Issues in Focus

Genomics in Cancer Care: Realizing Precision Medicine
Disclosure

The content of this report was prepared by Emron on Genentech’s request with the guidance of an editorial board and is based on published literature. Statements and opinions contained in the report do not necessarily reflect those of Genentech or the editorial board.
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>2</td>
</tr>
<tr>
<td>Precision Medicine or Personalized Medicine?</td>
<td>3</td>
</tr>
<tr>
<td>Applying Genomics to Cancer Care</td>
<td>4</td>
</tr>
<tr>
<td>Genetics- and Genomics-based Diagnostics in Cancer</td>
<td>5</td>
</tr>
<tr>
<td>Sequencing Methods to Molecularly Profile Cancer</td>
<td>8</td>
</tr>
<tr>
<td>Genomics as a Driver of Big Data</td>
<td>10</td>
</tr>
<tr>
<td>Genetic and Genomic Diagnostic Tests and Testing Sites</td>
<td>11</td>
</tr>
<tr>
<td>Molecular Genetics as Prognostic Biomarkers</td>
<td>16</td>
</tr>
<tr>
<td>Genetic Testing and Guidelines and Pathways</td>
<td>16</td>
</tr>
<tr>
<td>Integrating Genomic-based Testing Into Clinical Practice</td>
<td>17</td>
</tr>
<tr>
<td>Collaboration Between Oncologists and Pathologists</td>
<td>19</td>
</tr>
<tr>
<td>Advancing Precision Medicine Through Clinical Trials Innovation</td>
<td>20</td>
</tr>
<tr>
<td>Ethical Issues Related to Precision Medicine</td>
<td>22</td>
</tr>
<tr>
<td>Paying for Precision Medicine</td>
<td>24</td>
</tr>
<tr>
<td>Codes for Genetic Testing and Molecular Diagnostics</td>
<td>28</td>
</tr>
<tr>
<td>Economic Value of Sequencing</td>
<td>29</td>
</tr>
<tr>
<td>What Lies Ahead</td>
<td>29</td>
</tr>
<tr>
<td>Glossary of Terms</td>
<td>30</td>
</tr>
<tr>
<td>Appendix</td>
<td>31</td>
</tr>
<tr>
<td>References</td>
<td>35</td>
</tr>
</tbody>
</table>

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*Issues in Focus: Genomics in Cancer Care: Realizing Precision Medicine.*

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Introduction

Scientific discovery and innovation over the last decade are bringing about a transformation in clinical cancer research and the understanding of how these diseases are both diagnosed and treated. We now understand that, fundamentally, cancers are diseases of the human genome—the entire set of genetic instructions found in a cell—and that understanding the disease begins by identifying the abnormal genes and proteins that confer the risk of developing cancer. Recent research has led to the discovery of hundreds of genes that harbor variations contributing to cancer and other illnesses and has identified genetic variability in patients’ responses to various treatments. In addition, two broad classes of genes—proto-oncogenes and tumor-suppressor genes—play a key role in cancer induction. These genes encode many kinds of proteins that help control cell growth and proliferation; mutations in these genes can contribute to the development of cancer. As a result, cancer care providers today increasingly may rely on comprehensive genomic data to add a unique level of personalization or precision to individual patient care planning.

Advanced genomic profiling refines our understanding of cancer and presents a complex landscape for providers and payers tasked with utilizing and funding these tests and services for cancer patients.

This second edition of the Issues in Focus series serves as a primer regarding this landscape by taking a closer look at the opportunities and challenges to practice and policy that are central to realizing the potential of a broader spectrum of genomic advances and technologies in a new era of precision medicine that is changing cancer care in the United States.

Upgrading Technology to Improve Care Delivery

The advances in personalized medicine overlap with health care reform goals laid out in the Affordable Care Act, which is designed, in part, to drive improvements in the quality of care and the value proposition across all of health care delivery. The 2013 Institute of Medicine (IOM) report, Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis, identified several ways to improve the quality of cancer care in the United States. One of the tactics focused on efforts to upgrade the nation’s health information technology (HIT) infrastructure, which the report said would enable more effective diagnosis and prognosis and better quality and delivery of care.

The IOM report also addressed the progress made toward the recommendations included in its groundbreaking 1999 report on cancer in the United States. That earlier report found that cancer care is not as patient-centered or evidence-based as it could be. Enhancing the quality of care fits with the IOM’s goal of transforming the cancer care continuum, which includes efforts to identify better tools for cancer diagnosis and more effective targeted treatments.

The Obama administration also has taken steps to support the effort to make cancer care more patient-centered with the Precision Medicine Initiative, a coordinated national research effort to catalyze a new era of data-based and more precise medical treatment that considers the genetic, lifestyle, and environmental differences of individuals. An allocation of $215 million in the 2016 fiscal year proposed budget will fund the National Institutes of Health (NIH), the National Cancer Institute (NCI), the Food and Drug Administration (FDA), and the Office of the National Coordinator for Health Information Technology (ONC) to pursue the following activities:

- NIH to develop a voluntary national research cohort of more than 1 million Americans to transform participation in disease research and support open, responsible data sharing
- NCI to accelerate identification of cancer genomic drivers to propel new cancer treatment discovery
- FDA to develop high-quality curated databases and modernize the regulatory structure, as needed, to support the new research framework and protect public health
- ONC to develop interoperability standards that address privacy and secure information exchange.

These efforts are just the beginning of the increasing shift to personalized care that is based on better utilization of genome-based technology. It is believed that this technology will lead to a transition over time of the entire approach in medicine to more personalized and preventive care.

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*The terms and procedures printed in bold-faced blue type are defined in the Glossary of Terms, which begins on page 30.
However, there are challenges in effectively and efficiently developing new targeted cancer therapies and testing for tumor markers or biomarkers that indicate which patients will be responsive to them, and in implementing them appropriately in clinical practice. These challenges include policy issues, such as the level of oversight needed for test development and use, levels of evidence necessary for reimbursement decisions, and ways to meet informational needs of providers and patients (Figure 1).

Precision Medicine or Personalized Medicine?

The concept of precision medicine requires an understanding of the terminology involved to better focus on how to accomplish individually tailored, whole-person care. The clinical benefits of personalized medicine are evolving, with the goal of providing the right treatment, at the right dose, at the right time to the right patient.

A Better Understanding of Precision Medicine

The terms “precision medicine” and “personalized medicine” are often used interchangeably but may take on different meanings across different stakeholder groups. Both terms appear in this report. The lack of standardized definitions and implications for the scope of care delivery is the subject of published papers. Some experts maintain that personalized medicine, often referred to as personalized care, is not a new concept, as medicine has always considered the needs of the individual. Others view the concept more narrowly through the lens of genomic-based testing and targeted therapy.

Precision medicine is a concept that emerged in the writing of Clayton Christensen of the Harvard Business School in his book, The Innovator’s Prescription: A Disruptive Solution for Health Care. According to the authors, precision medicine incorporates the precise diagnosis of diseases, so that therapies that are predictably effective for each patient can be developed and standardized. The national Precision Medicine Initiative views precision medicine as an innovative approach to disease prevention and treatment that takes into account individual differences in people’s genes, environments, and lifestyles.

Some health care providers prefer the term “precision medicine” because it implies a more accurate diagnosis of a person’s disease. However, the term “personalized medicine” might imply the creation of drugs or medical devices that are unique to a person, rather than to the subpopulation(s) to which a person belongs, which are uniquely or disproportionately susceptible to a cancer or a specific treatment. While tumors might be distinct at a DNA level, it is not practical to assume each person would receive a customized therapy for his or her cancer.

Terminology matters. A narrow view of personalized or precision medicine focused on the application of genetics, genomics, and other types of “omics” alone may eclipse the broader construct of individually tailored, whole-person care, which is the bedrock of what people need and want when they are ill.

Clinical Benefits of Precision Medicine

Precision or personalized medicine includes the ability to classify individuals into subpopulations that are uniquely or disproportionately susceptible to a particular disease or responsive to a specific treatment. Therapeutic interventions then can be concentrated on those who will benefit, possibly sparing expense and some side effects for those who will not. The clinical benefits of personalized medicine are still evolving, but there are five areas of present development that show great promise:

- **Diagnosis/prognosis** — assess particular subtypes of a disease or the unique characteristics of a condition
- **Treatment prediction** — analyze whether a patient, infectious agent, or tumor with particular characteristics will respond to a certain treatment
- **Dosing** — determine appropriate amounts or strengths of treatments to administer to a particular individual
- **Safety** — anticipate adverse treatment reactions in certain subpopulations
- **Monitoring** — track and observe a patient’s response to a course of treatment, in part to evaluate any necessary modifications to the chosen treatment course
Replacing a One-Size-Fits-All Approach

Many stakeholders agree that regardless of the terminology applied, the underlying fundamental philosophy is the idea of providing the right treatment, at the right dose, at the right time to the right patient. This may counter prevailing trends toward standardized decision making and measurement and treatment pathway adoption in the current “one-size-fits-all” approach to patient care. Replacing this approach with one designed to meet the precise needs of the patient offers the possibility of producing better health outcomes and may provide cost-effectiveness benefits.

The prospect of broadly applying the concept of precision medicine has been dramatically improved by the recent development of large-scale biologic databases (such as the human genome sequence), powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology), and computational tools for analyzing large sets of data. What is needed now is a broad research program to encourage creative approaches to precision medicine, to test them rigorously, and ultimately to use them to build the evidence base needed to guide clinical practice.

Applying Genomics to Cancer Care

Sequencing of the human genome has greatly accelerated the process of linking specific genetic variants with disease. This linking process is likely to expand as genome sequencing plays an increasingly larger role in health care. Researchers estimated that 228,000 human genomes had been completely sequenced worldwide at the end of 2014, and they expect this number to double about every 12 months before reaching 1.6 million genomes by 2017.

Genome sequencing—which deciphers the order of DNA bases in an entire genome—first began in the 1970s. The first time scientists sequenced a person’s entire genome, it took more than a decade and cost hundreds of millions of dollars. In 2014, Illumina introduced a new machine that can sequence a human genome for $1,000. However, it is important to note that additional costs and time are necessary for analysis and annotation in a clinical setting.

New technologies now enable the rapid sequencing of large amounts of DNA at lower costs than was previously possible. These new technologies, often called next-generation sequencing (NGS) or massively parallel or high-speed sequencing, are distinguished by their ability to rapidly examine many genes simultaneously, using a single test. This multiplex biomarker testing approach provides significant opportunity in the clinical care setting for oncology patients.

Advantages of NGS Technologies

Benefits of NGS over traditional biomarker testing methods include:

- Provides the ability to sequence small quantities of DNA without manipulation
- Offers sequencing "coverage" of each gene to interrogate multiple areas of the gene concurrently
- Aids molecular diagnoses in patients with novel diseases when standard diagnostic approaches have been exhausted
- Helps expand the characterization of genetic contributions to different diseases
- Offers insights into the mutational processes and gene regulatory networks implicated in disease progression
A Testing Ground for Molecular Diagnostics

Through analysis and identification of abnormal genes, researchers have developed a collection of molecular diagnostics designed to guide disease treatment and management. Many of these tests are aimed at determining the optimal treatments for specific forms of cancer, making oncology a valuable testing ground for the use of molecular diagnostic tests. As a result, the stage is set for wide-ranging changes in how cancer is diagnosed, how targeted therapies are developed and utilized to treat cancer, and how strategies to prevent cancer are refined.

The result is that, after decades of research, health care is on the precipice of a new era of precision medicine in which detailed genetic information may be routinely used to deploy potentially more effective, patient-specific remedies to treat a patient’s cancer.

Genomics and Immunotherapy

Advances in genome sequencing also have led to other unprecedented opportunities to treat diseases. For cancer, most genome sequencing studies have focused on identifying new driver mutations that promote neoplastic development and metastasis. This same technology can be used to identify expressed mutations in cancer cells that result in expression of tumor-specific antigens. These can be targets for immune-mediated therapies (ie, immunotherapy) that control and/or eliminate cancer. This approach may also be useful in identifying subsets of patients whose tumors express antigens that can be most effectively targeted by immunotherapy, and may provide a mechanism to longitudinally evaluate changes in the antigenic profile of tumors as a consequence of ongoing immunotherapy. Some researchers predict that a genomic approach to tumor antigen identification may provide new opportunities for individualized cancer immunotherapy directed at tumor-specific—rather than simply cancer-associated—antigens in the future.

The link between the immune system and cancer was noticed more than 100 years ago, and the first immunotherapy was approved in 1992 for metastatic renal cancer. Today, many different kinds of immunotherapies for a variety of cancers are in testing. Nonetheless, experts agree that immunotherapy is still in its early stages.

Immunotherapy treats the immune system and not the cancer, which is the target of most current treatments, including chemotherapy, radiation, and genetically targeted therapy. Current approaches have been seen to succumb to cancer’s uncanny ability to develop resistance through mutation. Most experts believe it will take combinations of immunotherapy drugs—or combinations of immunotherapy with other cancer treatments—to optimize their impact and fight the ever-changing cancers. Finding safe and effective combinations is a daunting undertaking. Innovations in genomic sequencing can help the scientific community determine who are the patients most likely to benefit from these treatments and how to develop more treatment options to improve care for patients.

Genetics- and Genomics-based Diagnostics in Cancer

An ever-expanding understanding of the molecular basis of the more than 200 unique diseases collectively called cancer, combined with efforts to apply these insights to clinical practice, is forming the foundation for precision medicine.

Fundamentals of Cancer

Cancer is extremely complex and involves profound changes in the basic genome and changes of cellular machinery that control cell reproduction, differentiation, and death. Six fundamental changes are required for a cell to turn cancerous:

- Self-sufficiency in growth signals
- Insensitivity to growth-inhibitory or antigrowth signals
- Evasion of programmed cell death (apoptosis)
- Limitless potential to replicate
- Sustained angiogenesis (self-ordering of a blood supply)
- Tissue invasion and metastasis

Each of these alterations allows the cell to escape immune-system detection and overcome the natural defense mechanisms of cancer prevention.
Diagnosing Cancer

The primary tools for diagnosing cancer today are laboratory tests, imaging, endoscopy, physical exams, and biopsies. Additionally, precision medicine utilizes genetic and genomic clinical laboratory testing to identify molecular markers that signal disease risk or presence before clinical signs and symptoms appear. It offers the opportunity to focus on prevention and early intervention rather than on reaction at advanced stages of disease (Figure 2).

The introduction of NGS technologies, which enable the quick analysis of many genes simultaneously, is dramatically changing how genetic testing can be used in clinical care. However, the complexity of sequencing far exceeds that of most other testing in health care.

Genetic and molecular screening and testing can help:

- Identify a person with a predisposition for a given disease
- Detect whether a person has a disease, often in earlier stages of illness than was previously possible
- Predict the potential effectiveness of a particular drug therapy for an individual with a particular condition
- Describe a more precise nature of a disease, such as condition severity and the characteristics of an organism

Testing can also inform prognosis (see page 16).

Using Molecular Tests in Oncology

An increasing number of molecular diagnostic tests are helping to guide drug treatment and management. Patients may not necessarily benefit from the first drug they are offered in treatment, and responses to the same drug can differ across patients. One study estimates that as many as one-fourth of the cancer patient population will not respond to any known chemotherapy drug.

The use of genetic and other forms of molecular screening allows the physician to select a more likely optimal therapy at the outset, thus potentially avoiding the frustration and costs associated with trial-and-error prescribing potentially resulting in improved quality of care received. Even when single-analyte tests — tests that detect only one specific marker of tumor response — are accurate, patients can still be resistant to the targeted therapies or acquire such resistance after a favorable initial response to treatment. Understanding the cause of the primary or acquired resistance of these patients is becoming more of a possibility due to technological advances that have made it feasible and economical to decipher much or all of the entire genome of tumor cells. NGS has uncovered co-occurring genetic mutations in tumors, including molecular backup pathways that can emerge when a major tumor driver is blocked from acting by a specific treatment.

NGS has uncovered co-occurring genetic mutations in tumors, including molecular backup pathways that can emerge when a major tumor driver is blocked from acting by a specific treatment.
Many cancer drugs in the pipeline target specific mutations. However, the tumor genomic landscape is heterogeneous (e.g., breast cancer can be expressed differently within a patient, as well as in different patients), and researchers are finding that it changes with the progression of cancer. Multiple driver mutations (actionable targets) may be present within individual patients and tumors between patients with the same form of cancer.\(^{34}\)

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By 2013, comprehensive sequencing studies had discovered

- 71 tumor suppressors and
- 54 oncogenes, which when mutated contribute to cancer development.\(^{35}\)

All of the known driver genes can be classified into one or more of 12 cellular signaling pathways.\(^{35}\) Targeted therapies are used to affect the pathways during tumor growth. Single-analyte companion diagnostics exist for many drugs, but are costly and require additional time to develop. However, NGS-based panels can simultaneously detect the presence of multiple analytes in human samples and capture a complete view of the tumor landscape, potentially making measurements easier and more economical.\(^{35}\) Notably, these panels may test for genetic alterations that do not yet translate into better clinical outcomes and do not fit payers’ evidentiary standards for payment.\(^{17,20}\)

With an increasing emphasis on more patient-centered, personalized, and preventive approaches, genetically personalized strategies might address the patient and physician frustrations that sometimes result from the one-size-fits-all paradigm of evidence-based medicine.\(^{36}\)

With an increasing body of knowledge about underlying genomic alterations, tumor classification is shifting away from anatomic (i.e., tissue of origin) and toward molecular taxonomy, which has a profound effect on the way that oncology treatment decisions are made.\(^{7}\) Bringing diagnostic tests to market previously required developing evidence of technical feasibility, analytic validity, and clinical validity. However, considering the use of molecular diagnostics in oncology requires decision makers to answer questions pertaining to clinical utility (see box).\(^{18}\) The addition of clinical utility questions has changed the traditional path and altered the processes involved in developing molecular diagnostic tests.\(^{18}\)

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**Key Questions in Considering the Use of Molecular Diagnostics in Oncology**\(^{18}\)

- **Analytic validity:** Does the genomic application provide correct information and measure what it is supposed to measure?
- **Clinical validity:** Is there a significant association between the results of the genomic application and the clinical phenotype (i.e., observable condition of the individual)?
- **Clinical utility:** Does the genomic application provide clinically significant information? Does it lead to improved patient outcomes as compared with the alternatives?

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Market uptake of precision medicine depends on identifying molecular markers and developing clinically useful diagnostic tests, according to assessments of biopharmaceutical and diagnostic companies reported in the May/June 2015 Impact Report by the Tufts Center for the Study of Drug Development (CSDD).\(^{37}\) While commitment remains high, developers face...
As the development and commercialization of biomarkers and companion diagnostic testing continues to rise, clinicians need up-to-date and succinct information to guide selection of appropriate testing. The NCCN Biomarkers Compendium® is one such source that provides the essential details for nearly 1,000 biomarker testing recommendations linked to the NCCN Clinical Practice Guidelines in Oncology. The choice of specific test kits or methodologies remains that of the treating oncologists and pathologists. Table 1 summarizes the subset of tests with clinical utility regarding responsiveness to targeted therapy. Other groups (some listed in the Resource Appendix) are assessing the clinical and analytic validity for specific test methodologies. The NCCN Biomarkers Compendium® is complementary to these other efforts.

### Table 1. Predictive Biomarker Tests Used for Treatment Decision Making From the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) and Biomarkers Compendium

<table>
<thead>
<tr>
<th>Test</th>
<th>NCCN Guideline or Disease</th>
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<tr>
<td>21-gene RT-PCR</td>
<td>Breast cancer</td>
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<tr>
<td>BCR-ABL1 translocation</td>
<td>Ph+ acute lymphoblastic leukemia, CML</td>
</tr>
<tr>
<td>ABL1 mutation</td>
<td>Ph+ acute lymphoblastic leukemia, CML</td>
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<tr>
<td>ALK rearrangement</td>
<td>NSCLC</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>NSCLC, melanoma, colon cancer, rectal cancer</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td>NSCLC</td>
</tr>
<tr>
<td>ERBB2 amplification/overexpression</td>
<td>Breast cancer, esophageal and esophagogastric junction cancers, gastric cancer</td>
</tr>
<tr>
<td>ESR1 expression</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>KIT mutation</td>
<td>Soft tissue sarcoma: GIST</td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>Colon cancer, rectal cancer, NSCLC</td>
</tr>
<tr>
<td>MGMT promoter methylation</td>
<td>CNS cancers: anaplastic glioma/glioblastoma</td>
</tr>
<tr>
<td>MLH1, MSH2, MSH6, PMS2 expression and/or mutation, MSI testing</td>
<td>Colon cancer, rectal cancer</td>
</tr>
<tr>
<td>PDGFRA mutation</td>
<td>Soft tissue sarcoma: GIST</td>
</tr>
<tr>
<td>PGR expression</td>
<td>Breast cancer</td>
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<tr>
<td>ROS1 rearrangement</td>
<td>NSCLC</td>
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The NCCN Biomarkers Compendium® identifies biomarker tests—tests measuring gene and gene products used for cancer diagnosis, screening, monitoring, surveillance, or predictive or prognostic information—recommended for use by the NCCN Guidelines® panels. This table summarizes the tests, as of February 2014, which are predictive of responsiveness to a targeted therapy and included in current guidelines.

*Based upon analysis of NCCN Biomarkers Compendium ©2014 National Comprehensive Cancer Network, Inc. Accessed February 14, 2014. Records may have been updated since then as guideline changes have been recorded.

*Data from NCCN.

CML=chronic myelogenous leukemia; CNS=central nervous system; GIST=gastrointestinal stromal tumor; MSI=microsatellite instability; NSCLC=non-small cell lung cancer; PDGFRA=platelet-derived growth factor receptor alpha; Ph+=Philadelphia chromosome-positive; RT-PCR=reverse transcription-polymerase chain reaction.

**Sequencing Methods to Molecularly Profile Cancer**

The purpose of genetic and genomic clinical laboratory testing is to look for variants or mutations in the genetic code that may indicate specific health conditions. Most testing, until recently, was performed on a limited number of known genes, such as the analysis of the *BRCA1* and *BRCA2* genes for determining risk for breast and/or ovarian cancer.

New genomic sequencing technologies have enabled advances in the diagnosis and treatment of cancer. For example, cancer is no longer identified primarily by the location in the body where it begins. Cancer also is identified by the complex combination of patient-specific molecular characteristics that drive the development and behavior of each cancer.

This is part of the molecular biology revolution that began in the 1990s and early 2000s when several molecularly targeted...
therapies became available. Single-analyte tests were used to assess the likelihood of responding to specific treatments targeted to the genetic alterations in the tumors that were driving their growth.\textsuperscript{11}

Such tests have been followed by the development of more comprehensive genomic profiling enabled by NGS technology. Distinguished by their ability to rapidly examine many genes simultaneously, using a single test, this technology has opened the door for use in clinical care, instead of only for research purposes, and ultimately to replace many current tests on specific genes.\textsuperscript{21} Other novel techniques, such as RNA-sequencing tests and “liquid biopsies” that sample the DNA of tumor cells circulating in the blood, are being developed as methods for molecularly profiling cancers. The rapidly changing nature of the technologies used to develop tests adds to the complexity of assessing new tests as they arise.\textsuperscript{11}

**Sequencing as a Continuum**

Sequencing encompasses an evolving range of methods and approaches that can be used in a variety of ways.\textsuperscript{20} Thus, it is helpful to think of sequencing as a continuum:

- **Targeted sequencing** involves sequencing specific genes, often as a panel of multiple genes\textsuperscript{20}

- **Whole exome sequencing (WES)** involves the determination of the DNA sequence of the protein encoding regions—collectively known as the exome—which constitute about 1\% of the genome\textsuperscript{30}

- **Whole genome sequencing (WGS)** involves the determination of the sequence of most of the DNA content constituting the entire genome, which has about 22,000 genes\textsuperscript{20}

- **RNA sequencing** focuses efforts on the DNA portion of the genes that are being transcribed into RNA and then into proteins that play an active role in tumor cells. Most mutations in oncogenes—a mutated gene that contributes to the development of cancer—are easier to detect in RNA\textsuperscript{11}

WES, an abridged version of the more complete but more costly WGS, has the potential to identify clinically relevant variations in genes at a lower cost than WGS.\textsuperscript{20} Once a patient’s DNA is extracted and the exons—the DNA segments that code for proteins—are sequenced, computer programs identify differences between the patient’s DNA and a reference sequence for the human genome. These variants may point to the cause of the patient’s disease.\textsuperscript{41}

**Liquid Biopsies**

Other innovative molecular diagnostic tests on the horizon are those that measure tumor DNA circulating in the blood and are called liquid biopsies. They analyze a small blood sample to detect and screen the naked DNA released by tumor cells during cell turnover, circulating tumor cells, and/or cell-free tumor DNA. Although these DNA fragments are small, they can contain genetic mutations.\textsuperscript{11}

For these biopsy tests, circulating tumor DNA must be separated from the DNA of normal cells in the bloodstream, a challenging process. Such liquid biopsies are advantageous because they are non-invasive, enabling the collection of multiple specimens with minimal burden to patients.\textsuperscript{11} The tests also avoid the potential for DNA degradation associated with testing of paraffin-embedded tissue samples. Another advantage is that the DNA from multiple genetically diverse metastatic tumors can be collected in a single blood sample, unlike surgical biopsies that only sample the DNA of the specific tumor site covered in the biopsy.\textsuperscript{11}

Liquid biopsy tests have many potential uses in oncology, including determining the mutation status of the tumor, monitoring tumor burden, and tracking the development of resistance to targeted therapies. However, studies indicate that these tests may work better in certain cancers and in higher-stage tumors.\textsuperscript{11}

If liquid biopsies are sensitive enough, oncologists could potentially use the tests to detect residual disease after treatment and early recurrence. Circulating tumor DNA also could reveal how the genetics of the tumor changes over time and be used to track the emergence of new mutations that might influence responses to treatment.\textsuperscript{11}
Genomics as a Driver of Big Data

Decreases in the costs of computing power and storage, the proliferation of smart devices, and the growth of electronic communication are generating an explosion of health care data, often referred to as “big data.” By 2020, this health care data worldwide is estimated to reach 25,000 petabytes (1 petabyte = 10^15 bytes of data) of digital information, or the equivalent of the contents of 500 billion four-drawer file cabinets. While definitions of big data vary, at least three defining features of it — volume, variety, and velocity — are widely accepted. Massive amounts of disparately formatted and constantly refreshed data from sources, including electronic health records (EHRs), diagnostic imaging, and laboratory testing, as well as data streaming from social media and mobile applications, must be efficiently and flexibly linked, managed, and analyzed to economically extract value — through insights that improve health.

By 2020, this health care data worldwide is estimated to reach 25,000 petabytes of digital information, or the equivalent of 500 billion four-drawer file cabinets. The proliferation of genomics data through sequencing technologies is a key driver of big data. The amount of data from a single person’s whole genome is equivalent to the information in over 100,000 photos. Many future medical discoveries will depend on the ability to process and analyze large genomic data sets. The American Society of Clinical Oncology (ASCO) has predicted that by 2030, HIT will be the major mechanism for collecting, analyzing, and learning from big data in order to drive change in the delivery of care.

The combination of improved methods of genomic analysis, decreasing genotyping costs, and increasing computing resources has led to an explosion of clinical genomic knowledge in the past 10 years. Similarly, health care systems are increasingly adopting robust EHR systems that can be used to improve health care. These EHR systems contain a vast repository of disease and treatment data that could be mined for genomic research. Kaiser Permanente manages up to 44 petabytes of data about its 9 million members through its EHR system alone — 4,400 times the equivalent of data stored in the Library of Congress.

Information about the interaction between genes and environment that results in disease has been elusive to date, according to NIH leadership. Advances in EHR technology, implementation by physicians’ practices, and the more affordable cost of DNA analysis paves the way for the Precision Medicine Initiative to move forward, which was unlikely 10 years ago. In 2013, 78% of office-based physicians reported using any type of EHR system, a significant increase from 18% of physicians using an EHR in 2001.

Institutions are creating EHR-linked DNA biobanks (ie, a type of repository that stores biologic samples for use in research) to enable genomic and pharmacogenomic research, using EHR data for clinically relevant phenotypic information. However, EHRs at this time are designed primarily for clinical care, not research, which leads to challenges when attempting to reuse clinical EHR data for research purposes. Significant information remains locked within EHR unstructured narrative text documents, including clinical notes and certain categories of test results, such as pathology and radiology reports.
In the IOM 2013 report, *Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis*, the committee on improving the quality of cancer care recommended the development of a learning health care system for cancer, an IT system that would continually and automatically collect and compile information from clinical practice, disease registries, clinical trials, and other sources, in order to deliver the best, most up-to-date care, personalized for each patient. This IT system would be a large clinical data resource that could be used for observational research. The potential for a learning cancer care system to improve research and the generation of new knowledge about cancer care is enormous.6

Genetic and Genomic Diagnostic Tests and Testing Sites

The human genome comprises 23 paired chromosomes with 6 billion bases, which are molecules that form the building blocks of DNA, arranged around a double helix in 400 trillion cells, containing around 23,000 protein-coding genes. Only 0.4% of the human genome differs between individuals. Insights into these differences hold great promise for disease prevention and treatment. Increasingly, an understanding of these differences is enriched by information derived from a subset of clinical laboratory screening and testing performed on cells, tissue, and other samples at the genetic and molecular levels, particularly in cancer.32

Genetic information is critical in the diagnostic process for cancer tumors. Genetic and genomic clinical laboratory testing includes diagnostic tests involving an analysis of various facets of human genetic material (eg, DNA, RNA, chromosomes, and genes). Beyond analyzing genetic material directly, tests also may analyze the molecular products of genes. Those gene byproducts may include proteins, enzymes, or metabolites, which are molecules involved in metabolism.32 Testing techniques are often categorized across three major categories30:

- **Molecular genetics**—applications focused on the identification and measurement of single or multiple genes associated with a disease, disorder, or potential drug response
- **Cytogenetics**—applications that examine chromosomes and chromosomal abnormalities
- **Biochemical techniques**—applications that detect markers of changes to proteins and certain metabolites linked to genetic function

The potential for a learning cancer care system to improve research and the generation of new knowledge about cancer care is enormous.6
Types of Molecular Diagnostic Tests

The identification and measurement of changes in DNA, RNA, or specific genes are accomplished using molecular tests—clinical laboratory testing that analyzes organisms at the molecular level. These tests often focus on single genes or mutation or gene byproducts, such as proteins.32

**Fluorescence and flow cytometry:** Quantitative measurements of DNA began in the 1930s in work using ultraviolet absorption methods to identify the areas of interest. Techniques emerged in the 1960s, called fluorescence, which were used in combination with flow cytometry methods. The flow cytometry process suspends particles in a fluid for analysis and is used primarily to analyze proteins. Next-generation applications of this type are used in cancer diagnosis and risk assessment.47

For hematologic malignancies, flow cytometry and molecular genomics have been integral to cancer diagnosis.48

**DNA and sequencing tools:** Forty years after their discovery, some molecular testing techniques are still common in genetic testing today. These testing tools manipulate (cut and copy) the DNA material itself. One such technique allows scientists to “cut” DNA strands at specific places using enzymes. The cuts produce fragments that scientists can separate and reproduce. This tool became important in the ability to detect disease-related mutations and in sequencing or analyzing the nucleotides that create the genetic code in DNA or RNA, so genetic disorders can be identified and further studied.32

The sequencing process is important in lung cancers. The identification of oncogenic drivers has redefined how these illnesses are described and treated.49

**Comparing DNA, hybridization, and fluorescence in situ hybridization (FISH):** Another common molecular testing technique uses a process called hybridization, which compares complementary sequences of two strands of DNA, or of DNA and RNA. One of the strands is given a fluorescent tag, which allows for detection of mutations, deletions, and other genetic changes on the other comparison strand. Hybridization is combined with a more basic analysis of chromosomes to do advanced analysis of chromosomal abnormalities using a modern technique called FISH, which again builds on the original labeling and staining approach to studying genetic materials.32

FISH-based testing in breast cancer has focused primarily on the assessment of the copy number of the HER2 gene and on the selection of anti-HER2-targeted therapies. However, a new multicolor FISH assay, the eXagenBC™ (eXagen Diagnostics, Inc.) has been developed as a pure prognostic test to predict breast cancer outcome in lymph node-positive or lymph node-negative patients.50

Comparative genomic hybridization is related to FISH testing technology, focuses on chromosomal abnormalities, and is useful for complex tumor analysis.46 It is the technique of choice for future cytogenetic tests because of its technical performance and its comparable cost relative to older techniques.32

**Microarray technology, DNA amplification, and polymerase chain reaction (PCR):** The analysis of multiple sequences of DNA, RNA, and proteins, rather than the analysis of single genes or proteins, represents a key laboratory advance. Testing techniques still rely on comparisons, but on a much larger scale. Multiple tests are performed at the same time using an analysis platform of microarrays. Microarrays can consist of up to thousands of different DNA sequences (or other molecular-level organisms).32

Microarrays of DNA depend on DNA amplification, in which strands are replicated by many orders of magnitude, sometimes millions of times, for analysis. The process used for replication is called PCR, in which enzymes are used to copy DNA in a technique that involves repeated heating and cooling. PCR is a powerful tool that can help scientists detect and measure certain DNA sequences or note their absence. It has applications in analysis of the sex chromosomes; infectious disease diagnosis; and the diagnosis, prognosis, and treatment planning for cancers, such as non–small-cell lung cancer.32
The science of genetic and genomic testing, as well as its use in clinical practice, has evolved rapidly over the last 2 decades. As a result, clinical labs now offer a wide and growing selection of tests that clinicians can order. Laboratories have voluntarily registered over 26,000 tests for clinical and research use across 5,600 conditions and 3,800 genes in the National Center for Biotechnology Information’s Genetic Testing Registry (GTR) as of June 1, 2015.¹ This total includes 20 labs across the United States that have registered 197 tests for clinical use (eg, diagnostic, prognostic, predictive, therapeutic management, and drug response) regarding 362 cancer/somatic conditions.¹

Annual spending on testing is difficult to measure in light of how testing is defined, categorized, and measured across markets. Analyses of claims and clinical information from UnitedHealthcare, along with additional analyses of Medicare and Medicaid fee-for-service spending, estimated that the US health care system spent more than $5 billion on genetic testing and molecular diagnostics in 2010, and projected that the amount spent on these tests could increase to between $15 billion and $25 billion by 2021.²

Testing ordered by a physician may occur in several different settings, including during the physician office visit at the point of care, at a hospital laboratory, or—as is most common today—in a laboratory facility.³ These labs may use FDA-approved tests or develop their own tests. Many lab tests currently use proprietary methods, known as laboratory-developed test (LDT) offerings. LDTs can be used to measure or detect a wide variety of analytes (substances such as proteins, such chemical compounds as glucose or cholesterol, or DNA) in a sample taken from a human body. Some LDTs are relatively simple tests that measure single analytes. Others are complex and measure or detect numerous analytes, such as DNA variations used to diagnose genetic disease.⁴

Due to the reduced costs and increased efficiency of genomic sequencing tests over the last 20 years and the advent of other new technologies, the business climate for developing diagnostic tests is seen as more encouraging now than in previous years. Interest in developing genetic tests has grown since a Supreme Court ruling in June 2013 (Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.) invalidated patents of isolated genes that occur in nature.⁵ Smaller labs today have access to better technology, which has leveled the playing field and enabled many laboratories to do genomic testing. Prior to the Human Genome Project, genetic testing was mainly the purview of large academic/medical centers or specialized laboratories. Now, smaller academic hospitals are expressing interest in doing tumor profiling.⁶

Types of Laboratories and Business Models

In the laboratory sector, there are different types of facilities and business models. Labs affiliated with a health care institution provide testing directly to patients in a clinical setting. A reference lab (also known as a referral, diagnostic, or commercial testing laboratory) receives samples sent by physicians for testing. Hybrid labs are large institutional reference labs that have outreach programs, for example, to acquire samples from the community.⁷

Reference labs can be more efficient and reduce cost compared to institution-affiliated labs because of the high volume of tests. Reference labs tend to perform tests for esoteric conditions; that is, to diagnose rare disorders that only a thousand patients may have. Because these patients are scattered across the country, there is an advantage to having only one central reference lab that offers the test for a rare disease.⁸

Pathway to Regulatory Approval

How a test is regulated is determined by how it comes to market. A test may be marketed as a commercial test “kit,” a group of reagents used in the processing of specimen samples that are packaged together and sold to multiple labs.⁹ More commonly, a test comes to market as an LDT, where the test is developed and performed by a single laboratory, and where specimen samples are sent to that laboratory to be tested. The FDA currently regulates only tests sold as kits and generally has practiced “enforcement discretion” for LDTs, which it defines as in-vitro diagnostics manufactured, developed, validated, and offered by a single laboratory. There are tens of thousands of LDTs in clinical use, and most cancer diagnostics are LDTs.¹⁰ The FDA’s involvement in the regulation of LDTs is likely to change (see sidebar on pages 14 and 15).
Oversight of Laboratory-Developed Tests (LDTs)—A Variable Landscape

Regulatory oversight of the development and use of biomarker tests, including the latest genomic tests, is currently in an unsettled state. Most tests used in clinical practice have not been reviewed by the FDA, but instead are offered as LDTs. Labs that perform these tests are subject to quality assurance requirements under the Clinical Laboratory Improvement Amendments (CLIA), which are administered and implemented by the Centers for Medicare and Medicaid Services (CMS). State laboratory certification programs and professional accrediting bodies also play a role in regulating labs and their tests.

The FDA has acknowledged that it has generally not enforced premarket review and other applicable FDA requirements because LDTs have tended to be relatively simple lab tests and generally are available on a limited basis. However, technology advances, along with new business models, have led to a more complex and wider reach of LDTs, which now present higher risks than were present in 1976, when the FDA first gained comprehensive authority to regulate all in vitro diagnostics (IVDs) as devices.

LDTs in Diagnosis and Targeted Treatment Planning

LDTs are a type of IVD test designed, manufactured, and used within a single hospital, academic, and/or clinical lab. These tests are often created in response to unmet clinical needs and are commonly used for early and precise diagnosis, monitoring, and guiding of patient treatment. LDTs are also used to diagnose and assess diseases and disorders for which no FDA-authorized test kit exists, such as rare and emergent diseases or those with small patient populations.

LDTs can be used to measure or detect a wide variety of analytes, including DNA. The FDA’s definition of LDTs encompasses a wide range of diagnostics, including complex multigene panels that are performed in a single laboratory, and basic diagnostic tests, such as a complete blood count, which are performed in thousands of laboratories nationwide.

Estimates by the FDA suggest that tens of thousands of diagnostic tests, including the majority of genetic tests, are currently available as LDTs. As long as the manufacturer of an LDT does not make and sell a kit for use in other labs, the test can be provided as an LDT.

The LDT pathway may facilitate rapid innovation in test development, but concerns have been raised about whether greater oversight is necessary for more complex tests. Even when a drug and a companion diagnostic test are co-developed and co-approved by the FDA, with the companion diagnostic listed in the drug label, clinical laboratories may quickly develop similar tests as LDTs and offer them to patients without FDA review.

A Risk-Based Regulatory Framework

To help health care providers and patients more comfortably rely on the thousands of LDTs that are used daily, in July 2014, the FDA notified Congress that it planned to issue a draft oversight framework for LDTs based on risk to patients, rather than whether the tests were made by a conventional manufacturer or a single laboratory. The draft guidance framework, issued in October 2014, included a requirement for premarket review of higher-risk LDTs, such as those used to guide treatment decisions, including the many companion diagnostics that have entered the market as LDTs.

In taking this action, the FDA said it had identified problems with several high-risk LDTs, including claims that are not adequately supported with evidence and a lack of appropriate controls.

Regulating LDTs is something the agency had been contemplating for more than 4 years, and when the agency finally issued its draft guidance last year, it was met with intense reaction from groups on each side of the issue. The FDA is currently reviewing public comments on the October 2014 draft guidance that it received through an open public docket and a 2-day public meeting. In response to public comments, the FDA may modify the proposed framework when issuing final guidance.

Opposing aspects of the FDA’s plan to play a larger role in regulating LDTs are small laboratories, academic officials, and professional organizations, such as the Association for Molecular Pathology. Their rationale includes that the proposed policy changes could potentially stifle innovation by not allowing professionals the flexibility to improve and adapt already approved tests (essentially freezing outdated tests in time). In addition, some opponents believe the FDA’s proposed regulations could add new, and in some cases, duplicative requirements on clinical labs.
Under the assumption that new regulations would increase the costs of developing LDTs, there may be a significant reduction in the number of clinical labs that offer molecular tests. This has the potential to negatively impact the health care system, including creating barriers to innovation, restricting direct interaction between molecular professionals and clinicians, limiting patient access to medically necessary testing, and reducing opportunities for specialized training around complex LDTs, although this is all to be determined based on the passing of regulations to be seen.

From the other perspective, proponents of the FDA’s proposed guidance include the American Society of Clinical Oncology (ASCO). The central theme of their argument is that the risks to patients are significant when an LDT fails to perform as claimed, and that a company that develops its own LDT currently does not need to conduct any research to make a claim. Supporters of the FDA proposal also note that CLIA regulations require labs to demonstrate the analytical validity of their tests (meaning the test accurately and reproducibly measures what it claims to measure), but CLIA does not evaluate the clinical validity of a test (the test’s ability to detect the clinical condition for which the test is intended). Nor does CLIA evaluate the clinical utility of a test.

The FDA has argued that a laboratory that develops an LDT has created a “device” that can be regulated under the Federal Food, Drug, and Cosmetic Act, separate from the performance of per-patient testing, which would remain a service regulated under CLIA. Under the FDA’s position, laboratories performing LDTs might potentially be subjected to two regulatory frameworks applicable to the same test.

Neither development pathway, as an LDT or as an FDA-approved diagnostic test, requires evidence of clinical usefulness (clinical utility), which is often expected for reimbursement. Furthermore, there is concern that prevailing reimbursement rates for diagnostic tests often do not reflect the value of clinically useful biomarker tests. Thus, developers may be reluctant to invest the time and resources necessary to demonstrate clinical utility and support reimbursement decisions.

In comments submitted on the FDA’s draft guidance, the American Society of Human Genetics noted that regulation of genomics as a medical product raises many ancillary legal issues, such as potentially subjecting genomics to the states’ strict product liability tort regimes. Separately, the American Clinical Laboratory Association (ACLA) filed a citizen petition with the FDA in June 2013, arguing that the FDA has no authority to regulate LDTs. According to the ACLA, if there is concern about regulatory gaps around LDTs, the most logical and appropriate solution would be to amend the current CLIA regulation, rather than developing an additional layer of regulation based on a different statute that was written to address products, rather than laboratory testing. The contemplated new oversight by the FDA will superimpose a new bureaucracy on an already highly regulated industry that serves highly trained physicians and professionals. As of July 2015, the FDA had not responded to the public comments on its draft guidance for LDT regulation. The likelihood of the success of the FDA’s efforts is unclear, given the influence of the opposition, including members of Congress, industry groups and their representatives, and academic scientists. Regardless, many questions about implementation of a new FDA regulation are likely to remain.

Regulating Companion Diagnostics

In 2014, the FDA stepped up its oversight of companion diagnostics when it issued final guidance covering these in vitro diagnostic (IVD) products. Generally, the regulatory model for companion diagnostics is one in which a pharmaceutical company partners with a manufacturer of diagnostic tests to achieve FDA approval of the product combination.

The benefits to both companies and the FDA are clear. For regulators, the use of the diagnostic tests offers to make it easier to determine which patients will likely benefit from the companion products, and this is expected to reduce the chance of a drug being used off-label in untested populations. For drug and diagnostic companies, the use of companion diagnostics theoretically makes it easier to obtain approval by allowing regulators to see who stands to benefit from a drug, and why.

Yet, the need to have both a drug and a device ready to be brought to market at the same time can potentially delay approvals, even as smaller and more targeted trials may provide companies the hope of saving time (and money).
According to the FDA, LDTs are supposed to be simple, well-understood pathology tests, tests used to diagnose rare diseases, or tests for which testing outside the institution would be prohibitive to patient care due to delays between test ordering and delivery of test results. The FDA does not consider a diagnostic test an LDT if it was designed or manufactured completely or partly outside of the lab that offers and uses the test.11

The FDA approval of diagnostic tests involves more rigorous oversight along two main regulatory pathways.11 One, called the premarket notification (510k) process, requires showing that the test (which is considered a device) is substantially equivalent to a device that is already on the market or was on the market before 1976, and that the test meets quality standards set by the FDA. The 510k pathway can only be employed for tests with moderate levels of risk, as deemed by the FDA, linked to their use. For more complex tests that pose more risk to patients, manufacturers must submit an application for Premarket Approval (PMA) to the FDA that details the safety and effectiveness of their test. The test cannot enter the market until after the FDA reviews and approves this application. In its review of tests, the FDA considers analytical and clinical validity, but not clinical utility.11

Conducting the studies required for either the 510K or PMA regulatory pathways may be quite expensive. Although the 510K route is the less-expensive route, it can still cost millions of dollars to carry out, and no NIH grants or other public funds are allocated for this purpose. As a result, private-sector involvement is often required. Part of the expense of acquiring FDA approval for a biomarker test can be due to having to submit to FDA review not just the test, but the platform on which the test was performed. For RNA sequencing tests, for example, the FDA has only reviewed one machine used for the tests, but there are several other platforms on which the tests can be run.11

Accurately predicting a patient’s prognosis once a malignancy has been diagnosed is of great importance to both patients and their physicians.67 Many factors affect a patient’s prognosis68.
- The type, location, and grade of the cancer
- Certain traits of the cancer cells
- The patient’s age
- How healthy the patient was before cancer
- The patient’s response to treatment

DNA sequencing technologies increasingly will play a role in the implementation of cancer prognosticators, as well as predictors.66

Genetic Testing and Guidelines and Pathways

Providers increasingly will be asked to interpret more complex genomic data and make evidence-based recommendations to their patients.17 However, the increased personalization of patient care facilitated by NGS may counter existing trends toward care decision standardization and treatment pathway adoption. Integrative, multitarget NGS features, such as comprehensive tumor characterization, are not yet conducive to incorporation into a treatment pathway or a decision algorithm. This potentially could contribute to increased variation in decisions and treatments, which is considered unfavorable in the current health care environment striving for practice standardization.17

What tests to order and when, how to interpret and communicate the results, and how to apply those results to patients are all decisions providers need to make regarding molecular diagnostic testing. Two forms of decision support for providers include practice guidelines and treatment pathways.11

Molecular Genetics as Prognostic Biomarkers

Technological advances have greatly increased an understanding of the molecular basis of tumor progression and treatment response and have led to the identification of numerous tumor biomarkers. These biomarkers can be divided into two types66:

- **Prognostic markers**, which aim to objectively evaluate the patient’s overall outcome, such as the probability of cancer recurrence after standard treatment. The presence or absence of a prognostic marker can be useful for the selection of patients for treatment but does not directly predict the response to a treatment

- **Predictive markers**, which aim to objectively evaluate the likelihood of benefit from a specific clinical intervention, or the differential outcomes of two or more interventions, including toxicity

Evidence-based guidelines addressing the use of molecular diagnostic tests are not widely available. Professional medical societies and other independent and research entities may need to refine existing guidelines to reflect appropriate uses of genetic testing and molecular diagnostics.32 These guidelines could identify and report genetic variants as clinically actionable and specify what level of evidence is needed to take clinical action in response to a test result.11

Professional medical societies and other independent and research entities will need to refine existing guidelines to reflect appropriate uses of genetic testing and molecular diagnostics.32
The adoption of genomic medicine into routine clinical care has been relatively slow compared with the growth of genomic discovery. With WGS and WES moving from the laboratory to the clinic and the shifting paradigm of single-gene testing to more multiplex tests that examine tens to hundreds of cancer-related genes, it is important to understand physician knowledge and readiness to integrate this technology into patient care. In late 2010, physicians spanning all disciplines (eg, primary care, surgeons, internal medicine/pediatric specialists, and other specialists) within a community-based health system participated in one of the first studies to assess physician preparedness to integrate genomic medicine into practice. These physicians identified their perceived lack of knowledge and time to keep updated as their greatest barriers to incorporating genomic testing and pharmacogenetic testing into practice.

Clinically active adult cancer physicians at a comprehensive cancer center were surveyed in early 2012 about their level of confidence in their genomic knowledge before the initiation of enterprise-wide multiplex testing (Figure 3). Many participants were not confident at all or not very confident in their knowledge of genomics (22%), ability to explain genomic concepts to patients (14%), and ability to make treatment recommendations based on genomic data (26%).

Participants reported that they would use a variety of terms to describe testing to patients, including tumor testing (77%), molecular testing (72%), genetic testing (62%), and biomarker testing (41%). On open-ended questioning, participants identified an additional 28 terms that they would use, including tumor fingerprinting, treatment target testing, molecular biology testing, scanning for actionable mutations, and personalized therapy testing. It is important to standardize the language used to explain multiplex testing in order to avoid patient confusion and increase test acceptance.

To incorporate genomic technology into clinical practice, physicians will need to be convinced of its clinical utility. In addition, they need insights into how to order such testing, interpret the results, and communicate evidence-based results to their patients. Because the success rate of clinical genome and exome sequencing (CGES) for the identification of a causative variant is approximately 25%, it is important to understand the basis of this testing and how to select the patients most likely to benefit from it. Some CGES laboratories can assist by offering advice about the testing strategy for a given clinical scenario, but this is no substitute for a robust understanding of these issues.
Role of Board-Certified Physician Geneticists and Genetic Counselors

Medical geneticists are uniquely qualified and trained to assume overall responsibility for the genetic health care of the patient and family, which involves diagnosing, treating, case managing, coordinating, and supervising the care for individuals and families with known and suspected genetic disorders over the entire lifespan. Board-certified clinical medical geneticists should oversee any provider who provides genetic services so that the same standard of care is provided in the delivery of that service. According to the American College of Medical Genetics and Genomics (ACMG), only about 50% of the available clinical genetics training slots in the United States are filled. This may be due to a lack of medical geneticists at most medical schools and teaching hospitals who could serve as role models for medical students and encourage them to consider clinical genetics as a career path, rather than other specialties. The number of trainees who pass the ACMG exam to become board certified basically has remained the same since 1999.

According to ACMG, only about 50% of the available clinical genetics training slots in the United States are filled.

The shortage of medical geneticists can be challenging for both physicians and patients, especially with the increase in the use of CGES. Medical geneticists help keep physicians up to date on new tests and treatment options.

Genetic counselors play a key role in helping patients and their families get appropriate care, especially as medicine becomes more personalized and treatment plans increasingly are tailored to a patient’s individual needs.

Genetic counselors are members of the medical genetics team that is led by a clinical medical geneticist or other physicians. They are involved in development, documentation, and assessment of family histories; facilitation of genetic testing decision making; patient/family education; and addressing the psychosocial needs of their patients. Genetic counselors may function independent of the medical genetics team and are directed by physicians in the areas in which they practice. Genetic counselors are increasingly used directly in molecular laboratories to help with test selection and guidance.

When Cancer Patients Should See a Genetic Counselor

- Early age onset of disease (eg, less than 50 years of age for breast and colon cancer)
- Personal history of more than one cancer diagnosis
- Three or more relatives on the same side of the family with the same type of cancer
- Triple-negative breast cancer
- Ovarian cancer
- Male breast cancer
- Aggressive form of prostate cancer (Gleason grade 7 or higher)
- A genetic mutation confirmed in a family member
Collaboration Between Oncologists and Pathologists

There are various challenges related to effectively implementing molecularly targeted cancer diagnostics and therapies in a clinical setting. Among these challenges are complexity of test selection, insufficient or inadequate tissue specimens, and reporting and interpreting the abundance of genetic data. For example, tumor samples obtained for diagnosis may be of poor quality and insufficient for conducting multiple tests that are needed downstream to select the appropriate targeted drug treatment and/or monitor patient response over time. In addition, NGS is producing what some providers call a “tsunami of genetic data,” which is coming into the clinic so quickly that providers are becoming overwhelmed and do not know what to do with all of the information they are receiving. For that reason, some clinicians are staying away from ordering genomic tests.

As these new technologies come into play, the tissue specimen will always be critical because of its variability. The pathologist is the key interface between the specimen and the test, between patients and the choices oncologists will have to treat them. Collaboration between oncologists and pathologists is key. In addition, optimal interpretation and integration of genomic test results for clinical management requires a team approach through which molecular laboratory directors function collaboratively with the other clinical caregivers to bridge inevitable gaps in knowledge and differences in expertise.

ASCO and the College of American Pathologists have together announced a new partnership, with the goal of improving the development, application, interpretation, and dissemination of pathology tests, so that patients and their oncologists can obtain the most accurate diagnoses, and so that optimal treatments can be individually tailored. Projects include expansion of ongoing joint guideline development on molecular testing for cancer; development of point-of-care guidance statements regarding the appropriate molecular work-up of newly diagnosed patients; the launch of a multidisciplinary, virtual molecular tumor board; and planning a joint workshop on cancer diagnostic services in developing countries.

Projected Pathologist Shortage

In the United States, physician shortages, including pathologists, have been predicted for some time (Figure 4). Through 2010, approximately 18,000 pathologists were actively practicing in the United States (5.7 per 100,000 population) and most were board certified. According to a recent comprehensive workforce analysis, pathologist numbers will decline steadily, beginning in 2015, leading to a net deficit of about 5,700 pathologists by 2030. A major cause is believed to be generational. The clinical pathology specialty has the second-largest proportion of physicians over 55 years when compared with all other specialties.

Cigna’s Genetic Counseling Program

Cigna is the first national health service company to require independent board-certified genetic counseling before approving coverage for genetic testing through its national program implemented in September 2014. The requirement applies to individuals at heightened risk for certain hereditary conditions, such as breast cancer, colorectal cancer, or long-QT syndrome.

Additional data collected from individuals seeking genetic testing through pre-test counseling may result in a better match between those who can benefit from testing and those who are approved for it, according to Cigna. This enables more informed decision making and may help to ensure that health care dollars are wisely spent. The services of a genetics specialist, which includes taking a complete, three-generation family history, helping individuals understand if a test is right for them, and then helping them understand test results if they proceed with testing, can take hours. The program is an added resource that supports doctors whose patients may need genetic testing, freeing them to concentrate on providing medical care to their patients.
It is common for pathologists-in-training to pursue at least 1 year of fellowship training in their career and sometimes more. As recently as 2013, a 15% vacancy among molecular genetics pathology fellowship programs across the country was reported by the Accreditation Council for Graduate Medical Education. The demands for pathology services will rise in light of the health care needs of an aging population. New and enhanced services include genomics and bioinformatics, outcome assessment/utilization management, in vivo microscopy, biorepository management, preventive health management, and provider consults. A pathologist shortage may have a negative impact both on patient access to laboratory services and health care providers’ abilities to deliver more-effective care to their patients.

Advancing Precision Medicine Through Clinical Trials Innovation

The ability to detect numerous genetic anomalies in cancers is not equally matched by the ability to understand what those molecular flaws mean clinically. Conducting more clinical studies to assess this is challenging. Reasons cancer patients with profiled tumors do not participate in clinical trials for targeted therapy are varied—lack of experimental drugs, a decline in health status, unwillingness to travel to a trial site, and/or lack of patient or provider awareness of available studies for which they might be eligible. Various public and private efforts (see Appendix) are underway to address the evidence gap regarding the roughly 1,000 to 1,300 newer and more complex genetic tests.

ASCO released its Blueprint for Transforming Clinical and Translational Cancer Research in November 2011, coinciding with the 40th anniversary of the National Cancer Act. The blueprint focuses on three critical areas: improved understanding of the molecular processes that drive tumors and how best to measure the pharmacologic perturbation of these processes; the design and conduct of clinical trials; and harnessing HIT so that every patient’s experience can seamlessly inform research and improve outcomes. ASCO recognizes the need to prioritize targets for therapeutic development; identify and validate biomarkers early in drug development; and overcome legal, financial, and regulatory barriers in the pursuit of the most promising clinical applications.

Many institutions have genetic profiling programs, but taking the next step to translate the profiling into value in patient care is a high bar to reach. New research models may provide alternatives to traditional clinical trial design that include a less-expensive mechanism for evaluating genetic and molecular diagnostic tests. Possible models include those that involve rapid repetitive cycles, practice-based interventions, observational studies, prospective and retrospective studies, and comparative-effectiveness research.

Researchers are trying to better match their genetically profiled cancer patients to experimental therapies by using two types of innovative clinical trial designs, umbrella trials and basket trials. People with rare tumors are likely to be studied in basket trials, whereas people with more common cancers might do better in umbrella trials. Both basket and umbrella trials enable the testing of multiple treatments using the same protocol, which offers economical benefits and may support financial stability. While an exhaustive review of current trials is outside of this report’s scope, examples of trials underway include the NCI-MATCH basket trial and the Lung-MAP umbrella trial.

**Umbrella Trials vs Basket Trials**

**Umbrella trial:** Enrolls patients with one specific tumor type, profiles the tumors, and treats them with different therapies, each targeting a different biomarker profile, in the same trial

**Basket trial:** Usually groups together patients with several different types of cancers, but with a similar biomarker profile in their tumors so they can receive a treatment that targets those molecular drivers

**Challenges Presented by Basket and Umbrella Trials:**
- Difficulty finding adequate numbers of patients with cancer subtypes
- Collaboration between competing institutions and drug sponsors
- Tumor heterogeneity that presents a dynamic and moving target to treat
- Prioritizing genetic targets for treatment
NCI-MATCH

NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) is a national 10-arm basket trial open for enrollment in July 2015, with each arm enrolling adults with advanced solid tumors and lymphomas that are no longer responding/never responded to standard therapy and whose tumors have begun to grow.

The goal is to screen via tumor biopsy about 3,000 patients in order to enroll 1,000 patients in the various treatment arms, and for at least 25% of the enrollees to have rare cancers. Additionally, common cancers under study include non–small-cell lung, breast, colorectal, and prostate cancers.

Biopsy specimens will undergo DNA sequencing to analyze for more than 4,000 different variants across 143 genes to identify those that contain actionable genetic mutations that may respond to targeted drugs selected for the trial arms. Patients selected for enrollment based upon a second level of eligibility requirements will be treated with the targeted drug for as long as their tumor shrinks or remains stable. Patients can be considered for a second arm, as appropriate, if the first treatment is not successful.

The trial will have more drugs available than most trials: 20 to 25 drugs are anticipated to be ultimately tested, each in a different arm or sub-study of the trial. The drugs have all been FDA approved for another cancer indication or have shown some effectiveness against particular genetic alteration(s) in other ongoing clinical trials.

Seeking Evidence of Effectiveness

NCI-MATCH seeks to determine whether treating cancers according to molecular abnormalities will show evidence of effectiveness. Assessments will include objective response rate (primary endpoint), 6-month progression-free survival (secondary endpoint), as well as time to progression and treatment side effects.

Up to 2,400 clinical sites across the United States that are part of NCI’s National Clinical Trials Network and Community Oncology Research Program and four genetic testing labs are involved in the trial. A pediatric version of the trial led by the Children’s Oncology Group is expected to launch in 2016.

Lung-MAP

The Lung Cancer Master Protocol (Lung-MAP) clinical trial study is an innovative multi-arm, biomarker-driven umbrella trial launched in June 2014 to study patients with advanced squamous cell lung cancer, a form of lung cancer with few established treatment options beyond surgery.

Using comprehensive genomic profiling, patients are tested simultaneously according to a master protocol for many biomarkers connected to several different investigational drugs, and every patient tested is enrolled into one of the sub-studies. This master protocol sidesteps the significant recruitment and infrastructure burdens imposed on researchers and patients by traditional trial design that investigates single biomarkers and only enrolls a small portion of patients tested.

Screenings for Lung Cancer-Related Genes

The modular design of the protocol is designed to be nimble, with sub-studies closing and new ones opening as promising new targeted therapies become available for testing. At launch, the trial will test five drugs, and between 500 and 1,000 patients will be screened annually for over 200 cancer-related genes for genomic alterations. The trial infrastructure is capable of testing as many as five to seven additional drugs over the next 5 years and will cost up to $160 million.

The trial will be conducted at medical centers in NCI’s National Clinical Trials Network funded partially by NCI, with significant additional funding by participating companies. Lung-MAP is an unprecedented public-private collaboration among the NCI, SWOG Cancer Research, Friends of Cancer Research, the Foundation for NIH, five pharmaceutical companies (Amgen; Genentech; Pfizer; AstraZeneca; and AstraZeneca’s global biologics research and development arm, MedImmune), Foundation Medicine, and several lung cancer advocacy organizations. As of March 2015, the trial remains open and enrolling patients at over 400 sites in 42 states.

The trial has the potential to change and accelerate the way investigational biomarker-defined therapies are tested and approved for lung cancer, and possibly for many other diseases in the future.
Ethical Issues Related to Precision Medicine

Today, we are on the cusp of a revolution in health care delivery where clinicians may be able to access patients' genetic information cheaply, quickly, and entirely. With the availability of this information come numerous ethical issues somewhat different from targeted genetic testing. Areas of clinical and ethical importance include:

- Return of results and, in particular, disclosure of incidental findings
- Structuring the informed consent process given decisions about return of results
- Special situations with relatives and children, including “duty to warn” at-risk relatives and family communication issues
- Privacy and confidentiality

Structuring the Informed Consent Process

Traditional models of informed consent for genetic testing have taken a conservative approach, often using genetic counseling (such as clinical geneticists and genetic counselors) to discuss in great detail the testing options and related risks, benefits, and limitations of genetic tests. Because patients vary in their preference toward receiving specific results, two approaches have been proposed—a generic consent approach and a preference-based approach where patients can choose to receive information based on categories of disorders. Research studies are needed to assess the effectiveness and patient satisfaction with a range of informed consent processes.

Return of Results

The results of WGS or WES go beyond the specific clinical testing indication, offering incidental or secondary findings (eg, beyond the intention of the testing). This creates ethical issues surrounding what findings should be disclosed, in what manner, and to whom. Some believe patients have a right to receive all the genetic information from a test, whether or not it is clinically relevant. Others support limiting the return of results to those that are medically actionable as part of screening, surveillance, or treatment to improve morbidity or mortality. A third group supports rolling results out in stages over a person's lifetime.

The 2013 ACMG recommendations for the return of incidental findings suggest a small list of conditions, genes, and variants that should be considered “obligatory” to return when performing exome or genome sequencing. These are based on their significant potential for preventing disease morbidity and mortality, if identified in the presymptomatic period. However, variants of unknown significance, variants associated with low or unknown penetrance, and variants associated with disorders not currently amenable to intervention should not be reported.

Clinically active adult cancer physicians at a comprehensive cancer center were surveyed in early 2012 before the initiation of enterprise-wide multiplex testing about their attitudes concerning such testing. Disclosure of uncertain genomic findings to patients was endorsed by 42% of them.

ACMG also recommends that pretest counseling include a discussion of possible incidental findings, with the understanding that patients cannot opt out of the laboratory’s reporting of incidental findings to the ordering clinician. The clinician is responsible for contextualizing these findings to the clinical circumstances, such as the nature of ongoing clinical problems, their knowledge of personal and family history, patient preferences, and other issues. This shared decision making is similar to that which is undertaken by patients and physicians any time complex medical testing is considered; patients are informed that data generated can reveal unexpected results.

Research studies are needed to assess the effectiveness and patient satisfaction with a range of informed consent processes. Obtaining informed consent in the clinical setting may be challenging. Although health care providers may wish to ensure that their patients have an understanding of the implications of agreeing to the return of results from genomic testing, the limited time spent in patient care may be a barrier. The mean duration of ambulatory visits for cancer from 2006 to 2007 was 22.9 minutes. Since cancer patients are likely to be one of the largest patient groups to undergo clinical genomic sequencing, the ability of health care providers to obtain informed consent has important implications for considering return of secondary findings. Spending more time on educating patients about genomic testing and the implications of the results may come at the expense of other conversations related to clinical care. Some experts suggest more emphasis should be put on engaging patients, rather than educating them. While patients want their physician to make decisions, they want to be engaged in the decision and understand it.
“Duty to Warn” Family Communication Issues

Genomic testing expands the potential health knowledge that may be obtained, and which will almost universally impact relatives. In some cases, genomic testing may identify a predictive risk that is not significantly relevant to the patient, but rather is of value to other relatives. As more and more genetic predispositions to disorders that will almost always be apparent in an individual carrying the disease-causing mutation are discovered in the absence of clear family history, clinicians should identify a range of ways to assist family members in conveying accurate genomic risk information to relatives. If a patient is unwilling to inform at-risk relatives, clinicians may take the approach of disclosing relevant genetic information without identifying the specific affected family member.

ACMG has reaffirmed in a recent joint statement with the American Academy of Pediatrics that diagnostic genetic testing should be “driven by the best interests of the child” and that carrier screening and presymptomatic testing of children at risk for adult-onset diseases should be deferred until the child reaches maturity. Genome sequencing in children should be ordered and performed as a diagnostic test only if there are clear clinical indications. However, some incidental findings would clearly benefit the child and justify the disclosure of an incidental finding of a severe, actionable, pathogenic mutation that predicts an adult-onset condition, such as a BRCA1 gene mutation.

Privacy and Confidentiality

As larger amounts of genomic sequence data can be obtained from individuals, privacy and confidentiality becomes of greater concern. This is not only because obtaining more information and storing it in a larger number of databases may be more likely to lead to an unauthorized or accidental release, but because larger amounts of genetic information about any individual becomes increasingly uniquely identifying.

In 2012, the Presidential Commission for the Study of Bioethical Issues offered 12 recommendations to improve current practices and to help ensure privacy and security as the field of genomics advances. Recognizing that ethical obligations reach beyond what is legally enforceable, the Commission examined both the relevant ethical principles and the relevant legal requirements to offer guidance as to what (ethically) ought to be done and what (legally) must be done, which is the foundation of the recommendations they offered. The Commission states: “Privacy protections should guard against unauthorized access to, and illegitimate uses of, WGS data and information, while allowing for authorized users of these data to advance individual and public health.”

For protection from harm associated with breaches of privacy of genomic data collected for clinical use, patients and consumers must rely on policymakers to adapt laws and regulations, however imperfect, to technological advances and eventual use of genomics data in mainstream clinical practice.

Patients’ Perspectives on Clinical Genomic Testing

Recent research identified a variety of views that genetics patients and their caregivers have about the promises and perils of clinical genomic testing. A 2009 study was conducted that consisted of 66 interviews with patients or parents of patients younger than 21 years who had presented for clinical genetic testing but had not yet received the results or received a diagnosis of a specific genetic condition. Participants expressed moderate levels of enthusiasm for clinical genomic testing, which was much greater for diagnostic application than for nontargeted forms of genetic risk assessment. Participants expressed moderate levels of enthusiasm for clinical genomic testing, which was much greater for diagnostic application than for nontargeted forms of genetic risk assessment. Participants voiced numerous concerns about the potential misuse of genomic results. These concerns included emotional and psychosocial burdens that genomic risk information could pose to themselves and others, concerns about genetic discrimination, and worries about genetic privacy. These findings suggest that patient response to new forms of clinical genomic testing may not be completely positive and that many patients will have mixed opinions on the extent to which genomic testing reflects their personal values and goals.

Familiarity, Perspectives, and Expected Value of Personalized Medicine (based on a 2013 survey of 602 US consumers)

- 73% Unfamiliar with the term “personalized medicine”
- 95% Expected personalized medicine to have a positive benefit after understanding the term
- 84% Would seek a second opinion or want therapy anyway, if testing was unfavorable

Consumers’ willingness to pay was associated with impact on survival, rather than predicting disease risk.
There are a number of reasons why a patient may want to learn about some, but not all, genomic health risks:

- The net benefit of testing for some genetic conditions, such as hereditary breast and ovarian cancer, ranges from minimal to potentially harmful for asymptomatic individuals without a medical or family history of the disease.

- Potentially harmful mutations found in asymptomatic individuals could generate anxiety and defensive medicine leading to unnecessary medical procedures, overtreatment, and iatrogenic (ie, complication caused by medical treatment) effects.

- Individuals may be concerned about the way genomic risk information could impact their ability to qualify for affordable life, disability, or long-term care insurance, which are not protected by the Genetic Information Nondiscrimination Act.

- Individuals may want to avoid the psychological burden of learning about genomic risks.

Several barriers that may pose challenges to patient comprehension of genetic and genomic test reports include health literacy, genetic literacy, e-health literacy (for reports reported via an online patient portal), and risk perception.

Paying for Precision Medicine

The time and costs associated with examining human genetic variations across the entire genome have been greatly reduced by NGS. However, it has substantially increased the amount of data to be stored and the complexity of both interpreting the information and using it effectively to improve health care. In addition, there is a need for technical confirmation of potentially significant findings and supplementation with other genetic assays to achieve clinical grade sensitivity and specificity. The associated bioinformatics infrastructure, computational tools, data storage, and ongoing data evaluation represent a care service not paid for under current reimbursement and coding systems.

Increasingly, hospital and reference laboratories are sequencing patient’s tumors in order to better target therapy. However, many are not comparing matched normal DNA to tumor DNA to filter out noncancer-related alterations that could lead to false-positive findings not specific to the tumor. In a recent study of DNA from tumor and normal cells of patients with various cancers, 31% and 65% of the genetic alterations identified in targeted and exome analyses, respectively, were false positives and not related to the patient’s cancer. These study results suggest that matched tumor-normal sequencing analyses are essential to precise identification and interpretation of tumor-specific (ie, somatic) and inherited (ie, germline) alterations and have important implications for the diagnosis and therapeutic management of cancer patients. Sequencing of normal tissue can add additional costs, patient privacy concerns, and payer coverage issues. However, inaccurate genetic information that leads to inappropriate therapies may cause serious side effects, lack of useful targeted treatments, and increased cost of care.

31% and 65% of the genetic alterations identified in targeted and exome analyses, respectively, were false positives and not related to the patient’s cancer.

Payers’ policies play a key role in the adoption of new technologies, such as NGS, because ultimately such technologies have to be covered and reimbursed if they are to be widely adopted. Uses of NGS may require adaptation of existing payer policy frameworks and/or require new approaches. Particularly in oncology, the utility of big data is derived from research, as well as clinical applications, which can confound the development of payer coverage policies. Not uncommonly, multigene panels can include genes with and without clinical validation, thereby blurring the lines between clinical interventions, which are typically covered by payers, and research applications, which are typically not covered.

Payer Coverage and Reimbursement Policies

Most US payers have not issued formal coverage policies for genomic profiling via NGS. Although it is possible to receive reimbursement for NGS from payers on a case-by-case basis, the lack of a formal coverage policy causes payment uncertainty and variability, and may limit patient access. Understanding insurance coverage considerations for NGS is vital for all oncology stakeholders, including oncologists, pathologists, laboratories, researchers, and patients.

Priority Health, a Michigan-based regional health plan, has been a leader in oncology reimbursement and treatment reform. It is the first insurer to issue a formal coverage policy for NGS in cancer for a narrow set of circumstances (see box on page 25).

Payers likely see the potential benefits of NGS of cancer tumors and recognize it as an evolutionary trend in health care, but it poses disruptive challenges to existing coverage policy frameworks, and payers may not be sure how to pay for it. Key challenges to developing a positive coverage policy for NGS were identified in possibly the first study to directly interview US private payers on NGS reimbursement conducted in 2013 (see box on page 25).
Priority Health’s Multimarker Tumor Panel Medical Policy\textsuperscript{98,99}

Priority Health is the first insurer in the United States to implement a formal coverage policy for the use of genomic profiling. For most insurers, genomic profiling is billed as out-of-network services, requiring patients to pay higher out-of-pocket fees for this potentially lifesaving test. Priority Health has changed this by offering coverage for genomic profiling for its members diagnosed with aggressive forms of cancer through Foundation Medicine.

While NGS to personalize cancer treatment has only been endorsed by the NCCN Guidelines for Non-Small Cell Lung Cancer (NSCLC) at the time of policy development, several factors converged to warrant reconsideration of this standard by Priority Health in selected patients and tumor types outlined in their policy. These factors include the Affordable Care Act’s (ACA) requirements regarding the coverage of Phase 1 to Phase 4 clinical trials, NCCN’s recommendations for clinical trials as standard of care even when other options exist, the use of emerging biomarkers to often determine eligibility for ACA-eligible cancer clinical trials, and high unmet needs and limited therapeutic options for certain malignancies.

Priority Health will cover the use of NGS to provide additional insights into the therapeutic options available to cancer patients and their physicians in the following seven circumstances, according to its medical policy originated in November 2014, regarding multimarker tumor panels:

1. Newly diagnosed Stage IV NSCLC
2. Newly diagnosed cancer of unknown primary site
3. Newly diagnosed hematologic malignancies with high-actionable mutations or limited treatment options in defined clinical guidelines
4. Tissue to perform evidence-based tumor genome mutation analysis is unavailable
5. Newly diagnosed selected Stage IV rare solid tumors with limited/no systemic treatments in clinical guidelines/pathways
6. Newly diagnosed selected Stage IV solid tumors with poor prognosis, very limited benefit from standard of care chemotherapies, and high prevalence of actionable mutations
7. Stage IV solid tumors in patients who desire further treatment, having exhausted guideline-driven systemic therapy and requisite molecular testing

Additional requirements include an Eastern Cooperative Oncology Group performance status grade of 0, 1, or 2; completion of advance care planning; and for numbers 5 to 7 above, patient willingness to participate in a clinical trial.

Key Challenges to NGS Coverage\textsuperscript{17}
(based on interviews with 10 major payers representing >125 million enrollees)

- **Not fitting definitions of “medically necessary” and “experimental/investigational”**—80% of payers stated one or more reasons why NGS does not fit the concept of “medically necessary” to grant coverage versus “experimental/investigational.”
  - Additionally, 70% commented that inclusion of novel targets among the medically necessary targets renders the entire NGS tumor panel experimental/investigational

- **Misalignment with single-test/single-result approach to coverage**—70% of payers will evaluate each target included in an NGS panel individually using single test/single result approaches, while acknowledging the daunting task
  - They do not perceive the integrated benefit of NGS, such as comprehensive tumor characterization

- **Evidence methods proposed for NGS do not fit payers’ evidentiary standards**—100% of payers require evidence of analytic validity, clinical validity, and clinical utility (including outcomes from treatments guided by the diagnostic)
  - All of them will apply these requirements to NGS coverage

- **Adoption and care delivery concerns**—80% of payers believed that implementing NGS in practice will face difficulties and expressed concerns that these difficulties will preclude the promised advantages
One study examined Medicare reimbursement of 10 drug-companion diagnostic combinations used in cancer on the basis of a formulary review and a survey in 2013. The authors found that payers managing reimbursement under Medicare Part B and Part D did so for all 10 drugs, but with variable and relatively high patient coinsurance, as well as imposition of formulary restrictions. Payer reimbursement of companion diagnostics is highly variable. Ideally, a personalized drug would not be reimbursed without an appropriately defined or identified subpopulation. However, the authors observed that drugs are being reimbursed independent of companion diagnostic coverage.

Payers typically cover only interventions that are for clinical use, not those that are for research. But in some cases, the distinction between clinical and research uses is blurred, such as determining a person’s eligibility to participate in a clinical trial in conjunction with his or her standard treatment. NGS supports integration of all care for a particular patient, both standard and experimental. This facilitates choice of existing treatments and determination of trial eligibility in a clinically relevant time frame. The current model of financing patient care requires separating standard-of-care from experimental activities for reimbursement purposes. Experimental activities are further fragmented because pharmaceutical trial sponsors require single-marker testing and may not finance NGS as a shared utility.

Questions Payers May Consider When Determining Coverage Decisions

- What is the strength of the clinical evidence that this technology is safe and effective?
- What group of patients, if any, would benefit most from using a given technology for preventing, diagnosing, or treating a particular condition?
- Under what circumstances and conditions, if any, would the technology be most appropriately used? Does our policy need to specify certain providers or facility types?
- How does the new technology compare to other available treatments for the same condition?

Part of the reason more genetic tests have not been reimbursed may be because most of the “actionable” genetic alterations these tests uncover do not yet translate into better clinical outcomes. Those that do can potentially spare patients the cost and side effects of using therapies that are not likely to benefit them.

A clear timeline and process exist for the review of newly approved drugs on a periodic basis by payer Pharmacy & Therapeutics Committees, but no such formal process exists for the evaluation and coverage of diagnostic tests. Also, there is no standardized method of preparing evidence of clinical utility, establishing whether a diagnostic is covered, or setting reimbursement rates for companion diagnostics.

Coverage With Evidence Development

Coverage with evidence development (CED) is a paradigm whereby CMS decides, after a formal review of the medical literature, to cover an item or service only in the context of an approved clinical study or when additional clinical data are collected to assess the appropriateness of an item or service for use with a particular beneficiary. In November 2014, a prostate cancer epigenetic test gained conditional Medicare coverage with data development—the first instance of this conditional payment mechanism for a molecular diagnostic test. Similar to CED, the mechanism specifies clinician qualifications and collection of specified registry data as part of the accrual of evidence of clinical utility.

In the commercial space, CED was developed to give payers some leverage in making sure studies are designed to answer the sorts of questions they are interested in, such as clinical utility. To be considered for CED, a medical diagnostic or treatment must address an important health need and/or specific payer priority, and the existing evidence on the intervention must be adequate to conclude that the technology is promising.

As a caveat, it usually takes longer to acquire the evidence than it does to gather the data needed for standard coverage decisions. In addition, it is a lot of work for payers to make decisions about what constitutes medical necessity and to establish the criteria for what is considered “promising.” It is also difficult to ascertain the kind of study that will provide sufficient evidence for permanent coverage of the intervention.

Different Approach to Medicare Reimbursement for Laboratory Testing

On April 1, 2014, President Obama signed into law the Protecting Access to Medicare Act of 2014, which creates a completely different approach to paying for laboratory testing—considered by health care policymakers to be the most substantial overhaul to the clinical laboratory fee schedule created nearly 30 years ago. Currently, CMS sets rates for new tests based on its system of comparing new tests to old—also known as crosswalking. Test rates remain unchanged unless there are across-the-board updates, such as for inflation or cuts by Congress. Beginning in 2017, Medicare will rely on average
payer rates to set Medicare’s fee schedule for laboratory testing and will give special treatment to single-source proprietary tests. For the initial cycle, this means that CMS will set new, market-based rates on January 1, 2017, based on what private payers paid in 2015. The new market-based system includes a reasonable level of transparency, which is expected to result in a more definitive and predictable pricing system.104

The law creates a special category for advanced diagnostic tests (see box below); however, NGS tests would not meet the algorithmic requirement, which poses a large unanswered question for a key area driving innovation. In addition, the law does not guarantee that Medicare will cover NGS tests—only set payment for them if and when they are covered.104

The law promises to speed payment and force CMS to make more deliberate decisions on initial rates and code assignments for new tests that fall outside the special advanced diagnostics criteria. Further clarification and details await the regulations yet to be written.92

### Advanced Diagnostic Test104

An advanced diagnostic test is provided only by a single lab, not sold for use by other labs, and meets one of three criteria:

1. The test is an analysis of multiple biomarkers of DNA, RNA, or proteins combined with a unique algorithm to yield a single, patient-specific result
2. The test is cleared or approved by the FDA
3. The test meets other similar criteria that the Secretary of Health and Human Services sees fit to create

### MolDX® Approach to Test Reimbursement

Developed in 2011, the Molecular Diagnostic Services (MolDX®) Program by Palmetto GBA, a Medicare Administrative Contractor, created a new paradigm for reimbursement. It was created in recognition of the challenges in gathering evidence for genomics, particularly through clinical trials directed at rare patient subsets where there are substantial unmet needs.105 The goal of the program is to develop and use an evidence framework to evaluate molecular diagnostic testing for CMS, with an emphasis on clinical utility evaluations. Instead of dividing up interventions into the traditional two categories “standard” and “experimental,” MolDX recognized a new category, called “transitional,” for treatments and tests that are in between. In addition, MolDX established a pathway for provisional coverage for interventions that fall into this transitional space.11

To determine which genetic tests are considered transitional, MolDx has high-level discussions with multiple stakeholders with the aid of its Partner Specialty Societies (specialty groups and societies that help to advance appropriate molecular testing).11 A MolDX Executive Committee, comprised mostly of molecular pathologists from academic institutions and selected from this group, makes the coverage decisions in an expedited pathway. The committee reviews every dossier that has been registered and submitted to identify tests that address a significant unmet clinical need, could potentially have widespread acceptance by the medical community, but do not yet have robust evidence of clinical utility. The experts decide if the tests should be covered, have limited coverage, or have coverage with data development.11 The MolDX program plans to evaluate each genetic panel and laboratory in which it is performed separately until accepted standards for these tests are available. Each genetic panel test or groups of tests must show analytic validity, as well as clinical utility, and be disease specific.11

Effective July 2015, MolDX granted limited coverage for comprehensive genomic profiling (CGP) on tumor tissue-only for patients with metastatic non–small-cell lung cancer who are never-smokers or former light smokers and who have tested negative for specific genomic alterations. Participating laboratories that meet Palmetto’s analytic validity criteria must report deidentified patient data every 6 months that include patient demographics, sample testing, gene alterations, and treatment response and duration following CGP testing.106

### Functions Performed by the MolDX Program105

- Facilitates detailed and unique identification through registration of molecular diagnostic tests and Z-code identifier assignment to facilitate claims processing and to track utilization
- Establishes clinical utility expectations
- Completes technical assessments of published test data to determine clinical utility and coverage
- Establishes reimbursement
Overcoming Reimbursement Barriers

To help close the clinical utility evidence gap and help ensure access to NGS tests that are likely to benefit patients, while avoiding the clinical and economic harms of potentially ineffective tests, three medical ethics experts suggested a four-pronged approach. Test developers should:

1. Invest in robust validation studies to determine analytic and clinical validity, which should be made readily available to payers and technology assessment groups.

2. Establish a system for prioritizing research to assess clinical utility and the quality of existing evidence and give priority to tests that have demonstrated analytical and clinical validity, some existing evidence of clinical utility, and for which it is feasible to conduct additional utility studies.

3. Use existing evidentiary frameworks, such as those recommended by technology assessment groups and large payers, for assessing clinical utility as a starting point for designing clinical utility studies.

4. Evolve the evidence review process to account for the full range of benefits that are theoretically possible with NGS, characterized as “compound utility.”

Compound utility includes the concepts of personal utility (value of information to the patient and/or family beyond its intended clinical use), as well as the unique potential value of this type of testing that is likely to occur over the long term.

Resources for Creating Coverage Policies

The National Business Group on Health (NBGH) has published an issue brief that describes eight actions employers can take to incorporate precision medicine into a benefit plan. In addition, NBGH and NCCN have worked together to create resources designed to help employers design cancer-related health benefits.

The NIH is currently funding the development of a publicly available registry of reimbursement coverage policies that will include what and where tests are available, how much they cost, and what insurers are paying for them.

Understanding quantitative tumor biology and applying this knowledge, along with an understanding of drug responsiveness, may lead to what is described as the “sweet spot” for payers — using the right cancer drug for the right patient at the right time.

Codes for Genetic Testing and Molecular Diagnostics

Providers and laboratories today commonly use a procedure-based approach to identify genetic tests and molecular diagnostics by the steps involved in the test rather than the nature of the test itself. Currently, specific technical steps for molecular analysis are encoded separately and then a single Current Procedural Terminology (CPT) code is given for interpretation. A gene, such as CFTR, may involve as many as 88 separate molecular probes for known mutations resulting in 88 CPT codes. The aggregation of the many CPT codes to describe “one” genetic test is known as a “code stack.” For a CPT system that was designed to assign one code to one medical procedure, genetic testing has proven to be confusing. A starting point for the evolution of the CPT coding system has been collapsing the coding system into bins with varying numbers of probes.

Payer Difficulties With Stacking Codes

- Payers are unclear about what they are paying for.
- Clinical laboratories are not consistent with CPT coding.
- High multiple units of service are confusing and may be viewed with suspicion by payers.
- Payers face challenges aligning ICD-9 justifications for payment with numerous CPT codes generated by molecular testing.
- Problems are created with targeted insurance coverage policies, since once a CPT code is linked to a limited set of ICD-9 codes, that particular CPT code is unavailable for molecular testing associated with other ICD-9 codes.

In some cases, laboratories identify the codes that best represent their own processes for genetic testing services, making variation in code use common. Even when laboratories use the same procedure codes for a test, they may include different services in those procedures, making comparisons or aggregation of data across laboratories difficult.
Often, health plans have had to address the lack of coding by developing their own identifying codes for specific genetic and molecular tests, particularly when the tests are commonly used in clinical practice. For example, some payers use alphanumeric codes (S-codes) to identify certain tests for a variety of conditions, such as tests for breast and ovarian cancer genetic mutations, including \textit{BRCA1} and \textit{BRCA2}.\textsuperscript{32}

In addition to the difficulties involved in identifying the tests themselves through codes, identifying the therapeutic area in which genetic and molecular tests are being used is also a challenge. Claims submitted for laboratory services may use a diagnosis code that reflects the immediate issue facing the patient, rather than the result of a genetic test or subsequent diagnosis. Therefore, diagnosis codes, or a combination of diagnosis and procedure codes, cannot confidently be relied on as a source for information on the use of a genetic or molecular test or a test result.\textsuperscript{32}

Over 100 molecular pathology (MoPath) CPT codes were implemented in 2013. However, they may not adequately address changes in molecular diagnostic testing due to the advent of NGS technology. To address this concern, the Association for Molecular Pathology developed an NGS-coding proposal in March 2013 and submitted it to the American Medical Association (AMA) for review. In this proposal, the Association for Molecular Pathology coined the term “genomic sequencing procedure” (GSP) to describe both current and future diagnostic technologies that analyze the human genome in complex and diverse ways, such as NGS.\textsuperscript{112}

In January 2015, the AMA implemented a significant number of changes to CPT coding. The CPT code set was expanded to include a new subsection for reporting these analyses, “Genomic Sequencing Procedures (GSPs) and other Molecular Multianalyte Assays.” This new subsection includes introductory guidelines that describe some of the characteristics of GSPs and other molecular multianalyte assays, including their unique features, functions, and applications. The new subsection includes 21 new codes.\textsuperscript{113}

The updated coding system for diagnosis (ICD-10) to be implemented October 1, 2015, will eventually allow for combinations of codes and is structured to capture additional detail about diagnoses and related procedures. For genetic testing and molecular diagnostics, the increased detail, such as genetic susceptibility to disease, will enable providers to better understand how tests relate to their patients’ conditions.\textsuperscript{32}

### Economic Value of Sequencing

The adoption of NGS will ultimately depend on the value that it provides not only to individuals, but also to the health care system.\textsuperscript{20} Cost-effectiveness is about improving patients’ lives as efficiently as, or more so than, current clinical practice.\textsuperscript{114}

Payers must make informed choices about whether or not to pay for testing. Some genetic testing, such as to determine if a patient is a rapid metabolizer of clopidogrel or of warfarin, may not be considered clinically justified by the payer community, which may not reimburse for it.\textsuperscript{111}

The following three major components to the economic value of NGS in clinical care—clinical sequencing—need to be better understood\textsuperscript{114}:

1. What are the patient and economic impacts of improved clinical diagnosis, prognosis, and prediction through the clinical use of clinical sequencing?

2. What are the near- and long-term impacts of returning incidental findings to patients?

3. What value do patients place on both intended and incidental findings from clinical sequencing that is not captured by clinical measures?

These evidence needs will likely influence recommendations for future research and policy development.

### What Lies Ahead

Much has been discovered since 2003 when the real drive toward personalized or precision medicine occurred with the complete sequencing of the human genome.\textsuperscript{11} To capitalize on the momentum of the last decade, systems-level innovations are needed to further integrate basic molecular science with clinical science via innovative clinical research, bioinformatics, decision-support infrastructure, and effective regulatory and health policies. Many private and publicly supported initiatives and partnerships across sectors and stakeholders are underway to address unmet needs. The appendix includes a sampling of these activities currently underway. Only through the translation of the evolving science of genomics into meaningful outcomes for patients with cancer by deliberate and collaborative efforts on the part of all stakeholders will the promising impact of precision medicine in cancer be realized.
Glossary of Terms

Analytic validity: How well the molecular diagnostic test predicts the presence or absence of a particular gene or genetic change

Biobank: A large collection of biologic or medical data and tissue samples, amassed for research purposes

Bioinformatics: Using computers to solve information problems in the life sciences, primarily involving the creation of extensive electronic databases on genomes, protein sequences, and other biologic data

Biomarker: See “tumor marker”

Clinical Laboratory Improvement Amendments (CLIA): The legislation that gives the Centers for Medicare & Medicaid Services authority to regulate all laboratory testing (except research) performed on humans in the United States. CLIA covers approximately 251,000 laboratory entities

Clinical utility: An expression — preferably in a quantitative form — of the extent molecular diagnostic testing improves health outcomes relative to the current best alternative, which could be some other form of testing or no testing at all

Clinical validity: The accuracy with which a molecular diagnostic test identifies a patient’s clinical status

Companion diagnostic: An in vitro diagnostic device that provides essential information for the safe and effective use of a corresponding therapeutic product

Driver genes: Contain driver gene mutations (mut-driver gene) or are expressed aberrantly (epi-driver gene) in cancer and confer selective growth advantage

Genetic and genomic clinical laboratory testing: Analysis of DNA to look for a genetic alteration that may indicate an increased risk for developing a specific disease or disorder

Gleason grade: The Gleason grading system for prostatic carcinoma is the dominant method used around the world in research and in daily practice, and is based entirely on the histologic pattern of arrangement of carcinoma cells in hematoxylin-and-eosin (H&E) stained prostatic tissue sections

Human genome: The entire set of genetic instructions found in a cell. The human genome was completely mapped and sequenced by April 2003, through the international efforts of the Human Genome Project

Immunotherapy: The prevention or treatment of disease with substances that stimulate the immune response

Incidental findings: Undiagnosed medical conditions that are discovered unintentionally

Laboratory-developed test (LDT): A type of in vitro diagnostic test that is designed, developed, validated, and offered by a single laboratory

Metabolomics: The scientific study of the set of metabolites present within an organism, cell, or tissue

Molecular diagnostics: The detection and/or analysis of nucleic acid molecules (DNA or RNA) to provide clinical information

Molecular marker: See “tumor marker”

Next-generation sequencing (NGS): Also known as massively parallel or high-speed sequencing, these new technologies are distinguished by their ability to rapidly examine many genes simultaneously using a single test

Oncogene: A mutated gene that contributes to the development of cancer

Pharmacogenomics: The study of genetic variations that influence individual responses to drugs

Phenotype: A description of a person's actual physical characteristics (ie, height and eye color), along with overall health, disease history, and even behavior and general disposition

Proband: The first affected individual in a family who brings a genetic disorder to the attention of the medical community

Proteomics: A branch of biotechnology concerned with applying the techniques of molecular biology, biochemistry, and genetics to analyzing the structure, function, and interactions of the proteins

Proto-oncogenes: Genes within a cell’s nucleus that code for proteins and help regulate cell growth. A change in the DNA sequence of the proto-oncogene gives rise to an oncogene, which produces a different protein and interferes with normal cell regulation

Reference lab: A laboratory that performs quality and cost-effective high-volume and esoteric testing of biologic samples for physicians, hospitals, and other laboratories. Also known as a referral, diagnostic, or commercial testing laboratory

Reflex testing: Follow-up testing automatically initiated when certain test results are observed in the laboratory; used to clarify or elaborate on primary test results

Single-analyte test: A traditional immunoassay performed as a discrete test (ie, one analyte per assay tube), such as a test that measures the over-expression of human epidermal growth factor receptor 2 (HER2) in breast cancer

Tumor-suppressor genes: Genes in the body that can suppress or block the development of cancer

Tumor marker: Also called a biomarker or molecular marker. A substance present in, or produced by, a tumor or by the host, which can be used for differentiating neoplastic from normal tissue based on measurements of biomolecules, such as DNA, RNA, protein, peptides, and biomolecule chemical modifications, in body fluids, secretions, cells, and/or tissues. Can be classified as predictive, prognostic, and/or diagnostic
Appendix

Below is a sampling of the public and private organizations, as well as public-private collaborations, underway to advance precision medicine through comprehensive genomics data in cancer care. Initiatives underway include clinical research, bioinformatics, health policy, practice standards and guidelines, and educational activities. These organizations and described initiatives are provided solely for information and convenience. Genentech does not endorse the views they express or the products/services they offer.

**Actionable Gene Consortium**
(www.genomeweb.com/sequencing/actionable-genome-consortium-forms-guide-use-ngs-clinical-oncology)

Gene sequencing company Illumina has joined with four founding major cancer centers (Dana-Farber Cancer Institute, Fred Hutchinson Cancer Research Center, MD Anderson Cancer Center, and Memorial Sloan Kettering Cancer Center) to found the Actionable Genome Consortium, an organization dedicated to publicizing standards for the use of next-generation sequencing in clinical oncology that can be broadly shared across care providers. This will include a list of actionable events; recommendations for best practices for biopsy, sample storage and transport, and extraction; and technical performance standards for DNA sequencing. It will also make recommendations for standards for variant calling, annotation and interpretation, and guidelines for the format and content of clinical reports. The consortium will also include a research arm to coordinate cross-institutional projects.

**American College of Medical Genetics and Genomics (ACMG)**
(www.acmg.net)

Founded in 1991, ACMG advances the practice of medical genetics and genomics by providing education, resources, and a voice for more than 1,600 biochemical, clinical, cytogenetic, medical, and molecular geneticists and genetic counselors and other health care professionals committed to the practice of medical genetics. ACMG's activities include developing laboratory and practice standards and guidelines; advocating for quality genetic services in health care and in public health; and promoting the development of methods to diagnose, treat, and prevent genetic disease. In May 2015, ACMG unveiled the ACMG Genetics Academy for Genetic and Genomic Education, an online educational portal for health care professionals and scientists. It offers self-paced interactive learning, Webcasts, live streaming courses, and online archived courses. Also included are the ACMG Genomics Case Conferences, which began in 2014.

**Association for Molecular Pathology (AMP)**
(www.amp.org)

AMP is a not-for-profit scientific society that advances the clinical practice, science, and excellence of molecular and genomic laboratory medicine through education, innovation, and advocacy to enable highest quality health care.

A number of initiatives are underway in 2015 and include the following. AMP published its vision paper for the evolving role of molecular laboratory directors in the age of genomic sequencing in March. It also released its micro-cost and health economic models and template for use by members to effectively communicate value and cost of genomic sequencing procedures to payers. In April 2015, it published a substantial digest of research to-date on the minimally invasive “liquid biopsy” approaches to cancer diagnostics.

**ASCO CancerLinQ**
(cancerlinq.org)

CancerLinQ is the American Society of Clinical Oncology's (ASCO) pioneering initiative to develop a learning health care system that will help oncology professionals analyze and share data on every patient with cancer. A prototype was completed in March 2013, with a subset of practices and deidentified data on more than 150,000 breast cancer patients. Phase 2 development of the full systems is underway. ASCO is developing strong data governance policies and protocols to assure ethical stewardship of this resource.

**National Cancer Institute's Cancer Trends Progress Report**
(progressreport.cancer.gov)

This report summarizes advances against cancer in relation to Healthy People targets set by the Department of Health and Human Services; it includes key measures of progress and uses national trend data to illustrate where improvements have been made.

**Center for Medical Technology Policy (CMTP)**
(www.cmtpnet.org)

CMTP is an independent nonprofit dedicated to developing a health care system where patients, clinicians, health care policymakers, and payers have the evidence they need to make informed health decisions. They convene and collaborate with a national and international network of thought leaders, patients, patient advocates, clinicians, policymakers, and payers to support the next generation of clinical research. This is done by providing methodological guidance, shaping health policy solutions, and transforming clinical research. Among its multistakeholder partnerships is The Green Park Collaborative–USA.
Center for Translational and Policy Research on Personalized Medicine (TRANS Perez)
(pharm.ucsf.edu/transpers)
TRANS Perez is the premier research organization for developing evidence-based information about the use of personalized medicine. Launched in 2008 and based at the University of California San Francisco, TRANS Perez brings together a broad spectrum of experts from across the world—from academia; government; and groups representing patients, providers, and payers—to examine critical issues that impact the translation of personalized medicine into practice and policy. Using an evidence-based approach, they launch projects and establish working groups to explore key areas, including health care utilization, patient preferences, costs and cost-effectiveness, evidence development and evaluation, patient diversity, decision making (patient, provider, payer, and government), and policy. Among its ongoing initiatives is the development of a registry of public and private payer coverage policies for new and emerging genetic tests, as well as the factors that determine coverage. Guided by an expert advisory group, including a broad range of stakeholders, the registry will build on Tufts Medical Center Cost-Effectiveness Analysis Registry.

CEO Roundtable on Cancer
(ceoroundtableoncancer.org)
The mission of the CEO Roundtable on Cancer is to make continual progress toward the elimination of cancer as a personal disease and public health problem. Members of the CEO Roundtable work collaboratively to develop and implement initiatives that reduce the risk of cancer, enable early diagnosis, facilitate better access to best-available treatments, and hasten the discovery of novel and more effective diagnostic tools and anti-cancer therapies. The CEO Cancer Gold Standard™ (www.cancergoldstandard.org) provides a framework for employers to have a healthier workplace by focusing on cancer risk reduction, early detection, and access to clinical trials and high-quality care.

ClinGen
(clinicalgenome.org)
ClinGen, funded by the National Institutes of Health, is a resource dedicated to harnessing both research data and data from the hundreds of thousands of clinical genetics tests being performed each year. ClinGen will engage the genomics community in data-sharing efforts, develop the infrastructure and standards to support curation activities, and incorporate machine-learning approaches to speed the identification of clinically relevant variants in order to build a genomic knowledge base to improve patient care.

ClinVar
(http://www.ncbi.nlm.nih.gov/clinvar/)
ClinVar is a publicly accessible database launched in April 2013 at the National Center for Biotechnology Information, which archives up-to-date information submitted about genetic variants with medical relevance.

College of American Pathologists (CAP)
(www.cap.org)
As the leading organization of board-certified pathologists, CAP serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide. CAP provides a number of resources, including accreditation of laboratories, guidelines development, educational resources, and patient resources. CAP is the publisher of Archives of Pathology & Laboratory Medicine, the monthly, international, peer-reviewed journal, which is the most highly read journal title among US practicing pathologists. Among its 2015 initiatives, CAP has joined a partnership with the American Society of Clinical Oncology (ASCO) and the Association of Molecular Pathology in the creation of the Molecular Oncology Tumor Boards series (university.asco.org/motb), a crowd-sourced, online and user-driven resource designed to help cancer care providers with the interpretation and understanding of tumor molecular profiling tests and studies. Each month a case-based discussion involving genomics in cancer through an open forum is available through the ASCO Connection website. This allows oncologists and pathologists to share the latest information and best practices in a real-time format.

Genetic Testing Registry
(www.ncbi.nlm.nih.gov/gtr)
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.

List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)
(www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm#.VOuKA3zo66g.email)
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 in vitro 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.

MEDCAC was established to provide independent guidance and expert advice to the Centers for Medicare and Medicaid Services (CMS) on specific clinical topics. MEDCAC reviews and evaluates medical literature; reviews technology assessments and public testimony; and examines data and information on the benefits, harms, and appropriateness of medical items and services that are covered under Medicare or that may be eligible for coverage under Medicare. MEDCAC judges the strength of the available evidence and makes recommendations to CMS based on that evidence.

MyCancerGenome.org (www.mycancergenome.org)

My Cancer Genome is a personalized cancer medicine knowledge resource for physicians, patients, caregivers, and researchers. It gives up-to-date information on what mutations make cancers grow and related therapeutic implications, including available clinical trials. My Cancer Genome is a one-stop tool that matches tumor mutations to therapies, making information accessible and convenient for busy clinicians.

NCCN Biomarkers Compendium (NCCN.org)

Based directly on the NCCN Guidelines, the NCCN Biomarkers Compendium contains information designed to support decision making around the use of biomarker testing in patients with cancer. The goal of the NCCN Biomarkers Compendium is to provide essential details for those tests which have been approved by NCCN Guideline Panels and are recommended by the NCCN Guidelines.

NCCN Outcomes Database (NCCN.org; Flatiron.com)

The NCCN announced in January 2015 a collaboration with Flatiron Health to create a cloud-based data repository of NCCN member institution data—the NCCN Outcomes Database. Through this collaboration, electronic health record data will be aggregated for cancer quality and outcomes assessment, as well as identification of key trends and patterns in the care of cancer patients, using Flatiron's OncoAnalytics™ tool.

Oncology Research Information Exchange Network (ORIEN) (www.ORIENCancer.org; m2gen.com)

ORIEN is a unique research alliance among North America’s top cancer centers, launched in May 2014 to amass and exchange data to drive research collaborations in oncology and personalized medicine. Through ORIEN, founding members Moffitt Cancer Center, the Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital, and the Richard J. Solove Research Institute have agreed to use Moffitt’s standardized protocol, Total Cancer Care®, for tracking patients’ molecular, clinical, and epidemiologic data throughout their lifetime. ORIEN members have access to one of the world’s largest clinically annotated cancer tissue repositories and data from more than 100,000 patients who have consented to the donation for research. M2Gen, an informatics company created by Moffitt, guides ORIEN operations, data management, clinical trial matching and biobanking, and infrastructure to maximize federal and industry-sponsored research.

Personalized Medicine Coalition (PMC) (www.personalizedmedicinecoalition.org)

PMC membership encompasses a broad spectrum of academic, industrial, patient, and health care provider constituencies. By joining PMC, organizations ensure that they are afforded the opportunity to advance and shape the future of personalized medicine by identifying and building consensus on the most important issues, forging relationships with other stakeholders, sharing best practices, and creating a favorable public policy environment for the advancement of this field. The PMC has published in 2014 the fourth edition of its signature report, The Case for Personalized Medicine.

Program for the Assessment of Clinical Cancer Tests (PACCT) (www.cancerdiagnosis.nci.nih.gov/scientific_programs/pacct)

An initiative of the Cancer Diagnosis Program of National Cancer Institute’s (NCI) Division of Cancer Diagnosis and Treatment, PACCT has been developed to ensure that development of the next generation of laboratory tests is efficient and effective. The PACCT strategy group, which includes scientists from academia, industry, and NCI, is developing criteria for assessing which markers are ready for further development. PACCT also aims to improve access to human specimens, make standardized reagents and control materials, and support validation studies. A new program, the Clinical Assay Development Program, allows NCI to assist in the development of promising assays that may predict which treatment may be better or that will help indicate a particular cancer’s aggressiveness.
Talking Glossary of Genetic Terms App from the National Human Genome Research Institute (Available at the App Store) (www.genome.gov/Glossary)

The National Human Genome Research Institute created the Talking Glossary of Genetic Terms to help everyone understand the terms and concepts used in genetic research. In addition to definitions, specialists in the field of genetics share their descriptions of terms, and many terms include images, animation, and links to related terms.


The TAPUR study—sponsored by the American Society of Clinical Oncology (ASCO)—is a prospective, observational, nonrandomized clinical trial that aims to describe the performance (both safety and efficacy) of commercially available, targeted anticancer drugs prescribed off-label for treatment of patients with advanced cancer (ie, solid tumor, multiple myeloma, or non-Hodgkin lymphoma), which have a potentially actionable genomic variant. The study also aims to simplify patient access to approved targeted therapies that are contributed to the program by collaborating pharmaceutical companies, catalogue the choice of genomic profiling test by clinical oncologists, and learn about the utility of registry data to develop hypotheses for additional clinical trials.

At least 13 drugs that target more than 15 genomic variants will be provided by five pharmaceutical companies (AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Genentech, and Pfizer) at no charge to participants. ASCO expects more companies to support the collaboration. ASCO expects to submit the completed trial protocol and consent form to an institutional review board in July 2015 and begin enrollment by year-end.

The Cancer Genome Atlas (TCGA) (cancergenome.nih.gov)

TCGA is a comprehensive and coordinated research effort to accelerate an understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. TCGA is a joint effort of the National Cancer Institute and the National Human Genome Research Institute. Since its launch as a pilot in 2006, results from TCGA analyses to date have led to more than 2,700 articles in research journals. Two new projects underway are PanCanAtlas and Pan-Cancer Analysis of Whole Genomes, which expand on data to date about the complex relationships across cancer types.

The Green Park Collaborative–USA (www.cmtptnet.org/resource-center/category/green-park-collaborative)

This collaboration was initiated in 2013 between drug and device developers, private and public payers, and clinicians and the patients they serve to improve clinical research. Among its initiatives in 2014 is the exploration of coverage and reimbursement challenges related to next-generation sequencing (NGS)-based testing in oncology. Multistakeholder work will continue in 2015 regarding the methods and standards for evaluation of the clinical utility of NGS-based testing, and culminate in the issuance of an Effectiveness Guidance Document on the Clinical Utility of NGS in 2015.

The Molecular Evidence Development Consortium (MED-C) (www.med-c.org)

MED-C was formed as a nonprofit public charity in February 2015 to organize all the major stakeholders—patients, physicians, payers, pharmaceutical companies, laboratories, and regulators—into a consortium to undertake work in a shared and scientific manner to advance personalized medicine through data collection and education. All stakeholders will derive a net benefit from participation.

MED-C will use existing infrastructure to introduce molecular testing to patients and also increase numbers of patients for existing clinical trials, and where trials do not exist, access to advanced testing and promising treatments. This will be achieved through a robust and highly standardized prospective observational outcome registry (SOR). The goal is to dramatically increase the numbers of patients participating in the advancement of care through trials first and the SOR second. The MED-C SOR compliments current and future clinical trials.

The high degree of standardization will differentiate the MED-C SOR from other registries. Standards include patient characteristics, testing methodology, treatment pathways, physician and patient outcome reporting, and toxicities. An independent oversight body will use the data gathered to allow iterative learning and refinement of testing and treatment pathways so that the complexity of personalized medicine is unlocked in a stepwise fashion. Given its open nature, shared governance, and cross-specialty focus, MED-C has the potential to impact a broader community than any single group. Activities are underway regarding infrastructure and the first pilot project to gather data about next-generation sequencing in metastatic non–small-cell lung cancer.


Issues in Focus:
Genomics in Cancer Care:
Realizing Precision Medicine

An informational white paper
provided by Genentech,
South San Francisco, CA

Produced by Emron, Wayne, NJ
www.emron.com