Advancing Biomarkers to Screen and Diagnose Preeclampsia:
A Report to Stakeholders

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This document includes background on the state of molecular biomarkers for preeclampsia screening and diagnosis, identification of the needs and challenges facing the field, the proceedings and participants of the Biomarkers Consortium (convened by the Preeclampsia Foundation in December 2012) and the resulting calls to action, broken out by stakeholders (research and academia, manufacturers and laboratories, clinical, regulatory, and patient organizations).

Introduction

Biomarkers and diagnostic tests facilitate evidence-based individualized medicine, improve providers' ability to provide quality and targeted healthcare services, and enable the early detection of diseases and conditions, ultimately saving costs through improved health outcomes. As the United States seeks to reduce healthcare expenditures and improve the quality of care, policymakers, patients, and healthcare providers search for opportunities to better diagnose and manage costly conditions. More precise testing options can improve a clinician's decision-making and provide patients better awareness and understanding of what is needed to manage their healthcare needs at a reduced overall cost.

In the field of obstetrics and gynecology, the potential for new biomarkers is viewed optimistically by many – from scientific researchers to clinicians – as they seek an opportunity to improve maternal safety. The interest in biomarkers stems from a need to better detect significant impending disease in order to make care decisions prior to the deterioration of a pregnancy. There is a specific desire for such testing options to improve maternal and infant health outcomes when faced with the risk of preeclampsia, suspected preeclampsia, or confirmed preeclampsia.

Preeclampsia complicates approximately five to eight percent of pregnancies in the western world, and remains a leading cause of maternal morbidity and infant and maternal mortality across the globe. Data from the National Center for Health Statistics and from the National Hospital Discharge Survey show a consistent increase in preeclampsia diagnosis of approximately 25 percent over the last two decades. Clinicians and researchers surmise that this increase may be due to an increase in the prevalence of obesity, diabetes, and chronic hypertension within the pregnant population - all risk factors for preeclampsia.

Finding either a common definition for preeclampsia or a one-stop approach for diagnosis and management of the disease has thus far proven impossible, given the syndromic nature of the disease process. Reliance upon traditional methods of diagnosis or assessment of risk for preeclampsia,

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including frequent measurement of hypertension and proteinuria, has been the standard of care for prenatal assessment since the 1960's. Delivering the baby, at times extremely premature, has been the only known option for protecting the mother's (and often baby's) health when preeclampsia threatens significant health complications or death.

A broad community of providers, patients, researchers, and manufacturers came together in 2012 as a consortium in an effort to get beyond current thinking and clinical practice and advance change. Clinician and patient communities no longer want to rely on antiquated protocols as the only standard of care for those with preeclampsia or those suspected of having preeclampsia. Many desire a better approach, even without complete elucidation of preeclampsia's pathophysiology. Ultimately, the goal of advancing new biomarker tests for preeclampsia detection is to significantly improve patient care and reduce adverse maternal and infant outcomes. Those looking to advance biomarkers in this field want to better address both immediate health outcomes and the life-long consequences for a woman and her baby's health.

Statement of Need

The United States is in serious need of accurate biochemical/biomarker-based screening and diagnostic tools that can ultimately lead to better patient healthcare management and improved health outcomes for women with – or at risk of – preeclampsia, and their babies. An evidence-based clinical pathway that leads to improved patient health outcomes is the goal. In such a pathway, clinical risk factors and biomarkers are used to inform patient and clinician choices on appropriate health interventions. There is a particular need for accurate tests that can screen, predict, diagnose, and risk stratify the most severe forms of preeclampsia, which is where the preeclampsia community sees the risk to both the mother and the baby to be the highest.

Scope of the Issue

- Hypertensive disorders of pregnancy are one of the most common medical disorders of pregnancy, occurring in 12-22% of pregnancies. Preeclampsia, more specifically, occurs in 5-8% of all pregnancies.
- Preeclampsia is serious condition of pregnancy that can lead both immediate and long-term adverse outcomes for the mother and her baby.
- The incidence of preeclampsia has seen a small but consistent increase in the United States over the past two decades.
- Preeclampsia is currently diagnosed by sustained, new onset hypertension ($\geq$140 systolic OR $\geq$90 diastolic) and the presence of new onset proteinuria (protein to creatinine ration of $\geq$0.30) or one or more severe features of disease (i.e., renal insufficiency, thrombocytopenia, impaired liver function, pulmonary edema, cerebral or visual symptoms).
- Despite decades of research, the specific etiology of preeclampsia and its complete pathogenesis remains unknown. This has led to unresolved debates surrounding the classification, diagnosis, and management of hypertensive disorders of pregnancy.
- Preeclampsia is a major cause of preterm birth. Preterm birth can be associated with immediate neonatal morbidity and has been linked to remote cardiovascular and metabolic disease in newborns.
- Women who survive preeclampsia are two to eight times more likely to have future cardiovascular and metabolic diseases.
- Worldwide, there remain an estimated 76,000 preeclampsia-related maternal deaths and 500,000 perinatal deaths every year. In addition, in the United States, for every maternal

death related to preeclampsia, it estimated that there are 50 mothers who suffer "near miss" life threatening events.

- Several states, including California where 13% of the countries births occur, found that all maternal deaths related to preeclampsia had at least "some" chance of being altered, and half of those were determined to have a strong-to-good chance to alter the outcomes.

Impact on Health Today

- Imperfect identification of preeclampsia or risk for adverse outcomes can lead to an unnecessary intervention (e.g., early delivery) or delayed diagnosis and management, both affecting pregnancy outcomes.
- Due to the many unknowns, pregnant women cannot be safely reassured or appropriately advised about the risk of preeclampsia and its consequences to the mother and baby. Women with preeclampsia cannot be accurately counseled on expected pregnancy outcomes.
- Extensive monitoring for the development of preeclampsia and inappropriate preeclampsia management or intervention lead to significant healthcare costs.

Challenges Ahead

Although there is general clinical recognition that more tools are needed to appropriately and accurately screen, risk stratify, and diagnose preeclampsia, there are hurdles that must be addressed. Physicians have differing perspectives on what type of test would be most helpful in the management of prenatal care. The economic burden of disease and potential cost savings from better tests are not well understood or documented. All too frequently, patients (both pregnant and post-partum) who experience pregnancy complications from preeclampsia do not understand what preeclampsia is, why they may have had a negative pregnancy outcome, or what preeclampsia means for future pregnancies or their long-term health. On a broader scale, the public does not generally know what preeclampsia is, and those who have heard of it often have very little appreciation for how devastating it can be to both short- and long-term health. A recent market survey found fewer than half of today's pregnant women know what symptoms of preeclampsia warrant medical attention.

It is the responsibility of all communities – provider, patient, and test manufacturer – to overcome these hurdles and work to advance women's health tests and treatments. However, the challenging market as described and the complex U.S. regulatory environment create immense challenges in getting a new preeclampsia biomarker into the United States.

Developing awareness for an unmet health need can be extremely difficult. A new way of thinking and collaboration is needed if we are to get all stakeholders to think of preeclampsia as more than "just a pregnancy thing." Much work must occur to get stakeholders to mutually understand that preeclampsia is a complication that affects a woman's overall health immediately postpartum, as well as for the rest of her life and potentially her child's life. A commitment from researchers, academics, physicians, allied health providers, patients, and diagnostic companies is needed to move preeclampsia research and new preeclampsia testing methods forward.

The clinical and economic potential for improved maternal and infant health through new biomarker tests for preeclampsia is immense. New tests have the potential to improve the level of and timing of diagnosis so that appropriate interventions are undertaken. Effective biomarker tests could support the provision of appropriate prenatal care and help to ensure better health outcomes overall, leading to enhanced management of healthcare resources. Health providers need improved tools for

expectant management so they do not deliver babies too late or too soon. Quite simply, women and their families deserve better.

Approach of the Biomarkers Consortium Meeting
In December 2012, the Preeclampsia Foundation facilitated a consortia meeting with government regulatory representatives, healthcare providers, patient representatives, academics, researchers, and representatives of the diagnostic manufacturing and laboratory communities who are actively engaged in the field of preeclampsia. (See Appendix A for a detailed description of the proceedings and Appendix B for list of participants.) The intention was to host a symposium focused on how the audiences represented could collectively begin to partner to advance the development of biomarkers that can eventually be used to screen for, risk stratify, and diagnose preeclampsia. At the onset of the meeting, the assumption was that questions existed about the proof of benefit to a preeclampsia screening and/or diagnostic biomarker as well as proof of efficacy. Those questions led participants to ultimately identify and develop a plan to overcome three key barriers and challenges that exist today to the advancement of preeclampsia biomarkers:

- Patient/consumer understanding of preeclampsia biomarkers
- Individual clinician and medical society acceptance of preeclampsia biomarkers
- Regulatory and policy processes to attain approval of preeclampsia biomarkers.

Calls to Action – By Community
Movement toward the establishment of biomarkers for preeclampsia whether diagnostic markers specifically for high risk patients, screening markers for patients that present with specific indications, or markers that can be used across the entire population, requires the support of a multi-stakeholder community. Over 10 manufacturers and laboratories along with academics, educators, clinicians, and patient representatives convened at the consortium meeting to begin this process (see Appendix B for list of participants), but successfully extending that productive exchange hinges on continued advocacy across and by various audiences including: medical educators, research institutions, professional medical, nursing, and other healthcare associations, patient advocates, and industry (manufacturers and laboratories).

The following provides an outline of where each industry is in relation to the development of preeclampsia biomarkers – the challenges and opportunities. The consortia participants identified priority actions and additional steps that can and should be taken by stakeholder communities in an effort to advance the establishment and use of new preeclampsia biomarkers within the United States.

RESEARCH AND ACADEMIA
For the research and academic communities, establishing preeclampsia biomarkers hinges on the advancement of new studies and the creation of evaluations that can both support clinical trial development and provide evidence for consideration by the FDA during analysis of new preeclampsia testing devices. Collaboration is needed to establish a focused process for studying biomarkers over time and in a diverse patient population.

Recommended Priorities

- Support a comprehensive review of current research evidence on the need for screening, prognostic, and diagnostic preeclampsia tests and recommendations on additional studies that should be undertaken to provide necessary information and evidence.

- Support a multi-center, multi-national clinical trial of differing preeclampsia biomarkers to examine clinical outcomes, potentially with the support of the National Institutes of Health (NIH) and/or through collaboration with academic medical centers to launch a multi-center clinical trial through an existing maternal-fetal network.
- Create a preeclampsia-focused clinical trials network in the United States to undertake clinically important investigations of interventions and biomarkers.
- Conduct government-sponsored and/or private studies on the clinical utility of biomarker tests to determine what clinicians need to have for healthcare management and what clinicians must understand to use such tests.
- Produce a healthcare economics report that quantifies the short-term and long-term financial burden of disease to mothers and babies.

Other Actions

- Promote evidence-based guidelines for consistent care and clinical practice in relation to preeclampsia management.
- Work with medical education institutions to change current training programs about preeclampsia, focusing on the need for different ways to screen and diagnose.

MANUFACTURERS AND CLINICAL LABORATORIES

For manufacturers and clinical laboratories, the regulatory environment in the United States can cloud the path forward toward the development of biomarkers for the screening and/or diagnosis of preeclampsia. Many manufacturers have found that the current system prohibits the ability of companies to bring new innovative technology into the U.S. market. The perception by many companies is that the U.S. regulatory approval process is restrictive and costly, and new opportunities for a regulatory pathway to market are needed.

Some manufacturers have experienced that the time needed to receive FDA approval creates lengthy, cumbersome, and sometimes extraordinarily costly delays. For small manufacturers in particular, the expense and time to get to market can override the opportunity. These experiences and concerns have resulted in some manufacturers looking to pathways that have not historically required FDA approval, such as collaboration with clinical laboratories. As of January 2015, these laboratories do not undergo FDA review for the approval of laboratory-developed tests. However, on October 14, 2014, the FDA issued a proposed federal guidance on a process to oversee and approve laboratory developed tests (LDTs) based on their level of risk to a patient's health and safety. If the FDA's guidance is finalized, this could potentially have a dampening effect on investment in the development of LDTs for preeclampsia, as there is concern about the burden and costs associated with a formal FDA regulatory process for LDTs. Manufacturers have also expressed specific concerns about FDA-imposed limitations on the use and credibility of clinical data and biological samples that are collected outside of the United States as clinical data to support biomarker tests under consideration for approval. If U.S.-based and European-based manufacturers could combine forces under an agency-approved protocol, many manufacturers believe that this could save resources and move preeclampsia markers forward in a more expeditious manner across the globe.

The following is a summary of expressed concerns from some manufacturers on the U.S. regulatory approval system as it relates to moving forward with the review for preeclampsia screening and diagnostic devices:

- If a device is considered Class III, requiring Premarket Notification (PMA) status, many manufacturers (especially small manufacturers) may find the PMA approval too lengthy and expensive given their current financial investment.
- It is unclear whether the FDA would provide different risk categorizations for diagnostic tests versus screening tests; and if so, this could affect a manufacturer's decision to move forward.
- Large clinical databases exist around the world to support testing of various types of biomarkers for preeclampsia, yet it is the experience of some manufacturers that there are perceived FDA limits or objections to using such non-U.S. data to assist manufacturers in their device approval process.

Recommended Priorities

- Engage in a collaboration with the clinician community to understand concerns about the utility of a screening biomarker test for preeclampsia, including the overall reliability of such tests and at what intervals a test should be used and considered reliable in the clinical management of the patient, (e.g., how long a given test can be relied on across gestational periods) and to develop research protocols and studies that will answer clinician questions.
- Join with clinicians in approaching the FDA on development of an agency-approved protocol for the use of data and samples that exist in individual biobanks, potentially establishing collaboration between the European Union and a biobank in the United States to share data samples and conduct clinical trials. Such a collaboration for a defined specification (e.g., screening or diagnostic marker) could be considered to design studies by indication. Data could be used to show linkages to reviews for specific populations and geographic locations.
- Join with clinicians in approaching the FDA on the topic of appropriate consideration of predicate devices related to new types of preeclampsia biomarker tests. Provide insight and evidence to support claims of how new innovative tests should be considered so they are not inappropriately classified by the FDA and can be fairly evaluated and considered for approval.

CLINICIANS

For clinicians, the primary interest in preeclampsia biomarkers is in how such markers can help improve patient diagnosis, patient management, and health outcomes over the current standard of care or where the current standard of care is not being practiced. Evidence demonstrating clinical value and better results than management without the benefit of biomarkers will help build confidence in the use of such biomarkers as a standard part of patient care.

Recommended Priorities

- Acquire access to inexpensive, generally available, rapidly performed, sensitive, and specific biomarker tests that reliably assist in the diagnosis of a patient who is at risk of or has preeclampsia.
- Have key opinion leaders publish papers demonstrating interest in this field and guide the FDA to understand the clinical benefit of having a new type of preeclampsia screening and/or diagnostic test.
- Utilize information published by the ACOG Hypertension in Pregnancy Task Force to formulate recommendations to the FDA on issues to consider in regard to additional preeclampsia tests and associated patient risk.

PATIENT ORGANIZATIONS

Patient advocacy groups and consumer organizations are essential to the continued advancement of preeclampsia biomarkers and can be instrumental in gaining the attention, awareness, and support of government agencies and private payers to approve, cover, and appropriately reimburse for preeclampsia testing. Patient advocates are also critical in the effort to reach out to all women and their families to educate about the risk of preeclampsia both during pregnancy and post-pregnancy.

Priorities

- Collaborate with organizations that directly communicate with pregnant women (e.g., BabyCenter.com, Text4Baby) to improve communications aimed at consumers about preeclampsia, its risks, and the need for improved research and clinical trials on new biomarker tests for screening, risk stratification and diagnosis.
- Collaborate with clinicians and approach government and private payers to explore coverage of new tests and support demonstration projects and clinical trials of such tests within the payer community.
- Collaborate with manufacturers and clinicians to provide a better understanding of what patients would embrace for biomarker testing options.
- Collaborate with manufacturers to assess cost data associated with preeclampsia management and treatment to develop economic data on the need for improved measurement and testing for demonstration to government and commercial payers.
- Establish a coalition of patient groups around various interests to showcase examples of successful marker developments where lessons can be learned to support the growth of new markers (e.g., cancer, osteoporosis, diabetes/artificial pancreas). Form a set of core recommendations to the FDA to expedite the review and approval process for novel biomarkers.

Other Actions

- Advocate before the FDA for a demonstration project to pilot use of biomarker tests within a defined population.
- Engage potential funding partners in an effort to support global data collection on preeclampsia biomarker development.
- Use a patient-driven research network (such as The Preeclampsia Registry™) to conduct comparative effectiveness research on biomarkers and their impact on health outcomes, either retrospectively or prospectively.
- Provide insight to manufacturers and laboratories on consumer comfort with the out-of-pocket cost for preeclampsia-related tests to understand what patients would be willing to directly spend in the absence of insurance coverage.

GOVERNMENT REGULATORS

Government agencies have an important role in the continued development of preeclampsia biomarkers and the research needed to support the markers. Agencies of interest include the Food and Drug Administration for device/diagnostic test approval; the Centers for Medicare and Medicaid Services to address payer consideration; the Agency for Health Research and Quality to provide research support of the potential for markers to reduce hospital expenditures through improved care management; the Centers for Disease Control and Prevention to support biobank development and counsel for clinical trial development; the National Institutes of Health to support continued growth in research for biomarker development; and the Health Resources and Services Administration's

Maternal and Child Health Bureau to support public awareness about preeclampsia and care/treatment protocols.

Priorities

- Work with stakeholders to consider biomarker tests using the 510k or 510k DeNovo pathway to approval, considering different thresholds for claims regarding different types of tests (e.g., thresholds for risk stratification and prediction).
- Work with stakeholders to consider protocols for the acceptance of clinical trials and evaluations conducted outside the United States when evaluated by regulatory bodies for additional use and evaluation in the United States.

Appendix A

Biomarkers Consortium Meeting
December 2, 2012 | Washington, DC

Goals and Objectives of the Biomarkers Consortium Meeting

The Preeclampsia Foundation hosted the consortium with the central goal of identifying the barriers to moving preeclampsia biomarkers forward and options for overcoming those barriers. For many years, the Foundation has heard of interest from clinicians, patients, and diagnostic manufacturers in new tests that can either identify women at high risk for developing preeclampsia and its advere outcomes, or providing a more definite diagnosis of preeclampsia when signs or symptoms are present – all to avoid tragic outcomes for mom and/or baby. Using the call to action recommendations outlined from the meeting, it is the expectation of the consortium members that action steps will be identified to address the outlined priority recommendations and that an ongoing collaboration can be formed among partners to move preeclampsia biomarkers forward in the U.S. in the near future.

The consortium meeting included planned presentations from representatives of scientific, medical, patient, and regulatory organizations, followed by moderated discussions. The participants were then divided into workgroups that focused on a series of thematic questions and issues to identify concerns and mutual interests within the various communities present, with report back on direct calls to action within each of those communities.

Consortium Meeting Agenda

The meeting agenda to guide the day-long consortium meeting and its discussion was as follows:

I.   Outlined Purpose of Consortium Meeting
II.   Where We Are –The Status of Preeclampsia Biomarker Development for Screening and Diagnosis
III.   The Necessity of Preeclampsia Biomarkers – Health Consequences and Physician Decision Making
IV.   The Necessity of Preeclampsia Biomarkers –Data from A Patient Perspective
V.   FDA Approval and Collaboration: The Agency Perspective
VI.   Gaining Physician Acceptance
VII.   Breakout Discussions: Identification of Specific Challenges and Potential Solutions
      A. Patient Acceptance of Biomarkers
      B. Clinician Acceptance of Biomarkers
      C. Regulatory and Policy Barriers to Approval of Biomarkers
VIII. Report Back from Breakouts – Recommended Actions by Community

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. Those participating in this meeting were instructed to avoid discussion of competitively sensitive subjects, including confidential marketing, sales, and pricing information.

Overview of Biomarkers Consortium Presentations and Discussion

Where We Are – The Status of Preeclampsia Biomarker Development for Screening and Diagnosis *– By Ravi Thadhani, MD, MPH, Director of Clinical Research in Nephrology, Massachusetts General Hospital, Professor of Medicine, Harvard Medical School*

Understanding the Terminology

When seeking to understand what types of markers or evaluations can be most helpful in supporting clinician screening and diagnosis of preeclampsia, it is important to understand the terminology and reflect on how efforts can be most constructive in supporting clinician management of preeclampsia risk and the onset of the condition. The following is meant to break down the terms.

Biological Marker (Biomarker) – A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a diagnostic and/or therapeutic intervention (NIH Biomarkers Definitions Workgroup, 2001). For example, liver function tests, platelet counts, and serum creatinine would be examples of biomarkers that are used in the diagnosis of preeclampsia.

Surrogate Endpoint – A biomarker intended to substitute for a clinical endpoint. A clinical investigator uses epidemiologic, therapeutic, pathophysiologic, or other scientific evidence to select a surrogate endpoint that is expected to predict clinical benefit, harm, or lack of benefit or harm. Examples in this category for preeclampsia are being worked on extensively, and while not definitively proven, may include uric acid, soluble Flt-1, and/or PlGF.

Clinical Endpoint – A characteristic or variable that reflects how a patient feels or functions, or how a patient survives. For example, clinical endpoints that could be used in preeclampsia include cerebral or visual symptoms.

A biomarker can be a surrogate, but does not have to be. It must provide objective measurement and provide an indication of normal response, pathologic response, or response to intervention. The community interested in development of new preeclampsia biomarkers must clearly distinguish between biological markers and surrogate endpoints for purposes of credibility and understanding within the clinician community.

A surrogate is a laboratory value or a physical sign (e.g., cholesterol, blood pressure) used in therapeutic trials as a substitute for a clinically meaningful endpoint. It is a direct measure of how a patient feels, functions, or survives, and can predict the effect of therapy. To be effective, a surrogate must be reproducible and easy to perform. Not all biomarkers are surrogates.

Clinicians may consider using a surrogate marker because otherwise hard endpoints require large, long and more expensive trials. Surrogate markers can be most helpful when addressing aggressive diseases and when no effective therapies typically exist.

The Need for Preeclampsia Biomarkers Today

The current risk factors used by clinicians (in the absence of new biomarkers), including elevated blood pressure and proteinuria to assess for preeclampsia, only identify some cases of preeclampsia.

There are many false positives, and current risk factors are not typically enough to guide a clinician toward a care management plan.

When considering the need for a preeclampsia biomarker, one should consider the various stages of preeclampsia development and where a marker can have the greatest effect:
- EARLY = Screening/Risk Stratification
- NEAR/APPROACHING DISEASE = Prediction and Diagnosis
- AT TIME OF DISEASE = Prognostication of adverse outcomes

Focus Needed – Learn from Other Biomarker Experiences

One example for development of preeclampsia-related biomarkers is the development of Troponin for myocardial infarction (MI) diagnosis. Like preeclampsia, MI offered non-specific symptoms, and non-specific or varied test readings (false positives and false negatives) but yet the strong need for timely diagnosis, prognostication, and an understanding of what type of patient would benefit from an intervention and at what point in their care that intervention is most beneficial.

Troponin took 20 years to come fully into practice from the initial development phase to the production of clinical guidelines for mandatory use. Development followed a certain trajectory:
- Robust assays needed to run tests
- Medical and economic utility research needed
- Clinical management guidelines released

The tipping point for movement forward with development of Troponin included a number of successful clinical trials to validate it as a surrogate marker. Troponin was approved as a 510k device and in 2012, 20 years after approval, became integral in the diagnosis and management of MI in patients.

When evaluating preeclampsia as a candidate for a surrogate or other type of marker, one should reflect on whether the clinical community already has a number of successful clinical trials to validate a surrogate (e.g., use of low dose aspirin in women at high risk of preeclampsia). We should also consider the types of biomarker approaches that are currently in play or being developed and how those can help support a more defined marker. These include and may not be limited to:
- Protein
- Proteome
- Metabolite
- Metabolome
- Gene
- Genome
- MiRNA
- New Analytic Techniques

The Necessity of Preeclampsia Biomarkers – Health Consequences and Physician Decision Making *– By James N. Martin, Jr., MD, Immediate Past President, American Congress of Obstetricians and Gynecologists (ACOG), Chief of Maternal-Fetal Medicine, University of Mississippi Medical Center*

Incidence Rising
The incidence of preeclampsia within the U.S. is around three percent of pregnancies on average; however, some tertiary centers see the incidence at far greater rates as high as 10 percent of pregnancies. Prevalence is tied to a whole host of other health issues including obesity, diabetes mellitus, multiple births, increased maternal age, lack of prenatal care, and racial health disparities (particularly among the African American female population). The overall increase in the incidence of preeclampsia by 25 percent over the last two decades may also be attributed to better data collection efforts that capture statistics on preeclampsia incidence and outcomes.

Preeclampsia is the leading cause of maternal mortality in many countries across the world. In the United States, hypertensive disorders of pregnancy are responsible for approximately 17% of maternal mortality.

Preeclampsia is also the leading cause of maternal morbidity. It is estimated that for every death, there are 10-50 near misses, where negative outcomes fell just short of death but with dire consequences for the mother and baby. Preeclampsia is the leading reason for pre-term births, which come with significant health and economic consequences.

Preeclampsia has also been identified through research and clinical practice to be a signal for patient risk of cardiovascular disease, so we are just starting to understand as a medical community that preeclampsia also impacts future survival. Mothers who experienced preeclampsia, even if they had a healthy pregnancy outcome, have a higher risk of hypertension that persists, as well as higher death rates from cardiovascular issues. A woman's individual risk ranges from two to eight times higher, depending on factors such as the severity of her preeclampsia, its recurrence, and if the baby suffered from growth restriction..

Clinical Management Challenges
Preeclampsia is recognized by most healthcare providers as a "syndromic condition," since it can present differently in every woman and is characterized by a series of events or pregnancy challenges. The placenta is the root of the problem, and with its removal, after delivery recovery begins. Most women do not have obvious risk factors for preeclampsia and some women never show patient-identifiable signs of having preeclampsia during pregnancy. Given this, many times preeclampsia is a surprise diagnosis that causes unexpected emergency clinical situations as a pregnancy continues or even in the immediate postpartum period. In the absence of an objective biomarker or set of biomarkers it can be impossible to screen or sometimes extremely difficult to diagnose preeclampsia. Preeclampsia should be considered to be like an iceberg. Clinicians can see the tip of it clinically, but they do not see all the underpinnings of it in most patients in the absence of biomarker tests.

In the fall of 2013, the American College of Obstetricians and Gynecologists (ACOG) produced new recommendations on the diagnosis and management of preeclampsia that differ somewhat from past clinical recommendations. These markers will be slightly adjusted from the traditional health signs and symptoms used to date, including hypertension and proteinuria. For example, the new recommendations do not include proteinuria as a lead, required marker with new-onset hypertension

in recognition of the syndromic nature of the disease. ACOG recommends that proteinuria OR one of several indicators of maternal compromise be considered to indicate the presence of preeclampsia. Such evidence, when linked with hypertension, may include: mild thrombocytopenia, renal insufficiency (liver or kidney concerns), cardiopulmonary edema, or cerebral or visual disturbances. ACOG no longer make reference to the "mild" classification of preeclampsia, given that research shows that any form of preeclampsia has the potential to have consequences of maternal and infant morbidity and mortality and should be treated as such. Preeclampsia can fulminate from mild to severe disease over a very short period of time, and differentiation of severe disease from mild disease remains a constant challenge particularly when linked to co-morbidities or if a clinician is managing early onset preeclampsia. To date, clinical symptoms, when assessed together, have been more predictive of maternal outcome than laboratory parameters. This is one area where a new biomarker may be able to help clinicians in making better determinations.

Pregnant women with vascular disease, chronic hypertension, connective tissue disorders, diabetes mellitus, or renal disease are at highest risk to develop preeclampsia, and clinicians have an extremely difficult time differentiating preeclampsia from their underlying diseases. A biomarker is also needed that could indicate risk for placental abruption from preeclampsia.

> **Clinical Tools Used to Evaluate Patients at Risk For or With Preeclampsia:**
> - Blood Pressure
> - Urinary Protein
> - Laboratory Tests (specify)
> - Ultrasound
> - Physical Findings
> - Impedance Cardiography
> - Seizure
> - Headache
> - Visual Problems
> - Epigastric Pain
> - GI Complaints
> - Excessive Edema

At this time, ACOG has not made any clinical recommendations on new biomarker screening or diagnostic tests. ACOG supports research and data that can offer demonstrated improvement in maternal-fetal outcomes. There is a need for prospective clinical trials of preeclampsia-related markers. ACOG needs and wants to see that use of a new marker will positively impact care. To move forward in support of new biomarker tests for preeclampsia screening or diagnosis, ACOG would require the following:

- Properly designed and undertaken clinical investigations showing that a biomarker has high likelihood ratio[3] (LR) > 10 for a positive result and a very low LR < 0.2 for a negative result, with
- Documentation of improved maternal/perinatal outcomes, lower healthcare-associated costs, and a clear benefit to provide "best care" that is verified by multiple investigators.

Patient and Family Challenges
For every maternal death related to preeclampsia in the U.S., it is estimated that there are 50 mothers who suffer major life-threatening morbidities that stop short of death.

Research Challenges
Despite decades of research investment in both the public and private sectors and throughout the globe, the specific etiology of preeclampsia and its complete pathogenesis remain unknown. More

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[3] Likelihood ratios (LRs) are one of the best measures of diagnostic accuracy. Likelihood ratios of any clinical finding is the probability of that finding in patients with disease divided by the probability of the same finding in patients without the disease. The bigger the LR, the more certain the findings suggest that disease. Positive LRs increase probability and negative LRs decrease it.

research is needed to determine whether there is a clear association with disease presence, its severity and progression and changes in pro-angiogenic and anti-angiogenic biomarkers.

Preeclampsia and other hypertensive disorders of pregnancy remain among the most understudied and underfunded research areas as compared with other diseases in terms of disability-adjusted life years.

Economic Effect
The cost in dollars and cents of pregnancy hypertensive disorders is so great that improved management of pregnancies and the application of treatment would lead to large healthcare savings. This is largely because a major contributing factor to prematurity is preterm preeclampsia, eclampsia, HELLP syndrome and other related hypertensive complications in pregnancy that frequently require very early delivery and intensive care.

Inconsistent, inadequate, and sometimes inappropriate care of pregnant women with preeclampsia is a recurring cause of medical liability actions in the U.S.

Second or additional pregnancies following a pregnancy with preeclampsia constitute a further need for a biomarker test to assess risk and manage pregnancy health.

Possible Biomarker Options – Prediction/Screening, Prognostic or Diagnosis
To have clinical utility, even the most reliable prediction test must have one or both of the following:
- Associated effective preventive approaches and therapeutic interventions; and/or
- Demonstrated improved maternal or fetal outcomes after close follow-up indicated by the positive prediction test versus no test/no intervention. Such tests must be considered for their sensitivity and specificity so that there are not too many false positive test results that could lead to a higher risk pathway.

Potential applications of predictive/screening markers include:
- Follow the effect of preeclampsia management
- Predict fetal risk potential from preeclampsia
- Develop a marker for potential future cardiovascular disease risk
- Develop a marker for maternal morbidity
- Develop a marker for potential HELLP Syndrome risk
- Establish an index for placental health and risk of abruption
- Develop a marker to predict risk potential for eclampsia or stroke in the patient with preeclampsia
- Identify the patient at risk for postpartum preeclampsia/eclampsia/stroke/cerebral hemorrhage in the absence of evidence for preeclampsia during the intrapartum period

What Is Needed in a Biomarker Test Today
- A test or panel of tests with high positive and very low negative likelihood ratios.
- A test or panel of tests that apply to a multitude of various clinical scenarios concerning patient health condition, age, ethnicity, and other concurrent health indications
- Large prospective trials evaluating the clinical utility of the biomarker(s)
- A demonstration of improved maternal/fetal outcomes with utilization

The Necessity of Preeclampsia Biomarkers – Data from the Patient Perspectives Survey *– By Ms.
Caryn Rogers, Senior Science Writer, Preeclampsia Foundation*

Background – Understanding of Patient Values and Beliefs
In 2012, the Preeclampsia Foundation sought to better understand patient values and preferences
when it comes to screening and diagnosing preeclampsia. Conducting a survey of women throughout
the U.S., the Foundation's survey aimed to assess whether women who have been pregnant since
1990 (both those who have had preeclampsia and those who have not) desire a way to screen for
preeclampsia early in pregnancy, and if so, how a test might change their healthcare decisions. The
survey also explored whether women find current diagnostic methods for preeclampsia adequate.

Results
Of the 1,065 women who responded to the voluntary survey, 953 were from the United States,
representing nearly every state. 62 percent had a history of preeclampsia (affected), leaving a
substantial number of unaffected controls. Those with a history of preeclampsia were queried for
additional pregnancy complications that could further group them into more and less severely
affected populations. The survey also sought to understand the backgrounds of the respondents,
including their age, race and ethnicity, religion, education level, past parity; and number of living
children. Values-based questions were framed both positively and negatively.

Diagnostic Tests
Questions sought patients' attitudes about the adequacy of current diagnostic methods and the degree
of importance of a biomarker diagnostic test (e.g., would patient be willing to pay out-of-pocket
fees). There was a statistically significant difference ($p<.001$) between the views of affected and
unaffected women on the adequacy of current diagnostic tests with affected women indicating lack
of confidence in current methods of diagnosis; however, a majority of both populations reported a
willingness to pay out-of-pocket for a better test.

Screening/Prediction Tests
Affected and unaffected were consistent in their desire to take a screening test for preeclampsia early
in pregnancy. The majority of affected women believe they would have managed a previous
pregnancy differently with predictive information from a screening test, whereas the majority of
unaffected women responded that they they would not have made different choices in relation to
pregnancy management. Presumably this is because the unaffected population had normal
pregnancies and a screening test would have indicated likewise. That said, neither group anticipated
being more relaxed about their prenatal care if a test indicated they were at low risk for developing
preeclampsia. This suggests that a test would not cause harm by discouraging women from obtaining
routine prenatal care. Neither group believed test results would add to their anxiety. Both groups
strongly disagreed with the idea that a predictive test was of no use, despite there being no cure for
preeclampsia.

Conclusions
Women, particularly those with a history of preeclampsia, want screening and diagnostic tests for
preeclampsia so they/their loved ones can better evaluate their health situation and make care
decisions. The majority of unaffected women valued screening and diagnostic tests for preeclampsia,
though those with a history of complications more so. While women with no history of preeclampsia
did not think their care plans in prior pregnancies would have changed in response to a preeclampsia
test, presumably the test would have predicted a normal pregnancy sequence.

FDA Approval and Collaboration: The Agency Perspective *– By Alberto Gutierrez, Ph.D.,*
Director, Office of In Vitro Diagnostics and Radiological Health, U.S. Food and Drug
Administration

Types of Tests and FDA Oversight
Dr. Gutierrez presented that the FDA sees preeclampsia as an area where there is a "huge clinical need" for new tests. The FDA would like to see more companies getting into this space and tackling the different areas where a diagnostic could be very useful for patients and clinicians, and the agency wants to be helpful in making sure there is a smooth path to market.

The FDA representatives emphasized that in thinking through potential markers for preeclampsia, descriptive language about the type of marker(s) sought is critically important. The community must be clear on whether it seeks a diagnostic, a prognostic (i.e., risk of future development of preeclampsia), or a screening marker(s).

FDA Classifications of Devices
The FDA assesses biomarker tests intended for clinical use as devices, based on specific classifications. A "Class I" device is considered low risk to a patient's health and well-being. A "Class II" device is considered moderate risk to a patient and requires additional regulatory oversight. "Special controls," or specific device related requirements, can also accompany the Class II designation, such as performance data, labeling requirements, or surveillance. A "Class III" device is considered highest risk to the patient's health and well-being and must have premarket approval (PMA). The FDA conducts a manufacturing inspection before Class III devices go to market along with continued monitoring of clinical data. There are many more controls in place with a Class III device, making this more costly for a company. Also, unlike for Class I or II devices, the agency approves all device modifications for Class III devices.

Intended Use
The intended use of a laboratory test is the most critical factor to determining regulatory classification, which ultimately affects the device's regulatory pathway. The manufacturer's stated intended use tells the FDA how a device is intended to be used. One important factor in determining in vitro diagnostic device classification is the impact of undetected false negative and false positive results during patient testing. This information is helpful to understand because the FDA uses it to assess how crucial it is that the test work properly once on the market, and what types of controls are necessary to assure safety and effectiveness. For low risk tests, perhaps only manufacturing controls are necessary, while for high risk tests, close control over device modifications and manufacturing may be necessary.

Regulatory Pathway Options for Preeclampsia
To date, the FDA has considered the risk of premature delivery an area of high risk in relation to patient safety, and as a result, has previously classified assays for the prediction of preterm delivery as Class III. Any new device as intended to diagnose preterm delivery would be assessed to determine the impact of an incorrect result (e.g., the risk of patient mismanagement based on an undetected incorrect result), and whether it may also fall under a Class III category. Based on current patient management in clinical practice, misdiagnosis of preeclampsia (e.g., a false negative result that may lead to greater risk of maternal and infant mortality and morbidity) can have a significant impact on the patient, and these tests may be appropriately regulated as Class III. However, the classifications may vary between tests depending on their exact intended use (e.g., how they may be used in the (screening, diagnosis, or the prognosis of preeclampsia).

A mechanism does exist for manufacturers to justify that their novel test should be in a lower regulatory Class. Known as the "de novo" process, this pathway allows the agency to consider whether a device should be classified as Class I or Class II instead of Class III. Whether de novo is a legitimate option for a device's approval ultimately depends on the device's intended use and the clinical risks of an undetected false negative/false positive result, and whether those risks can be adequately mitigated by "special controls."

No matter which regulatory pathway is used, any new device for preeclampsia testing would likely be discussed in public in an FDA Advisory Meeting, in which a panel of experts could weigh in on the safety and effectiveness of the device submitted for FDA review.

Recommendations for Manufacturers on FDA Consideration
Any manufacturer planning to seek FDA approval for a new device intended to screen for or diagnose preeclampsia is strongly encouraged to(contact FDA early in the(development process for interactive discussion. The following should be described when contacting the FDA to discuss a new test to assess preeclampsia:

- What is the intended use of the device/test?
- What are the potential benefits and risks of the device?
- What possible risk mitigations did you consider?
- What is your proposed development path (e.g., studies to be conducted)?

Primary Regulatory Concerns by Manufacturers
There is a perception by manufacturers that the time needed to receive FDA approval creates lengthy, cumbersome, and sometimes extraordinarily costly delays. For small manufacturers in particular, the expense and time to get to market sometimes overrides the opportunity. This has resulted in manufacturers looking to pathways that to date have not required FDA approval, such as collaboration with clinical laboratories that currently do not undergo FDA review for the approval of laboratory developed tests. The following is an outline of expressed concerns from manufacturers on the U.S. regulatory approval system as it relates to moving forward with the review for preeclampsia screening and diagnostic devices:

- If a device is considered Class III, requiring Premarket Notification (PMA) status, many manufacturers (especially small manufacturers) may find the PMA approval too lengthy and expensive given their current financial investment.
- It is unclear whether the FDA would provide different risk categorizations for diagnostic tests versus screening tests; and if so, this could affect a manufacturer's decision for going forward.
- Large clinical databases exist around the world to support testing of various types of biomarkers for preeclampsia, yet there are perceived FDA limits or objections to using such non-U.S. data to assist manufacturers in their device approval process.

Gaining Physician Acceptance *– By Arun Jeyabalan, MD, Magee Women's Hospital, University of Pittsburgh School of Medicine, Associate Professor, Department of Obstetrics and Gynecology and Reproductive Science, Division of Maternal-Fetal Medicine, University of Pittsburgh*

The Physician Perspective
When we consider how to get physicians to accept new preeclampsia biomarkers, it is essential that we evaluate this through the eyes of the practicing community physician, namely a general practicing physician who does not have additional training in preeclampsia management. This could include general practice obstetricians, family physicians, or emergency room physicians.

Today, several biomarkers are already utilized by physicians to identify preeclampsia, including: routine laboratory data (e.g., substances in blood, urine), ultrasound characteristics, or a combination of these markers. Given that preeclampsia is a syndrome, spanning a wide spectrum of clinical features, much of the diagnostic criteria used today is just a description of the clinical features of a patient. Many physicians recognize that new markers could help with early prediction or risk stratification, clearer diagnosis, and more effective therapeutic interventions. Physicians are looking for: (1) a good test that is clinically useful and that impacts management (usually for the better); (2) a test that is practical in its use; (3) a test that has gained endorsement by governing professional organizations and societies; and (4) a test that has limited medical-legal implications.

Clinically Useful and Practical Tests
To gain physician acceptance, a test must not only be good from the perspective of its sensitivity and specificity, but its performance must be precise at the individual patient level. A test should have clear positive predictive valuations: a probability that the outcome is present when the test is positive, and negative predictive valuations: a probability that the outcome is absent when the test is negative. Current tests used to diagnose preeclampsia do not rely on predictive valuations but rather sensitivity and specificity. The limitation here is that sensitivity and specificity do not predict the probability of an outcome.

Under ideal circumstances, physicians would seek a new test that could detect all cases of preeclampsia. However, obstetricians are very comfortable with tests that are not perfect, as they understand that patients are unique and there is rarely a one-size-fits-all approach to disease management. Some leading examples of tests that are not perfect, but have been very effective in identifying problems that can be paired with therapeutic interventions include tests to determine such things as the risk of preterm birth using fetal fibronectin. To ensure physician comfort with new tests, test manufacturers must go further than test development itself. Management strategies must be applied along with the tests, including outlined therapeutic interventions and preventative interventions so that physicians understand how testing can lead to improved management of a pregnant woman and her baby.

A good test must be accurate and reliable, but also reproducible. Most obstetricians desire clear guidelines to understand if a test is positive or negative and have it readily available. This is particularly vital in the third trimester of managing a woman with or suspected of having preeclampsia where testing could be needed not only in a tertiary care setting but also in a community hospital. Tests would also need to be easy to administer and allow for quick results. Tests would likewise need to be universally available and reasonable in cost. There would need to be clear recommendations on when to use the test and not to use the test and clear recommendations based on the results of the test to guide management.

Endorsement of Professional Organizations
Support of governing organizations is essential. This includes support for both use of new tests and support regarding the appropriate standard of care that accompanies use of the tests. To attain this support, strong prospective studies with large numbers of patients that support test characteristics and test performance in varied populations will be required. The governing bodies will need to provide clear guidance to practicing clinicians. Some tests take a long time to secure such endorsement and support from professional organizations, and we have examples in the field of some tests needing to have a stronger endorsement from an NIH Consensus Conference, for example, before physicians began to utilize a test regularly.

Medical-Legal Implications
It is challenging to move new tests forward in the field of obstetrics without addressing the medical/legal climate where obstetricians practice. The proportion of physicians facing medical malpractice claims annually show OB/GYN in the top 10. When a new test comes to market, there is risk to the manufacturers that produced it, but the individual practitioners that use the test face the greatest risk. The best way to mitigate risk is to ensure there are clear guidelines for the use of any new test, particularly for a syndromic disease like preeclampsia where there can be immense variation in the patient base and presentation of disease.

Outline of Identified Challenges and Areas for Focus – Workgroup Discussions

The following is an outline of the primary perceived and actual barriers that communities of interest believe will affect the advancement of preeclampsia biomarkers at this time. Barriers are broken down into three key groups: patient acceptance; clinician acceptance; and regulatory and policy hurdles. The barriers identified have been considered and were utilized to outline a call to action in order to proactively address these barriers.

Patient Acceptance of Preeclampsia Biomarkers
- Patient education on the frequency and severity of preeclampsia during pregnancy and postpartum is lacking, along with the long-term health consequences of the disease.
- The costs associated with obtaining additional testing during pregnancy that may not be covered through insurance generate concern about affordability and subsequent access to uncovered tests.

Clinician Acceptance of Preeclampsia Biomarkers
- No randomized controlled trials currently exist to demonstrate the utility of preeclampsia biomarker tests.
- Provider awareness over how biomarkers can improve screening and diagnosis, and reliability of patient care decision-making is not universal and needs to be expanded.
- Professional provider associations have not yet issued guidelines or recommendations on use of biomarkers in place of, or in tandem with, traditional markers for preeclampsia screening and diagnosis (e.g., how to use the tests and under what circumstances).

Regulatory and Policy Barriers to Approval of Preeclampsia Biomarkers by Agency
- (FDA) Lack of a predicate device to use for approval of new biomarker tests.
- (FDA) No clear delineation between risk assessments for screening versus diagnostic tests.
- (FDA) Complexity of device approval process and time delay in moving through the process.
- (FDA) Lack of fair consideration for international data and biobank samples in the establishment of clinical data to support biomarker applications.
- (NIH and AHRQ) Reduced investment in research on preeclampsia and related clinical trials.

Outline of Consensus Items and Priorities
- Preeclampsia is a relatively common serious disease/syndrome of pregnancy, but health outcomes for both mom and infant are frequently negatively affected by the absence of accurate pathophysiological biomarkers that could be used to better inform clinical decision-making.
- The current diagnostic criteria used to identify preeclampsia in a pregnant woman can frequently cause both false positives and false negatives. False positives can misclassify pregnant women as having preeclampsia when they might have a benign or an otherwise serious condition requiring a different clinical protocol, often leading to unnecessary delivery of a premature baby. False negatives can cause missed detection altogether, increasing the risk for adverse pregnancy outcomes to both mother and baby.
- Current management of preeclampsia by clinicians requires the attending clinician to interpret multiple, unspecified criteria to inform decision-making. These markers have not evolved to any great extent since 1998 when advanced by the National Blood Pressure Education Program and ACOG. These markers are non-specific, have arbitrary thresholds,

do not predict adverse outcomes on their own, and measurement methods to evaluate results can be inaccurate.

- Current markers do not accurately assess the severity of preeclampsia or provide insight on the timing of and need for clinical intervention. These markers do not accurately stratify health risk or predict the speed of preeclampsia progression.
- Negative maternal and infant health outcomes due to preeclampsia lead to significant healthcare costs that could potentially be averted through the development and consistent use of accurate preeclampsia screening and diagnostic biomarker tests.
- The threshold for approval of a new screening or diagnostic biomarker test for preeclampsia by the U.S. Food and Drug Administration remains unclear (e.g., 510k or PMA), or possibly unattainable. Questions exist as to how a new test for preeclampsia should be evaluated and validated, and what clinical research data can be used to support regulatory acceptance.

Appendix B

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