Institution: King's College London		
Unit of Assessment: 3		
Title of case study: Biomarkers and tools to enable personalised care and improve outcomes in high risk pregnancy		
Period when the underpinning research was undertaken: 2010-2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Lucy Chappell Laura Magee Kypros Nicolaides Caroline Ovadia Liona Poon Lucilla Poston Jane Sandall Andrew Shennan Rachel Tribe Peter von Dadelszen Catherine Williamson	NIHR Professor Professor Professor Chadburn Lecturer Professor Professor Professor Professor Professor Professor Professor	2006 - ongoing 2017 - ongoing 1991 - ongoing 2014 - ongoing 2013 - ongoing 1987 - ongoing 2000 - ongoing 1998 - ongoing 1995 - ongoing 2017 - ongoing 2013 - ongoing
Period when the claimed impact occurred: 1 Aug 2013-2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Reduction of maternal mortality and stillbirth are national and international priorities. Globally, more than 10% of maternal and fetal morbidity/mortality is caused by spontaneous preterm birth (PTB), pre-eclampsia, and intrahepatic cholestasis of pregnancy (ICP). Practice-changing King's-led research developed diagnostic markers and tools to improve stratification and care pathways of pregnant women according to risk. The impact has been disseminated globally to pregnant women via our international reach, collaborations with charities, health policies and the media. The research has influenced national and international guidelines, changed clinical practice and informed management.

2. Underpinning research

There is an unmet meet need for strategies to identify women and babies at risk of serious complications of pregnancy. The most common gestational disorders, affecting approximately 130,000 UK births annually (20,000,000 globally), are preterm birth (PTB; 6-8%), hypertension/preeclampsia (10%) and intrahepatic cholestasis of pregnancy (ICP; 0.5-1%). Since 2010, King's academics have conducted research that has advanced understanding of the underlying causes of these disorders, and led to new ways of identifying high risk women who will benefit from specific care pathways or treatments, and models of care.

Spontaneous preterm birth globally causes over 1 million deaths annually. King's researchers established an evidence-based clinic at Guy's and St Thomas' NHS Trust in 2004 for women at risk of prematurity – since emulated nationally; research centred on this clinic has led to new tests for prediction and management of PTB. These tests include quantification of cervico-vaginal fetal fibronectin (released when the fetal sac detaches from the uterine lining) and measurement of cervical length (which shortens prior to preterm labour). King's researchers combined these tests with maternal history to create an algorithm that provides a high-performing rule in/out test for PTB **(1)**. Now incorporated into a web and smart phone-based App (QUIPP; NHS App of the Year Commendation 2018), this algorithm is widely used to guide clinical management. We showed that 92% of women found the App provided understanding and reassurance and 95% found the score helpful; and that clinicians found it accessible and acceptable for triage, improving their confidence and changing their perception of risk . Treatments

developed by King's include the insertion of an abdominal stitch at the base of the womb to reduce PTB, where clinicians need to treat just 5 women to save a baby's life **(2)**.

Pre-eclampsia affects ~3% of pregnant women. Pre-eclampsia was traditionally diagnosed by raised blood pressure and the presence of urinary protein, but neither are adequately specific to enable accurate diagnosis. King's-led research demonstrated in NHS patients that a low value of a biomarker of placental dysfunction, placental growth factor (PlGF), is associated with pre-eclampsia; and when combined with clinical history, blood pressure and ultrasound, it can accurately predict in early pregnancy those women that will subsequently develop pre-eclampsia (early PlGF research was included as a REF2014 case study). A national King's-led trial then showed that PlGF measurement in high-risk women reduced the time to diagnosis and maternal complications of pre-eclampsia **(3)**. Furthermore, a King's-led European trial showed that treatment with aspirin following risk assessment with an algorithm including PlGF reduced the incidence of early-onset pre-eclampsia by 80% **(4)**. In a global health setting, King's researchers developed and validated a robust blood pressure monitor with a novel traffic light alert system (CRADLE VSA) that reduced maternal mortality by >50% in Sierra Leone **(5)**.

Intrahepatic cholestasis of pregnancy is the most common liver disorder of pregnancy. Using international datasets, King's researchers established that maternal serum bile acid concentrations above a specific threshold can identify women at increased risk of stillbirth **(6)**, providing much needed evidence for making decisions about timing of delivery to avoid this devastating complication. From 2013-2019, King's researchers led an NIHR-funded ICP whole genome sequencing study that identified pathological mutations in liver transporter genes (ABCB4/ABCB11) in 20% of women with pregnancy cholestasis **(7)**.

3. References to the research (indicative maximum of six references)

1. Watson HA, Seed PT, Carter J, et al. (2020). *Development and validation of predictive models for QUiPP App v.2: tool for predicting preterm birth in asymptomatic high-risk women.* Ultrasound Obstet Gynecol. 55(3):348-356. doi:10.1002/uog.20401

2. Shennan A, Chandiramani M, Bennett P, David AL, Girling J, Ridout A, Seed PT, Simpson N, Thornton S, Tydeman G, Quenby S, Carter J. (2020). *MAVRIC: a multicenter randomized controlled trial of transabdominal vs transvaginal cervical cerclage.* Am J Obstet Gynecol. 222(3):261.e1-261.e9. doi: 10.1016/j.ajog.2019.09.040. PMID: 31585096

3. Duhig KE, Myers J, Seed PT, Sparkes J, Lowe J, Hunter RM, Shennan AH, Chappell LC; PARROT trial group. (2019). *Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial.* Lancet. pii: S0140-6736(18)33212-4. doi: 10.1016/S0140-6736(18)33212-4. PMID: 30948284

4. Rolnik DL, Wright D, Poon LC, …Nicolaides KH. (2017). *Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia.* N Engl J Med. 377(7):613-622. doi: 10.1056/NEJMoa1704559. PMID: 28657417

5. Vousden N, Lawley E, Nathan HL, Seed PT, Gidiri MF, Goudar S, Sandall J, Chappell LC, Shennan AH; CRADLE Trial Collaborative Group. (2019). *Effect of a novel vital sign device on maternal mortality and morbidity in low-resource settings: a pragmatic, stepped-wedge, cluster-randomised controlled trial.* Lancet Global Health; 7(3):e347-e356. doi: 10.1016/S2214-109X(18)30526-6. PMID: 30784635

6. Ovadia C, … Chappell LC*, Williamson C*. (2019). *Adverse perinatal outcomes of intrahepatic cholestasis of pregnancy and association with biochemical markers: results of aggregate and independent patient data meta-analyses.* Lancet. 393(10174): 899-909. Doi: 10.1016/S0140-6736(18)31877-4. PMID: 30773280.

7. Turro E, …Williamson C, …Raymond FL, Ouwehand WH. (2020). *Whole-genome sequencing of patients with rare diseases in a national health system.* Nature. 583(7814):96-102. doi: 10.1038/s41586-020-2434-2. PMID: 32581362.

4. Details of the impact (indicative maximum 750 words)

King's-led research has informed national and international policy and guidelines on high risk pregnancy, thereby influencing the clinical management strategies of >8,000 obstetricians and ~45,000 midwives in the UK (and >1,500,000 practitioners globally).

Public policy

Preterm birth: The specialist clinic model developed at Guys and St Thomas' NHS Trust was recommended for roll-out in NHS England's Saving Babies Lives Care Bundle (V2; 2019) **[A.1]**, now rapidly being adopted (currently 50 UK clinics and expanding). The clinic provided the basis of the UK PTB Clinical Network and Research database **[A.2]** (> 29 UK and international contributing clinics), a forum for clinicians, scientists, and researchers committed to improving the care of women and babies at risk of preterm birth. The UK PTB Network and King's research influenced guidance for UK commissioners **[A.3]**, led to a Department of Health report recommending a reduction preterm birth from 8% to 6% by 2025, and was instrumental in creating and writing guidance for NHS England **[A.4]**. The prediction tests and intervention strategies we developed and validated have all been incorporated into National guidance **[A.5-7]**. Additionally, we contributed to the WHO guideline group on PTB **[A.8]**. The Tommy's National Centre for Maternity Improvement is integrating the QUIPP App into a new digital tool for rapid implementation in NHS practice **[A.9]**.

Pre-eclampsia: King's research providing evidence for PlGF testing was incorporated into the 2016 and 2019 NICE guidelines, **[B.1-2]**, and in the 2020 International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines **[B.3]**. NHS England supported widespread implementation of the test (2019) through the Accelerated Access Collaborative and Innovation Technology Payment programmes **[B.4]**, the NHS Directory for general public access **[B.5]** and the NHS England MedTech Funding Mandate policy 2021/22 **[B.6]**. Following demonstration of PlGF efficacy in Mozambique, the government introduced PlGF screening as a national policy **[B.7]**. Early aspirin treatment for prevention of pre-eclampsia in high-risk women has been incorporated into International Federation of Gynecology and Obstetrics (FIGO] (2019) and ISSHP 2020 guidelines **[C.1-2]** and the NHS England Saving Babies lives care bundle V2 **[C.3]** and NICE guidelines 2019 **[C.4]**. The Sierra Leone Government has deployed 3,000 CRADLE VSA devices across its health system **[D.1-3]**; the VSA was awarded the Inaugural Newton Prize for excellence in research and innovation in support of economic development and social welfare in less developed countries (2017) **[D.4]**, and was amongst the top 30 high impact innovations in global health (PATH-led Award 2015) **[D.5]**. It has also been recommended for roll-out in refugee camps **[D.6-7]**.

Cholestasis: King's-generated evidence that serum bile acids are implicated in stillbirth is cited in the Society for Maternal and Fetal Medicine (USA) guideline **[E.1]**, the American Association for the Study of the Liver Practice Guideline **[E.2]** and in the pre-publication draft of the RCOG Obstetric Cholestasis guideline **[E.3]**. It influenced the newly released American College of Obstetrics and Gynaecology guidance **[E.4]** and was voted the most impactful paper of 2019 **(6)** by the North American Society of Obstetric Medicine **[E.5]**. Based on King's research a new NHS Genomic Medicine Service was approved (2019) for screening of women with ICP to identify those with mutations in hepatobiliary disease genes, and at risk of cirrhosis, gallstone pancreatitis or biliary malignancy; with relevance to ~750 women/year in the UK and their relatives **[E.6]**.

Health and Wellbeing

Impact on women's lives: King's-led biomarker research for high-risk pregnancy (preterm birth, pre-eclampsia and cholestasis) has had a marked influence on women's lives. The impact is demonstrated through testimonials from patients attending research-led clinics **[F.1-5]**. An example from feedback for the King's preterm birth clinic: *"We owe so much to Professor Shennan and his team at Tommy's Preterm Surveillance Clinic. Without their research and their care, my story would be so different".*

Impact through working with charities: King's research is made available to the public via charities, e.g. Tommy's charity, Action on Pre-eclampsia (APEC), The Preeclampsia Foundation (North America), ICP Support and the Borne Charity **[G.1-5]**. King's researchers also participate in Facebook sessions with patients via Tommy's; a video arising from a joint session with ICP Support reached 32,125 people within a week, and was viewed 5024 times **[G.6-8]**. The CEO of

Tommy's charity stated, *"We believe the work we have done with KCL researchers through the Tommy's Research Centre has had a major clinical impact to improve clinical care and education of women based on the research performed at KCL"* **[G.1]**.

Impact through training and teaching: Health and wellbeing has been improved via training informed by our research. Following recommendation for national roll-out of the preterm birth clinic model (National Maternity Ambition), we have held regular training sessions. Nicolaides and Williamson deliver webinars every 2-4 weeks (typically 10-12,000 registrants) that include education about King's research **[H.1]**. King's researchers regularly deliver research-based training (examples include **H.2-4**). For cholestasis, King's researchers validated the Royal College of Midwives (48,000 members) i-learn package on cholestasis, that used King's biomarker research to inform the education of midwives across the UK **[H.5]**.

Commercial

Kings biomarker research has benefited from strong and long-term commercial collaborations. We worked with HOLOGIC in development of the fetal fibronectin quantitative test **[I.1]**; the company have stated, "*your research has helped physicians … better manage their patients presenting with symptoms of preterm labour"*, and *"the test has become the gold-standard across both the UK and Australia…and many other countries including the USA"*, and with Mirvie to develop additional biomarkers for preterm birth prediction **[I.2]**. Research leading to the development of the cradle BSA device was in collaboration with MicroLife, and >35,000 have been made **[I.3]**. King's work on PlGF has been carried out over many years with the manufacturer of the test, Quidel (previously known as Alere) who commented: *"On behalf of Quidel I would personally like to thank the KCL team for making such an important contribution to pregnancy care"* **[I.4-5]**. King's cholestasis research influenced a main producer of the clinically-used bile acid assay, Diazyme, to alter their laboratory protocol such that testing should be performed to determine peak (prandial), rather than fasting, serum bile acid levels, a change proposed by affected women based on the research **[I.6-7]**.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[A]. Pre-term birth: The evidence in this bundle includes the national and international clinical practice guidelines that refer to King's research.

[B]. Pre-eclampsia: The evidence in this bundle demonstrates the adoption of PlGF-based testing in clinical practice, national/international guidelines, public policy and further impacts.

[C]. Pre-eclampsia: This bundle includes evidence of the impact of King's-led research on recommendations for use of aspirin treatment for pre-eclampsia prophylaxis in clinical practice, and in national/international guidelines.

[D]. Pre-eclampsia: This bundle includes evidence of the impact of the CRADLE VSA device in a Global Health context.

[E]. Cholestasis: This bundle includes evidence for the impact of King's cholestasis research on national/ international guidelines and on clinical practice.

[F]. Patient Testimonials: Evidence from patient testimonials to show the impact of King's research-led clinics on patient experiences.

[G]. Charities: This bundle provides evidence for the impact of King's research on the work of charities.

[H]. Education: This bundle provides evidence for the impact of King's-led research through research-orientated education of professionals in the UK and internationally.

[I]. Commercial: The evidence in this bundle shows the impact of King's research on commercial enterprises.