Preeclampsia risk stratification early in pregnancy: Conversion of a promising metabolomics discovery into a LC-MS based clinical assay.

Liz Bond1, Charline Lenaerts2, Christopher Benton3, Phil Baker4, Louise Kenny5, Robin Tuytten1

1Metabolomic Diagnostics, Little Island, Cork, Ireland
2Lab. of Pharmaceutical Analysis, Faculty of Medicine & Pharmacy, University of Mons, Belgium
3Agilent Technologies, Life Sciences & Chemical Analysis Group, Stockport, UK
4Gravida: National Centre for Growth and Development, The University of Auckland, New Zealand
5The Irish Centre for Fetal and Neonatal Translational Research, Cork University Maternity Hospital, Cork, Ireland

Short Abstract (fewer than 100 words)

Basic metabolomics research has uncovered that combinations of blood borne metabolites can risk-stratify women early in pregnancy according to their risk of developing pre-eclampsia later in their pregnancy. Since then, a company has been established which is dedicated to translating this finding into a tool for health care providers and pregnant women. A targeted approach is being developed whereby ca. 40 metabolites are (semi-) quantified using liquid chromatography-tandem mass spectrometry. An update on the method development progress as well as an overview of the clinical studies lined-up to verify and validate the pre-eclampsia risk stratification test will be discussed.

Long Abstract

For the many discovery studies published heralding novel biomarkers with potential clinical utility, only a handful are further pursued for translation into a diagnostic product. It is only when putative biomarkers are further credentialed and developed into commercial assays that health care providers, patient and the society at large benefit from the investments made in funding biomarker discovery research.

Expediting biomarker discovery findings requires co-evolution of test format refinement, analytical validation, clinical qualification, regulation as well as the appropriate patient cohorts in support of these tasks.

Here we report on the progress made in migrating the discovery finding that specific combinations of blood-borne metabolite biomarkers can risk-stratify pregnant women early in pregnancy (~15 weeks) according to their risk to develop pre-eclampsia during the remainder of their pregnancy into a commercial LC-MS based clinical assay.

The original biomarker discovery study relied on metabolite profiling using Ultra-Performance Liquid Chromatography (UPLC) with High Resolution Mass Spectrometry. To accommodate the large install base of quadrupole mass spectrometers (QqQ-MS) in clinical laboratories world-wide, a platform migration was performed. A single step metabolite extraction and a targeted LC-QqQ–MS approach using stable isotope labelled metabolites for relative quantification has been developed. Herewith, the (semi-) quantitative analysis of circa 40 metabolites with very disparate physicochemical characteristics is achievable in a single run. Performance metrics derived from pre-validation study results will also be discussed.
In order to support both the further refinement of the metabolites-based pre-eclampsia prediction algorithm and the subsequent technical and clinical validation of the test, access to appropriate patient samples collected in dedicated prospective cohorts is warranted. As pre-eclampsia affects only about 1 in 20 (first) pregnancies, large cohorts are warranted.

Public-private partnerships wherein supranational government funders, clinicians and dedicated small and medium size companies collaborate on the establishment of the requisite sample biobanks is proving a cost-efficient way to enable both additional basic biomarker research and progressing biomarkers to market. Metabolomic Diagnostics is therefore an active collaborator\(^2\) and partner\(^3\) of 2 large scale international prospectively collections of first-time pregnancy biobanks, i.e. SCreening fOr Pregnancy Endpoints (SCOPE\(^2\)) and IMproved Pregnancy Outcomes by Early Detection (IMPROvED\(^3\)). Sample contributions and the roles of the respective biobanks towards the product development path of Metabolomic Diagnostics pre-eclampsia risk stratification product will be outlined.

