

The FNIH Biomarkers Consortium embraces the BEST

Joseph P. Menetski¹, Christopher P. Austin², Linda S. Brady³, Guy Eakin⁴, Chris Leptak⁵, Abbey Meltzer¹ and John A. Wagner^{6*}

The Biomarkers Consortium aims to facilitate drug development with biomarkers across a range of diseases. Here, we briefly highlight its accomplishments so far and its recent expansion in scope to include related tools along the lines of the Biomarkers, EndpointS and other Tools (BEST) resource, such as patient-reported outcomes and clinical outcome assessments.

The Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium (BC) was formed in 2006 in collaboration with the National Institutes of Health (NIH), the FDA, the Centers for Medicare and Medicaid Services (CMS), the Biotechnology Industry Organization (BIO) and the Pharmaceuticals Research and Manufacturers Association (PhRMA). The BC is set up to address specific biomarker projects in the precompetitive space, and its 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, with all stakeholders having a voice in the direction of projects. The spirit of collaboration extends beyond individual projects; an important aspect of all the BC projects is that the project results and data are made available to the entire scientific community. In this article, which is based on a recent strategic review of the BC, we discuss the achievements so far, as well as new opportunities created by challenges that have developed in the last 12 years, including the need to expand the scope of the BC to formally include projects beyond biomarkers such as patient-reported outcomes and clinical outcome assessments (COAs).

Accomplishments of the BC

The BC has had several notable accomplishments, addressing biomarkers that have facilitated drug development for important unmet medical needs and thereby directly benefited patients. As a first example, the development of new antibacterial drugs for skin infections and bacterial pneumonia had been severely hampered by the lack of a measurable end point for early treatment effects, particularly effects that would be relevant to the patient and provide data to improve the design of clinical trials. As part of its projects on community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections, hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia¹, the BC

confronted this issue by generating new COA measures that allow sensitive and robust assessment of infection and report on outcomes important to the patient. The sensitivity and consistency of these measures has allowed the FDA to confidently assess the utility of new treatments. These measures have aided the approvals of seven drugs so far (dalbavancin, delafloxacin, tedizolid, oritavancin, ceftaroline fosamil, telavancin, and ceftazidime plus avibactam).

A second BC accomplishment has been improving clinical trials and biomarker use for breast cancer, which affects a heterogeneous set of subpopulations, increasing the challenge of identifying effective treatments. The BC launched the trailblazing I-SPY 2 trial 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 design². Successful drugs may graduate to smaller registrational trials, reducing the time and cost of drug development. I-SPY 2 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 six therapies in breast cancer to date (neratinib, veliparib, pembrolizumab, MK-2206, pertuzumab, and TDM1 and pertuzumab in combination).

Third, assessing kidney injury early in drug development trials continues to be a major concern for drug developers. The BC Kidney Safety Project has analysed and validated many urine biomarkers and identified several that can outperform the current standards for monitoring acute drug-induced kidney injury. The project team developed a composite panel of six urine biomarkers to assess kidney injury in healthy control subjects in drug development clinical trials that was recently qualified by the FDA (see Related links). Several companies are now using this composite measure to augment their current approaches to assessing kidney injury. These biomarkers will enable decisions about the renal safety of candidate drugs in phase I and phase II trials.

¹Foundation for the National Institutes of Health, North Bethesda, MD, USA.

²National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD, USA.

³National Institute of Mental Health, Bethesda, MD, USA.

⁴Arthritis Foundation, Atlanta, GA, USA.

⁵Center for Drug Evaluation and Research, Food and Drug Administration, MD, USA.

⁶Takeda Pharmaceuticals International, Cambridge, MA, USA.

*e-mail: John.Wagner.md.phd@gmail.com

doi:10.1038/d41573-019-00015-w

Finally, the BC has taken a key role as a leader in driving consensus to define how to collect and describe evidence needed for biomarker qualification. In April 2016, the BC and the FDA co-sponsored a workshop to define and evaluate a general framework for assessing the evidentiary criteria needed for biomarker qualification using safety biomarkers as real-world examples³. The BC and the FDA also co-sponsored a follow-up workshop in July 2018. The vigorous discussion at the workshop has refined the path for assessing what kind of data and how much are needed during the qualification process, including a more detailed description of the biomarker itself and describing how collected data relate to important characteristics of biomarker utility.

Current status and challenges

The BC Executive Committee carried out an extensive analysis of the state of the biomarker and regulatory science field, starting with an analysis of how the current projects were developed and have been executed. Through the work of external consultants, the committee also assessed opinions on public-private partnerships, biomarker development and the BC itself by carrying out more than 30 interviews with leaders in the field, analysing 121 surveys of BC committee and project team members, and benchmarking similar organizations.

Two main themes emerged in this analysis. First, the survey and interview responses made it clear that biomarker science is harder and more complex than was appreciated 10–12 years ago. Initial expectations of biomarker discovery and development fell short of generating decision-making tools with sufficient technical and biological validation to allow them to be confidently used in drug development. Important advances with ‘omics’ technologies such as next-generation sequencing have emerged, but data produced using such technologies only provide initial hints of their potential to be used as decision-making tools. Partly because of the availability of these biomarker discovery platforms, there has been a proliferation of unvalidated biomarkers, which require validation and standardization in order to be used as drug development tools. Like the drug development process itself, however, in which the vast majority of ‘hits’ are not ultimately validated or developable into drugs, most biomarker candidates will probably not meet the rigorous requirements of a drug development tool.

Second, as the need for validation and standardization has been recognized, there has been a proliferation of consortia in the biomarker space. Although there is skepticism about what might be accomplished in some partnerships, the need for collaboration remains great, and the rationale for BC-type consortia holds strong. Testifying to this need, interviewees advocated not simply continuing the BC in its current form, but expanding its remit to include additional types of drug development tool beyond biomarkers; for example, along the lines of Biomarkers, EndpointS, and other Tools (BEST; see Related links). The BC Executive Committee has now endorsed this expansion, resulting in a new mission and vision for the BC.

New vision, mission and strategic priorities

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 the following strategic priorities.

- Broaden the BC’s scope to validate and qualify biomarkers, as well as drug development tools along the lines of BEST, that can leverage the BC’s infrastructure, experience and expertise.
- Engage in projects and events that will further establish the BC as a thought leader in the field of regulatory science. The BC as an infrastructure excels at convening multiple stakeholder groups to drive consensus in areas where collaboration will lead to better results for all stakeholders and the public. One example described above is the creation of a general framework for assessing the evidentiary criteria needed for biomarker qualification³. The partnership will continue to search for such leadership opportunities, as exemplified by the qualification workshop focused on surrogate end points.
- Streamline and clarify the process by which the BC is governed. The public dissemination of the results from the BC projects into the scientific community, with as few barriers as possible, will continue to be a keystone of how the BC operates.

In summary, the needs in the biomarker science community have increased since the inception of the BC. The BC strategy discussion has reaffirmed the utility of an infrastructure where biomarker challenges can be addressed in a project-by-project approach. The expanded scope is expected to provide for projects focused on biomarkers and other drug development tools and lead to continued accomplishments and further impact for the biomarkers community.

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Acknowledgements

The authors acknowledge the contribution of J. Altshuler and S. Staats from Altshuler and Staats for their work on the strategic analysis, as well as the support and feedback from the members of the Biomarkers Consortium executive committee, particularly P. Herrling, chair of the executive committee and FNIH board member.

Competing interests

J.A.W. is an employee of Takeda Pharmaceuticals. J.P.M., C.A., L.S.B., G.E., C.L. and A.M. declare no conflicts.

RELATED LINKS

Biomarkers, EndpointS, and other Tools (BEST): <https://www.ncbi.nlm.nih.gov/books/NBK338448/>
 FDA letter of support in response to the submission by Critical Path Institute’s Predictive Safety Testing Consortium on urinary biomarkers for kidney safety monitoring: <https://c-path.org/wp-content/uploads/2014/09/PSTC-NWG-2014820-FDA-LetterOfSupport.pdf>
 FDA qualification page for kidney safety markers: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm>