

# The Foundation for the National Institutes of Health Biomarkers Consortium: Past Accomplishments and New Strategic Direction

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The Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium (BC) is a public–private partnership that aims to facilitate drug development with biomarkers across a range of therapeutic areas. The BC is organized to address specific precompetitive biomarker projects, giving participating stakeholders a role in the design and conduct of projects and making the results freely public. Ultimately, the goals of the BC are to accelerate the development of new medicines, inform regulatory decision making, and improve patient care. Here, we describe how the BC works and briefly highlight its accomplishments. The BC has had many notable successful biomarker projects in the past 12 years, including I-SPY2, which has improved clinical trials and biomarker use for breast cancer, and an evidentiary framework for biomarker qualification. Recently, the BC has undergone a strategic expansion of its scope to include related drug development tools along the lines of the Biomarkers, Endpoints, and other Tools (BEST) resource.

Biomarkers have become an increasingly impactful part of the biomedical landscape, including both drug development and medical practice. A biomarker has been defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic process, or pharmacologic responses to a therapeutic intervention”<sup>1</sup> and “A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.”<sup>2</sup> The original comprehensive definition of biomarkers arose from the April 1999 US Food and Drug Administration (FDA)/National Institutes of Health (NIH) consensus conference on “Biomarkers and Surrogate Endpoints: Advancing Clinical Research and Applications,”<sup>1</sup> and emphasized that biomarkers are medical measurements, including physiological measurements, blood tests, molecular analyses of biopsies, genetic or metabolic data, and measurements from images. The more recent definition was from a sustained FDA and NIH effort to refine biomarker and drug development tool nomenclature, resulting in the Biomarkers, Endpoints and other Tools (BEST) resource.<sup>2</sup> Biomarkers serve as the language that adheres many of the component translational and biomedical disciplines together. Increased interest in the field of biomarkers include activities, such as US Congressional scrutiny (in the form of the 21st Century Cures legislation), the FDA’s Critical Path Initiative and the biomarker qualification pathway, the NIH-FDA biomarker taxonomy effort, the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium, Brookings/

FDA, Center of Excellence in Regulatory Science and Innovation, Critical Path Institute, National Biomarkers Development Alliance, and the National Academy of Medicine surrogate end points. Biomarkers are expected to have a substantial positive impact on drug development, and coordinated efforts to identify biomarkers are a major focus of research and discussion.<sup>3</sup>

## HISTORY OF THE FNIH AND THE BIOMARKERS CONSORTIUM

The FNIH was founded through an act of Congress in 1990 to “support the mission of National Institutes of Health (NIH) and to advance collaboration with the biomedical researchers from universities, industry and nonprofit organizations.” Through the years, the FNIH has built alliances and public–private partnerships that have transformed the research landscape and focused on areas in which there is special scientific need for input from the private sector. Many partnerships have been initiated by the FNIH, each with unique characteristics determined specifically for the need to better enhance and enrich public health. These include global health initiatives, such as the Grand Challenges to Global Health supported by the Bill & Melinda Gates Foundation, and the Genetic Association Information Network), which set the stage for the National Center for Biotechnology Information database of Genotypes and Phenotypes (dbGaP).

The FNIH Biomarkers Consortium (BC) was formed in 2006 in collaboration with the NIH, the FDA, the Centers for

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Medicare and Medicaid Services (CMS), the Biotechnology Industry Organization (BIO), and the Pharmaceuticals Research and Manufacturers Association (PhRMA). This founding group recognized that converting a biomarker discovery into a confident decision-making tool required a diverse set of skills and experience. Deep knowledge of the biology of the biomarker is necessary to place the biochemical or structural changes observed into context of the physiological and pathological changes observed in the disease or treatment. The deep knowledge about the biology generally requires expertise in the biochemistry and molecular biology of the pathway and rests in the basic research that generally resides in academic institutions. The pathology and the clinical utility of a biomarker use are best assessed by a clinical research specialist that sees patients and runs clinical trials in therapeutic development. This clinical expertise rests at the interface of the basic clinical researcher and the drug development clinician. The mathematical validity of the relationship between the biomarker and the relevant clinical or biochemical outcome requires knowledge of the variables associated with the physiology and the regulatory expectations of the agency in charge of using the biomarker to make regulatory decisions. Logically and statistically, validation is typically defined in terms of consistency of the biomarker to repeated measurement of itself and a clinically relevant gold standard measurement. This statistical and regulatory expertise is generally found in the private industry setting or the government regulatory agency. Thus, to develop a decision-making tool that can be confidently used requires a community of experts.

The BC was set up to address biomarker projects in the precompetitive space, where all stakeholders have a voice in the direction of projects, share resources, costs, and risks and the results are made public for the entire field to use. The focus is on developing biomarkers for specific applications that accelerate drug development, inform regulatory decision making, and improve clinical practice. These open and collaborative projects foster precompetitive exchange of knowledge and expertise among industry, academic, and government scientists in a way that is not generally available outside of this unique setting. The spirit of collaboration extends beyond individual projects; an important aspect of all the BC projects is that the consortium project results and data are made broadly available to the entire scientific community. This open sharing with the scientific community means that these projects do not generate intellectual property that is for the exclusive use of only one entity (public or private).

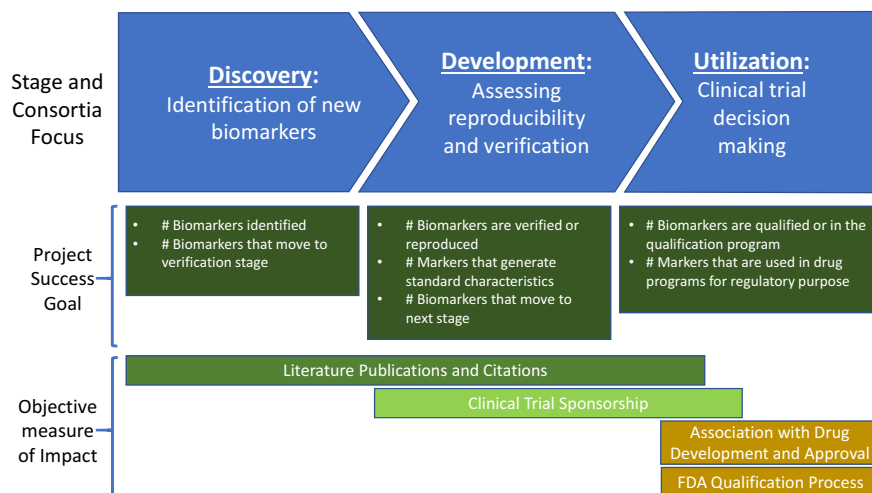
The governance for the BC is provided by committees that ensure that (i) there is a clear medical and regulatory need for the biomarker project, (ii) the scientific project plan is well thought out, supported by the current understanding in the field, (iii) the likelihood of success and the expected impact upon completion is high, and (iv) there is clear advantage to the project being done as a consortium effort with combined resources from public and private partners. The structure is separated into two committee areas. The executive committee is responsible for the strategic direction of the BC and is ultimately responsible for maintaining the success of the projects that are approved by the BC and updating the FNIH Board of Directors about its progress. The executive committee is also responsible for ensuring that the projects completed by the BC

are the best use of FNIH resources and will support the mission of the NIH in projects that clearly benefit from a public-private partnership. Reporting to the executive committee, the steering committees manage a portfolio of concepts and projects that focus on an area, or areas, of therapeutic interest, as determined by the executive committee strategy for the BC. Currently, there are four steering committees (Neuroscience, Inflammation and Immunity, Cancer, and Metabolic Disorders) that identify areas of need in the field, define concepts to develop as a consortium, and oversee the execution of projects that will provide the tools needed for clinical trial and regulatory decision making. The steering committees are at the interface of the medical need with representatives from all stakeholder groups. Thus, concepts are conceived and refined by the steering committees so that private support can be requested, and then the executive committee ensures that these projects adhere to the expectations of the strategy and the FNIH mission.

At its core, the BC is a membership organization, with members from biotechnology and pharmaceutical industry, not-for-profit foundations, and patient advocacy groups. Each committee and team consists of scientists from these private entities, government agencies (e.g., the NIH and the FDA), and academic institutions. The membership of each committee reflects the commitment of the BC to broad stakeholder input. In addition, the executive committee composition reflects the genesis of the BC and has equal representation from senior leadership of the NIH, senior leadership of the FDA, and scientific executives in the pharmaceutical industry. The executive committee also has a patient advocate representative and a member from PhRMA. The executive committee is led by an FNIH Board Member, and all committees are managed by FNIH staff. The steering committees are comprised of scientists from private member organizations and government and academic scientists in the field of interest. In addition, as the steering committee recognizes new areas of medical need, the composition of the committee can change to accommodate the appropriate scientific talent. Thus, the steering committee has the flexibility to recruit experts in the fields where new projects could grow.

Project selection and development is a critical portion of the consortium activities and is nurtured and encouraged by the steering committees. Because of the broad depth and expertise, the steering committees can identify areas of need in a general way. However, the generation of a defined and milestone-driven project requires focused work on plan development. The steering committee can set up subgroups or working groups to more clearly define a concept or outline of a plan that could be addressed to generate a usable decision-making tool. Thus, the first step of project identification is the generation of this concept and presentation to the steering committee. If the steering committee believes it is a viable project for the consortium to pursue, the working group is asked to prepare a detailed plan for obtaining the desired goal, including scientific plan, budget, potential team members, and expectations for probability of success. After the generation of this detailed plan, the team returns to the steering committee for additional feedback, and then the plan is presented to the executive committee to ensure strategic fit, overall merit, and assess the expected impact to the field. Currently, only after executive committee approval, does the

Stages of Biomarker development and associated impact measures



**Figure 1** Stages of biomarkers discovery and development. Different stages of biomarker discovery and development are expected to produce different results and therefore expected impact and success. FDA, US Food and Drug Administration.

FNIH begin to raise the resources to carry out the project. The BC has found that providing a clear, complete plan and a defined deliverable tool at completion makes it more likely that the private partners asked will be able to decide about funding.

Projects are launched when all the resources necessary to execute the project have been acquired or contractually obligated. At that point, the execution of the project is under the supervision and management of the project team, which consists of the investigators involved in carrying out the laboratory work, representatives from the funding partners, FDA representatives, and members of the FNIH staff, including project management. Early in the tenure of the BC, project management was identified as a critical role in execution of cross-stakeholder projects.<sup>4,5</sup> The project team is responsible for meeting and approving milestones and making any decisions about the conduct of the project as needed. An important feature of the BC project teams is that the public and private sector scientists have an equal voice in decision making, which is very different than the NIH or single investigator grants. In addition, all projects are milestone driven with clear deliverables built into the project plan. These milestones are not paid until the whole project team agrees that they have been met. Although this type of “team science” can bring up differences of opinion and style, the ultimate outcome from these projects is a tool with a broad base of support and input.

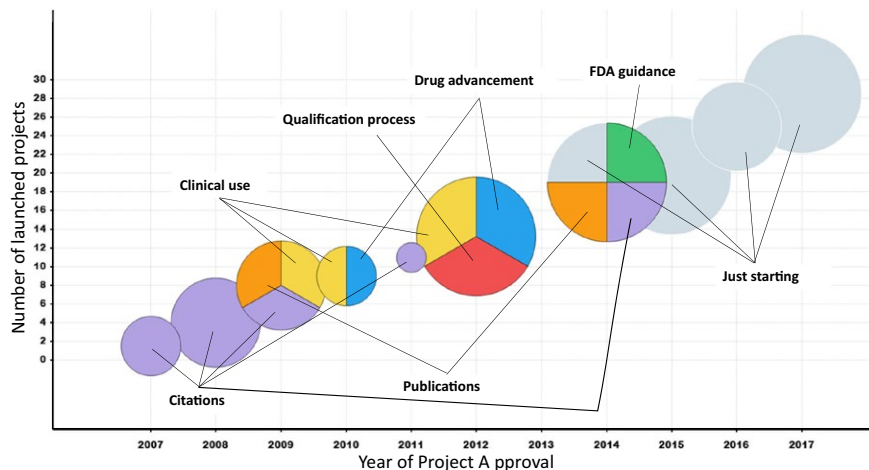
#### OVERVIEW OF PAST PROJECTS: STAGES OF TOOL DEVELOPMENT AND LEVEL OF SUCCESS

Biomarker development can be separated roughly into three stages: (i) biomarker identification, (ii) biomarker development, and (iii) biomarker utilization (**Figure 1**). Biomarker identification projects are designed to find new molecular characteristics that may relate to a disease or symptoms of a disease. Biomarker early development is designed to confirm the correlation between the biomarker and disease (or physiological process), generally by reproducing the original result(s) in an unrelated dataset. Finally, biomarker utilization shows

that the potential biomarker can be used with some degree of confidence in a particular clinical setting for decision making. Each stage involves very different metrics of success. The BC focuses efforts in the last two areas of biomarker development and the most successful projects have been in delivery of tools that can be used for making decisions in clinical settings, primarily drug development trials. To date, the BC has supported projects in all facets of biomarker development from early disease definition to late stage FDA Qualification. The ultimate goal and measure of success for a project is to generate tools and knowledge that definitively and visibly moves the field forward. As a general overview, the statistics for success in the BC show over 30 launched projects. These projects have generated over 50 project team publications and have been cited in publications over 800 times. Importantly, these projects have generated nine tools that are being used by the pharmaceutical industry in drug development to make clinical trial decisions. Given that the goal is to make useable tools, this is a particularly important result. Finally, the work of BC projects has contributed to 5 FDA Guidance documents, 1 FDA Biomarker Qualification, and the advancement of 12 therapies toward FDA approval. The therapies have been in cancer and bacterial infections. Thus, in the past 12 years, the consortium has been very successful in all aspects of biomarker development by having direct impact on advancing the scientific fields that are addressed and providing tools that help bring new therapies to patients. It would be difficult to provide details of the impact for all the projects that the BC has supported. A figure of the timeline that projects were approved and the general output type that the project made are shown in **Figure 2**, and the projects are summarized in **Table 1**. What follows is a selection of projects that highlight the types of impact that has been observed across the span of biomarker development.

#### EXAMPLES OF ACCOMPLISHMENTS OF THE BC

The BC has had many notable successes in the past 12 years. Several have been published and will only be highlighted here, including the I-SPY2 trial and the Kidney Safety Biomarkers project.



**Figure 2** Timeline of projects that were approved and initiated in the Biomarkers Consortium. The projects that have been approved in the Biomarkers Consortium are shown as a function of year of Executive Committee approval. The size to the marker is proportional to the number of projects approved during that calendar year (4 is the largest). The color of the marker sectors represents the highest level of success that the project has attained as of the writing of this review. FDA, US Food and Drug Administration.

The I-SPY2 trial has improved clinical trials and biomarker use for breast cancer, in which tumor heterogeneity increases the challenge to selecting effective treatments. The BC launched the I-SPY2 trial in 2007 to assist in identifying the right drug for the right patient by incorporating biomarker analysis early in the phase II testing process and using an innovative adaptive trial design.<sup>6</sup> I-SPY2 has been instrumental in establishing a new clinical end point, pathological complete response, as a powerful predictor of breast cancer survival, and has helped advance the development of multiple therapies in breast cancer to date.<sup>7</sup> In addition, the BC Kidney Safety project has recently obtained FDA Qualification for a composite biomarker of six urine analytes to identify acute kidney damage in early drug development trials with normal healthy volunteers.<sup>8</sup> This represents the first FDA Qualified clinical safety biomarker and will undoubtedly assist identifying safe drugs for patients that need new life-saving medicines. These two projects are not the only success stories; four additional examples are provided below.

### BACTERIAL INFECTION CLINICAL OUTCOME ASSESSMENTS

A strong example of an impactful project that has resulted in direct benefit to patients and improved standards of care is evident from the results of the BC projects in community-acquired bacterial pneumonia (CABP), acute skin and skin structure infection (ABSSSI), hospital-acquired bacterial pneumonia (HABP), and ventilator-associated bacterial pneumonia (VABP).

Due to increasing antibiotic resistance, many bacterial infections are very difficult to treat, and new antibiotics are urgently needed to save patient lives. The traditional measures of treatment success in clinical trials of antibiotics for skin infections and pneumonia have not kept pace with the evolving standards of regulatory science, which has led to substantial uncertainty and delays for companies developing these important drugs. Historically, efficacy end points for antibiotic registrational trials were based on resolution or improvement of signs and symptoms of infection at a time point after completion of therapy.<sup>9</sup> By design, these end points included

assessments at earlier time points as an element of outcome. As novel drug development understanding moved forward, the FDA and the scientific community realized the design of noninferiority trials evaluating antibiotics could be improved by defining more reliable outcome measures that reduced dependence on subjective elements and by evaluating outcomes at time points for which prior evidence had demonstrated well-defined, reliable, and reproducible drug effects.<sup>10</sup> The ability to measure known treatment effects on these outcome measures is essential for noninferiority (NI) trial designs. NI clinical trials are designed to determine whether the effectiveness of a new treatment is not unacceptably worse than the current or control treatment regimen.<sup>11</sup> In addition, the “patient voice” has become a critical component of drug development, and the FDA stipulates that outcome measures for studies that support drug registration should be direct measures or established surrogates of how patients feel, function, or survive.

To address these shortfalls in trial design and outcomes, in 2010 the FDA asked the BC to form a project team from a broad array of stakeholders, including the FDA, the National Institute of Allergy and Infectious Diseases, academic researchers, the Infectious Diseases Society of America, and industry sponsors. The team embarked on an effort to advance the scientific process of developing well-defined and reliable outcome assessments for use as end points in clinical trials and to recommend a more standardized and modernized approach to the design of CABP/ABSSSI trials.<sup>12,13</sup> The primary goal of this project was focused on improving the process, providing better information to patients and clinicians, increasing trial efficiency by limiting costs, and shortening the time to bringing new, safe, and efficacious antibiotics to patients. More recently, in 2012 the FDA asked the BC to expand these efforts into HABP and VABP.<sup>14</sup>

Considering the FDA's standards for drug approval, the project team evaluated historical evidence for treatment effects from the established literature, outlined research gaps, evaluated outcomes from recent biopharmaceutical clinical trials, and proposed recommendations for improved FDA Guidance for outcome assessments

**Table 1 Approved FNIH Biomarkers Consortium projects and accomplishments**

Steering Committee	Project title	Status	Year approved	Project stage	Current highest accomplishment
Cancer	Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) Lung and Lymphoma	Completed	2007	Development	Cited in publications
Metabolic disorders	Evaluation of the Utility of Adiponectin as a Biomarker for Predicting Glycemic Efficacy	Completed	2007	Development	Cited in publications
Metabolic disorders	Carotid MRI Development and Validation via an AIMHIGH Sub-Study	Completed	2008	Development	Cited in publications
Neuroscience	Comparison of Two PET Radioligands to Quantify the Peripheral Benzodiazepine Receptor	Completed	2008	Development	Cited in publications
Neuroscience	Use of Targeted Multiplex Proteomic Strategies to Identify Plasma-Based Biomarkers in Alzheimer's Disease	Completed	2008	Development	Cited in publications
Cancer	I-SPY TRIAL-2 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis): An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy	Ongoing	2010	Utilization	Advanced drug development
Neuroscience	Use of Targeted Multiplex Proteomic Strategies to Identify CSF-Based Biomarkers in Alzheimer's Disease	Completed	2009	Development	Cited in publications
Metabolic disorders	Establish Guidelines for Initial Diagnostic Criteria for "Sarcopenia with Clinically Important Weakness" and Associated Evidence for Treatment Benefit	Completed	2009	Discovery	Clinical use
Neuroscience	Placebo Data Analysis Project in Alzheimer's Disease/Mild Cognitive Impairment Clinical Trials	Completed	2009	Discovery	Cited in publications
Executive committee	Clinical Evaluation and Qualification of Translational Kidney Safety Biomarkers	Ongoing	2012	Utilization	Qualification process
Metabolic disorders	<i>In Silico</i> Modeling of Biomarkers of Atherosclerosis: Estimating Risk Reduction and Residual Risk from Statin Therapy	Ongoing	2011	Discovery	Cited in publications
Metabolic disorders	Diabetes Drug Development: Identification and Validation of Markers That Predict Long-Term Beta Cell Function and Mass	Completed	2010	Development	Clinical use
Inflammation and Immunity	Osteoarthritis Project	Completed	2012	Development	Qualification process
Executive Committee	Developing Endpoints for Clinical Trials in CABP and Skin Infections	Ongoing	2012	Utilization	Advanced drug development
Neuroscience	The Autism Biomarkers Consortium for Clinical Trials	Ongoing	2015	Development	Early project
Metabolic disorders	Bone Quality Project	Ongoing	2012	Utilization	Clinical use

(Continues)

**Table 1 (Continued)**

Steering Committee	Project title	Status	Year approved	Project stage	Current highest accomplishment
Executive committee	Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia Clinical Endpoint Development	Ongoing	2014	Utilization	Advanced drug development
Metabolic disorders	The Performance of Novel Cardiac Biomarkers in the General US Population	Ongoing	2014	Development	Early project
Metabolic disorders	Sarcopenia as a Valid Biomarker for Identifying Individuals at Risk of Disability	Completed	2015	Development	Early project
Cancer	Minimal Residual Disease Detection in Adult Acute Lymphoblastic Leukemia	Ongoing	2014	Development	Cited in publications
Cancer	Vol-PACT: Advanced metrics and modeling with Volumetric CT for Precision Analysis of Clinical Trial results	Completed	2014	Development	Cited in publications
Inflammation and immunity	Treatments Against RA and Effect on FDG PET-CT (TARGET Biomarker Study)	Ongoing	2015	Development	Early project
Cancer	High Definition Single Cell Analysis of Blood and Tissue Biopsies in Patients with Colorectal Cancer Undergoing Hepatic Metastasectomy	Ongoing	2015	Development	Early project
Cancer	Vol-PACT Phase II: Advanced metrics and modeling with Volumetric CT for Precision Analysis of Clinical Trial results	Ongoing	2016	Development	Early project
Neuroscience	Longitudinal Proteomic Changes in CSF from ADNI: Toward Better Defining the Trajectory of Prodromal and Early Alzheimer's Disease	Ongoing	2016	Development	Early project
Neuroscience	Inflammatory Markers for Early Detection and Subtyping of Neurodegenerative and Mood Disorders	Ongoing	2016	Development	Early project
Inflammation and immunity	PROGRESS OA: Clinical Evaluation and Qualification of Osteoarthritis Biomarkers	In fundraising	2017	Utilization	Early project
Cancer	Determining the impact of chemotherapy on tumor immunity by systematic dissection of the tumor microenvironment with single cell genomics	In fundraising	2017	Discovery	Early project
Cancer	Identification and Validation of ctDNA Reference Materials	In fundraising	2017	Utilization	Early project
Metabolic disorders	Non-Invasive BioMarkers of MetaBolic Liver Disease (NIMBLE)	Ongoing	2017	Development	Early project

ADNI, Alzheimer's Disease Neuroimaging Initiative; CABP, community-acquired bacterial pneumonia; CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; FNIH, Foundation for the National Institutes of Health; MRI, magnetic resonance imaging; OA, osteoarthritis; PET, positron emission tomography; RA, rheumatoid arthritis; VolPACT, Advanced metrics and modeling with Volumetric Computer-aided tomography for Precision Analysis of Clinical Trial results Project. Further information on these projects can be found on the FNIH BC Website, <<https://fnihi.org/what-we-do/biomarkers-consortium/programs>>.

in antibacterial trials. Through parallel discussions around each disease, the team focused on standardized assessments of patient response (symptoms) in the first few days after initiation of antibiotic therapy, which might provide key insights into drug effect and

options for trial design. These symptoms may then be used as early clinical response end points and provide a scientific basis for NI hypotheses in antimicrobial registrational trials.<sup>15-17</sup> For CABP, progressive improvement in four symptoms (cough, dyspnea, chest

pain, and sputum production), reported during the first 4 days of therapy was sufficiently well-documented that an early response end point measure was recommended.<sup>14</sup> For ABSSSI, recommendations focused on the need for clear definitions in the types of skin infections (abscesses vs. cellulitis vs. wound infections) while supporting a primary end point focused on  $\geq 20\%$  reduction in lesion size from baseline at 48 hours. In addition, initial FDA ABSSSI Guidance noted data demonstrating treatment effects at 48–72 hours after initiation of antibiotics, including body temperature, pulse, respiratory rate, and other measures that are biomarkers (i.e., not direct measures of how a patient feels, functions, or survives).<sup>14,18</sup> However, these biomarkers are not on the causal pathway of the disease (i.e., temperature), cannot be obtained reliably in outpatients, and the team recommended that these biomarkers may have a secondary role in long-term assessment of disease resolution during patient care but are insufficient as early end points for regulatory decision making.<sup>12,14</sup>

For the HABP Guidance, the current end point is all-cause mortality (ACM) at 28 days. Pharmaceutical developers have argued that measuring ACM at day 28 captures deaths unrelated to HABP or VABP and does not truly reflect a drug's efficacy. Analyses of factors predicting greater mortality failed to identify strong prognostic variables beyond unsurprising results that older age and negative standard clinical laboratory assessments generally correlated with greater mortality.<sup>19</sup> Other factors, such as baseline oxygenation and prior antibiotics, were also inconsistently predictive. By taking a similar approach highlighted for CABP, the project team explored the consideration of a “mortality-plus” end point (i.e., use of a multicomponent assessment of ACM “plus” selected serious adverse events and adverse events/complications).<sup>20,21</sup> Various approaches to determine which “plus” events to use were examined, and the team chose an approach using a widely available and accepted method for identifying events that impact how a patient feels and functions: the Toxic/Septic Shock Standardized MedDRA Queries (SMQs), which contains a variety of clinically important events, such as sepsis, other infection-related events, and respiratory failure.<sup>14,21</sup> SMQs are highly specific and standardized medical terminology that facilitate harmonization and sharing of regulatory information internationally and across scientific and industry sectors.<sup>22</sup> These events reflect events plausibly related to HABP/VABP that could be seen as a consequence of inadequate antibiotic therapy but did not necessarily have to be rigidly pneumonia-related, such as pleural empyema or respiratory failure requiring mechanical ventilation. A clinical trial database could be readily interrogated using this SMQ to define the “plus” in a mortality-plus end point. Therefore, in each of the CABP, ABSSSI, and HABP projects, FNIH team members advocated for more standardized, prospective validation of the “patient voice” to better appreciate and consider other potential symptomatic end points for clinical trials and drug development.

The project team conclusions for each disease were submitted to the relevant FDA dockets,<sup>15–17,20</sup> and these considerations led to publication of new or updated FDA Guidances for CABP/ABSSSI and HABP/VABP trials,<sup>23–25</sup> which focus on assessment of efficacy at earlier time points or include expanded patient-focused end points to mortality than previously

recommended. These symptomatic end points have proven themselves as beneficial and essential, qualified outcome measures and improvements to patient care, allowing clinicians and patients to understand the similarities and differences between therapeutic agents in development or posttreatment. Overall, eight antibacterial drugs (dalbavancin, delafloxacin, tedizolid, oritavancin, omadacycline, ceftaroline fosamil, telavancin, and ceftazidime/avibactam) have been approved, or approved for expanded use, based on clinical studies incorporating recommendations from these BC projects.

As promoted above, a second phase of these BC projects has been the development of draft patient-reported outcomes (PROs) for CABP, ABSSSI, and HABP that are currently in psychometric validation for FDA regulatory approval as a defined tool to assess these symptomatic end points in a standardized mechanism.<sup>26</sup> PROs capture the “patient voice,” measuring how patients describe and quantify their symptoms of illness. For pneumonia, these could include painful or difficult breathing, fever, chest pain, social isolation, and the inability to perform the tasks of daily living. Having the patient record these data fulfills the FDA obligation to capture how patients “feel and function,” as well as survive, and PROs achieve this imperative by capturing the patient voice reproducibly and verifiably.<sup>27–29</sup> The availability of validated and FDA-qualified drug development PROs would add to the “toolbox” of options for sponsors to use in future registrational trials in these indications. In addition, appropriately evaluated PROs can be used outside the setting of clinical trials evaluating medical interventions, standardize measurements in epidemiological studies evaluating natural history and burden of disease, as well as form part of development of “severity” scales that could be included among the inclusion criteria for future trials.<sup>30</sup> An overview of the project workflow and key inputs and achievements from the BC project teams is shown in **Figure 3**.

The outcome measures and PROs developed in these impactful BC projects are being made broadly available to clinicians and the research community. The contributions of these projects are particularly important at a time when the incidence of treatment-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* and many gram-negative bacteria, are increasing. Giving the FDA and clinical researchers better tools to measure the impact of treatments helps spur the development of new therapies (or expand the utility of existing drugs labels) and ensures that these therapies are effective: an obvious benefit to patients, their families, and their healthcare providers.

### OSTEOARTHRITIS STRUCTURE AND DISEASE ACTIVITY BIOMARKERS

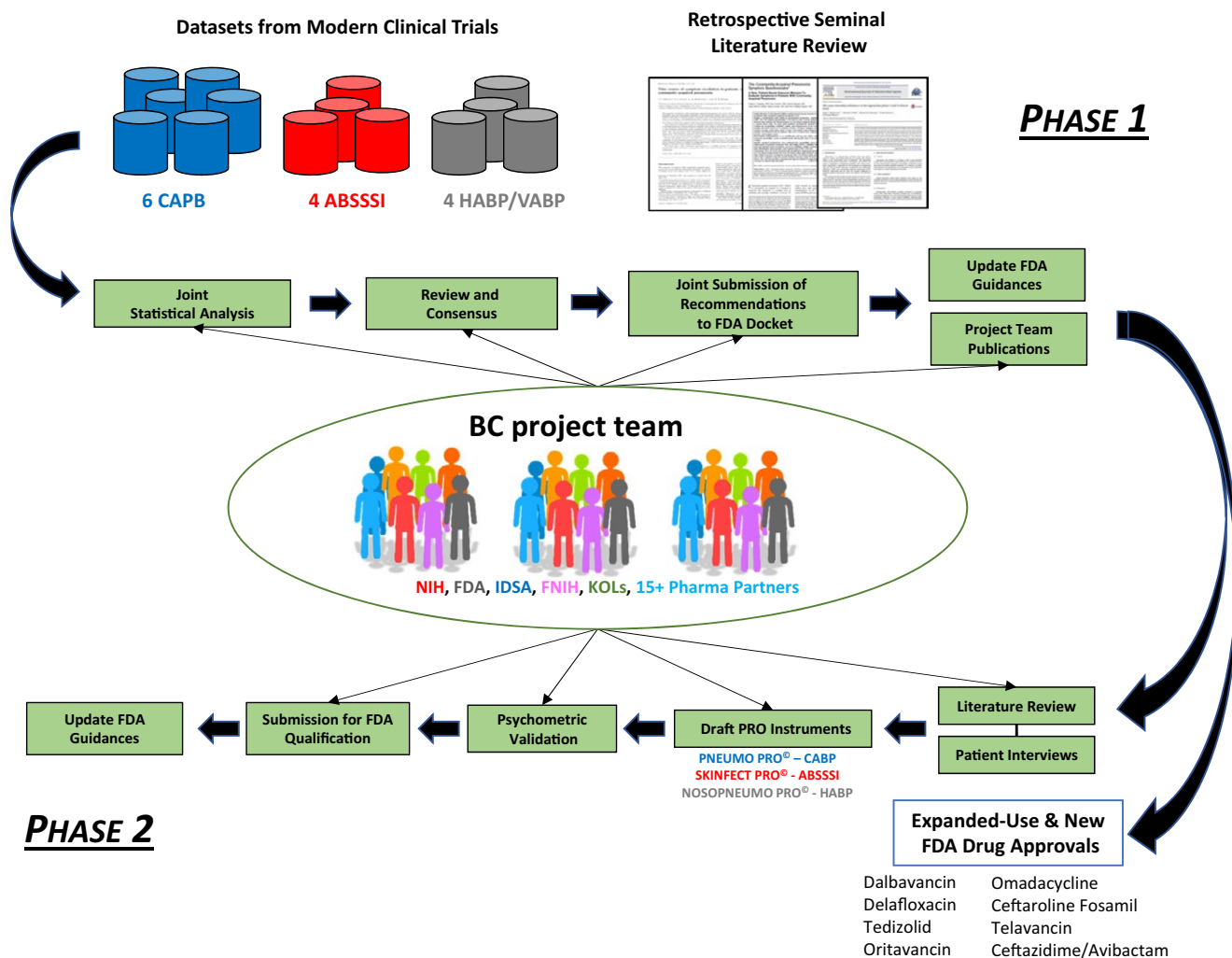
Osteoarthritis (OA) is a highly prevalent, disabling disease, with a tremendous individual and societal burden. Recent estimates suggest that 250 million people worldwide are affected by knee OA, and that number is expected to increase due to increased life expectancy and rates of obesity.<sup>31</sup> Historically, treatment innovation in OA has been slow compared with other common medical conditions. One of the many reasons for this slow pace is the lack of biomarkers to ascertain disease progression and efficacy of treatments for the disease.<sup>32</sup> Pharmaceutical drug development of

therapeutics that have disease-modifying effects is greatly hampered by the lack of clinical end points for OA. There are presently no therapies approved by regulatory authorities that modify the onset or progression of OA structural damage.

The Osteoarthritis Research Society International (OARSI), the leading medical society for advancing the understanding, early detection, treatment, and prevention of OA, launched an OARSI-FDA OA Assessment of Structural Change working group in response to the 2007 Federal Register notice posted by the FDA to address the lack of OA biomarkers. The working group was comprised of experts in the field of OA biomarker research from both academia and industry. After a series of meetings, the OARSI-FDA Assessment of Structural Change working group developed a consensus document between 2007 and 2009 that laid the groundwork for the need for biomarker development in OA.<sup>33</sup>

The identified unmet need in OA biomarker discovery and development was well-suited for a consortia-based approach in which

multidisciplinary teams of scientific experts work together to achieve a common goal that advances the field forward. A formal FNIH BC Project Plan, led by Dr David Hunter at the University of Sydney and Dr Virginia Byers Kraus at Duke University, was developed based on the biomarkers described in the consensus document. The overall objective of the FNIH BC OA Biomarkers Project was to evaluate the predictive validity of multiple imaging and biochemical disease progression biomarkers with the goal of finding more precise and sensitive measures of OA disease progression and the effectiveness of new treatments. Importantly, the project analyzed both biochemical markers that can elucidate the underlying molecular mechanisms of OA disease progression, as well as imaging biomarkers that measure the structural change within the joint. The biomarkers were selected in an effort to overcome the limited responsiveness of existing imaging biomarkers. One such limitation is the poor relationship in individual patients between joint structural pathology (e.g., joint space narrowing on radiographs) and symptomatic disease.



**Figure 3** Project flow for the antibacterial clinical outcome measure project. ABSSSI, acute skin and skin structure infection; BC, Biomarkers Consortium; CABP, community-acquired bacterial pneumonia; FDA, US Food and Drug Administration; FNIH, Foundation for the National Institutes of Health; HABP, hospital-acquired bacterial pneumonia; IDSA, Infectious Diseases Society of America; KOLs, key opinion leaders; NIH, National Institutes of Health; PRO, patient-reported outcome; VABP, ventilator-associated bacterial pneumonia.



The project made use of the NIH Osteoarthritis Initiative (OAI), a public-domain repository of medical images, patient data, and biospecimens. The OAI was funded by a public-private partnership, including seven NIH institutes, led by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute on Aging, and four pharmaceutical companies, in which FNIH coordinated the private sector participation for OAI. This project evaluated imaging data and biospecimens from a nested case cohort (200 cases and 400 controls) within the OAI progression cohort, a unique longitudinal cohort (~4,700 men and women ages 45–79, including 3,285 in the incidence subcohort, at the 4 OAI clinical sites) that contains a longitudinal repository of imaging data and serum and urine biospecimens together with the clinical profile data. The FNIH BC OA Biomarkers Project Team included experts from the NIH, FDA, pharmaceutical industry, and nonprofit sector. Scientific and financial contributions to support the study were provided by pharmaceutical and biotech companies. In-kind donations to support biochemical tests were provided by several diagnostic companies.

A first major successful outcome of the project was determining the best-case control criteria for the OAI longitudinal cohort, which is continually used as the standard comparator for the OAI datasets. The analysis of the OAI datasets found 9 biochemical biomarkers and 12 magnetic resonance imaging (MRI) biomarkers that performed well in multivariable models to predict the longer-term clinical outcome of clinically relevant (pain and radiographic worsening) knee OA progression. The biochemical markers included serum and urinary markers of cartilage and bone resorption, degradation, as well as biomarkers of skeletal matrix synthesis and formation. The imaging biomarkers were derived by semiquantitative analysis (cartilage morphology, meniscus morphology, synovitis, and osteophytes), quantitative cartilage morphometry (medial tibio-femoral compartment and central medial femur), and bone surface area (medial and lateral femur) of MRI scans. Altogether, over 20 publications have resulted from the FNIH BC OA Biomarker Project.<sup>34</sup> The learnings from this project have also been successfully disseminated to the broader scientific community and have been incorporated into industry-sponsored clinical trials for OA drug development.

Biomarker validation and biomarker qualification are interrelated but distinct processes; validation refers to the establishment of an accurate and reliable measure both analytically and clinically, and qualification refers to the establishment of acceptable performance in a specific context of use for a biomarker in drug development for regulatory decision making.<sup>35</sup> The FNIH BC OA Biomarker Project achieved the first step in the biomarker development process by systematically validating a set of biomarkers that could predict the longer-term clinical outcome of clinically relevant (pain and radiographic worsening) knee OA progression. To begin the biomarker qualification process, and moving into the utilization phase, the results of the MRI data were submitted to the FDA in a letter of intent in 2015.

The FDA released draft OA Guidance for Industry in July 2018 that recognizes OA as a serious disease and acknowledges difficulties in developing drugs for OA due to the lack of structural end points that translate into clinically meaningful benefit to patients.

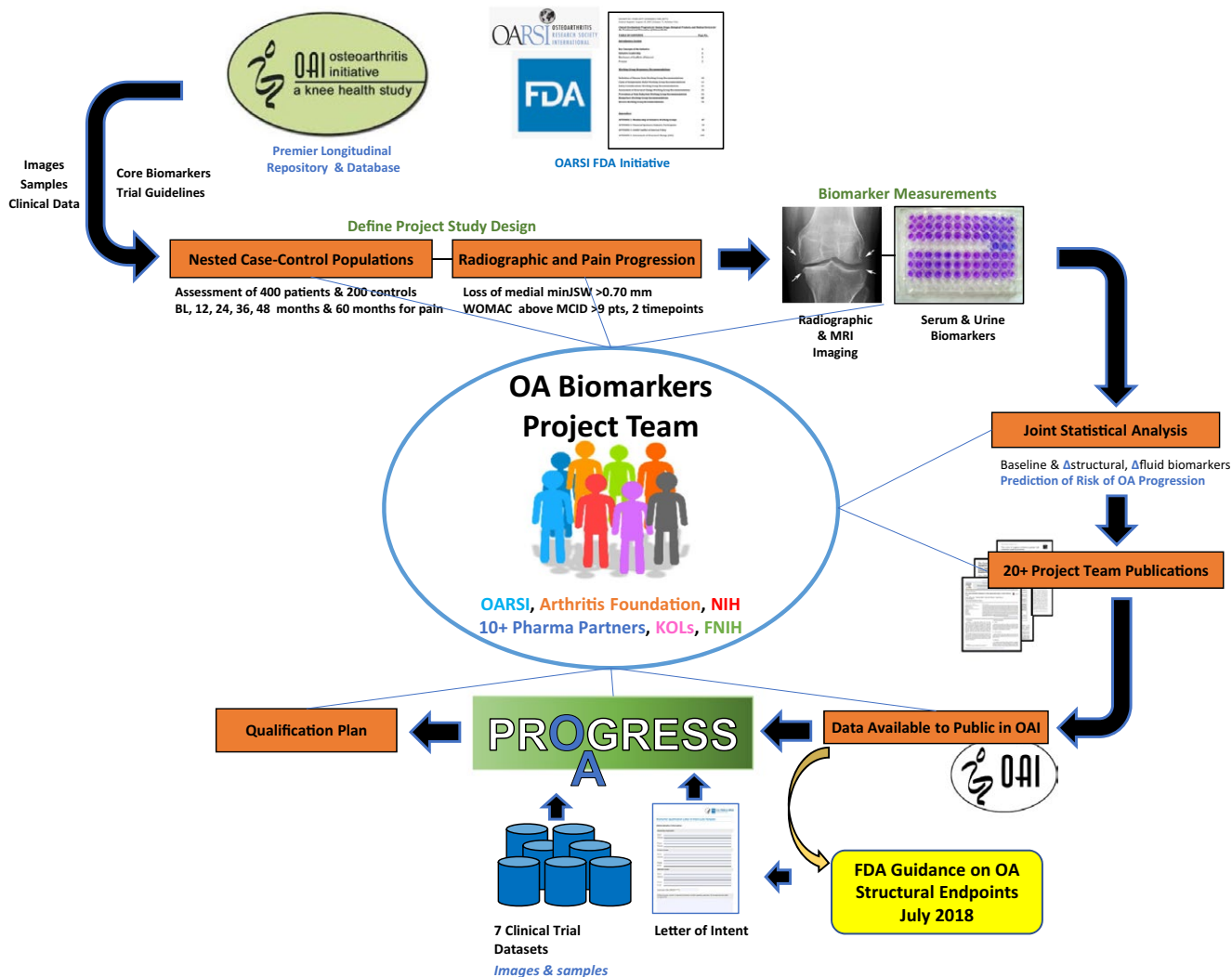
The guidance also describes the FDA's willingness to engage with stakeholders to better address the gaps. Serendipitously, the FNIH BC Clinical Evaluation of OA Biomarkers for Regulatory Qualification "PROGRESS OA" was developed to build upon the successes and confirm the results found in the first phase of the project with a novel set of datasets distinct from the original OAI dataset. The overarching goal of this 3-year project is to verify the novel radiographic measures, MRI measures, and biochemical markers discovered in phase I of the FNIH BC OA project that can be used as prognostic biomarkers of disease progression. The data generated will be submitted to the FDA and European Medicines Agency to qualify the imaging and biochemical biomarkers pertinent to knee OA for use in OA drug development. The results of the project, estimated to be completed by 2020, will verify and qualify the biomarkers to be used in clinical trials to develop disease-modifying regimens in OA. The results will impact the planning and design of OA clinical trials by providing a set of biomarker tools that will decrease the number of patients needed and decrease the time and costs needed for OA drug development. **Figure 4** illustrates the foundational resources that support the FNIH BC OA Biomarkers and PROGRESS OA projects and the strategic involvement of the multisector consortium guiding the projects and field toward the validation and regulatory consideration of select biomarkers of risk for OA progression.

#### SARCOPENIA DISEASE DEFINITION PROJECT

The BC has occasionally spearheaded identification of biomarkers for poorly understood and, therefore, unevenly diagnosed conditions like sarcopenia. In this section, we describe how FNIH has supported the identification, validation, and establishment of an objective evidence-based biomarker for diagnosis of sarcopenia through two sequential projects, sarcopenia 1 (2010–2015) and sarcopenia 2 (2016–2018). The study has come to its conclusion with presentation of final data for a consensus by an independent body of experts in November 2018 and subsequent publications and guidelines development.

The aims of the sarcopenia projects are to identify, validate, and establish an objective biomarker for diagnosis of sarcopenia in elderly population and define a "cut-point" for diagnosis in a targeted population in which clinical intervention will be likely required.

Sarcopenia is commonly found in older populations and characterized by reduced mobility, functional disability, and increased mortality.<sup>36</sup> In spite of its recognition as a significant geriatric syndrome, it has been poorly understood outside of the geriatric community. Lack of objective diagnosis criteria has prevented the development of any therapies to treat this condition that limits the quality of life in our fast-growing elderly population. In addition to its impact, it was recognized in the early 2000s that many pharmaceutical products on the market can potentially impact muscle mass. Although the exact effect of these drugs on the muscle was not known, increased recognition of the disease, anticipation of drug side effects, and an inability to develop treatment created a perfect storm in which a larger population of impacted individuals will have to live with potentially worsening muscle impairment and no means to objectively diagnose or develop treatments.



**Figure 4** Project flow for the osteoarthritis (OA) biomarker project. BL, baseline; FDA, US Food and Drug Administration; FNIH, Foundation for the National Institutes of Health; KOLs, key opinion leaders; MCID, minimal clinically important difference; minJSW, minimal joint space width; MRI, magnetic resonance imaging; NIH, National Institutes of Health; OAI, Osteoarthritis Initiative; OARS, Osteoarthritis Research Society International; WOMAC, Western Ontario and McMaster Universities.

In response to this need, the FNIH launched a program in 2010<sup>37</sup> on developing definitive guidelines to outline objective diagnosis criteria for sarcopenia through a consortium-based effort. The study was designed to take advantage of existing data from observational and interventional studies to analyze and provide the basis for a consensus definition of sarcopenia. With stakeholders from National Institute on Aging, the FDA, academia, and industry contributing their expertise, the study evaluated data from nine sources of community-dwelling older persons with a total sample of ~ 26,000 individuals. It was concluded from a consensus meeting in 2014 that diagnosis of sarcopenia is most sensitive to grip strength and low lean muscle mass adjusted for body mass index. These findings were of significant interest to all the constituents of the group for initial diagnosis of the disease. Publications resulting from the effort are listed at the FNIH website.<sup>38</sup>

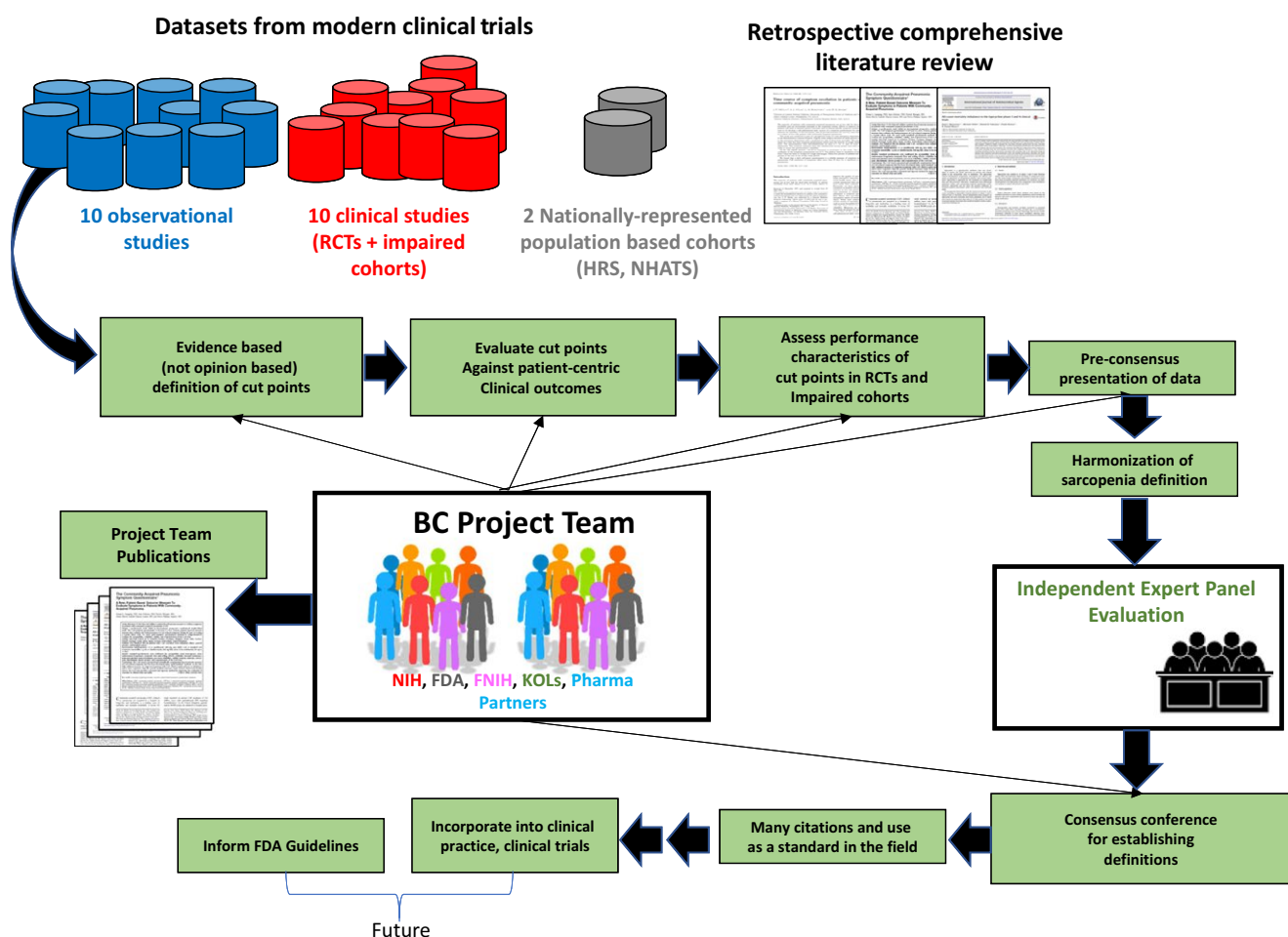
To further nuance the context of use for these biomarkers, FNIH expanded and refocused the project in 2016. Sarcopenia 2 (completed in 2018) evaluated a subset of community-dwelling elderly patients who were functionally limited and, therefore, would likely be targeted for function-improving therapies. These individuals would typically have slower gait and be at high risk for falls and fractures. Sarcopenia 2 expanded to include additional cohorts of patients with functional limitations and reassessed grip strength-related biomarkers with a focus on studying their predictive value in outcomes important to patient well-being, including activities of daily living disability, fractures, hospitalization, falls, and death. The Sarcopenia 2 project has continued to refine the definition of sarcopenia by systematically comparing various definitions and studies in the field. An international, independent panel of experts met in late 2018 to discuss and vote on the final consensus definition. A series of publications will follow in 2019 (results will appear in ref. 39). A schematic of the project path is shown in **Figure 5**.

**AN EVIDENTIARY CRITERIA FRAMEWORK FOR BIOMARKER QUALIFICATION: ENGAGING THE ENTIRE BIOMARKER DEVELOPMENT COMMUNITY**

The BC has taken a leading role in driving consensus to define an evidentiary framework for biomarker qualification. Drug development is an increasingly time-intensive and cost-intensive endeavor.<sup>40</sup> Biomarkers have been touted as one avenue to enhance development and regulatory processes.<sup>3</sup> However, defining a more clear and predictable process to qualify biomarkers has been challenging. In April 2016, the FNIH BC and the FDA cosponsored a workshop to define and evaluate a general framework for assessing the evidentiary criteria needed for biomarker qualification using safety biomarkers as real-world examples.<sup>41</sup> More recently, the FNIH BC and FDA cosponsored a follow-up workshop in July 2018 to refine the framework for defining evidentiary criteria for surrogate end-point qualification.

A general, updated evidentiary criteria framework is summarized in **Figure 6** and includes a Need Statement, Description of Biomarker, Context of Use (COU) Statement, Assessments of Benefit and Risk, and an evidentiary criteria map. The intent of the framework is to support constructive discussions between

biomarker developers or potential submitters to the biomarker qualification program and regulators that allow for refinements of the COU as the data mature. The Need Statement is a concise description of the knowledge gap or drug development need a biomarker developer plans to address. The COU statement is central to a biomarker qualification submission. The COU statement is greatly simplified from past regulatory guidance to a concise drug development use description, comprised of two elements. (i) What BEST category of biomarker is proposed, and what information content would it provide? (ii) What specific question is the biomarker intended to address? Once the COU is determined, benefit and risk to both the patient and society are assessed. Quantification of precise benefits and risks is not feasible, but a thorough semiquantitative assessment of the reasonable benefits and risks is possible. Categorical descriptions for what constitutes a high and minimal level of evidentiary criteria can be linked to a level assessment map<sup>42</sup> based on the semiquantitative framework. This visual representation of an evidence map can be used as a communication tool for gaining alignment between biomarker developers and FDA reviewers at key milestones and leads to a process with enhanced clarity and predictability.



**Figure 5** Project flow for the Sarcopenia biomarker project. BC, Biomarkers Consortium; FDA, US Food and Drug Administration; FNIH, Foundation for the National Institutes of Health; HRS, Health and Retirement Study; KOLs, key opinion leaders; NHATS, National Health and Aging Trends Study; NIH, National Institutes of Health; RCTs, randomized controlled trials.

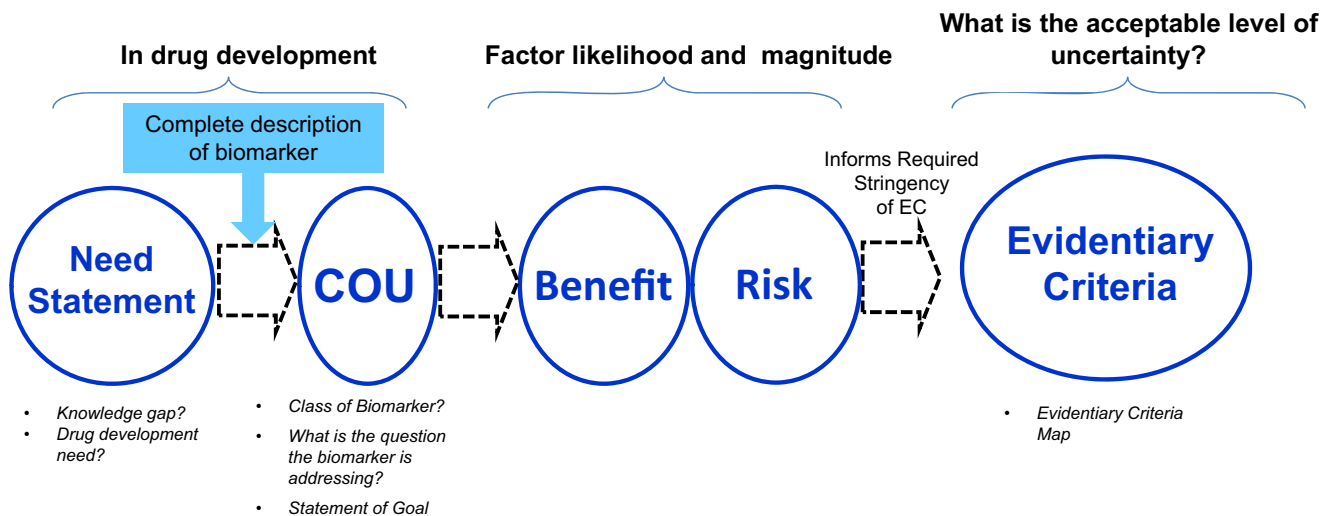


Figure 6 Evidentiary criteria framework for safety biomarkers qualification. COU, context of use.

**LOOKING TO THE FUTURE: ASSESSMENT OF THE CURRENT LANDSCAPE AND STRATEGIC PLANNING**

In 2006, the BC was a pioneering public-private partnership, a true innovator as described above. However, the world has dramatically changed since the BC was launched. Medical and technological advances since 2006 have been legion. That was before the advent of approved RNA therapeutics, gene therapy, or the iPhone. Nor did we have potentially innovative biomarkers, including exosomes, liquid tumor biopsies, or Ribonucleic Acid Sequencing. How many versions of the iPhone or advances in Ribonucleic Acid Sequencing have we seen since then? The pace of medical and technological change has been rapid; has the BC kept up with that change?

We asked exactly that question in a strategic planning exercise. More specifically, we asked who are we today, and in what context are we operating? In addition, who do we want to be? Then we asked: how do we get there? The answer to the last question sets our BC strategic priorities going forward. In order to understand who we are today, we took a multipronged approach. (i) We reviewed existing BC analyses, including current success metrics analysis and

composition of funders. (ii) We conducted key stakeholder interviews, soliciting direct, candid one-on-one input from over 30 key leaders, both those currently associated with the BC and those not directly associated. (iii) We implemented a participant survey to solicit input from a larger number of individuals who have been directly involved with the BC, including all BC staff, as well as members of Executive Committee, steering committee, working groups, and project teams. The approach was an anonymous, web-based survey sent to > 500 current and past BC participants. The questions were very similar to those in interviews, but with quantitative ranking or rating. We received 121 completed surveys for 24% response rate with equal representation across disease areas. (iv) Finally, we engaged in a benchmarking exercise to learn from public-private partnerships in related fields or with similar approaches, such as the FNIH Accelerating Medicines Partnership and Critical Path Institute, and TransCelerate.

Interviews and the survey results revealed similar observations. Biomarker science is more difficult than was initially appreciated 2006. The science is more complex, and important

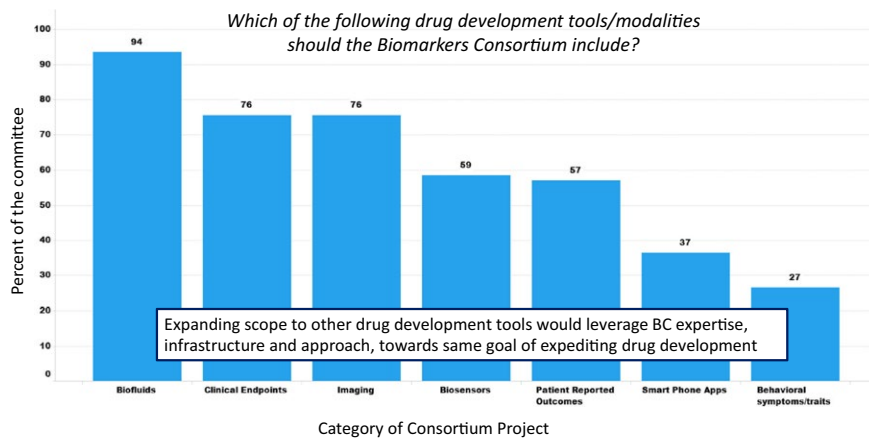


Figure 7 Results of Biomarkers Consortium (BC) Committee Member Survey. The Biomarkers Consortium Executive and Steering Committee members were asked to provide a perceived level of importance on different areas of drug discovery tool development. The results of this survey are shown and are reported a percent of members that thought that the particular area was important for the consortium to address.

technology advances are needed. In addition, there has been a proliferation of unvalidated biomarkers, a subset of which requires translation and/or validation. The needs remain great, and rationale for BC-type consortia still holds. The BC is appreciated for its rigor, project management, and deep engagement of the FDA. The “bottom-up” approach, in which projects originate from stakeholders and steering committees, differentiates the BC from other efforts, but many would also like more strategic guidance, particularly around focus or high priority areas. The impact is generally seen as strong. Clearly, there are many successes, but the question arose as to whether the successes are sufficient. In fact, many would like to see BC seize the mantle of biomarker thought leadership. Thus, there is an opportunity to do more.

All that said, there are perceived issues that arose from interviews and the survey. Funding is generally tougher with a proliferation of consortia, many with biomarker focus. There is “consortia fatigue” with the BC not clearly differentiated vs. other consortia. Another critical issue for the BC is clarity around what is in and out of scope. Interviewees and survey results saw value to projects beyond biomarkers (e.g., BEST drug development tools), an area that the BC has inconsistently engaged (Figure 7). As mentioned, it is currently difficult to identify and ensure focus on the most critical projects. A lack of prioritization stymies fundraising efforts, and the current model makes it difficult to surface or launch strategic, cross-disease projects. The current funding model is limiting, and needs to be revamped, particularly if a more strategic approach is chosen. The proposal process is seen as protracted, and it is possible to streamline via earlier executive committee, and funder input. Funding is sought late in the proposal cycle, which results in delays to projects. In addition, many interviewees would like to see public funding, as is implemented with other consortia. A related point is that the current membership has key gaps, selected large pharmaceutical companies in BC disease areas, as well as technology companies and adjacent industries. Besides funding, some of the BC processes, including roles of the executive committee and steering committee, lacked clarity. Finally, the communication of the BC, either internally or externally, is perceived as limited and inadequate.

## GOING FORWARD

Based on the extensive research and strategic planning, a new vision of “improving health through meaningful measurements” and a mission “to create and lead cross-sector efforts that validate and qualify biomarkers and other drug development tools to accelerate better decision-making for the development of new therapeutics and health technologies” was developed along with corresponding strategic priorities.

The BC’s scope and differentiation—the first strategic priority—are clarified to a collaboration infrastructure that responds nimbly to needs of the field, as well as biomarker and drug development tool thought-leadership. This affirms and embraces a broader BC scope that includes drug development tools that can best leverage the BC’s infrastructure, experience, and expertise. The broader scope is defined by the BEST resource.<sup>2</sup> In turn, a scope defined by the BEST resource aligns what is in/out of scope and allows agreed-upon criteria for evaluating projects.

The second strategic priority is to become more strategic and adaptive in defining projects and initiatives. One important aspect of this priority is to undertake periodic landscape reviews (e.g., every couple of years) to identify the greatest needs across the biomarker science ecosystem for biomarker and drug development tool validation and qualification. Such a landscape review should be in collaboration with many of the BC stakeholders, including PhRMA, NIH/National Center for Advancing Translational Sciences, the FDA, and FNIH. A rigorous landscape review is critical to set the executive committee priorities and inform annual steering committee priority setting and could be a valuable resource to members. In addition, the BC should leverage project experience and knowledge to impact the field as thought leader and trusted convener. A valued thought leader endeavor includes the evidentiary criteria workshops, and consideration should be given to expanding the role of the BC in this forum.

The third priority is to revamp the funding model to support a more strategic approach to project development and execution. Rather than wait to begin raising funds for completed project plans, the factors that influence fundability need to be addressed and incorporated into the actual process of project plan generation. The expectation is that, if project plans are developed closely with potential supporters, the needs of the project and the resource providers will be aligned. Although the alignment will not necessarily lead to a fundable project, the project development team will be able to gauge the likelihood of success for bringing the project to fruition. This will avoid possible frustrating situations in which good scientific projects that could be funded other ways are delayed because they do not fit into the strategies of potential funding partners.

The fourth priority is to enhance and optimize the governance process to ensure projects fulfill the strategic direction and mission of the BC. It was brought up during the information gathering stage of the evaluation process that the roles of the executive committee and the steering committee can overlap and create situations in which the decision making is confused. During the strategic assessment process, the team redefined and clarified the roles of the committees. In addition, the BC is implementing earlier discussions between the steering committee and executive committee to ensure alignment. This earlier alignment will allow more confident early sponsorship discussions and provide the executive committee with a higher-level strategic view of the consortium portfolio, allowing the executive committee to focus on the mission and strategic aspects of the field biomarker development.

Finally, the fifth strategic priority is to improve communication with all stakeholders. The BC must more clearly communicate its prioritized vision and mission, disseminate findings, and tout successes. Communications among different groups of stakeholders have different priorities. Communications should include steering committees project team participants, with the specific goals to more clearly communicate what is in the BC scope, process refinements, and roles of executive committee/steering committee. Communications with current member and partner organizations need to reinforce the value of their participation in, and support of, the BC. Finally, with regard to relevant external stakeholders, there is a need to disseminate findings beyond journal publication as well as reach out to new potential members, patient groups, and others.

## CONCLUSION AND NEXT STEPS

The landscape of the biomarker science community has substantially shifted since the inception of the BC in 2006. Based on the new vision of “improving health through meaningful measurements” and a mission “to create and lead cross-sector efforts that validate and qualify biomarkers and other drug development tools to accelerate better decision making for the development of new therapeutics and health technologies, the BC now has defined its strategic priorities, the utility of the BC has been reaffirmed, and new directions have been suggested, including a broadened scope.

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## CONFLICTS OF INTEREST

The authors declared no competing interests for this work.

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