AACC-FDA-NCI Cancer Biomarkers Collaborative Consensus Report: Advancing the Use of Biomarkers in Cancer Drug Development

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Abstract

Recent discoveries in cancer biology have greatly increased our understanding of cancer at the molecular and cellular level, but translating this knowledge into safe and effective therapies for cancer patients has proved to be a challenge. There is a growing imperative to modernize the drug development process by incorporating new techniques that can predict the safety and effectiveness of new drugs faster, with more certainty, and at lower cost. Biomarkers are central to accelerating the identification and adoption of new therapies, but currently, many barriers impede their use in drug development and clinical practice. In 2007, the AACC-FDA-NCI Cancer Biomarkers Collaborative stepped into the national effort to bring together disparate stakeholders to clearly delineate these barriers, to develop recommendations for integrating biomarkers into the cancer drug development enterprise, and to set in motion the necessary action plans and collaborations to see the promise of biomarkers come to fruition, efficiently delivering quality cancer care to patients.

Clinical phase of development can cost hundreds of millions of dollars and take nearly a decade to complete (2). Furthermore, the failure rate of clinical trials has increased, with one half of oncology drugs entering phase III trials never making it to U.S. regulatory approval (2). Many drug candidates fail in early clinical development because outdated trial designs are used for their clinical testing and evaluation. Although advances in technology and genomic information have fueled the use of innovative tools, methods, standards, and approaches—including those using biomarkers—throughout the drug development process, the incorporation of cutting-edge science and evidence-based knowledge into regulatory decision making has lagged behind. The resulting uncertainty in the drug approval process can make it difficult to get targeted therapies approved and implemented into clinical practice. Thus, both the drug development and regulatory approval processes are often constrained by outdated assessment tools.

The model for development of “blockbuster” drugs, that is, drugs given to an unselected population even though they may only be effective in a small percentage of the population, may not be sustainable. Traditional population-based models of clinical trials used for drug approval are designed to guard against bias of selection, which may form the antithesis of personalized medicine, and accordingly, these trials expose large numbers of patients to drugs from which they may not benefit. In oncology, where treatments are costly, life expectancy is limited, and the risk of drug toxicity is often high, there is a pressing need to identify and treat those patients for whom a given drug is most likely to be beneficial.

Knowledge of cancer at the cellular and molecular levels has grown exponentially in the past two decades and has resulted in significant improvement in the characterization of human tumors, which in turn has catalyzed a shift toward the development of targeted therapies. Advances in technology are increasingly leading to large-scale, high-throughput research and to the development and improvement of the tools capable of analyzing the whole genome, proteome, transcriptome, and metabolome (often referred to as the “omics” approaches). This tremendous revolution in biomedical sciences and technology produces massive amounts of data and has unprecedented potential to fuel the pipeline of therapeutics in development. Unfortunately, the degree to which this knowledge is translated into safe and effective cancer therapies is not keeping pace, in large part because the current drug development process is increasingly costly, inefficient, and unpredictable.

Despite a major increase in investment by government and industry over the last two decades, the overall U.S. approval success rate for cancer therapeutics has remained low (1). The cost and time required to evaluate and develop drug candidates have increased dramatically; the clinical phase of development can cost hundreds of millions of dollars and take nearly a decade to complete (2). Furthermore, the failure rate of clinical trials has increased, with one half of oncology drugs entering phase III trials never making it to U.S. regulatory approval (2). Many drug candidates fail in early clinical development because outdated trial designs are used for their clinical testing and evaluation. Although advances in technology and genomic information have fueled the use of innovative tools, methods, standards, and approaches—including those using biomarkers—throughout the drug development process, the incorporation of cutting-edge science and evidence-based knowledge into regulatory decision making has lagged behind. The resulting uncertainty in the drug approval process can make it difficult to get targeted therapies approved and implemented into clinical practice. Thus, both the drug development and regulatory approval processes are often constrained by outdated assessment tools.

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Biomarker: A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (34).

- **Diagnostic Biomarkers**
- **Predictive Biomarkers**
  - Early detection biomarkers
  - Predict patients likely to respond to a specific agent
  - Predict patients likely to have an adverse event to a specific agent
- **Metabolism Biomarkers**
  - Dose defining
  - Outcome Biomarkers
  - Forecast response
  - Forecast progression
  - Forecast recurrence

**Analytic validation or assay validation:** The process of assessing the assay and its performance characteristics and determining the optimal conditions that will generate a reliable, reproducible, and accurate biomarker assay for the intended application (3).

**Clinical qualification:** The evidentiary process of linking a biomarker (using data obtained by a biomarker assay) with meaningful biological or clinical outcomes (3).

**Known valid biomarker:** A biomarker that is measured in an analytic test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results (35).

Prospectively identifying populations of responders requires the development of predictive biomarkers, that is, biomarkers that predict the likelihood of response to a particular pharmaceutical agent(s). Such biomarkers can also be used to identify patient populations that are likely to have an adverse event. Development of a drug and companion diagnostic (i.e., an assay or test that detects relevant biomarkers) can aid in patient selection and forms the basis of what is referred to as personalized medicine—using molecular diagnostics of disease to prescribe the right treatment to the right patient. Biomarkers are also useful throughout the drug development process (3), not only to better determine drug efficacy with fewer patients by identifying critical responder subpopulations but also to provide early information about unpromising candidates such that a company can abandon its efforts sooner, saving valuable time and resources.

Like drug discovery and development, the discovery and development cycle for biomarkers can be defined as a set of linked processes in a pipeline: hypothesis generation, research study design, sample collection, data collection, data analysis, assay development, assay validation, clinical qualification, regulatory approval, and clinical use. Over the last several years, remarkable effort by the biomedical research community has gone into discovering and developing biomarkers for the diagnosis and treatment of cancer. Although this research has paid off in a plethora of novel biomarkers (4–7), most of them are stalled in a research setting, unable to be exploited for widespread clinical use. To date, it has been difficult for individual research laboratories to determine which biomarkers have the greatest potential for use in a clinical setting and to develop them, independently or concomitantly with companion drug development, to standards that regulatory agencies would find acceptable. The biomarker field needs a clear path for taking biomarkers from the research discovery phase, through validation, qualification, and the global regulatory approval process, and then on to use in clinical practice. Achieving the goal of using validated biomarkers to accelerate drug approvals will require a collaborative, multidisciplinary effort that brings together those in the basic, clinical, translational, and regulatory sciences.

Recognizing the great promise of personalized medicine but seeing that forward momentum was slow, in March 2004 the Food and Drug Administration (FDA) unveiled the Critical Path Initiative, a nationwide effort to modernize the scientific process through which potential therapeutics or devices are transformed from discoveries into medical products. The initiative was launched with the release of a report entitled "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products" (8), which detailed the scientific reasons for the recent decrease in the number of innovative medical products submitted for FDA approval. The Critical Path Initiative identified biomarkers as one of the most important areas for improving progress in therapeutic drug development.

Numerous other organizations and agencies worldwide have launched efforts to address the complexities of cancer drug development, and many have also identified biomarkers as a key component for accelerating progress along the critical path from the laboratory bench to the patient bedside. Yet despite this broad interest, considerable public and private research spending, and the drive toward personalized medicine, surprisingly few biomarkers have been successfully translated into fully validated diagnostic tools. Indeed, less than two dozen cancer biomarkers have been approved by the FDA (9).

**Accelerating Progress along the Critical Path: The AACR-FDA-NCI Cancer Biomarkers Collaborative**

A major factor contributing to the lack of progress in the biomarker field seems to be the diversity of stakeholders...
involved at the different phases of the biomarker lifecycle. Each stakeholder may have a particular agenda that is not well aligned, and is often in direct conflict, with others' agendas. In an effort to understand how disparate stakeholder motivations and perspectives contribute to the stagnation of biomarker development and clinical integration, the American Association for Cancer Research (AACR), in partnership with the FDA, the National Cancer Institute (NCI), and the Pharmaceutical Research and Manufacturers Association (PhRMA), convened a 2-day workshop to discuss the use of biomarkers in oncologic drug development and therapy in November 2006. The AACR-FDA-NCI Cancer Biomarkers Workshop catalyzed interactions among stakeholders from academia, industry, government, and the patient advocacy community. This workshop, along with insightful discussions with FDA leadership about how the AACR could help advance the Critical Path Initiative, led to the establishment of the AACR-FDA-NCI Cancer Biomarkers Collaborative (CBC) in April 2007.

The goal of the CBC is to accelerate the translation of cancer therapeutics into the clinic by shaping the processes for the effective development of validated biomarkers and their use in clinical trials for maximum patient benefit. Paramount to the success of the CBC is that it seeks input from and develops consensus among distinguished experts and key stakeholders—academia, pharmaceutical and diagnostics industries, government agencies, regulators, and patient advocates—worldwide. The CBC currently consists of more than 120 experts in all areas of cancer biomarker research working in four committees to address the priority areas of biospecimens, assay validation, bioinformatics, and information sharing (listed in no order of importance).

The objectives of the four CBC committees, which conducted their work over the course of the following 18 months, were (a) to identify the barriers to developing biomarkers for clinical use; (b) to define best practices and make recommendations to hasten the integration of biomarkers into drug development and clinical practice; and (c) to develop action plans with short- and long-term solutions to help move these vitally important areas forward. These action plans and related activities form the groundwork for a comprehensive strategy to facilitate the development of the methodologies, infrastructure, and policies necessary for effective and efficient use of biomarkers during cancer therapy. The processes addressed by the CBC’s work are relevant to the development of most biomarkers. Nonetheless, the CBC discussed the importance of other diagnostic techniques (e.g., imaging modalities) and other intended uses of biomarkers (e.g., forecasting response, progression, or recurrence) and noted the potential for future expansion based on its initial work.

The imperative to develop and apply quality standards, quality criteria, and quality systems for biospecimens and biomarker assay validation, as well as to construct an enabling environment of infrastructure, regulations, and policies that foster efforts to meet these goals, emerged from the CBC discussions. An enabling environment would include, among other things, a system for harmonizing terminology and standards, a supportive bioinformatics platform, incentives for following standards and sharing data, and improved awareness among stakeholders.

Specifically, the CBC committees identified eight critical areas for efficient and effective biomarker development and came to consensus on 27 recommendations (Table 1) that span these areas and address the most pressing barriers to the advancement of biomarkers in the development of cancer therapeutics. For ease of discussion, the CBC’s recommendations are categorized into eight critical areas for biomarker development: (a) biospecimens, (b) analytic performance, (c) standardization and harmonization, (d) bioinformatics, (e) collaboration and data sharing, (f) stakeholder education and communication, (g) regulatory issues, and (h) science policy. For each recommendation, a corresponding action plan toward overcoming these barriers was developed. The CBC recognizes that many of the recommendations need to be addressed contemporaneously, with continual feedback and dissemination of progress to the broader community, especially in light of the rapidly evolving technologies and scientific advances that pervade the biomarker field.

Accomplishing the recommendations is no trivial undertaking and cannot be implemented by a single sector or a single group working in isolation. It will require the close involvement and cooperation of governmental agencies, legislative bodies, industry, academia, and advocacy and nongovernmental not-for-profit organizations. The CBC recognizes and applauds the hard work of the numerous agencies and organizations worldwide that are already making strides toward surmounting barriers to biomarker development. The unique structure of the CBC, which boasts a deep interest and participation from the entire gamut of stakeholders engaged in the biomarker pipeline, means its greatest contributions are through its roles as a convener and an educator—the CBC can act as a catalyst for the numerous efforts that require coordination of multiple stakeholders, can build consensus and speak as a strong, collective voice to advocate for necessary process and policy changes, and can serve as a valuable resource for the cancer research community. The CBC will continue to organize workshops and working groups to advance the development of white papers, best practice documents, and educational materials to meet the specific challenges of individual recommendations. Furthermore, the CBC, which has primarily focused on the United States, will broaden its purview by seeking out additional international partners to collaborate on the many areas requiring global participation and harmonization. To make progress on the recommendations herein will require a substantial investment of resources—intellectual, personnel, time, and fiscal—and a committed, collective action from...
Without engagement and collaboration from stakeholders across the entire cancer research community, the promise of biomarkers to hasten the arrival of better, more effective cancer therapies may remain beyond reach.

Each of the following eight sections introduces the identified priority area, discusses the current problems and specific need for the recommendation, and details the anticipated outcomes of the action plans. They are presented herein in no order of importance.

### Table 1. The AACR-FDA-NCI Cancer Biomarkers Collaborative consensus recommendations in eight critical areas to advance the use of biomarkers in cancer drug development

**Biospecimens**
- Establish quality standards and promote routine quality assessment of biospecimens acquired for research
- Develop a publicly available national oncology resource of biospecimen reference standards for biospecimen quality assessment and analytic validation
- Promote an infrastructure and climate supportive of biospecimen research

**Analytic Performance**
- Develop best practices for analytic validation of various analytes and technologies
- Define and implement quality systems for use in assay validation
- Develop universal physical reference standards

**Standardization and Harmonization**
- Harmonize biomarker validation and qualification terminology
- Develop a set of common data standards in which the community has influence and input
- Define a universal data element set to accompany all high-quality biospecimens
- Create a simple, standard, and efficient informed consent process and document

**Bioinformatics**
- Implement a common workspace in a federated application environment
- Establish a collection of use cases (i.e., working models) for biomarker development to facilitate the development of appropriate bioinformatics tools

**Collaboration and Data Sharing**
- Form a model pre-competitive consortium to facilitate sharing scientific information and research operations
- Develop incentives to encourage collaborations among drug sponsors, clinical research sponsors, and regulatory authorities
- Encourage contribution of biospecimen methods data and experimental data to public databases

**Regulatory Issues**
- Develop best practices on codevelopment of therapeutics and diagnostics
- Develop best practices on evidentiary standards for changes in drug labeling and developing companion diagnostics
- Develop best practices for biomarker assays based on a composite of multiple individual biomarkers
- Develop best practices for retrospective-prospective study designs for clinical qualification of biomarkers
- Develop best practices on adaptive clinical trial designs for using biomarkers in drug development
- Develop best practices on alternative prospective trial designs for companion diagnostics

**Stakeholder Education and Communication**
- Educate patients and health care providers about the value and need for biospecimen collection
- Increase awareness and understanding of the importance of analytic validation and quality control
- Educate stakeholders in regulatory pathways to accelerate codevelopment of therapeutics and diagnostics

**Science Policy**
- Identify areas and/or processes that could enhance the environment for biomarker development
- Explore ways to improve reimbursement for biospecimen handling and diagnostic tests
- Address the barriers to biomarker research produced by the HIPAA Privacy Rule

**Biospecimens**

Biospecimens provide the raw material for biomarker discovery and development. Accurate detection of biomarkers using state-of-the-science research techniques requires high-quality biospecimens with intact, accessible proteins and nucleic acids as well as appropriate, informative annotation. The absence of high-quality biospecimens is widely believed to be one of the most significant roadblocks to developing and validating biomarkers (10).
The reasons leading to low-quality biospecimens are numerous and broad-ranging, but the use of low-quality specimens often results in the same unfavorable outcome: variability in assays that causes erroneous conclusions and failure to advance the translational process. Improving the quality and consistency of biospecimen resources was identified by the CBC as a top priority for action. CBC recommendations aim to improve universal biospecimen collections by addressing quality, reference standards, and the field of biospecimen research.

Quality—Establish quality standards and promote routine quality assessment of biospecimens acquired for research Biological samples used in clinical hypothesis testing must be validated before use to ensure their adequacy for the proposed analytic platform. The physical state of biospecimens is affected by many factors, including pre-acquisition (e.g., type of anesthesia given to the patient), acquisition (e.g., type of biopsy), and post-acquisition (e.g., how biospecimen is processed, stored, and prepared for analysis) variables. Currently, there is little quality assurance or quality control on newly collected or archived biospecimens, and collections used for retrospective studies most frequently are composed of biospecimens of unknown and often poor quality. Although numerous guidelines and recommendations for biospecimen collection exist (11–14), there are no uniformly applied standards for biospecimen quality. Neither international consensus nor widespread implementation has been achieved. The extent of this problem was highlighted when The Cancer Genome Atlas (TCGA) project of the NCI surveyed specimens for its large-scale sequencing effort. Many large collections of biospecimens previously assumed to be of high quality were found to be unacceptable for use in the TCGA pilot project (15). Thus, from the initial stages of biomarker discovery research, low-quality samples hinder progress. To address the lack of high-quality biospecimens, consensus documents on evidence-based best practices for biospecimen collection, evaluation of biospecimen quality, and quality control are needed. Best practices are dependent, to some degree, on the biospecimen type, the molecular analysis to be performed, and the goal or application of the research, and efforts in this area must aim to address the implausibility of applying a “one-size-fits-all” approach. Understanding that limited data exist on which to base best practices, efforts to bolster biospecimen research are also needed (see “Research” below). Changes in biospecimen collection methods and implementation of quality testing to comply with best practices will require a commitment of laboratory time and resources. Thus, universal uptake of best practices is not likely to happen without added incentives or appropriate disincentives. The idea of an accreditation program for biospecimen repositories should also be explored. Annotation of biospecimens with associated clinical data and the permitted use of biospecimens based on ethical, legal, and policy issues also affect the quality of biospecimen resources and are discussed in the appropriate sections below.

Reference standards—Develop a publicly available national oncology resource of biospecimen reference standards for biospecimen quality assessment and analytic validation A critical component of quality control is having access to reference standards that enable methodologic standardization, increase the confidence with which quality control data are interpreted, and provide material for proficiency testing of personnel. No such reference standards exist for biospecimens, and as a consequence, routine and reliable quality assessment is severely impeded. A reference repository of carefully characterized biospecimens that would include blood for genomic DNA, tumor tissue, and adjacent “normal” tissue of known molecular content and integrity would be valuable for control and comparison purposes. Additionally, availability of carefully annotated reference biospecimens appropriate for use in analytic validation would result in better, faster analytic validation of new biomarker assays. These specimens would need to be representative of those that will be used in clinical testing and be available in sufficient numbers to allow meaningful statistical analysis. The NCI Office of Biorepositories and Biospecimen Research (OBBR) has invested considerable time and effort toward this goal and is in the early stages of developing a national, standardized human biospecimen resource called the cancer Human Biobank (cHUB). To facilitate the establishment of a publicly available resource of biospecimen reference standards for quality assessment and assay validation, best practices for storage and use of biospecimen reference standards should be developed, as should best practices needed to facilitate such a resource, which agencies could utilize to improve national infrastructures. Standardized measures of biospecimen quality plus the availability of reference biospecimen standards would improve individual studies and facilitate cross-repository studies and sample sharing by allaying the common concern that specimens from other facilities are of unknown quality and thus potentially unreliable.

Research—Promote an infrastructure and climate supportive of biospecimen research The lack of evidence to define best practices for biospecimen use is a barrier to establishing universal standards for use in biomarker research. Biospecimen science, wherein the biospecimen itself is the subject of research, is perceived to be undervalued by the scientific community. Moreover, most empirical methods used currently in biomarker research do not incorporate data-driven biospecimen practices. The generation of large collections of high-quality biospecimens necessary for biomarker research and development may require significant changes to the current infrastructure and research climate. Initiatives aimed at educating researchers, funding agencies, scientific journals, and other stakeholders on the merits and necessity of biospecimen research are needed. A coordinated effort to alter the publication process to encourage researchers to communicate optimized biospecimen practices will require a commitment of laboratory time and resources. Thus, universal uptake of best practices is not likely to happen without added incentives or appropriate disincentives. The idea of an accreditation program for biospecimen repositories should also be explored. Annotation of biospecimens with associated clinical data and the permitted use of biospecimens based on ethical, legal, and policy issues also affect the quality of biospecimen resources and are discussed in the appropriate sections below.
protocol details is also warranted. Wider access to background biospecimen research should promote better sample procurement practices and avoid duplication of effort.

Biospecimens of known high quality would enable researchers to take full advantage of the newest, most exacting analytic platforms. As discussed above, to achieve universal high quality for biospecimens requires collective progress in quality measures and assessment, development of reference standards, and advancement of the scientific knowledge that drives best practices. The CBC will help to drive the field toward establishing rigorous standards for biospecimen procurement and storage by working with the NCI OBBR and reaching out to other U.S. and international agencies and organizations to help develop consensus needed to establish best practices in the aforementioned areas. The CBC will also dedicate efforts toward initiating and supporting the needed culture shift by encouraging compliance with best practices and building on the ongoing efforts of other organizations to coordinate and augment initiatives aimed at educating researchers, funding agencies, scientific journals, and other stakeholders on the merits and necessity of biospecimen research. Progress will also require standardization of quality measures, terminology, and annotation. Once high-quality biospecimens are routinely collected, reaping their full potential to advance biomarker development will be dependent on increased collection of and broader access to samples and will involve improvement in the informed consent process and in educating the public. Recommendations to address these challenges are discussed in the appropriate sections below.

**Analytic Performance**

Another major reason that cancer biomarkers are not better incorporated into the drug development process, and therefore clinical practice, is the challenge of developing, using, and communicating proper information about biomarker diagnostics. Without proper determination of analytic performance and biological and/or clinical relevance, biomarkers cannot have the expected and desired impact on improving the quality of cancer care. The diversity of perspectives among groups and individuals in the field has complicated efforts to achieve well-founded and understandable analytic validation methods. Indeed, the term “biomarker assay validation” remains one that is controversial and is defined differently depending on the stakeholder using the term. Defining, optimizing, and standardizing the processes used to validate biomarker assays will improve biomarker integration into clinical trials and encourage acceptance by regulatory agencies.

**Assay validation methodologies—Develop best practices for analytic validation of various analytes and technologies**

Analytic validation is necessary to demonstrate that an assay is accurate and reliable and that it meets the experimental objectives in a reproducible and comparable manner. There are significant differences in approaches and evidentiary standards required by regulatory agencies, accrediting organizations, granting agencies, scientific journals, professional organizations, and others. Only recently has a standardized template for defining diagnostic accuracy, the STARD initiative (16), been encouraged by biomedical journals. The paucity of specific guidelines for analytic validity may lead to omissions or failures that are detrimental to ensuring that an assay is accurate and reliable. Moreover, it is becoming increasingly clear that assay development should account for the analytic variability in testing and for the pre-analytic (e.g., biospecimen acquisition and handling) and post-analytic (e.g., reporting methods) factors that may affect the generation of reliable results and proper use of these results. Widely accepted standards and methodologies for analytic validation of analytes and technologies would benefit the cancer research community. Validated biomarker assays would provide the confidence with which data could be interpreted and would allow standardization to facilitate the pooling of data across investigational sites. Additionally, physician understanding and clinical uptake of new tests may be aided by standardized methods of analytic validation.

**Quality systems—Define and implement quality systems for use in assay validation**

Analytic validation of an assay does not ensure continual high-performance results unless supported by an integrated system to implement and maintain quality objectives. Studies to validate biomarker assays that are carried out in research laboratories lacking defined quality systems may generate inconsistent results leading to a reduced level of confidence in the assay. Thus, a quality system should be in place and functioning effectively before attempting to validate the biomarker assay or initiating clinical services that use the biomarker. A quality system approach will make this aspect of the pipeline more efficient and reliable. Guidelines for quality system requirements are needed, along with appropriate incentives or disincentives and educational programs to encourage laboratories to adopt model quality system approaches. The application of quality system principles to all levels of biomarker work, from discovery to clinical qualification, should help streamline the process, providing assurance that data are reliable and minimizing the unexpected failures that result from poor quality approaches.

**Physical standards—Develop universal physical reference standards**

Often, results from clinical trials using biomarker measurements cannot be directly compared because there are few universally available physical standards on which to base such comparisons. Physical standards for analytes and matrices relevant to cancer biomarker measurement would be a valuable resource during biomarker development and during clinical trials. Ideally, a universal standard would be available for each individual biomarker; however,
time and cost constraints limit the number of standards that can be generated and will force prioritization of standards, their most useful form, and their biological and chemical features. In addition, the organizations responsible for developing, characterizing, curating, and distributing the standards will need to be identified. Achieving a resource of physical standards would expedite inter-study comparisons by promoting cross-referencing of biomarker measurements within and between clinical trials.

The CBC recommendations on improving the process of analytic validation of biomarkers address major problems in the quality and reproducibility of methods. To facilitate their implementation, the CBC will help develop consensus needed to establish best practices and provide educational activities and resources to encourage laboratories to follow best practices for assay validation and adopt model quality system approaches. The CBC’s consensus approach is particularly valuable for prioritization because the needs among user groups and communities are quite varied. Similar to the burdens of improving biospecimen quality, engaging stakeholders to comply with best practices, incorporate quality systems into research activities, and contribute to and utilize universal physical standards will require additional expenditures of personnel and fiscal resources. Widespread adoption and implementation of new practices may require considerable stakeholder education and outreach and/or appropriate incentives or disincentives from regulatory and funding agencies.

**Standardization and Harmonization**

Every dimension of biomarker translation—from discovery to clinical practice—is riddled with the problems of heterogeneity and an absence of universal standards. Each stakeholder may use a different language and methods of operating, restricting the potential for collaboration, utilization of others’ samples, and building on previous work. The expansion of the global economy, the prevalence of diagnostic manufacturers with worldwide distribution, and the increased regulatory oversight at local, regional, and national levels have significantly increased the need for harmonization. Yet, currently there is no comprehensive effort to develop the necessary standards. The CBC recommends action in four areas in need of standardization and harmonization: terminology, data standards, biospecimen annotation, and informed consent.

**Terminology—Harmonize biomarker validation and qualification terminology**

Considerable differences exist in the nomenclature and definitions used at the various stages of biomarker discovery, development, and clinical use. Further complicating matters is the lack of consistency within each of these stages, in which terminology varies depending on the scientific specialty or the specific analytic technique used for measurement of the biomarker. Some nomenclature and definitions have been introduced by federal legislation [e.g., the Clinical Laboratory Improvement Amendments (CLIA) of 1988], whereas other terminologies have been proposed by outside organizations (e.g., the International Federation for Clinical Chemistry, the International Organization for Standardization, and the International Union of Pure and Applied Chemistry, among others) seeking to establish appropriate standards. Unfortunately, few of these documents can be immediately and freely accessed, limiting their potential for widespread adoption. International, national, and other organizations should continue to collaborate to develop harmonized terms and definitions. Existing databases should be improved and/or other resources should be created that are user-friendly and publicly accessible. Harmonizing biomarker validation and qualification terminology will lay the foundation for collaboration and will improve the interactions with regulators and the education of stakeholders.

**Data standards—Develop a set of common data standards in which the community has influence and input**

Semantic interoperability (i.e., the ability of two or more systems or components to exchange information and to use the information that has been exchanged) allows the exchange and use of information across platforms and between institutions and is a prerequisite to a functional biomedical cyber-infrastructure and a collection of common analysis tools. The field of informatics and its applications in biology have benefited greatly from the adoption of common data models for maturing technologies. Obtaining data is a costly endeavor; however, establishing databases that provide interoperability affords the ongoing opportunity for data mining and retrospective studies and, thus, enhances the value of the collected data. Developing a set of common data standards that address data elements, domain level data, metadata (i.e., data that describe the content of a document, image, or website; examples include the date created, image resolution, keywords, and security features), data ontologies (i.e., common vocabulary for researchers to aid in understanding the structure of information shared among people or software components), and models would support the development of interoperable bioinformatics processes. Although the informatics framework to support cancer biomarker discovery is still evolving, existing community and network-based efforts such as the Cancer Biomedical Informatics Grid (caBIG) and the EDRN (Early Detection Research Network) Knowledge System at the NCI have already defined many of the key components required to address challenges associated with cyber-infrastructure, such as data heterogeneity, data integration, data analysis, and data sharing. The NCI meta-thesaurus system provides a model for semantic mappings between representations. The work of these programs should be used as starting points for
a larger-scale standardization initiative to develop a set of common data standards in which the community of researchers has influence and input. The development of standards will require the participation and acceptance of the biomedical research and regulatory communities, particularly at the interface between communities where different vocabularies, ontologies, data elements, and data collection instruments currently exist. As the field is continually and rapidly changing, the end product must be flexible enough to address evolving technical, analytic, and protocol requirements. A process for reviewing and amending the standards must also be developed.

**Biospecimen annotation**—Define a universal data element set to accompany all high-quality biospecimens

The lack of universal standards for biospecimen annotation that meet the diverse needs of the various stakeholders often compromises the biomarker validation and qualification process. Currently, there is no consensus on established standards for the type or amount of clinical data that should be collected for biospecimens, nor is there a common vocabulary or formatting standards (as discussed in “Terminology”). Minimal and comprehensive data sets must be defined and a template document should be generated and provided to institutions. Defining a universal data element set that should accompany all high-quality biospecimens would facilitate the collection and recording of data at individual sites and set a universal template on which investigators and repositories could build. As electronic medical records (EMR) are developed and implemented universally, these biospecimen data should be linked to the clinical information contained in EMRs. A further challenge in biospecimen annotation involves the lack of standardized labels that facilitate biospecimen identification and tracking. A system for a legible, durable, coded label for each sample with certain minimum information must be defined. Forward progress will have to contend with complex cyber-infrastructure requirements as well as tackle intricate ethical and legal concerns such as informed consent, patient privacy, and intellectual property. Ultimately, standardized annotation of biospecimens will increase their research value by facilitating data sharing for comparison among studies and for consolidation of data from different studies. Universal standards for biospecimen annotation will help ensure the quality of biospecimens and accelerate the integrated cyber-infrastructure that is fundamental to the advancement of personalized medicine.

**Informed consent**—Create a simple, standard, and efficient informed consent process and document

Another major challenge to widespread use of biospecimens in cancer research is the lack of a common informed consent document (ICD) for use in biospecimen collection. Current ICDs vary substantially, in part because there is no consensus on the definitions and terms related to biospecimen collection. There is also a lack of agreement among stakeholders regarding the level of detail to be included to adequately address genomic research issues and to explain coding, confidentiality, and the “honest-broker-system” in a way that a majority of research participants can understand (17). A related problem is the process by which informed consent is obtained. Whereas studies have shown that patients generally are willing to provide biospecimens for research (18), the timing of introduction of the ICD to the patient is important. Typically, consent is sought immediately before surgery when patients are more focused on their pending medical care and may be less willing to confront complex consent issues in the limited time available. Broad-based consent programs are being tested at various institutions across the country to address the many challenges associated with the informed consent process. Consensus is needed on the elements to be contained in a common ICD, and a template ICD should be generated and provided to institutions and institutional review boards, along with recommendations on how to implement the common ICD. Essential to the success of a common ICD is the standardization of biospecimen terminology (as recommended above) and addressing issues of patient privacy (see below) and intellectual property rights. Widespread adoption of a simple, standard, and efficient ICD and process has the potential to increase the number of biospecimens collected, clarify authorized research use based on participant choices, lessen the variability in institutional review board rulings, and facilitate sharing of biospecimens and associated data among the cancer research community—all of which would facilitate biomarker research and development.

The CBC determined that steps must be taken to solve the lack of standardization and harmonization in the aforementioned areas. Again, the CBC will facilitate progress by helping appropriate agencies and organizations to develop consensus needed to achieve harmonization, develop standards, and create template documents for use by the cancer research community. The CBC will also play a key role in educating stakeholders about the existence and use of these standards and documents and can assist the community in aligning its efforts with the Department of Health and Human Services (HHS) and other agencies. Resolution of these differences will greatly facilitate progress in the critical areas described throughout this report, in particular analytic performance, biospecimens, and bioinformatics. Reconciling differences to achieve successful, broad-based harmonization will be challenging because it will require both intellectual contribution and compromise on the part of multiple stakeholders.

**Bioinformatics**

The biomarker discovery and development cycle is a data-intensive enterprise where informatics capabilities and cyber-infrastructure play critical roles in the collection, organization, management, and analysis of very large volumes of heterogeneous, unstructured data from
constantly evolving experimental modalities. Informatics solutions need to ensure a cyber-infrastructure that provides interoperability and data access to a diverse range of stakeholders while simultaneously exhibiting flexibility and robustness to meet the rapidly evolving needs and technological advances in instrumentation and procedures. The CBC recommends addressing challenges surrounding biomarker bioinformatics by developing a universal set of data standards (see “Standardization and Harmonization”), implementing a common workspace for data sharing, and establishing a collection of use cases to guide effective strategies for bioinformatics designs.

Common workspace—Implement a common workspace in a federated application environment

Standard infrastructure at most institutions is inadequate for storing, moving, mining, and manipulating—in real time—the terabytes worth of complex data generated by -omics research approaches. As discussed above in “Standardization and Harmonization,” interoperability of diverse cyber-infrastructure and informatics tools is essential to facilitate the exchange of data across platforms and across institutions, and efforts such as caBIG and EDRN have invested considerable time and effort toward this goal. A publicly accessible common workspace (or set of workspaces) in a federated application environment would leverage individual efforts within the cancer research community. The application environment must encompass the full spectrum of informatics needs for biomarker discovery, validation, and qualification, facilitating the flow of data, information, and knowledge across each component of the pipeline. Further development and increased use of caBIG and EDRN can support the needs of discovery, validation, and qualification. A collection of use cases will help address the disconnect between the tool maker and the tool user. This effort should include both academic and industry stakeholders in order to achieve a smooth transition along the discovery-development pipeline.

The above CBC recommendations are designed to advance the biomarker bioinformatics field by enhancing efficiency through standardizing and reducing duplicative efforts. Large-scale implementation of cyber-infrastructure to support biomarker research will require institutional commitments to adopt new technologies, to train new scientists in its deployment and use, and to share information technology resources and data available through them.

Collaboration and Data Sharing

Most stakeholders agree that working collaboratively and sharing data and resources would speed biomarker discovery and development; however, the need to establish viable, profitable business models is at times in direct conflict with such an approach. Discovering, validating, and qualifying biomarkers is costly, and companies are often unwilling to take the investment risk unless they can be assured of intellectual property protection as a means of maximizing their return on investment. Additionally, researchers in many academic institutions need to independently publish their novel findings to be considered for promotion. Developing protected environments to share data and resources and incentivizing collaboration are critical to accelerating progress in biomarker use.

Use cases—Establish a collection of use cases (i.e., working models) for biomarker development to facilitate the development of appropriate bioinformatics tools

In addition to being data-intensive, the biomarker discovery and development cycle is neither fixed nor linear. Biomarker development strategies and study designs are determined by the intended clinical application and the types of samples available or to be collected. Such designs and the associated workflows influence the use of bioinformatics tools in the biomarker development process. To take into account the unique attributes of an individual biomarker study and the limitations of existing infrastructure available for that study, bioinformatics tools are often developed both ad hoc and de novo, neither of which is efficient. Moreover, informatics developers may not be fully conversant in the unique constraints, limitations, or compromises during the data collection process and, thus, may not account for these when building the tools. Similarly, the researcher using the tools may not fully understand the assumptions inherent in many analytic algorithms that could bias the analysis. The process from candidate biomarker to known valid biomarker requires a bioinformatics platform that can support the needs of discovery, validation, and qualification. A collection of use cases will help address the disconnect between the tool maker and the tool user. This effort should include both academic and industry stakeholders in order to achieve a smooth transition along the discovery-development pipeline.

Pre-competitive consortium—Form a model pre-competitive consortium to facilitate sharing scientific information and research operations

To obtain the broadest intellectual property protection in the form of worldwide patents, information must remain undisclosed to the public until the appropriate patent applications have been filed. This nondisclosure requirement conflicts with the need to publish and freely share information among individuals, institutions, public-private partnerships, and consortia in a timely manner to avoid duplication of effort and to build rapidly on the growing knowledge base. The semiconductor industry provides precedence for a successful cooperative and collaborative pre-competitive consortium that can facilitate scientific information sharing and research collaboration.
Incentives—Develop incentives to encourage collaborations among drug sponsors, clinical research sponsors, and regulatory authorities

Sharing biomedical research and health care data is vital, and many efforts have addressed the technical approaches to data sharing for willing parties. However, these efforts must also be complemented by appropriate ethical, legal, and social frameworks. Some communities, notably the genomics, structural biology, and clinical trials communities, have established policies and practices to facilitate data sharing, but few have focused on incentives for key stakeholders to encourage innovation and enhance collaborations among drug sponsors, clinical research sponsors, and regulatory authorities. The necessary incentives will vary depending on the risk (real or perceived) of sharing data. Well-designed incentives should have immediate benefit, especially for those individuals who are judged on recent performance. Potential economic, strategic, logistic, or legislative incentives and disincentives must be identified and a priority list of opportunities for providing these incentives should be generated along with recommendations to appropriate organizations for implementation. Increasing data sharing and collaboration will improve the speed with which biomarkers can be validated and incorporated in clinical research and clinical practice.

Public accessibility of biospecimen data—Encourage contribution of biospecimen methods data and experimental data to public databases

Broader accessibility to biospecimen research protocols and data through public databases would prevent duplication of efforts by minimizing the need for investigators to conduct optimization studies that have been completed by others. Making biospecimen data collected with public funds publicly available could be accomplished by further developing and encouraging the use of the Biospecimen Research Database (BRD) established by the NCI Office of Biorepositories and Biospecimen Research. BRD is a searchable, web-based curation tool designed to help investigators maximize the quality and utility of biospecimens by analyzing existing data on how biospecimens are affected by pre-analytic handling variables such as acquisition, processing, storage, and distribution. The database is being populated with evidence curated from published studies, unpublished results, and ongoing BRD experimentation. Additionally, methods information from industry submissions to the FDA will populate the BRD. Wider adoption of caBIG would also improve interoperability and would promote accessibility of biospecimen research data for laboratories worldwide.

The CBC itself is composed of members representing sectors facing the conflicts associated with data sharing and is thus positioned to educate and engage the cancer research community across all levels to define ways to collaborate productively.

Regulatory Issues

In the area of biomarkers, as with any burgeoning field, clarity, transparency, and direction from regulatory agencies are essential to help industry, to avoid confusion, and to efficiently meet regulatory requirements for approval or clearance of medical products. Although draft guidances have been put forth in some relevant areas and interest has been expressed for guidances in other areas, many regulatory processes have not yet been developed for this rapidly evolving field. This may be one factor contributing to the speed of integration of biomarkers into the drug development process. Regulatory agencies such as FDA will need to continue to provide clear direction to the cancer research community that provides the stability in the regulatory process necessary for industry participation. The CBC believes it is important for regulatory agencies to continue to issue guidance documents on multiple aspects of the biomarker process, including codevelopment, labeling, composite biomarkers, and novel trial designs.

Codevelopment guidance—Develop best practices on codevelopment of therapeutics and diagnostics

Codevelopment of biomarker diagnostics and therapeutics will involve complex interactions between investigators with different skill sets as well as between different regulatory work groups—for example, the FDA Center for Devices and Radiological Health (CDRH) and the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER)—applying different regulatory statutes. In addition to concerns over harmonizing the work done under different regulatory systems (i.e., outside of the United States), there have been concerns about how sponsors should interact with the FDA when biomarker assays require clearance versus approval, and what administrative and evidentiary standards apply to new biomarker development, particularly those connected to drug use. The FDA issued draft guidance in 2005 (20), providing a starting point for discussion of the numerous issues involved in this complex area; however, further clarification is needed. A best practices document on codevelopment that addresses the scientific,
regulatory, and administrative issues that are important for bringing new biomarkers to market is warranted.

**Evidentiary standards**—Develop best practices on evidentiary standards for changes in drug labeling and developing companion diagnostics

The inclusion of pharmacogenomics information in FDA-approved drug labels is increasing (21). When the FDA introduced a series of labeling changes to include new pharmacogenomic information in drug labeling for at least three new biomarkers (e.g., CYP450 2D6/2C19, UGT1A1, and CYP450 2C9/VKORC1), it prompted the development of new FDA-cleared diagnostics for these biomarkers. It should be noted that although the FDA has changed labels based on evidence, it does not require that the biomarker assays be approved or cleared. This nascent area is in need of clarification from regulatory agencies with regard to the kinds of pharmacogenomic information that are needed on both drug and diagnostic test labels and the evidentiary standards that should be applied when making changes to drug labels in the future. A best practices document based on case studies for drug labels and evidentiary thresholds needed to inform a drug label change for adding new biomarker information; whether evidentiary thresholds should vary with biomarker use as described in the drug label; and possible approaches to assess the risk of the biomarker assay to determine its regulatory path (see “Regulatory Policy” below) could expedite progress in this area. Clarification of the similarities or differences between FDA-mandated data requirements and those used by payers and health care providers in setting standards for quality care is also needed to promote smooth integration of new biomarkers into clinical practice.

**Composite biomarkers**—Develop best practices for biomarker assays based on a composite of multiple individual biomarkers

A composite of numerous biomarkers, each individually identified with respect to its significance to various end points, can be more predictive and accurate collectively than individual markers. However, biomarker assays developed from a multiplicity of measurements introduce specific scientific questions related to analytic validation. For example, the statistical significance assigned to each marker individually should take into account the multiplicity in terms of the large number of other markers that were also analyzed. Even when the number of markers is small, what constitutes appropriate evaluation of a composite marker is unclear. Additionally, there is uncertainty with regard to when it is appropriate to report only the composite marker result versus all individual biomarker results in addition to the composite results. Clarification on how regulatory decisions will be made for biomarker assays based on a composite of multiple individual markers should address the current situation. Careful consideration of appropriate methodologies and techniques for testing new signatures and identification of areas of particular concern for proper analytic validation of composite biomarkers will help the cancer research community more rapidly identify and validate real and useful biomarkers.

**Retrospective study designs for clinical qualification**—Develop best practices for retrospective-prospective study designs for clinical qualification of biomarkers

For new biomarkers to rapidly enter clinical practice, it may not always be desirable or necessary to await the completion of long-term prospective studies. In some cases, it may be possible to provide interim credentialing of the biomarker using archived samples from external sample banks, recent randomized clinical trials, or both to identify biomarkers for certain intended uses. It may then be possible to build from an initial study to strengthen claims and understanding of its clinical relevance by adding samples from a well-studied cohort or by initiating a more robust prospective study. At least two biomarker assays—the Oncotype Dx (22, 23) by Genomic Health and the MammaPrint (24, 25) by Agendia, both for breast cancer prognosis—have been brought to the market based on data gathered in this manner. Using banked samples, clinical studies of both assays provided preliminary estimates of clinical relevance, and both are the subject of ongoing, more extensive prospective trials to further establish performance. Retrospective studies can present limitations. For example, populations studied retrospectively may be too narrow for broad application of results, or samples identified and studied may represent either convenience sample collections or banks with collection bias. A guidance document on clinical qualification of biomarkers that addresses the numerous issues that must be considered when applying retrospective studies to regulatory decision making will help the cancer community navigate this area in the most expeditious manner. A best practices document that describes several approaches to the use of retrospective-prospective trial designs and archived specimens in the evaluation of predictive biomarkers and addresses the tradeoffs of traditional comprehensive designs with the potential increase in speed of new study designs is warranted; one such document was recently published (26). If designed and implemented properly, retrospective studies can be highly beneficial in enabling more rapid and parsimonious development of biomarkers and more rapid clinical uptake.

**Adaptive clinical trial designs**—Develop best practices on adaptive clinical trial designs for using biomarkers in drug development

The use of biomarkers for early forecasting with regard to study parameters and study end points may create a need to revisit the traditional four-phase sequential models used in the process of drug development. Adaptive clinical trial designs allow for changes to a study in progress based on interim results, with the goal of streamlining and enhancing the study without losing scientific rigor. Whereas there is a growing literature base on adaptive designs (27, 28), and the FDA and other groups have growing experience with the use of enrichment studies (see below), to date there...
has been no consensus generated on which approaches might work best or specifically enunciating good practices for this process. Best practices in the use of adaptive clinical trial designs as they apply to both drugs and diagnostic devices used in the codevelopment process should be defined. A best practices document should include a road map for introduction of adaptive designs, including specific examples for modeling application of the methodology, should identify situations in which adaptive designs are of particular value, and may move beyond the traditional drug-diagnostic codevelopment model to consider prognostic use of biomarkers and novel designs for promoting these uses. It is hoped that such designs will foster rapid development of new drug-diagnostic combinations.

**Alternative prospective trials**—Develop best practices on alternative prospective trial designs for companion diagnostics

Prospective trials for new drug-diagnostic combinations can be performed in a variety of configurations. Randomization in such prospective studies may be performed by biomarker status, by treatment status, or by sequential randomization of both. The FDA has historically requested clinical trial studies in which the drug and diagnostic interactions are well established; however, an increasingly requested and applied alternative design is one in which an enriched patient population (e.g., only biomarker positive) is studied with the therapeutic (27, 28). This approach allows rapid accumulation of data to support the approval of the therapeutic and device in parallel and allows for the biomarker-drug combination product to move to market relatively quickly to benefit the identified subset of the population. However, this type of trial cannot assess drug effectiveness in biomarker negative patients. It also does not provide for evaluation of diagnostic sensitivity or specificity of the bioassay or the predictive value of a negative result. Among the requisites discussed at a recent NCI-FDA-Industry Workshop (29) for when an enriched patient study would be useful in establishing the safety and efficacy are a well-established biomarker assay and a clear understanding of the biology of the biomarker and its relationship to the target(s) of interest. Although these seem like reasonable requirements and the difficulties of full population (all-comers) studies are easy to recognize, the issue remains highly contentious. The lack of consensus within the cancer community underscores the need for best practices that will address the disconnection between the scientific and regulatory requirements for enriched designs and identify the circumstances that warrant enrichment studies to evaluate the clinical relevance of biomarkers.

The unique ability of the CBC to convene a comprehensive group of stakeholders enables the CBC to help develop consensus documents that will address some of the outstanding regulatory issues related to biomarker development and speak to the concerns of the cancer community. Such information should assist regulatory agencies in developing the necessary guidance documents to provide stakeholders with much needed clarity and direction.

**Stakeholder Education and Communication**

As more information is generated, new standards are developed, and new guidance documents are released, there is need to communicate this progress to various stakeholders and educate them about their potential roles and about the importance of compliance with guidance or adoption of new standards. To address this growing need, the CBC plans to help coordinate the production and dissemination of educational materials and other initiatives beginning with those areas deemed to be in the most immediate need of outreach: biospecimen collection and use, the importance of analytic validation, and the specifics of the regulatory process.

**Biospecimen collection**—Educate patients and health care providers about the value and need for biospecimen collection

A significant factor undermining biospecimen collection is the general lack of knowledge and awareness among primary care physicians, patients, and families about the value of biospecimen research in improving clinical practice and public health. In general, members of the public are more likely to contribute biospecimens when they fully understand the benefits and are presented with the opportunity to do so (18). Without appropriate education, however, patients entering hospitals may view biospecimen collection programs as being in competition with routine procedures that are part of health care, and may fear that their care will be compromised if they consent to contribute specimens for research. Patients also may be sensitive to privacy issues or have other concerns about the risks of contributing biospecimens to research. Educational initiatives from patient advocacy groups and other communities could mitigate many of these concerns and increase the acceptance of biospecimen collection. If health care providers are more aware of the relevance of biospecimen collection, they would be better able to participate in the education of their patients. Moreover, if patients and families better understand the purpose of and need for biospecimen research, they may be more likely to choose to contribute. A successful public education effort must address issues of public trust, alleviate individuals’ concerns, and emphasize potential benefits. Education and increased awareness of relevant stakeholders should increase the number of biospecimens contributed to research.

**Analytic validation**—Increase awareness and understanding of the importance of analytic validation and quality control

A number of professional organizations are addressing issues of assay validation and analytic quality control, but considerable stakeholder education is still required to enable implementation of solutions for establishing good laboratory practice (GLP) and for reporting of the data by
cancer researchers. The cancer research community would benefit from clear, specific information about analytic validation approaches—including the criteria of GLP that are requisite for valid data and the measures for maintaining quality control assurance for the accuracy and reproducibility of validated analytic methods—that have been developed and recognized by academia, government, and industry. Toward increasing awareness and understanding of the importance of analytic validation, educational programming and other materials for all stakeholders regarding drug and device regulations should be developed. Although it will require time for the complexities inherent in the basic principles of analytic validation to become properly understood by the cancer research community and for GLP to become more fully integrated into research, new educational forums on assay validation in cancer research will certainly facilitate robust credentialing of biomarkers for investigations, which will, in turn, lead to better cancer interventions.

**Regulatory pathways—Educate stakeholders in regulatory pathways to accelerate codevelopment of therapeutics and diagnostics**

Drug, biologic, and device regulations are markedly different, in part because they are performed under different legislative mandates and because of cultural and administrative differences among work units at the FDA. Drug stakeholders tend to know less about device regulation and vice versa. If the field of codevelopment of therapeutics and biomarkers is to move forward quickly, it is imperative that as much information as possible be shared with interested stakeholders so that there is a clear and comprehensive understanding of the regulatory processes for both drugs and devices. An enunciation of differences may help outside stakeholders better understand how to develop new products and may also assist the FDA and global regulatory agencies in considering mechanisms for harmonizing regulatory policies and finding mechanisms to ensure that drug and diagnostic work is as consistent as possible under existing regulations and statutes. The FDA already has useful educational materials for explaining regulatory policy, including a yearly workshop and web-based and printed materials; however, many stakeholders currently are not aware of them or do not use them consistently. Thus, additional efforts and alternative approaches must be taken to reach the intended audiences. This would require a commitment of time and resources on the part of the regulatory agencies to create educational videos and other materials on the various regulatory pathways, and numerous outside organizations and additional venues could be utilized to provide the FDA and other regulatory agencies with the greatest opportunities for knowledge sharing. These and other efforts to communicate the specific regulatory requirements should help accelerate codevelopment of therapeutics and diagnostics.

Stakeholder education and communication are areas of ongoing need in the dynamic biomarker field, and are particular strengths of the AACR. The CBC will leverage AACR venues, including its numerous scholarly publications, the CR advocacy magazine, its Annual Meeting and many other international meetings, educational workshops, and website resources to educate and engage these stakeholders and the general public.

**Science Policy**

A final area for consideration for the advancement of biomarker use in drug development is science policy. It is typical for the discoveries and applications of a rapidly advancing and evolving scientific discipline to outpace the necessary policy development that protects public health and safety. This is certainly the case for the role of biomarkers in the drug development process. Given the potential for biomarkers to improve and accelerate the drug development process and the subsequent delivery of quality care to patients, it is vitally important to develop policies that also cultivate innovation while safeguarding the public. The CBC has identified several areas in which current policies fall short of promoting biomarker development, including laboratory-developed tests, *in vitro* diagnostic multivariate index assays, reimbursement, and the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). The CBC believes it is important that relevant federal agencies engage in a process to address these areas and take necessary action through regulatory or statutory changes.

**Regulatory policy—Identify areas and/or processes that could enhance the environment for biomarker development**

There is a dichotomy between the approval pathways for commercially marketed laboratory diagnostic tests at the FDA and at the Centers for Medicare and Medicaid Services (CMS) under CLIA. Before entering the marketplace, the FDA review process assures that new assays have been validated for both analytic and clinical performance and have adequate instructions for use. Alternatively, when individual laboratories develop assays for use at their own unique site, called laboratory-developed tests (LDT) or "homebrew" tests, the laboratories are subject to CMS regulatory oversight under CLIA, which requires that, at the time of a scheduled inspection, assays developed during the review cycle are subject to ad hoc sampling to assure analytic validity and quality control. Although there is nothing to preclude laboratories from establishing clinical relevance for new LDTs, CLIA does not mandate this requirement and, for this reason, is perceived as a less burdensome pathway for rapid promulgation of new tests. Despite common practice, the FDA has viewed LDTs as medical devices subject to FDA oversight, but has traditionally applied enforcement discretion and not actively regulated them. In 2004, however, the FDA formally recognized a subtype of LDTs that involve integration of multiple signals into a composite clinical result, categorized as *in vitro* diagnostic multivariate index assays (IVDMIA). FDA published draft guidance that defined this niche set of LDTs and clarified...
its authority to regulate them (30), thereby creating great uncertainty in the industry. In 2008, in response to a change from the U.S. Department of Health and Human Services Secretary, the Secretary's Advisory Committee on Genomics, Health, and Society (SACGHS) evaluated federal oversight of genetic tests and recommended that the FDA consider regulating all LDTs on a risk-defined basis to assure clinical relevance and public health safety (31). Given the considerable, ongoing debate surrounding this issue (32), independent input from a diverse group of stakeholders on the IVDMIA guidance, the SACGHS recommendations, and other relevant sources would add a useful voice and broad-based perspective to the ongoing dialogue in this complex and controversial area, with the goal of helping regulators move forward the public health agenda in support of personalized medicine.

Reimbursement policy—Explore ways to improve reimbursement for biospecimen handling and diagnostic tests

Discussing above were some of the many challenges in biospecimen procurement, such as the need for high-quality samples, proper annotation, and patient education. Pathologists are central to the process, yet there is little incentive for them to participate in biospecimen procurement for research. An additional change to current policy that would increase the collection of high-quality biospecimens is the establishment of a billing code and reimbursement rate for pathologists’ handling of biospecimens. There is a need for improvement of the reimbursement process for diagnostic tests as well, as billing codes are often not sufficiently specific for novel biomarker assays and the reimbursement rates for these tests often do not reflect their value. By providing incentives for key stakeholders and setting precedent for other third-party payers’ coverage and reimbursement decisions, adequate CMS reimbursement for biospecimen handling and diagnostic tests would accelerate the widespread use of biomarker assays in clinical settings.

HIPAA—Address the barriers to biomarker research produced by the HIPAA Privacy Rule

Hospitals, health plans, and other U.S. organizations that handle medical records and samples must comply with the Privacy Rule of the HIPAA of 1996. Implemented to protect the privacy of an individual’s health information, HIPAA provisions also have unintentionally affected the performance of biomedical research, including cancer biomarker studies. In many instances, access to existing biospecimen collections and the acquisition of new biological samples have been hampered by current interpretation of HIPAA law. Also, the informed consent process is influenced by these federal stipulations, as are the ways in which researchers are permitted to share data and the types of data that can be shared. It is important that a thorough evaluation of the impact of HIPAA provisions on biomarker research be conducted. The Institute of Medicine (IOM) recently published a report “Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health through Research” (33), which identifies issues and problems with interpretation of HIPAA regulations as they pertain to research. This new report could serve as a starting point for discussions on how to overcome the unintended restrictions, including those that may be perceived, of the Privacy Rule.

The policy areas discussed in this section, as well as possible legislative incentives (or disincentives) to encourage collaborations (see “Collaboration and Data Sharing”), hold clear opportunities to initiate change that would accelerate biomarker research. The CBC is uniquely suited to serve as a resource for these agencies by assessing the range of stakeholder perspectives, collecting and synthesizing information, and ultimately, providing recommendations for effective policy changes with respect to areas in need of further exploration and attention. In addition, the AACR government relations and science policy capacity, along with its network of patient advocacy groups, will allow it to advocate for necessary legislative, regulatory, or other process and policy changes relevant to biomarker development. The CBC intends to leverage the important ongoing efforts of other organizations engaged in similar initiatives as well.

Summary

The AACR-FDA-NCI Cancer Biomarkers Collaborative is a stakeholder-driven effort to inform and accelerate the FDA Critical Path Initiative and the work of the broader cancer community. CBC committees identified eight critical areas for biomarker development—biospecimens, analytic performance, standardization and harmonization, bioinformatics, collaboration and data sharing, regulations, stakeholder education and communication, and science policy—and put forward 27 recommendations with corresponding action plans to address and overcome barriers in each of these areas. CBC recommendations address the need to develop and apply quality standards, criteria, and systems for biospecimens and biomarker assay validation; to create a supportive bioinformatics platform and a system for harmonizing terminology and standards; to identify incentives for following standards and sharing data; and to educate and improve awareness among stakeholders and the public.

The CBC serves as a valuable resource for the FDA, NCI, and other organizations, agencies, and individuals in the cancer research community. Through its work, the CBC has brought to the forefront many key issues with regard to biomarker development that need to be addressed. It has convened stakeholders from around the world to develop consensus on these important issues and continues to seek U.S. and international input. Furthermore, the CBC serves as a catalyst to initiate collaborative projects to implement solutions to improve biomarker validation and integration into clinical trials and, ultimately, into clinical use. Collectively, these efforts should not only improve the treatment of cancer
but also lead to advances in the treatment of other diseases in which biomarkers increasingly play important roles. The CBC will rely on the ongoing, active participation of a broad spectrum of stakeholders to continue its work to accelerate progress along the critical path in oncology drug development and will leverage and complement the ongoing efforts of numerous other groups. Successful integration of biomarker research and cancer drug development will require that all sectors engage, collaborate, and comply with best practices and guidance. Success also requires that educational efforts result in changes in attitudes, such as stakeholder compliance with standards or patient involvement. Importantly, success requires overall collaboration—whether to build and contribute to national common resources or to share data, a willingness of all stakeholders to engage is essential. While other groups have identified similar barriers to biomarker use, the CBC intends to take action and help lead the cancer community in the joint forward movement that is necessary to surmount the barriers by changing the current inefficient paradigms. The recommendations described within this report aim to accelerate the speed with which biomarkers can be used to fulfill their great promise to the personalized medicine revolution that cancer patients so critically await.

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