Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Delivery of new methods for safer prenatal diagnosis: non-invasive testing using cell free fetal DNA in maternal blood

1. Summary of the impact

Until recently, prenatal diagnosis of genetic conditions required analysis of fetal genetic material obtained following invasive testing, with a risk of miscarriage. Non-invasive prenatal diagnosis (NIPD) using cell-free fetal DNA in maternal plasma has transformed prenatal diagnosis for many women. Testing the maternal blood sample avoids the miscarriage risk. At UCL, we have led the implementation into clinical practice of NIPD for serious sex-linked and autosomal dominant disorders. After a successful application for UK Gene Testing Network (UKGTN) Gene Dossier approval for fetal sex determination in 2011, this is now the standard of care across the UK.

2. Underpinning research

Work led by Lyn Chitty at the UCL Institute of Child Health from 2005-10 was initially focussed on determining the clinical impact of NIPD for fetal sex determination in women considering an invasive diagnostic test because they were at risk of carrying a baby with a serious sex-linked disorder (e.g. Duchenne muscular dystrophy) or might require dexamethasone treatment because of a risk of congenital adrenal hyperplasia (CAH). The established approach to prenatal diagnosis requires an invasive test (e.g. chorionic villous sampling) to obtain fetal genetic material for analysis, procedures associated with a 0.5-1% risk of miscarriage. NIPD allows analysis of cell-free fetal DNA (cffDNA) in the blood of pregnant mothers. Our early clinical work, funded by an EU FP6 award, clearly showed that NIPD reduced the rate of invasive testing by 46% as well as reducing unnecessary administration of dexamethasone to some mothers **[1]**. These results led to the delivery of NIPD for fetal sex determination on a research basis from 2006.

We also established a bank of plasma samples collected from parents with pregnancies at risk of aneuploidy or genetic disorders. This now contains >11,000 samples and is a resource which has underpinned the developments described here. In 2009, Chitty was awarded an NIHR programme grant (RAPID: Reliable Accurate Prenatal non-Invasive Diagnosis) to investigate the feasibility of wider use of cffDNA and to develop standards for implementation into NHS clinical practice. Since then, the RAPID team has led the development of laboratory standards and performed a national evaluation of NIPD for fetal sex determination that demonstrated a high sensitivity and specificity for the method **[2]**.

We subsequently showed that it is cheaper than traditional invasive testing **[3]**, and that it is highly valued by patients **[4]**. This research formed the basis for the development of the standards required for formal approvals necessary to implement NIPD for fetal sex determination for serious sex-linked disorders as a clinical test. From 2009 onwards we also developed and implemented NIPD for single gene disorders including achondroplasia, thanatophoric dysplasia, and apert syndrome as well as developing several tests on a bespoke per patient basis **[5, 6, 7]**.

3. References to the research

[1] Hyett JA, Gardener G, Stojilkovic-Mikic T, Finning KM, Martin PG, Rodeck CH, Chitty LS. Reduction in diagnostic and therapeutic interventions by non-invasive determination of fetal sex in early pregnancy. Prenat Diagn. 2005 Dec;25(12):1111-6. http://doi.org/fbpfq9

[2] Hill M, Taffinder S, Chitty LS, Morris S. Incremental cost of non-invasive prenatal diagnosis versus invasive prenatal diagnosis of fetal sex in England. Prenat Diagn. 2011 Mar;31(3):267-73. http://dx.doi.org/10.1002/pd.2680

[3] Hill M, Finning K, Martin P, Hogg J, Meaney C, Norbury G, Daniels G, Chitty L. Non-invasive

prenatal determination of fetal sex: translating research into clinical practice. Clin Genet. 2011 Jul;80(1):68-75. http://dx.doi.org/10.1111/j.1399-0004.2010.01533.x

[4] Lewis C, Hill M, Skirton H, Chitty LS: Non-invasive prenatal diagnosis for fetal sex determination - benefits and disadvantages from the service users' perspective. Eur J Hum Genet. 2012 Nov;20(11):1127-33. http://dx.doi.org/10.1038/ejhg.2012.50

[5] Chitty LS, Griffin DR, Meaney C, Barrett A, Khalil A, Pajkrt E, Cole TJ. New aids for the non-invasive prenatal diagnosis of achondroplasia: dysmorphic features, charts of fetal size and molecular confirmation using cell free fetal DNA in maternal plasma. Ultrasound Obstet Gynecol. 2011 Mar;37(3):283-9. http://dx.doi.org/10.1002/uog.8893

[6] Lench N, Barrett A, Fielding S, McKay F, Hill M, Jenkins L, White H, Chitty LS. The clinical implementation of non-invasive prenatal diagnosis for single gene disorders: challenges and progress made. Prenat Diagn. 2013 Jun;33(6):555-62. http://dx.doi.org/10.1002/pd.4124

[7] Chitty LS, Khalil A, Barrett AN, Pajkrt E, Griffin DR, Cole T. Safer, accurate prenatal diagnosis of thanatophoric dysplasia using ultrasound and cell free fetal DNA. Prenat Diagn. 2013 May;33(5):416-23. http://dx.doi.org/10.1002/pd.4066

NIHR Programme Grant: **RAPID**- **R**eliable **A**ccurate **P**renatal non-**I**nvasive **D**iagnosis RP-PG-0707-10107, sponsor GOSH 2009-2014, £2 million

4. Details of the impact

Guidelines and adoption

The research on non-invasive prenatal diagnosis (NIPD) contributed to a report from the PHG Foundation in 2009, giving a service-based overview of the implications for the NHS of implementing this technology **[a]**. We also produced a opinion paper on NIPD using cell free fetal DNA in maternal blood for the Royal College of Obstetricians and Gynaecologists (RCOG) in 2009 which was supported by their scientific advisory committee **[b]**. We then led the Gene Dossier submission to the UKGTN which was approved formally in April 2011 **[c]**. Furthermore from 2012 the approval of Gene Dossiers for Achondroplasia and Thanatophoric dysplasia was gained **[d, e]**. Chitty has also co-led the FP7 work package of Eurogentest 2, which has developed and published guidelines for service delivery in Europe **[f]**. The technology has attracted further interest from policy makers, including a report on genomic technology in healthcare by the Human Genomics Strategy Group for the Department of Health **[g]**.

Service provision and patient benefit

NIPD for fetal sex determination is now the recognised standard of practice in UK genetic services allowing equity of access for all women in the UK at high risk of sex-linked disorders. The service at Great Ormond Street Hospital (GOSH) performs >100 tests per annum (Table 1) and, using samples in the RAPID sample bank, has helped other laboratories establish this as a standard of care, with Manchester offering this test from 2010, Birmingham from 2011 and Cambridge, Edinburgh and Salisbury from 2013. Fetal sex determination using NIPD is now the most common prenatal molecular test performed in the UK **[h]** and has reduced the invasive testing rate by nearly 50% for women at high risk of sex-linked disorders.

We have established a large unique/comprehensive bank of samples that is a resource for academic and commercial collaborators, which has already helped establish NIPD for sex determination in four other UK laboratories, and is being used to develop NIPD for Duchenne Muscular Dystrophy, Tuberous Sclerosis and Huntingdon Disease in Birmingham, Cambridge and Edinburgh regional genetics centres, as well as developing non-invasive prenatal testing for aneuploidy and other chromosomal rearrangements. We are the only public service laboratory offering a clinical service for NIPD for single gene disorders – not just in UK, but beyond, and we receive referrals from Europe, Canada and North America (Table 1).

	NIPD for fetal sex determination	Prenatal tests for Achondroplasia		Prenatal tests for Thanatophoric dysplasia	
		Invasive	NIPD	Invasive	NIPD
2008 - 9	96	21		4	
2009 - 10	118	28		16	
2010 - 11	103	27	13	21	0
2011 - 12	124	28	14	25	2
2012 - 13	163	20	22	17	11
2013 – now	79	10	4	4	11

Other tests performed clinically	Apert syndrome (n=7) Osteogenesis Imperfecta (n=1) Torsion dystonia (n=4) Fraser's syndrome (n=1) Autosomal Recessive Polycystic Kidney Disease (n=1)
Sources of referrals	UK, USA, Canada, Netherlands, Italy, Norway, Switzerland

Table 1. Details of clinical NIPD tests performed by our Regional Genetics Laboratory (figures given by financial year). Note the steady increase in numbers of tests done over time, with the trend to decreased invasive testing following gene dossier approval in 2012 **[i]**.

These tests can be offered earlier in pregnancy further relieving parental anxiety. The benefits are summed up by the supporting statement one patient gave us when we submitted our application for an NIHR programme grant to further develop this work and has been further supported in our work with patients who have undergone NIPD [reference 4 in section 3 above]:

"It is only three weeks since the termination, though the experience is still raw I wanted to share with you that the pain is very much mixed with a great sense of gratitude for the opportunity of having early non-invasive testing. Having experienced both procedures, I am enormously appreciative of developments in cffDNA diagnosis. Even with its unfortunate outcome, my second testing experience was a significantly less distressing process than the CVS with extended waiting period and associated risks. I would sincerely love to see the service and support I experienced expanded as far as possible, so that others can benefit as I did" **[j]**.

Patient and Practitioner Engagement

Our third impact is the engagement with practitioners and patients, particularly through our website www.rapid.nhs.uk which provides an information resource required to implement this safer approach to prenatal testing whilst maintaining the informed patient consent. In partnership with the National Genetics Education and Development Centre, Birmingham (RAPID co-applicants) and lay organisations such as Genetic Alliance UK, Sickle Cell Association and Antenatal Results and Choices (ARC) using information acquired from patient interviews and surveys, we have developed health information packages, including e-learning modules **[k]**. We have also contributed to practitioner-facing journals **[l]**.

5. Sources to corroborate the impact

[a] PHG foundation Steering Group Wright, C. Cell-free fetal nucleic acids for non-invasive prenatal diagnosis, Report of the UK expert working group, PHG Foundation (2009): http://www.phgfoundation.org/download/ffdna/ffDNA_report.pdf

[b] Chitty LS, Crolla JC. Non-invasive prenatal diagnosis using cell free fetal DNA in maternal blood. Scientific Advisory Committee Opinion Paper 15, RCOG June 2009: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/SIP_No_15.pdf

[c] Gene Dossier submission to the UKGTN which was approved formally in April 2011 Approval:
- http://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/test-service/x-linked-conditions-excluding-haemophilia-nipd-602/
- Best Practice guidelines: http://ukgtn.nhs.uk/fileadmin/uploads/ukgtn/Documents/Resources/Library/NIPD/BPCAREP

ATWAYSNIPDCAHFINAL.pdf

[d] Approval of Gene Dossiers for Achondroplasia and Thanatophoric dysplasia:
- http://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/test-service/achondroplasia-nipd-600/
- http://ukgtn.nhs.uk/uploads/tx_ukgtn/Achondroplasia_FGFR3_TC_Sept_12.pdf
- http://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/test-service/thanatophoric-dysplasia-nipd-599/
- http://ukgtn.nhs.uk/uploads/tx_ukgtn/TD12_FGFR3_TC_Sept_12.pdf

[e] Corroboration of our impact on the approval of the gene dossiers is available from the Chair of UKGTN Clinical and Scientific Advisory Group. Contact details provided.

[f] Skirton H, Goldsmith L, Jackson L, Lewis C, Chitty L. Offering prenatal diagnostic tests: European guidelines for clinical practice guidelines. Eur J Hum Genet. http://doi.org/pds

[g] Building on our inheritance: Genomic technology in healthcare. A report by the Human Genomics Strategy Group. January 2012 gives NIPD as an example that needs to be developed (quotes and Chitty acknowledged for contribution): http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_132382.pdf

[h] CMGS audits 2010-11 and 11-12: www.cmgs.org/CMGS%20audit/cmgs_audit.htm

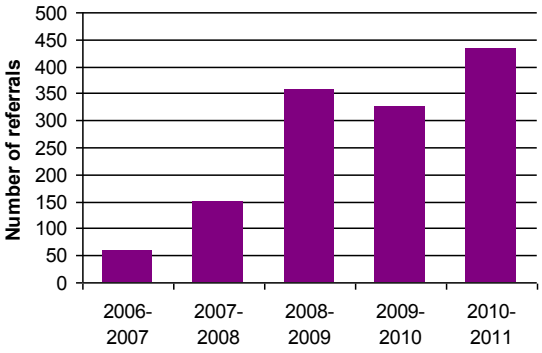

Fig 1a. Histogram showing increase use of NIPD for fetal sex determination

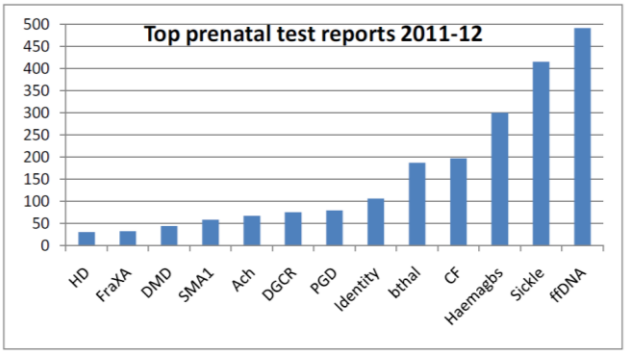

Fig 1b. Molecular prenatal tests performed

[i] Data can be confirmed by Lead Scientist NIPD section, North East Thames Regional Genetics Service, Great Ormond Street Hospital NHS Foundation Trust. Contact details provided.

[j] Anonymised patient feedback available on request from Great Ormond Street Hospital. Contact details provided. Further quotes from interviewed patients who have undergone NIPD and these are published in Lewis C, Hill M, Skirton H, Chitty LS. Fetal sex determination using cell-free fetal DNA: service users' experiences of and preferences for service delivery. Prenat Diagn. 2012; 32(8):735-41 and Lewis C, Hill M, Chitty LS: Non-invasive prenatal diagnosis for single gene disorders: experience of patients. Clin Genet 2013. http://doi.org/pdt

[k] See www.rapid.nhs.uk. Activities include:
- RAPID dissemination meetings at ICH for laboratory and clinical staff across England – July 2009, January 2010, November 2011, November 2012
- RAPID laboratory workshop on free fetal DNA Extraction methods involved 13 NHS labs from around the UK

[l] Director, Antenatal Results and Choices can vouch for support and dissemination to patients. Contact details provided.

[m] Rafi I, Chitty L. Cell-free fetal DNA and non-invasive prenatal diagnosis. Br J Gen Pract. 2009 May;59(562):e146-8. http://dx.doi.org/10.3399/bjgp09X420572.