**Institution:** Plymouth University

**Unit of Assessment:**
1 (Clinical Medicine)

**Title of case study:** Improving screening during pregnancy

**1. Summary of the impact** (indicative maximum 100 words)

Research on risk assessment and screening led by Wright at Plymouth University and including clinical participants from the Centre for Fetal Medicine at King's College Hospital and Tübingen University, has improved fetal and maternal healthcare. This research and work supporting the Fetal Anomaly Screening Program (FASP) has contributed to reductions in the number of unnecessary invasive diagnosis procedures in the UK, and has improved screening performance through the implementation of the NHS-endorsed Down's syndrome screening Quality Assurance Support Service (DQASS). The research has also contributed to the risk algorithms of the Fetal Medicine Foundation (FMF) which are used by the NHS and national and international companies that provide technologies for the clinical management of pregnancies by identifying high-risk groups for chromosomal abnormalities and preeclampsia.

**2. Underpinning research** (indicative maximum 500 words)

Statistical research conducted by Wright (Professor of Applied Statistics at Plymouth University, 2006-present) with Amy Baker (Senior Research Fellow) and in association with clinical researchers established more realistic models for risk assessment of fetal anomalies and of preeclampsia. It also considered the way measurement errors of various components in risk assessment impacted on performance risk assessment and screening. This research raised the importance of quality assurance in laboratory and ultrasound measurements.

The body of research began in 2005 with an investigation into non-invasive screening for Trisomy 21 (T21), a form of Down's syndrome (DS), demonstrating that false positive rates are influenced by the extent to which factors such as smoking status are taken into account in the calculation of risk pre-diagnosis (1). Building on this earlier research, Wright et al. worked on understanding the effect of ubiquitously used Nuchal Translucency (NT) median values in relation to the performance of screening for T21. The research found that high quality screening is dependent on accurate measurement of NT for which there was wide regional variation (2), while further work in 2012 on the under/over estimation of Crown Rump Length in first trimester combined screening concluded that individual sonographer variability must be taken into account when calculating patient specific risk of chromosomal fetal abnormality (3).

Alongside this work, Wright introduced a mixture model for the distribution of NT in chromosomally normal and abnormal pregnancies. The model uniquely accounted for the fact that a minority subgroup of chromosomally abnormal pregnancies can present in the same way as the majority of chromosomally normal pregnancies. The mixture model was found to be compatible with clinical findings of the pathophysiology of increased NT in both chromosomally normal and abnormal fetuses, providing a more realistic method of assessing the risk of fetal abnormalities relative to other non-invasive screening models (4). Wright et al. validated the model in 2009, demonstrating that the new risk algorithm for T21 could achieve a 90% detection rate (for a 3% false-positive rate) when NT is used in combination with maternal age and the biochemical markers PAPP-A and free *β-hCG* (5). This combination of markers is now widely used as standard practice.

More recently Wright developed a competing risk survival model (3) that estimated the time of delivery (birth) in cases of maternal preeclampsia (PE). The work reflected some of the underlying principles and assumptions about existing risk models as demonstrated in his NT research. Based on a study of 1,426 PE pregnancies and 57,458 normal pregnancies, Wright combined maternal characteristics with data collected at 11-13 weeks gestation, namely uterine artery pulsatility index and mean arterial pressure. The research showed that treating the time of delivery with PE as a 'continuous variable', statistically dependent on characteristics such as maternal weight, ethnic origin and medical history, provided a more efficient and effective way of assessing risks during early pregnancy. Using the gestation at the time of delivery with PE meant that the model could capture the severity of the condition on a continuum rather than arbitrarily grouping into early and

late PE (which were formerly considered separate conditions with separate outcomes). This model for effective first-trimester screening for PE has recently been extended to include biochemical markers (6) and is undergoing validation for adoption.

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


1. **Nix, B., Wright*, D., Baker,* A. (2007) The impact of bias in MoM values on patient risk and screening performance for Down syndrome. Prenat Diagn; 27: 840–845.** *Prenatal Diagnosis* communicates peer-reviewed research in prenatal and pre-implantation diagnosis. The journal ranks 22nd of 78 in the ISI Journal Citation Reports Ranking (Obstetrics and Gyneacology, 2011), while its impact factor is 2.106.

2. Kagan, K.O., Wright*, D., Etchegaray, A., Zhou, Y., Nicolaides, K.H. (2009) Effect of deviation of nuchal translucency measurements on the performance of screening for trisomy 21. Ultrasound Obstet Gynecol; 33: 657-664. *Ultrasound in Obstetrics & Gynecology* is an international, peer-reviewed journal including original papers, case reports, reviews, opinion articles, and letters. The journal ranks 11th of 78 in the ISI Journal Citation Reports Ranking (Obstetrics and Gynaecology, 2011), while its impact factor is 3.007.

3. Kagan, K.O, Hoopmann, N., Baker,* A., Huebner, M., Abele, H., Wright*, D. (2012**) Impact of bias in crown–rump length measurement at first-trimester screening for trisomy 21. Ultrasound Obstet Gynecol; 40: 135–9.** *Ultrasound in Obstetrics & Gynecology* is an international, peer-reviewed journal including original papers, case reports, reviews, opinion articles, and letters. The journal ranks 11th of 78 in the ISI Journal Citation Reports Ranking (Obstetrics and Gynaecology, 2011), while its impact factor is 3.007.

4. Wright*, D, Kagan KO, Molina FS, Gazzoni A, Nicolaides KH. (2008) A mixture model of nuchal translucency thickness in screening for chromosomal defects. *Ultrasound Obstet Gynecol.* 31(4):376-83. *Ultrasound in Obstetrics & Gynecology* is an international, peer-reviewed journal including original papers, case reports, reviews, opinion articles, and letters. The journal ranks 11th of 78 in the ISI Journal Citation Reports Ranking (Obstetrics and Gynaecology, 2011), while its impact factor is 3.007.

5. Kagan KO, Etchegaray A, Zhou Y, Wright,* D, Nicolaides KH. (2010) Prospective validation of first-trimester combined screening for trisomy 21. *Ultrasound Obstet Gynecol.* 34(1):14-8. *Ultrasound in Obstetrics & Gynecology* is an international, peer-reviewed journal including original papers, case reports, reviews, opinion articles, and letters. The journal ranks 11th of 78 in the ISI Journal Citation Reports Ranking (Obstetrics and Gynaecology, 2011), while its impact factor is 3.007.

6. Akolekar R, Syngelaki A, Poon L, Wright,* D, Nicolaides KH. (2013) Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther.* 33(1):8-15. *Fetal Diagnosis and Therapy* presents original, peer reviewed, papers covering both basic research and clinical investigations into all aspects of fetal diagnosis leading to therapy, including relevant technical advances and procedures. The journal ranks 61st of 78 in the ISI Journal Citation Reports Ranking (Obstetrics and Gynaecology, 2011), while its impact factor is Impact factor: 1.05.


*Current Plymouth University staff. Other institutional affiliations at time of publication as follows:
Kings College Hospital: Akoleka, Ethchegarary, Gazzoni, Kagan, Nicolaides, Poon, Syngelaki, Zhou, Molina (also Tübingen University).
Tübingen University: Abele, Hoopmann, Huebner.
Cardiff University: Nix .

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

Wright's research on screening for fetal anomalies and health conditions during pregnancy has improved international healthcare provision. In 2004 Wright was commissioned by UK (NHS) Fetal

Anomaly Screening Programme to develop-implement a quality assurance tool for DS screening in the UK, based on his NT and combined test research. As a result Wright formed, and currently leads, DQASS. DQASS provides support for screening laboratories and sonographers in all UK NHS hospitals, which are now required to submit screening information and data to the Service according to its national schedule. The analysis of this data focuses on identifying NT measurements that are greater than expected (red flags - implying unacceptable bias in sonographer performance), prompting the implementation of an action plan aimed at improving sonographer performance: as recommended by FASP/DQASS, practitioners are required to complete 25 supervised NT measurements in addition to three accurate paired NT and CRL measurements against the set UK standards. Upon successful completion of these tasks, the sonographer is permitted to return to independent practice.

Through DQASS, Wright's research has contributed to the improvement in the efficacy of fetal anomaly screening in the UK NHS by enhancing the quality of laboratory and sonographer practice, which has in turn contributed towards a reduction in the number of women proceeding to invasive testing where there is risk of fetal loss. Working with Wright, the FASP established eight regional ultrasound coordinators tasked with coordinating the recommended quality improvements and some 200 screening support sonographers at hospitals throughout the UK to disseminate information (specifically red flags) provided by DQASS. A series of regional workshops were also held between 2006 and 2010 on standardising and modernising practice, engaging over 2,000 sonographers and healthcare workers in obstetrics and gynaecology, representing 30 NHS laboratories.

As a result, UK DS screening performance has significantly improved. In 2003, 36,968 invasive tests for suspected fetal anomaly were carried out in the UK, whereas in 2009 only 13,595 were performed. This represents a reduction of 63% in the previous over-investigation of chromosomal abnormality, translating to 233 miscarriages avoided (based on a 1:100 invasive-test-linked miscarriage rate) (source: ACC, 2013). As stated in a joint letter from Annette McHugh, Programme Manager for FASP, and Val Armstrong, Deputy QA Lead (National), "Both the improvement in the performance of the [Down's Syndrome screening] test and the development of new strategies has been supported by the work undertaken by [Wright], contributing to the decreasing requirement for women to undergo unnecessary invasive testing.

Wrights work with DQASS has also influenced screening programmes in other countries. In Ontario, Canada, for example, it has been recognised that accurate NT measurement is fundamental in DS screening, as the Director of its national quality assurance agency, BORN, states: "I am submitting a letter of thanks to Prof. Dave Wright and the DQASS team for their support in our efforts to implement a quality assurance programme for NT ultrasound in Ontario, he has provided technical and statistical support, advice and credibility [to the Ontario QA programme] … the partnership with Wright and DQASS has been invaluable in this project… we can only hope to achieve the same results Wright has enabled across the UK".

Wright's research has also improved screening in private sector healthcare worldwide: the FMF is a global charity aiming to improve the health of pregnant women through research and training to support professional groups and certified obstetricians. Historically, the FMF supplied these groups with NT risk algorithms for a range of anomalies using the Delta method, based on a singular distribution of NT measurements. Recognising Wright's more accurate use of NT in trisomy risk calculations, the FMF replaced Delta with the mixture model in 2008. Since its introduction to the FMF, the mixture model has been commercially applied by major equipment/software companies operating in Europe and Asia: GE Healthcare uses the model in its nine ultrasound machines, which have been distributed to healthcare providers across the world while Astraia Obstetrics use the model in its first trimester anomaly risk calculator. Thermo Fisher Scientific Inc., one of the largest scientific instruments companies in the world, use the mixture model on screening for preeclampsia and state "the work of Dave Wright has had a major impact on the methodology and quality improvements of screening for fetal anomalies and preeclampsia. The mixture model for NT is used throughout the world by our customers". They also state that "the research of Dave Wright has been instrumental in the introduction of our assay for PIGF (Placental Growth Factor) in

screening for preeclampsia using the competing risk model". Thermo Fisher has recently (2013) bought an asset purchase agreement including a patent license for the exclusive rights of PIGF to diagnose preeclampsia.

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

DQASS:

Joint written statement from Programme Manager and Deputy QA Lead (National), UK National Screening Committee, Fetal Anomaly Screening Programme, 344-354 Gray's Inn Road, London WC1X 8BP, tel +44 (0)207 1642100

List of DQASS resources on the NHS website explain the role of DQASS and how the NHS works with Plymouth University: http://fetalanomaly.screening.nhs.uk/qualityassurance

Written statement from Director, BORN, Ontario, 401 Smyth Road |Ottawa, ON, K1H 8L1. A statement confirming the impact the research of Wright has had on the introduction of quality assurance programme for NT ultrasound in Ontario screening programme.

FMF and private sector healthcare providers:

Written statement from Director R+D, ThermoFisher Scientific. A statement highlighting the major impact Wright's research has had on screening for fetal anomalies and preeclampsia and that it is used by ThemoFisher Scientific throughout the world.