Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: National implementation of safer and rapid, prenatal testing for genetic conditions

Period when the underpinning research was undertaken: 2000 - 2020

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:
Lyn Chitty	Professor of Genetics and Fetal Medicine	2009 - present

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

A UCL team led by Professor Lyn Chitty has transformed patient care for families at risk of genetic diseases. Building on new molecular genetic techniques, the team has developed: (1) safer non-invasive prenatal diagnosis (NIPD) based on analysis of cell-free DNA in maternal plasma; and (2) rapid exome sequencing to diagnose genetic conditions in fetuses with unexpected ultrasound abnormalities. Since 2013, NIPD has allowed more than 1,950 pregnant women to avoid amniocentesis, eliminating the associated risk of miscarriage. Rapid exome sequencing requires amniocentesis, but has increased genetic diagnostic yield by 47% already in the first few months of the service. Sequencing test results, available within two weeks, have informed pregnancy management and parental decision-making. Every pregnant woman in England can now access these tests via the National Genomic Test Directory.

2. Underpinning research

Professor Lyn Chitty's team at the UCL Great Ormond Street Institute of Child Health (GOS ICH) has led development and implementation of (1) safe non-invasive prenatal genetic tests for families at known high risk (family history or relevant ultrasound findings) and (2) rapid genetic sequencing of parental and fetal DNA to diagnose genetic conditions in fetuses with unexpected abnormalities detected during pregnancy. Together, these tests are improving patient management and decision-making for parents and healthcare teams.

Developing non-invasive prenatal diagnostic tests based on analysis of cell free DNA in maternal plasma

Chitty's team at GOS ICH was among the first to develop maternal blood tests to detect genetic abnormalities in the unborn fetus and was the first laboratory worldwide to deliver an accredited non-invasive prenatal diagnosis (NIPD) service for monogenic conditions,

The tests exploit cell free fetal DNA that circulates in maternal plasma. At first, tests were limited to detection of genetic abnormalities that arose de novo in the fetus (not inherited from either parent) or that were inherited from the father. In these circumstances, the mother does not carry the abnormal gene and if it is detected in the plasma it comes from the fetus. The first test to be developed and accredited was for conditions caused by defects in the Fibroblast Growth Factor Receptor 3 gene (*FGFR3*), including achondroplasia, the most common short stature syndrome (**R1**).

The team subsequently extended NIPD to include recessive conditions where, to be affected, the fetus inherits the abnormal gene from both parents. In these cases, the mother's abnormal gene circulates in her blood. The team used sensitive counting methods to measure the ratio of mutant to normal allele in the maternal plasma, which is slightly higher if the fetus carries two copies of the mutant gene. In 2016 NIPD for the recessive disorders cystic fibrosis (CF) (**R2)** was approved for clinical use in the NHS.

GOSH was the first laboratory to be accredited to deliver the service and uptake has been much higher than for invasive testing (**R2)** demonstrating parents' preference for the safer non-invasive test.

The team also assessed the costs and acceptability of offering NIPD for genetic conditions such as CF and sickle cell disorder. They found that for de novo and paternally inherited conditions, where NIPD molecular techniques are straightforward, NIPD costs less than invasive testing. NIPD for autosomal recessive and X-linked conditions is technically more complex and currently costs more than invasive testing (**R3).** The team found that safety of NIPD is welcomed by parents and uptake is high (**R2**). Early access to testing was also valued as NIPD can be done from 9 weeks gestation, earlier than amniocentesis, with results available in 5 days or less **(R4)**. But safety is not the parents' only concern and some mothers may feel pressured into getting a diagnostic test. The research showed that to promote informed choice, pre-test counselling should be balanced, not exclusively focused on test safety and be delivered by fetal medicine or genetic health professionals **(R5).**

Rapid fetal genomic sequencing for prenatal diagnosis of monogenic disorders

When a pregnant woman's ultrasound scan picks up structural abnormalities, amniocentesis may be discussed. The UCL team has developed a rapid sequencing test – rapid trio exome sequencing – that sequences DNA from both parents and the fetus, using an analytical pipeline that can deliver the results in two weeks, such that results can be used to inform parental decisions and pregnancy management. The test was initially developed using a cohort of 16 cases with skeletal anomalies. A diagnosis was made in 80% of cases (80% diagnostic yield) (**R6**). Subsequently the team were co-applicants on a nationwide study that found diagnostic yield varied by the type of anomaly, with the highest yield being in fetuses with multiple anomalies, skeletal anomalies or hydrops (**R7**). These studies informed NHSE's decisions to implement this test and in the first few months of the NHS service there has been a 47% increase in diagnostic yield over standard tests.

These complicated tests have significant implications for parents. Throughout the research programme, the team has sought families' perspectives to ensure the tests meet their needs (eg **R4 and R5**), with parent advocates also included as co-applicants on key grant applications. The team also conducted mixed-methods research on the delivery of genome sequencing in the 100,000 Genome Project, evaluating informed decision-making, experiences of testing and receiving results. The work highlights positive attitudes and experiences for parents, families and professionals, but also raised concerns and misunderstandings that can guide implementation of genome sequencing in the NHS Genomic Medicine Service (**R8**).

3. References to the research

R1 Chitty LS, Mason S, Barrett AN, McKay F, Lench N, Daley F, Jenkins LA: (2015) Non-invasive prenatal diagnosis of achondroplasia and thanatophoric dysplasia: next generation sequencing allows for a safer, more accurate and comprehensive approach. *Prenat Diagn* Jul;35(7):656-62 DOI: 10.1002/pd.4583.

R2 Chandler NJ, Ahlfors H, Drury S, Mellis R, Hill M, McKay FJ, Collinson C, Hayward J, Jenkins L, Chitty LS. (2020) Noninvasive Prenatal Diagnosis for Cystic Fibrosis: Implementation, Uptake, Outcome, and Implications. *Clin Chem*. 66:207-216. PMID:3155131 DOI: 10.1373/clinchem.2019.305011.

R3 Verhoef TI, Hill M, Drury S, Mason S, Jenkins L, Morris S, Chitty LS. (2016) Non-invasive prenatal diagnosis (NIPD) for single gene disorders: cost analysis of NIPD and invasive testing pathways. *Prenat Diagn*.Jul;36(7):636-42. doi: 10.1002/pd.4832.

R4 Hill M, Compton C, Karunaratna M, Lewis C, Chitty LS. Client views and attitudes to non-invasive prenatal diagnosis for sickle cell disease, thalassaemia and cystic fibrosis. J Genet Counsel 2014;23:1012-1021 doi: 10.1007/s10897-014-9725-4.

R5Hill M, Oteng-Ntim E, Forya F, Petrou M, Morris S, Chitty LS. (2017) Preferences for prenatal diagnosis of sickle-cell disorder: A discrete choice experiment comparing potential service users and health-care providers. *Health Expect.* Dec;20(6):1289-1295. doi: 10.1111/hex.12568.

R6 Chandler N, Best S, Hayward J, Faravelli F, Mansour S, Kivuva E, Tapon D, Male A, DeVile C, Chitty LS. (2018) Rapid prenatal diagnosis using targeted exome sequencing: a cohort study to assess feasibility and potential impact on prenatal counseling and pregnancy management. *Genet Med* 20:1430-1437. https://doi.org/10.1038/gim.2018.30.

R7 Lord J, McMullan DJ, Eberhardt RY, Rinck G, Hamilton SJ, Quinlan-Jones E, Prigmore E, Keelagher R, Best SK, Carey GK, Mellis R, Robart S, Berry IR, Chandler KE, Cilliers D, Cresswell L, Edwards SL, Gardiner C, Henderson A, Holden ST, Homfray T, Lester T, Lewis RA, Newbury-Ecob R, Prescott K, Quarrell OW, Ramsden SC, Roberts E, Tapon D, Tooley MJ, Vasudevan PC, Weber AP, Wellesley DG, Westwood P, White H, Parker M, Williams D, Jenkins L, Scott RH, Kilby MD, Chitty LS, Hurles ME, Maher ER; (2019) Prenatal Assessment of Genomes and Exomes Consortium. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. *Lancet.* Feb 23;393(10173):747-757. https://doi.org/10.1016/S0140-6736(18)31940-8.

R8 Lewis C, Sanderson S, Hill M, Patch C, Searle B, Hunter A, Chitty LS. (2020) Parents' motivations, concerns and understanding of genome sequencing: a qualitative interview study. Eur J Hum Genet. 2020 Jul;28(7):874-884. DOI: 10.1038/s41431-020-0575-2.

3. Details of the impact

Invasive testing, amniocentesis or chorionic villus sampling, is offered to women where the fetus is at risk of a genetic disorder. These tests usually involve inserting a needle into the womb and carry a small risk of miscarriage, causing psychological stress to women. Further, fetal anomalies occur in around 2% of all pregnancies and many arise from genetic disorders. The inability to diagnose the underlying cause in fetuses with ultrasound abnormalities results in parental anxiety and difficulties in decision making. Research at UCL, to develop non-invasive genetic tests and rapid prenatal genome sequencing, is transforming patient care by reducing the psychological stress associated with these high-risk pregnancies, offering safer diagnosis to high-risk families and improving the diagnosis of genetic conditions in fetuses with abnormalities. Consequently, since 2013, more than 1,950 pregnant women in England have avoided invasive testing and more are now benefiting from timely prenatal genetic diagnosis that is informing pregnancy management and decision-making. These tests are now included in the National Genomic Test Directory in England's new Genomic Medicine Service, enabling access for all women who could benefit from these tests.

Increasing patient access to safer, non-invasive prenatal tests

GOSH, with UCL's GOS ICH, was the first centre in the world to deliver an accredited NIPD service for monogenic conditions. Since 2013, the UCL team has extended the availability of safer prenatal tests for conditions where the pregnancy is at risk of a monogenic disorder, including many very rare conditions and definitive diagnosis for recessive conditions, even when parents carry the same mutation. In 2018 there were approximately 840,000 conceptions in England and Wales and approximately 640,000 live births (ONS figures). The tests developed at UCL, are now available through the NHS, to every at-risk woman in England (**S1**).

This earlier, safer analysis of maternal plasma to identify fetuses with these abnormal genes is more acceptable to parents who seek testing, as it removes the anxiety and risk of miscarriage, associated with invasive testing (**S2**). Since 2013, in the UK, more than 1,950 women at risk for

>160 conditions have benefited from these non-invasive tests. A third of all prenatal molecular diagnostic tests offered by GOSH are now non-invasive (**S3**).

The tests are increasing uptake of prenatal diagnosis; approximately 40% of parents said they would undergo invasive prenatal testing for CF, whereas 94% said they would opt for NIPD, including those who had previously declined invasive testing (**S4**). The GOS ICH team receives requests for testing from as far afield as Canada and Australia.

Implementation of the prenatal diagnostic tests developed at UCL is allowing parents to receive appropriate care, sooner. The director of Antenatal Results and Choices (ARC) said, "For parents who carry single gene disorders, every pregnancy is fraught as they face testing to find out whether their baby has inherited the condition. We have supported many such parents and for them the possibility of having NIPD early in their pregnancy rather than undergo invasive testing is of huge benefit. The work you [Professor Chitty] have done to make this a reality for a number of conditions makes a real difference to the parent experience. We know that, for some, availability of such testing actually influences their decision to embark on a pregnancy"(**S5**).

The UCL team has also created a repository of plasma samples collected from parents with pregnancies at risk of chromosomal defects (aneuploidy) or genetic conditions (RAPID biobank). Since 2013, RAPID has almost doubled in size and now includes over 20,000 parental blood samples. This provides a valuable resource for service development at GOSH, across the UK, and for quality assurance schemes. The National Laboratory and Scientific Lead (Genomics Unit) for NHS England & NHS Improvement said, "The UK National External Quality Assessment Service (UK NEQAS) for Molecular Genetics runs an external quality assurance scheme for laboratories worldwide for fetal sexing, common aneuploidies and most recently common microdeletions. The RAPID biobank was instrumental in supporting the development, and now annual delivery of this international programme and has thus played a key role in ensuring the quality of cell free fetal DNA testing globally." (**S6**).

Providing rapid diagnostic testing through rapid fetal exome sequencing

Having an accurate diagnosis during pregnancy supports decision making and facilitates improved clinical management. Difficult decisions about continuing or terminating a pregnancy can be made with more certainty and inform pregnancy and early neonatal management to improve long-term outcomes.

One healthcare professional said, "In the last 12 months, you and your team have provided timely diagnostic information in several complex prenatal cases which has been truly transformational. We can only hope that this standard of care can become standard practice, nationally and internationally in not-too-distant future". Another clinician said, "Being able to offer couples genomic testing to help make a diagnosis empowers them to take a decision about their pregnancy with much clearer information than from scans alone". Prospective parents who had been given the results of tests felt that testing made "a very difficult decision much easier as they knew the prognosis for the baby would be very poor. Having this information for the decision helped them emotionally deal with it and with their recovery. They were extremely grateful for the service." (**S7**).

Rapid fetal exome sequencing was launched in 2020 as an accredited service at GOSH and is increasing the number of families receiving an accurate diagnosis for the abnormality identified in their unborn child. The team's research has also influenced national guidance for this new service. Approximately 2200 families a year can now access the service, with better information, pregnancy management and improved outcomes (**S8**).

Raising public awareness of non-invasive prenatal diagnosis and the importance of genome sequencing

The UCL team engaged the public through the media, publications and discussion groups to gauge parental and societal opinion. Chitty regularly delivers lectures to lay society annual meetings for organisations such as Antenatal Results and Choices (ARC) and the Brittle Bones

Society. The team has developed an animation for young people describing whole genome sequencing that was evaluated with 554 school pupils (11-15 years) and shown to increase objective knowledge scores. Interviews with 12 young people and 14 parents offered genome sequencing found positive views and feelings of empowerment to take an active role in decision making (**S9**). These animations are widely available on public websites including Genomics England (**S10**) and have been translated into Turkish, Chinese and Bengali. The animation has received almost 30,000 views on YouTube and when uploaded on Sina Weibo (Chinese Twitter), it received a further 136,800 views in one week.

NHS implementation

Chitty has advised NHS England Rare Disease Working Group on the implementation of these tests and through extensive engagement with patients, the public, health professionals and commissioners this multidisciplinary research programme has led to inclusion of the tests in the new NHS National Genomic Test Directory (**S1**). The NHS now funds NIPD and rapid fetal sequencing as part of the new national Genomic Medicine Service, making the tests available to all women across England.

5. Sources to corroborate the impact

S1. https://www.england.nhs.uk/publication/national-genomic-test-directories/

S2. Lewis C, Hill M, Chitty LS. Non-invasive prenatal diagnosis for single gene disorders: experience of patients. Clin Genet 2014 Apr;85(4):336-42. doi: 10.1111/cge.12179.

S3. GOSH laboratory records (via email)

S4. Hill M, Twiss P, Verhoef T, Drury S, McKay F, Mason S, Jenkins L, Morris S, Chitty LS:(2015) Non-invasive prenatal diagnosis for cystic fibrosis: detection of paternal mutations, exploration of patient preferences and cost analysis. *Prenat Diagn* Oct; 35(10):950-8. doi: 10.1002/pd.458

S5. Testimonial email from the Director of Antenatal Results and Choices

S6. Testimonial email from the National Laboratory and Scientific Lead (Genomics Unit) for NHS England and NHS Improvement

S7. Quotes from clinicians who had referred patients for exome sequencing at GOSH

S8. Guidelines for implementation of accredited rapid fetal exome sequencing service (2015) p. 13.

S9. Lewis C, Sanderson SC, Hammond J, Hill M, Searle B, Hunter A, Patch C, Chitty LS. Development and mixed-methods evaluation of an online animation for young people about genome sequencing. Eur *J Hum Genet.* 2020 Jul;28(7):896-906. doi.org/10.1038/s41431-019-0564-5.

S10.https://www.youtube.com/watch?v=sn3_FIEbe0U&ab_channel=GreatOrmondStreetHospitalandCharity