Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration

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Introduction

The emerging field of precision medicine continues to offer hope for improving patient health outcomes while also controlling the overall cost of health care. Precision medicine has also been recognized for its potential to improve the efficiency and overall productivity of the medical product development process by providing information on promising drug targets, optimal doses, and which patients are likely to exhibit favorable outcomes. Together, these strategies allow for a more biology-driven approach to drug development and may enable time and cost savings through leaner, more focused clinical trials that have a higher overall probability of success.

However, the overall impact of precision medicine in clinical practice and medical product development has been circumscribed due to limits in scientific understanding and the absence of well-characterized and reliable biomarkers for many disease areas. Biomarkers are defined as characteristics (e.g., a molecular, histologic, radiographic, or physiologic characteristic) that are measured as indicators of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. This definition broadly captures a variety of biomarkers that serve several important functions in the nonclinical and clinical settings of medical product development and clinical practice.

While advances in genomics, proteomics, metabolomics, and their associated technologies have propelled the discovery of novel biomarkers, the regulatory use of these biomarkers has been limited in large part by the lack of reproducible and clinically meaningful data. In addition, the pace of this discovery has largely outstripped the broader scientific and biomedical community’s ability to systematically validate and develop the evidence base to support their use. Biomarker development is a time-consuming and resource-intensive process, and there are several challenges that hinder progress in the field.

Numerous legislative and policy initiatives have been launched to facilitate the development and use of biomarkers in medical product development. In 2006, the U.S Food and Drug Administration’s (FDA) Critical Path Initiative identified biomarker development as a high priority area for future research and collaboration among stakeholders. Since then, FDA has worked to engage the stakeholder community through public meetings, issued guidance documents on the development and use of biomarkers in medical product development, established a voluntary submission process for pharmacogenomic data, and, most recently, implemented a biomarker qualification program as an additional pathway for the regulatory acceptance of biomarkers.

Improving the regulatory review of biomarkers was also a key commitment for FDA under the fifth reauthorization of the Prescription Drug User Fee Act. More recently, the 21st Century Cures Act (which is currently making its way through Congress) calls on FDA to take a number of additional steps to collaborate with the broader scientific community to facilitate the development and regulatory acceptance process.\textsuperscript{1,2}

More broadly, a diverse range of consortia are working to accelerate the discovery and development of publicly-accessible medical product development tools and methods, including better predictive tools, methods for clinical trials, procedures for biospecimen handing, and collective research resources (molecular libraries and tissue repositories). As many as one in four of these consortia are involved in biomarker research.\textsuperscript{3} The emergence of the consortia model indicates that stakeholders are increasingly open to sharing data, knowledge, resources, and capital to address pressing needs in biomedical research, especially in the area of biomarkers.

Several remaining challenges to effective communication and collaboration need to be addressed in order to make progress in the field. These challenges include a lack of consistent and coherent set of definitions for biomarkers and their uses; confusion surrounding the various regulatory pathways for biomarker acceptance; the need for data standards, rigor in data practices, and improved collaboration in data sharing between interested stakeholders; and the lack of coordination and prioritization of limited public and private resources.
This white paper, based in part on an expert workshop convened in October 2015, highlights key priority areas where further multi-stakeholder collaboration is required and ideas for adopting a more cohesive national strategy to advance biomarker development and precision medicine. The workshop was held under a cooperative agreement with FDA* and included leaders from various stakeholder groups, including, but not limited to, government, industry, consortia, academia, and patient advocacy groups.

Developing and Implementing a Universal Language for Biomarker Development

The use of biomarkers across different disciplines and settings (e.g. medical product development versus clinical practice versus scientific research) has naturally resulted in a great deal of variability in how different types of biomarkers (and their uses) are defined. Though varying definitions may capture important distinctions and situational nuances, the lack of a standard, universally agreed terminology has hampered effective communication among stakeholders and impeded the development of new biomarkers. Unclear or inconsistent definitions often lead to the misinterpretation of evidence and have complicated discussions around the development of evidentiary standards for biomarker qualification and regulatory acceptance. Inconsistent definitions also impede downstream decision-making related to clinical use and reimbursement.

Establishing a carefully defined, widely accepted biomarker-related glossary of terms would significantly improve communication and collaboration among stakeholders who are working to address barriers to biomarker development. In particular, a consistent set of definitions could facilitate the process of defining specific contexts of use for biomarkers in medical product development and regulation, which could in turn help build consensus on the evidentiary standards needed to endorse a biomarker for a specific use.

As a first step in driving this process, a joint working group of representatives from FDA and the National Institutes of Health (NIH) developed a proposed glossary that can serve as a starting point for broader standardization. The principal goal of this effort was to create a document that will serve as public resource to clarify biomarker terminology and that will capture the diverse range of biomarker types and their uses along the continuum of scientific discovery, therapeutic development, and patient care. An initial draft of select terms included in the glossary was presented at the workshop, along with an overview of the general approach that was taken by the working group to assemble the glossary. This approach involved reviewing existing definitions in statute, guidance documents, web resources, and a scan of the literature to identify existing terminology, a grouping of related terms, definitions and concepts, followed by the proposal of new definitions that underwent several iterations before being finalized. Ultimately, the goal is to align definitions that could be used consistently between regulatory, scientific, and clinical communities.

During this process, the working group followed three guiding principles. First, it was important for the proposed glossary to be sufficiently flexible in order to accommodate new concepts, methodologies, technologies (e.g. novel imaging techniques, biosensors, wearable monitors), and regulatory domains. Second, while harmonizing comparable terms, the working group also wanted to preserve important distinctions which would be useful when seeking to develop the evidentiary standards needed to establish a particular type of biomarker for a specific use. For example, the term susceptibility/risk biomarker was separated from the term prognostic biomarker to maintain important distinctions. Risk biomarkers measure a healthy individual’s likelihood of developing a particular disease or sensitivity to an exposure, whereas prognostic biomarkers provide information on disease behavior and the likely natural course of progression once an individual has been diagnosed with the disease. While both are used to guide clinical risk assessment, differences in the emphasis on the clinical status of the individual (i.e. absence versus presence of the disease) are important to highlight because they are likely to dictate the types of study designs and levels evidence needed to support the use of a biomarker for one specific use over another. Finally, the working group sought to use language and develop definitions that would

* At the time of convening, the FDA cooperative agreement was held by the Center for Health Policy at the Brookings Institution. In January 2016, the cooperative agreement was transferred to the Duke-Robert J. Margolis, MD, Center for Health Policy.
be all-inclusive and amenable to unification across stakeholder communities. The glossary has since been published on the National Library of Medicine website as an eBook, with the opportunity for public comment and feedback as soon as all definitions are complete. It is intended to be a living document that will be periodically updated.

Participants at the workshop agreed that a standardized glossary is a valuable public resource, and that the seven categories of use included in the glossary (e.g. susceptibility/risk, diagnostic, prognostic, predictive, pharmacodynamic, monitoring, and safety) adequately captured the range of applications in drug development and clinical practice. It was suggested that the group consider the inclusion of a specific term to capture the concept of screening, though others noted that this might be captured within one of the existing categories of biomarkers. As the glossary is developed and refined, further granularity of the categories can be considered, although participants cautioned against breaking down categories to the point where the use cases are too specific to be helpful or useful.

In order to ensure the broad acceptance and use of this terminology by all relevant groups, participants outlined a number of strategies and next steps that should be considered. First, the list should be updated regularly to reflect community input. It is also critical that this new set of terminologies be consistently used across federal agencies and reflected in all relevant documents, including FDA guidance documents, federal register notices, NIH Funding Opportunity Announcements, and in the grant application process. To the extent possible and appropriate, the terms should also be harmonized across international regulatory agencies. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) could play a critical role in driving this process.

It is also important to engage leadership from other relevant stakeholder groups, including consortia, professional societies, publishers, and journal editors, to ensure that these terms are incorporated into each group’s existing vocabulary. In order to achieve buy-in from these groups, it is important to clearly articulate the intent behind this effort and demonstrate how non-harmonized terminology has hindered progress in biomarker development. It may be helpful to include explanatory text in the glossary along with examples of ways these terms have been improperly applied, as well as tables that can map current terminology to the new definitions.

**Achieving Greater Clarity on the Different Pathways for Biomarker Development and Regulatory Acceptance**

Regulatory acceptance for biomarkers generally occurs through three pathways. The first involves general acceptance by the clinical, scientific, and regulatory communities, often after years or decades of debate on the clinical utility of a biomarker as evidence accrues organically through scientific research. The second involves the traditional marketing authorization process for medical products (i.e., the Investigational New Drug/New Drug Application pathway for drugs and biologics, or the Investigational Device Exemption/Premarket Approval pathway for devices), in which a sponsor may engage with FDA to reach agreement on the use of a biomarker in a given development program. The third involves qualification of biomarker for a given context of use (COU) that is independent of a specific drug development program.

Participants noted that these pathways are not isolated but instead exist in parallel, often informing one another and simultaneously contributing to the broader scientific body of knowledge. All of the pathways are data-driven and rely on consistency and reproducibility of the data to inform a given understanding and use of the biomarker. In addition, all of the pathways are associated with strengths and limitations and, depending on the biomarker and its COU, one pathway may have advantages over another (See Table 1). Because all pathways are voluntary, pathway selection will largely depend on the needs and available resources of the sponsoring organization.
Table 1: A comparison of the three general pathways for biomarker evidence development and regulatory acceptance

<table>
<thead>
<tr>
<th></th>
<th>Product-specific Development Pathway</th>
<th>Biomarker Qualification Pathway</th>
<th>Community Consensus Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>• Biomarker COU usually has well-defined purpose (limited scope/less generalizable)</td>
<td>• Biomarker COU usually more generalizable (drug classes, diseases)</td>
<td>• Extensive knowledge base for idea and hypothesis generation</td>
</tr>
<tr>
<td></td>
<td>• Data (clinical trial information) available to the biomarker developer</td>
<td>• Opportunities to pool resources and share costs</td>
<td>• Multitude of published studies</td>
</tr>
<tr>
<td></td>
<td>• Opportunities to bring in outside experts (for both FDA and company)</td>
<td>• Opportunities to bring in outside experts (for both FDA and company)</td>
<td>• Cost-sharing and public approach (e.g., NIH grant funding to support research)</td>
</tr>
<tr>
<td></td>
<td>• Company retains marketing advantage (real or perceived)</td>
<td>• Leverage outside stakeholder groups (e.g., patient advocacy, foundations)</td>
<td>• Opportunity for broad and multiple community inputs</td>
</tr>
<tr>
<td></td>
<td>• If the drug is approved, labeling and reviews made public (opportunities for others to use). May also inform recommendations to other companies working in the same area.</td>
<td>• Outcome results in a guidance (public availability for use)</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>• Biomarker may not be generalizable to other drug classes or diseases</td>
<td>• Data (clinical trial information) may not be available to the submitter</td>
<td>• Much of the information is not reproducible, data is difficult to organize/compare/pool, and process is not defined</td>
</tr>
<tr>
<td></td>
<td>• More limited opportunities for additional data sources</td>
<td>• If part of a group effort (e.g., consortium), member’s may have differing goals, level of commitment, and desire to share information</td>
<td>• Different study designs, populations, and analytics limits conclusions that can be drawn (data/goal mismatch)</td>
</tr>
<tr>
<td></td>
<td>• Company responsible for full development costs</td>
<td>• May take additional time to set up governance for group</td>
<td>• Protracted period of time</td>
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<tr>
<td></td>
<td>• May not have expertise for any analytical validation needs</td>
<td></td>
<td>• Many times do not have direct applicability to regulatory paradigms</td>
</tr>
<tr>
<td></td>
<td>• More limited opportunities for engagement with other outside stakeholder groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Likely Sponsor</strong></td>
<td>Individual company</td>
<td>Consortia of companies and/or academic groups</td>
<td>Community-wide effort</td>
</tr>
<tr>
<td><strong>Example of Biomarker</strong></td>
<td>EGFR mutation status as a predictive biomarker of response to EGFR-targeted therapies</td>
<td>Total kidney volume as a prognostic biomarker for autosomal-dominant polycystic kidney disease</td>
<td>Blood pressure as a prognostic biomarker for cardiovascular outcomes</td>
</tr>
<tr>
<td>Developed through this Pathway</td>
<td></td>
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</table>

Emerging regulatory experience with these various pathways suggests that some types of biomarkers are more appropriate for one pathway over another. However, this choice is not always clear, particularly in early development stages. More clarity is needed as to when regulatory acceptance of biomarkers could follow one pathway over another. Ultimately, since biomarker development is a voluntary activity, the developer retains the choice of which pathway to pursue.

Toward that end, the workshop included discussion of two biomarker case studies: Total Kidney Volume (TKV) in autosomal-dominant polycystic kidney disease and Epidermal Growth Factor Receptor (EGFR) in lung cancer. TKV was
recently qualified for use as a prognostic enrichment biomarker in studies for the treatment of autosomal-dominant polycystic kidney disease, while EGFR–related biomarkers (mutation status, protein expression) have been included as predictive biomarkers of drug response in a range of individual drug development programs and in the labels of several FDA-approved drugs that treat non-small cell lung cancer (NSCLC), including erlotinib, gefitinib, and afatinib. These two cases provided contrasting examples of the pathways towards regulatory acceptance. Of note, both the TKV qualification effort and the development of therapies targeting EGFR relied on consensus scientific understanding made possible through scientific publications and clinical experience.

Participants noted some similarities but also several important differences between the two case studies. Both biomarkers represent disease areas of unmet medical need, although the development space for autosomal-dominant polycystic kidney disease (ADPKD) has been considerably less active. Similarly, interest in TKV and EGFR emerged from early observations from the literature in the early 2000s that demonstrated their value as prognostic and predictive biomarkers, respectively. However, participants noted some important underlying differences between the two biomarkers that may explain why the development of TKV followed a structured, multi-stakeholder concerted effort under the biomarker qualification pathway, whereas EGFR’s status as a predictive biomarker was reached through separate IND development programs.

In the case of TKV, the qualification process was initiated by the PKD Foundation, which, in collaboration with FDA, the Critical Path Institute, academia and industry, launched the PKD Outcomes Consortium (PKDOC) to facilitate clinical trial development for ADPKD therapies. The role of the PKD Foundation in driving the qualification process highlights the important potential leadership role that patient organizations can play in collaborative biomarker qualification efforts. However, as with other qualification efforts mentioned during the discussion, participants noted that industry interest and multi-stakeholder engagement was also important for driving the process and seeing it through to completion. Representatives of the PKDOC noted that the motivation for the development of TKV stemmed from the lack of treatments for PKD, despite years of biomedical research on the disease. Because patients with PKD live several decades before changes to primary clinical endpoints are noticed, the PKDOC understood that the lack of drug development for this disease area was largely due to the absence of an acceptable outcome which made the disease area prohibitively risky and uncertain.

It was hoped that TKV would eventually serve as a surrogate endpoint, but the group decided to qualify the marker as a prognostic biomarker because that process would entail a lower and therefore more feasible evidentiary requirement. However, it is hoped that TKV can eventually be qualified as a surrogate endpoint through a step-wise evidence development approach. Representatives of the PKDOC noted that selection of the qualification pathway was most appropriate because little to no data existed. The qualification program allowed stakeholders to collaborate to piece together data from three patient registries and two observational cohort studies. A considerable amount of time was spent on developing a data standard for PKD and mapping disparate sources of data to a usable format. Participants noted that future data-sharing and qualification efforts would benefit from the availability and use of data standards for various disease areas. Nevertheless, participants emphasized the value of the qualification process as a safe harbor for bringing together the trove of existing biomarker data housed within academia, industry, and regulatory agencies.

Compared to TKV, the development of evidence for EGFR as a predictive biomarker for EGFR-targeted therapies in non-small cell lung cancer followed a largely unstructured and unexpected path under different IND development programs. Several EGFR-targeted therapies were approved prior to the realization that EGFR mutations could serve as a predictive biomarker for response to these drugs. Over the span of more than a decade, a number of retrospective analyses combined with prospective trials in patient populations enriched for EGFR mutations confirmed initial suggestions that EGFR mutation status could predict response to EGFR-targeted treatments. The results of these studies prompted efforts to develop and validate companion diagnostics for patient selection for EGFR-targeted therapies. Concordance studies were used to validate companion diagnostics and to ensure agreement between the two tests in order to bridge the clinical data to evaluate the drug efficacy in the intended use population.
It is difficult to say whether a predictive biomarker like EGFR could have been pursued through an alternative pathway, although participants noted that collaborative data sharing could have more readily identified EGFR mutations predictive of response to treatment had there been a safe harbor for companies to pool their data. Unlike the case of TKV, no neutral third party exists to facilitate collaboration among different stakeholders. Furthermore, the context of use for EGFR was limited, with various therapies targeting different activating mutations. Nevertheless, some participants noted that similar predictive biomarkers could be pursued through collaborative efforts in the future. Participation in the biomarker qualification program can occur alongside the traditional product development pathway, allowing companies to share certain data but also compete in other aspects of product development. This will require industry to reexamine the boundaries of pre-competitive collaboration. Meanwhile, participants noted the importance of having a neutral third party; declaring a biomarker qualification effort may provoke sponsors who would not have otherwise considered sharing data to partake in collaborative efforts.

Promoting Data Standardization and Sharing

Biomarker development and qualification can be data and labor-intensive activities, often requiring the aggregation of data from multiple sources to sufficiently power studies. While genuine progress has been made in the areas of pre-competitive collaboration and data sharing, participants expressed a desire for greater data sharing among stakeholder groups. Participants noted that the biomedical community has yet to unlock the full potential of current biomarker information and datasets that exist across stakeholder communities and geographic areas, while numerous opportunities are available for enhancing prospective data collection and sharing activities. Despite clear recognition of the benefits of collaborative data sharing, several technical, legal, commercial, and cultural barriers prevent stakeholders from pooling data and resources. Participants highlighted several guiding principles for data sharing, examples of data-sharing models that have effectively addressed these barriers, and strategies to encourage broader participation in data-sharing activities.

Implementing a systems-wide approach to encourage the adoption of data standards and improve data quality

Workshop participants noted that many of the challenges with biomarker discovery and development stem from a lack of standards in biospecimen collection and handling, biomarker analysis, and data reporting. Underlying data quality issues continue to pose a major obstacle for biomarker development by compromising downstream data reproducibility and analysis efforts. Participants emphasized the need for a systems-wide approach to adopt standards to address this issue, to ensure data reproducibility, and to enable the integration of biomarker information. Standardization not only provides benefits to individual institutions, including budget savings, cost avoidances, and improved efficiency, but can also improve collaborative data sharing efforts. Participants outlined several recommendations for harmonizing biomarker procedures across institutions to ensure that biomarker data can be readily generated and aggregated.

Standardization of pre-analytical variables

As the source of biomarker data and information, high-quality human specimens, such as cells, tissues, blood, and serum, are essential for accelerating the development of novel biomarkers. However, participants noted that current biospecimen practices, including specimen acquisition, handling, and storage, are diverse and lack standardization, which has contributed greatly to variability in the quality of specimens and, consequently, the reliability of the data produced from these samples. Participants emphasized the need to implement guidelines to promote standardized operating procedures for pre-analytical variables and to ensure compliance with these procedures. Several institutions have begun to implement standardized approaches and procedures for tissue acquisition, handling, and storage. However, further collaboration is needed to ensure harmonization across institutions and to develop best practices for specific disease areas. Several national and international bodies and consortia have endorsed the adoption of best practices guidelines. For several years, for example, the National Cancer Institute (NCI) has undertaken several initiatives to develop best practices and to improve the quality of biospecimen research with the establishment of the Biorepositories and Biospecimen Research Branch. To
ensure the broad implementation of best practices, however, participants indicated that better policies are needed to promote accountability, commitment, and quality assurance.

**Standardization and validation of bioanalytical tools and methods**

Selective, sensitive, and validated analytical tools and methods are needed to accurately and reliably measure biomarkers of interest. Analytical validation involves a number of different procedures that are undertaken to demonstrate that a particular method or tool used for the measurement of a biomarker is reliable and reproducible for its intended use. Variability in biomarkers tests and platforms used across institutions has significant consequences for the reliability of the data generated from these tools and downstream attempts to aggregate data from different sites. To maximize the utility of biomarker data, workshop participants stressed the need for the standardization and analytical validation of biomarker assays and tools to ensure concordance between data and results obtained at different testing sites. Because biomarker testing will most likely occur across different institutions and geographic locations, greater communication and collaboration is essential. Partners could work together to develop standardized procedures, physical reference materials, and protocols.

**Adopting data standards to streamline information exchange**

To gain maximum scientific knowledge from the totality of biomarker data generated across the biomedical research community, standardized data formats are needed to help facilitate data exchange and communication among partners. Standardization also offers several other benefits, enabling more effective analyses of shared data, allows for the reusability of data, and improves the efficiency of the regulatory review process. While legacy data can be converted to common standard elements, it can be both time- and resource- intensive and critical information may be lost in the process. Participants noted that upstream implementation of standards – rather than conversion from legacy data – is optimal. Toward that end, the Clinical Data Interchange Standards Consortium (CDISC), a global non-profit, has been working to develop and promote open, consensus-based clinical data standards to streamline the clinical research process. Despite progress in the development of standards for many different therapeutic areas, adoption and use of these standards has been slow. Participants noted that greater resources could go towards educating the broader community on the importance and value of data standards and to provide technical assistance in the implementation of standards.

**Incentives and investments for sustainable data collection and sharing**

Participants also discussed some of the cultural barriers to collaborative data sharing. Despite awareness of the benefits of data sharing, historical norms and existing incentives prevent stakeholders from readily sharing and pooling their data and resources. Industry, academia, and regulators produce and store vast amounts of data that could potentially accelerate biomarker development if shared. Participants emphasized the need for additional incentives to utilize this existing data, to improve the rigor and quality of prospective biomarker data collection, and to encourage stakeholders to share their data in a timely manner. Targeted incentives and enforcement mechanisms are needed to overcome specific barriers to data sharing for each stakeholder group (i.e., academia, industry, and regulatory) and encourage more team-based or collaborative approaches to scientific research.

There are several promising guiding principles and models for data sharing that could address these concerns. For example, advance planning can address intellectual property and other legal concerns upfront, while mechanisms for controlled access to research data and data anonymization can address patient privacy concerns. The Biomarkers Consortium, among other partnerships, has been able to manage these risks effectively. Participants noted that future efforts should focus on educating stakeholders on promising data sharing models to encourage greater participation in these activities. Growing participation in precompetitive consortia indicates a cultural shift within industry and academia. In 2014, for example, Pharmaceutical Research and Manufacturers of America (PhRMA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) endorsed guiding principles for responsible clinical trial data sharing that provide qualified researchers with access to clinical trial. However, representatives from industry indicated that
requests for access to data has been limited, suggesting greater communication is needed between researchers and sponsors to identify opportunities for future research. Meanwhile, the National Institutes of Health is exploring policies to require NIH-funded researchers to have rigorous data management strategies and plans for sharing their data in a timely manner.

With increasing data requirements for biomarker development, sustainability is a major challenge for all stakeholders. Greater resources and investments are needed to support rigorous data collection practices and infrastructure. Consortia representatives noted that many of their members lacked not only financial resources for data management but also the qualified personnel. Participants suggested that some grant resources should be dedicated specifically to supporting data management, which could help to address some of these issues.

Platforms for Improving Communication and Collaboration across Existing Consortia and Partnerships

Multi-stakeholder collaborations have become an integral component of the biomedical innovation ecosystem. The rising number of public-private partnerships reflects a mutual understanding that the growing costs, risks, and complexities of biomedical research can no longer be effectively addressed by any one entity or stakeholder group. Over the past decade, diverse stakeholder groups have launched partnerships to address bottlenecks throughout the innovation process, from early-stage product development to post-market surveillance. Many have yielded tangible results, demonstrating the potential value of collaboration. To date, however, existing consortia and partnerships have largely operated in isolation rather than as coordinated components of an overarching national and global strategic plan. Participants noted that the current state of fragmentation can largely be attributed to the disparate funding streams supporting various collaborations. Moving forward, meeting participants stressed the need for high-level collaboration and coordination among existing partnerships to minimize inefficiencies and duplication of effort and to ensure that limited public and private resources are strategically allocated to high priority areas of unmet need. Toward that end, participants explored various policy options for improving collaboration and coordination among stakeholders.

In 2012, The U.S. President’s Council of Advisors on Science and Technology (PCAST) released a report on improving biomedical innovation that recommended the formation of a U.S. counterpart to the European Union’s Innovative Medicines Initiative (IMI). Like the IMI, a broad-based umbrella consortium would act as a high-level organizing body that could facilitate cross-consortia communication and collaboration. More specifically, an umbrella consortium could take on several key roles including: 1) coordinating existing partnerships and consortia so that they effectively direct efforts to the development and regulatory acceptance of high priority biomarkers identified by FDA and the scientific community; 2) developing and maintaining the infrastructure for biomarker data collection and curation; 3) conducting reviews and making recommendations to FDA on the adequacy of data packages submitted by sponsors; 4) supporting biomedical research needed to advance the discovery and development of new biomarkers. In addition to supporting research and development, such a consortium could promote the use of common biomarker terminology and standards, and serve as a forum for the broader community to reach consensus on an evidentiary framework for biomarkers and their diverse uses. The idea of a broad-based consortium recently resurfaced in the 21st Century Cures Act, which includes provisions for the establishment of a public-private oversight committee that would bring together leadership from across the stakeholder community to advance a strategic research agenda for biomedical innovation.

Some participants agreed that a public-private partnership as discussed in the PCAST report and modelled after the IMI could address the challenge of sustainability by providing a stable source of funding for collaborative biomarker research. IMI’s unique model provides the organization with the dual functions of identifying high-priority needs and oversight of funding and implementation of consortia around these needs so that projects are adequately financed and seen through to completion. Others questioned the need for another consortium, or whether there is enough experience to date that can inform how such an umbrella consortium should be structured or governed. An alternative model would be to establish an independent scientific body to better coordinate and channel existing resources, from government funding to contributions from industry and patient groups, to existing consortia activities. Such a scientific body could also convene
leadership from across the biomedical community to develop consensus on an evidentiary framework for biomarker qualification.

**Precision Medicine – The Path Forward**

The above priority areas offer tangible next steps for achieving the goals of precision medicine and improved patient outcomes. Initial harmonization of terminology, for example, can help begin a community-wide discussion on the development of an evidentiary framework for biomarker acceptance by regulatory bodies. Meanwhile, effective data sharing and partnerships can help generate the data needed for exploratory exercises aimed at characterizing evidentiary standards for various biomarkers and their contexts of use. Greater interactions between stakeholders will be needed to ensure that meaningful progress is made on these objectives.

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