



**Biomarkers Consortium Meeting
February 3, 2016
Summary of Proceedings**

On February 3, 2016, the Preeclampsia Foundation convened a second Biomarkers Consortium meeting in Atlanta, Georgia. Attendees included representatives from the biomarker industry, academia, patient representatives, clinicians, researchers, Preeclampsia Foundation staff and members of the Board of Directors, and professional societies.

This meeting built upon the work of the 2012 Biomarkers Consortium meeting which sought to establish core recommendations in the primary areas inhibiting advancements in the development of biomarkers as diagnostic or screening tests for preeclampsia (research, clinical, industry, patients).

As the conversation was among and included several diagnostic manufacturing companies, all participants were informed that their discussions were subject to the antitrust laws applicable in the United States. Nothing discussed at the meeting was intended to restrict the individual decision-making of any participating company or to represent an agreement to coordinate marketing or sales conduct.

Meeting Agenda/Goals

The agenda of the 2016 meeting was as follows:

1. Hear from ACOG regarding recent Committee Opinion on biomarkers
2. Provide updates since the 2012 Biomarkers Consortium meeting
3. Define Working Groups to address calls to action
4. Define a Governance Committee
5. Determine the resources needed to move forward based on a collective vision

American College of Obstetrics and Gynecology (ACOG) Opinion

ACOG Vice President of Practice, Dr. Christopher Zahn, was invited to present rationale for and respond to questions related to ACOG's September 2015 Committee Opinion #638, "First Trimester Risk Assessment for Early Onset Preeclampsia" which advised against the use of biomarkers in early pregnancy. Dr. Zahn outlined the extensive review process the organization's committees use to provide guidance. In regard to biomarkers, ACOG says it's necessary for screening tests to be useful, be able to predict, be of consequence, be an acceptable minimal burden, and needs to affect outcome. As of September 2015, no studies were available that demonstrated the effects and outcomes of using preeclampsia screening tools in meaningful ways to patients and clinicians.

Discussion of the new interim review process, which allows the Committee to make expedited changes, followed and it was acknowledged that substantive data to support opinions would drive the standard of care.

Updates

Since the 2012 meeting, there has been some movement in the field. New research continues to uncover new directions in biomarkers and diagnostics, particularly with respect to the emerging field of precision medicine; some players have dropped out of the preeclampsia biomarkers space while several new players have entered; research is underway for interventions for preeclampsia, which will drive the urgency for a viable diagnostic tool.

We've watched both the Administration and Congress embrace the promise of precision medicine and begin to support ways to address the challenges raised in the first Biomarkers Consortium meeting. The *Advancing Breakthrough Therapies for Patients Act* was signed into law (2012) to create a breakthrough pathway to safely shorten the development and approval time for drugs. This process led to the FDA issuing guidances on development and use of biomarkers in medical product development, mainly through the Center for Drug Evaluation and Research (CDER). Dozens of consortia from other fields have formed to accelerate new biomarkers and work in collaboration with the FDA, NIH, industry, academia, patients and payers. The 21st Century Cures Act began moving through Congress in 2015 to help address regulatory hurdles, and legislation titled "Advancing Breakthrough Devices for Patients Act" was introduced (2015) with the goal of shortening development time and regulatory review of breakthrough medical devices (both 510k and PMA). The Preeclampsia Foundation and many of the organizations represented on this Consortium had a hand in these legislative and policy efforts.

The ACOG Task Force on Hypertension in Pregnancy (2013) identified biomarkers as an area in need for additional research¹. The Bill and Melinda Gates funded Global Pregnancy Collaboration (CoLab), an international multi-center group, published the results of its efforts to analyze a set of biomarkers using data from several biobanks (2016)²; further efforts are underway by CoLab to advance the study of biomarkers.

While much has changed for the better, some things have remained the same or stalled. Support for diagnostic and biomarker guidelines is still slow in coming from the key medical societies and our efforts to publish an opinion piece in a peer-reviewed journal by members of this consortia was unsuccessful.

State of Biomarkers

Dr. Ravi Thadhani (event moderator) reviewed what could be accomplished at this meeting and in the future by members of the Consortium. The 2012 meeting took place at a time when demand, research, and need were all aligned; regulators were there to help define a sensible benchmark and to hear input from clinicians, investigators and patients. Interest in biomarkers research grew exponentially after that meeting. The FDA issued expedited review status via its breakthrough designation.

Interventions

The role of biomarkers to facilitate research for and eventually implementation of therapeutic interventions was discussed.

¹ American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol.* 2013;122(5):1122-1131.

² Burke Ó, Benton S, Szafranski P, et al. Extending the scope of pooled analyses of individual patient biomarker data from heterogeneous laboratory platforms and cohorts using merging algorithms. *Pregnancy Hypertens.* 2016;6(1):53-59.

Rick Finnegan (rEVO) discussed the ongoing PRESERVE-1 trial into antithrombin replacement.

Dr. Ravi Thadhani (Kaneka) and Dr. James Smith (Advanced Prenatal Therapeutics) discussed the ongoing work in apheresis to filter soluble factors from the maternal bloodstream.

Review and Update Challenges and Priorities

Dr. Arun Jeyabalan, (MFM, University of Pittsburgh Medical Center) outlined a strategy to create a biomarker test with FDA approval and broad public uptake. Given the need for data to support the use of biomarker tests, academia and researchers need to focus on multicenter international trials, the creation of evidence-based guidelines for use, and evidence for quantified, defined benefits. Questions raised include: Should we plan for research trials that show effects from changes in expectant management, considering both NIH funding priorities for therapeutics, and the ability of tests to drive practice changes?

Manufacturers and Clinical Laboratories Perspective

Ursula Klause (Roche) discussed challenges and strategies for bringing biomarkers through clinical use to FDA's attention. FDA only considers US studies, which can be cost-prohibitive, and considers use in pregnant women to be risky. But doing nothing is also risky. Collaboration between manufacturers and clinicians to design data acceptable to FDA will move biomarkers tests towards FDA acceptance. We need to stop working independently, and collaborate to develop a strategy with a value proposition worthwhile to everyone and that addresses FDA's concerns and requirements.

Ensuing discussion included a review of effective biomarkers available outside the US and the apparent disconnect between the FDA and Laboratory Developed Tests (LDTs).

Clinical Perspectives

Dr. James Martin (ACOG Past President; MFM, University of Mississippi) observed that preeclampsia management is currently challenging because of the absence of a quantitative test. Biomarkers could provide quantitative support for prediction, diagnosis, and prognosis, but currently are not at this stage. Low dose aspirin as an intervention is not enough. Biomarkers have the potential to help us diagnose correctly and prevent discharges of women who will worsen after delivery. We need a diagnostic bundle that will work for all women regardless of the stage when they are tested, and standardized studies that can convince the world.

Discussion followed which emphasized the importance of a test for OB/GYN generalists, versus MFMs.

Patient Perspectives

Caryn Rogers (Preeclampsia Foundation patient representative) reported strong patient support for clear and complete information that could improve education and preparation for complicated outcomes, even if no therapies exist currently. Data from the Preeclampsia Registry suggests that there is high demand for a screening and diagnostic tests.

Regulatory Perspectives

Diarmuid Cahalane (Metabolomic Diagnostics) reported from their experience that the FDA is anxious to see a test brought to market and has expedited access due to the unmet medical need. We need to demonstrate clinical utility. Is one pathway to this the US Preventive Services Task Force? Can we change precedent? Can we discuss as a unified group with the FDA?

Healthcare Economics

Matthew Cooper (Progenity, Preeclampsia Foundation Board of Directors) reported on the need to understand the costs associated with preeclampsia and how biomarkers tests can benefit payers. This can highlight the need for more research dollars and support financing for product manufacturers. The Preeclampsia Foundation has convened a task force to develop a manuscript with available data, framing the key questions, data sources, and providing analysis. Efforts are underway to publish this economic impact data.

Rick Finnegan (rEVO Biologics) discussed their work in therapeutic development and the role of economic analysis, since prolonging gestation will shape healthcare economics. Adding more time in the hospital and the cost of therapeutic drugs but reducing morbidity, mortality, and long-term outcome costs will need to be quantified.

The group agreed that healthcare economics work needs to be done. How many unnecessary prenatal visits can be avoided for women who screen negative? How many iatrogenic preterm deliveries can be avoided? The Preeclampsia Foundation can convene this task force, but will need input from stakeholders with their own data. Rana, Cahalane, and Cooper mentioned ongoing work that can be contributed, as well as possible contributions from USPSTF, California, and the UK.

Conclusion

Several issues are common to all stakeholders and, as a result, suggestions were made to work together to make progress. A discussion is needed on maximizing stakeholder cooperation, bringing patients into the process, managing competition, and the role of the Preeclampsia Foundation in assisting with the process. Perhaps a regulatory strategy, a sample repository, education and outreach, a US study, and work on healthcare economics would be possible to determine the best way to get tools to market. There was also discussion about the Consortium's effectiveness and what would be needed to continue its work.

A post-meeting survey was conducted to prioritize efforts and ascertain ongoing interest.

Summary of Post-Meeting Survey Results

In their responses to a post-meeting survey, participants agreed that the Consortium had been a good use of their time. In response to questions about how to advance biomarkers development, more than half the participants viewed regulatory support for biomarkers development as their primary need. Increasing support from clinicians, patient education and awareness, updates on developments in this area, addressing payer concerns, access to serum samples, and research on best practices were also areas where participants reported unmet needs.

In the future, participants believed the Consortium should continue to meet as one group with topic subgroups, and that it should engage a program manager experienced with these sorts of colloquia to speed advances. While the thought of breaking the initiative into multiple initiatives received support from about a quarter of participants, there were no clear theoretical joints along which to divide the group.

Almost all participants agreed that producing an estimate of the economic burden of preeclampsia that could be used in lobbying, reimbursement, and other advocacy efforts should be a high-priority initiative for the group. Roughly two-thirds agreed that a biobank should be a high-priority as well. More than half wanted to identify and address challenges to acceptance of biomarkers for screening, and three-quarters wanted to identify and address challenges for diagnostic use. Ninety percent hoped to see a White Paper and publication of the Consortium findings. Ninety percent also wished to focus on regulatory concerns and to expand patient education and awareness programs in this area. Participants expressed interest in providing various forms of financial support for the Consortium's activities, mostly in support of traveling to future meetings, and covering direct costs for future consortia meetings.

Unfortunately, sufficient financial support was not prioritized by the participants and the Preeclampsia Foundation does not have any dedicated funding to maintain this initiative at this time.

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