No Time to Wait: Women Need Accurate Tests for Preeclampsia Now

A Call To Action

It is with great urgency that we call upon leaders in research, industry, regulatory bodies, policy makers, professional societies, and payers to engage and address this call to action, removing barriers and accelerating the development and clinical adoption of biomarkers for preeclampsia.

Preeclampsia is a heterogenous maternal syndrome recognized ultimately by the development of high blood pressure and multi-organ dysfunction or injury. Its clinical presentation can be quite varied and confusing: elevated BP may precede or follow proteinuria, other symptoms may be obscured; its onset may be gradual, quite sudden, or even present postpartum. It is the most common severe obstetrical complication in the U.S.[1], affecting 2 to 8 percent of pregnancies, and leading to multiple adverse maternal outcomes including seizure, stroke, heart disease, and death, as well as neonatal outcomes that include growth restriction, preterm birth, and death[2,3]. The estimated cost of preeclampsia in the United States was $2.18 billion dollars in 2012[4], the average preeclamptic pregnancy cost three times more than normotensive pregnancies[5], and the incidence of preeclampsia – especially its severe variants – has been increasing[6], underscored by the unacceptable disparities we are seeing in both higher prevalence and worse outcomes amongst Black and American Indian/Alaskan Native women[7,8]. It has now been over 100 years since the term 'preeclampsia' was first coined to define the syndrome of hypertension, proteinuria and edema[9] – clinical endpoints that have not markedly changed, and yet still the cause of the disease remains elusive, hampering efforts to predict, diagnose, and manage this scourge of pregnancy. **Clearly, we must do better**.

A key component needed in the fight against preeclampsia, and perhaps the most urgently needed, is the development of tests for simple, rapid, and accurate diagnosis and prediction. Sadly, health care providers are still struggling to diagnose the syndrome of preeclampsia and stratify women's risks using antiquated tools and schemes of the 19th Century. Blood pressure, proteinuria, maternal symptoms, and basic blood chemistries are highly variable, nonspecific, and poorly predictive of outcome. The resulting diagnostic uncertainty is pervasive and shameful – rare or atypical cases are overlooked with potentially devastating

consequences, while a great many unaffected patients are subjected to worrisome, repetitive, and wasteful surveillance or possibly even to unnecessary iatrogenic delivery. Rapid, reliable and clinically useful biomarkers for preeclampsia are urgently needed as decision aids to improve pregnancy outcomes[10].

Biomarkers are powerful laboratory tools that can be used to detect or predict pathology before symptoms, such as elevated blood pressure, are present. These unique biological products are found throughout our body and may be quantifiable by a simple blood, urine, or even a saliva test at various points in the disease process. There are several important benefits to introducing biomarkers into the fight against preeclampsia: 1) Screening pregnant women for pre-symptomatic disease to enable interventional research studies, accelerating progress toward therapeutic drugs or biologics; 2) Determining disease severity and risk stratifying women to improve surveillance and management, such as timing of delivery; 3) Reducing costs associated with short and long term medical care by eliminating unnecessary testing and surveillance[11]; 4) and most importantly, saving the lives and well-being of mothers and their babies.

Clinically relevant biomarkers of preeclampsia can be divided into placental, inflammatory, endothelial and metabolic categories[12]. A few promising biomarkers include Placenta Growth Factor (PlGF) which is involved in the modulation of the placental and maternal vascular system[13], soluble FMS-like tyrosine kinase-1 receptor (sFlt-1) which antagonizes blood vessel formation and promotes endothelial dysfunction[14], asymmetric dimethylarginine (ADMA), which interferes with nitric oxide production and leads to abnormal vascular function[15], Congo Red, a test of protein-folding abnormalities in the urine of preeclamptic women[16], and others. Combined with usual clinical and ultrasound surveillance during pregnancy, these biomarkers have been shown to diagnose preeclampsia and predict adverse outcomes with an even greater accuracy than traditional tests[17,18], and some have even been shown to reduce medical costs associated with evaluations of suspected preeclampsia[19].

In 2015, the American College of Obstetricians and Gynecologists (ACOG) released a committee opinion stating that, although commercial tests were available to predict preeclampsia during the first trimester, there was a lack of evidence supporting their use clinically[10]. Since then, ongoing research studies have further refined biomarker strategies, which are now capable of predicting over 75 percent of cases of preterm preeclampsia with a low false positive rate of 10 percent[20] and others which have led to effective 'rule out' strategies[21,22]. In other countries, serum biomarkers have already been adopted for clinical use and incorporated into management guidelines[23].

Efforts to bridge the gap between biomarker research and widespread clinical use led to the Preeclampsia Foundation hosting two biomarker consortia, in 2012 and 2016. An

interdisciplinary team of experts convened to debate the current state of the biomarker field, present challenges, such as regulatory hurdles, define the need through both clinical and patient perspectives, and develop recommendations to move forward. Detailed findings of the consortia proceedings are summarized in our 2012 Report to Stakeholders and our 2016 Meeting Proceedings. As a result of these dynamic conversations, the FDA recognized some tests may provide substantial improvement over currently available clinical and diagnostic testing to diagnose preeclampsia and, hence, made an expedited review and approval process available to manufacturers pursuing commercial development.

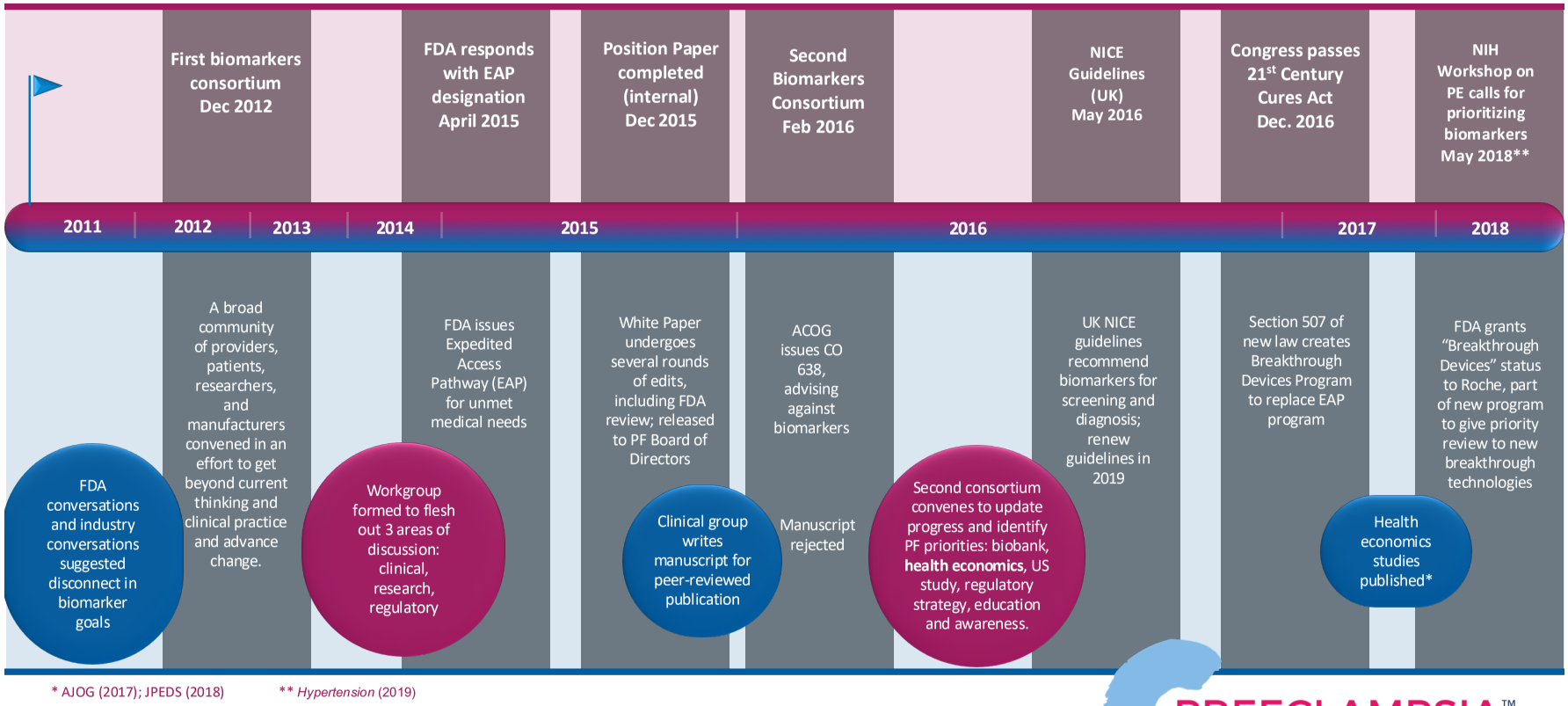
This designation and other key milestones in the evolution of the biomarker field are illustrated in *Figure 1*. As U.S. policymakers look to expand beyond legislative efforts to support cures and therapy breakthroughs, they should consider ongoing regulatory reforms that will allow expedited approval for new screening tests, coverage, and clinical screening guidelines. Professional societies must encourage the use of these important decision aids as clear markers of placental dysfunction.

The Preeclampsia Foundation, a patient advocacy organization, represents the nearly 300,000 pregnant women per year affected by hypertensive disorders in the US and Canada. Its purpose is to reduce the burden of preeclampsia and related complications by educating, supporting, and engaging the affected community, improving healthcare practices, and finding a cure. As such, **the Preeclampsia Foundation is a strong advocate of biomarker research and clinical utilization.** The Foundation has extended its support of biomarkers by awarding biomarker-based research grants, using patient surveys to demonstrate the importance of biomarkers to preeclampsia survivors, and encouraging industry to engage in biomarker development.

The status quo is inadequate. It is time to move to the molecular era. Biomarker studies and clinical adoption must be prioritized and accelerated if we are going to save the lives and improve health outcomes of preeclamptic mothers and their babies. It is with great urgency that **we call upon leaders in research, industry, regulatory bodies, policy makers, professional societies, and eventually payers to engage and address this call to action, removing barriers and accelerating the development and adoption of biomarkers** to improve screening and diagnosis of hypertensive and placental disorders of pregnancy.

Preeclampsia Foundation Board of Directors
September 17, 2020

Biomarkers Consortium Timeline



* AJOG (2017); JPEDS (2018) ** *Hypertension* (2019)

PREECLAMPSIA™ FOUNDATION

Figure 1 - Timeline of Key Milestones

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