of genetic and genomic technologies into health care and public health; the clinical, public health, ethical, economic, legal, and societal implications of these technologies; gaps in research and data collection; the impact of patent policy and licensing practices on their accessibility and availability; and how genetic and genomic technologies are used in other settings such as education, employment, insurance, and law. (For more on SACGHS see http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/genetics-health-and-society/sacghs-archives [accessed June 6, 2016].)

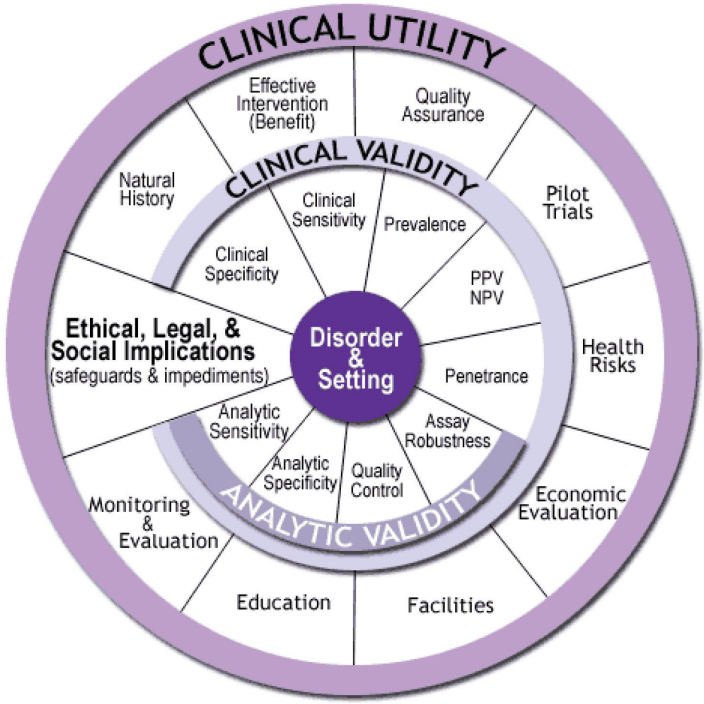

FIGURE 3-2 ACCE Model process for evaluating genetic tests.
NOTE: NPV = negative predictive value; PPV = positive predictive value.
SOURCE: http://www.cdc.gov/genomics/gtesting/ACCE (accessed June 4, 2015.

while test developers are hesitant to invest in evidence development without reasonable certainty such expenditures of resources will be supported by a level of market access that produces a reasonable return on investment. Clearer and more consistent evidence requirements would significantly improve manufacturers' incentives to develop biomarker tests (Faulkner, 2009; Goldman et al., 2013).

The Centers for Disease Control and Prevention (CDC) developed a useful framework known as the ACCE Model,[4] which presents a process for evaluating scientific data on emerging genetic tests. ACCE refers to four main evaluation criteria: analytic validity, clinical validity, clinical utility, and ethical/legal/social implications (see Figure 3-2). The ACCE Model process is based on a standard set of 44 targeted questions related

[4] See http://www.cdc.gov/genomics/gtesting/ACCE (accessed June 4, 2015).

to the four main evaluation criteria.[5] According to this model, the clinical utility of a biomarker test always rests on established analytic validity and clinical validity. A test's analytic validity reveals how well the test detects the specific analytes it was designed to detect and includes assessment of the test's range, accuracy, precision, bias, and reproducibility when used by different operators or instruments across different settings. Clinical validity is a measure of the accuracy of a test for a specific clinical purpose, such as correlation with the presence of a disease or prediction of response to a targeted therapy in a specific patient population. Clinical validity involves assessment of the clinical sensitivity, specificity, and other parameters of a test (Febbo et al., 2011; IOM, 2015; Parkinson et al., 2014; Teutsch et al., 2009). Demonstration of a test's clinical validity is critical to reducing patients' risk of harm from false-positive or false-negative results (Hwang et al., 2015). Both analytic validation and clinical validation lay the foundation for demonstration of clinical utility. The committee's definitions for these terms, as used throughout this report, are outlined and clarified in Box 3-1.

CDC's Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, building on the ACCE Model, defined clinical utility as a test's "evidence of improved measurable clinical outcomes, and usefulness and added value to patient management decision making compared with current management without genetic testing" (Teutsch et al., 2009, p. 11). Clinical utility encompasses evidence of utility in clinical settings as well as the balance of benefits and harms of the test (Teutsch et al., 2009). This understanding of clinical utility has been broadly used to explore policy, research, and clinical care issues related to the use of biomarker tests and corresponding molecularly targeted therapies (CMTP, 2013; Hayes et al., 2013; IOM, 2012a; Parkinson et al., 2014). No consensus currently exists, however, about the evidentiary standards that should be applied to assess the clinical utility of new technologies such as biomarker tests for molecularly targeted therapies (Woodcock, 2010).

Assessing Clinical Utility

Establishing a linkage to improved patient outcomes requires clear, consistent, and reasonable standards of evidence. The lack of such common standards of evidence of clinical utility represents a significant challenge in the implementation of effective biomarker tests for molecularly targeted therapies into routine clinical practice, with significant consequences for patient access to tests, as well as potential for patient harm if

[5] See list of questions at http://www.cdc.gov/genomics/gtesting/ACCE/acce_proj.htm (accessed June 4, 2015).

BOX 3-1
Defining Validity and Utility of Biomarker Tests for Molecularly Targeted Therapies

The clinical use of biomarker tests for molecularly targeted therapies depends upon reliable performance characteristics, a well-defined clinical purpose, and evidence of improved outcomes associated with the test. The definitions used in this and other Institute of Medicine reports are drawn from earlier work by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, and provide a widely accepted framework for evaluating the validity and utility of biomarker tests. These definitions are repeated and briefly clarified below.

Analytic Validity

EGAPP defines the analytic validity of a genetic test as "its ability to accurately and reliably measure the genotype (or analyte) of interest in the clinical laboratory, and in specimens representative of the population of interest" (Teutsch et al., 2009, p. 8). This report uses an adaptation of this definition that defines analytic validity as the accuracy of a test to detect the specific entity that it was designed to detect. This accuracy by itself does not imply any clinical significance, such as diagnosis.

Clinical Validity

EGAPP defines the clinical validity of a genetic test as "its ability to accurately and reliably predict the clinically defined disorder or phenotype of interest. Clinical validity encompasses clinical sensitivity and specificity (integrating analytic validity), and predictive values of positive and negative tests that take into account the disorder prevalence (the proportion of individuals in the selected setting who

tests with limited evidence of clinical utility are used to direct treatment, or if effective tests are not being used clinically due to lack of reimbursement. Such evidentiary standards are also critical for test development as they enable test developers and investors to assess the risk and potential returns on investment in biomarker tests; the lack of such standards may constrain the development of biomarker tests (IOM, 2013d).

The concept of reasonable evidentiary standards hinges on the importance of designing valid studies that can generate evidence in a timely manner that is broadly applicable to real-world clinical situations. Thus, the development of clear, consistent, and reasonable evidentiary standards should focus on evidence that is adequate for rational decision making instead of "ideal" or "best" evidence approaches. At the same time, such standards must be sufficient to address payers' decision-making

have, or will develop, the phenotype/clinical disorder of interest)" (Teutsch et al., 2009, p. 10). For the purposes of this report, clinical validity refers to the accuracy of a test for a specific clinical purpose, such as diagnosing or predicting risk for a disorder. A clinically valid biomarker test for a molecularly targeted therapy is able to define a patient population for which a specific therapy or class of therapies would or would not be beneficial.

Clinical Utility

EGAPP defines the clinical utility of a genetic test as "the evidence of improved measurable clinical outcomes, and its usefulness and added value to patient management decisionmaking compared with current management without genetic testing. If a test has utility, it means that the results (positive or negative) provide information that is of value to the person, or sometimes to the individual's family or community, in making decisions about effective treatment or preventive strategies" (Teutsch et al., 2009, p. 11). In this report, the committee has further expanded the concept of clinical utility to refer to a continuum of evidence, as opposed to a specific moment in time at which point clinical utility is demonstrated.

For biomarker tests for molecularly targeted therapies, this report uses the phrase "improved patient outcomes" to refer to a wide variety of health care benefits associated with the use of a test, including increased survival or quality of life associated with use of a specific therapy, avoidance of unnecessary therapy or toxicity, cost savings, and improved clinical management and decision making. Traditional levels of evidence demonstrating improvement in these areas may be unavailable or require time to develop, and mechanisms need to be in place to facilitate the clinical use of these tests and treatments when appropriate, along with collection of data to further support or refute continued use.

requirements and ensure that patients are not harmed by the introduction into clinical use of new tests that lack adequate evidence (Faulkner, 2009).

Various approaches to systematically establish clinical utility have been proposed over the past two decades, including conducting prospective clinical trials that assess the test or by conducting prospective or retrospective studies using archived specimens collected from previous clinical trials or registries (IOM, 2012a) (see Table 3-1). The assessment of the clinical utility of a biomarker test generally requires applying the test to a large number of patients or patient samples and generation of data on the association of the test result with clinical decisions that lead to improved patient outcomes. Less rigorous studies can result in bias, or conclusions of limited generalizability (IOM, 2011b). The collection of such data requires long-term patient follow-up and collection of outcomes data from an adequate number of patients, which can be challenging

TABLE 3-1 Examples of Study Designs to Assess the Clinical Utility of a Biomarker Test

Type of Trial Design	Description	Advantages and Limitations
Prospective, test-directed randomized controlled studies		
Test-guided versus non-guided, with randomization ("All-comers")	Patients are randomly assigned to the test-guided arm or the non-guided arm. Patients randomized to the test-guided arm are directed to therapy as dictated by the test (test-positive to new therapy, test-negative to standard of care). Patients randomized to the non-guided arm undergo a second randomization to receive either new therapy or standard of care.	**Advantages:** Can be used to evaluate complex test-directed treatment strategies using a large number of treatment options or test categories. **Limitations:** Requires a larger number of patients to be enrolled relative to other designs.
Enrichment studies	The test is applied to all patients, but only test-positive patients are randomized and/or treated. Test-negative patients are either off study or followed prospectively in a registry.	**Advantages:** Useful when clinical utility of some of the test-designated categories is already established or assumed and need not be re-evaluated, while other categories require prospective evaluation in a clinical trial. Acceptable in circumstances where a certain subgroup of patients is thought so unlikely to experience an event with standard of care, or to benefit from the new therapy, that it would be unethical to randomize those patients. **Limitations:** Cannot assess the treatment benefit in test-negative patients. Cannot definitively establish the predictive ability of a marker.

TABLE 3-1 Continued

Type of Trial Design	Description	Advantages and Limitations
Other pragmatic/adaptive studies		
Prospective–retrospective studies	Uses archived specimens from a previously conducted clinical trial with treatment(s) that are relevant to the intended clinical use of the test.	**Advantages**: Despite being less resource- and time-intensive, study design may have evidentiary value close to a prospective study under certain conditions (Simon et al., 2009). Study design can be used if prospective trial is not feasible for ethical or other reasons. **Limitations:** Archived specimens may be unavailable; uncertainty in collection, storage, or processing methods may render test assessment unreliable. Statistical inference concerns due to original trial likely not pre-specifying a plan to study treatment effect in subgroups.
Single-arm studies	Test is applied to all patients, and test-positive patients are uniformly treated with the existing, approved therapy believed to provide a differential benefit based on the test result. Test-negative patients are either off study or followed prospectively in a registry.	**Advantages:** Can be used to identify a subset of patients who may benefit differentially from an existing FDA-approved therapy (with a disease-specific indication in the labeling that would make subsequent RCTs unethical), where archival tissue from the original trial is not available. **Limitations:** It must be feasible to use complete or overall response as an endpoint, and comparable data must be available from a suitable noncontemporaneous cohort. Single-arm studies only provide data on test-positive patients. Due to a lack of a control arm, test-negative patients cannot be assumed not to benefit from the treatment.

continued

TABLE 3-1 Continued

Type of Trial Design	Description	Advantages and Limitations
Longitudinal observational studies	A variety of possible designs, which do not include any study-directed testing or intervention and instead prospectively collect clinical and outcomes data, including "Quasi-experimental": collection of clinical outcomes data pretest and posttest for at least two groups under investigation. Prospective cohort: broad enrollment criteria to facilitate examination of heterogeneity in test- or treatment-related effects.	**Advantages:** Can help generate hypotheses related to large hypothesized effect sizes, evolving treatment strategies, real-world clinical use of tests and multiple corresponding therapies, patient/provider preferences related to test use, long-term outcomes, and very large required sample sizes. **Limitations:** Careful consideration of the rationale for performing an observational study instead of other study types, as well as methods to address bias and confounders, is needed. Observational studies are particularly vulnerable to time-varying confounders. A fully defined research protocol (including hypotheses, intervention groups, outcome and subgroup definitions, power calculations, and analysis plan) is required to approximate a randomized study's objective of causal inference.

TABLE 3-1 Continued

Type of Trial Design	Description	Advantages and Limitations
Detection-analytic modeling techniques	For tests meeting an agreed upon plausibility threshold for clinical utility, modelling techniques can estimate overall downstream outcomes. Such models would include all relevant risks and benefits related to remaining survival and quality of life.	**Advantages:** In cases where explicit evidence of clinical utility is absent, these techniques can estimate the effect of tests on patient outcomes using a variety of sources of evidence as input, through metrics including quality of life and life expectancy. **Limitations:** Tests to be assessed need to meet an established threshold for plausible evidence of clinical utility. Good modeling techniques are labor- and time-intensive to develop and validate (including establishing links between surrogate and final outcome measures), and are not recommended when there is a high degree of uncertainty about the underlying disease process or the link between test results and treatment effectiveness.

NOTE: FDA = Food and Drug Administration; RCT = randomized controlled trial.
SOURCES: CMTP, 2013; Freidlin et al., 2010; IOM, 2012a; McShane, 2011; Sargent et al., 2005; Simon et al., 2009. Adapted from Freidlin et al., 2010; IOM, 2012a.

in light of the rarity of some of the mutations the tests are designed to identify. For example, *BRAF* gene mutations occur in 1 percent or less of lung cancer patients. For one study, researchers screened more than 11,000 lung cancer patients in order to enroll 23 patients with a specific *BRAF* mutation (IOM, 2015). Randomized controlled trials, considered the gold standard of evidence, typically focus on more restricted patient populations and thus do not capture broader patient groups more representative of "real-world" patients with co-morbidities and other issues that render treatment of the patient's condition more complex (Lewis et al., 2015; Perlmutter, 2015; Sniderman and Furberg, 2009; Treweek et al., 2015), as discussed further in Chapter 5.

Currently no agency or organization in the United States is charged with the responsibility of developing evidentiary standards for the clinical

utility of biomarker tests (Schott et al., 2015). As discussed further in the next section, the current regulatory oversight structure for biomarker tests for molecularly targeted therapies does not include assessment of clinical utility. Given the critical need for evidentiary standards of clinical utility to ensure the implementation of appropriate biomarker tests into routine clinical practice to improve patient care, and the absence of a dedicated body responsible for developing such standards, many have called for public–private collaborations to take the lead (Parkinson et al., 2014; Sawyers, 2008). Organizations such as the Center for Medical Technology Policy (CMTP) have worked to fill the void by bringing together a range of public and private stakeholders to work together toward consensus on evidentiary standards for clinical utility (CMTP, 2014; IOM, 2013d, 2015).

REGULATORY CHALLENGES

The regulatory framework for biomarker tests for molecularly targeted therapies presents a number of challenges. First, there is concern over the adequacy of the current approach to the regulation of biomarker tests for molecularly targeted therapies. Second, the processes for regulatory and reimbursement decisions are not currently aligned. Finally, there is a lack of clearly communicated information about the performance characteristics and intended use of biomarker tests, particularly given the availability of multiple tests for the same purpose. All these challenges cause uncertainty and confusion among health care providers, patients, test manufacturers, and payers, and in some cases may potentially expose patients to harm.

Regulatory Oversight of Biomarker Tests for Molecularly Targeted Therapies

The current regulatory structure for biomarker tests for molecularly targeted therapies features key oversight authority by two federal agencies: the Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS). Numerous state regulatory bodies and professional and accreditation organizations also are involved and provide complementary oversight of diagnostic tests and laboratory operations (see Table 3-2).

FDA is charged with overseeing the safety and effectiveness of drugs and medical devices under the Federal Food, Drug, and Cosmetic Act of 1938 and the Medical Device Amendments of 1976. FDA's Center for Drug Evaluation and Research (CDER) regulates drugs, while the Center for Devices and Radiological Health (CDRH) regulates medical devices, including in vitro diagnostics (IVDs). FDA has defined IVDs as tests,

TABLE 3-2 Selected Examples of Entities Involved in Quality Improvement and Oversight of Clinical Laboratories

Entity	Role in Quality Improvement or Oversight
Centers for Medicare & Medicaid Services (CMS)	CMS regulates laboratories under the Clinical Laboratory Improvement Amendments (CLIA) (CMS, 2015a). To ensure CLIA compliance, laboratories undergo review of results reporting, laboratory personnel credentialing (i.e., competency assessment), quality control efforts, and procedure documentation. Laboratories are also required to perform proficiency testing (PT), a process in which a laboratory receives an unknown sample to test and report the findings back to the PT program, which evaluates the laboratory's performance. CMS also approves programs to perform PT. CMS grants states or accreditation organizations the authority to deem a laboratory as CLIA-compliant. Approved accreditation organizations include: American Association of Blood Banks, American Association for Laboratory Accreditation, American Osteopathic Association/Healthcare Facilities Accreditation Program, American Society for Histocompatibility and Immunogenetics, Commission on Office Laboratory Accreditation, College of American Pathologists, and The Joint Commission.
Centers for Disease Control and Prevention (CDC)	CDC performs research on laboratory testing processes, including quality improvement studies, and develops technical standards and laboratory practice guidelines. CDC also manages the Clinical Laboratory Improvement Advisory Committee, a body that offers guidance to the federal government on clinical laboratory quality improvement and revising CLIA standards (CDC, 2014).
Food and Drug Administration (FDA)	FDA reviews and assesses the safety, efficacy, and intended use of in vitro diagnostic tests (IVDs) (FDA, 2014c). FDA assesses the analytic validity (i.e., analytic specificity and sensitivity, accuracy, and precision) and clinical validity (i.e., the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition), and it develops rules and guidance for CLIA complexity categorization. FDA has stated that it has statutory authority for the regulatory oversight of all tests used in patient care, but has used its enforcement discretion (meaning it has chosen not to exercise that authority) for the oversight of laboratory-developed tests (LDTs). However, FDA signaled its intent to begin regulating LDTs in draft guidance released in 2014 (FDA, 2014a).

continued

TABLE 3-2 Continued

Entity	Role in Quality Improvement or Oversight
College of American Pathologists (CAP)	CAP accreditation ensures the safety and quality of laboratories and satisfies CLIA requirements. CAP also offers an inter-laboratory peer PT program, which includes (1) Q-Tracks: a continuous quality monitoring process; (2) Q-Probes: a short-term study that provides a time-slice assessment of performance, and (3) Q-Monitors: customized programs that address process-, outcome-, and structure-oriented quality assurance issues.
American Academy of Family Physicians (AAFP)	AAFP offers a number of CMS-approved PT programs (AAFP, 2015).
American Society for Clinical Pathology (ASCP)	ASCP certifies medical laboratory professionals. ASCP also manages a CMS-approved PT program for gynecologic cytology (ASCP, 2014).
New York State Department of Health (NYSDOH)	NYSDOH's Clinical Laboratory Evaluation Program (CLEP) seeks to ensure the accuracy and reliability of results of laboratory tests on specimens obtained within the state through on-site inspections, proficiency testing and evaluation of the qualifications of personnel of state permit-holding clinical laboratories and blood banks (NYSDOH, 2015a).

SOURCE: Adapted from NASEM, 2015.

reagents, instruments, and systems used to diagnose medical conditions. FDA's jurisdiction does not cover laboratory facilities or functions; rather, it focuses on individual IVD safety and effectiveness.

The regulatory pathways for clinical laboratory tests differ from that for drugs. Clinical laboratory tests such as biomarker tests for molecularly targeted therapies are introduced into standard clinical practice through several pathways. Medical device manufacturers may market a commercial "test kit," which typically includes the necessary reagents, instructions, and statements regarding the intended use of the test. Such test kits are sold to laboratories, health care providers, or hospitals in interstate commerce, and they must be approved or cleared by FDA using the premarket approval or 510(k) process, respectively (see Box 3-2).

A test also may be developed for exclusive use within a specific laboratory; this is known as a laboratory-developed test (LDT), which FDA defines as an IVD manufactured, developed, validated and offered by a single laboratory. Although the uses of an LDT are often the same

BOX 3-2
Regulatory Pathways for Medical Devices

The Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act established three regulatory classes for medical devices based on the degree of control necessary to assure that the various types of devices are safe and effective. The most regulated devices are in Class III; a Class III device is defined as one that supports or sustains human life or is of substantial importance in preventing impairment of human health or presents a potential, unreasonable risk of illness or injury. Insufficient information exists on a Class III device so that performance standards (Class II) or general controls (Class I) cannot provide reasonable assurance that the device is safe and effective for its intended use. Under Section 515 of the act, all devices placed into Class III are subject to premarket approval (PMA) requirements. Premarket approval by the Food and Drug Administration (FDA) is the required process of scientific review to ensure the safety and effectiveness of Class III devices.

Section 510(k) of the Act requires device manufacturers who must register to notify FDA of their intent to market a medical device at least 90 days in advance. This is known as Premarket Notification or 510(k). This allows FDA to determine whether the device is equivalent to a device already placed into one of the three classification categories. Thus, "new" devices (not in commercial distribution prior to May 28, 1976) that have not been classified can be properly identified. Medical device manufacturers are required to submit a premarket notification if they intend to introduce a device into commercial distribution for the first time or reintroduce a device that will be significantly changed or modified to the extent that its safety or effectiveness could be affected. Such change or modification could relate to the design, material, chemical composition, energy source, manufacturing process, or intended use.

When FDA review is needed prior to marketing a medical device, two regulatory pathways exist:

1. FDA may decide to "clear" the device after reviewing a premarket notification, known as a 510(k) (named for a section in the Food, Drug, and Cosmetic Act), that has been filed with FDA. Whether a 510(k) needs to be filed depends on the classification of the medical device. To acquire clearance to market a device using the 510(k) pathway, the submitter of the 510(k) must show that the medical device is "substantially equivalent" to a device that is legally marketed for the same use.
2. FDA may decide to "approve" the device after reviewing a premarket approval application that has been submitted to FDA. The PMA applicant must provide reasonable assurance of the device's safety and effectiveness to obtain approval.

SOURCES (accessed May 12, 2016): http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194460.htm; http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances; http://www.fda.gov/Medicaldevices/Deviceregulationandguidance/Howtomarketyourdevice/Premarketsubmissions/Premarketapprovalpma/Default.htm.

as an FDA-cleared or approved IVD, many clinical laboratories choose to offer their own test. Indeed, the LDT pathway is a more commonly used route to market, enabling rapid test development and implementation into clinical use (IOM, 2015).[6] Any clinical laboratory that reports tests for clinical management of patients falls under the purview of CMS's Clinical Laboratory Improvement Amendments of 1988 (CLIA, as in a CLIA-certified laboratory) which provides a baseline level of oversight with respect to test performance and the quality of laboratory operations, discussed further below.

Importantly, review of tests by FDA focuses on demonstration of analytic validity and clinical validity; according to FDA guidelines, a "safe and effective" IVD has established *both* analytic and clinical validity. FDA's authority extends to regulate the design, manufacturing quality, labeling, and legitimacy of manufacturer claims concerning "intended use" of diagnostics and drugs designed for clinical use. FDA does not require evidence of a test's clinical utility prior to clinical use. Thus, FDA approval or clearance does not necessarily imply that the test improves clinical outcomes. LDTs performed in CLIA-certified laboratories also are not required to demonstrate clinical utility prior to use (IOM, 2010, 2012a, 2015).

FDA has stated that it has statutory authority for the regulatory oversight of all tests used in patient care, but has used its enforcement discretion (meaning it has chosen to not exercise that authority) for the oversight of LDTs.[7] While an LDT developed by a CLIA-certified laboratory currently does not require FDA approval or clearance, FDA has indicated in a draft guidance released in October 2014 its intention to gradually phase in regulation of high-risk LDTs, followed by moderate-risk LDTs, over a 9-year period, as discussed further below (FDA, 2014c).

Companion Diagnostics

Biomarker tests that will be used to identify patients likely to benefit from a specific investigational targeted therapy may be co-developed with the drug; the biomarker and drug are both tested simultaneously in clinical trials, and the safety and efficacy of the test and the drug are evaluated in the same trial. Biomarker tests that are co-developed with a drug and co-approved by FDA are known as companion in vitro diag-

[6] The alternative LDT pathway is not possible for drug development; premarket approval by FDA is required for all drugs.

[7] The majority of biomarker tests for molecularly targeted therapies currently in clinical use are LDTs.

nostics[8] (IOM, 2015). In oncology, for example, FDA has approved nearly two dozen companion diagnostics, most of which target the *HER2* gene, but also include tests for *BRAF* gene mutation, *EGFR* gene mutations, and other targets.[9] Companion diagnostics provide information that FDA considers necessary for the safe and effective use of a corresponding therapy and approved drugs and their companion diagnostics refer to each other in their labels (IOM, 2015). As Parkinson points out, "The approval in recent years of companion diagnostics developed with targeted therapies serve as the best available examples of successful clinical utility efforts" (Parkinson et al., 2014, p. 1439).

For a biomarker test that is co-developed with a drug (e.g., *HER2* for trastuzumab), the regulatory pathway enables concurrent approval of the test and the drug (Frueh, 2013). Although establishment of clinical utility for the drug–diagnostic combination would be expected to ensure reimbursement of the test, this is not always the case; one study found limited and variable reimbursement of drug–diagnostic combinations, stating that "even in cases of co-developed combinations, drug reimbursement does not necessarily imply diagnostic reimbursement" (Cohen and Felix, 2014, p. 171).

An important note is that challenges to the companion diagnostics model include the fact that LDTs can be used in place of an FDA-approved companion diagnostic. Moreover, when FDA initially developed the companion diagnostics model, single-analyte tests predominately were used to indicate treatment with a specific companion drug. Given the increasing use of newer technologies such as next-generation sequencing (NGS), the companion diagnostic model of single test for single drug may not be feasible for assessing a single small cancer biopsy for potential response to multiple drugs using multiple individual tests on different testing platforms (Blumenthal et al., 2016; IOM, 2015; Mansfield, 2014).

[8] According to FDA, "a companion diagnostic device can be an in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product." http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm (accessed May 22, 2015).

[9] See complete list at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm (accessed May 18, 2015).

Laboratory Oversight Under CLIA

All laboratories operating in the United States and involved in "the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings" fall under the jurisdiction of CMS laboratory oversight under CLIA.[10] Passed by Congress to ensure the quality of all clinical laboratories in the United States, the amendments were motivated in large part to target unregulated laboratories that were operating outside the authority of the earlier Clinical Laboratory Improvement Act of 1967 (CMS, 2006). Any laboratory performing biomarker testing used to guide treatment selection falls within the regulatory purview of CLIA.

The requirements for CLIA certification vary depending on the nature and complexity of the tests performed by a laboratory. This system is based on the degree of harm that an incorrect test could cause for a patient. Tests determined to be low-complexity tests such as urine pregnancy tests or fecal occult blood tests (for colorectal cancer screening) are granted waived status under CLIA (CMS, 2015c).

Laboratories performing medium- and high-complexity tests, including those for biomarker tests for molecularly targeted therapies, are subject to additional quality control and proficiency testing (PT) requirements in order to obtain the required CLIA Certificate of Compliance. These laboratories must participate in one of 13 national PT programs, which in turn are overseen by CMS or its approved accreditation organizations (see Table 3-2). Laboratories performing specialized testing (e.g., for hematology or toxicology) are further subject to specialty PT to ensure additional rigor in the assessment of the laboratory performance and quality (Astles et al., 2013).

The PT process assesses the analytic validity of laboratory tests: PT specimens are provided and the laboratory processes the samples in accordance with its standard operating procedures to detect certain analytes, then reports the results to the PT agency. To determine the quality of the laboratory, test results are evaluated according to CLIA's criteria for acceptable performance. These criteria are often based on the mean performance of other laboratories performing the tests by the same methods, or are tied to a reference value (SACGHS, 2008).

CMS[11] currently does not define specific standards for molecular pathology or genetics/genomics tests under CLIA, though requests for inclusion of specialty PT related to genetics have been made to CMS and

[10] 42 U.S.C. 263a.

[11] See https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/lccodes.pdf (accessed May 19, 2015).

the Clinical Laboratory Improvements Advisory Committee (Murphy et al., 2006).[12]

The current level oversight of laboratories under CLIA raises concerns in the context of the clinical use of biomarker tests for molecularly targeted therapies, given the minimum standards required to maintain compliance with CLIA. CLIA requires that laboratories analytically validate their tests prior to use; the criteria for adequate test validation and performance are defined by the laboratory director (IOM, 2015). CLIA regulations do not explicitly require laboratories to verify clinical validity of LDTs, although the regulations may be interpreted to mandate such verification (Ferreira-Gonzalez et al., 2014).

Given CLIA regulations only explicitly require demonstration of analytic validity, concerns have been raised that a CLIA-certified laboratory potentially could develop an analytically valid test for clinical use without demonstrating the clinical validity or clinical utility of the test to positively impact patient care. Moreover, CLIA's specialty areas that require a higher degree of oversight do not currently include genetic, genomic—or other omics—testing, raising concerns over the level of oversight of laboratories conducting highly complex biomarker tests (Hudson et al., 2007). Many laboratories are more highly regulated under frameworks defined by state laws and other accreditation authorities as discussed further below, but currently CLIA is the minimum national legal standard for clinical laboratories, including laboratories developing LDTs.

Evolving Regulatory Framework

Appropriate oversight and validation of LDTs has continued to be debated, driven by the need to ensure safe, accurate, and reliable biomarker tests without limiting patient access and quality of care. While FDA recognizes the importance of CLIA oversight of laboratories, concern over whether CLIA provides a sufficient regulatory framework for high-risk testing has arisen (FDA, 2014a). In the past, FDA attributed exercising enforcement discretion for LDTs to their simple, low-risk nature. FDA recognizes that current LDTs are:

- Manufactured with components that are not legally marketed for clinical use;

[12] Additional CMS testing oversight measures include educational publications in the CDC's *Morbidity and Mortality Weekly Report*, training of state surveyors in relevant technical and procedural issues, and requests for FDA assistance in validation of complex tests. https://www.genome.gov/Pages/About/OD/ReportsPublications/June2008_YostHoL.pdf (accessed June 21, 2015).

- Offered beyond local populations and manufactured in high volume;
- Used widely to screen for common diseases rather than rare diseases;
- Used to direct critical treatment decisions (e.g., prediction of drug response); and
- Highly complex (e.g., automated interpretation, multisignal devices, use of nontransparent algorithms and/or complex software to generate device results) (FDA, 2014b, p. 8).

The evolving complexity of LDTs propelled FDA to signal its intention to exercise its regulatory authority through issuance of draft guidance in October 2014 (FDA, 2014b). Certain stakeholder groups have reacted strongly to the proposed guidance (see Box 3-3 for an overview of selected stakeholder perspectives on increased oversight for laboratories and LDTs). Stakeholders' reaction focuses on the concern about the FDA's ability to regulate LDTs in a way that will not hamper innovation, concern that its processes are too slow to keep pace with the rapidly changing medical knowledge regarding the genetic and genomic causes of disease, as well as the lack of evidence that LDTs cause patient harm (Evans et al., 2015; Terry, 2014). FDA released a White Paper in November 2015 that examined 20 LDTs, which due to false-positive or false-negative results may have caused or did cause actual harm to patients. Other LDTs examined by FDA were found to have provided information that did not have any proven relevance to the disease or condition for which the test was intended for use (FDA, 2015c).

Once the FDA LDT guidance is finalized, all laboratories will have a 6-month grace period to notify FDA of all LDTs in clinical use, and begin to report significant adverse events to FDA. Notification details will include laboratory and test name, intended use, clinical use (e.g., prognostic, predictive), monthly test volume, disease or patient population, test method and analyte detected, and sample type(s) (FDA, 2014a). Test manufacturers and clinical laboratories developing tests would be required to continue to remove products from the market at any time if they are found to be unsafe.

FDA has stated that LDTs should be subject to further risk-based regulation requiring sufficient evidence to deem them safe and effective. The initial focus after the LDT guidance is finalized will be on premarket review of LDTs that have the same intended use as existing FDA-cleared or -approved companion diagnostics or high-risk medical devices (laboratories providing these LDTs will have a 12-month grace period to file for premarket approval [PMA] with FDA). FDA will determine further prioritization for review based on the notification data received for all

BOX 3-3
Selected Stakeholder Perspectives on FDA Draft Guidance on LDT Oversight

American Clinical Laboratory Association[a]

The American Clinical Laboratory Association (ACLA) retained expert legal counsel and threatened legal action against the Food and Drug Administration (FDA), citing a lack of statutory authority for their intent to regulate certain laboratory-developed tests (LDTs). A white paper released in 2015 outlines ACLA's rationale, which cites existing state and Centers for Medicare & Medicaid Services (CMS) oversight (through the Clinical Laboratory Improvement Amendments, or CLIA) of "laboratory-developed testing services" (LDTSs). The use of this alternative terminology defines LDTs not as medical devices, but as a valuable service provided by pathologists during the routine practice of laboratory medicine, which is beyond FDA's statutory purview. ACLA claims that FDA was never granted oversight of laboratories or laboratory testing services in the Federal Food, Drug, and Cosmetic Act, and furthermore was expressly forbidden from regulating the practice of medicine.

Additional justifications given by ACLA's counsel for potential legal action relate to the regulatory distinctions between medical devices and testing services (e.g., medical devices are defined as "physical articles or products," and LDTSs are not introduced into interstate commerce for commercial distribution). Additionally, ACLA asserts that FDA is attempting to circumvent requirements to "meaningfully consider and respond" to comments on draft guidance, rendering FDA noncompliant with federal administrative law as defined by the Administrative Procedure Act.

Association for Molecular Pathology[b]

The position statement from the Association of Molecular Pathology (AMP) redefines LDTs as laboratory developed procedures (LDPs), "a professional service that encompasses and integrates the design, development, validation, verification, and quality systems used in laboratory testing and interpretative reporting in the context of clinical care."[c] The AMP proposal affirms that existing CLIA oversight of laboratories, and required documentation, is sufficient for resolving LDP performance issues.

AMP proposes that CMS improve laboratory performance transparency by making public existing laboratory registries, and further expanding those registries to include information about adverse events on a per-laboratory basis. Furthermore, AMP asserts that for a certain class of high-risk LDPs (e.g., those predicting risk of disease or response to targeted therapy, AND used in diseases associated with significant morbidity/mortality, AND providing results through hidden or "black box" algorithms or otherwise not transparent to other laboratory professionals), third-party oversight through FDA or other entities may be required to assess analytic and clinical validity.

continued

BOX 3-3 Continued

College of American Pathologists[d]

The College of American Pathologists (CAP) position on LDTs emphasizes cooperation among CMS, FDA, and other accrediting bodies, and defines three risk categories (low, moderate, and high) that should be subject to varying levels of regulatory oversight. Low-risk tests, which are commonly used in concert with other clinical findings to establish diagnosis, prognosis, or predicted effective therapy, would remain subject to existing regular accreditor inspection. Moderate-risk tests, used independently to diagnose disease or predict therapeutic response, and performed through well-understood and independently verifiable methodology, would require accreditor review prior to clinical use to ensure analytic and clinical validity. The final category, high-risk tests, would require FDA review prior to clinical use, due to unclear or unverifiable testing methodologies, including use of proprietary algorithms that would limit interlaboratory comparability.

Diagnostic Test Working Group[e]

The Diagnostic Test Working Group (DTWG) defines a distinct regulatory category apart from medical devices, drugs, and biologics: the in vitro clinical test (IVCT). DTWG asserts that an IVCT differs from a traditional medical device in that analytic and clinical validity are the central regulatory attributes, rather than safety and effectiveness. Asserting that the development, validation, and clinical use of IVCTs also differs from medical devices, DTWG proposes FDA oversight for test development, including design, development, validation, kit or IVCT production, and postmarket activities. Laboratory oversight would be retained by CMS, and the practice of medicine, defined as "the medical judgment used for determining what tests are appropriate for a specific patient and the interpretation of test results and related consultations" (p. 9), would be regulated at the state level. DTWG classifies IVCTs based on high, moderate, and low risk, each with varying quality and pre- and postmarket requirements.

SOURCES (accessed May 12, 2016): [a] Clement and Tribe, 2015; [b] Ferreira-Gonzalez et al., 2014; [c] Ferreira-Gonzalez et al., 2014, p. 5; [d] http://www.cap.org/apps/docs/advocacy/ldt/oversight_model.pdf; [e] http://www.fdalawblog.net/DTWG_final_proposal.pdf.

LDTs, through the use of an advisory panel. The first phase of the regulatory process is expected to last 5 years (with an additional 4 years for moderate-risk devices) (FDA, 2014b).

FDA will continue to exercise enforcement discretion for three categories of LDTs: (1) those intended for use with rare diseases or conditions ("rare" as defined by FDA refers to cases where the number of persons who may be tested with the device is less than 4,000 per year); (2) "traditional LDTs," defined by FDA as being manufactured by a health care facility laboratory, interpreted by a qualified laboratory professional, used

in the treatment of a patient within the same health care system, composed only of components and instruments that are legally marketed for clinical use, and interpreted by qualified laboratory professionals without the use of automated instrumentation or software for interpretation; and (3) LDTs for unmet needs for which no FDA-approved diagnostic exists for its intended use. LDTs used in law enforcement and in determining transplant histocompatibility would also remain under enforcement discretion (FDA, 2014b).

This regulatory approach seeks to balance the dual goals of making LDTs available to patients in need, while also requiring accurate and reliable test performance. In an effort to improve transparency and efficiency in the regulatory process, FDA encourages laboratories to provide notification that they are developing tests. This early collaboration would enable advisory panels working in conjunction with FDA to better understand and prioritize tests in the pipeline according to risk (FDA, 2014a).

Newer technologies such as NGS also pose significant regulatory challenges. Such technologies are producing an unprecedented amount of omics data, which have the potential for both research and clinical use. However, variability in platforms, assay design, and bioinformatics approaches can complicate the validation of these vast amounts of often novel biological data (Boland et al., 2013; Ewing et al., 2015; Pant et al., 2014). FDA has proposed a collaborative approach to ensuring the accuracy and reproducibility of NGS tests and continues to work with the broader scientific community to refine its regulatory framework regarding these complex new technologies (Blumenthal et al., 2016; FDA, 2015a; Kass-Hout and Litwack, 2015).

REIMBURSEMENT CHALLENGES

As noted at the beginning of this chapter, the policy challenges to biomarker tests for molecularly targeted therapies must be viewed within the context of the broader U.S. health care system. Although the Affordable Care Act contained incentives to adopt alternative reimbursement models (Blumenthal et al., 2015)—such as global, bundled, or value-based payments, and accountable care organizations—the predominant reimbursement method in the U.S. health care system remains fee-for-service. Reimbursement systems have a significant impact on how care is delivered; fee-for-service reimbursement encourages volume of services and does not provide a strong framework for linking reimbursement to health outcomes or value (Patel et al., 2015). The Institute of Medicine's (IOM's) *Best Care at Lower Cost* report concluded that fee-for-service does not reward health care providers for quality of care and actually encourages wasteful and ineffective care (IOM, 2013a). In addition to an evolving

reimbursement structure, reimbursement for biomarker tests also must be viewed against the backdrop of ongoing broad-based efforts by payers to constrain health care spending (Deverka and Dreyfus, 2014).

The U.S. health care system features an array of private and public payers with different coverage and reimbursement policies (Chambers et al., 2015). Medicare is a key public payer, providing insurance coverage for more than 50 million beneficiaries (CMS, 2015b). The Medicare reimbursement system is governed by the "reasonable and necessary" standard. It cannot reimburse for experimental treatments, or most screening tests, and will not reimburse for biomarker tests for molecularly targeted therapies that are not the standard of care (IOM, 2015). Medicare at times makes coverage decisions that are applicable nationwide, known as national coverage determinations (NCDs) or more commonly, works with regional claims administrators known as Medicare Administrative Contractors (MACs) to make local coverage determinations (LCDs). The joint federal–state Medicaid program involves significant state-level flexibility and variability in benefits and reimbursement policies, and thus operationally is closer to 51 separate programs than one monolithic program[13] (Schneider and Wachino, 2013).

Private payers insure approximately two-thirds of the U.S. population (U.S. Census Bureau, 2014) and there are hundreds of different coverage and reimbursement policies and decisions—what is often likened to a crazy quilt of policies—underscoring the absence of a standardized approach to coverage and reimbursement of tests such as biomarker tests for molecularly targeted therapies (Graf et al., 2013; Gustavsen et al., 2010; Meckley and Neumann, 2010; Trosman et al., 2010).

Recent moves among large health care payers indicate the continuation of a consolidation trend, leaving three large corporations that dominate the U.S. health insurance market.[14] Once the proposed merger between Anthem and Cigna is finalized, one insurer will be responsible for coverage and reimbursement decisions for more than 50 million members. Such payer consolidation increases the large insurers' ability to negotiate fees with health care providers (Caffrey and Joszt, 2015), while intensifying consumers' and providers' concerns about the impact on competition (Japsen, 2015).

Decisions by payers—private insurers, private health plans, and public programs—are critical to the integration of biomarker tests for molecu-

[13] States are responsible for making Medicaid coverage decisions. Consequently there are significant state-by-state differences in Medicaid coverage for genetic tests and services (SACGHS, 2006), which can serve as a source of disparity in access to biomarker tests for molecularly targeted therapies, discussed further in Chapter 5 of this report.

[14] Aetna announced an agreement to acquire Humana in July 2015, and Anthem subsequently announced the purchase of Cigna in August 2015. Currently, the top three largest publicly traded U.S. health insurers are Anthem, UnitedHealth Group, and Aetna.

larly targeted therapies into routine clinical practice. Public and private health insurers and health plans seek to ensure that biomarker tests for molecularly targeted therapies provide information that is beneficial to the selection of treatment and leads to improved patient outcomes, and expect to use evidence of clinical utility to determine coverage and reimbursement decisions. However, evidence of clinical utility is often lacking, as discussed earlier (Frueh and Quinn, 2014; Parkinson et al., 2014; Schott et al., 2015; Simonds et al., 2013). Indeed, coverage decisions are often made in the context of a seemingly contradictory environment of a large volume of genetic and genomic information and relatively limited evidence of clinical utility (IOM, 2014). The lack of evidentiary standards for clinical utility influences payers' willingness to cover and reimburse the cost of biomarker tests for molecularly targeted therapies (Cohen and Felix, 2014; Hresko and Haga, 2012). Test developers, for their part, require adequate reimbursement levels to ensure sufficient return on their investment (Deverka et al., 2014).

Value of Biomarker Tests for Molecularly Targeted Therapies

New molecular test codes that took effect in 2013 (see Appendix B for a discussion of coding issues related to biomarker tests for molecularly targeted therapies) provide some clarity for biomarker tests manufacturers and payers, but the ongoing development and subsequent implementation of biomarker tests for molecularly targeted therapies hinges on the ability of test developers and investors to capture the value of their innovations through adequate reimbursement levels. As one observer points out, even with the assignment of the new Molecular Pathology codes, such cost-based reimbursement is "not grounded in systematic measurement of the value of diagnostic tests" and results in a significant imbalance between the high value of the tests and limited amount of reimbursement (Goldman et al., 2013, p. 130).

A biomarker test's clinical value lies in its potential to improve patient care by directing effective targeted therapy, or determining that such treatment would not prove to be beneficial to the patient. A biomarker test's financial value is linked to its ability to direct treatment to a specific subpopulation of patients most likely to respond to a specific and often expensive molecularly targeted therapy, optimizing patient care while containing costs that would otherwise be spent on ineffective treatments. The total financial cost of developing a biomarker test is typically calculated by adding the cost of discovery research and test validation as well as the cost of developing evidence of clinical utility. For test manufacturers to recoup the significant costs of these research efforts, a test needs to be reimbursed at a sufficient level, which varies depending on the volume of test use. Although the market historically has rewarded discovery and

development of molecularly targeted therapies with high levels of reimbursement, this has not necessarily been the case for biomarker tests to guide selection of those therapies, which has slowed their adoption into clinical practice (Hayes et al., 2013).

Indeed, reimbursement levels for biomarker tests are much lower than for targeted treatments, which impacts the ability to generate the high levels of evidence needed to demonstrate clinical utility, resulting in what Hayes et al. (2013) have termed a "vicious cycle" of undervaluation of biomarker tests by payers, leading to few biomarker tests with established clinical utility on the one hand, and adoption of tests into clinical practice without sufficient evidence of clinical utility, on the other (Hayes et al., 2013). Given the potential of biomarker tests to identify patients that are likely to respond to treatment, thereby avoiding ineffective treatments, many have called for policies to "reconcile the potential mismatch between innovator incentives and social value" (Goldman et al., 2013, p. 132). Moreover, the current focus on the cost of expensive drug therapies underscores the value of tools such as biomarker tests that are capable of identifying which patients are most likely to benefit from expensive therapies (Faulkner et al., 2012; Fugel et al., 2014).

Provisions in the Protecting Access to Medicare Act (PAMA) of 2014 (see discussion in Appendix B) call for the introduction of a market-based payment system for tests under the Clinical Laboratory Fee Schedule (CLFS). The law requires "applicable laboratories"[15] to report to CMS the rates paid by private payers for each clinical diagnostic laboratory test and the volumes of each test provided over a specified period of time. CMS will use this rate information to calculate a weighted median payment amount for each test. Applicable laboratories will have to begin to collect payment rates from private payers from July to December 2015 and report the rate information to CMS during the first quarter of 2016. CMS published its 2016 CLFS fee schedule, using two different fee-setting processes depending on the type of test (discussed further in Appendix B) and PAMA is scheduled to take effect on January 1, 2017 (Ray, 2015). It remains to be seen if the proposed market-based pricing approach for advanced laboratory tests, such as biomarker tests for molecularly targeted therapies, represents progress toward the goal of value-based reimbursement (Carey, 2014). There is concern, for example, that potential aggressive pricing of tests by laboratories may influence the final reimbursement rate calculated by CMS (Newcomer, 2015).

[15] An applicable laboratory is defined by CMS as a lab that receives more than 50 percent of its Medicare revenues as paid under the CLFS or physician fee schedule. This would exclude hospital labs. In addition, labs that have Medicare revenues of less than $50,000 would be excluded.

Information That Payers Use to Support Coverage and Reimbursement Decisions

Health plans, insurers, and other payers seek certainty and value for their health care reimbursement dollars when making coverage and reimbursement determinations, but such certainty is difficult to attain, particularly in the field of precision medicine with its promising, but complex and rapidly evolving, tests and associated targeted treatments. The explosion in the number of tests leaves payers and providers to navigate what has been referred to as a "wild West" environment of ever-increasing numbers and complexity of tests without the necessary evidentiary support required to make decisions about clinical use and coverage (IOM, 2013d). As discussed earlier in this chapter, the lack of common evidentiary standards for biomarker tests for molecularly targeted therapies may limit health care providers' and patients' access to such tests.

Payers' coverage and reimbursement policies are informed by evidence of analytic and clinical validity of a test, as well as evidence of clinical utility (Deverka and Dreyfus, 2014; Deverka et al., 2014; Meckley and Neumann, 2010). Payers expect to make coverage and subsequent reimbursement decisions based on evidence that the use of a biomarker test is: (1) medically necessary; (2) linked to improved outcomes for patients; and (3) better than the tests currently used in standard care or no test at all (IOM, 2015). Studies have found a significant variability of coverage of genomic testing among payers (Hresko and Haga, 2012; Meckley and Neumann, 2010; Trosman et al., 2010). One study found that lack of evidence or limited published studies demonstrating a test's clinical utility is a key factor in insurers' decisions to not provide coverage of disease-related genomic tests (Hresko and Haga, 2012).

In the absence of evidence of clinical utility, or consensus regarding evidentiary standards of clinical utility, payers rely on a variety of information sources to develop their coverage policies (Graf et al., 2013; Trosman et al., 2011). In addition to peer-reviewed studies published in medical journals, payers consider:

- Reviews of published studies on a particular topic, such as those conducted by the Agency for Healthcare Research and Quality (AHRQ), Blue Cross/Blue Shield Technology Evaluation Center, or Duke Evidence-based Practice Center.[16]
- Evidence-based consensus statements or guidelines from professional societies or other nationally recognized health care organiza-

[16] AHRQ: http://www.ahrq.gov (accessed June 20, 2015); BCBS: http://www.bcbs.com/blueresources/tec/tec_staff.html (accessed June 20, 2015); Duke: http://guides.mclibrary.duke.edu/c.php?g=158201&p=1036021 (accessed June 20, 2015).

tions, such as the American Society of Clinical Oncology (ASCO) or the National Comprehensive Cancer Network (NCCN) (IOM, 2015).
- Guidance documents developed by multistakeholder groups such as CMTP (McDonough, 2015).

Private payers are generally believed to often follow Medicare's coverage determinations. However, a recent study found that the coverage decisions for medical devices by 16 private payers aligned with Medicare decisions only half the time (Chambers et al., 2015). Most large health insurers have clinical policy divisions responsible for evaluating the evidence associated with medical technologies. Payers also consider a number of evidentiary frameworks in an effort to guide coverage and reimbursement decisions. For example, the ACCE process, supported by CDC's EGAPP initiative discussed earlier in this chapter, is considered useful for examining clinical validity and utility (McDonough, 2015; Veenstra et al., 2013).[17]

Randomized controlled trials are widely considered the gold standard for generating evidence, as noted earlier in this chapter, but they are costly and require tracking large numbers of patients over time; as a result they are not typically conducted to evaluate biomarker tests for molecularly targeted therapies. This is due in part to the thinner profit margins of IVD test developers relative to pharmaceutical companies, which makes it less likely they would be able to support clinical trials on the scale of those funded by pharmaceutical companies (Faulkner, 2009). Other types of studies that payers may consider in evaluating clinical utility to support reimbursement include prospective–retrospective and observational studies (McDonough, 2015). In cases where compendia, which are summaries of drug information based on expert reviews of clinical data, indicate the need for a specific test to use a drug for a specific indication, payers tend to cover those tests. However, research indicates that information contained in compendia is of variable quality and often not supported by sufficient evidence (Abernethy et al., 2010).

Payer Use of Clinical Guidelines

Health care providers often rely on clinical practice guidelines (CPGs) to translate research findings into actionable steps for providing care (IOM, 2011a, 2013b). Payers, for their part, often turn to CPGs to help

[17] Other initiatives include a recently developed tool to help payers assess the clinical and economic evidence for companion diagnostics associated with targeted drug therapies (Canestaro et al., 2015).

inform coverage and reimbursement decisions (Graf et al., 2013; Meckley and Neumann, 2010). CPGs are important sources of information for health care providers as well as payers, but there is significant variability in the quality of the underlying evidence base for the guidelines, and as the IOM has pointed out, "the CPG development process is often fragmented, lacking in transparency, and plagued by potential conflicts of interest in the membership of the CPG panels that might bias the resulting product" (IOM, 2013b, p. 294).

The IOM convened a consensus committee to develop CPG standards. The committee concluded that to be trustworthy, CPGs should be based on a systematic review of the evidence; be transparently developed by a knowledgeable and multidisciplinary panel in conjunction with patients and reflects patient preferences; provide ratings of evidence and strength of recommendations; and be updated regularly (IOM, 2011a). Further discussion of the development of CPGs, as well as the committee's recommended approach to CPGs related to biomarker tests for molecularly targeted therapies, is presented in Chapter 5 of this report.

Payer Use of Clinical Pathways

In addition to clinical guidelines, payers have increasingly turned to the use of clinical pathways to guide care decisions. Such clinical or treatment pathways are developed by health insurers or provider organizations and tend to present fewer options than guidelines. Pathways reflect the evidence base as well as the total cost of care (IOM, 2013b). Given significant variation in clinical practice and differences in treatment costs, payers view clinical pathways as a way to control costs, with the potential to also improve quality (DeMartino and Larsen, 2012; IOM, 2013b,c, 2015).

Private health insurance plans provide financial incentives to health care providers for adherence to prescribed pathways, generally in the form of a per member/per month case management fee. Studies have shown that pathways can limit variation in treatment use, in the case of chemotherapy, for example, contributing to lower overall costs with no significant difference in overall survival rates (Patel et al., 2015). One of the largest U.S. health insurers, Anthem, manages a clinical pathways program for treatment of cancer that it developed through a process that includes review of national guidelines (e.g., NCCN, ASCO) and peer-reviewed evidence from clinical trials, supplemented by input by an external group of experts. The process results in the development of treatment pathways specific to tumor type, biomarkers, and patient characteristics. These pathways are updated quarterly to reflect new information, changes to guidelines, and new FDA-approved indications. The pathway treatment information is made available to health care providers when

they enter biomarker test results into the patient's electronic health record (EHR). Though adherence to the pathways is not mandatory, health care providers receive an additional monthly reimbursement of $350 for each cancer patient treated through a recommended pathway. The insurer estimates a 3 to 4 percent annual reduction in the cost of treatment by using treatment pathways (PMC, 2015).

Patient advocates have raised concerns about payer use of clinical pathways and the linkage to financial incentives, pointing to significant differences in the evidence used and the processes by which payer organizations develop and update treatment pathways, and the limited transparency of pathway development. Patients and health care providers are concerned that such programs could have a negative impact on patient access to treatments designated as off pathway, and that such pathways may prevent health care providers from customizing care plans to individual patient needs (Avalere Health, 2015; Balch et al., 2015). The Personalized Medicine Coalition notes that clinical pathways and other decision support tools will be "challenged to keep pace" with changes in evidence and, importantly, what works for an individual patient (PMC, 2015).

Medicare's Coverage with Evidence Development

As noted earlier in the chapter, CMS requires that tests be "reasonable and necessary," which CMS links to improvement in health outcomes. Medicare's coverage with evidence development (CED) program is a policy tool through which CMS agrees conditionally to cover new medical technologies provided that sponsors/manufacturers collect additional data to support more informed coverage decisions (CMTP, 2010, 2013). CED offers conditional coverage—in essence a third option between denial and approval of coverage—for promising medical tests, technologies, etc., that would not otherwise meet Medicare's standards of evidence for "reasonable and necessary" treatment. CED represents an approach to balancing the competing priorities of—and inherent tensions between—access to emerging technologies and evidence-based medical policy to protect patients from harm.

CED first appeared on a formal basis in 2005 with CMS draft guidance describing its new CED approach, developed in the context of the use of CED for Medicare's coverage of implantable cardioverter defibrillators (Tunis and Pearson, 2006). CMS released revised guidance in 2006[18] clari-

[18] See https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/ced.pdf (accessed May 1, 2015).

fying the specifics of the new policy, and issued revised draft guidance as recently as 2014[19] to better define CED in an effort to expand its use.

Essentially, CED creates a direct link between coverage of certain new technologies and the development of evidence through collection and analysis of clinical data to assess more fully the potential risks and benefits to patients. CED provides temporary reimbursement as the evidence is further developed by requiring patients to participate in a registry or clinical trial[20] to qualify for coverage of the technology. This is particularly important for biomarker tests for molecularly targeted therapies, given the time and financial resources required to collect data on the impact of testing on patient management and clinical outcomes. Indeed, high research costs and extended timelines needed to conduct clinical trials are often viewed as major obstacles by manufacturers developing novel diagnostic tests (Schulman and Tunis, 2010). CED facilitates discussion and collaboration between payers and product developers about clinical trial design with the goal of efficiently developing data with which to assess clinical utility. Thus, CED offers a pathway to enable coverage for promising new technologies that are still considered experimental or investigational under CMS evidence requirements, and thus are excluded from traditional coverage (CMTP, 2010).

However, despite its potential public health benefits, many private payers are reluctant to embrace CED. Though CED has been used in a number of different areas, including Positron emission tomography imaging and treatment of localized prostate cancer, it has faced numerous challenges ranging from legal and limited funding to lack of sufficient data and problems with reaching consensus on clinical study designs (Tunis et al., 2011). As a result, CED has had limited application, with CMS implementing CED policies fewer than two dozen times to date, though the majority of recent NCDs issued by CMS have applied the CED approach. CMS has only twice used evidence generated through the CED process to revise an NCD (*Health Affairs*, 2015). Some observers argue that additional support for CED studies from research funding organizations such as the Patient-Centered Outcomes Research Institute (PCORI) and the National Institutes of Health (NIH), as well as collaboration with other federal agencies such as the FDA, is necessary in order for CED to transition successfully from a "one-off" tool to a more broadly and systematically

[19] See https://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=27 (accessed May 19, 2015).

[20] The statutory basis for requiring these studies is not under CMS's authority, but that of AHRQ. AHRQ is authorized under the Social Security Act to conduct and support research on outcomes, effectiveness, and appropriateness of services for Medicare beneficiaries (*Health Affairs*, 2015).

used approach to developing evidence for novel technologies (Daniel et al., 2013).

CMTP has done extensive work in the area of CED, conducting research and analysis, and convening several multistakeholder working meetings on the topic, through which they have identified a number of improvements that could enhance the ability of CED to achieve its stated objectives. Given an intensified focus on constraining health care spending, the use of CED could help to meet the greater demand for evidence of comparative effectiveness of promising new technologies. CMTP cautions, however, that despite the potential role for CED application by private health plans, CED studies will often need to be coordinated across multiple health plans, requiring an independent party to align the approach across plans, as well as stakeholder groups to focus on study design and implementation (CMTP, 2010).

A recent IOM report suggests that the CED policy lever could be applied to create incentives for device industries to participate in evidence generation comparable to the pharmaceutical industry's research efforts related to new drug development (IOM, 2013b). Others have suggested CED be used to pay for innovative therapies such as proton beam treatment for patients with prostate and other cancers, providing they are enrolled in a randomized trial to compare outcomes to other treatment approaches (Emanuel and Pearson, 2012).

CED holds the promise of an effective approach to providing coverage while simultaneously strengthening the evidence base for emerging technologies such as biomarker tests for molecularly targeted therapies. The application of CED to date, however, has yet to realize its full potential. CED studies have been found to have significant design flaws, including lack of rigorous data collection, which can fail to produce evidence that is of sufficient quality to inform sound coverage policy (Tunis et al., 2011). Other implementation challenges include significant staff reductions within CMS's Coverage and Analysis Group that is responsible for CED implementation (Jacques, 2014) and lack of funding for CED studies (*Health Affairs*, 2015). While some private insurers, such as Priority Health of Michigan, are developing policies similar to CED to cover biomarker test–directed, off-label use of targeted therapies in the context of clinical trials (IOM, 2015), many private insurers are unwilling to pay for what they perceive to be research activities that should be covered by the test manufacturers (Newcomer, 2015). CED does offer payers an effective approach to cost savings; however, if the evidence that is being collected indicates that a specific test is not useful, payers may then have a strong basis to no longer pay for that test.

Palmetto GBA, a MAC, implemented a pilot program in 2011 called MolDX to identify molecular diagnostic tests and determine coverage and

reimbursement. The program currently covers laboratory tests in states that fall within Palmetto GBA's geographic jurisdiction, and manufacturers and laboratories seeking coverage for their tests must provide Palmetto evidence of their test's analytic and clinical validity, as well as clinical utility.[21] Although several other MACs have followed MolDX's decisions, CMS has not determined how or whether MolDX will be expanded on a national basis (Hughes, 2014). Such programs may be viewed as vehicles to facilitate discussion between payers and test developers about trial design, with the goal of ongoing data collection to support the development of evidence of clinical utility (Radensky, 2015). As with any study approach, CED has its advantages as well as its limitations. Data obtained are more broadly representative of patient populations compared to clinical trials, though the observational nature of CED studies may serve as a potential limit to the generalizability of study conclusions.

Challenges Related to Next-Generation Sequencing

Though single-analyte tests currently are the most commonly used biomarker tests for molecularly targeted therapies, test technology is rapidly advancing with the introduction of next-generation sequencing. NGS includes a number of advanced sequencing technologies that are distinct from Sanger sequencing, which has been in use for 40 years. In contrast to what is viewed as conventional molecular diagnostics tests, which typically involve single-test/single-result assays and return a single biomarker result (Trosman et al., 2015), NGS platforms "perform massively parallel sequencing during which millions of fragments of DNA from a single sample are sequenced simultaneously" (Schott et al., 2015, p. 1930). NGS offers the benefit of performing DNA sequencing more extensively, quickly, and less expensively than Sanger sequencing, and uses a smaller amount of DNA compared to multiple separate molecular diagnostic tests. Though NGS technologies typically seek to identify DNA-based variations, they may also be used to probe for other omics variations[22] (Schott et al., 2015), which are likely to be integrated on an increasing basis with genomic data to refine precision medicine.

Laboratory use of NGS technologies (and related billing claims) may raise additional coverage and reimbursement challenges. Although NGS offers a relatively low incremental cost of assessing many molecular bio-

[21] See http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~General~8R5QUL0858?open&navmenu=Browse^By^Topic (accessed August 1, 2015).

[22] Such omics variations may include those in the proteome (protein), transcriptome (RNA), metabolome (metabolites), and the microbiome (organisms living within and on humans).

markers, payers typically evaluate and reimburse tests on a per-analyte basis and reimburse only the medically necessary components of gene panels. For this reason, a laboratory seeking reimbursement on a per-panel level may see those claims denied or pared back. In this context, some payers consider NGS technology to be investigational, while others are in the process of developing specific NGS coverage policies. According to a survey of large private health plans about next-generation tumor sequencing (NGTS), 80 percent of health plan representatives indicated that such tests do not meet their criteria for medical necessity. Seventy percent said they view gene panels as bundles of individual gene tests, and each gene marker needs to be evaluated separately (Trosman et al., 2015).

NGTS can be viewed as disruptive to the current coverage and reimbursement framework in that it supports an integrated approach to patient care, one that includes both standard and experimental elements. Though offering a potential broader choice of therapy options (which are often not grounded in a high level of evidence), NGTS runs against the grain of current approaches to reimbursement—most notably the separation of standard of care from experimental activities for reimbursement purposes. Large cancer centers such as MD Anderson Cancer Center have developed a sophisticated process to report NGS results to distinguish standard of care from investigational use for reimbursement purposes (Mendelsohn, 2013; Meric-Bernstam et al., 2013; Trosman et al., 2015).

CMTP recently released initial guidelines for coverage of NGS testing in oncology that were developed by the Center's Green Park Collaborative, a multistakeholder, public–private group. The guidelines represent a framework for coverage of targeted NGS gene panels that recognizes the unique evidentiary challenges of demonstrating clinical utility for a panel of tests rather than evaluating a specific diagnostic test for a well-defined clinical use. The initial draft coverage guidelines include two specific recommendations for payers: the first is that payers cover NGS panels with 5 to 50 genes when those panels include a subset of genes considered to be medically necessary,[23] and the second recommendation is for payers to rely on the College of American Pathologists' accreditation program and proficiency testing to assure the analytic validity of NGS tests (CMTP, 2015).

The National Institute of Standards and Technology recently developed and made available reference material to facilitate the validation of clinical NGS tests by laboratories, which may support coverage decisions. This new DNA reference material will enable clinical laboratories to

[23] The guidelines recommend payment for these panels at a rate not to exceed the cost of individual sequencing of the medically necessary genes by other methods.

determine whether they are providing accurate genomic analyses, which may in turn increase the confidence of health insurers in the accuracy and quality of such test results, thereby increasing the likelihood that payers will approve payment for NGS tests (Pear, 2015).

Lack of Alignment of Regulatory and Reimbursement Decision Processes

In addition to multiple regulatory pathways, the policy environment for biomarker tests for molecularly targeted therapies is further complicated by the existence of separate processes for regulatory and reimbursement decisions. FDA and CMS both play critical roles in the adoption of biomarker tests into clinical practice. Each agency has its distinct statutory mandate that in turn defines its evidentiary standards to guide approval decisions: FDA evaluates drugs and devices based on evidence that the product is safe and effective; CMS coverage determinations are based on whether the product is reasonable and necessary for Medicare beneficiaries (*Health Affairs*, 2015). In broad terms, FDA oversight is intended to ensure that the benefits of marketed products are greater than the risks under carefully defined circumstances. CMS looks for evidence that medical interventions are likely to improve outcomes for patients when available for broad clinical use.

The Medicare program is the largest single payer for laboratory tests in the United States, and therefore influences Medicaid and private payer coverage and reimbursement decisions (OIG, 2013). Medicare is required by law to pay only for items and services that are "reasonable and necessary" for its beneficiaries, which is interpreted generally as improving clinically meaningful health outcomes, although determining the precise definition of these terms has "proven to be an enduring challenge" (Neumann and Chambers, 2012, p. 1775). For example, in 1989, Medicare released a proposed regulation that defined reasonable and necessary as "safe, effective, non-investigational, appropriate, and cost-effective." The proposal was withdrawn after criticism from external stakeholders—including some medical professional societies and the medical device industry—who argued that such a definition would result in patients being denied necessary care. In addition, the use of "least costly alternative" in CMS reimbursement policy was successfully challenged in the courts in 2008. Efforts to clarify the terms continue, with some calling for a legislative remedy to provide definitional clarity (Neumann and Chambers, 2012).

The evidentiary requirements for regulatory decisions by FDA are viewed as less stringent than the evidence requirements for reimbursement decisions (Deverka and Dreyfus, 2014). As Walcoff and Pfeifer note

(2012, p. 305), "some stakeholders have suggested that FDA clearance or approval be the litmus test for meeting the reimbursement standard of reasonable and necessary" (Walcoff and Pfeifer, 2012, p. 305). Indeed, the findings of a 2013 study suggest that compared to FDA, CMS took a more restrictive approach to coverage of medical devices than of drugs, representing a significant challenge for device manufacturers (*Health Affairs*, 2015).

Given the different agencies' requirements, two separate evidentiary standards exist, requiring product developers to generate two separate sets of data. Clinical trials designed to generate the necessary evidence for FDA that a product is safe and effective tend to be conducted, for example, with tightly controlled patient populations. CMS, for its part is interested in knowing how the product performs in "real-world" Medicare patients who tend to be more diverse and have more comorbidities than the typical clinical trial patient. Given the two agencies' different statutory mandates and respective evidentiary requirements, FDA may approve or clear a product that does not meet Medicare's reasonable and necessary requirements. On the other hand, Medicare may approve a product for payment that FDA has not approved or cleared as safe and effective (as in off-label use of a product already on the market) (*Health Affairs*, 2015). These two separate review processes can lead to delays in getting a test on the market or limit the success of market entry—both of which potentially can have a negative impact on patients' access to new tests. Coordination of evidentiary standards would facilitate a streamlined decision process for biomarker tests and their associated targeted therapies.

Communication About Biomarker Test Performance Characteristics and Use

The availability of two paths to market for test developers discussed above creates challenges for health care providers who are faced with the difficulty of selecting the appropriate biomarker test and most effective treatment for their patients (IOM, 2010). Simply put, "it is clear that the performance of many new tests has not been well established or well documented" (Parkinson et al., 2014, p. 1430).

The increasing number of complex biomarker tests for molecularly targeted therapies being implemented in clinical practice has raised concerns about insufficient access to information about test performance and intended use. Health care providers need accurate information to support effective clinical decision making. In particular, they need such information to avoid use of biomarker tests with poor clinical validity or insufficient evidence of clinical utility that could result in harm to the patient—either through under- or overtreatment (Yu et al., 2015). Indeed,

given the complex nature of biomarker tests for molecularly targeted therapies, the continuous evolution of biomarker knowledge and emergence of new tests, and the impact of evolving evidence about new uses of existing tests, health care providers and patients as well as payers need information on test performance and intended use that is more transparent than currently available.

CREATING A SUPPORTIVE POLICY ENVIRONMENT FOR BIOMARKER TESTS FOR MOLECULARLY TARGETED THERAPIES

The committee identified a number of key regulatory and reimbursement challenges related to biomarker tests for molecularly targeted therapies, including the absence of common standards of evidence of clinical utility; the lack of alignment between the regulatory and reimbursement approval processes; the information gaps and communication challenges on the part of health care providers and patients; and the need for ongoing assessment of the clinical utility of biomarker tests. The committee subsequently developed a recommended set of associated policy measures. These recommendations represent important steps in the development of a supportive policy environment as one component of a rapid learning system for biomarker tests for molecularly targeted therapies. Progress toward achieving the promise of precision medicine is likely to be significantly enhanced by timely implementation of these recommendations.

Establishing Common Standards of Evidence

Clear, consistent, and reasonable standards of evidence for biomarker tests for molecularly targeted therapies are required in order for these promising technologies to realize their potential to improve patient outcomes (Faulkner, 2009). To ensure patient access to effective technologies, renewed focus must be brought to bear on the existing lack of common standards of evidence to assess clinical utility:

> Given that demonstration of clinical utility is currently often a missing element in the evaluation of new laboratory tests, there is a critical need to raise the consciousness about its importance, to encourage the use of better planning and methodologies in addressing the search for utility, and to create guidance that will be of value to all stakeholders working to medical care more effective. (Parkinson et al., 2014, p. 1440)

Of critical importance is that the federal government needs to play a key leadership role in raising awareness of the urgency of this need by bringing together a broad group of public and private stakeholders to work in a collaborative manner to achieve the establishment of clear, consistent, and reasonable evidentiary standards. As noted by Ginsburg

and Kuderer: "No organization has owned the evaluation of genetic testing; it has been a distributed process with widespread heterogeneity among stakeholders" (Ginsburg and Kuderer, 2012, p. 4237). Given the complexity of issues involved in establishing evidentiary standards for the clinical utility for biomarker tests for molecularly targeted therapy, "the convening power of a central body . . . will be required to achieve meaningful consensus" among diverse stakeholders (Callahan and Darzi, 2015, p. 1566).

The federal government should champion the effort, clearly articulating the urgency and value of the work to be done. This leadership role would align with and support the federal government's launch of its Precision Medicine Initiative (Collins and Varmus, 2015). Thus, the committee recommends that **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, multistakeholder bodies (Recommendation 1).**

Furthermore, the process for developing evidentiary standards should recognize that the standards being developed will be used as the basis for different types of decisions, including clinical, regulatory, coverage, and reimbursement, as well as guideline recommendations, and will evolve over time as more evidence accumulates through further research and clinical use of biomarker tests for molecularly targeted therapies. The development of a common evidentiary framework should focus on "sufficient" evidence for rational decision making instead of "ideal" or "best" evidence approaches, yet at the same time such standards must be strong enough to address payers' decision-making requirements and to ensure that patients are not harmed by the introduction into clinical use of new tests that lack adequate evidence (Faulkner, 2009). As a result, HHS should ensure the development of **consistent and coordinated evidentiary standards and study design approaches, including rapid learning systems, 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.**

The stakeholder community involved in biomarker tests for molecularly targeted therapies is a diverse group encompassing patients, health care providers, academia, industry, government agencies, and payers, each with their own perspective on what qualifies as "adequate" evidence for clinical utility. As Ginsburg and Kuderer further note: "more dialogue and coordination among stakeholders is needed to facilitate the develop-

ment of the necessary evidence base. It is equally apparent that test development and reimbursement need to focus on the clinical utility of the test and the net benefit to patients" (Ginsburg and Kuderer, 2012, p. 4237). Establishing common evidentiary standards would help ensure that all stakeholders—patients, health care providers, payers, test developers, and policy makers—are all "working from the same playbook" and have a clear understanding of expectations for evidence development (Faulkner, 2009). This type of multistakeholder dialogue to develop evidentiary standards for coverage and reimbursement can be viewed as "reimbursement science," which focuses on the development of new tools, standards, and approaches for comparative effectiveness research and the assessment of the value of products covered by public and private health plans. Thus it is similar to "regulatory science," which develops evidentiary standards to guide clinical research intended to inform regulatory decision making (IOM, 2015).

To serve as an effective forum for discussion and collaboration, the process for developing evidentiary standards must include the diverse range of stakeholder perspectives and policy priorities, as is also the case for regulatory science discussions. In encompassing a broad array of participants, such a process provides a framework for public engagement; "transparency and accountability can be expressed in a dialogue between those who determine policy and those who are affected by it" (Callahan and Darzi, 2015, p. 1567). Collaborative, multistakeholder approaches are critical to the integration of complex biomarker tests for molecularly targeted therapies into clinical practice. The broadest possible coalition of public and private perspectives—government, policy makers, payers, test developers, health care providers, and patients—will ensure balanced, pragmatic, and viable approaches to the development of a common evidentiary framework (Faulkner, 2009; Hoffman et al., 2010). The committee recognizes that **the 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 CMS), FDA, test developers, pharmaceutical companies, molecular pathologists, clinical laboratory geneticists, informaticians, and research funders (e.g., PCORI, NIH, AHRQ).**

The committee acknowledges the considerable challenges involved in bringing together diverse perspectives to establish common standards of clinical utility across all stakeholders, but believes it is imperative that this initiative be undertaken to enable biomarker tests for molecularly targeted therapies to achieve the promise of precision medicine. This is

consistent with the long-term approach required to establish clinical utility: the need to plan from the early stages of development and anticipate the different types of data that will be necessary to build on evidence of analytic validity and clinical validity (Deverka et al., 2014; Parkinson et al., 2014), as well as ensuring that new evidence thresholds are sensitive to the value of ongoing research (Veenstra et al., 2013). **The committee recommends that analytic and clinical validity of biomarker tests should be assured prior to assessing clinical utility.**

In addition, the committee recognizes that evidentiary standards for clinical utility may vary across different diseases. For example, although most biomarker tests are currently used to guide treatment for cancer, the rapid rate of advances in understanding the molecular basis of disease likely will lead to their increased use to direct therapies for a range of diseases, potentially requiring distinct evidentiary standards. Therefore, **HHS could determine that more than one advisory body may be necessary to develop disease-specific evidentiary standards of clinical utility for biomarker tests for molecularly targeted therapies.**

The evidentiary standards for clinical utility developed in collaboration with multiple stakeholders will be used to **guide the creation of new labels for biomarker tests and corresponding therapies (see Recommendation 3).** Such standards will also be useful in the context of the **collaborative development of clinical guidelines (see Recommendation 10).**

The committee stressed in its deliberations the progressive nature of establishing evidentiary standards of clinical utility. The committee strongly views this as an ongoing, iterative process with standards evolving over time as evidence strengthens, methods and data infrastructure are improved, and the field of precision medicine itself evolves. This may initially appear counterintuitive as standards are often considered to be fixed in time, and to have some degree of stability over time in order to be useful. In light of the evolving nature of the process of establishing evidentiary standards, the committee recommends that **HHS continue to support the ongoing refinement of common evidentiary standards as they evolve.** Establishment of standards will require ongoing and sustained discussion across all stakeholders as new scientific discoveries and technological advances influence the development of new biomarker tests as well as new uses for existing tests.

Many effective multistakeholder partnerships exist in the genomics domain that may serve as models for, or provide input to, the process for developing evidentiary standards for biomarker tests for molecularly targeted therapies. The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) exemplifies a multistakeholder effort to facilitate consensus, and has as its focus the devel-

opment of standards for newborn screening for genetic disorders.[24] Consistent with this IOM Biomarkers consensus committee's recommendation, the SACHDNC brings together multiple stakeholders with different perspectives, including state health officials, laboratory medicine experts, researchers, academics, private foundations, and representatives from federal agencies including CDC, the Health Resources and Services Administration, NIH, AHRQ, and FDA to discuss which disorders should be included in the Recommended Uniform Screening Panel (RUSP).

The SACHDNC meets approximately three times per year to discuss and vote on whether additional disorders should be added to the panel. Once a new disorder has been nominated to be added to the RUSP, the committee reviews the nomination to see if there is sufficient evidence to support further investigation. If there is, they send the nomination to an external evidence review board. If the nomination moves on, then work groups conduct a full review of the research on the disorder in question. If they find sufficient evidence to recommend screening, they propose that the Secretary of HHS include the specific disorder in the panel (Kemper et al., 2014).

The SACHDNC developed an evidence-based approach to recommending whether a condition or disorder should be included in the RUSP, which could prove informative for this committee's recommendation. An external group of experts is consulted for each condition being considered, and provides the SACHDNC with an evidence-based assessment of the risks and benefits of screening for each condition. The SACHDNC reviews the expert report and assigns one of five ratings based on the evidence presented and the consensus of the committee. The SACHDNC collaborated to develop a RUSP that includes screening for 32 core disorders and 26 secondary disorders (HRSA, 2015; Kemper et al., 2014). This group's experience developing standards and evaluating tests on a case-by-case basis in the context of variability in state-level regulations serves as a relevant model for the committee's recommended process for developing standards.

Other examples of independent, multistakeholder collaborations exist, such as the partnership that was formed between Friends of Cancer Research and the Engelberg Center for Health Care Reform at the Brookings Institution. These two organizations joined forces to convene an annual conference on clinical cancer research, which brought "together a diverse group of experts in cancer drug development from academic and clinical research centers, federal health and regulatory agencies, patient advocacy organizations, and the private sector to develop practi-

[24] See http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders (accessed July 22, 2015).

cal, consensus-driven solutions to critical challenges in the development of drugs for cancer."[25] Importantly, many of the conference panels contributed to significant changes in cancer drug development, including the Advancing Breakthrough Therapies for Patients Act of 2012, which facilitated the expedited development of exceptional new drugs, and the development of the Lung-MAP trial, a biomarker-driven clinical trial that matches patients with investigational new treatments.[26]

Another multistakeholder collaborative group is CMTP's Green Park Collaborative (GPC), a multistakeholder forum that brings together patients, health care providers, payers, researchers, regulators, life sciences companies, and other stakeholders to develop recommendations to guide the generation of evidence needed to inform both clinical and reimbursement decisions (CMTP, 2013). GPC's most recent effort focuses on guidelines for clinical use of NGS in oncology (CMTP, 2015). GPC's multistakeholder process and proposed policy framework could serve as a model for the recommended process to develop standards of evidence required for biomarker tests for molecularly targeted therapies.

A final example is the Molecular Evidence Development Consortium (MED-C), a nonprofit public–private partnership of stakeholder representatives—including patients, payers, providers, regulators, industry, laboratories, and pharmaceuticals—collaborating to establish policy on the validation of genomic tests by creating a standardized outcome registry. The overarching goal of MED-C is to apply a systematic approach to large-scale data collection to advance evidence of clinical utility for molecular diagnostic tests and treatment (Dickson, 2015). The initial pilot program, a registry for NGS in patients with non-small cell lung cancer, has recently been funded. As this program expands, it is hoped that the registry can serve to drive accrual on clinical trials and other precision medicine-related research efforts (MED-C, 2015).

These are only a few examples of the multistakeholder approach recommended by the committee. These and other working partnerships may serve as a guide for HHS as it addresses the long-standing and increasingly urgent need for a common evidentiary framework for current and emerging biomarker tests for molecularly targeted therapies—to facilitate patient access to appropriate tests, and to protect them from potential harm as well.

[25] See http://www.focr.org/conference-clinical-cancer-research (accessed October 11, 2015).

[26] See http://www.focr.org/about-us (accessed October 11, 2015).

Creating an Integrated Review Process for Regulatory and Reimbursement Decisions

Another significant challenge to the appropriate and effective clinical adoption of biomarker tests for molecularly targeted therapies is the lack of alignment between the regulatory and reimbursement decision processes. This misalignment creates significant inefficiencies, and "if the practice of clinical medicine is to benefit from the biological and technical advances resulting from the new 'omics' era, regulatory and reimbursement expectations need to be more aligned" (Parkinson et al., 2014, p. 1440). Thus, the committee recommends that **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 multianalyte tests performed using current or new technologies, and any corresponding molecularly targeted therapies[27] (Recommendation 2).**

In crafting its recommended FDA[28]–CMS integrated review process for biomarker tests for molecularly targeted therapies, the committee was cognizant of the different statutory authority of the two agencies, as discussed earlier in this chapter. The committee is not calling for statutory reconciliation of the two agencies, which would require congressional action and would go beyond the narrow context of the committee's charge: biomarker tests for molecularly targeted therapies. Rather, the committee is calling for the two agencies to work closely together, to coordinate their review approaches with the goal of creating a streamlined decision-making process for biomarker tests for molecularly targeted therapies that developers could voluntarily choose to undergo.

The committee's recommended integrated review process is a voluntary, multifaceted process encompassing regulatory, coverage, and reimbursement review, which applies to a limited subset of all clinical tests: biomarker tests for molecularly targeted therapies. This integrated review process is, by design, sufficiently flexible to accommodate a variety of scenarios, as depicted in Figure 3-3. For example, tests could be reviewed simultaneously with an associated targeted therapy: This could be the case when a sponsor is seeking initial approval for a novel drug, or seeking expansion of intended clinical use of an approved drug. Tests could also be submitted separately for integrated regulatory and reimbursement

[27] This coordinated pathway is designed to reflect the current predominant fee-for-service reimbursement system for clinical tests.

[28] Given that the committee's recommended review process could incorporate both test and drug review, both the drug (CDER) and device (CDRH) centers of FDA would be involved.

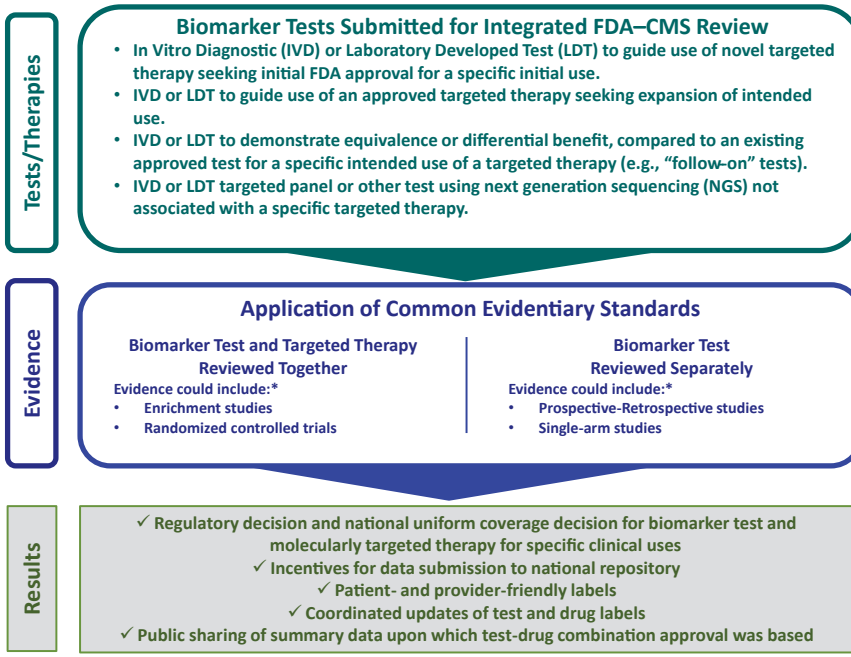

FIGURE 3-3 FDA–CMS Integrated Review Process.
NOTE: CMS = Centers for Medicare & Medicaid Services; FDA = Food and Drug Administration.
* See Table 3-1 for descriptions of various approaches to evidence generation.

review. For example, where regulatory approval of an intended use of a drug already exists based on an existing biomarker test, a test to demonstrate further or differential benefit may be submitted in order to secure regulatory and reimbursement approval. Multianalyte tests using technologies such as NGS not associated with a specific therapy, or linked to multiple therapies, could be submitted separately. Thus, the integrated review process recommended by the committee acknowledges the expanding use of newer testing technologies such as NGS that are typically not linked to a single treatment, and in so doing, offers a more comprehensive framework than FDA's current companion diagnostic model. The committee's recommended integrated review process does not replace that model—which as discussed earlier in this chapter is likely to evolve given the increased use of newer technologies such as NGS—rather it serves as a complementary review pathway.

Indeed, while a version of this integrated process exists in a somewhat related form in the companion diagnostic model, as noted earlier

in this chapter, drug–test co-development may facilitate, but does not guarantee, reimbursement. Of critical importance, developers of biomarker tests for molecularly targeted therapies—whether IVDs or LDTs, and including multianalyte tests using technologies such as NGS—that choose to undergo the committee's proposed integrated review process (and successfully reach the approval stage) would be guaranteed reimbursement by CMS through a national uniform coverage decision. In contrast, tests that do not go through this integrated review process will not have the benefit of guaranteed reimbursement and will need to seek reimbursement through traditional avenues. Application of common evidentiary standards of clinical utility will be required for coordinated regulatory, coverage and reimbursement decisions; these standards should be developed through the process as described in Recommendation 1 above.

The committee is not expecting FDA to become a payment organization, nor for CMS to become a regulatory authority. CMS will maintain its authority to set payment levels through its usual mechanisms, but it will work closely with FDA to conduct a coordinated review for coverage, reimbursement and regulatory decisions. Consistent, transparent evidentiary standards should span regulatory and reimbursement considerations and lay the groundwork for a more streamlined, efficient review process.

Once FDA and CMS have made their coordinated decision regarding regulatory and reimbursement approval for a test or test–drug combination, other payers are encouraged to make a similar decision regarding test reimbursement on a national basis. As noted earlier in this chapter, CMS covers a large patient population and private payers often follow the lead of CMS in terms of reimbursement decisions, and the committee hopes this continues to be the case in regard to its recommended integrated review process. For this to occur, it will be important for private payers to have confidence in the rigor of the integrated review process, including the standards of evidence that are being applied when making such decisions.

The process for developing evidentiary standards described in Recommendation 1 above will determine a minimum level of evidence of clinical utility to enable a biomarker test for molecularly targeted therapy to enter into clinical use, with the understanding that stronger evidence may be generated through the monitoring of the test's clinical use and patient outcomes, including potential changes to patient management, over time. Incentives to continue to refine tests, in the form of increased reimbursement as evidence of clinical utility is generated, may be an option if considered feasible and effective.

The committee's recommended integrated review process is designed

to address the lack of clarity and consistency of reimbursement decisions by payers, which are considered to be variable and opaque. The committee's recommended coordinated pathway would enable concurrent regulatory and reimbursement decisions for test–drug combinations, thus developing a more efficient, streamlined review process for both regulators and payers, and creating greater certainty for test and drug manufacturers and more rapid reimbursement decisions for health care providers and patients needing to make treatment decisions. Consistent with the committee's envisioned rapid learning system, the committee recommends that summary data—upon which approval decisions are made within the context of the integrated review process—will be made publicly available.

The integrated review process also includes requirements for standardized test labeling and data collection efforts. As discussed further below, a new type of test label will include standardized test information to enhance provider and patient communication and understanding of test performance and intended use. Moreover, labels for biomarker tests and their associated therapies will be updated in a coordinated fashion.

Finally, as an important initial step in the committee's vision of a rapid learning system for biomarker tests for molecularly targeted therapies, the integrated review process will include financial incentives designed to encourage health care providers and health systems to submit test data on patient use and outcomes to a national data repository, as discussed further below.

Thus, in summary, **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 (Recommendation 3).**
- **Drug review and approval with detailed labeling that includes standardized biomarker test information (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 (Recommendation 7).**
- **A defined process for coordinated updates of biomarker test and drug labels (Recommendation 3).**
- **Public sharing of the summary data upon which the review process based the approval and coverage decisions for a biomarker test and drug combination.**

An important note is that the committee crafted this recommendation to reflect the reality of the current dominance of the fee-for-service reimbursement approach in the U.S. health care system. If alternative payment arrangements and mechanisms such as accountable care organizations or global, bundled, and value-based payments make deeper inroads into the U.S. health care system, such an integrated regulatory and reimbursement review process would need to be reassessed, based on a clearer understanding of the impact of the new payment models.

The committee's call for FDA and CMS to work closely together in an effort to streamline the decision-making process for biomarker tests for molecularly targeted therapies builds upon existing precedent. Indeed, FDA and CMS are well positioned to work together to support timely review, coverage, and reimbursement of new advanced tests; a key example of interagency collaboration is the FDA–CMS parallel review pilot program.[29] Historically, FDA and CMS have worked independently, with separate staff focused on different points of a product's development lifecycle, and with different evidentiary expectations from FDA's focus on safe and effective, to CMS's focus on reasonable and necessary. In 2010, FDA and CMS introduced the concept of a parallel review process and officially launched a pilot program the following year (Gaffney, 2014).

The pilot parallel review program was developed in response to the fact that attaining FDA approval of a product based on safety and efficacy does not necessarily result in a timely determination by Medicare that the product is medically necessary and therefore should be covered (Pomager, 2014a,b). The stated goal of the program was to reduce the time between FDA approval and CMS national coverage determinations, which are important for products to be integrated broadly into clinical practice (Messner and Tunis, 2012).

The pilot parallel review program is only available for certain qualifying technologies[30] and offers three key advantages: (1) it targets products deemed innovative by developers, FDA, and CMS, with the capacity to improve patient care; (2) it provides product developers with a clearer sense of the evidence expectations of both regulators and payers; and (3) it promotes better evidence generation for clinical decision makers about novel technologies (Messner and Tunis, 2012). A notable success

[29] See http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm274833.htm (accessed September 11, 2015).

[30] The parallel review program is only available for qualifying new medical device technologies that must meet certain criteria. See http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHInnovation/ucm456149.htm#parallelreview (accessed September 9, 2015).

that emerged from the parallel review pilot program is Cologuard,[31] the first non-invasive colorectal DNA screening test, and the first product to receive simultaneous decisions from FDA (premarket approval) and CMS (national coverage decision) (Pomager, 2014a,b).

FDA's CDRH established the Payer Communication Task Force (PCTF) to manage the parallel review program with CMS and to examine potential ways to reduce the time between FDA approval or clearance and payer (public and private) coverage decisions. PCTF has incorporated key lessons learned from the parallel review program to identify ways for payers to interact with FDA and medical device manufacturers earlier in the development process: "The PCTF believes … that early engagement between device manufacturers, CDRH, and payers will allow for the design of clinical trials that may produce required outcomes for both regulatory approval or clearance and positive coverage determinations" (FDA, 2015b).

The pilot program was designed to run through the end of 2015, and it is unclear at this time whether it will be extended. Significant staff reductions within CMS's Coverage and Analysis Group that oversees the parallel review program have had a limiting impact on the implementation of the program (*Health Affairs*, 2015; Jacques, 2014). Increased CMS staff resources may be necessary to adequately support the coordination required to implement the committee's recommended integrated review process.

Another existing group that could help to inform the FDA–CMS integrated review process recommended by the committee is the FDA–CMS Task Force on LDT Quality Requirements. The interagency task force was established in the spring of 2015 to leverage the resources of the two agencies involved in the oversight of LDTs, with the goal of avoiding duplication of efforts and increasing efficiency through greater collaboration (Shuren and Conway, 2015). Such collaborative efforts between FDA and CMS are critically important and should be expanded.

The development of a pathway for coordinated regulatory and reimbursement decisions has the potential to create a more harmonized process for market entry for biomarker tests for molecularly targeted therapies. Such FDA–CMS integrated review with simultaneous regulatory and reimbursement decisions will serve to reduce delays inevitable with dual decision-making processes, and by clarifying requirements for coverage and reimbursement will enable test and drug manufacturers to plan accordingly, which in turn will help to increase the rate at which new

[31] See http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm409021.htm (accessed September 9, 2015).

technologies are made available to health care providers and their patients (Hwang et al., 2015).

In summary, the integrated review process recommended by the committee is a voluntary process that applies to a small subset of all clinical tests—biomarker tests for molecularly targeted therapies—represents a complementary pathway to the current companion diagnostic model, and builds on an existing precedent of cooperation between FDA and CMS. The committee recognizes that its recommended approach may entail implementation challenges, but the current lack of coordination between the two agencies is detrimental to patients and test and drug manufacturers. The coordinated review process would provide benefits to both patients and manufacturers: test and drug manufacturers could receive FDA approval and meet evidentiary standards for payment in parallel, providing patients with faster access to appropriate biomarker tests for molecularly targeted therapies. Broader health care system and societal benefits from such a coordinated review process also should be acknowledged as some biomarker tests in clinical use and covered by insurers have been found to be ineffective and/or harmful to patients (FDA, 2015c).

Enhancing Communication and Information About Tests

Given the proliferation and complexity of biomarker tests for molecularly targeted therapies, it is challenging for health care providers to understand fully the performance characteristics and evidence for specific intended uses of biomarker tests and molecularly targeted therapies. Detailed information should be contained in the biomarker test's label, which should state in clear language the test's use, the specific actions to be taken, the relevant clinical condition as well as information on analytic validity, clinical validity, and clinical utility, if available. Moreover, given the speed at which predictive tests are evolving, test information needs to be updated regularly and reflect new information as the tests are continuously evaluated for their impact on patient outcomes (IOM, 2010).

Transparent labeling of biomarker tests for molecularly targeted therapies designed to provide useful information will help physicians make effective decisions, enable patients to be engaged in the decision-making process, and help payers seeking information on which to base coverage and reimbursement decisions. **Thus, the committee recommends that 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. FDA or laboratory accrediting bodies should approve the label for each biomarker test, including tests not reviewed through**

the integrated process (specified above) (Recommendation 3). The committee recommends a two-step process. First, FDA develops a uniform, transparent labeling system, defining the specific contents of the biomarker test label. Second, although the committee recognizes the product label as the property of the drug or device manufacturer or developer, the contents of the label are to be approved by either FDA or laboratory accrediting bodies. This standardized labeling system will apply to all biomarker tests for molecularly targeted therapies—regardless of whether the tests undergo the integrated review process described above.

The committee recommends that **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.** The analytic validity of a biomarker test is assumed as part of the labeling process; however, the analytic sensitivity and specificity will be included on the label. The proposed star system is similar to the system used to rank variants that are reported to NIH's ClinVar database (Rehm et al., 2015).[32] A single star would signify limited or single-source validation of clinical validity or utility for a given intended use, while 3 or 4 stars would indicate widespread acceptance of clinical validity or clinical utility commensurate with an expert panel recommendation or clinical practice guideline. This would enable the labels to be flexible enough to accommodate emerging intended uses (while maintaining transparency as to their level of validation) as well as enabling analytically valid "follow-on" panels and other multianalyte tests, such as NGS tests of well-established single-analyte tests to label themselves with 3 or 4 stars, as appropriate. Such evidence ranking standards could be developed in conjunction with the standards for clinical utility.[33]

[32] ClinVar is a freely accessible, public archive of reports of the relationships among human variations and phenotypes, with supporting evidence. ClinVar facilitates access to and communication about the relationships asserted between human variation and observed health status, and the history of that interpretation. ClinVar collects reports of variants found in patient samples, assertions made regarding their clinical significance, information about the submitter, and other supporting data. The alleles described in submissions are mapped to reference sequences, and reported according to the Human Genome Variation Society standard. ClinVar then presents the data for interactive users as well as those wishing to use ClinVar in daily workflows and other local applications. See http://www.ncbi.nlm.nih.gov/clinvar (accessed June 6, 2016).

[33] Other ranking systems relevant to biomarker tests for molecularly targeted therapies exist, such as the Clinical Pharmacogenetics Implementation Consortium. See https://www.pharmgkb.org/page/cpic (accessed June 6, 2016) for guidelines for gene/drug pairs. The strength of these recommendations (strong, moderate, or optional) is based on a consideration of the quality of supporting evidence and any additional clinical implications,

The committee's labels provide opportunity for manufacturers to specify potential intended uses of their biomarker tests for those tests that have not undergone integrated review. For this reason, these claims of clinical validity, or clinical relevance, will need to be evaluated. Multiple methods of clinical validation exist; some interpret current CLIA regulations to require clinical validation of tests prior to their use (Ferreira-Gonzalez et al., 2014), the New York State Department of Health requires such information as part of their approval process for tests, and the IOM and other multistakeholder groups have discussed the need for tests to have a defined intended use population and associated outcomes (Deverka et al., 2015; IOM, 2012a). These sources stress the need to clinically validate a test using a number of specimens commensurate with the complexity of the test, and which are representative of the population to be treated in real-world clinical scenarios (e.g., not using primarily Caucasian specimens when the underlying disease overwhelmingly affects African Americans).

The committee recognizes that it will be important for the proposed labeling process to include not only the development of labels, but the periodic review and updates of labels for biomarker tests and any corresponding molecularly targeted therapies. The committee suggests that developers of biomarker tests and manufacturers of the drugs with which they are paired, CMS, other payers, and PCORI could potentially collaborate to fund rapid learning approaches to assessing the clinical utility of biomarker tests. Thus, the committee recommends that **labeling should be subject to expedited revision as further evidence develops, providing an incentive for developers to establish the clinical utility of their products.**

The proposed labels would provide information on test performance and clinical use that is intelligible and useful to each group of stakeholders, namely patients, health care providers, and directors of laboratories and institutions that administer such tests, the vendors of such tests, payers, and health technology assessors. Thus, the committee recommends that **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.**

The structure of such a label should be uniform for all biomarker tests for molecularly targeted therapies used in clinical practice, regardless of their status (i.e., whether evaluated and labeled by FDA or not). The label could include multiple "intended uses," each with different levels

including morbidity, potential for harm, and impact on current practice (Relling and Klein, 2011). This system is similar to those used in other guidelines, as discussed in Chapter 5.

of evidence. Linkage to these labels should be built into the patient-facing portals of EHRs, as well as laboratory websites and existing national test information sites such as NIH's Genetic Test Registry.[34] Moreover, training about the new labels should be included in educational efforts for providers (e.g., health care providers and genetic counselors) who will become resources to patients for using the information.

Two illustrative example labels are provided in Figures 3-4a and 3-4b. Figure 3-4a depicts a label for a test directing cancer therapy with a well-established evidentiary base, and Figure 3-4b depicts a label for a test directing multiple emerging therapies related to cystic fibrosis. In addition to briefly describing the purpose, accuracy, limitations, and methodology, the ranking system provided on the label would enable providers and patients easily to determine the relevance to their clinical condition and outcomes. The label also would specify whether or not the test was approved or cleared by FDA. The committee appreciates that the process for developing standards may necessitate modification to the rating system for clinical utility in the proposed labels, and offers the label examples below for illustrative purposes only.

The committee proposes that the test labeling process be initiated as a pilot program for biomarker tests for molecularly targeted therapies, given that such tests are the focus of the committee's statement of task. The impact of the pilot labeling program would be monitored and tracked in a formal evaluation process designed to determine the program's effectiveness and whether it has the potential to improve transparency of test information and could be expanded beyond biomarker tests for molecularly targeted therapies and implemented on a broader scale to apply to all biomarker tests. The stakeholders described in Recommendation 1 above could be instrumental in developing specific evaluation criteria, which would be tailored to the different target audiences, including health care providers, patients, and payers.

The evaluation should determine, for example, if the labels are achieving the stated goal of patient friendliness by testing patient comprehension of the label information with patient focus groups and surveys. Other stakeholder-specific assessments should be undertaken to determine whether the labels are improving provider, payer, and other stakeholders' understanding about the performance and use of biomarker

[34] The Genetic Testing Registry (GTR®) provides a central location for voluntary submission of genetic test information by providers. The scope includes the test's purpose, methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials. The overarching goal of the GTR is to advance the public health and research into the genetic basis of health and disease. See http://www.ncbi.nlm.nih.gov/gtr (accessed June 6, 2016).

TEST FACTS	
***BCR/ABL1* Fusion**	**Laboratory: Ajax Clinical Laboratory**
Test Purpose	Determine whether a patient's leukemia has a translocation between the *BCR* and *ABL1* genes.
FDA Approved or Cleared	☐ Yes ☑ No
Test Accuracy[a]	*[Test will not be marketed if not analytically valid. This placeholder is for analytic sensitivity and specificity (with confidence intervals)]*
Limitations	This test will not detect some types of translocations.
Method Used	FISH (fluorescence in situ hybridization) using probes ABC and XYZ.
Sample Type	Peripheral blood; bone marrow aspirate.
Intended Use	Predicts response of chronic myelogenous leukemia to treatment with imatinib
Clinical Relevance[b] ****[c]	**Does this improve health outcomes?**[d] ***[c]
Intended Use	Predicts response of acute lymphoblastic leukemia to treatment with imatinib.
Clinical Relevance[b] ****[c]	**Does this improve health outcomes?**[d] ***[c]

FIGURE 3-4a Mock label for a biomarker test directing molecularly targeted therapy for leukemia.

[a] Analytic Validity, or the accuracy of a test to detect the specific entity that it was designed to detect.

[b] Clinical Validity, or the accuracy of a test for disease diagnosis or predicting response to specific drug therapy.

[c] Ratings indicate:

*: Single source criteria provided;

**: Multisource consistency;

***: Expert panel consensus;

****: Practice guideline.

[d] Clinical Utility, or evidence of improved measurable clinical outcomes, usefulness, or added value.

tests for molecularly targeted therapies. The evaluation should identify specific areas where adjustments may be needed.

Update and Strengthen Laboratory Oversight and Accreditation

The fourth recommendation proposed by the committee to create a supportive policy environment for biomarker tests for molecularly targeted therapies is intended to enhance laboratory accreditation standards

TEST FACTS	
CFTR G551D Mutation	**Laboratory: Ajax Clinical Laboratory**
Test Purpose	Detect a germline variant p.G551D in the CFTR gene associated with cystic fibrosis (CF) disease or carrier status.
FDA Approved or Cleared	☐ Yes ☑ No
Test Accuracy[a]	**Analytic sensitivity**[b]**:** 99% **(**95% CI 90%-100% when compared against referent method). **Analytic specificity**[b]**:** 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[c] ****[d]	**Does this improve health outcomes?**[e] ********[d]
Intended Use	Predict response of CF patients to treatment with lumacaftor.
Clinical Relevance[c] ****[d]	**Does this improve health outcomes?**[e] ********[d]

FIGURE 3-4b Mock label for a biomarker test directing molecularly targeted therapy for cystic fibrosis.

[a] Analytic Validity, or the accuracy of a test to detect the specific entity that it was designed to detect.

[b] Analytic sensitivity refers to the ability for a test to discern a specific low concentration from background noise; analytic specificity refers to how well a test only detects the entity of interest instead of other, similar entities.

[c] Clinical Validity, or the accuracy of a test for disease diagnosis or predicting response to specific drug therapy.

[d] Ratings indicate:

****: Single source criteria provided;

****: Multisource consistency;

****: Expert panel consensus;

****: Practice guideline.

[e] Clinical Utility, or evidence of improved measurable clinical outcomes, usefulness, or added value.

to a level appropriate for complex biomarker tests, such as NGS tests. As noted earlier in this chapter, given the current environment of highly complex biomarker tests, CLIA is not perceived to be up to date. Other organizations have developed laboratory accreditation standards that exceed CLIA standards and have developed voluntary laboratory quality control accreditation programs and provide further quality assurance to address CLIA's limitations.

The specific standards of these accrediting programs may deviate from the CLIA requirements as long as they meet or exceed CLIA standards, as determined by CMS; as noted earlier in the chapter, such accrediting organizations are granted "deemed status" to review laboratories in lieu of CLIA inspection.[35] The College of American Pathologists (CAP), for instance, has instituted a comparatively stringent accreditation program, which has been granted authority by CMS to inspect laboratories in lieu of a CMS inspection. CAP also requires documentation in its Molecular Pathology Inspection Checklist that is related to clinical validity (American Clinical Laboratory Association, 2009). CAP's authority also is recognized by The Joint Commission (a nonprofit U.S. health care accrediting organization) and certain state certification programs.

States traditionally have taken responsibility for regulating medical practice, and some states have developed independent laboratory certification programs that entail licensure, and in some cases, inspection. The New York State Department of Health (NYSDOH), for example, operates a state certification program that currently has been deemed by CMS to meet or exceed CLIA standards, rendering laboratories under its jurisdiction exempt from specific CLIA oversight.[36]

NYSDOH's Clinical Laboratory Evaluation Program (CLEP) entails regular inspection and PT, and additionally reviews all non-FDA-cleared or -approved tests for evidence of analytic and clinical validity (SACGHS, 2008). Through this rigorous test approval policy, CLEP has issued specific requirements for molecular genetic testing and guidelines for the NGS testing for germline genetic variants (NYSDOH, 2013, 2015b). Moreover, NYSDOH's Clinical Laboratory Reference System (of which CLEP is a part) oversees both clinical and forensic testing on all specimens originating in the state of New York. Therefore, even laboratories outside of New York that handle specimens originating in the state require New York licensure.[37]

Regardless of FDA's final guidance regarding regulation of certain

[35] See https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Accreditation.html (accessed May 15, 2015).

[36] 63 FR 26732 § 493.551.

[37] See http://www.wadsworth.org/docs/clrs.shtml (accessed November 4, 2015).

LDTs, the committee's view is that although CLIA functions as a minimal standard for the operation of a clinical laboratory, it is not up to date and is inadequate for the oversight of more complex biomarker tests to guide selection of molecularly targeted therapies. **Moreover, CLIA standards are inadequate for current NGS tests and other emerging technologies.** Thus, the committee recommends that **the Secretary of HHS should establish and enforce up-to-date laboratory accreditation standards for biomarker tests for molecularly targeted therapies, either through CMS's CLIA or in collaboration with an existing up-to-date accreditation organization. Reimbursement for such biomarker testing should be dependent on meeting these standards (Recommendation 4).** These standards should exceed current CLIA standards, similar to those of existing voluntary accreditation programs and other state-level regulatory bodies, as described above. **These standards should comply with test labeling requirements** as discussed earlier (see Recommendation 3).

Ongoing Assessment of the Clinical Utility of Biomarker Tests

The committee highlights the importance of viewing evidence generation for biomarker tests for molecularly targeted therapies as an ongoing process that takes place along a continuum (depicted in Figure 3-5), where

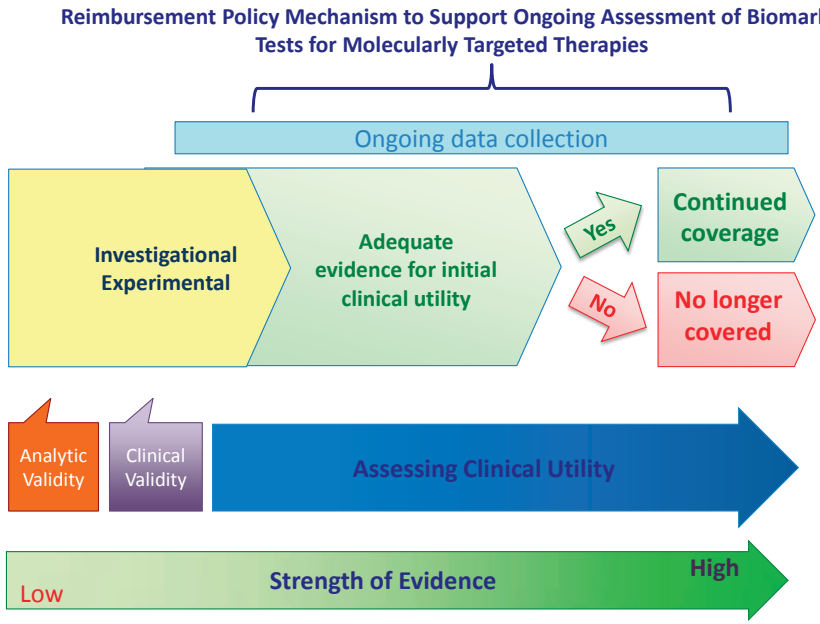

FIGURE 3-5 Evidence continuum.

evidence increases in amount and quality through additional studies and well-documented clinical use over time. The continuous accumulation of evidence enables a change in designation from investigational/experimental to adequate to make an initial determination regarding the clinical utility of the biomarker test for molecularly targeted therapy. This initial determination is subsequently supported and strengthened by additional clinical studies as well as ongoing data collection to provide greater certainty about the optimal use of the biomarker test for molecularly targeted therapy.

The process for developing evidentiary standards described above could be relied on to determine what level of evidence of clinical utility is sufficient for initial determination that a biomarker test is reasonably likely to benefit patients, and thus could be used effectively in clinical practice and be reimbursed by payers. In most cases, however, additional evidence will be needed to confirm the impact of the test based on longer-term clinical outcomes, to define the patient subgroups for whom testing is most useful, and to compare the outcomes achieved with use of the test to alternative approaches to patient management. Thus, it will be extremely valuable for payers to apply policy mechanisms designed to promote the ongoing assessment of evidence of the clinical utility of biomarker tests for molecularly targeted therapies.

An important note is that initial clinical use of biomarker tests should only proceed if basic assessments of test validity have been conducted, and there is sufficient evidence to demonstrate that these tests are reasonably likely to benefit patients. Ongoing collection and evaluation of data may be the most effective way to fully assess biomarker tests. In the words of one expert: "If you get stuck with either the highest level of evidence or nothing at all, genomics will never really come to light" (IOM, 2012b, p. 55).

Importantly for payers, assessment of postmarket data could support decisions for continued reimbursement of a biomarker test or alternatively, provide the rationale for discontinued reimbursement. In the former case, payers will have reassurances that coverage of the test is beneficial to patients. In the latter case, payers will benefit from cost savings associated with no longer paying for a test that has been determined to not be effective in directing targeted therapy. Thus, the committee recommends that **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 (Recommendation 5a).** It is critical that CMS takes the lead regarding these CED efforts, assuming primary responsibility for the data registries

and analysis associated with CED. Other payers should follow CMS's lead and support data collection efforts because the data will be used to refine clinical use and reimbursement policy decisions related to biomarker tests for molecularly targeted therapies.

The committee recommends that payers could develop several potential approaches to support such ongoing assessment of clinical utility. For example, payers could **pay for biomarker tests that meet predefined clinical and evidentiary criteria (Recommendation 1), with the requirement for ongoing postmarket data collection and assessment (through the national database as proposed in Recommendation 7,** discussed in Chapter 4).

Consistent with the committee's vision of a rapid learning system, and recognition of the evolving nature of a biomarker test's ability to direct therapy to different targets than originally intended, the committee recommends that payers support **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.** Also consistent with the committee's proposed rapid learning system, the committee further recommends that **payers consider innovative incentives to promote the submission of data to a national repository for biomarker tests and molecularly targeted therapies that have initial evidence of clinical utility** (discussed further in Chapter 4).

Coverage with Evidence Development

As noted at the outset of this chapter, the current fee-for-service reimbursement system does not provide incentives to improve quality, nor does it reward value. Alternative reimbursement methods are emerging that focus on improving quality, rewarding value, and containing health care costs. Such reimbursement models that focus on value are needed, particularly as precision medicine becomes more widely implemented, for as McClellan and Thoumi note: "As care becomes more personalized, fee-for-service reimbursements are likely to become increasingly misaligned with high-value treatment and service combinations for particular patients" (McClellan and Thoumi, 2015, p. 225). Some observers caution, however, that the shift from traditional fee-for-service to risk-based reimbursements may have an impact on care delivery, particularly for newer technologies such as biomarker tests for molecularly targeted therapies, in that the increasing emphasis on achieving quality and cost benchmarks may make health care professionals reluctant to use newer, not yet fully proven technologies (PMC, 2015).

The adoption of innovative reimbursement approaches such as

performance-based risk-sharing arrangements (PBRSAs) would be consistent with the committee's recommendations. Such approaches have the potential to support continuous collection of evidence to enable progressive approval while the strength of the evidence base becomes more robust (Carlson et al., 2010; Ramsey and Sullivan, 2014). The International Society for Pharmacoeconomics and Outcomes Research Task Force on PBRSAs has defined two general types of arrangements: (1) reimbursement is linked to product performance in the real world, and (2) limited access to a promising therapy is based on strategies to collect and evaluate additional evidence (Garrison et al., 2013). Under the latter of the two arrangements, known alternately as managed entry or coverage with evidence development, the payer provides coverage and reimbursement of a biomarker test for molecularly targeted therapies if the patients receiving the test agree to enroll in a clinical study to generate the additional evidence required for ongoing assessment of clinical utility. The ongoing collection of data is viewed as the best solution to resolve the uncertainty regarding the clinical utility of the test; critical evidence would not be made available without such an approach. A number of ongoing efforts to capture data for evidence development are discussed further in Chapter 4 of this report.

As discussed earlier in this chapter, CED is a policy tool that ties coverage of an emerging technology with a requirement that patients receiving the service are enrolled in clinical studies—either patient registries or clinical trials with the express purpose of systematically gathering data to inform future coverage decisions (*Health Affairs*, 2015; Neumann and Chambers, 2013; Tunis et al., 2011). In this way, CED is consistent with the rapid learning system envisioned by the committee, as research and clinical practice are interrelated and reinforce one another (Jacques, 2014; Lewis et al., 2015).

CED can be viewed as representing a win–win for all stakeholders: Patients would be able to access promising new biomarker tests before full evidence is available as to their clinical utility; payers share responsibility for generating evidence necessary to make informed coverage decisions; and manufacturers gain reimbursement for their products during the period when they are developing further evidence to support full coverage decisions by payers (CMTP, 2009; Lewis et al., 2015). Importantly, CED can facilitate the collection of clinical data of those patients underrepresented in traditional clinical trials (e.g., minorities or the elderly), and allow Medicare and other payers to develop more relevant, evidence-based coverage policies (MedPAC, 2010). CED is also beneficial for patients with rare diseases where a strong evidence base has not yet, and may never be, developed due to the lack of clinical trials when only a limited number of patients would be eligible (Lewis et al., 2015).

Policy makers continue to see value in CED as a policy tool as evidenced by the Medicare Payment Advisory Commission's (MedPAC's) recommendation to grant Medicare clear statutory authority to implement innovative strategies such as CED (MedPAC, 2010), and the Obama Administration's highlighting of CED as a viable approach to providing incentives for innovative technologies in its 2012 National Bioeconomy Blueprint[38] (Neumann and Chambers, 2013; OSTP, 2012). Moreover, an initial draft of the 21st Century Cures Act contained provisions to revise the statutory language relating to CED, though such provisions are not included in the final version of the bill (*Health Affairs*, 2015).[39]

Significant challenges limiting the effective implementation of CED include the requirement of CMS's "reasonable and necessary" authority to implement CED. CMS interprets reasonable and necessary under its standard statutory authority to mean there is adequate evidence to conclude that the item of service improves health outcomes, yet this is in opposition to the intended aim of CED to generate adequate evidence for promising new technologies and treatments, creating somewhat of a Catch-22 situation. Moreover, under current statute, CMS's implementation of CED depends on AHRQ's legal authority[40] to conduct research related to the outcomes, effectiveness, and appropriateness of health care services and procedures for the Medicare population (Tunis et al., 2011).

Experts note that the challenges facing CED are not design flaws; rather, the major limiting factor is the lack of a clear statutory basis to enable CMS to appropriately implement this critical policy tool (Jacques, 2014; Tunis et al., 2011). As noted by MedPAC, a solid statutory foundation could enable CED to overcome its current implementation challenges and realize its full potential as an effective approach to coverage of emerging technologies (MedPAC, 2010).

The committee recommends that **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.** Importantly, CED studies of biomarker tests should include coverage of treatment directed by those tests.

Finally, the committee recognizes the importance of rapid learning approaches to support the assessment of clinical utility for biomarker tests

[38] See https://www.whitehouse.gov/sites/default/files/microsites/ostp/national_bioeconomy_blueprint_april_2012.pdf (accessed September 1, 2015).

[39] See http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/114/Analysis/Cures/20150127-Cures-Discussion-Document.pdf (accessed May 4, 2015).

[40] Section 1862(a)(1)(E) of the Social Security Act references AHRQ's authority to conduct research for Medicare.

for molecularly targeted therapies and encourages funders to develop granting mechanisms to support such efforts. A number of existing programs within NIH examine issues related to clinical utility, and could potentially implement the committee's research recommendation. For example, the NCI's Implementation Science Program, under the Division of Cancer Control and Population Sciences, supports research grants examining the dissemination and implementation of evidence-based treatment in clinical practice settings (NCI, 2014). In addition, the Implementation Science Research Program under NIH's Fogarty International Center seeks to "understand the behavior of healthcare professionals and other stakeholders as a key variable in the sustainable uptake, adoption, and implementation of evidence-based interventions" (NIH, 2013). NCI's Community Oncology Research Program performs multidisciplinary cancer care delivery research on outcomes (including patient health, costs, quality of care, and access), as a result of financial, organizational, and behavioral factors related to adoption of new health care technology (NCI, 2015). The Biomarkers Consortium, a broad multistakeholder initiative managed under the Foundation for the National Institutes of Health, currently has a wide variety of active and upcoming research projects specifically related to evaluating the use of biomarkers in clinical practice (Biomarkers Consortium, 2015). The Consortium may therefore serve as an ideal organization to assist with research into clinical utility for biomarker tests for molecularly targeted therapies.

The independent PCORI was created to fund comparative effectiveness research (CER).[41] According to a 2014 analysis by the Center for American Progress, few PCORI studies focus on CER priority areas identified by the IOM, and PCORI has not funded any CER studies of medical devices (Tanden et al., 2014). Notably, research on "biomarker testing versus usual care in preventing and treating cancers and other conditions for which promising biomarkers exist" is among the top quartile[42] CER priority areas identified by the IOM (IOM, 2009, p. 4). The Center for American Progress called on PCORI to increase CER funding to at least 80 percent of its total research funding by fiscal year (FY) 2016, and

[41] PCORI's activities are financed through the PCOR Trust Fund, which includes funds from general appropriations, transfers from the CMS trust fund, and fees (approximately $2 for each covered individual) assessed on private insurance and self-insured health plans. PCORI's annual funding more than doubled from $320 million in FY 2013 to approximately $650 million for FY 2014. This level continues until the organization's funding expires in 2019 (PCORI, 2015).

[42] The IOM CER committee grouped the 100 individual CER topics into quartiles according to the number of votes each received during the committee's voting process. Topics within the first quartile were considered higher priority than those in the fourth quartile, but the order within quartiles does not signify rank (IOM, 2009).

to prioritize CER that focuses on the top quartile topics identified by the IOM (Tanden et al., 2014).

PCORI-funded CER studies of promising biomarkers for molecularly targeted therapies would be a natural complement to clinical efficacy research funded by NIH. Therefore, the committee recommends that **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 5b).**

SUMMARY AND RECOMMENDATIONS

The committee examined a number of key regulatory and reimbursement policy challenges influencing the adoption of biomarker tests for molecularly targeted therapies into clinical use, and crafted an interrelated set of recommended approaches to tackling those challenges. In so doing, the committee laid the foundation for one component of its vision of a rapid learning system for biomarker tests for molecularly targeted therapies: the development of a supportive policy environment.

The committee's interrelated policy recommendations are expressly designed to develop a rapid learning system to promote the development, assessment, and use of precision medicine's powerful tools—biomarker tests for molecularly targeted therapies. Such tests have the potential to improve health outcomes and lower overall health care costs by avoiding the use of therapies that are not effective and may in fact cause harm to the patient. A supportive regulatory and reimbursement policy environment—such as the one recommended here—is required for biomarker tests to realize their full potential.

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 the Department of Health and Human Services (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 the development of these evidentiary standards could be convening one or more independent, public–private, multistakeholder 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, informaticians, and research funders (e.g., the Patient-Centered Outcomes Research Institute, the National Institutes of Health, and the Agency for Healthcare Research and 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 the Department of Health and Human Services should facilitate the development of a new integrated federal review process involving the Food and Drug Administration and the Centers for Medicare & Medicaid Services, as a pathway for coordinated regulatory, coverage, and reimbursement decisions for biomarker tests for molecularly targeted therapies (including in vitro diagnostics, laboratory developed tests and multianalyte tests performed using current or new technologies,

and any corresponding molecularly targeted therapies).[43] 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 the 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: The Food and Drug Administration (FDA) should develop a patient- and provider-friendly standardized label for biomarker tests (including in vitro diagnostics and laboratory developed tests) to facilitate transparency of test performance characteristics and the level of evidence for the intended use(s) of the test. 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 would 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.**

[43] This coordinated pathway is designed to reflect the current predominant fee-for-service reimbursement system for clinical tests.

- **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 oversight and accreditation of laboratories providing biomarker tests for molecularly targeted therapies.

Recommendation 4: The Secretary of the Department of Health and Human Services should establish and enforce up-to-date laboratory accreditation standards for biomarker tests for molecularly targeted therapies, either through the Centers for Medicare & Medicaid Services' Clinical Laboratory Improvement Amendments (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 next-generation sequencing 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, the Centers for Medicare & Medicaid Services (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 further to 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 reimburse-**

ment 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: The Patient-Centered Outcomes Research Institute and the National Institutes of Health, 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.

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4

Supporting Data Infrastructure for Biomarker Tests for Molecularly Targeted Therapies

The rapid accumulation of disease-relevant molecular data following the complete sequencing of the human genome led the National Research Council (NRC) to explore the creation of a new taxonomy of human disease (NRC, 2011). The report outlined a framework based on broad access to patient data (through an "Information Commons"), to facilitate observational studies of emerging connections to evolving biological research (through a "Knowledge Network"). The hypotheses that would emerge about disease in various subpopulations could be validated in subsequent studies, ultimately establishing new taxonomies of disease that would lead to improved patient outcomes through more accurate diagnosis, clinical decision making, and treatment (NRC, 2011).

Although the NRC committee refrained from overspecifying the infrastructure necessary to create this new taxonomy, the collection, storage, and sharing of data were central to their vision. In a related report, *Best Care at Lower Cost*, the Institute of Medicine (IOM) recommended leveraging technology and policy mechanisms to address health care delivery's rapidly mounting complexity, while maximizing value (IOM, 2013a). The report stated that a focus on clinicians alone was insufficient, and that health care tools, resources, and systems were all needed to create a "coordinated system of care" (IOM, 2013a, p. 135).

As discussed in Chapter 2, numerous experts have described an unmet need for a robust data infrastructure and the associated challenges with implementing a rapid learning health care system (Chute and Kohane, 2013; Etheredge, 2014; French and Kampfrath, 2014; Friedman et al., 2015;

Ginsberg, 2014; IOM, 2013a; Miriovsky et al., 2012). This chapter explores the ways in which overcoming current obstacles in health information technology and data sharing will provide the necessary infrastructure to support a rapid learning system for the clinical use of biomarker tests for molecularly targeted therapies.

ELECTRONIC HEALTH RECORDS

The goals of documentation in electronic health records (EHRs) and laboratory information systems (LISs) are complex, and reflect functions apart from clinical care, including billing and quality improvement; ensuring usefulness for these various functions requires properly structured data fields (Hripcsak and Vawdrey, 2013). The Office of the National Coordinator for Health Information Technology (ONC) reported in 2014 that more than half of office-based health care professionals, and more than 80 percent of hospitals in the United States, meaningfully use EHRs (ONC, 2014). Meaningful use in this context is defined by a set of criteria established by the Centers for Medicare & Medicaid Services (CMS) and divided into progressive implementation stages (i.e., Stage 1 criteria should be satisfied before advancing to Stage 2), which encompass broad data-related objectives that range from recording patient health information in structured formats, to sharing summary records, to protecting electronic health information (CMS, 2015). The adoption of meaningful use-compliant EHRs has been motivated, in part, by incentive payments by CMS to those providers who meet these criteria.

However, the widespread adoption of EHRs reported by ONC belies a critical gap relevant to precision medicine: structured -omics data fields are not currently required under criteria for meaningful use (CMS, 2014). Currently, omics test results and subsequent treatment and outcomes data are stored primarily in report or open-text formats (e.g., physician notes), and this precludes full integration into EHRs (IOM, 2012; Miriovsky et al., 2012). This is despite the need for structured data[1] to support a rapid learning system that integrates genetics into the clinic (Manolio et al., 2013). This gap is at least partially explained by the increasingly data-intensive nature of omics-based testing, requiring storage capacities that are orders of magnitude larger (Pelak et al., 2010) than for other ancillary EHR functions (e.g., radiology), and also by the persistent difficulty in

[1] Structured data, further discussed below, are part of CMS Meaningful Use criteria and help to improve data quality and to support data sharing for clinical care and research. Structured data are sometimes defined as a set of Common Data Elements (CDEs) that can standardize the names, definitions, and possible values of clinical information (Fridsma, 2013; NIH, 2013).

applying these data to improve health outcomes, as outlined in Chapters 3 and 5 of this report. Determining the optimal method of integrating these data into EHRs will be challenging. Distinct clinical and research needs must be considered; efficient decision support, based on actionable biomarker test results, must be balanced against the need to preserve access to the complete molecular test results that will enable research and discovery (Masys et al., 2012).

EHRs as Clinical Support

The increasing number of omics tests and the growing complexity of test results require tools to support health care providers in the evaluation of these relevant clinical data (IOM, 2015a; Masys, 2002; Stead et al., 2011; Welch and Kawamoto, 2013). One potential approach, explored in Chapter 5 of this report, is collaboration between community physicians and larger health care centers to evaluate complex clinical cases. However, a complementary role exists for decision support related to well-established clinical uses of biomarker tests and targeted therapies. This section of the chapter explores the data infrastructure needed for the use of such systems to reinforce evidence-based precision medicine within a rapid learning system.

The Role of Information Technology and Structured Data

Information technology has radically changed the way health care is practiced and documented. Currently, health care practices generate, exchange, and store vast amounts of patient-specific information. Apart from traditional clinical narratives, data generated in modern health care centers related to laboratory test results, diagnoses, imaging, and treatments are automatically captured in structured databases (Jensen et al., 2012). The interdisciplinary fields of bioinformatics and biomedical informatics, which involve managing, analyzing, and interpreting information from biological structures and sequences, have enabled the continual consolidation of systems that bear large-scale biomedical data (Sethi and Theodos, 2009). Crosscutting bioinformatics tools and techniques have led to exponential growth in the analysis of DNA and protein sequence databases, which in turn leads to a better understanding of disease mechanisms through not only genetics and proteomics, but by associating them with clinical data (Sethi and Theodos, 2009). When existing structured health care data are linked with biobanks and genetic data, the assimilation of biomedical informatics in a centralized EHR format can facilitate the exploration of genotype-phenotype associations, ultimately informing the use of genomic test results to improve patient care.

The American Medical Informatics Association (AMIA) defines bioinformatics as "the development of storage, analytic, and interpretive methods to optimize the transformation of increasingly voluminous biomedical data into proactive, predictive, preventative, and participatory health" (AMIA, 2006). Indeed, the objective of bioinformatics is to design and implement novel methodologies and tools that monitor and predict future health through identifying genetic mutations and protein interactions. More relevant to the implementation of precision medicine is the broader AMIA term biomedical informatics, defined as "the interdisciplinary field that studies and pursues the effective uses of biomedical data, information, and knowledge for scientific inquiry, problem solving, and decision making, driven by efforts to improve human health" (Kulikowski et al., 2012, p. 931). Although progress has been achieved at the level of genomic data exploration, incorporation into health care records has yet to be fully realized (Sethi and Theodos, 2009). This is in part due to the nature of the data implementation. Health care providers using EHR systems have two primary methods for converting their observations into machine-computable and reusable data. The first method, qualitatively known as expressivity, includes unstructured data in which clinical narratives provide the medical reasoning behind various treatments and/or medications. This free-text form is convenient for recording impressions and concepts, but it is difficult for searching, summarization, decision support, and statistical analysis (Meystre et al., 2008). The second method consists of structured data entry that conforms to predefined or conventional syntactic organization and supports data reuse and comparison across multiple groups and timeframes.

The process of extracting structured patient data from clinical narratives "generally requires named entities or concepts in the text to be recognized and mapped to codes in a relevant controlled vocabulary, such as the Systematized Nomenclature of Medicine's Clinical Terms (SNOMED CT) or 1 of the 100-plus vocabularies in the Unified Medical Language System" (Jensen et al., 2012, p. 398). Typically this is carried out through natural language-processing tools, which combine a range of linguistic, statistical, and heuristic methods to analyze free text and extract structured data (Jensen et al., 2012). The use of genomic data in standard clinical practice has commonly consisted of tests such as those for sickle cell anemia, cystic fibrosis, or cancer genomics (Green et al., 2011). The representation of actual genetic sequence information, generally stored in the LIS or related bioinformatics tools, is not widely implemented in EHRs. However, with increasing efforts toward integration of genomic and clinical data, semantic interoperability will be necessary for mapping between both platforms (i.e., the EHR and the LIS) (Sethi and Theodos, 2009). The Observational Health Data Sciences and Informatics

Initiative is one example of a project developing a common data model for interoperability that intends to be particularly well suited to scalable, distributed databases (OHDSI, 2016). As genetic research continues to pave the way for personalized medicine, researchers will be able to apply tools and technologies to better understand disease mechanisms that progress from molecular, cellular, tissue, and organ levels to the personal, and, ultimately, population level (Frueh et al., 2008).

Data sources with repeated and structured measurements are an attractive resource for assessing the relationship between changes in biological markers and risks of a clinical event. Improving patient outcomes through the application of genomic data will depend upon data structures that can easily integrate into EHRs, as well as provide a linking mechanism for genotype-phenotype data (Sethi and Theodos, 2009). The combination of detailed EHR-based patient phenotyping and genetic data has resulted in the emergence of a novel reversal of the genome-wide association study (GWAS) approach to gene-disease association (Jensen et al., 2012). A phenome-wide association study (PheWAS) instead starts with the individual variant[2] and checks for statistical association against hundreds of disease phenotypes of patients that have been genotyped for that variant, and has demonstrated usefulness as a tool to explore associations between genetic biomarkers and disease (Denny et al., 2013). Pharmacogenomics is an additional field that has recently embraced the assimilation of EHR data and genetic data (Wilke et al., 2011). The patient profile that can be constructed from an EHR, consisting of clinical data over a period of time, allows drug exposure profiles to be correlated with treatment outcome measures, such as efficacy and toxicity. Linked biobank and genetic data, properly structured, can then find associations of such correlations within the underlying genotype (Jensen et al., 2012). Dynamical modeling approaches, iteratively corrected and refined by translational science over time, can be derived from such data to develop predictive paradigms of disease evolution and drug response across the lifespan (Iyengar et al., 2015). The intersection of novel methods in translational biomedical informatics has the potential to greatly enhance clinical decision support.

Clinical Decision Support Systems

Clinical decision support systems (CDSSs), alternatively called clinical decision support tools, are "any electronic system designed to aid directly in clinical decision making, in which characteristics of individual patients are used to generate patient-specific assessments or recommendations

[2] In this example, the variant is a single nucleotide polymorphism (SNP).

BOX 4-1
Pilot Projects Integrating Electronic Health Records (EHRs) and Genomic Data

DIGITizE[a]

The Displaying and Integrating Genetic Information Through the EHR (DIGITizE) Action Collaborative is an ad hoc activity within the National Academies of Sciences, Engineering, and Medicine's Roundtable on Translating Genomic-Based Research for Health. Established in 2014, the purpose of DIGITizE is to engage the various stakeholders involved in health care and health informatics to develop a scalable framework for genomic data integration and related decision support for adoption across existing EHR platforms. In undertaking this task, DIGITizE has used a three-pronged strategy: assembling the right organizations, often those who are in competition with each other (including vendors, laboratories, patients, government, etc.), focusing on areas of agreement on what can and should be done, and finally, initiating interinstitutional project coordination.

This coordination among interdependent entities has been critical to move data from laboratories into patient EHRs. Laboratories are not always located within the same organization, and often use different software, which requires EHR vendor support to be reconciled. Those vendors rely on standards bodies for direction, which in turn rely on labs and health care providers in a cyclical feedback loop that the Action Collaborative has successfully engaged to address this problem. Reliable incentives or funding are needed to sustain this cooperation as it scales up, particularly for standards-making bodies. Demonstrable success in this pilot project may ultimately lead to support from government or other funding agencies.

Pilot projects to test the framework have thus far focused on pharmacogenomic applications, including adding tests into clinical order sets and reporting test results to the EHR. Pre- and post-test alerts are also used to optimize test use with

that are then presented to clinicians for consideration" (Kawamoto et al., 2005, pp. 1-2). Biomarker test results that are structured to interact with decision-support algorithms, which in turn are based on an evolving synthesis of evidence, are critical for CDSSs (Pulley et al., 2012). Pilot projects to integrate and represent primarily pharmacogenomic biomarker data into EHRs for clinical use are underway. These examples illustrate the complex, interdisciplinary process of operationalizing CDSSs for guiding molecularly targeted therapy (see Box 4-1).

Varying approaches to implementation of CDSSs within EHRs exist, and can be combined as appropriate on an institutional or practice level. Passive CDSSs, for example, rely on clinicians to identify a knowledge gap, and seek educational resources embedded or linked within EHRs; active CDSSs can either be presented outside the clinical workflow (e.g.,

corresponding therapy; physicians can be prompted to order tests for drugs that require test results prior to use, and can also be prompted to align clinical decision making based on returned test results. The lessons learned from these cases will further the goal of facilitating effective flow of genomic information through a health care system.

eMERGE[b,c,d]

The Electronic Medical Records and Genomics (eMERGE) network is a multiphase consortium funded by the National Institutes of Health and was established in 2007. The consortium, currently composed of 10 institutions, originally used genome-wide association studies to examine the relationship between genetic variation and human health conditions of interest. In 2012, the project began systematically examining pharmacogenomic gene variants through collaboration with the Pharmacogenomics Research Network (PGRN) and the PGRN-seq sequencing panel.

Phase III of the project, begun in late 2015, will examine methods to incorporate clinically relevant genetic variants into EHRs and clinical care decisions and further explore the health outcomes associated with the use of knowledge generated during the earlier phases of the project. Areas of particular interest include characterizing additional pathogenic variants through sequencing samples stored in biobanks and linked to clinical records, as well as refining relevant clinical decision support systems and other EHR tools.

SOURCES (accessed May 12, 2016): [a] Aronson, 2015; [b] http://www.genome.gov/27540473; [c] Rasmussen-Torvik et al., 2014; [d] https://www.genomeweb.com/sequencing/new-phase-emerge-link-ngs-emr-study-clinical-outcomes-individuals-rare-variants.

monthly reporting with relevant education) or at defined points within the clinical workflow (e.g., computerized order entry for a targeted therapy that requires a biomarker test result) (Williams, 2015). Implementing active CDSSs requires close collaboration with experts who have domain expertise with the target patient population, as well as careful and continuous consideration of the evidence to support specific drug/genotype associations (Pulley et al., 2012). This collaboration, inclusive of pathologists, clinicians, and bioinformaticians, can also be used to streamline and standardize test ordering and result reporting, while collecting feedback data to ensure the system provides value (e.g., lower unnecessary testing or higher necessary testing) (Stead, 2015). Given the potentially increasing role of CDSSs in routine clinical practice, implications for Continuing Medical Education (CME) and Specialty Board Maintenance of Certifica-

tion (MOC) may arise (see Chapter 5 for further discussion of CME and MOC).

In addition to ensuring routine testing for well-established clinical uses, CDSSs within a rapid learning system for biomarker tests for molecularly targeted therapies would also facilitate the matching of patients to clinical trials, where appropriate. In oncology, for example, strong evidence linking certain biomarker test results with effective therapy is growing, but currently limited; where no treatment alternatives exist, CDSSs could be leveraged to match patients to clinical trials evaluating the effectiveness of targeted agents (Meric-Bernstam et al., 2015). This functionality could enroll patients from increasingly small subpopulations, often studied together due to shared molecular characteristics across many cancer types (IOM, 2015b) (see Box 4-2).

Research to examine improvements in health care processes and health outcomes as a result of using CDSSs has produced mixed results. A health care process is defined as "a health care-related activity per-

BOX 4-2
Examples of Clinical Trials of Biomarker Test–Driven Molecularly Targeted Therapy

ALCHEMIST[a]

The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST) is a set of trials testing the use of adjuvant chemotherapy in early stage lung adenocarcinoma and related lung cancers. Specimens removed during surgery will be screened for mutations in the *ALK* and *EGFR* genes, in order to direct treatment with drugs that are currently approved by the Food and Drug Administration only for advanced lung cancer. A separate study will follow those patients whose tumor lacks either mutation.

Lung-MAP[b,c]

The Lung Cancer Master Protocol (Lung-MAP) uses a genomic profiling platform to assign patients with late stage squamous cell lung cancer to one of five experimental drugs. Lung-MAP is designed to enroll patients faster than is typical for trials for molecularly targeted therapies due to the multiple treatment options, and will use a centralized Institutional Review Board to enable rapid modifications to the trial design, if necessary. Additionally, pre-specified safety and efficacy endpoints for a combination of biomarker test and targeted therapy will facilitate their FDA approval.

formed for, on behalf of, or by a patient" (AHRQ, 2015b). Evidence exists for improvements in process measures, provided the CDSS operates well within the existing workflow, is computer based and provided at the time of clinical decision making, is based on good evidence, is applied to demonstrated inappropriate variability, and provides recommendations rather than assessments (Kawamoto et al., 2005; Williams, 2015). Health outcomes are more difficult to measure than processes, and although initial data are consistent with the potential for improvement through the use of CDSSs (Bright et al., 2012; Jaspers et al., 2011), further research is necessary to ensure optimal support of clinical care within rapid learning systems.

The recent *Improving Diagnosis in Health Care* report from the National Academies of Sciences, Engineering, and Medicine emphasized that CDSSs, while promising, must be used strategically in order to assist clinicians during their existing workflows and environments, and most importantly to ensure the CDSSs themselves do not introduce novel sources

M-PACT[d]

The National Cancer Institute (NCI) Molecular Profiling Based Assignment of Cancer Therapy (M-PACT) trial is investigating whether receiving relevant targeted therapy improves response rates and progression-free survival of patients whose tumors exhibit certain mutations. Patients with mutations of interest (MOIs) in one of three pathways will be randomized to receive either treatment targeting that pathway, or treatment not associated with that pathway. Patients whose tumors lack any MOIs relevant to the study will not be enrolled.

NCI-MATCH[e,c]

The NCI-Molecular Analysis for Therapy Choice (MATCH) trial opened for enrollment in August 2015. NCI-MATCH differs from classic clinical trials in cancer by enrolling patients from across different tumor types, depending on the specific molecular characteristics of their cancer. As a result, more drugs than is typical for a single study are being used, and patients who progress while on study will have the opportunity to have their tumor retested and possibly be enrolled on another arm of the trial.

Another important feature is the enrollment of patients with rare cancer types in addition to the more common cancers of the lung, breast, prostate, and colon. The estimated mutation prevalence for each biomarker directing therapy in NCI-MATCH is less than 10 percent.

SOURCES (accessed May 12, 2016): [a] http://www.cancer.gov/types/lung/research/alchemist; [b] http://www.lung-map.org; [c] IOM, 2015b; [d] http://dctd.cancer.gov/MajorInitiatives/M-PACT_Slides.pdf; [e] http://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match.

of error into the decision-making process (NASEM, 2015). Of particular concern for the rapidly moving field of molecularly targeted therapies is ensuring that CDSSs are based on reliable and up-to-date evidence to avoid delivering incorrect recommendations to clinicians (AHLA, 2013).

Patient-Friendly EHRs

Potential challenges to patient-shared decision making in the context of omics-based tests and targeted therapies are discussed in Chapter 5 of this report; telemedicine in particular is explored as a mechanism to overcome barriers to patient access and clinician expertise. Similarly, patient-friendly EHR portals are well positioned to provide timely access to educational materials supportive of shared decision making. Research has demonstrated that patient attitudes are generally positive regarding the move toward precision medicine, but this is accompanied by a lack of knowledge about the nature of biomarker testing and implications for treatment (Blanchette et al., 2014; Issa et al., 2009). Additionally, health care providers and researchers are faced with ethical issues concerning the return to patients of incidental findings uncovered during clinical biomarker testing (see Box 4-3). Beyond reporting relevant test results in patient-readable formats, a number of online resources could be accessed from within the EHR portal to assist patients in understanding their test results and relevant treatment decisions (see Table 4-1).

Clinically Relevant Reporting

Certain considerations to ensure clinical relevance must be taken into account for biomarker test results to be used effectively to guide selection of molecularly targeted therapy; structured data fields should be reported for variants with an established effect on genes or protein variants associated with phenotypes, and implications for treatment (IOM, 2012). Historically, clinical laboratories have had primary responsibility for interpreting and reporting actionable test results, but the growing complexity of molecular testing, exacerbated by the lack of clinical data provided to clinical laboratories, is diffusing some of this responsibility to physicians and other health care providers (IOM, 2012). At the institutional level, multidisciplinary tumor boards or other interdisciplinary clinical conferences can help interpret test results and recommend treatment decisions for complex cases (Schilsky, 2014). Genetic counselors and other members of the health care team with relevant expertise will be essential to help health care providers and patients navigate this transition, and are discussed in Chapter 5.

More broadly, the task of defining the clinical utility of biomarkers for

BOX 4-3
Incidental Findings

Although not unique to molecularly targeted therapies, genomic sequencing technologies, particularly next-generation sequencing technologies, provide an abundance of data that is not always relevant to the clinical questions under investigation. The importance of addressing the return of incidental findings has become apparent with the expansion of genomic testing and research showing that such incidental findings will not be rare (Johnston et al., 2012). Concerns have been raised about returning results within the context of research where resources and time to adequately inform participant consent are both scarce (Berg et al., 2011). Additionally, patients may find information about incidental findings confusing, or pursue aggressive follow-up for genetic variants that would never have caused harm (Kohane et al., 2006).

In the research setting, several major policy statements (Jarvik et al., 2014; NHLBI Working Group et al., 2010; Robson et al., 2010; Wolf et al., 2008) agree that researchers should return incidental findings when (1) the finding has important health implications for the participant, and the associated risks of the health implication are established and substantial; (2) the finding is actionable; (3) the study participant opts to receive results; and (4) the test is analytically valid. Each policy statement raises other considerations as well. Wolf and colleagues (2008) further describe three types of results: (1) those that offer a strong net benefit to patients if returned, that is, the actionable findings are for conditions that are likely to be life-threatening or grave, including reproductive conditions that will affect the offspring; (2) those that offer a possible net benefit such as results about a nonfatal condition that is likely to be grave and for which the research participant would likely think the information important; and (3) results about conditions that are not likely to be serious. The authors recommended disclosure in case 1, allowing, but not requiring, disclosure in case 2, and recommended against disclosure in case 3 (Wolf et al., 2008). This "three bin" approach has been recommended by others as well (Berg et al., 2011; Reilly, 1980)

Although a basic consensus has been reached that at least certain incidental findings should be returned to both patients and research participants, much work remains to be done. There is no agreement on what counts as "actionable," (Wolf, 2012) and few have actually attempted to set up a working system for returning these results (Berg et al., 2013).

the purposes of directing molecularly targeted therapy will be a continuous research endeavor. Larger collaborative efforts such as the American Society of Clinical Oncology's (ASCO's) Targeted Agents Profiling and Utilization Registry (TAPUR), the Actionable Genome Consortium,[3] and

[3] The Actionable Genome Consortium includes Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, MD Anderson Cancer Center, and Fred Hutchinson Cancer Research Center, in a partnership with the sequencing company Illumina.

TABLE 4-1 Examples of Web-Based Resources to Assist Patients with Shared Decision Making

Resource	Description and URL
American Society of Clinical Oncology's (ASCO's) Advanced Cancer Care Planning Booklet	This booklet offers patients with advanced cancer information about treatment options, clinical trial participation, palliative care and hospice care, the role of family in the decision-making process, and end-of-life planning (e.g., creating an advanced directive, developing a living will, and how to find religious or spiritual support if desired). http://www.cancer.net/navigating-cancer-care/advanced-cancer/advanced-cancer-care-planning
ASCO's Cancer.Net Mobile	This application helps patients plan and manage their cancer treatment and care, including tools to assemble questions for clinicians and record their responses, track symptoms and side effects during treatment, among other resources. http://www.cancer.net/navigating-cancer-care/managing-your-care/mobile-applications
Genetics Home Reference	This resource provided by the National Library of Medicine contains consumer-friendly information on the effect of genetic variants on human health. http://ghr.nlm.nih.gov
Informed Medical Decisions Foundation	This foundation does not provide direct medical advice, but provides resources to help patients better engage their health care providers. This includes methods to obtain information relevant to health care decisions and other shared decision-making resources. http://www.informedmedicaldecisions.org/patient-resources
John M. Eisenberg Center for Clinical Decisions and Communications Science	This center translates comparative effectiveness research findings into plain language that patients can understand. It creates a variety of products, ranging from research summaries to decision aids and other materials, for use by patients, clinicians, and policy makers. http://effectivehealthcare.ahrq.gov/index.cfm

TABLE 4-1 Continued

Resource	Description and URL
Leukemia & Lymphoma Society's Information Booklets	These guides provides detailed information about the biology of various types of leukemia and lymphoma, considerations in treatment planning (e.g., choosing a specialist, risks and benefits of various treatment options, clinical trial participation, follow-up care), and general strategies for maintaining health (e.g., maintaining a healthy diet and seeing a doctor regularly). It also includes definitions of medical terms. https://www.lls.org/resource-center/download-or-order-free-publications
National Cancer Institute's Patient Education Publications	These resources include a wide array of materials on topics including treatment options and side effects, in addition to clinical trials, screening, survivorship, and overviews of the natural progression of various types of cancer. http://www.cancer.gov/publications/patient-education

NOTE: URL = Uniform Resource Locator, an address to a resource on the Internet.
SOURCES: AHRQ, 2015a; ASCO and CancerNet, 2015a,b; *Healthwise*, 2015; Leukemia & Lymphoma Society, 2015; NCI, 2015b; NLM, 2015. Adapted from IOM, 2013b.

the Molecular Evidence Development Consortium (MED-C) are seeking to expand the availability of omics-based testing and treatment through demonstration of clinical utility for certain biomarker tests and molecularly targeted therapies (Dickson, 2015; Schilsky, 2014; Solit, 2014). The clinical utility of a biomarker test and corresponding targeted therapy is dependent on the interaction of treatment on phenotype and various outcomes, including survival and quality of life. Many of these data, including valuable patient experiences and reported outcomes, are only known by the patient and not always captured in the EHR; nevertheless, they are essential to the implementation of a value-driven rapid learning health system (Berenson et al., 2013; Millenson and Berenson, 2015). Methods to capture phenotype and exposure information from patients, as well as patient-reported outcomes, are therefore necessary to facilitate ongoing learning about the effectiveness of molecularly targeted therapies (see Box 4-4). EHR functionality will need to go beyond the support of clinical decision making, and enable rapid learning based on continuously aggregated data from "real-world" clinical practice and patient experience to facilitate the evaluation of outcomes associated with the use of biomarker tests and molecularly targeted therapies.

BOX 4-4
PROMIS

The Patient Reported Outcomes Measurement Information System (PROMIS) is a National Institutes of Health–funded system of measures designed to provide precise and reliable patient-reported data on symptoms, quality of life, health status and other patient experiences. These measures are being validated in a number of studies across a variety of conditions, in order that they may serve as endpoints in clinical studies related to interventions. PROMIS instruments are available in multiple formats, including paper forms and computer adaptive testing (which can adapt the instrument in real-time based on patient input in order to refine the result obtained for that patient).

Additionally, PROMIS measures are standardized across diseases and conditions, to facilitate broader research into health outcomes among distinct patient populations. The measures are also designed to accommodate patients without respect to literacy, language, physical function, or life course. Additional instruments under development include gastro-intestinal symptoms, and self-efficacy for management of chronic disease for adults, as well as pediatric instruments for pain behavior, pain quality, pain intensity, physical activity, experience of stress, subjective well-being, impact of child illness on family, and family belongingness.

The PROMIS measures can be used in settings apart from interventional or clinical studies as mentioned above, including: observational studies, comparative effectiveness studies, and research into health care delivery and health policy. PROMIS also facilitates research through online tools for managing study data.

SOURCE: http://www.nihpromis.org (accessed May 12, 2016).

EHRs as Research Tools

With an increasing trend toward precision and personalized medicine, the omics world (including genomics, proteomics, metabolomics, lipidomics, transcriptomics, epigenetics, microbiomics, fluxomics, phenomics, etc.) has the potential to become a source of data-driven hypotheses and evidenced-based medicine. Clinical data, when properly captured in EHRs and correlated with data from biobanks or clinical laboratories, can be used as a tool to confirm genetic associations (Ritchie et al., 2010). Once established, such integrated health informatics systems can serve as "inexhaustible sources" of data for rapid learning (Krumholz, 2014, p. 1163). These rapid learning systems can leverage a wide variety of information, including individual patient data, clinical trials and other population-level data, and operational data (Yu, 2015). For molecularly targeted therapies in particular, generating evidence to support the use of a biomarker or associated therapy will require structured data fields

beyond the test results necessary for a CDSS as described above. Moreover, clinical use of potentially beneficial molecularly targeted therapies (through compassionate use programs, or general "off-label" use) do not currently produce usable outcomes data, which represents a tremendous loss of information that could be used to further assess the utility of the therapy (Schilsky, 2014). Thus, data on the treatments prescribed and used as well as longitudinal clinical patient data will need to be more rigorously captured, in a manner that is minimally burdensome to health care providers (Kullo et al., 2013).

Ensuring the ease of use of EHRs for this purpose is as important as data functionality. Results from a survey of physicians by the RAND Corporation further emphasize this point: Despite a general preference for EHRs over paper records, current EHR implementations decrease professional satisfaction due to a combination of perceived poor usability, disruption to workflow, and diminished quality of clinical documentation (Friedberg et al., 2013). The *Improving Diagnosis in Health Care* report stated that technologies such as speech recognition and natural language processing (which extracts data into structured formats from free text) may serve to bridge the gap between the need for structured data and clinician preference for more free-form documentation (NASEM, 2015). The diversity of clinical workflow environments may be best served by offering multiple solutions within the EHR, to enable clinicians to select an option based on their specific needs and preferences (Rosenbloom et al., 2011).

Data infrastructure supporting a rapid learning system for biomarker tests and molecularly targeted therapies requires linkages among the specific test ordered, the reported results, the treatments prescribed (whether based on the test result or not), and longitudinal clinical patient data. Diverse longitudinal data collected routinely during clinical practice would enable assessments of usage and multiple outcome measures to meet the evolving needs of clinical utility as defined by the broader health care stakeholder community (see Chapter 3). Therefore, to support the data infrastructure needs of a rapid learning system, the committee recommends that **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 (Recommendation 6a).** Data structured in the EHR should include, at a minimum, biomarker test specimen requirements, specific test results and interpretation (particularly of actionable next-generation sequencing, or NGS, variants), treatments prescribed and other diagnostics ordered (including the reason for such orders, e.g., further need to refine treatment options), and longitudinal clinical patient data. Similarly, structured data within the LIS would include specific biomarker test descriptions,

including assay method, analytes assessed, test performance characteristics, quality metrics, and bioinformatics tools, when applicable. Taken together, these structured and linked data would provide the backbone of the infrastructure to facilitate clinical decision support development and ongoing research. As discussed previously, these fields should be populated in a manner that facilitates easy entry of data by clinicians in order to ensure consistency and use.

The committee further recommends that **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 (Recommendation 6b).** Decision support should be flexible, employing both highly focused prompts during clinic visits as well as more detailed educational support before or after the visit. EHRs should allow for the incorporation of practice guidelines or other treatment pathways into decision support systems, and include mechanisms for tracking compliance. Patient-facing EHR portals should provide biomarker test results in a patient-friendly format, and include linkage to relevant educational materials and the committee's proposed pilot test labels (discussed in Chapter 3).

The committee recommends that **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.** Because each practice will need to customize the EHR for their specific use, the customization of point-of-care decision support should align with available evidence-based clinical practice guidelines.

Finally, given the increasing educational role provided by CDSSs in a rapid learning system for biomarker tests and targeted therapies, the committee recommends **licensing and specialty boards should recognize Continuing Medical Education (CME), Continuing Education Units (CEUs), and Maintenance of Certification (MOC) achieved through interaction with point-of-care decision support educational materials (Recommendation 6d).** Professional schools, training programs, and specialty boards should ensure that clinicians are skilled in the use of these tools.

BIG DATA

In oncology, a relatively modest number of "driver" mutations are thought to underpin each patient's cancer (Vogelstein et al., 2013). However, each patient's cancer also harbors a long "tail" of mutations that, though infrequent, make each case unique (Garraway, 2015). This fact complicates efforts to define which biomarker test results may truly be clinically actionable for any given patient. Solving this challenge likely

will depend on the ability to leverage very large sample sizes coupled with detailed phenotype and clinical data in order to distinguish meaningful outcomes associated with the use of certain therapies (Abernethy, 2015). Recent research into genomic correlates of response to cancer immunotherapy likewise concluded that "detailed integrated molecular characterization of large patient cohorts may be needed to identify robust determinants of response and resistance to immune checkpoint inhibitors" (Van Allen et al., 2015, p. 207). The existing distributed and data-driven initiatives described in this chapter reflect these needs. Moreover, a small number of medical school curricula, with funding from the American Medical Association, are beginning to incorporate big data coursework to train physicians who are comfortable using such evaluations to explore and improve health care delivery (AMA, 2015). However, medical research in general has lagged behind other fields in the use of big data analytics, despite the potential usefulness of the vast amounts of data generated daily in clinical care (Krumholz, 2014).

Data Sharing

For large-scale data analysis to generate knowledge effectively, it will be important to aggregate evidence on promising biomarker tests and targeted therapies. Capture of clinical and other data from the off-label use of targeted therapies was discussed in the context of EHRs above, but data on biomarker tests or therapies that never make it to market due to failure to demonstrate benefit for patients in clinical trials also will need to be consistently documented. Studies have shown that despite obligations to do so, not all clinical trials are properly reported or updated on national registries such as ClinicalTrials.gov (Anderson et al., 2015), and the lack of widespread reporting of negative studies may impede research to develop effective molecularly targeted therapies. Furthermore, published medical research does not completely reflect all data generated during clinical trials (Riveros et al., 2013). Ensuring that clinical research data is made publicly available, when appropriate, is a first step toward building a culture of data sharing that would enable "big data" analysis.

The challenges and benefits of ensuring that clinical trial data are properly shared were described in the IOM report *Sharing Clinical Trial Data*. Acknowledging that the clinical trials landscape is changing, the report made broad recommendations, including the fostering of a data-sharing culture; adhering to pre-specified timeframes for sharing types of study data; and enhancing security and transparency through development of strategies, independent review panels, and data use agreements (IOM, 2015c). However, precision medicine may represent a blurring of the line between clinical care and clinical research; one example is treat-

ment for advanced cancer, which increasingly seeks to use the latest generation of molecularly targeted therapies when other treatments have been exhausted (IOM, 2015b). Comparative effectiveness research (CER), in which the relative benefits and harms of interventions are assessed, increasingly seeks to refine clinical practice through evaluating current clinical care options (see Box 4-5). Importantly, the clinical use of NGS platforms will require data sharing to ensure the validation of novel test results through assessment of concordance across clinical laboratories and patient care sites (IOM, 2012). The National Institutes of Health (NIH) considers data sharing integral to translating genomic discoveries to the benefit of human health, and has published a Genomic Data Sharing Policy[4] that applies to all NIH-funded research that generates large-scale genomics data.

The health care and clinical research communities have been largely responsive to these data-intensive requirements of precision medicine; many public, private, and academic initiatives to create resources to assess the clinical significance of biomarkers are under way (see Table 4-2). These initiatives, however promising, represent silos of knowledge and potential obstacles to the building of larger datasets. A critical prerequisite for successful data sharing is overcoming the institutional, organizational, or other opposition to making data available. *Sharing Clinical Trial Data* featured a prominent discussion on the disincentives to sharing data, particularly the potential for researchers unrelated from the initial data gathering to misuse data or use the data to undermine the primary research (IOM, 2015c). Recent movement toward building data-sharing culture, including requirements for data sharing as a condition for manuscript submission, has helped demonstrate the potential of "symbiotic" secondary research on shared datasets (Dalerba et al., 2016; Longo and Drazen, 2016; Taichman et al., 2016). Emerging best practices for secondary researchers seeking to ensure trust should include a focus on novel research ideas, the careful selection of collaborators whose data may help test a hypothesis, and shared responsibility for conducting the research and subsequent report authorship (Longo and Drazen, 2016).

Despite the barriers to large-scale collaboration, promising projects are demonstrating potential to leverage shared data and expertise. The Global Alliance for Genomics and Health (GA4GH) seeks to position itself as an "honest broker" through convening stakeholders, fostering innovation and data-sharing culture, and harmonizing institutional processes (Lawler et al., 2015). GA4GH working groups (focusing on clinical practice, data, regulation, and security) have released work products, including data analysis tools as well as consent and data sharing policies

[4] 79 CFR 51345.

BOX 4-5
Comparative Effectiveness Research

The Institute of Medicine (IOM) defined comparative effectiveness research (CER) as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care" (IOM, 2009b, p. 13). Some researchers consider the value of care to be a central component of CER, and additionally assess the relative cost of an intervention (Schilsky, 2015). Ultimately, the goal of CER is to empower patients, health care providers, payers, and others to make the most informed health care decisions to improve patient outcomes (IOM, 2009b).

Tools to assess CER include not only traditional randomized controlled trials, systematic reviews, and meta-analyses, but also population studies (e.g., through the use of disease registries), predictive association and other observational studies, quality-of-life assessments and patient-reported outcomes, and clinical decision models (including cost-effectiveness analyses) (Lyman and Levine, 2012). Many of these assessments, particularly for genomic medicine, can be facilitated through evidence extracted from a data infrastructure able to leverage clinical, research, and administrative data for the purposes of CER (Goddard et al., 2012). The IOM has described the importance of CER that reflects overall patient populations, particularly in diseases such as cancer where research participants typically are not representative of the general patient population (IOM, 2013b); CER on data from electronic health records may be well positioned to fill this role. Moreover, early research has demonstrated that CER data on the use of biomarkers tests for therapeutic decision making may be used to model long-term outcomes that would otherwise require many years to evaluate (Birnbaum et al., 2015). Thus, CER in parallel with broader clinical data sharing may enable valuable assessments related to the clinical utility of biomarker tests for molecularly targeted therapies.

Historically CER has been underused in the United States, but the Patient Protection and Affordable Care Act[a] created the Patient-Centered Outcomes Research Institute in order to help support CER of interventions for common and high-cost conditions (Tanden et al., 2014). Effective CER produces results that are able to inform decision makers, and a critical remaining challenge for the evaluation of biomarker tests for molecularly targeted therapies is agreement on standards for research methodology and outcomes that are able to meet the needs of all involved stakeholders (e.g., patients, providers, test and drug developers, payers, and regulators) (Deverka and Haga, 2015).

[a] Patient Protection and Affordable Care Act, Public Law 111-148, 111th Congress, 2nd Sess. (March 23, 2010).

(GA4GH, 2016). Initiatives under the umbrella of the GA4GH include an effort to globally pool BRCA research data to more rapidly establish therapeutic and preventive interventions for breast cancer patients, the development of a European "eCancer Hospital" through interoperable clinical laboratory processes and health information technology (IT) protocols, and the American Association for Cancer Research's Genomics

TABLE 4-2 Existing Data Resources for Assessing Clinical Significance of Biomarkers

Resource Name	Description	URL
Clinical and Functional Translation of CFTR (CFTR2)	Provide information about cystic fibrosis (CF) mutations to patients, researchers, and the general public. Specifically, information on whether a particular mutation will result in CF when combined with another mutation is provided. Clinical factors associated with a given mutation (e.g., lung function) are also catalogued.	http://www.cftr2.org
Clinical Interpretations of Variants in Cancer (CIViC)	Provides an open access, open source, community-driven Web resource for interpreting clinical significance of cancer variants.	https://civic.genome.wustl.edu
ClinVar	Aggregates information about both germline and somatic sequence variation and its relationship to human health.	http://www.ncbi.nlm.nih.gov/clinvar
dbVaR	Database of genomic structural variation; archives studies of structural variation and their interpretation.	http://www.ncbi.nlm.nih.gov/dbvar
DNA-Mutation Inventory to Refine and Enhance Cancer Treatment (DIRECT)	Catalogue of clinically relevant mutations found in lung cancer, namely *EGFR* mutations. Program has goals to expand this to all known mutations.	http://www.mycancergenome.org/about/direct
GeneReviews	Developed and maintained by the University of Washington. It contains phenotypic information and some clinical implications. Site focuses only on strongly implicated variations. Catalogues both germline and somatic variants.	http://www.ncbi.nlm.nih.gov/books/NBK1116

TABLE 4-2 Continued

Resource Name	Description	URL
Human Gene Mutation Database	Database of the first example of all mutations causing or associated with human inherited disease, plus disease-associated/ functional polymorphisms reported in the literature.	http://www.hgmd.org
My Cancer Genome	Freely available online resource for common molecular alterations within known cancer types. Provides oncogenic properties of genomic alterations as well as potential therapeutic options.	http://www.mycancergenome.org
NHGRI Genome Wide Association Study (GWAS) Catalog	Compendium of SNP-trait associations gleaned from published GWAS studies.	http://www.genome.gov/GWAStudies
NIH Genetic Testing Registry (GTR)	Provide a catalogue of genetic tests in clinical use for clinicians. While most information will be at the gene level, tests for single variants will be included. Assertions of AV, CV, and CU are made by test submitters.	http://www.ncbi.nlm.nih.gov/gtr
PharmGKB	Provide information about the impact of genetic variation on drug response for clinicians and researchers.	http://www.pharmgkb.org

NOTE: AV = analytic validity; CU = clinical utility; CV = clinical validity; EGFR = epidermal growth factor receptor, a common therapeutic target in some cancers; NHGRI = National Human Genome Research Institute; NIH = National Institutes of Health; SNP = single-nucleotide polymorphism, a type of genetic variant.
SOURCES: Adapted from Bailey et al., 2014; Ramos et al., 2014.

Evidence Neoplasia Information Exchange (GENIE) (Lawler et al., 2015). The recently announced GENIE project seeks to "fulfill an unmet need in oncology by providing the statistical power necessary to improve clinical decision-making, particularly in the case of rare cancers and rare variants in common cancers," and as such is a particularly relevant potential proof of concept for the committee's proposed rapid learning system for biomarker tests for molecularly targeted therapies (AACR, 2016).

The Food and Drug Administration (FDA) has also signaled its willingness to innovate in the field of "regulatory science," specifically stream-

lining evidence generation through the use of adaptive trial designs and by the incorporation of "real-world" patient data (Califf and Ostroff, 2015). FDA also recently announced that it intends to collaborate with the broader scientific community to develop future oversight of NGS and other data-intensive technologies through an open-access research infrastructure (Blumenthal et al., 2016; FDA, 2015b; Kass-Hout and Litwack, 2015).

The Common Rule[5] governing human subjects research may be undergoing a similar policy evolution. The Department of Health and Human Services (HHS) has proposed modifications[6] to the rule, including (1) a requirement for informed consent for all research on biospecimens, whether or not they are de-identified; (2) streamlining of the informed consent process; (3) the creation of uniform data security standards calibrated to the types of information being collected, thus removing the evaluation of privacy risks from Institutional Review Boards' oversight, a task they may have not been well-suited to perform; and (4) the creation of a central repository for submission of adverse event data across all relevant federal agencies. Taken together, these modifications indicate a willingness to respect the privacy of research subjects in an increasingly data-driven research environment, while helping to facilitate data sharing by minimizing regulatory ambiguity for researchers (Hudson and Collins, 2015).

Challenges for Data Sharing

The *Sharing Clinical Trial Data* report concluded with observations on challenges to broad sharing of data, some of which are relevant for a rapid learning system to assess biomarker tests and molecularly targeted therapies. The primary technological challenge, beyond structured data discussed previously, is the need for infrastructure to store such a large volume of data while remaining nimble enough to permit continuous research (IOM, 2015c). The report acknowledged that the volume of data and the diversity of stakeholders involved in clinical research likely precluded the creation of a single database; rather, a federated query model could bridge existing resources by connecting them "in such a way that they can respond to queries as if all the data were in a single virtual database" (IOM, 2015c, p. 166). The federated query model also maintains institutional ownership of shared data, which was crucial in the context of clinical trial data and may be equally crucial for a repository of data for biomarker tests and molecularly targeted therapies (IOM, 2015c).

[5] 45 CFR 46.
[6] 80 FR 53931.

The ability for distinct electronic resources to transmit and receive structured data successfully (i.e., interoperability) is also critical to data sharing. For example, initiatives such as ASCO's Cancer Learning Intelligence Network for Quality (CancerLinQ) program or the American Society of Radiation Oncology's National Radiation Oncology Registry are attempting to demonstrate the feasibility of leveraging heterogeneous clinical data to support adherence to practice metrics (Efstathiou et al., 2013; Hudis, 2015). However, lack of interoperability in EHRs has been cited as a major roadblock to leveraging big data analytics to improve health care (ASCO, 2015). Moreover, ONC reported that data-blocking activities[7] by health care providers or EHR vendors are potentially an additional obstacle to interoperability and widespread data sharing, though the report concluded that the scope of such activities is difficult to quantify (ONC, 2015b). The 21st Century Cures Act[8] passed by the House of Representatives includes provisions designed to address some of these obstacles, including a prohibition of data blocking, a mandate for complete access and exchange of health information, and a broadly outlined plan for the development of interoperability standards. The development of such standards for interoperability is essential to the use of clinical patient data stored within EHRs for research purposes (Jensen et al., 2012). An ONC task force to evaluate the role of health IT for the Precision Medicine Initiative (PMI) likewise recommended closing the existing gaps in data and interoperability standards in order to facilitate the exchange of clinical data (ONC, 2015a). Pilot projects in EHR data interoperability have been promising, but limited in scope (Rea et al., 2012; Warner et al., 2015).

There will be a need to ensure the quality of data, particularly genomic sequence data, that are submitted to a shared database for biomarker tests for molecularly targeted therapies. In some, but not all, of the existing data resources in Table 4-2 there may be concerns around the quality of submissions (i.e., the strength of genotype-phenotype associations of sequences submitted). More specifically, quality needs to be addressed with respect to both analytic validity and clinical validity. For analytic validity, historically the only quality control for data emerging from research databases is if the report of the variant has been published in peer review. This is a very low bar. However, the sequence interpreta-

[7] In the report, ONC described data blocking as activities beyond lack of coordination, divergent policy implementation, and inconsistency in standards that currently exist across health care systems and among states. Examples of health care providers or EHR vendors actively engaging in data blocking include: contractual terms that restrict access to health information, prohibitively expensive fees for information portability, and developing health IT in ways that will likely result in costly or complex data sharing or "locked in" users or data.

[8] H.R. 6, 114th Congress (2015-2016).

tions relevant for a proposed database of variants used in clinical care will come from a clinical laboratory variant report, and the lab will have established analytic validity through the Clinical Laboratory Improvement Amendments certification process (or other related oversight processes, as discussed in Chapter 3).

The curation of clinical validity (i.e., whether a variant is likely pathogenic or pathogenic, or represents a legitimate target for molecularly targeted therapy) is indeed a source of confusion in existing public databases. However, the underlying rationale for these databases is to make variant interpretations transparent and publicly accessible, to include the underlying data that supports the interpretation, and to highlight the existence of discrepancies. Having a variant interpretation in a database does not mean it is correct; unfortunately, there is no reliable method for fully pre-curating the clinical validity of variants and knowing the "truth" about such variants prior to submitting them to a database. It is the availability of multiple interpretations, and the underlying evidence for these interpretations, that allows us to highlight discrepancies and allow the most accurate clinical validity assessments (Rehm et al., 2015). The power of such comparisons will be enhanced by existing collaborative efforts such as the Green Park Collaborative (GPC) and the MED-C collaboration to develop a core set of clinical data elements that all such repositories should collect and to identify data commonalities that promote cross-database compatibility and comparisons (CMTP, 2016).

Sustainability of data sharing is also paramount, particularly because the assessment of outcomes associated with therapy requires the use of longitudinal clinical patient data. For clinical trial data sharing, it was concluded that costs were borne by a fraction of stakeholders; the IOM therefore recommended transitioning to a model with more equitable distribution of economic responsibility (IOM, 2015c). A rapid learning system for biomarker tests and molecularly targeted therapies could be sustained through a variety of methods; for example, Chapter 3 discusses reimbursement models that could facilitate data collection for the ongoing assessment of clinical utility of biomarker tests. Given the expanding role of EHRs for both decision support and research as described above, and their potential to provide valuable clinical data to larger repositories, an additional mechanism to sustain the development and use of data sharing may take the form of payments to health care providers who submit data, similar to those provided by CMS to early adopters of EHRs.

Data security and privacy may pose challenges to broad data sharing for the purpose of rapid learning for biomarker tests and molecularly targeted therapies. The collection of longitudinal clinical and other outcomes data to support the clinical utility of biomarker tests and molecularly targeted therapies will necessarily preclude certain levels of de-

identification. Additionally, for genomic test results, true de-identification may be impossible as these data are inherently identifiable (Gymrek et al., 2013; Homer et al., 2008). The Common Rule currently allows de-identified specimens and data to be shared or used for research without a requirement for informed consent; however, variability in interpretation of regulations, particularly in delineating when research is additionally subject to the Health Insurance Portability and Accountability Act of 1996,[9] has perpetuated an environment lacking in uniform standards for the use of data in research (IOM, 2009a). Given these facts, and the proposed changes to the Common Rule that will require informed consent for all research involving biospecimens and related data, the committee believes that patient consent measures are a reasonable requirement for data sharing to facilitate rapid learning for biomarker tests and molecularly targeted therapies. Such consent measures could take the form of the broad, open-ended consent documents suggested in the proposed Common Rule changes, and currently employed in some health care centers across the country.

Previous reports have addressed the competing needs of data sharing and privacy across varying health care research contexts, and in general have emphasized that privacy regulations should be prudently developed and deployed only when necessary and effective, in order to facilitate health care advances through research (IOM, 2009a, 2015c; NRC, 2011; Presidential Commission for the Study of Bioethical Issues, 2012). The NRC report *Toward Precision Medicine* stated that "there is little evidence that the public has the extreme sensitivity toward genetic data that many researchers anticipated 25 years ago" (NRC, 2011, p. 39). The Presidential Commission for the Study of Bioethical Issues likewise concluded that parsimonious regulation is justified because it will facilitate the sharing of data from autonomous research participants who desire to contribute to beneficial medical research (Presidential Commission for the Study of Bioethical Issues, 2012).

Nevertheless, data security and patient consent measures are insufficient to remove all concerns of potential breaches of privacy, and additional mechanisms could be used to minimize risk. In *Sharing Clinical Trial Data*, the IOM recommended data use agreements to govern the level of data sharing and potential uses for which data could be used, as well as transparency in policies and composition of any bodies that review research requests for shared data. Additionally, mandatory registration for researchers seeking to use shared data resources would facilitate penalties for willful re-identification of data or other misuse (IOM, 2015c). The PMI's Proposed Privacy and Trust Principles likewise include data

[9] Public Law 104-191.

use agreements and criminal penalties for the deliberate misuse of data. The PMI cohort paradigm seeks to create a new research model in which consented participants are equally as engaged as investigators, and the resulting focus is not on eliminating privacy risks but adequately communicating risk and minimizing such occurrences, with procedures in place for prompt notification and accountability in the event of a data breach (The White House, 2015).

Under the proposed changes to the Common Rule, standardized data security protections will be developed that are sensitive to varying clinical research scenarios, and the development of data-sharing repositories should reflect those standardized protections. Similarly, existing confusion regarding appropriate informed consent and requirements for sharing patient specimens and data will be clarified. However, existing research performed on stored and de-identified biospecimens may need to be re-evaluated in light of the proposed consent requirements. Moreover, whether or how specific data security, informed consent, and privacy modifications to the Common Rule will address potential discrimination on the basis of omics data is uncertain (see Box 4-6). Thus, the nature of the impact on translational research by the proposed updates to the Common Rule, while likely to be significant, remains unclear.

The Precision Medicine Initiative

The PMI, as described in the introduction to this report, reflects an appreciation for the scale of data and research infrastructure needed to explore associations between health and omics data. In a recently released PMI Working Group report on the PMI cohort study, the authors reflected on maximizing the opportunity to systematically study such a large research cohort, and recommended automated data collection whenever possible, rigorous data curation, centralized data resources, and coordination with CMS and other payers to facilitate integration of clinical data from EHRs (PMI Working Group, 2015). These recommendations are consistent with the role of supporting data infrastructure for biomarker tests for molecularly targeted therapies, as outlined in this chapter. The PMI is additionally relevant because of the funding set aside for the development of regulatory-grade databases to advance precision medicine (Blumenthal et al., 2016; OPS, 2015). FDA's pilot collaborative data-sharing platform, precisionFDA, represents the first step toward such regulatory tools.[10] NIH, through the National Human Genome Research Institute, is currently seeking multistakeholder input (including payers, patients, health care providers, researchers, professional organizations, policy makers, and

[10] See http://precision.fda.gov (accessed January 5, 2016).

BOX 4-6
Genetic Discrimination

The Genetic Information Nondiscrimination Act of 2008 (GINA) (Public Law 110-233) generally prohibits discrimination based on the use of genetic information for purposes of employment or health insurance (life, disability, or long-term care insurance are notably absent). The passage of this legislation reflects not only the increasing pervasiveness of genetic information in society, but also the potential for genetics to improve health provided that important future research is not obstructed by fears of genetic discrimination.

However, the extent to which the legislation has succeeded in both preventing discrimination and allaying public fears is not yet clear. Few cases of genetic discrimination, relative to other forms of employment discrimination, have been tested thus far; in general, the widespread use of genetic test results by insurers or employers has yet to materialize. Similarly, public understanding of the role of genetic tests and the potential for discrimination remains limited. Evidence suggests that fear of future discrimination may still present an obstacle to research participation, though distinguishing such cases from legitimate use of informed consent is challenging.

In the near future, omics data may become pervasive enough to warrant reexamination of GINA. Precision medicine also may provide avenues to remedy genetic risks that are currently perceived to be immutable. Moreover, in evaluating the genetic heterogeneity of large populations, insurers may prefer more unified pricing models to account for the wide variation in potential future risk. However, clarification of the relationship between genetic variation and health will require broad participation in future research. As legal and regulatory frameworks adjust to the influx of genetic and other omics information, consideration of the potential for misuse of these data will be necessary to ensure that the privacy of research participants is protected.

SOURCES: Green et al., 2015; Hellman, 2003; Varmus, 2010.

others) on the optimal design of a clinical sequencing program, including the ability to leverage existing and future data infrastructure to support the integration of genomics into clinical care (NHGRI, 2015). Similarly, the National Cancer Institute (NCI) intends to fund collaborative genomic and proteomic research networks across academic institutions in order to comprehensively characterize tumor types, investigate responses to drugs, and refine biomedical informatics approaches to working with these large omics datasets.[11]

Thus, a well-identified need exists for broader collaboration and data

[11] Funding Opportunity Announcement Numbers include RFA-CA-15-018, RFA-CA-15-019, RFA-CA-15-020, RFA-CA-15-021, RFA-CA-15-022, RFA-CA-15-023.

sharing among all stakeholders in the health care system; such collaboration would multiply the usefulness of current research through the positive economics of data sharing (IOM, 2015a). To capitalize on the initial momentum described in this chapter (among clinical researchers, health care providers, health information technology vendors, regulatory agencies, and others), and to facilitate the continuous assessment of the evidence supporting the clinical use of biomarker tests and molecularly targeted therapies, the committee recommends **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, the Patient-Centered Outcomes Research Institute, 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.** The repository would include data structured within EHRs (including biomarker test description, test results and interpretation, treatment decisions and outcomes, adverse reactions, and other relevant data generated during clinical practice), as well as clinical trial data, billing/reimbursement data, patient-reported outcomes, and other longitudinal clinical patient data. **Given the fact that widely accepted EHR interoperability standards do not currently exist, the committee expects that the Task Force may need to define and develop a repository-specific interoperability standard, in order to ensure the incorporation of data from as broad a pool of clinical practice settings as possible.**

In addition to data located in EHRs, this repository could also leverage data from other existing resources, such as FDA's Sentinel Initiative to track adverse events (see Box 4-7), or those resources for assessing the clinical use of biomarker tests listed in Table 4-2. The repository may ultimately be composed of discrete databases for different indications (e.g., separate and dedicated resources for oncology, cardiology, cystic fibrosis, etc.). **As mentioned above, the national repository should be built and made accessible with appropriate de-identification, data security, and patient consent measures, and sustainability should be provided, in part, through incentives put into place by HHS for data submission by all health care providers and health systems.** The committee believes such a resource should provide de-identified datasets freely to researchers, health care providers, payers, and regulators, and standards and best practices for data sharing and analysis could draw upon existing cloud-based programs (Stein et al., 2015). The NCI's Cancer Genomics Cloud Pilots are one such example of attempting to standardize access, analysis, and collaboration on large genomic datasets (NCI, 2015a).

BOX 4-7
FDA's Sentinel Initiative

A pilot program launched in 2008, the Sentinel Initiative aims to develop a national electronic system, compatible with existing systems that the Food and Drug Administration (FDA) can use to track reports of adverse advents stemming from the use of regulated products after they have entered the market. In the past, FDA has relied on passive collection of event reports and postmarket studies. FDA's Adverse Event Reporting System (FAERS) database is composed primarily of voluntary reports. Submission of an adverse event report is only required if the nature or severity of the event is inconsistent with previous documentation. FAERS data are available to the public, but have not been extensively validated. The Sentinel System will allow FDA to tap into automated health care data holders (e.g., electronic health records and insurance claims databases) and broad networks to safely and securely access the data necessary to respond to emerging risks.

FDA faces many challenges in postmarket risk assessment. Critics point to unresolved issues regarding data integrity, validity, reliability, and reproducibility. Additionally some argue that the usefulness of Sentinel is much more limited than FDA claims: It has not yet facilitated rapid drug safety assessment and improved regulation. The regulatory response of FDA to undesirable results of postapproval studies is not clearly defined, due in part to reliance on inconsistent input from FAERS, Sentinel, and other postmarket studies. Nonetheless, FDA has asserted that Sentinel holds tremendous promise for regulatory decisions based on big-data tools to organize and evaluate evidence and to maintain standards of safety and efficacy.

SOURCES: FDA, 2015a; *Health Affairs*, 2015.

SUMMARY AND RECOMMENDATIONS

The committee's vision for a rapid learning system to assess biomarker tests and corresponding molecularly targeted therapies depends on robust data infrastructure; many of the recommendations presented throughout this report relate to the capabilities outlined here for EHRs and a national repository for shared data. The systematic capture of relevant clinical data will serve the complex and occasionally competing needs of regulators, payers, health care professionals, patients, and drug and diagnostic developers. Continuous research on these data through an openly accessible national data repository will be instrumental in assessing value and ultimately improving patient outcomes.

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: Electronic health record (EHR) and laboratory information system (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).

The information to be structured in the EHR should include, at a minimum:

- **Biomarker test specimen requirements (type, amount, handling).**
- **Specific biomarker test results and interpretation (including actionable panel or next-generation sequencing test results).**
- **Treatments prescribed and diagnostic tests ordered (whether based on the biomarker test result or not).**
- **Longitudinal clinical patient data.**

The information to be structured in the LIS should include, at a minimum:

- **Biomarker test descriptions (assay method, analytes assessed, test performance characteristics, quality metrics, and bioinformatics tools).**

Recommendation 6b: Electronic health record (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.**
- **To enhance patient understanding, relevant educational materials should be accessible from within the portal.**
- **Portals should include linkage to test labels (see Recommendation 3).**

Recommendation 6c: Health care institutions and physician practices should use electronic health records (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.

Recommendation 6d: 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.

- **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: The Secretary of the Department of Health and Human Services (HHS) should charge the Food and Drug Administration (FDA) and National Institutes of Health (NIH) to convene a task force (comprising FDA, the Centers for Medicare & Medicaid Services, the Department of Veterans Affairs, NIH, the Department of Defense, the Patient-Centered Outcomes Research Institute, 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.

- **This prospective, integrated, and structured database should include biomarker test description, test results and interpretation, treatment decisions and outcomes, other relevant electronic health record 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.**

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5

Processes to Improve Patient Care

The well-being of patients is central to the practice of medicine. This is the focal point around which the efforts of all stakeholders in health care converge, with the goals of curing disease and extending life whenever possible, while also improving or preserving quality of life. As discussed throughout this report, precision medicine, defined as targeting therapies to patients through the use of biomarker tests, is being increasingly pursued as a path toward realizing this goal, particularly in those patients for whom current treatments have proven inadequate or are nonexistent. However, challenges associated with the rapid increase in potentially therapeutically relevant biomarkers have accompanied the molecular characterization of diseases. In addition, the number of tests offered by both academic institutions and private test developers has been steadily rising (Frampton et al., 2013; Meric-Bernstam et al., 2013). The growing list of options for biomarker tests, absent guidance, can be confusing not only for academic health care providers, but especially for providers in the community where, for example, the majority of U.S. cancer patients are treated (The Moran Company, 2013).

This chapter discusses processes to improve patient care in the context of biomarker tests and molecularly targeted therapies, including equity in access to testing and relevant expertise, ensuring patient safety and adequate test performance, and the implications for generating evidence-based clinical practice guidelines. The committee's specific recommendations are summarized in the conclusion of this chapter.

BOX 5-1
Pharmacogenomic Biomarker Tests

Pharmacogenomic tests, distinct from tests for biomarkers used to stratify patients for molecularly targeted therapy, are also used to inform treatment decisions made by health care providers and patients. These tests predict drug response or toxicity that is due to genetic variability in drug metabolism or drug action, and are typically performed only once, prior to initiation of therapy (Crews et al., 2012). One example is HLA-B*57:01 testing prior to abacavir treatment of patients with HIV/AIDS. A rare and life-threatening hypersensitivity reaction, occurring in approximately 6 percent of patients, can be avoided if patients are first tested for the HLA-B*57:01 allele. Positive test results inform a physician that abacavir administration is contraindicated. Such testing is now standard practice prior to initiation of abacavir therapy (Martin et al., 2012) and required per Food and Drug Administration labeling, and has resulted in the near elimination of incidents of the hypersensitivity reaction.[a]

Pharmacogenomic testing is also used in anti-platelet therapy. The drug clopidogrel is used to lower the risk of cardiovascular events, such as blood clots or heart attacks. A test for *CYP2C19* variants can identify patients for whom the drug will function less effectively (resulting in more cardiovascular events than expected, albeit with less risk of bleeding) (Mega et al., 2009, 2010), or more effectively (fewer thrombotic events, but with increased risk of bleeding) (Zabalza et al., 2012). Informed by pharmacogenomic testing results, physicians and patients can weigh the risks and benefits in deciding to use this antiplatelet therapy, or pursue treatment with alternative drugs.

[a] Personal communication, Simon Mallal, Vanderbilt University Medical Center, May 6, 2015.

CURRENT CHALLENGES IN TEST RESULT INTERPRETATION

In the current era of precision medicine, physicians seeking to incorporate emerging tools into the management of their patients will increasingly use advanced biomarker tests to guide treatment (Evans and Khoury, 2013). Certain predictive biomarker tests, known as pharmacogenomic tests,[1] evaluate genetic variations that affect pharmacokinetics (i.e., "what the body does to the drug") and pharmacodynamics (i.e., "what the drug does to the body"), and physicians and patients use these tests to optimize treatment selection and dosage (see Box 5-1). However, in diseases with complex somatic or germline genomic etiologies, such as cancer or cystic fibrosis (CF), the molecular subsets of these diseases may

[1] As defined in Chapter 1, pharmacogenomic tests are outside the scope of the committee's charge, but their distinct role is discussed briefly here in the interest of clarity.

have unclear or emerging relationships to molecularly targeted therapies. In CF, for example, approximately 5 percent of cases are caused by the p.G551D mutation in *CFTR* (the gene which, when mutated, can result in the disease) and can be treated effectively by the drug ivacaftor. For the patients whose disease is linked to the far more predominant *CFTR* mutation p.F508del (present in 90 percent of CF patients), treatment with ivacaftor alone, or in combination with another new drug named lumacaftor, has thus far produced comparatively limited results (Davis, 2015).

Similarly, tremendous advances have been made in basic and clinical cancer research, but many challenges to widespread implementation of targeted cancer therapeutics remain (Garraway et al., 2013). Cancer is now understood to be a diverse collection of distinct acquired or inherited genomic diseases, and despite initial successes with drugs targeting specific biological processes (e.g., trastuzumab for breast cancer overexpressing HER2,[2] and imatinib for chronic myelogenous leukemia with the *BCR-ABL* translocation), the success of new treatments depends, in part, on well-validated biomarker tests to optimally select patients for targeted therapies (Mendelsohn, 2013). Clear understanding of the biological mechanisms underlying response and resistance to molecularly targeted therapy remains incomplete; the existence of so-called exceptional responders are a testament to existing knowledge gaps (see Box 5-2). Increasingly, improving the survival of patients with advanced cancer may require targeting multiple oncogenic processes in order to overcome resistance due to tumor heterogeneity and cellular context (Vogelstein and Kinzler, 2015).

An early example of the paradigm of using a single biomarker test to select patients likely to benefit from a molecularly targeted therapy is the use of trastuzumab in breast cancer. Trastuzumab was a targeted therapy approved by the Food and Drug Administration (FDA) in 1998[3] for treatment of breast cancer patients. This approval was initially for patients with metastatic breast cancer that overexpressed the HER2 protein, as detected by immunohistochemistry (IHC), a technique that uses antibody-based staining to measure levels of protein expression. Subsequent studies eventually expanded approval to include use as adjuvant therapy[4] in patients with early-stage breast cancer exhibiting either HER2 protein overexpression by IHC, or *HER2* gene amplification (increased copies of

[2] There are multiple names for the protein and gene (including *ERBB2*), but *HER2* is the term commonly used in oncology practice.

[3] See http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5256lbl.pdf (accessed July 1, 2015).

[4] Adjuvant therapy is given to patients who have undergone potentially curative intervention for their cancer (e.g., surgery or radiotherapy) in order to minimize the risk of local recurrence or metastasis.

BOX 5-2
Exceptional Responders

Response to molecularly targeted therapies, as with all medical treatments, can vary from patient to patient. Particularly interesting for researchers are the rare patients who respond exceptionally well to therapies despite lack of existing scientific explanation for such a dramatic response.

The National Cancer Institute Exceptional Responders Initiative is a pilot phenotype-to-genotype study that reverses the typical biomarker-driven research paradigm by working backward from those patients who have a unique response to treatments that are not effective for most other patients. The initiative builds upon an earlier feasibility study demonstrating that exceptional responses do exist in sufficient numbers to establish this project. Patients exhibiting an exceptional response (either a complete response, or a partial response lasting greater than 6 months) will have their tumors analyzed through a variety of methods in an attempt to characterize the molecular underpinnings of the response. It is hoped that these analyses will help explore biological mechanisms of disease and lead to new predictive markers and improved drug and diagnostic development.

The Metastatic Breast Cancer Project is a related research initiative that seeks to use social media to recruit patients with metastatic breast cancer to further the understanding of patient genomics and response to therapy. Specifically, extraordinary response to treatment will be examined, as will lack of response to treatments predicted to have been of benefit to a patient. The project has a strong emphasis on rapid learning through data sharing with the broader cancer research community, as well as an emphasis on researcher-participant collaboration. Researchers plan to publish updates and discoveries at regular intervals as well as share those discoveries with patients who complete the initial study questionnaire.

SOURCES (accessed May 12, 2016): http://www.cancer.gov/news-events/press-releases/2014/ExceptionalRespondersQandA; https://www.mbcproject.org/faq.

a gene) as detected by a technique known as fluorescent in situ hybridization (FISH) (Hudis, 2007).

Despite the seemingly straightforward relationship between HER2 amplification/overexpression and response to the drug trastuzumab, the testing methodology continued to be refined over many years, and there is still no general agreement on optimal test methods and interpretation. As detailed in the Institute of Medicine (IOM) report *Evolution of Translational Omics* (IOM, 2012a), substantial discordance was reported for both IHC and FISH results performed in community laboratories compared to a central reference laboratory in the course of two clinical trials (Paik et al., 2002; Roche et al., 2002). A 2007 panel established by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) recommended HER2 testing for all invasive breast cancers, as well

as proposed guidelines to assist in test result interpretation and to reduce errors in the laboratory testing process (Wolff et al., 2007a,b). Additionally, the panel clarified some of the technical limitations of both IHC and FISH (Schmitt, 2009). HER2 testing has improved as a result of these guidelines and other efforts to standardize testing performance and interpretation criteria, although questions remain regarding whether some patients whose breast cancer is negative for HER2 overexpression might benefit from treatment with trastuzumab (Ithimakin et al., 2013).

A more recently FDA-approved cancer immunotherapy drug, the monoclonal antibody nivolumab, further demonstrates the ongoing difficulty in establishing well-validated biomarkers to guide treatment selection by health care providers and patients. Johnson and colleagues' review of nivolumab for treatment of patients with melanoma described the process by which evolving evidence shapes the implications for clinical use of the drug (Johnson et al., 2015). Nivolumab was originally reported to be effective only in those melanoma patients whose tumors tested positive for overexpression of PD-L1, an immune system biomarker. Subsequent studies reported response to nivolumab in a small but significant number of patients whose tumors tested negative for PD-L1. Given the durable nature of the response and relatively limited early toxicity (patients who respond to nivolumab treatment tend to survive longer than is typical for advanced cancer patients, with fewer serious side effects), as well as the still-developing evidence around the biomarker PD-L1, FDA-approved use of nivolumab currently does not require a PD-L1 biomarker test.[5]

Despite this finding, similar immunotherapies are being developed, each with their own distinct PD-L1 biomarker test. FDA has recently approved the first companion diagnostic for the PD-L1 inhibitor pembrolizumab (also a monoclonal antibody), and an industry working group has been convened to harmonize the validation process across PD-1/PD-L1 biomarker tests, using different antibodies and different interpretation criteria (Averbuch et al., 2015). However, it is not yet clear whether a single test can optimally stratify patients for treatment with the various immunotherapies targeting the same pathway. Additionally, the target population for these drugs has the potential to expand rapidly. Both nivolumab and pembrolizumab have been recently approved by FDA for treatment of metastatic non-small-cell lung carcinoma, and studies have reported significant response to pembrolizumab in a separate cohort of non-melanoma patients whose tumors have abnormally high mutation rates (Le et al., 2015).

The lessons learned through the incorporation of targeted therapeu-

[5] See http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125554lbl.pdf (accessed August 4, 2015).

BOX 5-3
Biomedical Imaging and Radiation Therapy

The use of biomedical imaging, in conjunction with treatment for diseases such as cancer, has historically been as a surrogate endpoint to assess the progression of disease or response to therapy (e.g., tumor size as reported by a variety of imaging modalities) (IOM, 2010a). More recently, the National Cancer Institute has announced intention to fund research exploring the integration of biomedical imaging with other biomarkers for a more unified approach to screening, risk assessment, and diagnosis (NCI, 2016). Biomedical imaging technology may also provide alternative methods for predicting response to treatment with molecularly targeted therapies. For example, molecular imaging using positron emission tomography (PET) tracers may be able to predict response to molecularly targeted therapies in a manner similar to current molecular pathology biomarkers, simultaneously across all lesions in the body (IOM, 2007). However, clinical applications are currently limited due to the sensitivity of existing assays for mutational status, and the variability in response to treatment associated with quantity of receptors (e.g., EGFR versus HER2) as detected by PET (Pantaleo et al., 2009; van Kruchten et al., 2012). Initiatives such as the Quantitative Imaging Biomarkers Alliance™ continue to optimize and standardize the detection of imaging biomarkers for certain clinical applications, and may lead to advances in radiological techniques that would enable better prediction of response to molecularly targeted therapies.[a]

Research into biomarkers that predict benefit from radiation therapy is in the early stages, but some molecular subgroups, such as human papillomavirus (HPV)-positive head and neck squamous cell carcinoma (HNSCC), have demonstrated higher sensitivity to radiation and better prognosis compared to HPV-negative HNSCC (Mirghani et al., 2015). The role for biomarker tests to guide the use of radiation therapy in combination with molecularly targeted therapy is largely unclear; similar to the original trials of molecularly targeted therapies in unselected patient populations, initial trials assessing this interaction were disappointing (Higgins et al., 2015; Morris and Harari, 2014). Nevertheless, radiation therapy is frequently deployed in the routine clinical treatment of cancer, and future assessment of biomarkers associated with response to molecularly targeted therapy may come to include studies of the synergistic effects of radiation. Such assessment is likely to be even more complex than investigating predictive biomarkers for either therapy independently, due to the complexity and heterogeneity of cancer, and the variety in biological mechanisms of action targeted by radiation and molecularly targeted therapies (Coleman et al., 2014; Yard et al., 2015).

For this reason, the rapid learning approach to assessing biomarkers for molecularly targeted therapies discussed throughout this report may represent a pathway toward further clarifying the complementary roles for biomedical imaging and radiation therapy in the era of precision medicine.

SOURCE: [a] http://www.rsna.org/QIBA (accessed May 12, 2016).

tics into clinical practice highlight the need for standardized and well-validated biomarker tests, as well as continued evidence generation for use of both the biomarker tests and corresponding therapies. Over time, a large body of high-quality evidence could be generated from clinical experience to support optimal clinical decision making and, ultimately, improved outcomes for patients. The central importance of using high-quality evidence to guide clinical care featured prominently in the 2013 IOM report *Delivering High-Quality Cancer Care*, with the committee recommending adherence to evidence-based clinical practices, and further expansion of evidence gathering beyond clinical trials into real-world patient outcomes (IOM, 2013; Psek et al., 2015; Yu, 2015).

The absence of a robust evidence base, due to the rapid development and incorporation of new biomarker tests and targeted therapies, often leaves health care providers with less rigorous, unclear, and occasionally conflicting information on which to base their testing and treatment decisions (FDA, 2015; IOM, 2015). In certain rare diseases, this lack of evidence may be balanced by high unmet need for effective therapy where none currently exists. However, evidence suggests that some targeted therapies are context specific: colon cancers with *BRAF* mutations are largely unresponsive to BRAF inhibition despite therapeutic effectiveness in *BRAF*-mutant melanoma (Hyman et al., 2015; Prahallad et al., 2012). Due to the evolving nature of the evidence for the clinical use of predictive biomarker tests, careful consideration of the use of molecularly targeted therapies in general clinical practice is necessary to avoid potentially exposing patients to unnecessary risk for uncertain benefit.

The era of molecularly targeted therapy has implications for the fields of biomedical imaging and radiation therapy, which continue to be critical components of the treatment of cancer (see Box 5-3). For example, gene signatures[6] may eventually be useful to identify patients for whom radiation therapy may not provide durable control of their disease, but more research is needed prior to adoption for clinical use (Ahmed et al., 2015; Torres-Roca et al., 2015).

EQUITY IN ACCESS TO TESTING AND EXPERTISE

Fair access is a key ethical concern in medicine. The bedrock ethical principle supporting fair access to health care is the principle of social justice: treat people as equals. Treating people as equals has been interpreted to mean access to opportunity (Rawls, 1971) and access to resources (Dworkin, 1981). Each interpretation entails equal access to health care,

[6] Gene signatures are indexes or scores derived from testing multiple genes from one specimen.

either as an opportunity that some have and therefore all should have or as a necessary resource that should be available to all (Daniels, 2013).

In the context of precision medicine, challenges to obtaining access may confront patients of particular economic, ethnic, and cultural backgrounds and geographic locations. These challenges include the ability of patients to access and interpret complex information, to obtain coverage for biomarker testing, and to receive treatment with targeted therapies, if appropriate. In such a data-driven field, datasets skewed by the differential access to new technologies threaten the generalizability of conclusions reached through analysis of those datasets. Additionally, fair access requires that health care professionals possess the expertise to properly order tests and interpret the results to determine optimal therapy selection, in spite of the challenges posed by the rapid pace of clinical knowledge development outlined previously.

Potential Obstacles to Public Access and Understanding

Fair access to effective biomarker testing for molecularly targeted therapies may be jeopardized by a number of factors. These include (1) technical limitations of the biomarker tests and the evidence underpinning interpretation and use of the test results; (2) attitudes and behaviors relating to people from underserved communities; and (3) income inequalities (Chadwick, 2013; McClellan et al., 2013). Preventing the growth of disparities in access to biomarker tests for molecularly targeted therapies, and the resulting disparities in beneficial health outcomes, may depend on lessons learned from disparities in access to other forms of genetic testing.

Research on patterns of genetic predisposition testing reveals that more variants of unknown significance are identified in test results from minority populations than in those of European descent (Oloparde, 2004), and as a result the usefulness of genetic tests is reduced for those populations. Also, prediction models tend to be Euro-centric. Some models in particular underestimate risk for African Americans (Adams-Campbell et al., 2009) and Hispanics (Banegas et al., 2012), thereby potentially limiting access to appropriate care for those populations (Kurian, 2010). Interestingly, in a Government Accountability Office investigation, none of the testing companies that were sent specimens could provide fictitious African American and Asian clients with complete test results, though none of the companies' advertising alerted the consumer to this testing coverage gap (GAO, 2010). The potentially harmful effect of advertising on the public's perception of precision medicine, particularly through false or misleading advertisements, is described in Box 5-4.

A second source of unequal access to effective tests emanates from characteristics of the people in underserved communities. For example,

African Americans historically have been reluctant to use genetic services due to fears of genetic discrimination and stigmatization, and racial discordance between physicians and patients remains a persistent obstacle to shared treatment decision making (Lin and Kressin, 2015; Peterson et al., 2002). Research also suggests that minority patients are more likely to report an unmet need for discussion of genetic testing with their physician (e.g., for breast cancer risk and corresponding risk-reducing treatment); this perceived need may be influenced by cultural or language barriers, and misconceptions about genetic testing (Jagsi et al., 2015). The health care facilities available to some minority patients may be less equipped with respect to medical technology, or present other institutional barriers to participation in clinical research (Hasnain-Wynia et al., 2007; Joseph and Dohan, 2009). Nevertheless, large datasets are needed to further develop the association between genetics and disease risk or treatment response for all patient populations, and varying desire or ability among different populations to use genetic services hinders the compilation of these datasets. Moreover, accurate family histories are crucial to health assessments in the genomics era, yet both low socioeconomic status and being a member of a minority community are correlated with lower accuracy of personal and family histories (Abraham et al., 2009; Dominguez et al., 2007; Soegaard et al., 2008).

Income inequality may also contribute to unfair access. A recent study found that among insured women, the use of a 21-gene expression assay in women with newly diagnosed breast cancer was highest in geographical areas that had the largest income inequality, whereas the use of the test was lower in areas with more equal income distribution[7] (Ponce et al., 2015). Furthermore, in areas with greater income inequality, the use of the test was significantly higher among high-income women compared to lower-income women, while there was no such disparity in the areas with less income variability. Other factors that correlated positively with the use of the 21-gene expression assay included being non-Hispanic white, being a younger age, having point-of-service insurance plans rather than other types of coverage, and having a lower Charlson score[8] (Ponce et al., 2015). The authors concluded that, even among the insured, high income may result in better access; this may be particularly problematic given that the United States ranks high in income inequality among developed economies (DeNavas-Walt et al., 2013). However, a similar study of Medi-

[7] The Gini index is a measure of statistical spread of income across a population, commonly used to describe income inequality. In this study, a Gini index variable was computed using Census tract-level average income in three categories: less than $50,000; $50,000-$100,000; and greater than $100,000.

[8] Charlson score is a measure of comorbidity, with a higher value indicating multiple co-occurring conditions and predicting higher 10-year mortality.

BOX 5-4
Advertising and Marketing Claims

The intersection of patients, laboratories, and biomarker tests used to guide molecularly targeted therapy is often encountered in marketing materials and advertisements. Using Google, Bing, Yahoo, a literature review, and exhibitor information from a national oncology conference, one study identified 55 websites marketing oncology germline testing, genomic interpretations, and/or personalized medicine, defined as individualized care based on genomic or tumor data (Gray et al., 2015). Fifty-six percent of the websites were sponsored by commercial entities, 20 percent by academic institutions, 15 percent by private institutions, and 5 percent by individual physicians. Eighty-eight percent of the 32 websites that offered somatic analysis marketed at least one nonstandard test lacking evidence of clinical utility. Thirty-one of the websites claimed they could find more effective treatments, with messages such as "Every option we present to you has passed rigorous scrutiny and has been proven to have a direct and positive impact on the treatment of your particular form of cancer." Furthermore, the websites provided more information on the benefits of personalized medicine than on the limitations ($p < 0.001$), as has been found previously (Caulfield and McGuire, 2012; Lachance et al., 2010). This type of marketing effort can influence patients' attitudes, knowledge, and decision making (Abel et al., 2009; Mouchawar et al., 2005a,b), so the unbalanced messaging is disconcerting.

In 2006, officials from the U.S. Government Accountability Office (GAO) testified that the companies offering direct-to-consumer genetic testing made disease predictions that were not supported by evidence (GAO, 2006). In 2010, GAO undertook a similar investigation by purchasing 10 tests each from 4 different companies, sending paired specimens from the same DNA donor, one with correct

care recipients, albeit a different population, did not reveal any disparities in test access among groups with different incomes or racial backgrounds (Dinan et al., 2015).

These studies did not examine access to testing among the underinsured or uninsured population, but research has shown, for example, that the costs of cancer treatment for the uninsured significantly exceed public and private payers' negotiated rates, and consequently may restrict access (Dusetzina et al., 2015). In 2006, the Department of Health and Human Services (HHS) Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) found that significant variation in coverage of genetic testing existed among state Medicaid programs, and moreover that the ease with which this coverage, as an optional benefit, could be rolled back may exacerbate heterogeneity in access to genetic testing (SACGHS, 2006). Subsequent analysis of data from 2011 by the Office of the Inspec-

identifiers (age, race, and select medical history) and one with fictitious identifiers (GAO, 2010). The GAO staff then made undercover calls to seek health advice from the companies based on the risk profiles in the test results. The GAO staff also called these companies and 11 additional companies to ask about supplemental sales, test reliability, and privacy. Genetic experts were consulted to verify or dispute the claims made. GAO found 10 egregious examples of deceptive marketing, including claims that the tests were diagnostic and prognostic.

The Federal Trade Commission (FTC) regulates the advertising of medical devices and tests. The FTC works to prevent fraudulent, deceptive, and unfair business practices by manufacturers of all medical products. The jurisdiction of the FTC does not include labeling of medical devices and tests approved by the Food and Drug Administration (FDA). However, because most tests are currently not regulated by FDA, claims made about such tests fall under the jurisdiction of the FTC. If an advertisement is deceptive, the FTC considers whether it is likely to mislead reasonable consumers and affect purchasing decisions. Additionally, the FTC examines advertised claims, both explicit and implicit, as well as the omission of important information that might mislead a consumer in his or her decision to purchase a product. The FTC has filed charges against a small number of genetic testing companies,[a,b] all of which reached a settlement with the FTC.[c,d] The FTC website also provides an excellent warning to consumers about the unreliability of the claims on direct-to-consumer testing websites (FTC, 2014).

SOURCES (accessed May 12, 2016): [a] https://www.ftc.gov/system/files/documents/cases/140512genelinkcmpt.pdf; [b] https://www.ftc.gov/system/files/documents/cases/140627lorealcmpt.pdf; [c] https://www.ftc.gov/news-events/press-releases/2014/05/ftc-approves-final-consent-orders-settling-charges-companies; [d] https://www.ftc.gov/news-events/press-releases/2014/06/loreal-settles-ftc-charges-alleging-deceptive-advertising-anti.

tor General (OIG) reported that all but one state Medicaid program provided some level of coverage for genetic testing, but policies remained non-specific, case-by-case, or were evaluated by a variety of factors that continued to perpetuate heterogeneity in access to testing (OIG, 2012).

The IOM has called repeatedly for policies to ensure health insurance coverage for all U.S. citizens (IOM, 2004, 2009). Health insurance coverage was discussed as a primary method to ensure access to care in *Delivering High-Quality Cancer Care*, though the report acknowledged that access alone would not ensure quality, and recommended the development of innovative, community-focused programs aimed at identifying and reducing disparities (IOM, 2013). Expanding U.S. health insurance coverage is a primary goal of the Patient Protection and Affordable Care Act,[9]

[9] Patient Protection and Affordable Care Act, Public Law 111-148, 111th Congress, 2nd Sess. (March 23, 2010).

and implementation of the legislation is ongoing. However, state-level variation in implementation policies can impact enrollment and access (Sommers et al., 2015), and a recent Census Bureau report states that 10.4 percent, or approximately 33 million persons, were uninsured for the entire 2014 calendar year (Smith and Medalia, 2015). Thus, the uninsured and underinsured remain a population that is vulnerable to lack of access to health care services in general and in particular to precision medicine and molecularly targeted therapies.

Gaps in Patient Understanding

Once a patient successfully gains access to the health care system to obtain treatment, the degree to which the patient understands his or her clinical condition and recommended options can influence their health outcomes (Ancker and Kaufman, 2007; Nelson et al., 2008). Ensuring that patients understand their treatment options is challenging, particularly in diseases such as cancer, given the severity of the disease and the complicated nature of the treatments (Fallowfield and Jenkins, 1999). Many cancer patients can be overwhelmed by the complex information and terminology related to their diagnosis; Tom Brokaw, while being treated for myeloma, likened the experience to being in a foreign culture, commenting that "most patients enter a doctor's office or hospital as if it were a Mayan temple, representing an ancient and mysterious culture with no language in common with the visitor" (Brokaw, 2015). The pervasive difficulty in understanding a cancer diagnosis and treatment options is magnified in genomic testing by patients' low level of overall health literacy, and lack of specific genetic knowledge.

Although patients do not need to understand all of the complex concepts involved in genomic testing in order to participate in shared decision making, persistent concerns exist about the degree to which variability in health literacy and numeracy affect patient engagement and health outcomes (Paolucci and Wicklund, 2015). In *Delivering High-Quality Cancer Care*, the IOM described challenges to patient-centered care that included failure on the part of clinicians to understand patient needs and preferences, and cultural or language barriers that inhibit effective shared decision making for often complex cancer treatments (IOM, 2013). The IOM has also emphasized that health literacy and particularly health numeracy, defined as "the degree to which individuals have the capacity to access, process, interpret, communicate, and act on numerical, quantitative, graphical, biostatistical, and probabilistic health information needed to make effective health decisions" (Golbeck et al., 2005, p. 375), are critical for understanding biomarker-related decision making and potential outcomes (IOM, 2010a). The report noted that because numeracy does not

correlate as closely with education as literacy does (Nelson et al., 2008), further research into solutions to improve patient numeracy are needed not only for the purpose of shared health care decision making, but also to enable the public to help shape and accelerate the adoption of relevant health policy.

Another factor that contributes to the difficulty in adequately communicating information about genomic testing to patients is the high expectations that have accompanied precision medicine. Government agencies, professional organizations, and researchers often discuss the promise of precision medicine without providing realistic assessments about the current capabilities and likely timeline for meaningful breakthroughs. For example, many cancer patients believe that having their tumor genome sequenced will result in the discovery of a mutation that will enable successful treatment of their cancer with a targeted therapy. However, recent studies have found that potentially actionable targets are identified in less than half of patients specimens sequenced (an exception is an abstract presented at ASCO's 2015 annual meeting, which reported identification of actionable targets in 77 percent of specimens), with limited data on patient outcomes (Meric-Bernstam et al., 2015; Mody et al., 2015; Nadauld et al., 2015).

Initial or highly cited scientific publications of biomarker effect sizes tend to report stronger associations with disease outcomes and risks than are demonstrated in subsequent meta-analyses (Ioannidis and Panagiotou, 2011). The media tends to disproportionately cover these publications due to their initial exciting findings, more than follow-up or conflicting studies, which can result in an unbalanced portrayal to the general public (Gonon et al., 2012). Historically, the manner in which the news media report scientific advances has been a major contributor to public understanding and expectations (Anderson et al., 2011); this can contribute to unrealistic expectations and/or fears in the context of genomic medicine (Condit, 2007; Condit et al., 1998; Lea et al., 2011). A decade ago, the Kaiser Family Foundation reported that 40 percent of the public at the time relied on news media (television, radio, newspaper) as their primary source of health and health care information (other primary sources included health professionals, friends and family, and the Internet) (Kaiser Family Foundation, 2005). More recent research shows the Internet and other new media technologies[10] are increasingly pervasive, particularly for younger people (Kaiser Family Foundation, 2010). Survey data from 2013 indicated that 35 percent of U.S. adults used the Internet to obtain information about a health condition, and nearly half of

[10] New media technologies include smartphones, laptops, and tablet devices, and these may serve as delivery platforms for electronic versions of television and print media.

those subsequently consulted a health care provider based on their online research, bringing their expectations into the clinic (Pew Internet, 2013).

The evolving field of precision medicine may carry with it the unintended consequence of intensifying disparities in access to advanced health care services. It is essential that during efforts to standardize the analytic and clinical validity and develop evidence of the clinical utility of biomarker tests for molecularly targeted therapies, resources be dedicated to a comprehensive investigation and assessment of disparities in access to both testing and expertise. These may be due to a variety of economic, ethnic, cultural, and geographic factors, and once identified, efforts should be focused on reducing such disparities. The Clinical and Translational Science Awards were established with many focus areas, one of which was community and health disparities research, and may serve an important role in ensuring health disparities do not increase with the widespread adoption of precision medicine (IOM, 2012b). The committee recommends that **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 (Recommendation 8a).** Existing evidence of differential understanding or access, as cited in this section of the report, is currently limited. Therefore, the committee acknowledges this research need as a first step to characterizing potential obstacles to access, which could help inhibit growth in disparities as a result of precision medicine.

Ensuring Provider Expertise

A health care provider's recommendation for a targeted therapy depends on patient preference, clinical condition, and reliable biomarker test results, and is guided by available practice guidelines that aim to improve patient outcomes (practice guidelines are discussed further in a separate section below). The interrelated effects on clinical practice of guidelines, other published clinical data, and FDA approval and labeling are difficult to separate. Studies of physician uptake of new targeted therapies over time have demonstrated their responsiveness to both regulatory decisions and evolving guidelines (Dotan et al., 2014; Neugut et al., 2012). However, even as biomarker tests for molecularly targeted therapies have become more common and physicians have grown more accustomed to their availability, lack of confidence in the use of genetic tests has persisted in a significant proportion of providers (Cox et al., 2012b; Freedman et al., 2003; Gray et al., 2014). In 2008, SACGHS found that health care providers have difficulties keeping current with which tests to order and how to apply the results to therapy (SACGHS, 2008). In the preceding year, Guttmacher and colleagues outlined the barriers

to educating non-geneticist physicians about genetics, including medical school curriculum deficiencies, misperceptions and incorrect physician attitudes toward genetics (i.e., that genetic information is peripheral to most clinical care), lack of bridges between basic sciences and clinical care, and a need for more practical, case-based continuing education (Guttmacher et al., 2007).

Although there have been long-standing concerns that primary care physicians lack training in genomics (Scheuner et al., 2008; Suther and Goodson, 2003), recently these concerns have extended to specialty providers as well, such as oncologists and pathologists. Gray and colleagues reported that even in a comprehensive cancer center, a significant minority of physicians described themselves as having "low genomic knowledge," and that even among those providers who were more comfortable with genomic tests, there was wide variation in the interpretation, disclosure to patients, and clinical use of genomic test results (Gray et al., 2014). Although physicians have always had to adapt to medical technology innovations, how well they can adapt to the increasing availability of omics test results remains to be seen (Vassy et al., 2015). Current variation in clinical practice points to the potential difficulties of implementing targeted therapeutics based on biomarker tests in various clinical settings.

Maintenance of Certification (MOC) is a process administered under the American Board of Medical Specialties (ABMS) that is intended to avoid limitations in training and knowledge for physicians in practice that may influence the health care of their patients (Batmangelich and Adamowski, 2004). The four components addressed by MOC are professional standing (i.e., licensure); lifelong learning and self-assessment, which is generally interpreted as a requirement for participation in continuing medical education; cognitive expertise, as assessed by a proctored examination; and performance in practice. Each of these components is adapted by the various specialty boards to meet their specific needs, though some physicians that affirm the value of recertification question the MOC process's relevance and effectiveness as it is currently structured (Drazen and Weinstein, 2010; Goldman et al., 2010). Research into MOC examination scores has demonstrated an association between higher scores and rates of evidence-based care processes for Medicare patients (Holmboe et al., 2008) as well as for patients with diabetes (Hess et al., 2012).

However, assessments of competency related to biomarker tests and their use for directing targeted therapies are lacking outside of certain specialties (e.g., pathology). This is complicated by the fact that board certification and MOC for some types of specialists (e.g., medical oncologists) are distributed across a variety of specialties such as internal medicine or obstetrics/gynecology. This distributed framework of responsibility

ensures flexibility for assessing competence in a highly complex profession, but may also require coordinated action by both ABMS and the independent specialty boards to ensure competence in the use of crosscutting medical technologies such as biomarker tests and molecularly targeted therapies. ABMS recently released updated standards for the MOC program that direct member boards to take action to increase program quality and relevance, to continuously monitor the quality and improvement of programs, and to "incorporate ways in which diplomates may engage in specialty-relevant, performance-in-practice assessment followed by improvement activities when practice gaps are identified" (ABMS, 2014, p. 12).

The role of ensuring competence of health care providers for improving patient care has featured prominently in previous IOM reports. In *Redesigning Continuing Education in the Health Professions*, the IOM similarly called for collaboration to assess the impact of continuing professional development on competence, health care outcomes, and patient safety (IOM, 2010b). *Delivering High-Quality Cancer Care* included recommendations to ensure the competence of both oncology and nononcology providers, and particular reference was made to the use of flexible cancer core competencies to improve cancer care delivery at a number of sites (Cox et al., 2012a; IOM, 2013; Smith et al., 2009). The report also drew from a National Cancer Institute (NCI) monograph on the value of patient-centered communication and shared decision making (Epstein and Street, 2007) in outlining recommendations for high-quality cancer care. *Improving Diagnosis in Health Care* further emphasized the value of interpersonal and communication skills to health care providers, including communication with patients (NASEM, 2015), citing the core competencies developed by ABMS and the Accreditation Council for Graduate Medical Education (ACGME) as evidence of the role played by licensing, certification, and MOC to improve health care delivery (ABMS, 2015; ACGME, 2015; NASEM, 2015).

The previous chapter discusses the committee's rationale and recommendations for using electronic health records (EHRs) and related tools to enhance clinician decision making, but as precision medicine continues to expand into medical practice in general, the committee recommends that **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 8c).** Particular attention should be given to competency in communication with patients about the therapeutic implications of their test results, and realistic expectations of resulting outcomes. In addition to the roles for ABMS and ACGME, ensuring competency will require medical education organizations, including the National Board of Medical Examiners, the

Liaison Committee on Medical Education, the Federation of State Medical Boards, and the Educational Commission for Foreign Medical Graduates, to integrate these concepts into medical school curricula.

Underlying challenges to the effective clinical use of biomarker tests and targeted therapies include the current ambiguity surrounding standards for clinical utility (discussed in Chapter 3 of this report), as well as an often immature evidence base, further complicated by issues with research reproducibility that limit the impact on health outcomes (Bowen and Casadevall, 2015). In addition, the ability for health care providers, particularly primary care physicians, to keep pace with the speed of new clinical research and knowledge continues to decline as the number of new publications increases (Williams, 2015). As discussed previously in this chapter and throughout this report, the validation of biomarker tests and their association with response to molecularly targeted therapies in select patient populations is a process that involves accumulating large amounts of clinical data over time. The clinical implications, whether for testing methodology or treatment recommendations, would ideally evolve in parallel with the evidence and ultimately be available within clinical decision support systems (as discussed in Chapter 4).

However, in the process of developing a mature evidence base for any given intended use of a biomarker test, unclear or emerging data could lead to clinical decisions that are ineffective or put patients at unnecessary risk. Policy mechanisms to ensure that clinicians and patients have access to additional expertise, as needed, are necessary to limit the inappropriate use of biomarker tests for molecularly targeted therapies. Larger health care centers and academic medical centers are able to leverage multidisciplinary expertise to ensure evidence-based treatment in the care of patients with complex conditions. A focus on multidisciplinary care, particularly in specialties such as oncology, is recognized by accreditation entities overseeing hospitals and other large health care institutions (ACS, 2012). Multidisciplinary conferences, also referred to as multidisciplinary tumor boards, can be convened to discuss treatment options given specific pathologic features, biomarker test results, and a variety of other clinical factors specific to an individual patient. However, there is variation in the implementation of these tumor boards. While some studies have documented improvement in some outcomes or increased clinical trial enrollment, the effect of widespread adoption will require further assessment (Blayney, 2013; Keating et al., 2013; Kehl et al., 2015; Kuroki et al., 2010). Nevertheless, there is an opportunity for smaller clinical practices to access multidisciplinary, molecular expertise needed to assess biomarker tests and determine appropriate molecularly targeted therapy.

The Role of Telemedicine

Collaboration among health care teams for the purposes of evaluating treatment options for individual patients can be facilitated by the use of telemedicine, also known as telehealth. Telemedicine is defined by the American Telemedicine Association (ATA) as:

> The use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status. Telemedicine includes a growing variety of applications and services using two-way video, e-mail, smart-phones, wireless tools and other forms of telecommunications technology. (ATA, 2015)

The Health Resources and Services Administration of HHS, which evaluates the use of telehealth through the administration of federal grants, defines telehealth in similar terms, as "the use of electronic information and telecommunications technologies to support long-distance clinical health care, patient and professional health-related education, public health and health administration" (HRSA, 2015). The terms "telemedicine" and "telehealth" today are generally used interchangeably, though historically telemedicine has been connected more closely to actual clinical services, while telehealth referred more broadly to health services including education and disease monitoring and management (ATA, 2015; CCHPCA, 2015; IOM, 2012c).

Telemedicine thus consists of multiple services, including primary care or specialist consultation, patient or provider education, and remote patient monitoring, which can be delivered through various methods. Live videoconferencing ("synchronous"), and store-and-forward systems ("asynchronous") can be used to deliver clinical consultation with or without real-time clinician and patient interaction, for example, and electronic communication and mobile technologies facilitate remote monitoring and health education of patients and health care providers (ATA, 2015; CCHPCA, 2015). However, variation exists among individual health payer policies related to coverage and reimbursement of these services.

Until recently, the Centers for Medicare & Medicaid Services (CMS) maintained a narrow interpretation of reimbursable telemedicine services. Payment to providers previously depended on patients living in rural areas, and only certain types of clinical services were permitted (e.g., tobacco cessation, behavioral counseling for obesity), often with requirements for real-time interaction between provider and patient (e.g., video- or teleconferencing) (CMS, 2014). However, under a new rule, additional Current Procedural Technology (CPT) codes will expand CMS coverage of telemedicine beyond rural populations, and will include services such as non-real-time analysis and interpretation of clinical or physiologic data for those patients with multiple (defined as two or more) chronic

conditions, including cancer, diabetes, asthma, and heart disease (CMS, 2015). Limitations to this new policy include the multiple required chronic conditions, and a lack of payment tied to the collection of the data to be analyzed (ATA, 2014).

In *Improving Diagnosis in Health Care*, the National Academies of Sciences, Engineering, and Medicine acknowledged the potential for telemedicine technology to improve coordination of diagnostic management teams, as well as affordability and patient access to health care (NASEM, 2015). Relevant to molecularly targeted therapies, the report described the use of telepathology to improve diagnosis through granting immediate access to off-site subspecialty pathologists, and cited research suggesting the educational potential of having the local and consulting pathologists examine a case simultaneously. Teleoncology likewise has the potential to improve care and access. European countries have begun to use and reimburse for such care management services in an attempt to address heterogeneity in cancer outcomes. In the United States, "twinning" partnerships between larger medical centers and local centers serving rural or underserved populations may serve a similar purpose (Hazin and Qaddoumi, 2010). Studies of the influence of specific components of teleoncology, including real-time video consultations and hereditary cancer screening, suggest the ability to deliver adequate services, but conclude that further evaluation is necessary (Kitamura et al., 2010; Zilliacus et al., 2010, 2011).

To ensure judicious use of biomarker tests and molecularly targeted therapies, the committee recommends that **the Secretary of HHS and CMS should conduct demonstration projects to design and assess the effectiveness of collaborative partnerships between community health care providers and larger health care centers and/or academic medical centers to be part of a rapid learning system (Recommendation 8b).** These demonstration projects should examine the use of reimbursement incentives by CMS for the multidisciplinary collection and review of patient data with clinical recommendations, using distance technology or telemedicine. This would bring appropriate expertise into diagnostic management teams such as multidisciplinary tumor boards, to promote parity of access to appropriate biomarker use and clinical decision making. Individuals with molecular genomics expertise, including molecular pathologists, medical geneticists, and genetic counselors, should be included.

The continued growth of the clinical genetics workforce is integral to the shared decision making processes used to select targeted therapies. As molecularly targeted therapies continue to expand into clinical practice, clinicians will increasingly seek support from these providers (i.e., molecular pathologists, medical geneticists, and genetic counselors) and current estimates suggest a need to expand training programs to accom-

modate this (Paolucci and Wicklund, 2015; Wicklund and Trepanier, 2014). Coverage and reimbursement policies in the U.S. health care system are variable across payers, particularly those related to genetic counseling; this variability may limit access to expert guidance by non-geneticist physicians and their patients. In addition to the above recommendation to explore collaboration between larger medical centers and community centers, the committee recommends that **these demonstration projects include reimbursement by CMS for genetic counseling services.**

SPECIMEN ACQUISITION AND QUALITY

The clinical use of reliable biomarker tests to guide molecularly targeted therapy selection depends on many related processes. The central process is the testing itself, the oversight of which is discussed in Chapter 3. However, a number of other processes before and following clinical laboratory testing need to be considered, which can affect the accuracy and reliability of test results and patient safety. The brain-to-brain loop model[11] for laboratory testing (see Figure 5-1) describes nine steps necessary to generate a laboratory test result, including test ordering, specimen collection, patient identification, specimen transportation, specimen preparation, analysis, result reporting, interpretation, and clinical action (Lundberg, 1981; Plebani et al., 2011). This model reflects the collaborative nature of clinical laboratory medicine, and provides a more granular understanding of the processes that lead to clinically useful test results. This section addresses interdisciplinary processes—including test ordering, specimen collection, processing, and handling—that are critical not only to the integrity of biomarker tests, but also to patient safety.

The acquisition of high-quality tissue specimens upon which to perform biomarker testing, as well as the development of sophisticated biobanks to store these specimens for ongoing research, is critical (Poste, 2011). High-quality specimen acquisition is particularly important for biomarker tests that use tissue-based somatic biomarkers (e.g., in cancer) because of the often discrete location of these tissues as well as specific specimen and methodological requirements of biomarker tests (Aisner and Marshall, 2012; de Gramont et al., 2015; Narmala and Boulmay, 2013). Low-quality, inadequate, or indeterminate specimens lack sufficient tissue for analysis, or lack the required tissue to be tested (e.g., obtaining normal tissue instead of tumor), and can delay a patient's access to molecularly targeted therapies or hinder collaborative research that requires specimen collection across diverse clinical settings (Dolgin, 2016). Such errors can

[11] The brain-to-brain loop model is named for the cycle of interaction among patients, physicians, and laboratory staff that can result in optimal laboratory testing and result reporting.

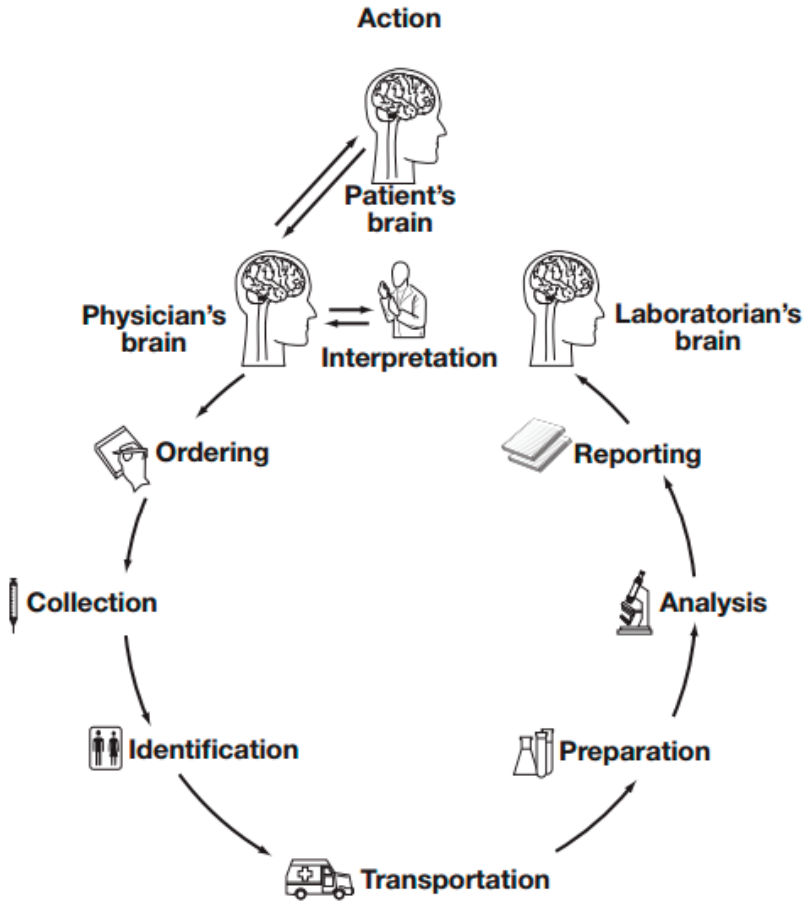

FIGURE 5-1 The brain-to-brain loop concept for laboratory testing.
SOURCE: Plebani et al., 2011.

be due to inexperienced personnel obtaining the specimen (Choi et al., 2011), or lack of a pathologist's involvement in the procedure to determine if diagnostic tissue has been obtained (ACR and ARRS, 2010; Gomez-Macias et al., 2009). The complexity involved in consistently obtaining adequate specimens requires communication throughout the entire health care team, including clinicians, surgeons, radiologists, and laboratory professionals, as well as consideration of the unique clinical conditions of each patient (Yamaguchi et al., 2012). The National Academies of Sciences, Engineering, and Medicine report *Improving Diagnosis in Health Care* also

emphasized the need for a team-based approach to reduce errors in the steps performed outside the clinical laboratory, particularly test ordering, specimen acquisition, and result interpretation (NASEM, 2015).

Across clinical practice settings, a variety of administrative, procedural, and billing issues arise when requesting biomarker tests on tissue specimens, particularly a test from a laboratory outside the institution with limited interaction with the practice. For example, typically several administrative steps are involved in establishing the relationship, including at least a brief vetting process regarding regulatory and compliance issues, or a more extensive due diligence (e.g., if the laboratory is a start-up); a formal, signed Laboratory Services Agreement[12] detailing many aspects of the relationship also may be necessary. In addition, clinical questions or concerns may arise (e.g., in what specific instances patient safety might override tissue requirements for testing), which may be best discussed in a multidisciplinary group meeting, or may even warrant establishing a dedicated workgroup.

When testing involves biopsy procedures to obtain tissue, clear communication regarding the tissue requirements for biomarker tests is necessary to reduce the incidence of inadequate or insufficient specimens, and to ensure the efficiency of the entire process among all involved health care providers. Each clinical laboratory defines its own processes and procedures for the majority of tests based on the most appropriate biomarker testing technologies (e.g., next-generation sequencing platforms); cancer biomarker tests for molecularly targeted therapies, for example, may be performed on specimens with varying requirements[13] (Dietel et al., 2015; IOM, 2015). Therefore, providers need to discuss the testing methodology and tissue or specimen requirements with their onsite pathologist and laboratory colleagues prior to specimen collection, and not assume they possess knowledge of the specimen requirements for a novel biomarker test. Also, special processes may be required for specimen handling (e.g., specific preservative or handling in the "gross room"[14]), particularly for fresh or flash-frozen tissue, which may vary with tissue type and specific biomarker test (Hatzis et al., 2011; Shabihkhani et al., 2014). Regardless of specific test requirements, requisition forms and any other required paperwork should be obtained from the specialty laboratory in advance of

[12] These contractual agreements may define provided services and related standards, procedures for specimen custody, confidentiality, compensation, indemnification, and other miscellaneous provisions related to the business relationship.

[13] Specimen requirements may include total tissue volume, tumor tissue volume, overall cellularity, percentage of viable cancer cells, tissue types, specimen format, fixative, and others.

[14] The gross room is the area where specimens from the operating room are transferred and processed for pathological review.

specimen collection and reviewed by ordering clinicians and pathologists. Any required shipping kits or labels should be obtained well in advance and made available appropriately (e.g., to the histology laboratory or to the referral laboratory staff).[15]

A role exists for professional societies to help ensure the integrity of biomarker testing for molecularly targeted therapies, through the development of specimen acquisition and testing guidelines for the most frequently ordered tests (Dietel et al., 2015; Schilsky, 2014). Similarly, the *Improving Diagnosis in Health Care* report recommended that payers provide coverage for time spent by pathologists advising health care providers on the selection, use, and interpretation of tests, which are not currently coded or covered (NASEM, 2015). To ensure the performance and accuracy of biomarker tests for molecularly targeted therapies, the committee recommends that **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 (Recommendation 9a).** Health care professionals who collect, process, and handle patient biomaterials for biomarker testing should ensure that adequate tissue is acquired to perform all necessary testing so patients are protected from unnecessary or repeated procedures, and that specimens are properly handled, with documentation in the EHR and the laboratory information system.

In making this recommendation, the committee looked to existing collaborative models of generating standards for new therapies. The Foundation for the Accreditation of Cellular Therapy (FACT) recently released common standards for cellular transplantation services, including a thorough discussion of personnel qualifications, quality controls, procedures, and processes for handling and storing cellular therapy products (FACT, 2015). The FACT standards also point out that institutions should examine their specific policies and procedures and determine what adjustments should be made or whether additional or different standards should apply. Similarly for biomarker tests for molecularly targeted therapies, the variability in specimen requirements and testing methodologies, even between tests for the same biomarker as well the number of tests needed to be performed on a given specimen, will require development of interdisciplinary best practices and workflows to ensure consistent acquisition of high-quality specimens to meet the testing needs of patients and health care providers. The NCI's *Best Practices for Biospecimen Resources* could

[15] Additionally, billing and reimbursement should be clarified on both sides—for the testing lab, the sending institution, and sometimes even for the ordering clinician's office.

serve as a useful starting point for development of such interdisciplinary institutional standards (NCI, 2007). Although these general guidelines and best practices will be useful, the requirements for each specific test will need to be addressed at an institutional level.

The committee considers patient safety the ultimate goal of standardized specimen acquisition and testing. Specimens that are insufficient for all ordered tests hamper timely access to the initiation of therapy, which is critical in diseases such as cancer. Repeat procedures to acquire sufficient tissue put patients at unnecessary risk of complications. To ensure compliance with the professional standards generated in Recommendation 9a, the committee additionally recommends that **the National Quality Forum (NQF) should develop quality measures that assess unnecessary repeat specimen collections (Recommendation 9b).** NQF is a nonprofit organization that convenes working groups to develop and endorse quality-related measures, with the goal of improving health outcomes and the efficiency of health care delivery (NQF, 2015). NQF is particularly suited to developing the quality measure recommended by the committee, given the diverse range of stakeholders represented on the forum (including the pharmaceutical and diagnostics industries, regulatory agencies, payers, health care providers, and patients and their advocates).

CLINICAL PRACTICE GUIDELINES

The relationship between biomarkers and health outcomes can be complex. An IOM report concluded that the optimal clinical use of biomarkers depended on contextual analysis of the evidence, and further that:

> It is most essential that this analysis be carried out by a panel of experts, as scientific and medical judgment is necessary to weigh the possible advantages and disadvantages of the proposed biomarker use. These evaluations should take place on a per use basis, because use depends on the context of use proposed and because knowledge and technology continually evolve. (IOM, 2010a, p. 10)

Molecularly targeted therapies represent promising treatment options for patients suffering from the conditions these drugs are approved to treat; however, the ability for biomarker test results to suggest the use of molecularly targeted therapies in other conditions (particularly in oncology) also represents a potential challenge for health care providers. For example, off-label use in oncology is relatively common and a small but growing number of oncologists choose to select treatments beyond their FDA-approved indications (i.e., "off-label") based on emerging biomarker test results (e.g., treatment with erlotinib in patients who have exhausted standard treatment options, but whose cancer contains epidermal growth

factor receptor [EGFR] mutations) (Carlson et al., 2015; Conti et al., 2013; Krzyzanowska, 2013). However, the potential benefit of selecting treatment based on emerging biomarker tests remains uncertain, though controlled clinical trials are under way (Andre et al., 2014; Le Tourneau et al., 2015) (see also Box 4-2 in Chapter 4). Clinical practice guidelines (CPGs), generated by professional and other organizations, attempt to meet this need for guidance and distinguish clinically meaningful options that clinicians and patients can consult when making health care decisions.

This is of particular importance given the rapid rate of technological innovation in the field of precision medicine, which will continue to outpace physician knowledge of interpretation and use of biomarker tests, driving both increased reliance on CPGs (Schully et al., 2015) and increased pressure for more frequent guideline updates. The inclusion of a biomarker test and corresponding molecularly targeted therapy in a trustworthy CPG can lead to more effective use in clinical practice. Research is beginning to assess adherence rates, and the impact on survival and quality of life associated with adherence to certain guidelines in clinical conditions such as breast (Cloud et al., 2015; Henry et al., 2014) and ovarian cancers (Lee et al., 2015). However, while inclusion in a CPG may suggest a biomarker test and corresponding targeted therapy have clinical utility when used together, formal assessment of clinical utility is beyond the scope of CPG development.

The IOM report *Clinical Practice Guidelines We Can Trust* defines CPGs as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of the evidence and an assessment of the benefits and harms of alternative care options" (IOM, 2011a, p. 4). The IOM report established standards for generating trustworthy CPGs (see Table 5-1), and a companion IOM report outlined the requirements for performing comprehensive systematic reviews of evidence to inform guideline development (IOM, 2011b). The IOM's CPG report also detailed challenges in existing guidelines development, including weak evidentiary standards, lack of methodological transparency, concerns with conflict of interest (COI), and inconsistency among related guidelines. The report stated that guidelines that successfully surmounted these concerns would "ultimately . . . give users confidence that guidelines are based on best available evidence, largely free from bias, clear about the purpose of recommendations to individual patients, and therefore trustworthy" (IOM, 2011a, p. 77).

Methodological transparency and COI continue to be refined on the organizational level, with many expert panels outlining the criteria used in the selection of data sources, the categorization of varying levels of evidence, the rationale for resulting recommendations, and the panel's composition with various methods for disclosure of potential COI (ACCF

TABLE 5-1 IOM Standards for Development of Trustworthy CPGs

Focus of Standard	Application to CPG Development
Transparency	Development and funding processes should be detailed and publicly accessible.
Management of Conflict of Interest	Whenever possible GDG members should not have COI; relevant COI should be disclosed, with potential for divestment if such interests could be affected by CPGs.
Panel Composition	Panels should be balanced, multidisciplinary, and inclusive of patients and patient advocates.
Systematic Review	GDGs should use systematic reviews that meet IOM standards.[a]
Rating of Evidence and Strength of Recommendation	Each recommendation should have: • A clear description of benefits and harms, • A summary of relevant evidence (quality, quantity, and aggregate consistency), • Ratings for level of confidence in and strength of recommendations, and • Description of any differences of opinion.
Articulation of Recommendation	A standardized and precise description of recommended action and applicable circumstances should be given; strong recommendations should be phrased to enable evaluation of compliance.
External Review	Reviewers should include a full spectrum of relevant stakeholders, and should be kept confidential unless waived; all reviewer comments should be considered; and a review draft should be made available for public comment.
Updating	Publication date, pertinent systematic review dates, and proposed future review dates should be documented. Literature should be monitored regularly to identify emergence of new and relevant evidence and to evaluate continued validity of the CPG.

NOTE: COI = conflict of interest; CPG = clinical practice guideline; GDG = guideline developing group; IOM = Institute of Medicine.

[a] IOM, 2011b.

SOURCE: Adapted from IOM, 2011a.

and AHA, 2010; ASCO, 2015; NCCN, 2015). However, despite the need to incorporate higher quality evidence into guideline development related to biomarker testing for molecularly targeted therapies, progress has been slow. The Centers for Disease Control and Prevention's Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working

Group published a summary of lessons learned from the group's publication of eight recommendation statements between 2005 and 2014. Among the testing scenarios examined, many of which addressed testing related to targeted therapies, EGAPP noted a lack of consistent demonstration of analytic and clinical validity, as well as clinical utility, resulting from the difficulty of applying traditional evidence review to rapidly advancing fields (Calonge et al., 2014). Similarly, Abernethy and colleagues examined the difficulty associated with traditional systematic review in technology assessment for off-label use of targeted therapies in cancer. Particularly problematic was the widespread heterogeneity of reviewed studies and data, and the tendency of review cut-off dates to exclude potentially practice-changing new research (Abernethy et al., 2010).

Recent CPG generation efforts reflect these difficulties. For example, a review of 16 current CPGs published jointly between the American College of Cardiology (ACC) and the American Heart Association (AHA) found that nearly half were based not on systematic review of evidence, but instead on expert opinion, case studies, or standards of care (Tricoci et al., 2009). The National Comprehensive Cancer Network's (NCCN's) default level of evidence category for recommendations (2A) similarly relies on lower-level evidence from "indirect comparisons among randomized trials, Phase II or non-randomized trials, or in many cases, on limited data from multiple smaller trials, retrospective studies, or clinical observations" (NCCN, 2015; Poonacha and Go, 2011) (see Table 5-2 for a summary of NCCN recommendations for biomarker testing to direct targeted therapy in common cancers). ASCO also publishes CPGs and states that "few guideline questions can be directly or completely answered only considering the evidence. Interpretation and extrapolation of evidence are often necessary" (ASCO, 2015).

Different interpretations of the relative value and harm of an intervention in the context of non-definitive evidence can result in inconsistency among related guidelines (IOM, 2011a). In contrast with NCCN guidelines, for example, a recent ASCO endorsement of a joint CAP/International Society for the Study of Lung Cancer/Association of Molecular Pathology (AMP) guideline related to testing for non-small-cell lung cancer patients prioritized *EGFR* and *ALK* testing above all other markers, but did explain that emerging tests for *ROS1* and *RET* are under investigation (Leighl et al., 2014). Similarly, a recent draft guidance document for molecular testing in colorectal cancer (released jointly by the American Society for Clinical Pathology, CAP, ASCO, and AMP) did not consider the evidence sufficient to recommend testing for *BRAF* mutations for predicting response to anti-EGFR therapy in colon cancer (*BRAF* and *KRAS* mutations are considered mutually exclusive in colon cancer), which conflicts with the current NCCN recommendation (AMP, 2015).

TABLE 5-2 NCCN Guidelines for Clinical Use of Predictive Biomarker Tests in Common Cancers

Cancer Type	Biomarker (Gene Symbol)	Quality of Evidence*
Non-Small Cell Lung Cancer	*ALK*	1, 2A
	EGFR	1, 2A
	ROS1	2A
	KRAS	2A
	BRAF	2A
	ERBB2 (HER2)	2B
	MET	2A
	RET	2A
Breast Cancer	*ESR1*	2A
	PGR	2A
	ERBB2 (HER2)	1
Prostate Cancer	-	-
Colon Cancer	*NRAS/KRAS*	2A
	BRAF	2A

NOTES: * Quality of Evidence can differ between mutations within a target biomarker; Category 1: Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate; Category 2A: Based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate; Category 2B: Based on lower-level evidence, there is NCCN consensus that the intervention is appropriate.
NCCN = National Comprehensive Cancer Network.
SOURCE: NCCN Biomarkers Compendium, http://www.nccn.org/professionals/biomarkers/default.aspx (accessed June 2, 2015).

Compounding the variability in evidence and the inconsistency among CPG recommendations is the fact that the studies on which CPGs are based are often conducted on more restricted populations than those to which the CPGs are applied (Treweek et al., 2015), particularly in molecularly driven trials (Kim et al., 2015). This can lead CPGs to focus too narrowly on clinical conditions without considering real-world patient scenarios, where comorbidities are commonplace (Sniderman and Furberg, 2009). Efforts to reduce bias and redundancy and better direct research and clinical care have fueled calls for centralized CPG generation under the auspices of the Agency for Healthcare Research and Quality (AHRQ) or the U.S. Preventive Services Task Force (Shaneyfelt and Centor, 2009). The AHRQ's National Guidelines Clearinghouse[16] currently aggregates guidelines, enables comparison, and has a limited number of syntheses drawn from multiple guidelines in a related setting.

[16] See http://www.guideline.gov.

Given the complexity of precision medicine, there is a growing need for clinician guidance from professional organizations (Manolio et al., 2014). Clinical decision making, particularly in cancer genomics, will increasingly benefit from comparing the incremental effectiveness of therapeutic options, a process that is necessarily interdisciplinary (Goddard et al., 2012; Simonds et al., 2013). The committee endorses the existing IOM standards for trustworthy clinical practice guidelines shown in Table 5-1 (IOM, 2011a), and further **recommends that guideline-developing organizations (e.g., CAP, AMP, the American College of Medical Genetics and Genomics [ACMG], ACC, NCCN, AHA, ASCO, the American College of Physicians [ACP], and others) should expand interdisciplinary collaborations to develop integrated guidelines on the appropriate use of biomarker tests for molecularly targeted therapies (Recommendation 10).** 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 IOM and Guidelines International Network. Additionally, 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.

Collaboration among guideline-developing organizations has the potential to save time and resources if redundant guideline development is avoided; it also adds clarity to clinical decision making by reducing guideline inconsistency. The need for cooperative guideline development is further highlighted by the fact that no single group can cover the extensive field of genomics as it relates to clinical practice (Schully et al., 2015). The National Guideline Clearinghouse should expand its work in reviewing and rating guidelines to help ensure this collaboration is effectively improving guidelines related to biomarker tests for molecularly targeted therapies. Additionally, EHR vendors and 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 labeling proposed in Recommendations 2 and 3.

SUMMARY AND RECOMMENDATIONS

Patients in remote or underserved areas without access to a larger health care center or academic medical center may have limited access to adequate biomarker testing technology. In addition, there is a significant lack of genetic/genomic knowledge among patients and health care providers. Rapid learning systems present a unique opportunity to

ensure evidence-based medical practice is widely available and continuously refined. Multidisciplinary conferences and specialty tumor boards have been shown to be useful vehicles for knowledge sharing and learning among health care providers. Genetic counselors have an important role to play as members of the care team, working to inform physicians about interpretation of test results and to explain biomarker test results to patients.

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 8b: The Secretary of the Department of Health and Human Services and the Centers for Medicare & Medicaid Services (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.

- **Providers should demonstrate competency in communicating with patients about biomarker tests for molecularly targeted therapies.**

Inadequate tissue may be collected from a patient, requiring repeat biopsy procedures to obtain specimens sufficient for testing and exposing

the patient to unnecessary risk. Uniform standards are needed regarding specimen acquisition, handling, and subsequent documentation in the EHR and/or laboratory information system.

Recommendation 9a: 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.

- **Health care professionals who collect, process, and 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 electronic health record and/or the laboratory information system.**

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

CPGs exist for some biomarker tests for molecularly targeted therapies, but may not be frequently updated, may not be sufficiently user-friendly or clinically relevant, and often conflict with related guidelines. Increasingly, a broader base of interdisciplinary expertise is needed to generate trustworthy guidelines related to biomarker tests for molecularly targeted therapies. Consistent with the committee's vision of a learning health care system, CPGs serve an important dual purpose, both for clinical decision making and for data input for decisions regarding test and drug labeling.

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 (e.g., the College of American Pathologists, Association for Molecular Pathology, American College of Medical Genetics and Genomics, American College of Cardiology, National Comprehensive Cancer Network, American Heart Association, American Society of Clinical Oncology, American College of Physicians, and others) 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, and developed with patient participation. They should conform to standards articulated by authoritative groups, including the Institute of Medicine and Guidelines International Network.**
- **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.**
- **Electronic health record (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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Appendix A

Committee Member and Staff Biographies

COMMITTEE MEMBER BIOGRAPHIES

Harold L. Moses, M.D. (*Chair*), was chair of the Department of Cell Biology at Vanderbilt for 13 years. He is now the acting chair of the Department of Cancer Biology. He was the founding director of the Vanderbilt-Ingram Cancer Center, which he led for 12 years; he is now director emeritus. He has served as president of the American Association for Cancer Research (AACR), president of the Association of American Cancer Institutes, chair of the National Institutes of Health Chemical Pathology Study Section, chair of the Molecular Oncogenesis Study Section, a member of the Integration Panel for the U.S. Army Breast Cancer Program, co-chair of the Breast Cancer Progress Review Group for the National Cancer Institute (NCI), and chair of the NCI Cancer Centers review panel. He is a member of the National Academy of Medicine and was founding chair of the National Academies of Sciences, Engineering, and Medicine's National Cancer Policy Forum, 2005 to 2011. Dr. Moses is a graduate of Berea College and Vanderbilt University School of Medicine.

Trained as a pathologist, Dr. Moses has devoted much of his career to basic research on growth factors and tumor suppressor genes and has received many awards for his research. These include two Outstanding Investigator Awards from the NCI, the Esther Langer Award for Meritorious Cancer Research from the University of Chicago, the Rous-Whipple Award from the American Association of Pathologists, the John H. Exton Award for Research Leading to Innovative Biological Concepts, the Harvey Branscomb Distinguished Professor Award, the Nakahara

Memorial Lecture Award from the Princess Takamatsu Cancer Research Fund, the T.J. Martell Foundation Lifetime Medical Research Award, the Earl Sutherland Prize for Achievement in Research, the Grant W. Liddle Award for Promoting an Interest in Research Among Physicians, the T.J. Martell Lifetime Scientific Achievement Award, and the AACR Lifetime Achievement in Cancer Research Award. He also has been elected Fellow of the AACR Academy. He is chair the Board of Trustees of Berea College, a position he will hold for the next 2 years.

John M. Carethers, M.D., is the John G. Searle Professor and Chair of the Department of Internal Medicine at the University of Michigan. As chair, he oversees more than 700 paid faculty in their academic, clinical, and teaching roles as they relate to the overall integration with the health system's missions of clinical excellence, education, and discovery. Dr. Carethers is a trained gastroenterologist and physician–scientist who focuses his research in the area of hereditary colon cancer genetics.

Dr. Carethers received his B.S. in Biological Sciences with a minor in Chemistry from Wayne State University, and his M.D. with high distinction from the same institution. Dr. Carethers did his internship and residency in Internal Medicine at Massachusetts General Hospital, followed by a fellowship in gastroenterology at the University of Michigan. He was then recruited to the University of California, San Diego (UCSD), where he grew his laboratory-based research in the area of DNA mismatch repair and colorectal cancer pathogenesis; and he saw medicine and gastroenterology patients, including serving as the main physician for hereditary colon cancer referrals in Southern California. He served in leadership roles, including the gastroenterology fellowship director, the gastroenterology section chief for the San Diego Veterans Affairs Hospital, then division chief for UCSD, before being recruited to Michigan. He was the founding director of the National Institutes of Health (NIH)-funded UCSD Gastroenterology Center grant, and was the director of the gastroenterology T32 training grant. His laboratory research continues to be funded by NIH. Dr. Carethers also has interests in colorectal cancer disparities as they relate to genetics and outcomes. He is the former Principal Investigator of the San Diego State University/UCSD Cancer Center Comprehensive Partnership U54 grant, which addresses cancer disparities.

Dr. Carethers has published more than 150 manuscripts and book chapters. He is a senior associate editor for *Gastroenterology*, the highest impact gastroenterology journal. He completed a 2-year appointment on the National Commission for Digestive Diseases, a U.S. Congressional Commission, after his appointment by Elias Zerhouni, M.D., then director of NIH. He was elected a member of the American Society for Clinical

Investigation and the American Association of Physicians (AAP), and serves on the AAP Council. He was elected a member of the National Academy of Medicine in 2012.

Molly Cooke, M.D., professor of medicine, is the inaugural director of education for Global Health Sciences across the five schools (Medicine, Dentistry, Pharmacy, Nursing, and the Graduate Division) at the University of California, San Francisco (UCSF). She is charged with developing a portfolio of high-impact educational programs for UCSF students, residents, fellows, post-docs, and faculty members and devising innovative and high-value ways to share UCSF's expertise in discovery science, health care delivery, professional education, and basic science with international partners.

Dr. Cooke has been active in medical education program development and educational research throughout her career. A distinguished teacher, Dr. Cooke has received numerous teaching awards including, in 2006, the AOA/Robert J. Glaser Distinguished Teacher Award from the Association of American Medical Colleges. As a senior scholar of the Carnegie Foundation for the Advancement of Teaching, she co-directed a national study of medical education. This work culminated in the text, *Educating Physicians: A Call for Reform of Medical School and Residency* (2010). Dr. Cooke has used education and faculty development to address the health problems of underserved populations throughout her career. A founding faculty member of the internal medicine residency at San Francisco General Hospital–UCSF, she developed graduate medical education curricula focused on the care of the urban underserved. She serves on the Training Advisory Committee of the University of Zimbabwe Medical Education Partnership Initiative and is a member of the Scientific Advisory Board of Accordia Global Health Foundation and the Infectious Diseases Institute of Makerere University, Kampala.

Dr. Cooke is a practicing internist with a special interest in HIV and other complex chronic illnesses. She has been repeatedly selected by her peers as one of "America's Best Doctors." She is active in the American College of Physicians, serving as governor of the Northern California chapter of the American College of Physicians from 2004 to 2009, regent from 2009 to 2014, president-elect from 2012 to 2013, and president of the College from 2013 to 2014. Dr. Cooke is a graduate of Stanford University and received her M.D. from Stanford University School of Medicine. She did her residency training at UCSF, where she also served as chief resident in medicine and did a Henry J. Kaiser Family Foundation Fellowship focusing on ethics. She was elected to the National Academy of Medicine in 2013.

Garret A. FitzGerald, M.D., professor of medicine and pharmacology, is the McNeil Professor in Translational Medicine and Therapeutics at the Perelman School of Medicine at the University of Pennsylvania, where he chairs the Department of Pharmacology and directs the Institute for Translational Medicine and Therapeutics. Dr. FitzGerald's research has been characterized by an integrative approach to elucidating the mechanisms of drug action, drawing on work in cells, model organisms, and humans. His work contributed substantially to the development of low-dose aspirin for cardioprotection. Dr. FitzGerald's group was the first to predict and then mechanistically explain the cardiovascular hazard from non-steroidal anti-inflammatory drugs (NSAIDs). He has also discovered many products of lipid peroxidation and established their utility as indexes of oxidant stress in vivo. Dr. FitzGerald's laboratory was the first to discover a molecular clock in the cardiovascular system and has studied the importance of peripheral clocks in the regulation of cardiovascular and metabolic function.

Dr. FitzGerald has received the Boyle, Coakley, Harvey, and St. Patrick's Day medals; the Lucian, Scheele, and Hunter Awards; and the Cameron, Taylor, Herz, Lefoulon-Delalande, and Schottstein Prizes. He is a member of the National Academy of Medicine and a Fellow of the American Academy of the Arts and Sciences and of the Royal Society.

Felix W. Frueh, Ph.D., is a respected thought leader in personalized medicine with 20 years of research and development, management, and policy experience. Dr. Frueh is executive partner at Opus Three, LLC, a position he has held since 2012. He provides strategic consulting to pharmaceutical and diagnostic companies on scientific, regulatory, and reimbursement strategies for medical products in the personalized health care space.

From 2014 to July 2015, Dr. Frueh was chief scientific officer (CSO) of Human Longevity, Inc. (HLI). As CSO, Dr. Frueh led all genomic operations, including nonclinical microbiome testing, high throughput, next-generation genomic sequencing, and research collaborations and partnerships, including the program with the University of California, San Diego/Moores Cancer Center. Dr. Frueh was also instrumental in guiding HLI's collaborations and partnerships with the pharmaceutical and diagnostic industry.

Previously, Dr. Frueh was an entrepreneur-in-residence at Third Rock Ventures, a Boston-based venture capital firm, where he provided scientific and strategic input for the formation of new and the advancement of existing portfolio companies. Before joining Third Rock, Dr. Frueh was president of the Medco Research Institute, leading Medco's real-world, health economics and outcomes research-oriented initiatives and collaborations after having formed Medco's personalized medicine research and

development organization. Before joining Medco, he was the first associate director for genomics at the Food and Drug Administration (FDA), where he built and led the core genomics review team in the Center for Drug Evaluation and Research, and chaired the first FDA-wide, interdisciplinary pharmacogenomics review group.

Dr. Frueh has been a member of various working groups on genetics and genomics at FDA and the Department of Health and Human Services. He is the recipient of numerous awards, including the FDA Commissioner's Special Citation. He serves on the board of the Personalized Medicine Coalition and is also a board member at Enterome Biosciences. Dr. Frueh is a Fellow of the American College of Clinical Pharmacology, adjunct faculty member at the Institute for Pharmacogenomics and Individualized Therapy at the University of North Carolina, and held faculty appointments in the Departments of Pharmacology and Medicine at Georgetown University. Dr. Frueh was a Postdoctoral Fellow at Stanford University and the University of Basel in Switzerland, where he also received his Ph.D. in Biochemistry (magna cum laude).

Debra Leonard, M.D., Ph.D., is professor and chair of the Department of Pathology and Laboratory Medicine at the University of Vermont College of Medicine and the University of Vermont Medical Center. Dr. Leonard is a leading expert in molecular pathology and genomic medicine, applying our understanding of the human genome and pathogen genomes to the diagnosis and treatment of human diseases, including inherited disorders, cancers, and infectious diseases. Dr. Leonard is certified by the American Board of Pathology in Anatomic Pathology and by the American Boards of Pathology and Medical Genetics in Molecular Genetic Pathology. She is a member of the National Academies of Sciences, Engineering, and Medicine's Roundtable on Translating Genomic-Based Research for Health. She is past chair of the Personalized Healthcare Committee of the College of American Pathologists. She previously served as a member of the Advisory Committee on Genetics Health and Society to Secretary of Health and Human Services Michael O. Leavitt, and was chair of the Stakeholders Group of the Centers for Disease Control and Prevention Program Evaluating Genomic Applications in Practice and Prevention. She has spoken widely on various molecular pathology testing services, the future of molecular pathology and the impact of gene patents on molecular pathology practice.

Dr. Leonard did her undergraduate education at Smith College and her medical and scientific training at New York University School of Medicine. She started her faculty career at Case Western Reserve University School of Medicine, where she was director of the Molecular Diagnostics Laboratory, and moved to the University of Pennsylvania

School of Medicine as director of the clinical Molecular Pathology Laboratory and director of the Molecular Diagnosis and Genotyping Core Facility at the Abramson Cancer Center. Prior to joining the University of Vermont, Dr. Leonard was at Weill Cornell Medical College and New York-Presbyterian Hospital-Weill Cornell Medical Center, where she was professor and vice chair for Laboratory Medicine in the Department of Pathology and Laboratory Medicine and director of Clinical Laboratories. She also served as chief diversity officer for Weill Cornell Medical College from 2009 through 2012. Dr. Leonard was a 2003 Fellow at the Executive Leadership in Academic Medicine Program at Drexel University. She is a member of the College of American Pathologists and a founding member of the Association for Molecular Pathology, serving as president in 2000 and receiving its Leadership Award in 2009. She is editor of 2 textbooks of molecular pathology and has published more than 80 peer-reviewed articles, book chapters, and reviews.

Gary H. Lyman, M.D., M.P.H., is co-director of the Hutchinson Institute for Cancer Outcomes Research and member of the Public Health Sciences and Clinical Research Divisions at the Fred Hutchinson Cancer Research Center. He is also an adjunct professor in the School of Pharmacy and the School of Public Health at the University of Washington as well as professor of medicine in the Department of Medicine in the University of Washington School of Medicine. Dr. Lyman is a medical oncologist and hematologist and a member of the Breast Cancer Program at the Seattle Cancer Care Alliance. He was most recently director of Comparative Effectiveness and Outcomes Research–Oncology at Duke University and the Duke Cancer Institute, where he also served as professor of medicine in the Duke University School of Medicine and a Senior Fellow at the Duke Center for Clinical Health Policy Research. In addition to his training in Internal Medicine at University of North Carolina at Chapel Hill and Hematology/Oncology at Roswell Park Cancer Institute, Dr. Lyman was a Postdoctoral Fellow in Biostatistics at the Harvard School of Public Health.

Dr. Lyman is active with the American Society of Clinical Oncology (ASCO), serving on the ASCO Board of Directors, co-chair of the Breast Cancer and Survivorship Guideline Advisory Groups as well as chair of the Guideline Methodology Committee and several individual clinical practice guidelines. Dr. Lyman is also a member of the ASCO Research Committee, Biomarkers Guideline Working Group, the Comparative Effectiveness Research Task Force, the Global Oncology Leadership Task Force, and the Value of Cancer Care Task Force, contributing to development of ASCO's Top Five as a part of the American Board of Internal Medicine Choosing Wisely Campaign. He is a member of the Committee

on Educational Affairs for the American Society of Hematology. He is editor-in-chief of *Cancer Investigation* and on the editorial board of the *Journal of Clinical Oncology* and several other specialty journals. He is an active grant reviewer for the National Cancer Institute, Conquer Cancer Foundation, American Association for Cancer Research, and Canadian Institute of Health Research.

Dr. Lyman's research interests include comparative effectiveness and outcomes research related to targeted therapies and biomarkers, efforts to integrate health economics into evidence-based medicine, health policies, and real-world research paradigms. His research group is also engaged in advanced methods of evidence synthesis in support of clinical practice guidelines and population studies of patterns of cancer treatment and the impact of health disparities on the quality of cancer care. Dr. Lyman has authored or edited more than 15 books and more than 450 articles in scientific literature.

Robert L. Nussbaum, M.D., joined Invitae, a genetic information and testing company based in San Francisco, as Chief Medical Officer in August 2015. Previously, he was co-director of the Program in Cardiovascular Genetics at the University of California, San Francisco (UCSF), Heart and Vascular Center and Medical Director of the Cancer Risk Program of the Helen Diller Family Comprehensive Cancer Center. He is a member of the UCSF Institute for Human Genetics, where he is studying if and how genetic and genomic information can be used to improve health care by improving outcomes, reducing adverse reactions, lowering costs, and promoting health through risk education.

Dr. Nussbaum is one of the leading medical geneticists in the nation. The focus of his expertise in genomics medicine is on the interpretation of genomic data and its use for patient care decision making in the clinical setting. As the director of the UCSF Genomic Medicine Initiative, he is exploring ways of applying genomics to clinical care at UCSF. For example, he launched and supports a project at UCSF Medical School to sequence DNA from tumors and use the genomic data to identify patients most likely to benefit from targeted therapies. He also helped establish an undiagnosed diseases clinic in which whole exome sequencing is being used to make diagnoses in patients with puzzling, likely genetic disorders. Dr. Nussbaum is interested in establishing partnerships among clinics, laboratories, and institutions that create and maintain electronic medical records regarding the collection and storage of genomics data.

Dr. Nussbaum also conducts research on Parkinson's disease to understand what causes the disorder and to develop treatments to prevent, slow, or stop its progression. A member of the National Academy of Medicine and a former president of the American Society of Human

Genetics, Dr. Nussbaum was co-discoverer of the first inherited form of Parkinson's disease. Prior to joining UCSF, he was chief of the Genetic Disease Research Branch of the National Human Genome Research Institute. Dr. Nussbaum served a full term as a member of the National Academies of Sciences, Engineering, and Medicine's Roundtable on Translating Genomic-Based Research for Health.

Rebecca D. Pentz, Ph.D., is professor of research ethics, Emory University School of Medicine. She specializes in empirical ethics research on genetic testing, confidentiality, biobanking, return of results, duty to warn, and informed consent ethical issues in early drug development. She has a special interest in pediatric bone marrow transplant and the effect on the family. Before coming to Atlanta, she designed and directed the clinical ethics program at The University of Texas MD Anderson Cancer Center.

Dr. Pentz received her Ph.D. in Philosophy from the University of California. During the early part of her career, she served as a clinical ethicist, helping patients, families, and the health care team at the bedside to resolve ethical dilemmas, working first in the community setting in Yakima, Washington, and then as the sole clinical ethicist at The University of Texas MD Anderson Cancer Center for a decade.

Edith A. Perez, M.D. joined Genentech in August 2015 as vice president and head of all BioOncology US Medical Affairs. Previously, she served as the deputy director at-large for the Mayo Clinic Cancer Center, group vice chair of the Alliance for Clinical Trials in Oncology, and chair of the Breast Cancer Specialty Council formed in 2012; she retains her academic appointment as a professor of medicine at Mayo Medical School and chair of the Mayo Clinic Breast Cancer Translational Genomics Program started in 2009. She is a cancer specialist and an internationally known translational researcher at Mayo Clinic. Her roles extend nationally, including positions with the American Association for Cancer Research, the American Society of Clinical Oncology, and the National Cancer Institute.

Dr. Perez has developed, and is involved in, a wide range of clinical trials exploring the use of new therapeutic agents for the treatment and prevention of breast cancer. She leads and has helped develop basic research studies to evaluate the role of genetic markers in the development and aggressiveness of breast cancer. She has authored more than 700 research articles in journals, books, and abstracts. Dr. Perez is invited frequently to lecture at national and international meetings and serves on the editorial boards of multiple academic journals.

A select list of awards Dr. Perez has received includes Breast Cancer Research Foundation Research Grant Award; Horizon Achievement Award in Cancer Research; Mayo Clinic Outstanding Faculty Award;

North Florida Hispanic of the Year Award; Mayo Clinic Distinguished Educator Award; Serene M. and Frances C. Durling Professorship of Medicine; Honorary Doctorate of Letters, University of North Florida; Mayo Clinic Distinguished Investigator; Florida State Biomedical Research Advisory Council; Alpha Omega Alpha Honor Medical Society; Mayo Clinic Outstanding Course Director; EVE Award for Lifetime Achievement; NFL Hispanic Heritage Leadership Award; 1 of the 75 Most Influential People in Jacksonville Healthcare from *Jacksonville Magazine*'s 904 (2012); The Girls Inc. Woman of Vision Award; Jacksonville University Woman of the Year; the Susan G. Komen® Brinker Award for Scientific Distinction in Clinical Research; the Claude Jacquillat Award; and the OncLive's Giants of Cancer Care Award.

Jane Perlmutter, Ph.D., M.B.A., is a long-term cancer survivor and has been involved in a number of organizations committed to educating the public about cancer, supporting people affected by it, and eradicating the disease. She is an advocate representative in several clinical trials consortia, multi-institutional grants, clinical guideline committees, grant review panels, and National Cancer Institute working groups. She has also been an active member of the Clinical Trials Transformation Initiative. She is especially committed to training less experienced patient advocates, has written articles and tutorials on this topic, and is often involved in advocate training.

Dr. Perlmutter started her career as an experimental cognitive psychologist at the University of Texas in Austin, and spent most of her career at Bell Labs. She has run the Bell Technical Training Center and held an officer position in DeVry Inc., a publicly traded for-profit higher education company. She currently runs her own consulting company—Gemini Group. Her consulting focuses on process improvement for small businesses, not-for-profits, and institutions of higher learning. She has a Ph.D. in Cognitive Psychology, a master's in educational psychology, a master's in computer and information science, and an M.B.A.

Victoria M. Pratt, Ph.D., FACMG, is a medical and clinical molecular geneticist board-certified by the American College of Medical Genetics. She is currently director of the Pharmacogenomics Laboratory at Indiana University School of Medicine. Prior to joining Indiana University, she was chief director, Molecular Genetics, for Quest Diagnostics Nichols Institute. Dr. Pratt served on the Secretary of Health and Human Services Advisory Committee on Genetics, Health, and Society for the Oversight of Genetic Testing, and the Advisory Committee on Hereditary Disorders in Newborns and Children. She also participated in the preparation of the *Morbidity and Mortality Weekly Report* for Best Practices in Molecular

Genetic Testing for the Centers for Disease Control and Prevention (CDC). Dr. Pratt continues to serve on CDC's GeT-RM program for reference materials for Molecular Genetics. She is now serving on the National Academies of Sciences, Engineering, and Medicine's Roundtable on Translating Genomic-Based Research for Health.

Dr. Pratt is past chair of the Clinical Practice Committee and currently a member of the Professional Relations committee for the Association of Molecular Pathology. She is an advisory member of EurogenTest for genetic test validation. Dr. Pratt serves on the American Medical Association's Molecular Pathology Current Procedural Terminology Advisory Committee. Dr. Pratt has authored more than 40 peer-reviewed manuscripts and book chapters. She is also an associate editor for the *Journal of Molecular Pathology*. She graduated with a Ph.D. in Medical and Molecular Genetics from Indiana University School of Medicine. Her fellowship training was in Medical and Clinical Molecular Genetics at Henry Ford Hospital in Detroit.

Yu Shyr, Ph.D., received his Ph.D. in Biostatistics from the University of Michigan (Ann Arbor) and subsequently joined the faculty at Vanderbilt University School of Medicine. At Vanderbilt, he has collaborated on numerous research projects; assisted investigators in developing clinical research protocols; collaborated on multiple grants funded through external peer-reviewed mechanisms; and developed biostatistical and bioinformatic methodologies for clinical trial design, high-dimensional data analysis, and other statistical and bioinformatic approaches, published in journals such as *Statistics in Medicine*, *Bioinformatics*, and *Clinical Trials* in the past 3 years.

Dr. Shyr is a Fellow of the American Statistical Association, an associate editor of *JAMA Oncology* and a Food and Drug Administration (FDA) advisory committee voting member. He has delivered more than 200 abstracts at professional meetings and has published more than 340 peer-reviewed papers. Dr. Shyr has served on numerous National Institutes of Health (NIH)/National Cancer Institute (NCI) Specialized Program of Research Excellence (SPORE), P01, and Cancer Center Support Grant (CCSG) review panels/committees and has been a member of the invited faculty at the American Association of Cancer Research (AACR)/American Society of Clinical Oncology (ASCO) Methods in Clinical Cancer Research Vail Workshop since 2004. He currently serves on the external advisory board for a dozen national cancer centers, and directs the biostatistics and bioinformatics cores for the NCI-funded Vanderbilt University Breast Cancer SPORE, Gastrointestinal Cancer SPORE, and other program projects. In addition, Dr. Shyr is the Principal Investigator of a U01 grant for the Barrett's Esophagus Translational Research Network Coordinating

Center (BETRNetCC). Dr. Shyr's current research interests focus on developing statistical bioinformatic methods for analyzing next-generation sequencing data, including a series of papers on estimating the sample size requirements for studies conducting RNA sequencing analysis.

Sean Tunis, M.D., M.Sc., is the founder and director of the independent, nonprofit Center for Medical Technology Policy (CMTP) in Baltimore. CMTP's main objective is to improve the quality, relevance, and efficiency of clinical research by providing a neutral forum for collaboration among experts, stakeholders, and decision makers. Dr. Tunis was a member of the Institute of Medicine Committee on Initial National Priorities for Comparative Effectiveness Research. He collaborates with a wide range of domestic and international public and private health care organizations on issues of comparative effectiveness, health technology assessment, evidence-based medicine, clinical research, reimbursement, and medical technology policy.

Through September 2005, Dr. Tunis was the chief medical officer at the Centers for Medicare & Medicaid Services, where he had lead responsibility for clinical policy and quality for the Medicare program. Previously, he served as the director of the Health Program at the Congressional Office of Technology Assessment and as a health policy advisor to the U.S. Senate, where he worked on pharmaceutical and device policy issues.

Dr. Tunis trained at Stanford University, the University of California, Los Angeles, and the University of Maryland in Internal Medicine, Emergency Medicine, and Health Services Research. He holds adjunct faculty positions at the schools of medicine of Johns Hopkins, Tufts, and the University of California, San Francisco.

Tracey F. Weisberg, M.D., is president of New England Cancer Specialists. Dr. Weisberg joined New England Cancer Specialists (formerly Maine Center for Cancer Medicine) in 1990 and began to establish a breast cancer–specific practice. In the early part of her career, she had a basic science research lab at Maine Medical Center Research Institute and studied tumor biology in severe combined immunodeficiency (SCID) mice. Dr. Weisberg was the medical director of the Maine Medical Breast Care Center from 1994 to 2013.

Dr. Weisberg serves as the president of her regional American Society of Clinical Oncology (ASCO) society, Northern New England Cancer Society. She also sits on the ASCO State Affiliates council and has been asked to serve on the Executive Board. New England Cancer Specialists is a "Vanguard" practice for ASCO's CancerLinQ project and Dr. Weisberg serves as the representative. New England Cancer Specialists is also a COME HOME practice. Dr. Weisberg currently serves on the Board of Directors of the Hospice of Maine.

INSTITUTE OF MEDICINE (IOM) STAFF BIOGRAPHIES

Laurie Graig, M.A., is a program officer for the National Academies of Sciences, Engineering, and Medicine's Board on Health Care Services. She is currently the study director for the Committee on Policy Issues in the Clinical Development and Use of Biomarkers for Molecularly Targeted Therapies. Ms. Graig has worked on a broad range of health care systems research and policy issue areas, within for-profit and not-for-profit consulting organizations. Most recently, she participated in an evaluation of state-level improvement partnerships as a consultant to AcademyHealth. Previously, she managed a large, multifaceted project designed to improve the operational efficiency of community health centers using the Lean process improvement methodology. She has contributed to studies and reports in the area of public health planning and emergency preparedness, such as mass casualty events and pandemic influenza. She also worked for more than 10 years in the research and information center of a worldwide management consulting firm and conducted research and analysis of health and retirement issues. Ms. Graig is the author of three editions of *Health of Nations: An International Perspective on U.S. Health Care Reform* published by CQ Books (1991, 3rd edition). She is a former Peace Corps volunteer, having served in Burkina Faso, West Africa. Ms. Graig received her B.S. from Georgetown University and M.A. from the University of Virginia.

Jonathan Phillips is a research associate for the National Academies of Sciences, Engineering, and Medicine's Board on Health Care Services. Previously, he worked in clinical research at The University of Texas MD Anderson Cancer Center, providing clinical trial and translational research support for Principal Investigators in the Department of Gastrointestinal Medical Oncology and the Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy. He received a B.A. in Anthropology from Texas A&M University in 2008, and plans to receive his M.P.H. from The George Washington University in 2017.

Sarah E. De Leo, Ph.D., is an American Association for the Advancement of Science Science & Technology Policy Fellow with the Department of Defense. Her primary interests are intellectual property and regulatory issues surrounding state-of-the art technologies in the defense and health care spaces.

She served as a Mirzayan Fellow and then as a Research Associate for the Board on Health Care Services at the National Academies of Sciences, Engineering, and Medicine. Dr. De Leo's doctoral work focused on determining optimal conditions for lymphocyte activation and designing a targeted T cell expansion platform for use in adoptive immunotherapy. During her graduate studies, Dr. De Leo worked in the Columbia Ventures Technology fellows program where she assessed the economic feasibil-

ity and impact of scientific advancements and researched the landscape of relevant markets for technology transfer. Dr. De Leo holds a Ph.D., M.Phil., and M.S. in Biomedical Engineering from Columbia University and a B.S. in Biological Engineering from Louisiana State University.

Celynne Balatbat is a senior program assistant for the National Academies of Sciences, Engineering, and Medicine's Board on Health Care Services. She received her B.A. in Neuroscience and Behavior from Vassar College in 2013. Previously, she interned in the advocacy department at AARP California and worked as a laboratory assistant in a medical microbiology lab at the University of California, Davis.

Sharyl Nass, Ph.D., M.S., is director of the National Academies of Sciences, Engineering, and Medicine's Board on Health Care Services and director of the National Cancer Policy Forum of the Academies. The work of the board is helping to shape the direction of health care in the United States and abroad. The board considers the entire health care system in order to ensure the best possible care for all patients. Its activities pertain to the organization, financing, effectiveness, workforce, and delivery of health care. The Cancer Forum examines policy issues pertaining to the entire continuum of cancer research and care.

For more than 15 years at the Academies, Dr. Nass has worked on a broad range of topics that includes the quality of care, clinical trials, oversight of health research, developing biomarkers and omics-based tests to guide patient care, technologies and quality standards for breast imaging, strategies for large-scale biomedical science, and contraceptive research and development. In addition, she studied developmental genetics and molecular biology at the Max Planck Institute in Germany under a fellowship from the Heinrich Hertz-Stiftung Foundation. She was the 2007 recipient of the Cecil Award for Excellence in Health Policy Research, the 2010 recipient of a Distinguished Service Award from the Academies, and the 2012 recipient of the Institute of Medicine staff team achievement award (as the team leader). With a Ph.D. in Cell and Tumor Biology from Georgetown University and postdoctoral training at the Johns Hopkins University School of Medicine, she has published papers on the cell and molecular biology of breast cancer. She also holds a B.S. in Genetics and an M.S. in Endocrinology/Reproductive Physiology, both from the University of Wisconsin–Madison.

Adam C. Berger, Ph.D., joined the Food and Drug Administration's Office of In Vitro Diagnostics and Radiological Health, Center for Devices and Radiological Health in July 2015 as Senior Staff Fellow on the Personalized Medicine Staff. Previously, he was a senior program officer and director of the Roundtable on Translating Genomic-Based Research for Health

in the Board on Health Sciences Policy at the National Academies of Sciences, Engineering, and Medicine. His primary interests focus on policy issues relating to translational medicine, including the development of biologic, drug, diagnostic, and clinical and public health applications. In his capacity at the Academies, Dr. Berger has facilitated numerous policy discussions on innovative, new health care technologies and applications, helped establish collaborative projects among stakeholder groups, and planned and conducted many public workshops and written resulting reports, such as *Stem Cell Therapies: Opportunities for Ensuring the Quality and Safety of Clinical Offerings*; *The Economics of Genomic Medicine*; *Genome-Based Diagnostics: Clarifying a Pathway to Clinical Use*; *Integrating Large-Scale Genomic Information into Clinical Practice*; *Genome-Based Therapeutics: Targeted Drug Discovery and Development*; *Assessing Genomic Sequencing Information for Health Care Decision Making*; and *The Value of Genetic and Genomic Technologies*. Dr. Berger received his doctorate from Emory University in the Biochemistry, Cell and Developmental Biology Program and his B.S. in Molecular Genetics from The Ohio State University. He completed his postdoctoral training at the National Cancer Institute of the National Institutes of Health (NIH). He is the recipient of the NIH Fellows Award for Research Excellence and a Ruth L. Kirschstein National Research Service Award.

Andrew M. Pope, Ph.D., is director of the Board on Health Sciences Policy at the National Academies of Sciences, Engineering, and Medicine. He has a Ph.D. in Physiology and Biochemistry from the University of Maryland and has been a member of the Academies staff since 1982 and of the Institute of Medicine (IOM) staff since 1989. His primary interests are science policy, biomedical ethics, and environmental and occupational influences on human health. During his tenure at the Academies, Dr. Pope has directed numerous studies on topics that range from injury control, disability prevention, and biologic markers to the protection of human subjects of research, National Institutes of Health priority-setting processes, organ procurement and transplantation policy, and the role of science and technology in countering terrorism. Since 1999, Dr. Pope has served as Director of the Academies' Board on Health Sciences Policy, which oversees and guides a program of activities that is intended to encourage and sustain the continuous vigor of the basic biomedical and clinical research enterprises needed to ensure and improve the health of the public. Ongoing activities include Forums on Neuroscience, Genomics, Drug Discovery and Development, and Medical and Public Health Preparedness for Catastrophic Events. Dr. Pope is the recipient of the IOM's Cecil Award and the National Academy of Sciences President's Special Achievement Award.

Appendix B

Coding: Payment Infrastructure for Biomarker Tests for Molecularly Targeted Therapies

As noted in this report, alternative payment systems are making inroads into the U.S. health care system, but the predominant payment model remains fee-for-service, which relies on diagnostic coding systems for coverage and payment of clinical laboratory tests (PMC, 2014). Coding systems (see Box B-1) facilitate the processing of health care claims and thus are key to coverage and payment policy as well as data tracking and outcomes/quality research (Radensky, 2015). Coding systems enable health insurers and other payers to determine whether a certain service, procedure, or supply is covered by the patient's health plan and whether the claim should be paid. Though closely interdependent, assignment of a specific code to a procedure or service does not determine coverage, set reimbursement rates, nor guarantee payment by health insurers and other payers (SACGHS, 2006, 2008).

Coding for the large number of complex and rapidly evolving biomarker tests for targeted therapies has undergone significant changes over the past 3 years, and is a process that itself continues to evolve. Prior to 2013, molecular diagnostics were billed as separate items using a combination of Current Procedural Terminology (CPT®) codes that described each step of the procedure used to perform the test. This process, known as "code stacking," reflecting the layering nature of the process, was a response to the fact that the coding system had not kept pace with new technologies, and specific codes for molecular diagnostics were not available.

Code stacking created great uncertainty and confusion, and was

BOX B-1
Overview of Coding

A standardized set of codes for payment of claims is provided by the Healthcare Common Procedure Coding System (HCPCS) in two related code sets. The HCPCS Level I code set includes the Current Procedural Terminology (CPT®) codes first developed by the American Medical Association (AMA) in 1966. Nearly all private and public payers in the United States have adopted the CPT system. CPT codes consist of a five-digit number associated with a concise description of the medical procedure or service. The HCPCS Level II set is maintained and distributed by the Centers for Medicare & Medicaid Services and consists primarily of medical supplies, durable medical goods, and nonphysician services and services not represented in the Level I code set. It is also used for outpatient hospital care, chemotherapy drugs, Medicaid, and other services.

CPT codes fall into three categories: Category 1 covers procedures; Category 2 includes performance measurement codes; and Category 3 includes temporary emerging technology codes. All new or revised CPT codes must be requested from AMA and the process of obtaining a new CPT code can take up to 2 years to complete.

Each molecular diagnostic procedure is assigned a molecular pathology CPT code, which fall into two tiers. Tier 1 includes commonly performed analyte-specific tests such as tests for BRCA or KRAS mutations associated with certain types of cancers. Less commonly performed tests (meaning the incidence of disease being tested is rare) are placed in Tier 2, which are not specific to any test, and are arranged according to levels (1-9) of increasing complexity and/or required clinical interpretation.

AMA's CPT® Editorial Panel adopted a new subsection of the CPT Pathology Section, and created 114 new analyte-specific codes in the Tier 1 category of commonly performed tests. As of January 2013, clinical laboratories are required to report molecular pathology tests using these newly introduced Molecular Pathology CPT codes. Additionally, in response to the Protecting Access to Medicare Act, new Multianalyte Assays with Algorithmic Analyses codes for Advanced Diagnostic Laboratory Tests have been developed, and these codes started being used in 2015.

SOURCE: AMA, http://www.ama-assn.org/ama/pub/physician-resources/solutions-managing-your-practice/coding-billing-insurance/cpt.page (accessed April 12, 2015).

unsatisfactory to payers who could not determine precisely what test was being performed, as different stacked codes could be used for the same diagnostic test or different tests would be billed using the same stacked codes (Deverka and Dreyfus, 2014; Faulkner et al., 2012). Calls for increased transparency and granularity by payers and test manufacturers resulted in the American Medical Association's (AMA's) CPT® Editorial Panel adopting a new subsection of the CPT Pathology Section

to describe molecular pathology procedures. The new codes replaced procedure-based code stacking with analyte-specific codes in the Tier 1 category of commonly performed tests. The requirement that laboratories report molecular pathology tests using the 116 new Molecular Pathology (MoPath) CPT codes took effect in January 2013.[1]

The development of new codes facilitates appropriate and consistent payment by ensuring greater accuracy and granularity, providing health plans and other payers with a clearer understanding of precisely which tests they are paying for, and may support payers' efforts to assess clinical utility by enabling tracking of the test in claims databases. It is important to note, however, that while the new codes offer greater accuracy in terms of the specific biomarker tests used, observers note that outstanding issues remain—such as performance variability among different laboratories testing for the same analytes—that the new codes do not address (IOM, 2015). Moreover, the coding system will be further challenged to keep up with the rapid pace of innovative new technologies such as next-generation sequencing (NGS). AMA is currently working on developing NGS-specific CPT codes (Deverka and Dreyfus, 2014).

MEDICARE CODING AND PAYMENT FOR LABORATORY TESTS

The Medicare program is the largest single payer of laboratory tests in the United States, and as such influences Medicaid and private payer coverage and payment decisions (OIG, 2013). Medicare is required by law to pay only for items and services that are "reasonable and necessary," which is interpreted generally as improving clinically meaningful health outcomes, although determining the precise definition of these terms has "proven to be an enduring challenge" (Neumann and Chambers, 2012, p. 1775). For example, in 1989, Medicare published a proposed regulation defining "reasonable and necessary" as safe, effective, non-investigational, appropriate, and cost-effective (Neumann and Chambers, 2012). The proposal was withdrawn after criticism from external stakeholders over the inclusion of the term "cost-effective." Furthermore, the Centers for Medicare & Medicaid's (CMS's) use of a "least costly alternative" reimbursement policy was successfully challenged in the courts in 2008. Efforts to clarify the terms continue, with some calling for a legislative remedy to provide definitional clarity (Neumann and Chambers, 2012).

Though some Medicare coverage determinations are made at the national level (referred to as national coverage determinations, or NCDs), the large majority are local coverage determinations (LCDs) and are

[1] See http://www.ama-assn.org/ama/pub/news/news/2012-09-17-cpt-code-changes-2013.page (accessed April 21, 2015).

decided upon by Medicare Administrative Contractors (MACs). The NCD process typically takes approximately 9 months, while the LCD process takes about 3 months. CMS is also authorized by statute to use a process for coverage decisions known as coverage with evidence development.

The implementation of the new set of MoPath CPT codes occurs under Medicare's clinical laboratory fee schedule (CLFS). CMS has two methods at its disposal to set the Medicare payment rate for a new MoPath CPT code. First, for tests for which a comparable test or code exists, CMS uses the *crosswalk* approach to benchmark Medicare payment for the new code to the same rate for a comparable, existing test or code. Second, the *gap-fill* method is used in situations where a comparable code or test does not exist.

CMS's 2014 Physician Fee Schedule Final Rule[2] specified that the rates for the new molecular pathology CPT codes were to be set using the gap-fill process,[3] which can take a year to complete, and requires MACs to set payment rates for new advanced tests based on a number of factors, such as local pricing patterns (what laboratories charge, including discounts), resources required to perform the test, and what other payers pay for the same test. CMS then determines a national payment rate for each new CPT code based on the contractor-specific median rate. The new gap-fill rates released by the MACs are significantly less than the previous code-stacked amounts. Moreover, professional associations raised their concerns with CMS about considerable reduction in payment or denial of test claims by MACs. The uncertainty surrounding the new gap-fill rates is viewed as having a potentially negative impact on investment in new test technologies, which generally requires "stability of payment over time" (Deverka and Dreyfus, 2014).

Protecting Access to Medicare Act of 2014

Further changes to Medicare's coding and payment of clinical diagnostic laboratory tests resulted from the passage of the Protecting Access to Medicare Act (PAMA) in 2014.[4] PAMA's Section 216 titled *Improving Medicare Policies for Clinical Diagnostic Laboratory Tests*[5] entails modern-

[2] Revisions to Payment Policies under the Physician Fee Schedule, Clinical Laboratory Fee Schedule and Other Revisions to Part B for CY 2014 (CMS-1600-FC).

[3] The criteria and process for gap-filling are specified in 42 CFR 414.508(b). A reconsideration process for tests that are gap-filled is specified in § 414.509.

[4] The Protecting Access to Medicare Act, P.L. 113-93, was signed into law on April 1, 2014. https://www.congress.gov/bill/113th-congress/house-bill/4302 (accessed June 1, 2015).

[5] Sec. 216 amends the Social Security Act's Title XVIII to prescribe requirements for establishment of Medicare payment rates for clinical diagnostic laboratory tests and new advanced diagnostic laboratory tests. https://www.congress.gov/113/plaws/publ93/PLAW-113publ93.pdf (accessed May 1, 2014).

ization of Medicare's payment process for laboratory services. In fact, PAMA's provisions represent the most significant changes to the CLFS in 30 years, and come after calls for reform by many stakeholders over the years. The Institute of Medicine's comprehensive study *Medicare Laboratory Payment Policy: Now and in the Future*, conducted 15 years ago, for example, recommended far-reaching changes to improve the outdated CLFS to ensure it was prepared for the new era of advanced clinical laboratory tests (IOM, 2000).

PAMA established a new market-based payment approach to paying for laboratory services, using the weighted median of rates paid by private payers for tests (Carey, 2014). This change was driven by the recognition that Medicare was paying significantly more for certain tests than other payers (OIG, 2013). To implement the new payment approach, laboratories are required, beginning in 2016, to report test market data that CMS will use to determine CLFS prices. This reporting requirement is viewed by laboratories as potentially problematic because most clinical laboratories do not have adequate IT infrastructure, staff, and other mechanisms in place to report such information (Klein, 2015).

PAMA also requires coverage of clinical diagnostics to be established through LCDs. The legislation grants the Department of Health and Human Services (HHS) the authority to designate one or more MACs to establish coverage policies and/or process claims for payment for laboratory tests for the entire Medicare program.

Finally, PAMA also created a new type of diagnostic test referred to as an advanced diagnostic laboratory test (ADLT). An ADLT is a clinical diagnostic laboratory test offered and furnished only by a single laboratory and not sold for use by any laboratory other than the original developing laboratory. An ADLT must meet one of the following criteria:

- The test is analysis of multiple biomarkers of DNA, RNA, or proteins combined with a unique algorithm to yield a single patient-specific result; or
- The test is cleared or approved by the Food and Drug Administration (FDA); or
- The test meets other similar criteria established by HHS.

PAMA outlines a sophisticated coding structure for laboratory tests that could include existing Healthcare Common Procedure Coding System (HCPCS) codes with some modification. The law calls for (1) temporary (not to exceed 2 years) HCPCS codes to identify new ADLTs or new laboratory tests that are cleared or approved by FDA; (2) unique HCPCS codes to identify and publicly report the payment rate for existing tests for which Medicare payment is made and which are ADLTs or clinical

diagnostic laboratory tests that are cleared or approved by FDA; and (3) a unique identifier, such as a HCPCS code or modifier, for certain ADLTs or FDA-cleared or -approved laboratory tests as requested by a manufacturer or laboratory.[6]

The Congressional Budget Office estimates that PAMA's clinical laboratory fee provisions will result in significant reductions in Medicare spending, with savings on the order of $2.5 billion over the 10-year period between 2014 and 2024 (CBO, 2014). CMS is in the process of developing the regulatory framework to implement the myriad legislative provisions of PAMA. Most recently, CMS released the CLFS for 2016, which shifted the pricing process for several Multianalyte Assays with Algorithmic Analyses to the gap-fill method, instead of the crosswalk method CMS had proposed in an earlier draft of the CLFS that would have likely resulted in cuts to the payment rates for those tests. Significant uncertainty as to the precise impact of PAMA's provisions on molecular diagnostics will remain until the regulations are finalized and fully implemented.

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Appendix C

Information-Gathering Sessions and Speakers

COMMITTEE MEETING 1 – JANUARY 29, 2015

JEFFREY S. DLOTT, Medical Director, Coagulation and Immunohematology, Quest Diagnostics
LEVI GARRAWAY, Associate Professor, Department of Medicine, Harvard Medical School
BRUCE G. HAFFTY, Chair of the Board, American Society for Radiation Oncology
STANLEY R. HAMILTON, College of American Pathologists
DANIEL F. HAYES, Clinical Director, Breast Oncology Program, University of Michigan Comprehensive Cancer Center
LOUIS JACQUES, Senior Vice President and Chief Clinical Officer, ADVI Consulting
LARRY NORTON, Founder and Scientific Director, Breast Cancer Research Foundation
KIRSTEN PAULSON, Senior Director, Research, Medical Device Development, Pfizer Inc.
RICHARD L. SCHILSKY, Chief Medical Officer, American Society of Clinical Oncology

COMMITTEE MEETING 2 – APRIL 1, 2015

SAMUEL ARONSON, Executive Director, IT, Partners Personalized Medicine

ROBERT CALIFF, Deputy Commissioner for Medical Products and Tobacco, Food and Drug Administration
BRIAN CAREY, Partner, Foley Hoag, LLP
JOSEPH CHIN, Senior Medical Advisor/Acting Deputy Director, Coverage and Analysis Group, Centers for Medicare & Medicaid Services
CURTIS HANSON, Professor of Laboratory Medicine and Pathology, Chief Medical Officer, Mayo Medical Laboratories, Mayo Clinic
JONATHAN W. HEUSEL, Chief Medical Officer, Genomics and Pathology Services and Medical Director of the Clinical Laboratory, The Genome Institute of Washington University, Washington University School of Medicine in St. Louis
ELIZABETH MANSFIELD, Deputy Office Director for Personalized Medicine, Office of In Vitro Diagnostics and Radiological Health/ Center for Devices and Radiological Health, Food and Drug Administration
LAWRENCE J. MEYER, Professor of Dermatology and Internal Medicine, University of Utah Health Sciences Center; Associate Chief of Staff, Research, Salt Lake City Veterans Affairs Medical Center; and National Director, Genomic Medicine, Veterans Health Administration
LEE N. NEWCOMER, Senior Vice President, Oncology, Genetics and Women's Health, UnitedHealthCare
MARISA PAPALUCA, Senior Scientific Advisor, Human Medicines Research & Development Support Division, European Medicines Agency
SCOTT RAMSEY, Professor, School of Medicine, School of Pharmacy, and the Institute for Public Health Genetics, University of Washington
WILLIAM W. STEAD, Associate Vice Chancellor for Health Affairs; Chief Strategy Officer, McKesson Foundation Professor of Biomedical Informatics, Professor of Medicine, Vanderbilt University Medical Center
SUZANNE TOPALIAN, Professor of Surgery and Oncology, Director, Melanoma Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University
JOHN A. WAGNER, Senior Vice President, Head of Clinical and Translational Sciences, Takeda Pharmaceuticals
SHEILA WALCOFF, CEO and Founder, Goldbug Strategies, LLC
MARC S. WILLIAMS, Director, Genomic Medicine Institute, Geisinger Health System
JANET WOODCOCK, Director, Center for Drug Evaluation and Research, Food and Drug Administration

COMMITTEE REIMBURSEMENT WEBINAR – MAY 4, 2015

ELAINE JETER, MolDx Medical Director, Palmetto GBA
ROBERT McDONOUGH, Head of Clinical Policy Research and Development, Aetna
LINCOLN NADAULD, Director, Cancer Genomics, Intermountain Healthcare
PAUL RADENSKY, Partner, McDermott, Will & Emery
ALAN ROSENBERG, Vice President, Medical and Clinical Pharmacy Policy, Anthem

COMMITTEE MEETING 3 – JUNE 11, 2015

STEPHEN FRIEND, President, Co-Founder, and Director, Sage Bionetworks
SARAH GARCIA, Clinical Genomics Applications Manager, Personalis, Inc.
CLIFFORD A. HUDIS, Chief, Breast Medicine Service, Memorial Sloan Kettering Cancer Center
ROBERT WILDIN, Chief, Genomic Healthcare Branch, National Human Genome Research Institute

Glossary

Accrual (in clinical trials)—the enrollment of qualified patients in clinical trials.

Adjuvant therapy—additional cancer treatment given after the primary treatment to lower the risk that the cancer will return. May include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

Allele—any one of a series of two or more different genes that occupy the same position (locus) on a chromosome.

Allelic variant—an alteration in the normal sequence of a gene, the significance of which is often unclear until further study of the genotype and corresponding phenotype occurs in a sufficiently large population. Complete gene sequencing often identifies numerous allelic variants (sometimes hundreds) for a given gene.

Amplification—a process by which specific genetic material is increased. For some cancers, the number of copies of specific genes is higher than normal. These genes are said to be amplified.

Analyte—a substance that is the subject of analysis.

Analyte-specific reagent (ASR)—antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents, which through specific binding or chemical reaction with substances in a specimen are intended to be used in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens.

Analytic validation—traditionally, assessing an assay and its measurement performance characteristics, determining the range of conditions under which the assay will give reproducible and accurate data. With respect to biomarkers, assessing a test's ability to accurately and reliably measure the analytes of interest in the clinical laboratory, and in specimens representative of the population of interest.

Analytic validity—the accuracy of a test in detecting the specific entity that it was designed to detect. This accuracy does not imply any clinical significance, such as diagnosis.

Archival tissue—biological specimens collected from patients and stored for possible future use in medical care or research.

Assay—a biochemical or other measurement developed to quantify a biomarker.

Bias—the systematic but unintentional erroneous association of some characteristic with a group in a way that distorts a comparison with another group.

Bioinformatics—a field of study focused on developing fast, efficient computational procedures for data reduction, data mining, and literature search techniques and developing biologically informative annotations related to DNA/RNA sequence, gene/protein expression, or the interaction of pathways, networks, phenotypes, and druggable targets.

Biological plausibility—data elucidating the biological pathways underpinning a causal association.

Biological products (biologics)—a category of products regulated by the Food and Drug Administration, including vaccines, blood, and blood components, allergenic compounds, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.

Biomarker—a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic sequences, or pharmacologic responses to an intervention.

Biomarker test—a biochemical or other measurement developed to quantitate a biomarker. These tests can evaluate biomarkers for the detection and treatment of asymptomatic individuals (screening), establishing the presence and precise description of disease (diagnosis), estimating the risk or time to clinical outcomes (prognosis), identifying patient likelihood to benefit from certain therapies (predictive) or to experience therapy-related risks (pharmacogenomics), or treatment and posttreatment monitoring purposes (e.g., the early detection and treatment of advancing disease or complications).

Biomedical informatics—the interdisciplinary field that studies and pursues the effective uses of biomedical data, information, and knowledge for scientific inquiry, problem solving, and decision making, driven by efforts to improve human health.

Biopsy—the removal of tissues or cells so they can be examined by a pathologist.

Biorepository—a collection of biological samples, such as tissue, that can be used for research.

Biostatistics—a field of study focused on applying experimental design and data analysis to a wide range of topics in biology.

Blinding (in a controlled trial)—the process of preventing those involved in a trial from knowing the comparison group to which a particular participant belongs. The risk of bias is minimized when as few people as possible know who is receiving the experimental intervention and who the control intervention. Participants, caregivers, outcome assessors, and analysts are all candidates for being blinded. Blinding of certain groups is not always possible; for example, if treatment involves active patient participation, such as attending a therapy session, the participant cannot be blinded to the type of treatment provided.

BRCA—a gene that when mutated increases a woman's risk of developing breast cancer. Two BRCA genes have been identified and are known as BRCA1 and BRCA2.

Cetuximab—a monoclonal antibody drug used to treat head and neck cancers, and advanced or metastatic cancer of the colon and rectum, usually in combination with chemotherapy or irinotecan, another cancer drug.

Chemotherapy—treatment with drugs that kill cancer cells.

Circulating tumor DNA (ctDNA)—small pieces of DNA in the bloodstream that are released from dead and dying tumor cells. Potential screening biomarker for detecting somatic mutations associated with progression of cancer.

Clinical/biological validation—validation assessing a test's ability to accurately and reliably predict the clinically defined disorder or phenotype of interest.

Clinical endpoint—a characteristic or variable that reflects how a patient feels, functions, or survives in response to an intervention.

Clinical Laboratory Improvement Amendments (CLIA)—amendments passed by Congress in 1988 that established quality standards for all nonresearch laboratory testing performed on specimens derived from humans for the purpose of providing information for the diagnosis, prevention and/or treatment of disease, or impairment of or assessment of health. CLIA established quality standards for laboratories to ensure the accuracy, reliability, and timeliness of patient test results regardless of where the test is performed.

Clinical trial—a formal study carried out according to a prospectively defined protocol that is intended to discover or verify the safety and effectiveness of procedures or interventions in humans.

Clinical utility—evidence of improved measurable clinical outcomes, and a test's usefulness and added value to patient management decision making compared with current management absent testing.

Clinical validity—the accuracy of a test for a specific clinical purpose, such as diagnosing or predicting risk for a disorder.

Companion diagnostic—Food and Drug Administration designation for a medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or

biological product. Co-development of a drug and companion diagnostic ensures faster access to promising new treatments for patients.

Conditional coverage—a policy by which insurers agree to preliminarily cover new tests with the proviso that data would be collected in conjunction with the use of the test, to assess the clinical utility and value of the test, and to create better evidence. Data collected during conditional coverage assessments are used in later decisions regarding full coverage and may be used for research purposes afterward.

Confidence interval—a measure of the uncertainty around the main finding of a statistical analysis. Estimates of unknown quantities, such as the odds ratio comparing an experimental intervention with a control, are usually presented as a point estimate and a 95 percent confidence interval. This means that if someone were to keep repeating a study in other samples from the same population, 95 percent of the confidence intervals from those studies would contain the true value of the unknown quantity. Alternatives to 95 percent, such as 90 and 99 percent confidence intervals, are sometimes used. Wider intervals indicate lower precision; narrow intervals, greater precision.

Conflict of interest—a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.

Confounding effects—a situation in which an intervention effect is biased because of some difference between the comparison groups apart from the planned interventions, such as baseline characteristics, prognostic factors, or concomitant interventions.

Coverage with evidence development (CED)—a Centers for Medicare & Medicaid Services (CMS) program whereby prospective data collection on a product is required for national Medicare coverage (see Conditional coverage). A product that has an insufficient evidence base for CMS coverage determination could be evaluated through CED.

Current Procedural Terminology (CPT®)—a listing of descriptive terms and identifying codes for reporting medical services and procedures, designed to standardize the terminology used for medical, surgical, and diagnostic services. CPT codes were first developed by the American Medical Association and are updated by the CPT Editorial Panel.

Cytotoxic therapy—any agent or process that kills cells (e.g., chemotherapy and radiotherapy).

De novo classification—a Food and Drug Administration classification of a device or diagnostic that is not equivalent to a legally marketed product.

Deletion—the loss of genetic material. Some cancers are triggered by the deletion of key genes, portions of genes, or their regulatory sequences.

Diagnosis—a conclusion as to the presence of a disease.

Diagnostic—the investigative tools and techniques used in biological studies or to identify or determine the presence of a disease or other condition. In this report, "diagnostic" is often used synonymously with "biomarker test." These terms refer to any laboratory-based test that can be used in drug discovery and development as well as in patient care and clinical decision making.

Diagnostic test—tools and techniques used to identify or determine the presence of a disease or other condition. Any laboratory-based test that can be used in drug discovery and development as well as in patient care and clinical decision making.

Disease risk stratification—placement of an individual into a risk category based on the likelihood that a disease will develop or recur.

Distant recurrence—occurs when a cancer has metastasized to another location in the body following initial cancer treatment and remission.

DNA sequencing—a laboratory technique used to determine the exact sequence of bases (A, C, G, and T) in a DNA molecule. The DNA base sequence carries the information a cell needs to assemble protein and RNA molecules. DNA sequence information is important to investigating the functions of genes.

Enrichment trial design—the only patients entered into the clinical trial are those with positive test results at screening. These patients are randomized and/or treated.

Epidermal growth factor receptor (EGFR)—a receptor that is overproduced in several solid tumors, including breast and lung cancers. Its overproduction is linked to a poorer prognosis because it enables cell proliferation, migration, and the development of blood vessels. Several

new drugs recently approved by the Food and Drug Administration specifically target EGFR.

Epigenome—the complete set of epigenetic modifications, which are heritable or transitory changes in phenotype or gene expression that result from mechanisms other than changes in the DNA sequence in a given individual, tissue, tumor, or population.

Equipoise—that state of genuine uncertainty in the expert medical community over whether a novel treatment will be beneficial. This forms the ethical basis for assigning patients to different arms of a clinical trial.

Exome—the portion of DNA that is transcribed into mature RNA in any type of cell in the body. Though only a small fraction of the whole genome, the exome is thought to harbor a high proportion of disease-causing mutations.

False negative—the error of failing to observe a difference when in truth there is one.

False positive—the error that occurs when a difference is observed even though in truth there is none.

FDA approval—the Food and Drug Administration (FDA) can approve a device after reviewing a sponsor's premarket approval (PMA) application that has been submitted to FDA. To acquire approval of a device through a PMA application, the applicant must provide reasonable assurance of the device's safety and effectiveness.

FDA clearance—the Food and Drug Administration (FDA) can clear a device after reviewing a sponsor's premarket notification, also known as a 510(k) submission (named for a section in the Food, Drug, and Cosmetic Act), that has been filed with FDA. To acquire clearance to market a device using the 510(k) pathway, the 510(k) applicant must show that the medical device is "substantially equivalent" to a device that is already legally marketed for the same use.

Fluorescence in situ hybridization (FISH)—a method for detecting the presence of DNA sequences through the use of fluorescent probes.

Formalin-fixed, paraffin-embedded (FFPE) tissue—a tissue sample that has been preserved to enable pathological or molecular analysis.

Genome—the complete sequence of DNA in a cell or organism.

Genomics—the study of all of the nucleotide sequences, including structural genes, regulatory sequences, and non-coding DNA segments, in the chromosomes of an organism or tissue sample. One example of the application of genomics in oncology is the use of microarray or other techniques to uncover the genetic "fingerprint" of a tissue sample. This genetic fingerprint is the pattern that stems from the variable expression of different genes in normal and cancer tissues.

Genotype—the genetic makeup of an organism or cell.

Germline mutation—a gene change in a body's reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. Germline mutations are passed on from parents to offspring. Also called hereditary mutation.

Health Insurance Portability and Accountability Act (HIPAA)—an Act passed in 1996 that includes privacy and security regulations regarding disclosure and use of medical information.

Herceptin—see human epidermal growth factor receptor 2.

High-dimensional data—large datasets characterized by the presence of many more variables than observations, such as datasets that result from measurements of hundreds to thousands of molecules in a relatively small number of biological samples. The analysis of such datasets requires appropriate computing power and statistical methods.

High-throughput technology—any approach using robotics, automated machines, and computers to process many samples at once.

Histopathology—examination of tissue samples in order to understand the manifestations of disease in the organism from which the samples were obtained.

Human epidermal growth factor receptor 2 (HER2)—a growth factor receptor that is used as a breast cancer biomarker for prognosis and treatment with the drug trastuzumab (Herceptin), which targets the protein.

Human Genome Project—a 13-year project coordinated by the Department of Energy and the National Institutes of Health and completed in 2003. The project completed its goal of sequencing the genome and map-

ping all 20,000-25,000 genes in human DNA 2 years earlier than anticipated, due to technological advances.

Imatinib—a small-molecule compound originally developed for treating chronic myelogenous leukemia and gastrointestinal stromal tumors, imatinib (STI571, Gleevec) is a selective tyrosine kinase inhibitor that binds to the ATP-binding pocket and blocks the tyrosine kinase activities of Abl, c-kit, and PDGFR.

Immunohistochemistry—the process of detecting antigens (e.g., proteins) in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biological tissues.

Immunotherapy—the treatment of disease by inducing, enhancing, or suppressing an immune response.

In vitro device—a test that can detect disease, infection, or other health conditions.

Institutional Review Board (IRB)—an institutional oversight body that protects human safety, privacy, and autonomy and ensures informed consent.

Intended use—a statement describing a device's intended application, taking into account whether such use could harm the patient or consumer. The product manufacturer's intended use should be clearly marked on printed and graphic materials for proposed labels and promotional claims.

Investigational device exemption (IDE)—a Food and Drug Administration designation that allows an investigational device to be used in a clinical study to collect safety and effectiveness data supporting a premarket approval application or a premarket notification submission.

Laboratory-developed tests (LDTs)—laboratory tests used in patient care that have been developed and are performed in a Clinical Laboratory Improvements Amendments–certified clinical laboratory, but have not been reviewed by the Food and Drug Administration.

Lipidome—the complete set of lipids in a biological sample.

Loss of heterozygosity—loss of one allele at a specific position on a chromosome.

Mechanism of action—the biological pathway by which a drug affects its target in the body.

Medical device—according to the Food and Drug Administration, an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory that is recognized in the official National Formulary, or the US Pharmacopoeia, or any supplement to them; or, is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or, is intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent on being metabolized for the achievement of any of its primary intended purposes.

Metabolome—the complete set of small-molecule metabolites found with a biological sample (including metabolic intermediates in carbohydrate, lipid, amino acid, nucleic acid, and other biochemical pathways, along with hormones and other signaling molecules, as well as exogenous substances, e.g., drugs and their metabolites).

Metabolomics—the systematic study of the unique chemical fingerprints that specific cellular processes leave behind, that is, small-molecule metabolites.

Metadata—information about a dataset and how it was generated.

Microarray—a high-throughput biological assay in which different probes are deposited on a chip surface (glass or silicon) in a miniature arrangement.

Molecularly targeted therapy—in contrast with cytotoxic therapy, molecularly targeted therapies exploit known "driver" biomarkers as therapeutic targets in diseases such as oncology. Determining the driver status of a biomarker is known as target validation.

Multivariate model—measuring the impact of more than one variable at a time while analyzing a set of data, for example, looking at the impact of age, sex, and occupation on a particular outcome.

Negative predictive value (NPV)—the probability that an individual with a negative test result is truly unaffected and/or does not have the particular disease or characteristic that the test is designed to detect.

Next-generation sequencing—non-Sanger–based high-throughput DNA sequencing. These technologies enable millions or billions of DNA strands to be sequenced in parallel, yielding substantially more throughput and minimizing the need for the fragment-cloning methods that are often used in Sanger sequencing of genomes.

Off-label use—using a drug that either has not been approved by the Food and Drug Administration or has not been approved for the purpose for which it is being used.

Omics—scientific disciplines comprising study of related sets of biological molecules. Examples of omics disciplines include genomics, transcriptomics, proteomics, metabolomics, and epigenomics.

Omics-based test—an assay composed of or derived from many molecular measurements and interpreted by a fully specified computational model to produce a clinically actionable result.

Overfitting—occurs when the model-fitting process unintentionally exploits characteristics of the data that are due to noise, experimental artifacts, or other chance effects that are not shared among datasets, rather than to the underlying biology that is shared among datasets.

Pathway biomarker—a biomarker that can be detected in one or several key steps along a biochemical pathway that may be perturbed in cancer cells. Because of their broad applicability, pathway biomarkers may be useful in assessing the effectiveness of multiple drugs in different types of cancers.

Patient management—decisions about the care and treatment of individual patients, based on information about their disease status and history.

Performance characteristics—the sensitivity, accuracy, and specificity of a biomarker-based test.

Pharmacodynamics—the study of the biochemical and physiological effects of drugs, the mechanisms of drug action, and the relationship between drug concentration and effect. Pharmacodynamics is the study of what a drug does to the body, as opposed to pharmacokinetics, which is the study of what a body does to a drug.

Pharmacogenomics—a biotechnological science that combines the techniques of medicine, pharmacology, and genomics to determine the effects

of genetic differences in patients on the metabolism and hence the potential toxicity or efficacy of drugs.

Pharmacokinetics—the study of the time course of substances, such as drugs, in an organism. Pharmacokinetics is used to determine how long a drug remains in the body.

Phase I clinical trial—clinical trial in a small number of patients in which the toxicity and dosing of an intervention are assessed.

Phase II clinical trial—clinical trial in which the safety and preliminary efficacy of an intervention are assessed in patients.

Phase III clinical trial—large-scale clinical trial in which the safety and efficacy of an intervention are assessed in a large number of patients. The Food and Drug Administration generally requires new drugs to be tested in Phase III trials before they can be put on the market.

Phenotype—the physical traits of an individual.

Polymerase chain reaction (PCR)—a technique for duplicating genetic sequences in vitro by as many as a billion times. This technique enables the detection of relatively scarce genetic material.

Polymorphism—existence of a gene in several allelic forms.

Positive predictive value (PPV)—the probability that an individual with a positive test result has, or will develop, the particular disease or characteristic that the test is designed to detect. It is a measure of the ratio of true positives to (false + true positives).

Positron emission tomography (PET)—a highly sensitive technique that uses radioactive probes to image in vivo tumors, receptors, enzymes, DNA replication, gene expression, antibodies, hormones, drugs, and other compounds and processes.

Precision medicine—tailoring of medical treatment to the individual characteristics of each patient to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

Predictive factor—a measure that identifies patients most likely to be sensitive or resistant to a specific treatment regimen or agent. [A predictive factor] is particularly useful when that measure can be used to identify the subgroup of patients for whom treatment will have a clinically meaningfully favorable benefit-to-risk profile.

Premarket approval (PMA)—a Food and Drug Administration approval for a new test or device that enables it to be marketed for clinical use. To receive this approval, the manufacturer of the product must submit the clinical data showing the product is safe and effective for its intended use.

Premarket notification or 510(k)—a Food and Drug Administration review process that enables a new test or device to be marketed for clinical use. This review process requires manufacturers to submit data showing the accuracy and precision of their product and, in some cases, its analytical sensitivity and specificity. Manufacturers also have to provide documentation supporting the claim that their product is substantially equivalent to one already on the market. This review does not typically consider the clinical safety and effectiveness of the product. (See also FDA clearance.)

Proficiency testing—laboratories performing non-waived tests must enroll laboratory personnel in tests specific to the subspecialty relevant to the tests they will evaluate. The Clinical Laboratory Improvement Amendments requires proficiency testing of personnel at least once every 2 years.

Prognosis—an assessment of the probable course of a disease given the risk factors present in an individual; this assessment may affect treatment decisions.

Prognostic factor—a measure correlated with a clinical outcome in the setting of natural history or a standard-of-care regimen; it is a variable used to estimate the risk of or time to clinical outcomes.

Prospective clinical trial—a clinical trial in which patients are identified and then followed forward in time.

Prospective–retrospective clinical study—an analysis using archived specimens from previously conducted prospective clinical trials that addressed the intended clinical use of the test.

Proteome—the complete set of proteins expressed by a cell, tissue, or organism.

Proteomics—the study of the structure, function, and interactions of the proteins produced by the genes of a particular cell, tissue, or organism. The application of proteomics in oncology may involve mass spectroscopy, two-dimensional polyacrylamide gel electrophoresis, protein chips, and other techniques to uncover the protein "fingerprint" of a tissue sample. This protein fingerprint is the pattern that stems from the various amounts and types of all the proteins in the sample.

PSA test—a blood test that detects prostate-specific antigen. The PSA test was approved by the Food and Drug Administration in 1985 for prostate cancer recurrence, and has also been widely used as a screening test for prostate cancer. Due to concerns of overdiagnosis and overtreatment, its value as a screening test is being examined.

Qualification—evidentiary process of linking a biomarker with biological processes and clinical endpoints.

Quality-adjusted life-year (QALY) index—an index that combines measures of quality of life with length of life.

Randomized block trial design—a test result needs to be available at the time of screening patients for accrual, and the result is used to stratify the randomization of patients to different therapies.

Risk stratification—the classification of patients into groups based on the likelihood of developing or suffering effects from a disease.

Sample bias—see Bias.

Sensitivity (analytic)—the lowest concentration that can be distinguished from background noise. This concentration is termed an assay's detection limit.

Sensitivity (clinical)—a measure of how often a test correctly identifies patients with a specific diagnosis. It is calculated as the number of true-positive results divided by the number of true-positive plus false-negative results.

Single nucleotide polymorphism (SNP)—a variant DNA sequence in which the purine or pyrimidine base (e.g., cytosine) of a single nucleotide has been replaced by another such base (e.g., thymine).

Somatic mutation—an alteration in DNA that occurs after conception. Somatic mutations can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. These alterations can (but do not always) cause cancer or other diseases.

Specificity (analytic)—how well an assay detects only a specific substance and does not detect closely related substances.

Specificity (clinical)—a measure of how often a test correctly identifies the proportion of persons without a specific diagnosis. It is calculated as the number of true-negative results divided by the number of true-negative plus false-positive results.

Standard of care—in medicine, treatment that experts agree is appropriate, accepted, and widely used. Also called best practice and standard therapy.

Standard operating procedures (SOPs)—instructions detailing steps and activities of a process or procedure.

Statistical and bioinformatics validation—verifying that the omics-based test can perform its intended task. Ideally, this involves ensuring that the test can accurately predict the clinical outcome of interest in an independent set of samples that were not used in developing the test. Such validation is particularly important because omics-based tests typically involve computational models whose parameters can be "overfit" in any single dataset, leading to an overly optimistic sense of the test's accuracy.

Statistical significance—a result that is unlikely to have happened by chance. The usual threshold for this judgment is that the results, or more extreme results, would occur by chance with a probability of less than 0.05 if the null hypothesis was true. Statistical tests produce a p-value used to assess this.

Surrogate endpoint—a biomarker that is intended to substitute for a clinical endpoint in a therapeutic clinical trial and is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

Systemic therapy—treatment using substances that travel through the bloodstream and reach and affect cells throughout the body.

Target validation—demonstration that a potential drug target plays a key role in the disease process.

Transcriptome—the complete set of RNA transcripts from DNA in a cell.

Trastuzumab—see human epidermal growth factor receptor 2 (HER2).

Tumor marker—substances that are produced by cancer or by other cells of the body in response to cancer or certain benign (noncancerous) conditions. Most tumor markers are proteins. However, more recently, patterns of gene expression and changes to DNA have also begun to be used as tumor markers.

Usage—contextual analysis based on the specific use proposed and the applicability of available evidence to this use. This includes a determination of whether the validation and qualification conducted provide sufficient support for the use proposed.

Validation—the process of assessing the assay or measurement performance characteristics.

Whole genome sequencing—a laboratory process that determines the complete DNA sequence of an organism's genome at a single time.