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SCIENCE MOVING
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Ethical aspects of non-invasive prenatal diagnosis (NIPD)

Special Interest Group Ethics and Law

9

3 July 2011
Stockholm, Sweden

Ethical aspects of non-invasive prenatal diagnosis (NIPD)

Stockholm, Sweden
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Organised by
Special Interest Group Ethics and Law

Contents

Course coordinators

Guido De Wert (The Netherlands) and Wybo Dondorp (The Netherlands)

Course description

AIM: to present an overview of present and possible future developments related to the introduction of NIPD (a non-invasive diagnostic test) in the context of prenatal screening (systematic offer of testing for foetal abnormalities made to all pregnant women) and to contribute to normative (ethical, legal) reflection and guidance.

BACKGROUND: NIPD (in cell-free foetal DNA/RNA from a maternal blood sample) promises to allow safe and easy diagnostic testing in early pregnancy (from 7 weeks of gestation or even earlier). The feasibility of NIPD for trisomies 21, 13 and 18 has already been shown, making it likely that NIPD will be introduced in the near future as a one-step alternative for current approaches to prenatal screening and testing for common aneuploidies.

PART I (larger part of morning session) will be devoted to these imminent applications of NIPD-based prenatal screening. Presentations will cover the scientific background, possible implications for counseling and decision-making, and ethical aspects.

PART II (end of morning session, afternoon session) will address the implications of further scientific developments, possibly enabling (forms of) genome-wide NIPD-based prenatal screening. There will be presentations on the state of the art, ethical implications and legal/societal/regulatory aspects.

Target audience

The target audience consists of congress participants involved in prenatal testing and/or interested in these developments and their ethical, legal and societal implications.

Scientific programme

Part I: NIPD-based prenatal screening: imminent possibilities and moral challenges

09.00 – 09.30	Medical/scientific aspects – **Lyn Chitty (United Kingdom)**
09.30 – 09.45	Discussion
09.45 – 10.15	NIPD-based prenatal screening: psychosocial aspects/dynamics of decision making – **Jenny Hewison (United Kingdom)**
10.15 – 10.30	Discussion
10.30 – 11.00	Coffee break
11.00 – 11.30	NIPD-based prenatal screening: ethical aspects – **Ainsley Newson (United Kingdom)**
11.30 – 11.45	Discussion

Part II: NIPD-based prenatal screening: possible future applications and moral/legal challenges

11.45 – 12.15	The future of NIPD and NIPS – **Diana W. Bianchi (USA)**
12.15 – 12.30	Discussion
12.30 – 13.30	Lunch
13.30 – 14.00	NIPD and the ethics of non-medical applications – **Antina de Jong (The Netherlands)**
14.00 – 14.15	Discussion
14.15 – 14.45	Widening the scope of NIPD-based prenatal screening: what to offer and by whom to decide? – **Dagmar Schmitz (Germany)**
14.45 – 15.00	Discussion
15.00 – 15.30	Coffee break
15.30 – 16.00	Widening the scope of NIPD-based prenatal screening: the ethics of predictive testing of (future) children - **Guido de Wert (The Netherlands)**
16.00 – 16.15	Discussion
16.15 – 16.45	Regulatory aspects; international normative frameworks and commercial context – **Aart Hendriks (The Netherlands)**
16.45 – 17.00	Discussion

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ESHRE – European Society of Human Reproduction and Embryology

What is ESHRE?

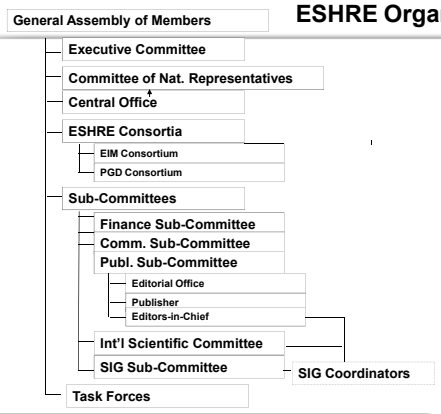
ESHRE was founded in 1985 and its **Mission Statement** is to:

- promote interest in, and understanding of, reproductive science
- facilitate research and dissemination of research findings in human reproduction and embryology to the general public, scientists, clinicians and patient associations.
- inform policy makers in Europe
- promote improvements in clinical practice through educational activities
- develop and maintain data registries
- implement methods to improve safety and quality assurance

Executive Committee 2009/2011

Chairman	• Luca Gianaroli	Italy
Chairman Elect	• Anna Veiga	Spain
Past Chairman	• Joep Geraedts	Netherlands
	• Jean François Guérin	France
	• Timur Gürgan	Turkey
	• Ursula Eichenlaub-Ritter	Germany
	• Antonis Makrigiannakis	Greece
	• Miodrag Stojkovic	Serbia
	• Anne-Maria Suikkari	Finland
	• Carlos Plancha	Portugal
	• Françoise Shenfield	United Kingdom
	• Etienne Van den Abbeel	Belgium
	• Jolieneke Schoonenberg-Pomper	Netherlands
	• Veljko Vlaisavljevic	Slovenia
	• Søren Ziebe	Denmark

ESHRE Organisation



ESHRE Journals

Human Reproduction with impact factor 3.859

Human Reproduction Update with impact factor 7.042

Molecular Human Reproduction with impact factor 3.005

Campus Activities and Data Collection

Campus / Workshops

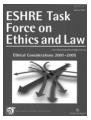
- Meetings are organised across Europe by Special Interest Groups and Task Forces
- Visit www.eshre.eu under CALENDAR

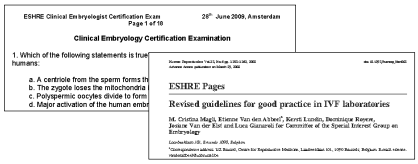
Data collection and monitoring

- European IVF Monitoring Group data collection
- PGD Consortium data collection

ESHRE Activities

- Embryology Certification
- Guidelines
- Position papers
- News magazine “Focus on Reproduction”




ESHRE Clinical Embryologist Certification Exam 20th June 2009, Amsterdam
Page 1 of 10

Clinical Embryology Certification Examination

1. Which of the following statements is true
humans:

a. A centriole from the sperm forms th
b. The zygote loses the mitochondria
c. Polyspermic oocytes divide to form
d. Major activation of the human embr

ESHRE Pages

Revised guidelines for good practice in IVF laboratories

M. Cristina Magli, Etienne Van den Abbeel, Kevrli Lundin, Dominique Royere, Jessica Van der Elst and Luca Gianaroli for Committee of the Special Interest Group on Embryology

ESHRE COMMUNITY

RSS feeds for news in reproductive medicine

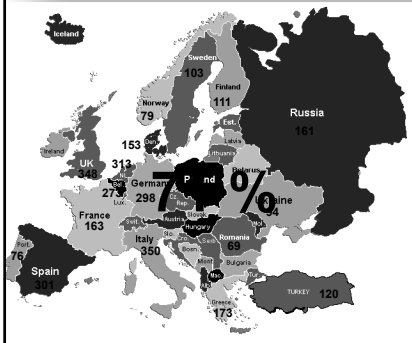
Since launch 12/2009: **1,360 Fans**

Since launch 12/2009: **190 followers** (journalists, scientific organisations, patient societies, governmental bodies)

Retweets to MHR

Find a member

ESHRE Membership (1/3)



4,017	Europe
476	Asia
372	North America
332	Middle East
221	Africa
142	Oceania
99	South America

TOTAL MEMBERSHIP*: 5 659 members

* as of July 2010

ESHRE Membership (2/3)

	1 yr	3 yrs
Ordinary Member	€ 60	€ 180
Paramedical Member*	€ 30	€ 90
Student Member**	€ 30	N.A.

*Paramedical membership applies to support personnel working in a routine environment such as nurses and lab technicians.
**Student membership applies to undergraduate, graduate and medical students, residents and post-doctoral research trainees.

ESHRE Membership – Benefits (3/3)

1) Reduced registration fees for all ESHRE activities:

Annual Meeting	Ordinary	€ 480	(€ 720)
	Students/Paramedicals	€ 240	(€ 360)
Workshops*	All members	€150	(€ 250)

2) Reduced subscription fees to all ESHRE journals – e.g. for Human Reproduction €191 (€ 573!)

3) ESHRE monthly e-newsletter

4) News Magazine "Focus on Reproduction" (3 issues p.a.)

5) Active participation in the Society's policy-making

*workshop fees may vary

Special Interest Groups (SIGs)

The SIGs reflect the scientific interests of the Society's membership and bring together members of the Society in sub-fields of common interest

- Andrology
- Early Pregnancy
- Embryology
- Endometriosis / Endometrium
- Ethics & Law
- Safety & Quality in ART
- Psychology & Counselling
- Reproductive Genetics
- Reproductive Surgery
- Stem Cells
- Reproductive Endocrinology

Task Forces

A task force is a unit established to work on a single defined task / activity

- Fertility Preservation in Severe Diseases
- Developing Countries and Infertility
- Cross Border Reproductive Care
- Reproduction and Society
- Basic Reproductive Science
- Fertility and Viral Diseases
- Management of Infertility Units
- PGS
- EU Tissues and Cells Directive

ESHRE – Annual Meeting

- One of the most important events in reproductive science
- Steady increase in terms of attendance and of scientific recognition

Track record:

ESHRE 2010 – Rome: 9,204 participants
ESHRE 2009 – Amsterdam: 8,055 participants
ESHRE 2008 – Barcelona: 7,559 participants

Future meetings:

ESHRE 2011 – Stockholm, 3-6 July 2011
ESHRE 2012 – Istanbul, 1-4 July 2012

ESHRE 2011, Stockholm, Sweden

When: **3 - 6 July 2011**
Where: **Stockholmsmässan, Mässvägen 1, Älvsjö, Sweden**
www.stockholmsmassan.se

Chair of conference: **Kersti Lundin**

Hotel and Travel:
MCI - Stockholm Office
Phone: +46 (0)8 54651500
E-mail: eshre@mci-group.com

For updates visit www.eshre.eu

ESHRE 2011, Stockholm

Keynote Lectures

Aneuploidy in humans: what we know and we wish we knew – Terry Hassold (USA)

Historical Lecture

A brave new world with a brave old humankind; quo vadimus – E. Diczfalusy (SE)

MHR Symposium – The paternal genome

Sperm chromatin packaging – B. Robaire (CDN)

The human sperm epigenome – B. Cairns (USA)

ESHRE 2011, Stockholm: Debates

This house believes that obese women should not receive treatment until they have lost weight

- **Yes: Mark Hamilton *(UK)***
- **No: Guido de Wert *(NL) - TBC***

Paramedical invited session: Should we pay donors?

- **Yes: Herman Tournaye (BE)**
- **No: Laura Witjens (UK)**

Annual Meeting – Pre-Congress Courses

- PCC 1: The challenges of embryo transfer (Paramedical Group)
- PCC 2: The blastocyst: perpetuating life (SIG Embryology and SIG Stem Cells)
- PCC 3: From genes to gestation (SIG Early Pregnancy and SIG Reproductive Genetics)
- PCC 4: Lifestyle and male reproduction (SIG Andrology)
- PCC 5: Ovarian ageing (SIG Reproductive Endocrinology)
- PCC 6: The impact of the reproductive tract environment on implantation success (SIG Endometriosis/Endometrium)
- PCC 7: Adhesion prevention in reproductive surgery (SIG Reproductive Surgery)

Annual Meeting – Pre-congress Courses

- PCC 8: Theory and practice update in third party reproduction
  (SIG Psychology and Counselling)
- PCC 9: Ethical aspects of non-invasive prenatal diagnosis
  (SIG Ethics & Law)
- PCC 10: Patient-centered fertility services
  (SIG SQUART)
- PCC 11: Clinical management planning for fertility preservation in female cancer patients
  (TF Basic Science and TF Preservation in Severe Disease in collaboration with the US OncoFertility Consortium)
- PCC 12: Opportunities for research in female germ cell biology
  (TF Basic Science)

Annual Meeting – Pre-congress courses

- PCC 13: Assisted reproduction in couples with HIV
  (TF Fertility and Viral Diseases)
- PCC 14: Prevention of infertility – from preconception to post-menopause
  (TF Reproduction and Society)
- PCC 15: Hot topics in male and female reproduction
  (ASRM exchange course)
- PCC 16: Academic Authorship programme
  (Associate Editors ESHRE journals)
- PCC 17: Science and the media, an introduction to effective communication with the media
  (Communications SubCommittee ESHRE)

Certificate of attendance

1/ Please fill out the evaluation form during the campus

2/ After the campus you can retrieve your certificate of attendance at www.eshre.eu

3/ You need to enter the results of the evaluation form online

4/ Once the results are entered, you can print the certificate of attendance from the ESHRE website

5/ After the campus you will receive an email from ESHRE with the instructions

6/ You will have TWO WEEKS to print your certificate of attendance

Contact

ESHRE Central Office
Tel: +32 (0)2 269 09 69
info@eshre.eu / www.eshre.eu

Non-invasive prenatal diagnosis
Current status and future prospects

Lyn Chitty

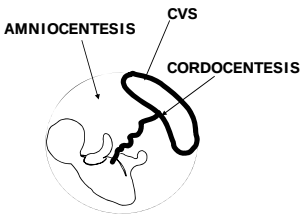
Professor in Genetics and Fetal Medicine

Clinical and Molecular Genetics, Institute of Child Health, London

Learning objectives

- Principals behind NIPD
- How it is done
- What we are doing currently
- Requirements for implemenation

Current prenatal diagnosis requires invasive procedures



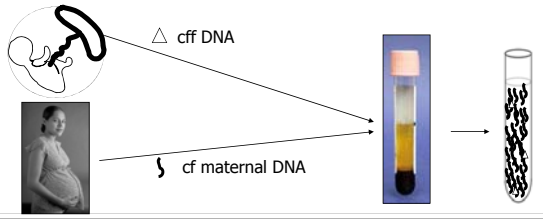
Aneuploidy
Single gene disorders
Metabolic conditions

Barriers to current PND

- **Risk of loosing a normal fetus**
- **Too late for intervention for some**
- **Much parental anxiety**

Cell free fetal DNA in the maternal plasma

- Detectable from 4 weeks
- Originates from trophoblast (placenta)
- Up to 10% of total circulating cell free DNA
- Cleared from circulation within 30 minutes of delivery



Cell free fetal nucleic acids for PND

Advantages

- No miscarriage risk
- Potentially earlier test and more acceptable
- Reduced parental anxiety

Problems

- Relative abundance of maternal cfDNA
- Emanates from the placenta - ?risk of mosaicism
- Unreliable in multiple pregnancies
- When used in early pregnancy, risks associated with 'vanishing twin'

How can we use cffDNA

- By identifying genes or alleles that are not present in the mother but are present in baby because they have been inherited from the father or arisen de novo at conception.
- Detection of paternally inherited alleles
  - Fetal sex determination - genes on the Y-chromosome
  - *RHD* in Rhesus negative mothers
  - Dominantly inherited genes carried by an affected father, e.g. Huntingdon's
  - Conditions arising de novo, eg Achondroplasia
  - Recessively inherited genes where the parents carry different mutations

Current use for NIPD in the UK

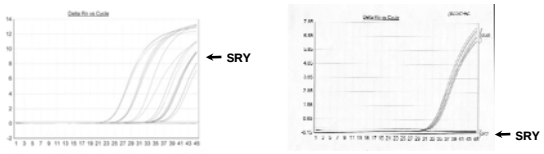
Detection of genes or alleles not present in the mother

- Fetal RhD status in high risk pregnancies
- Fetal sex determination
- Some single gene disorders

NIPD

Methods

Using targets on the Y chromosome, SRY or DYS14, and real time PCR accuracy of between 85-100% have been reported



male female

Hyett et al 2005. Prenatal Diagnosis 25:1111; Avent and Chitty 2006. Prenatal Diagnosis 26:598

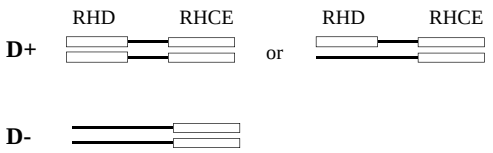
Problems with current methodology

- Determination of male fetus required positive signal, but female is indicated by absence of amplification:
  - Insufficient ffDNA present
  - Assay failure
- Independent fetal marker required

NIPD and RHD

NIPD and RHD

- D+ / D- phenotype is usually due to the presence or absence of the *RHD* gene, respectively
- If *RHD* gene sequences are detected in the plasma of a D- woman, the fetus is predicted to be D+
- If no *RHD* is detected, the fetus is predicted to be D-



NIPD for RHD
Current application in high risk women

- Useful in women with history of haemolytic disease of the newborn and those with RHD antibodies
- Maternal blood for ffDNA analysis of fetal RHD status
  - D- no need for further monitoring
  - D+ at risk and thus continue monitoring
- Small numbers using labour intensive methodology

NIPD and RHD
Potential in routine antenatal care

Check fetal RHD group

+ve

-ve

AntiD	28 weeks	**No Anti-D**
AntiD	34 weeks	**Potential for 40% reduction in Anti-D**
AntiD	40 weeks	**Prevent exposure to blood products** **Save >£4,000,000 pa**

High throughput analysis
1614 samples at 28 weeks

980 correct D+	(60.7%)	
579 correct D-	(35.9%)	
14 false D+	(0.9%)	
2 false D-	(0.1%)	
39 inconclusive	(2.4%)	Require further analysis

G. Daniels, K. Finning, P. Martin, I. Skidmore, J. Summers, C Wilkes
National Blood Service, Bristol & Birmingham, UK. BMJ 2008;336:816-

Finning et al BMJ. 2008;336:816-8.

Summary of preliminary study

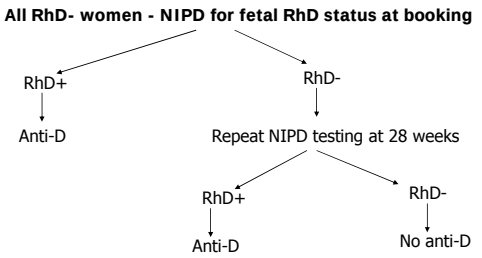
- High-throughput screening for fetal RHD blood group is possible and is highly accurate
- If current programmes remain unchanged, knowledge of fetal RHD status will be needed BEFORE 28 weeks
- The amount of fetal DNA in maternal plasma increases throughout the pregnancy

Finning et al BMJ. 2008;336:816-8.

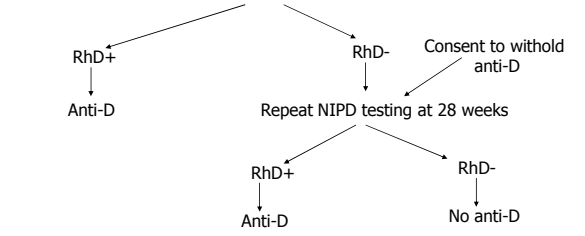
Opportunities for testing with minimum inconvenience or extra hospital visits

- At the time of booking for antenatal care
  - May be too early in view of low levels of cffDNA
- At the time blood is taken for Down's syndrome screening in units offering the 2nd trimester serum screening or the integrated test
  - Uptake only around 60-70% in most units
- At the routine fetal anomaly scan around 20 weeks gestation
  - Virtually 100% uptake but would require an additional blood sample

RfPB study at ULCH, Bristol and Birmingham
1440 RHD- women



NIHR study of routine fetal D typing ULCH and other UK units
1440 RHD- women



Prior to 28 weeks all women are given anti-D for sensitising events
Check RhD on all cord bloods

Fetal sex determination

Fetal sex determination

Indications

- Risk of X-linked disorders
- Risk of congenital adrenal hyperplasia
- Genital ambiguity detected on ultrasound
- As an aid to prenatal diagnosis in some renal anomalies or genetic syndromes

UCLH experience 2004-6

Effect on management

Indication	Male	Female	Failed	Effect on management
X-linked	29	25	2	22 avoided CVS 4 declined CVS
CAH	6	3	1	5 avoided CVS 2 avoided steroids 4 stopped steroids <11w
Ambiguous genitalia	2	1	0	2 avoided amniocentesis
Discordant genotype / phenotype	2		0	1 avoided amniocentesis
Total	**39**	**29**	**3**	**46% reduction in invasive procedures**

Hyett et al 2005, Prenatal Diagnosis 25:1111

Prospective Register of Outcomes Of Free-fetal DNA testing

PROOF

AIM: To determine the effectiveness of NIPD for fetal sex determination by performing a national audit of tests done by the two NHS laboratories offering this service

International Blood Group Reference Laboratory (Bristol)

- DYS14 RT- PCR

North East Thames Regional Molecular Genetics Laboratory (GOSH)

- SRY RT- PCR

Hill et al 2010, Clin Genet 2010 epub 15.10.2010

Audit Results: Phase 2

01.04.2007– 31.3.2009

Audit outcomes

- 512 pregnancies with 803 tests performed
- 497 pregnancy outcomes returned (97%)
- 30 - LTFU / 11 - miscarriage

Inconclusive results

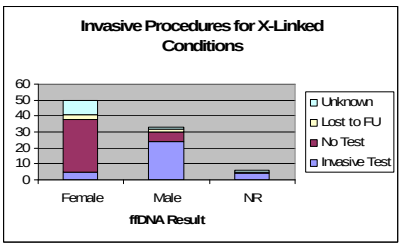
- Repeat testing - 12.4% (Bristol) and 10.6% (GOSH)
- No result issued in 22 pregnancies (4.3%)
  - 12 after one test and 10 after two or more tests

Accuracy

- 398 pregnancies where outcome known and result issued
- Overall: 99.5% (396/398)

Hill et al 2010, Clin Genet 2010 epub 15.10.2010

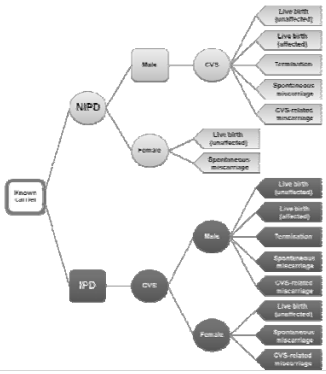
Effect on invasive testing



There was no invasive test in: 45% all pregnancies
18% of those with male fetuses
66% of pregnancies with female fetuses

Hill et al 2010, Clin Genet 2010 epub 15.10.2010

Care pathways and costs for DMD



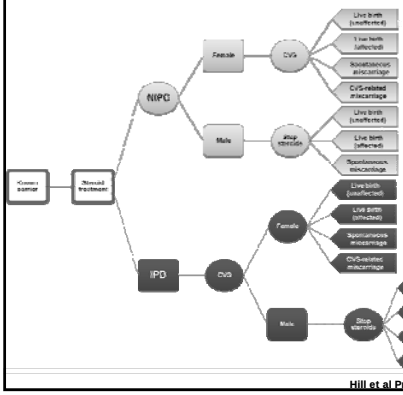
Mean cost per pregnancy: £2088

Mean cost per pregnancy: £2175

Difference: –£87
95% CI -£303 to £131

Hill et al Prenatal diagnosis 2011 31:267-72

Care pathways and costs for CAH



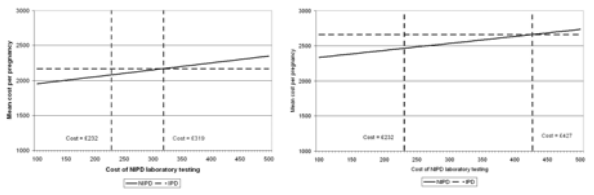
Mean cost per pregnancy: £2467

Mean cost per pregnancy: £2660

Difference: –£193
95% CI -£301 to -£84

Hill et al Prenatal diagnosis 2011 31:267-72

Impact of the cost of NIPD on total costs



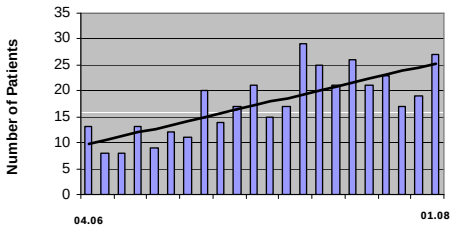
DMD CAH

Hill et al Prenatal diagnosis 2011 31:267-72

Conclusions

- **Fetal sex determination using cffDNA is very accurate when performed in NHS laboratories after 7 weeks but no result was issued in 4% of pregnancies**
- **NIPD needs to be used in conjunction with early ultrasound to exclude multiple pregnancies**
- **The use of NIPD has reduced the need for invasive testing**
- **It is no more expensive than invasive testing and may offer some cost benefits in pregnancies at risk of serious X-linked disorders or CAH**
- **These data have informed an application to UKGTN for a gene dossier and formal commissioning of NIPD for fetal sex determination**

Trends in use of ffDNA for fetal sexing



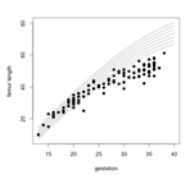
ffDNA testing accounted for for 25%-30% of all molecular prenatal diagnostic tests in 2007-8
(excl aneuploidy screening)

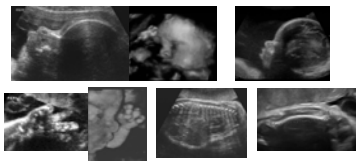
Single gene disorders

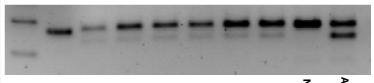
Detection or exclusion of paternal or de-novo mutation

- Myotonic dystrophy
- Achondroplasia
- Cystic fibrosis
- B-thalassaemia
- Congenital adrenal hyperplasia
- Huntingtons disease
- Aperts sydrome
- Torsion dystonia

cffDNA – an aid to sonographic diagnosis







Dilutions of maternal plasma

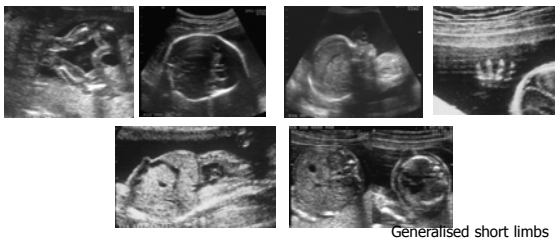
Normal

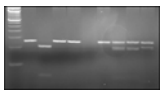
Achondroplasia

Achondroplasia

Chitty et al. Ultrasound O&G 2011;37:283-9

cffDNA – an aid to sonographic diagnosis





Thanatophoric dysplasia

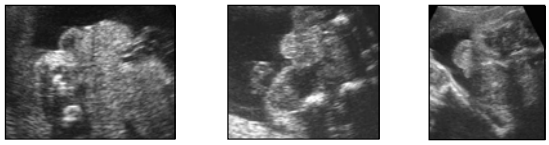
- Generalised short limbs
- +/- abnormal skull
- Frontal bossing
- Trident hands
- Small chest

Raymond et al Prenatal Diagnosis 2011 30:674-81

cffDNA – an aid to sonographic diagnosis

- Absent bladder
- Normal liquor
- Abnormal anterior abdominal wall
- Genital anomalies
- Short spine or hemivertebrae

Bladder exstophy

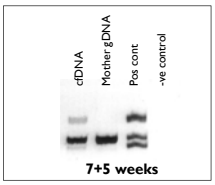


Single Gene Disorders GOSH Experience

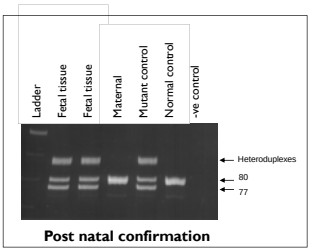
Condition	N	Gene + mutation	Indic	PCR + digest	Wks	cffDNA	Outcome
Achondroplasia	4 3	FGFR3, c.1138G>A	USS	Exon 8 / BsrGI	31-34 29-35	+ -	Affected IUGR LB
Crouzon	1	FGFR2, c.1040C>G	FH	Exon 10 / RsaI	12	-	Unaffected
Apert	1 2	FGFR2, c.755C>G	USS FH	Exon 8/Hae III	23 14	+ -	Affected Unaffected
Thanatophoric dysplasia	3 1	FGFR3, 742 C>T FGFR3, 1948 A>G	USS USS	Exon 10/AfeI Exon 15/BbsI	12-20 23	2 +/ 1- +	3 Affected Affected
Torsion dystonia	3 1	DYT1, c.946delGAG	FH	Exon 5 /3 bp del	7 & 9 7 & 9	+ -	Affected unaffected

Raymond et al Prenatal Diagnosis 2011 30:674-81

TOR1A c.904_906delGAG



7+5 weeks



Post natal confirmation

Norbury & Meany Prenatal Diagnosis 2009; 29:1218-21

A patient's perspective

- 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.
- As a patient, I am not qualified to comment on the many potential implementation benefits associated with this evolving technology, however, I can wholeheartedly express my appreciation of the procedure given my personal experience. 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

Views of service users and providers

- NIPD was viewed very positively by both service users and providers.
- Concerns that women would not consider the implications of NIPD due to the routine nature of blood tests during pregnancy.
  - Should not be offered with routine bloods
  - Formal consent process required to add gravity to the test

With a non-invasive test people might have it more readily with out thinking through whether they want that information.
Mary, Genetic counsellor

Pregnant women, they go for so many blood tests. Half of them are not even aware of what the tests are for – it's just, oh I'm pregnant yeah.
Anusha, carrier of β-Thalassaemia

Views of service users and providers

- NIPD was viewed very positively by both service users and providers.
- Concerns that women would not consider the implications of NIPD due to the routine nature of blood tests during pregnancy.
- Pre-test counselling, informed consent and results should be delivered through specialist teams (genetics and fetal medicine).

I have real reservations about my GP that they don't have access to specialist knowledge
Kate, carrier of ALD

Obviously if they had previous children and the results, maybe not for that person to see a specialist, but if its the first time they need to go to a specialist.
Phoebe, carrier of Sickle Cell/β-Thalassaemia

Additional concerns from service providers

- Concerns about misuses of NIPD
  - Sex selection
  - Anxiety resulting from "peer pressure" rather than actual risk

I feel that it would be also misused they might come up with some kind of a story about the family background and want to know the sex of the fetus for selection.
Louise, Fetal medicine consultant

Additional concerns from service providers

- Concerns about misuses of NIPD
  - Sex selection
  - Anxiety resulting from "peer pressure" rather than actual risk
- Concern about use of NIPD in the private sector or direct to consumer testing which could leave the NHS "picking up the pieces".
- There will be a "vacuum of expertise" as IPD becomes more rare.
- Parents may doubt the results of a blood test as it is very different from having a needle that goes into the abdomen next to the baby.

It could be hard to see the connection between the blood test and the baby. "It is my blood test it should be about me."
Louise, Fetal medicine consultant

Implementing NIPD into service

Factors to consider

- Small numbers reported in selected populations and reports need validating in larger numbers
- Technological development is required to produce machines that can cope with a high throughput of samples
- Laboratory standards will need to be developed
- The limits of gestation for testing will need to be determined
- Education and information to ensure that women and healthcare professionals understand the changes and women fully understand the implications of these tests.

Attitudes towards pre-test counselling for NIPD: An experimental vignette study

Aim
To test the hypothesis that NIPD may alter the delivery of pre-test counselling for screening or diagnosis.

Participants
250 obstetricians and midwives recruited at conferences in the UK.

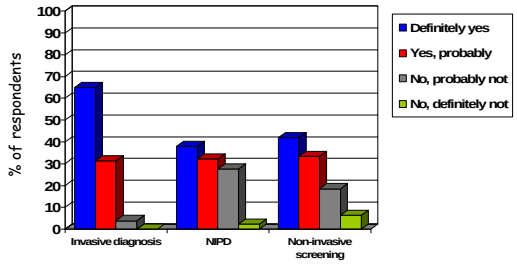
Method
Participants received one of three vignettes
- invasive diagnosis, NIPD, serum screening.

Outcome measures
- the need for written consent
- optimal gap between presentation of test and test (i.e. same day or return visit)
- the topics covered

Van den Heuvel et al. Patient Education and Counselling, 2010; 78:24-8

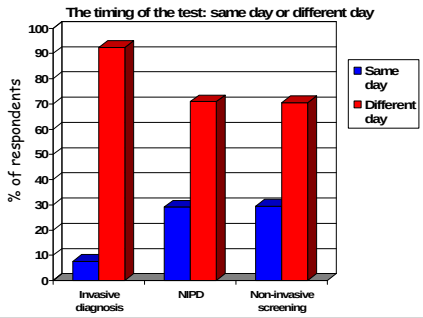
The perceived need for written consent

Should women undergoing the test sign a consent form?



Van den Heuvel et al. Patient Education and Counselling, 2010; 78:24-8

Preferred timing of presentation and test uptake (same day or return visit)



Van den Heuvel et al. Patient Education and Counselling, 2010; 78:24-8

Summary – vignette study

- Health professionals in the UK view NIPD as being very similar to screening rather than to invasive diagnostic testing
- NIPD has the potential to erode informed choice and care must be taken to educate health professionals prior to widespread implementation

Van den Heuvel et al. Patient Education and Counselling, 2010; 78:24-8

Remember
For safe implementation

- Development of laboratory protocols
- Careful evaluation of laboratory and clinical utility
- Health professional and public education
- Careful consideration of the ethical issues

Acknowledgements

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- All health professionals and patients who have helped with our research

The views expressed in this presentation are those of the authors and not necessarily those of the funders including the NHS, the NIHR or the Department of Health.

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ESHRE Stockholm 2011

NIPD-based prenatal screening: psychosocial aspects

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Advisor to UK National Screening Committee Fetal Anomaly Screening Programme

(No conflicts of interest)

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Learning Objectives

As a result of this session, participants will:

1. Understand the differences and similarities in the psychological aspects of invasive and non-invasive testing for Down's syndrome.
2. Understand the psychological and consent issues arising from offering tests for multiple conditions.
3. Be aware of limitations in the evidence base.
4. Understand the complexity of influences on uptake and hence the difficulties in anticipating future trends.

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Non-invasive prenatal diagnosis

"Unique Selling Point" is just what it says on the tin: it avoids miscarriage risk.

It is also a less daunting procedure and less unpleasant to undergo – no "big needles".

But psychologically, that is the beginning, not the end, of the story, so talk today has *three parts*:

- background and clarification of main issues,
- NIPD for Down's Syndrome,
- NIPD for multiple conditions.

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1. Background

Feature of NIPD that is shared with *all* other repro technologies?

It enables those who choose to do so to avoid the birth of a baby with a disabling condition.

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Features shared with *some* other reproductive technologies?

- Avoiding birth of affected baby entails termination of pregnancy, earlier or later.
- Can provide information on more than one condition.
- Even with definitive diagnosis, prognosis for child (and hence implications for parenting such a child) may be hard to predict.
- Informed consent challenge from multiple conditions, some of which are unpredictable in their effect.

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The NIPD versions of old questions

What should be offered, since we want to:

- offer women the choices reproductive technologies afford,
- while protecting people from foreseeable harm,
- and respecting the public interest?

What choices do women want to have, should they be allowed by law to exercise those choices, and if so, at public or private expense?

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What do we already know about:

•the information and choices women want to have,

•the ways they **trade off** potential benefits and harms,

AND hence

•the implications for women of new reproductive technologies which **change the basis of that trade off** and hence lower the "cost" of obtaining information?

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Literature on current two-stage process

Substantial psychological literature on women's **understanding, attitudes and responses** to the offer of two-stage prenatal testing.

However:

- Major gaps and shortcomings remain.
- Measurement problems abound.

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Understanding

- Whenever and wherever researchers have looked, major gaps have been identified in knowledge and understanding,
- These gaps almost certainly still exist, despite recent efforts to improve information provided, e.g. in UK.
- In UK, view is that woman needs to understand testing purpose and testing pathway, not just a specific procedure.

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Attitudes: to means or ends?

- Easier to measure attitudes to specific procedures than attitudes to whole pathway (i.e. package of technologies).
- Attitudes to current pathway and its limitations have to be "traded off" against attitudes to avoiding birth of a child with a disability.
- Test uptake is influenced by results of that trade off.

Until something changes, means and ends are inseparable.

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Knowledge, attitudes and behaviour

A lot of work has been put into trying to explain variations in test uptake ("behaviour"), but:

- It is still too early to apply theories and suggested measures outside of a research context
- Psychological models have poor predictive power.
- Measures not subjected to rigorous test evaluation procedures required in other medical contexts.
- Work to date has not addressed the trade off between means and ends.

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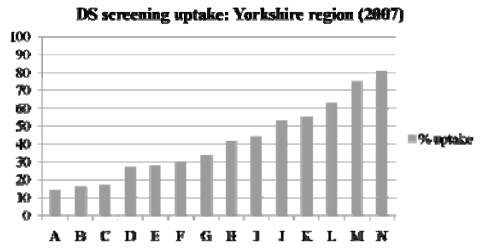
Variation in uptake (Unpublished audit data)



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Q: What is different about NIPD?

A: It fundamentally alters the trade off between means and ends.

Offering first trimester screening did that too:

- women undoubtedly prefer earlier results
- in part because many consider the option of ToP is more bearable to contemplate at that stage.

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Trade offs at policy as well as individual level

A reproductive technology which does not incur the risk of fetal loss also alters the whole equation on which prenatal testing is offered.

- DS diagnostic tests are only offered to a woman by the UK NHS if the likelihood of her baby having DS exceeds a particular threshold.
- The threshold is not determined by the woman's preferences, but by population based calculations which trade off FPRs and DRs.

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- A woman whose personal trade off led her to want a diagnostic test even though the likelihood of her baby having DS was lower than the official cut off would not be offered that test on the NHS, because the threat to the pregnancy would be deemed unjustifiable.
- Data from non-NHS facilities show that a lot of women would exercise this option.

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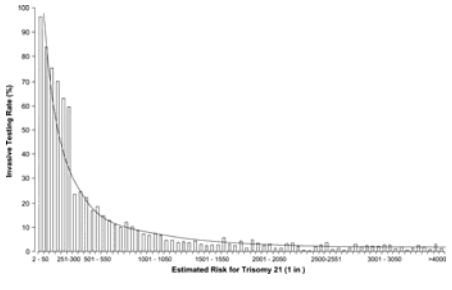

Nicolaides et al, 2005

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If "cost" (in terms of incurred risk to pregnancy) of acquiring information is taken out of the equation by NIPD, then the relevance of *both* DR and FPR changes:

- Relatively common conditions like DS can be tested for whatever the likelihood of occurrence in a specific pregnancy
- Rarer conditions can also be tested for, whatever their objective likelihood of occurrence (technology and finances permitting).

Rest of talk expands on these two points.

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2. NIPD for Down's Syndrome

Testing for same condition as before, offered to same people as before, at more or less the same time as before, but using a different technology.

- Information giving can focus on the tested-for condition rather than the testing technology
- Removes requirement for complex weighing up and comparing of two different types of probability estimates
- Uncertainty remains about degree of disability in affected child
- Available courses of action are unchanged: continue or end the pregnancy.

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With the result that:

- Knowledge and understanding are likely to be improved compared to low levels currently achieved
- Decision making is likely to be easier in terms of its cognitive demands (fewer factors to take into account) but not necessarily less stressful in emotional terms.

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Whose decisions about testing are likely to stay the same and whose to be different if NIPD was offered instead of a screening test for DS?

Decisions likely to be different?

People put off by some aspect of current technology.

And stay the same?

People not wishing to avoid the birth of a child with Down's syndrome.

People who would not consider a termination for DS.

People who accept the current testing technology.

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Proportions of people in each category?

Nobody knows - but they probably vary over time and place.

- In UK, the proportion of people not wishing to avoid the birth of a child with Down's syndrome has probably declined over time.
- We can't be sure that that explains reduced test uptake, because it might be that understanding and awareness of the drawbacks associated with current technologies have increased and changed the trade off for a lot of women.

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Psychological effects of current technology

- Anxieties – some of them enduring - associated with two stage process (probabilities not diagnoses, miscarriage risk, being a "false positive") are well documented.
- NIPD could reduce all of these in people who would have had tests anyway.
- But what about "new recruits"? And what about testing for new conditions?

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3. NIPD for other conditions

Test uptake rates and termination rates known to differ between conditions, but further interpretation limited by sample differences.

High termination rates in people currently obtaining a diagnosis may not apply to "new recruits."

What people say they want to do, and what they actually do often differ – but no "gold standard", because many influences involved in both.

But remember: what clinicians assume people will do is not a good guide to behaviour either.

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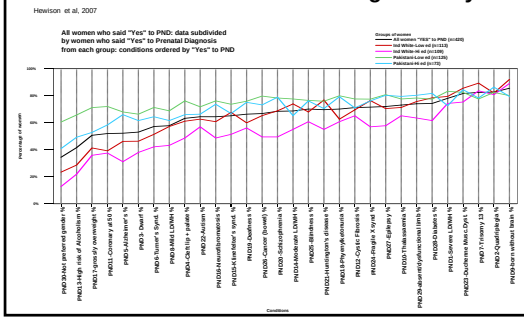
ESRC Innovative health technologies study

Hewison et al, 2007



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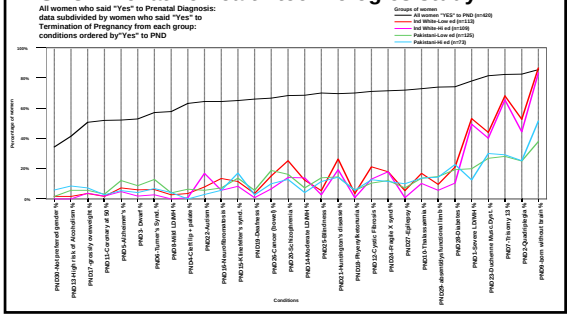
ESRC Innovative health technologies study

All women who said "Yes" to Prenatal Diagnosis: data subdivided by women who said "Yes" to Termination of Pregnancy from each group: conditions ordered by"Yes" to PND



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ESRC Innovative health technologies study

Summary of findings

1. Attitudes to testing

- A high level of interest in testing
- 6% of UK Pakistani women and 4% of white indigenous women wanted no prenatal testing at all

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ESRC Innovative health technologies study

2. Attitudes to termination

- For the great majority of conditions, fewer than a quarter of participants would consider a termination of pregnancy
- 25% of UK Pakistani women and 6% of white indigenous women would consider a termination for none of the conditions on the list

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Psychological implications?

People were strongly opposed to generic consent, and felt it was their right to decide for themselves which tests they wanted and which they did not.

Very substantial individual differences emerged but there was some consensus about conditions' relative severity, especially at the extremes.

Confronting newly exposed attitudes to different disabling conditions can be psychologically very disturbing - but is poorly understood.

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Course 9: Ethical aspects of non-invasive prenatal diagnosis (NIPD)
ESHRE Special Interest group on Ethics and Law

NIPD-based prenatal screening: ethical aspects

Dr Ainsley Newson, PhD
Senior Lecturer in Biomedical Ethics
(with Dr Z Deans)

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Conflict of interest statement

- Dr Newson and Dr Deans have no commercial relationships relevant to the content of this presentation
- Dr Newson is a co-investigator on the RAPID project: http://www.rapid.nhs.uk
  - RAPID is funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research (RP-PG-0707-10107). The views and opinions expressed are those of the authors and do not necessarily reflect those of the NHS, the NIHR or the Department of Health.

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Learning objectives

Following this presentation, delegates will be able to:

1. Place discussions of the ethics of NIPD prenatal screening in a wider context;
2. Discuss what might make NIPD based prenatal screening ethically distinct from existing PND;
3. Consider some of the moral implications of imminent clinical uses of NIPD prenatal screening;
4. Consider additional emerging issues for NIPD prenatal screening.

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‘NIPD based prenatal screening’

Two aspects:

1. Availability of NIPD to couples who wish to determine whether their fetus will develop a particular single-gene genetic condition;
2. Use of NIPD as a component of routine prenatal screening, which is offered to all pregnant women

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Existing ethical issues in PND

- Moral status of the fetus
- Assumptions about the value of life for those with the condition being tested for
- Threshold of ‘seriousness’ to justify testing

These issues are relevant to NIPD as well.

> “Some of these concerns exist today… But they will only become more immediate and more important with widespread NIPD.” (Greely, 2011)

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Moral status of the fetus

- In all PND there is an assumption that there may be circumstances when termination is acceptable
- For those who argue that…
  a) …a fetus has an inalienable right to life, NIPD will make no difference
  b) …there is a ‘gradualist’ position on fetal rights to life, NIPD will be advantageous
     - Earlier testing opens up the choice of earlier termination
  c) …a fetus has no right to life at any time in pregnancy, NIPD will make no difference

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Assumptions about value of life

- The 'disability rights critique' of PND remains active
- Might NIPD change this?
  - Simpler testing ➔ greater uptake
    - Women will no longer be able to use procedure-related risk as a reason not to test
  - Greater uptake ➔ increased detection
  - Increased detection ➔ (?) more terminations
  - Whether this also means devaluing of the lives of people with the condition being tested for is open to debate

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Threshold of 'seriousness' to test

- In PND there is also long-standing debate about what conditions should and should not be tested for and who should decide this
  - Couples' 'lived experience', professionals' considered views, or broader society?
- NIPD might re-ignite this debate, as low risk testing might mean more people would like to find out about a greater number of conditions, whether to inform the choice to continue a pregnancy, or merely 'for information'

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NIPD prenatal screening: new issues?

- So… NIPD prenatal screening raises existing ethical issues in a new context and with a potentially greater scale
- "The possibility [of NIPD] challenges all societies to decide for which ends and by what means they want such tests to be used…" (Greely, 2011)

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NIPD prenatal screening: further issues

1. Gender testing in NIPD for X-linked conditions
2. Informed decision-making in screening
3. Models of offer of NIPD prenatal screening
4. Effect on termination rates
5. Future/emerging issues

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1. NIPD gender testing in x-linked conditions

- Eg: haemophilia testing
  - Information can be for pregnancy management or (less commonly) termination
  - One audit showed apparent trend towards offering sexing with cffDNA, when information could have been found via other routine tests (eg ultrasound)
  - Is it appropriate to use state-funded NIPD to determine sex when this information can be found via other routes later in pregnancy?

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2. Informed decision-making in NIPD

"For parents who do choose NIPD, we will need to make sure they truly choose it." (Greely, 2011)

- Some health professionals believe that NIPD could change informed consent mechanisms to make them less rigorous, for example:
  - Offer and carry out the test on the same day
  - Remove need for written consent
- Would these changes be ethically problematic?

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2. Informed decision-making in NIPD

What do we mean by 'informed decision-making'?

- Informed consent:
  - Capacity
  - Appropriately informed
  - Voluntary
- Informed choice:
  - Relevant knowledge
  - Consistent with decision-maker's values
  - Behaviourally implemented (Marteau et al 2001)

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2. Informed decision-making in NIPD

- Why is this important?
  - Autonomy as an intrinsic good
  - Helps people get what they want and feel satisfied with and responsible for their decisions
  - Can protect against complaints and litigation
  - Ensures voluntariness

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2. Informed decision-making in NIPD

- Should consent to screening using NIPD be less rigorous than for invasive testing?
  - The 'Yes' view:
    - A less risky test will be simpler to explain
    - Intensive counselling for all women will be costly
    - Women may not have to deal with uncertainty of risk-based results (depending on screening model)
    - Not all women will want to make this decision over time; some will want the information straightaway and will find any wait difficult – given incidence rates, is it not paternalistic to make women wait?

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2. Informed decision-making in NIPD

- The 'No' view:
  - The impact of the information received will be no different whether the test is invasive or not
  - Consent procedures should reflect the importance of this decision and fully autonomous choice
    - Be mindful that lower test risk may mean women feel they 'ought' to have the test
  - If informed choice really is important, then resources to facilitate fully informed decision-making should be provided within budgets for roll-out of NIPD
    - Do not want this test to get 'lost' in the myriad other blood tests pregnant women choose to have

(Also see: Deans & Newson 2010)

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3. Models of offer of NIPD screening

- Assume NIPD for Down's syndrome or other conditions is feasible and satisfies requirements for a population screening programme…

  (And leaving to one side disability rights critique and resource allocation concerns)

- What model of NIPD screening best preserves informed decision-making?

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3. Models of offer of NIPD screening

- Three general models:
  1. NIPD as early as clinically feasible (≤10 weeks)
  2. NIPD to replace combined screening for all women who want it
  3. NIPD to replace invasive testing for women at high risk following combined screening, or who are not reassured by combined screening

(Deans and Newson, MS in preparation)

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3. Models of offer of NIPD screening

Model One: NIPD as early as clinically feasible

- Benefits:
  - Early diagnosis
  - Promotes reproductive autonomy
- Drawbacks:
  - Some women may have the test unnecessarily
  - Other clinical practicalities
  - Challenges to standards of informed consent

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3. Models of offer of NIPD screening

Model Two: NIPD to replace combined screening

- Benefits
  - No risk-based results to interpret
  - Reduced chance of false reassurance
- Drawbacks
  - Loss of 'thinking space'
  - Informed consent challenges
  - Poor compromise between promoting autonomy and protecting pregnant women?

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3. Models of offer of NIPD screening

Model Three: NIPD to replace invasive testing

- Benefits:
  - Mirrors current care
  - Allows 'thinking space'
  - Maximises informed decision-making
- Drawbacks:
  - More testing for some
  - Possibility of false negative results
  - Anxiety through enforced waiting time
  - Paternalism

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4. Effect of NIPD screening on termination rates

- Concern that greater uptake of NIPD will lead to increased terminations for fetal anomaly
- NIPD may also further 'normalise' screening and termination, potentially trivialising termination (de Jong *et al*, 2010)
- But also consider:
  - Uptake can be carefully considered when deciding which care model of NIPD to offer
  - No termination on medical grounds could ever be said to be trivial

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5. Future issues in NIPD screening

- Should there be a limit on the conditions NIPD is used for?
- What issues do pregnant women and couples perceive in this technology?
- Does NIPD need new or refined regulation or oversight?
- What role should the private sector play? What intellectual property rights should be granted over NIPD and how might this affect accessibility?

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Also see conference proceedings:

"The Coming Revolution in Prenatal Genetic Testing? Scientific, Ethical, Social and Policy Responses to Maternal Serum Cell-Free Fetal DNA Testing Conference", 7 May 2010,Stanford, USA.

http://go.nature.com/fbhahp

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The Future of NIPD and NIPS

Diana W Bianchi, M.D.

ESHRE Pre-Congress Course 9

"Ethical Aspects of Non-invasive Prenatal Diagnosis"

Disclosure:

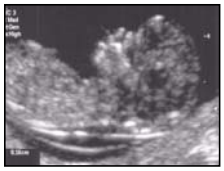
I am the Chair of the Clinical Advisory Board of Verinata Health, Inc. and I hold equity options in this company.

Learning Objectives

- **(Prof Chitty discussed current clinical uses)**
  - **Fetal sex determination**
  - **Fetal Rhesus D diagnosis**
  - **Impact on obstetrical management**
- **My focus: Learn about future clinical applications**
  - **Aneuploidy**
  - **Single gene disorders**
- **Understand uses of cell-free RNA in amniotic fluid**
  - **How can it advance knowledge of fetal pathophysiology?**
- **Discuss ethical aspects: are 90% of aneuploid fetuses really terminated?**
  - **Can we treat aneuploid fetuses?**

Non-invasive Prenatal Diagnosis of Aneuploidy Using Cell-Free Nucleic Acids in Maternal Blood

Trisomy 21



Current clinical approach: Combination of serum analytes and nuchal translucency measurement

Noninvasive Prenatal Diagnosis of Trisomy 21 Using Cell-Free Fetal Nucleic Acids

Here is one person's opinion:

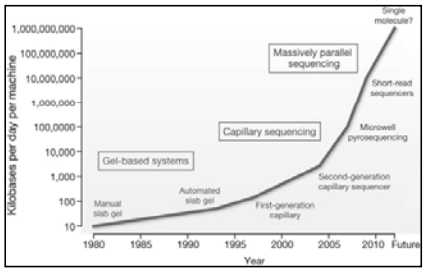
"Noninvasive prenatal diagnostics of aneuploidy is a solved problem - all that remains are the legal and business practicalities."

-Stephen Quake, December 2008

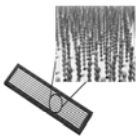
Multiple Approaches to NIPD of Aneuploidy

- **Cell-free DNA in maternal serum/plasma**
  - **Measure amount of fetal DNA: ~2-fold higher in trisomy 21 cases**
  - **Find differentially-methylated sequences on chromosome 21**
    - ***This reflects placental DNA***
    - ***Recent promising results using methylated DNA immunoprecipitation to examine fetal-specific DNA methylation ratios***
- **Cell-free RNA in maternal serum/plasma**
  - **Find gene sequences that map to chromosome 21, such as *PLAC4***
  - **Measure ratios of different alleles (SNPs) that reflect the number of chromosome 21s present**
    - ***Requires heterozygosity in DNA sequences from parental chromosomes***
- **Cell-free DNA in maternal serum/plasma**
  - **Measure amount of chromosome 21 DNA relative to a standard using next-generation sequencing**

Improvements in DNA Sequencing Technology: Implications for Prenatal Diagnosis

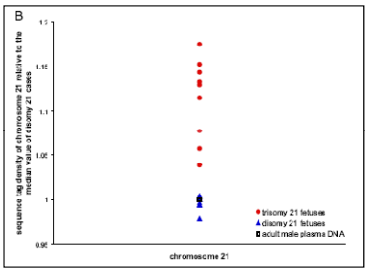


Advantages of high-throughput sequencing



1. **Entire process is automated**
2. **Multiple samples can be simultaneously analyzed**
3. **DNA is bound to a solid support, thousands of sequencing reactions can occur in parallel**

2008: Feasibility of Using Massively Parallel Sequencing Technology for NIPD of Trisomy 21 Shown



From Fan et al. Proc Natl Acad Sci USA 2008;105:16266

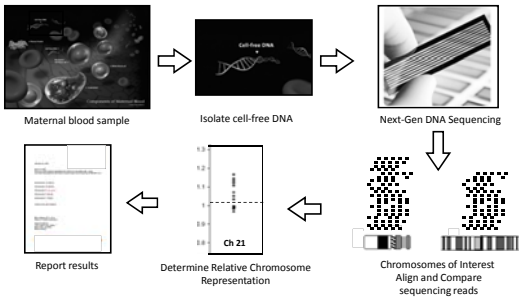
-Extremely sensitive

-Involves sequencing of 36 bp reads of DNA, mapping to chromosome of origin

-If extra 21 material is present it is readily apparent

-20-25 million sequence tags/sample

Diagnosis of Trisomy 21 by DNA Sequencing



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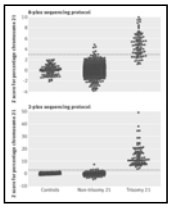
First Large-Scale Clinical Trial of NIPD of Trisomy 21 Using Sequencing
Chiu et al. BMJ 2011; 342:c7401

- 753 samples (prospective and retrospective)
- 86 cases of trisomy 21 included
- 8-plex approach 79% sensitivity, 99% specificity
- 2-plex approach 100% sensitivity, 98% specificity
- Conceived of as a way to reduce invasive procedure rate (2nd tier screen)
- Could reduce from 573 to 11 procedures in high-risk population



Chiu et al. BMJ 2011 study

- **Strengths**
- Diagnostic performance compared against karyotype
- Largest clinical study to date of high throughput sequencing
- Largely first trimester samples

- **Weaknesses**
- Mix of prospective and retrospective samples
- 100-fold increased prevalence of trisomy 21
- Positioned as 2nd tier screen, not diagnostic
- Cost=$700 per sequencing reaction, $6 million in equipment
- Could not dx trisomy 18

Second study from industry

REPORTS OF MAJOR IMPACT www.AJOG.org
UNDER EMBARGO UNTIL FEBRUARY 10, 2011, 12:01 AM ET

Noninvasive detection of fetal trisomy 21 by sequencing of DNA in maternal blood: a study in a clinical setting

Mathias Ehrich, MD; Cosmin Deciu, MSc; Tricia Zwiefelhofer; John A. Tynan, DPhil; Lesley Cagasan, MSc; Roger Tim, DPhil; Vivian Lu; Ron McCullough, DPhil; Erin McCarthy; Anders O. H. Nygren, DPhil; Jarred Dean; Lin Tang, DPhil; Don Hutchison, MSc; Tim Lu, DPhil; Huiquan Wang, DPhil; Vach Angkachatchai, DPhil; Paul Oeth, MSc; Charles R. Cantor, DPhil; Allan Bombard, MD; Dirk van den Boom, DPhil

- **Internal study performed at Sequenom**
- **449 High-risk samples**
- **All 39 trisomy 21 cases identified (100% sensitivity)**
- **409/410 euploid cases identified (99.7% specificity)**
- **Larger clinical validation study later this year**

Use of Chromosome Ratios Allows Noninvasive Diagnosis of Trisomies 21 and 18

Sehnert et al. Clin Chem 2011; in press

- **1014 samples collected prospectively pre-invasive procedure**
- **Ethnically diverse population**
- **Preparation and sequencing performed blindly**
- **Training set: 26 abnl + 45 nl = 71 samples**
- **Test set: 27 abnl + 21 nl = 48 samples**
- **Single end 36 bp reads sequenced and aligned to human genome assembly 18 UC Santa Cruz**
- **Normalized sequence reads on chromosome of interest to another chromosome (21 to 9, 18 to 8, etc.)**

The significance of normalizing chromosome ratios

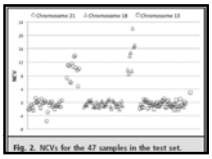


Fig. 2. NCVs for the 47 samples in the test set.

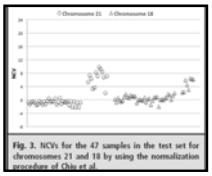


Fig. 3. NCVs for the 47 samples in the test set for chromosomes 21 and 18 by using the normalization procedure of Chiu et al.

Data from Sehnert et al. Clin Chem 2011

Table 3. Test set classification data.

	T21 classification		
	Classification		
Karyotype	Unaffected, n	T21, n	No call, n
Diploid Chr 21*	34		
47, XX, or XY, +21		13	
	T18 classification		
	Classification		
Karyotype	Unaffected, n	T18, n	No call, n
Diploid Chr 18	39		
47, XX, or XY, +18		8	

Noninvasive Prenatal Diagnosis of Aneuploidy: What is the Best Technique?

Current ultrasound/analyte approach	Future cell-free fetal DNA/approach
• Already in clinical practice	• Still in early stage trials
• Results validated in several large-scale clinical trials	• Unclear if existing IP will impede translation to practice
• First trimester scan gives additional information regarding CHD, other anomalies, single gene disorders	• Sequencing equipment, bioinformatics, data storage are expensive
• Less expensive, required equipment widely available	• Could be diagnostic (or an advanced screen)
• Not diagnostic	

What About Twin Gestations?

- **Sehnert et al. study included 5 sets of twins (4 in training set, 1 in test set)**
- **Asked question whether different amounts of fetal DNA in twin gestation would confound results?**
- **All twin gestations were correctly classified**
  - **In 3 sets both twins were unaffected**
  - **In one set both twins were affected with trisomy 21**
  - **One set was fraternal with one affected fetus (sample was called affected)**

High Throughput Sequencing to Noninvasively Diagnosis Single Gene Disorders

- **Proof of principle study for beta thalassemia**
- **Lo et al (Science Trans Med Dec 8 2010) sequenced a plasma DNA sample from a woman who underwent CVS**
- **Constructed a genome-wide genetic map**
- **Using information from the CVS diagnosis determined that fetus was a carrier**
- **Study cost $200,000 for this one case!**
- **Showed that entire fetal genome represented in maternal plasma at constant relative proportion**

Implications of Being Able to Noninvasively Diagnose Trisomy 21

- **Will more pregnant women opt for testing?**
- **What per cent of women will terminate affected pregnancies?**

From Egan et al. Prenat Diagn 2011; 31: 389-94

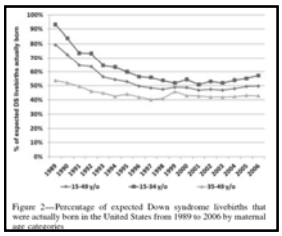
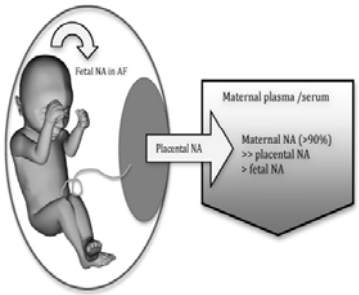


Figure 2—Percentage of expected Down syndrome livebirths that were actually born in the United States from 1989 to 2006 by maternal age categories

Translating the Transcriptome to Develop Novel Antenatal Therapies

- **Down syndrome occurs in 1 in 700 births**
- **The presumption is that many women who are diagnosed with an affected fetus will terminate**
- **Egan data suggest that is not true**
- **In many countries/continents termination is not an option**
- **Less attention has been paid to treatment options for women who continue pregnancies with Down syndrome**
- **Goal to use Down syndrome as an overall model for fetal treatment based on gene expression data**
- **Hypothesis is that even if treatment improves neurocognition by a few IQ points this would have major beneficial effects**

Fetal Cell-Free Nucleic Acids in Amniotic Fluid

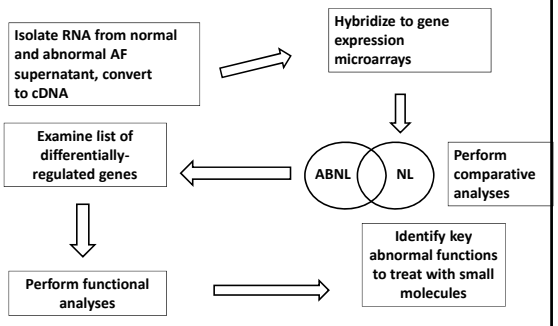


From: L. Hui and D.W. Bianchi, Hum Reprod Update 2010

The Advantages of Using Amniotic Fluid (AF)

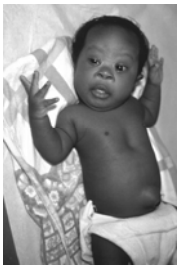
- Abundant source of cell-free DNA + RNA
- Unlike maternal blood, there is little (if any) maternal nucleic acid contamination in AF
- AF contains almost exclusively fetal (not placental) nucleic acids
- Tissues represented in AF: CNS, oropharynx, GI tract, pancreas, liver, lungs, skin
- Discarded material available for research, along with clinical and karyotype confirmation
- AF thus provides an opportunity to understand molecular pathophysiology in the living fetus

Overall approach to identification fetal biomarkers in amniotic fluid



Subjects

- Trisomy 21
  - AF from pregnant women with 7 second trimester fetuses with trisomy 21
  - 7 euploid cases matched for gender and gestational age
  - All singleton fetuses

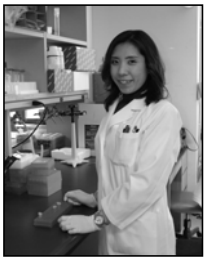


Gene Expression Analysis of 2nd Trimester Trisomy 21 Amniotic Fluid Supernatant Samples

- **Identified 414 probe sets that were differentially expressed between tri 21 and euploid samples**
  - **Corresponds to 311 genes**
- **54% of genes were up-regulated and 46% were down-regulated in tri 21**
- **Only 5 genes were actually located on 21, corresponding to the genes *CLIC6, ITGB2, RUNX1, C21orf67, C21orf86***
- ***CLIC6*= chloride intracellular channel *ITGB2*= integrin beta chain beta 2**

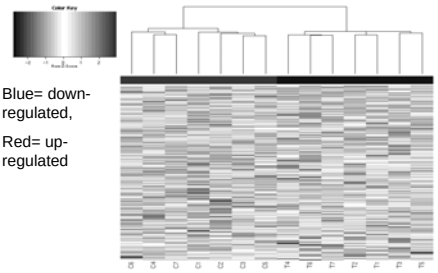
***RUNX1*= transcription factor associated with hematopoiesis**

- ***Many downstream effects***



Slonim and Koide et al. PNAS 2009;106: 9425-9

Heat Map Analysis of 409 Differentially-Regulated Genes NOT on 21 Correctly Grouped Samples by Karyotype



Blue= down-regulated,

Red= up-regulated

-Results show a consistent phenotypic pattern common to affected fetuses
-Not much individual variation
-Differs from normal in 2nd trimester

Control samples Trisomy 21 samples

Results of Functional Analyses using DAVID

Trisomy 21 compared to Euploid

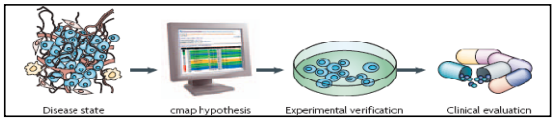
- **Oxidative stress**
- **Ion transport**
- **G-protein signaling**
- **Immune and stress response**
- **Circulatory system function**

Oxidative Stress

- Oxidative stress has been suggested to be the "bridge" between Down syndrome and Alzheimer disease
- Previously, Lockstone et al. (2007) found that oxidative stress response genes were over-represented in adult but not fetal brains with Down syndrome
- More recently, Esposito et al. (2008) identified oxidative stress and apoptosis genes in neural progenitor cell lines generated from the frontal cortex of 2nd trimester DS fetuses
- Perrone et al. (2007) examined AF and found biochemical evidence of oxidative stress in 2nd trimester DS fetuses. Nine-fold increase in isoprostanes, a new marker of free-radical catalyzed lipid peroxidation

Fetal Treatment and the Connectivity ("C") Map

- The Cmap is a publicly-available reference collection of gene-expression profiles from human cultured cells treated with bioactive small molecules along with pattern-matching software to mine the data
- Reveals "connections" between drugs, genes, and diseases
- Although the cell lines are derived from tumors, the elegance of the Cmap is that it uses genome-wide expression profiling as a common vocabulary



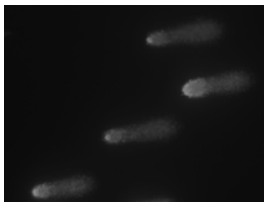
www.broadinstitute.org/cmap

In Silico: Novel Therapeutics for Trisomy 21

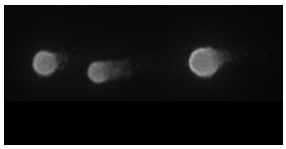
- Drugs suggested to "reverse" the phenotype of DS include apigenin (a naturally-occurring flavenoid), celastrol (potent antioxidant and anti-inflammatory drug suggested as possible treatment for Alzheimer's), dimethyloxalylglycine (DMOG), and scriptaid (histone deactetylase inhibitor)
- Can generate testable hypotheses to determine clinical value by co-culturing trisomy 21 cells with these compounds

From Lamb Nature Reviews Cancer 2007

Proof of principle that approach works COMET Assay



Trisomy 21 amniocytes with "comet tails" before treatment



Same Trisomy 21 amniocytes after treatment

In Vivo: Mouse Models of Down syndrome

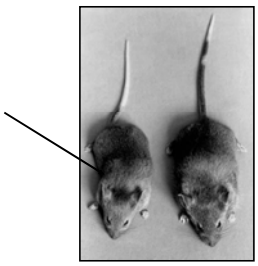


Image from www.jax.org

Late breaking data:

First treated pregnancies have occurred, neurocognitive experiments are ongoing.

If successful, intent is to start a human clinical trial following dx by CVS

Summary of My Talk Today-1

- **Noninvasive Prenatal Diagnosis of Trisomy 21**
  - **Made possible by advances in high-throughput DNA sequencing**
    - ***Technique is fully automated***
    - ***Does not require genetic marker heterogeneity between the parents (no need for a paternal sample)***
    - ***Costs are still high***
    - ***Multiple laboratories demonstrate accuracy and feasibility***
  - **Larger-scale prospective blinded clinical trials are still needed to evaluate performance**
  - **These are ongoing (mainly organized by industry groups)**
  - **It is unclear at present whether test will be better utilized as a second tier screen or a noninvasive diagnostic test**

Summary of My Talk Today-2

- **Comparative gene expression microarray analyses from amniotic fluid can provide novel information on normal and abnormal fetal functional developmental gene expression.**
- **Our studies in trisomy 21 fetuses suggest many complex but specific downstream effects.**
- **There are significant secondary adverse biological consequences such as oxidative stress that are in addition to congenital anomalies observed on prenatal sonography in aneuploidy.**
- **This discovery driven approach can lead to new hypotheses and novel treatment strategies**
  - **Could the mental retardation in trisomy 21 partly be the result of prolonged exposure to oxidative stress? Can this be ameliorated?**
- **We are currently testing treatments *in vitro and in vivo* using mouse models**

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NIPD and the ethics of non-medical applications

Antina de Jong MA LLM [1,2,3]

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2 GROW, School for Oncology and Developmental Biology, Maastricht University
3 Centre for Society and Genomics, Nijmegen

The author declares no commercial/financial or other conflicts of interest

Learning objectives

- Evaluate non-medical applications of NIPD:
  sex selection and paternity testing
- Inform on 'general' upheld cons
- Ethically reflect on tenability of arguments
- Suggest reasons for reconsidering rejection

Outline

- Context NIPD
- Sex selection
- Paternity testing
- Early moment: moral status embryo
- Conclusion

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Context

- Screening vs testing on request
- Clinical application vs commercial offer
- Severe vs minor conditions: distinction - trivialisation?
- Medical vs non-medical: clear distinction?

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Sex selection

Reasons

- Medical: sex-linked disorders
- Intermediate: avoid carrier daughters
- Non-medical: preference for one sex / gender
  personally/socio-culturally otivated

  family balancing

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Non-medical sex selection – Objections I

Sex selection

- Is unnatural
- Undermines human dignity
- Does not belong to the field of medicine
- Is inherently sexist and discriminatory / position women

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Non-medical sex selection – Objections II

Sex selection

- Generates unbalance in sex ratio
- Is emotionally harmful to child born
- What's next? -> slippery slope

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Beyond the objections

- No decisive objections, but not morally indifferent
- Reproductive freedom: if, when, number, … gender?
- Focus on preconditions:
  - Mixed family: at least 1 child of other sex
  - Follow societal consequences and reconsider if necessary

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Prenatal paternity testing

Reasons

- Medical: inherited disease and gene defect unknown
- Non-medical: ambiguous paternity, due to
  - more than one sexual partner
  - rape

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Paternity testing – Analoguous objections?

Paternity testing

- Is unnatural
- Undermines human dignity
- Does not belong to the field of medicine
- What's next? Slippery slope

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Prenatal paternity testing – Different case?

Paternity testing

- Is discriminatory -> against whom?
- Generates unbalance -> between what?
- Is emotionally harmful to child born -> or avoided?

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Paternity testing – Specific objections I

- Non-maleficence (WHO): whose harm?

  Foetus, mother, putative father, family
- Genetic discrimination (GenDG): genotype vs phenotype
- Privacy of putative father (GenDG / HTA)

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Paternity testing – Specific objections II

- Social paternity > biological paternity

Cf

- Accidental findings non-paternity
- Post-natal paternity testing: no ban

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Alternatives

- Continue (a possibly unwanted) pregnancy
  - knowledge and fear of child having 'wrong father'
  - discovered -> possible harm to woman, child and family
  - cf accidental finding of non-paternity
- Terminate (a possibly wanted) pregnancy
  - Burden of choice, decision; regret?

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Timing – moral status foetus/embryo

- CffDNA/RNA from maternal blood > 7 weeks of gestation

Ethically insignificant if
- absolute / high moral status from the start
- no independent status at all

Ethically relevant in
- dominant opinion: progressively increasing moral status (gradualist view)
- '40 days position' (8 weeks of gestation)

- Moral status early embryo relevant for evaluation both applications

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Conclusions

- Regulated setting
- Conditional
- Case to case basis
- Timing is ethically relevant
- In control of commercial offer?

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Thank you for your attention

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Widening the scope of NIPD-based prenatal screening

What to offer and by whom to decide?

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Outline

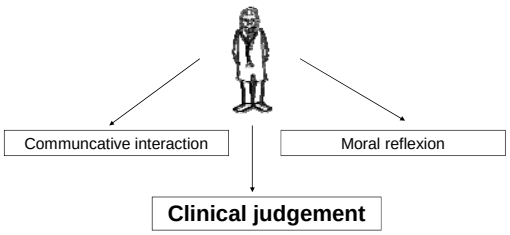
1. Prenatal genetic diagnosis - a special clinical action?
2. ...because it is medically justified ? The telos of (non-invasive) prenatal genetic diagnosis
3. ...because the woman wants it? Autonomy and privacy in NIPD and TOP
4. Consequences – who should decide?
5. Conclusion and questions

Objectives

1. To understand the teleologic nature of medicine, its influence on the structure of clinical actions and its relevance for moral agents in NIPD.
2. To compare the role of physicians as moral agents in termination of pregnancy and NIPD
3. To identify consequences for physician-patient interactions and responsibilities of physicians in NIPD

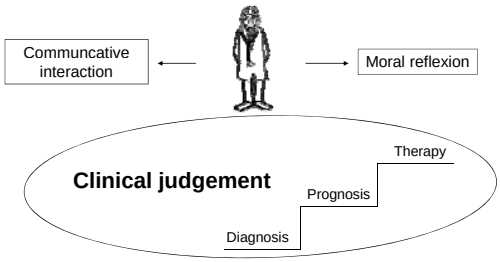
1. Prenatal genetic diagnosis – a special clinical action?

Characteristics of clinical actions:

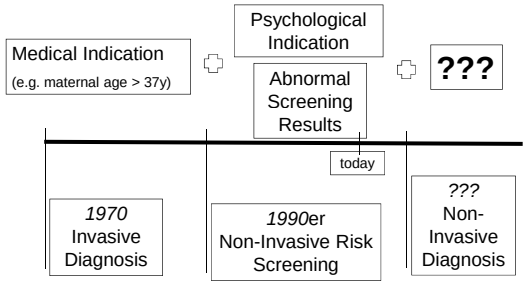


1. Prenatal genetic diagnosis – a special clinical action?

Characteristics of clinical actions:



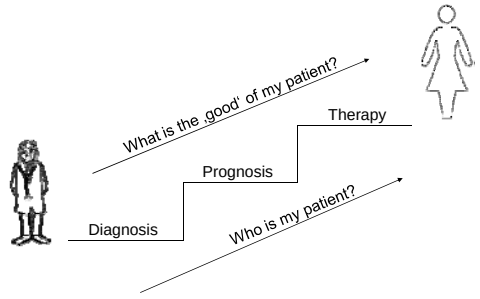
1. Prenatal genetic diagnosis – a special clinical action?



2. ...because it is medically justified ? The telos of (non-invasive) prenatal genetic diagnosis

- Medicine is a practical science
- As a practical science it is intrinsically directed towards a *telos* (healing, health, well-being of the patient)
- Clinical actions are also **perceived** as being directed towards a *telos*

2. ...because it is medically justified ? The telos of (non-invasive) prenatal genetic diagnosis



3. ...because the woman wants it? Autonomy and privacy in NIPD and TOP

Aims of prenatal diagnosis – the women's view

- Ensuring baby's health: 61.6%
- An aid to deciding wether to terminate the pregnancy in the event of a disability: 44.0%
- Part of general prenatal care: 36.8%
- My doctor wanted me to do so: 25.6%
- My doctor had (very) strong influence on my decision for or against prenatal diagnosis: 52%

(BZgA 2006, Representative Survey, Experience of pregnancy and prenatal diagnosis.)

3. ...because the woman wants it? Autonomy and privacy in NIPD and TOP

Council of Europe (Parliamentary Assembly) 2008

6. The Assembly affirms the right of all human beings, in particular women, to respect for their physical integrity and to freedom to control their own bodies. In this context, the ultimate decision on whether or not to have an abortion should be a matter for the woman concerned, who should have the means of exercising this right in an effective way.

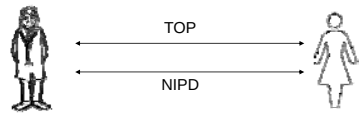
7. The Assembly invites the member states of the Council of Europe to:

7.2. guarantee women's effective exercise of their right of access to a safe and legal abortion;

7.3. allow women freedom of choice and offer the conditions for a free and enlightened choice without specifically promoting abortion;

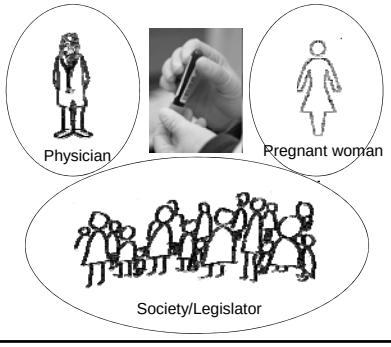
3. ...because the woman wants it? Autonomy and privacy in NIPD and TOP

Providing access to safe abortion



Providing information about a „third" person

4. Consequences – who should decide?



4. Consequences – who should decide?

- Prenatal genetic diagnosis is part of a clinical action, intrinsically directed towards a distinct *telos,* the *good* of the patient
- Physicians bear responsibility for identifying the *telos* of the clinical action and choosing the right means in order to achieve it

Who is my patient?

What is the *good* of my patient?

4. Consequences – who should decide?

- Physicians:
  Which kind of NIPD can/should be part of a clinical action?
- Society/legislator:
  What are the „rights“ of the pregnant woman and of the fetus and how can we secure them in NIPD?
- Pregnant woman/couple:
  What is my conception of a worthwile life and how can I pursue that conception with regard to NIPD?

5. Conclusion and questions

- Physicians have to decide what to offer.
- What should be offered, depends on the distinct *telos* of the clinical action.

- Is the fetus also a patient in prenatal care?
- Does „healing“ as a *telos* still play a role in the context of clinical actions in prenatal diagnosis?
- Should the „reproductive autonomy“ of the pregnant woman be a *telos* of clinical actions in prenatal diagnosis?
- What are the right means to pursue this *telos*?

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Widening the scope of NIPD-based prenatal screening: the ethics of predictive testing of future children

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ESHRE SIG Ethics & Law

Learning objectives

- to understand the dynamics of NIPD/NIPD-based prenatal screening and its moral implications
- to illustrate how prenatal testing for late-onset disorders might violate the future child's right not to know
- to refine the ethical framework regarding NIPD-based prenatal screening
- to stimulate further reflection on the difficulties involved in protecting the future child's right not to know

Widening the scope of NIPD: *late-onset* disorders

From testing for aneuploidy

to testing for causative genes/predispositions for Mendelian and complex disorders, including *late-onset* disorders:

A. NIPD for one single late-onset disorder (in case of high *a priori* risk)

B. NIPD-based screening for many disorders simultaneously by means of e.g. WGS/WGA

What about the ethics?

A. From aneuploidy to late-onset disorders: the paradigm case of HD

2 types of ethical issues: abortion-related and testing-related

1. Abortion because of HD: objections (cf Post)?

a. 'the child will have several decades of good living'
b. 'the parents are not immediately affected like in case of congenital disease' →
'the moral ambiguity of the quest for perfect babies'

These objections are invalid, as the disease is serious, the penetrance is high, and the prospect of the eventual fate imposes a severe burden

The paradigm case of HD (cont.)

2. Prenatal diagnosis of HD as such

Morally indifferent knowledge?

If a woman will carry the pregnancy to term anyway, prenatal testing for HD *de facto* amounts to predictive testing a (future) child for HD

What, then, about the ethics of predictively testing (incompetent) children for HD?

The paradigm case of HD (cont.)

Predictively testing incompetent children for HD?

The pros include:
- reassurance for the parents
- reassurance for the (older) children

The cons: a positive result would
- harm the child (the harm principle)
- violate its right not to know, a specification of the child's right to an open future (cf Feinberg)

Implications for *prenatal* testing for HD?

The paradigm case of HD (cont.)

Implications for good clinical practice:

1. Don't offer prenatal testing for HD (a morally unacceptable policy);
2. Provide *conditional* access, namely only to women intending to abort in case of a positive test result.

Objections to option 2 include (cf RCNRT):

- most women who reject the option of abortion will refrain from prenatal testing for HD;
- a commitment to selective abortion can not be enforced.

These objections are, however, unconvincing; the future child's right not to know should be protected as much as is reasonably possible (cf De Wert).

Formal justice: treat similar cases similarly

If we accept (only) *conditional* access to prenatal testing for HD, we should accept the same policy in similar cases
- but which cases are similar?

Of course: other late-onset, autosomal dominant, untreatable conditions, caused by full penetrance mutations
- but what is late-onset, what about variable age-of-onset, and what is untreatable?

What about (lower penetrance) predispositions for multifactorial (treatable or untreatable) late-onset disorders?

Minimal and *maximal* interpretations of the future child's right not to know? – that's the question

B. NIPD-based screening for many disorders simultaneously, incl. late-onset diseases?

Most of the ethical literature suffers from 'moral myopia';
it wrongly focuses only on problems reg. well-considered decision making of pregnant women and increased numbers of abortions
(cf Shuster)

Assuming that fetuses at risk for late-onset disorders will regularly be carried to term, one would *de facto* screen future children

Profiling newborns (or older minors) is, rightly, considered to be morally unjustified in view of the harm principle and the child's right not to know (cf HGC, Dondorp and De Wert)

NIPD-based screening for many disorders simultaneously, incl. late-onset disorders? (cont.)

Prenatal WGS/WGA (and other genome-wide approaches)

- will regularly (or even inherently) violate the future child's right not to know and
- blurs the distinction between reproductive/prenatal and non-reproductive/ neonatal screening (cf De Jong et al.; Dondorp and De Wert).

Implications for 'good screening practice':

- refrain from this type of prenatal screening, *or*
- use filters/target testing in order to avoid or at least limit getting information about late-onset disorders (to be further specified)

  unless this information is considered to be relevant for reproductive decision making by the pregnant woman involved …

NIPD-based screening for many disorders simultaneously, incl. late-onsert disorders? (cont.)

On what conditions could the latter policy (a *conditional* use of prenatal WGS/WGA or similiar testing approaches) be morally acceptable? Can the rights and interests of future children, then, be adequately protected?

Concerns regard

- the *systemic* nature of foetal risks for late-onset disorders;
- barriers for well-considered decision making by prospective parents, in terms of e.g. their lack of relevant experience and time constraints regarding (pre-test) counseling →

  an increased number of future children whose complete genotype has been tested *in utero,* and whose rights/interests have been violated.

The challenge: how, then, to minimize the latter risk

- and what standard to use for the moral evaluation of residual risks?

Conclusions

The ethics of prenatal testing should not be reduced to the ethics of selective abortion. The interests of future children, more in particular their right not to know, should be given due attention.

Giving only conditionally access to prenatal testing for a late-onset disease is morally justified.

Regarding possible future NIPD-based prenatal screening for many diseases simultaneously, the responsibility to respect the future child's right not to know is a strong argument for targeting.

The inclusion of late-onset disorders in such future prenatal screening should only be considered on the condition

- that it meets a reproductive interest of the prospective mother/parents;
- that adequate pre-test counseling is available, aimed at educating women/couples about the moral problems involved and at protecting the interests of future children;
- that such wider testing is embedded in empirical research reg. the effectiveness of such counseling.

Assuming that this effectiveness will be suboptimal, the question as to what standard should be used to evaluate this residual risk needs closer scrutiny.

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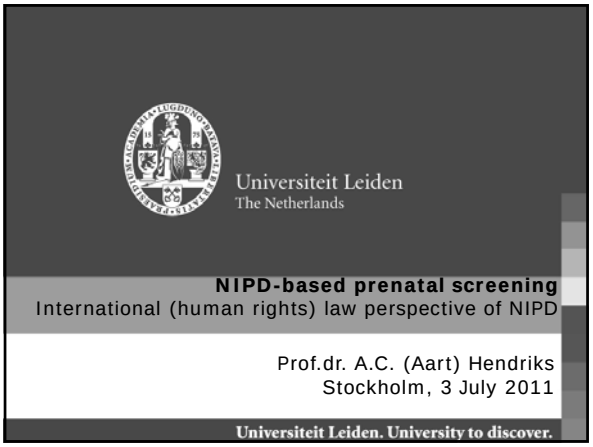

- I declare no conflict of interest.

Aims of Presentation

- Identify legal (human rights) questions involved;
- Examine applicable international and European instruments and case-law;
- Clarify why international law does not give clear norms?
- Discuss: (how) further?

Legal (h.r.) questions

- What is law? Why do we have law?

- What is human rights law? Why do we have it?

Legal (h.r.) questions

Human Rights:

Special role European Court of Human Rights (ECtHR)

Legal (h.r.) questions

NIPD-based prenatal screening can be used to reveal all kind of information - touching upon various rights/rights of different persons

Legal (h.r.) questions

Answer dependent on question: what is **aim** of NIPD-based prenatal screening and **kind of information** revealed

e.g. – Prevent harm – to woman and/or child???

- Earlier and safer means of prenatal screening (efficiency)?
- Avoid birth of foetus abnormalities?
- Facilitate preventive health measures/ adaptations?

Legal (h.r.) questions

Pregnant woman:

- Right to private life
  - Incl. personal autonomy (physical integrity, etc.), right to know, make use of legal abortion services
- Right (not) to establish a family
  - Incl. procreational freedom
- Right to health and life

Legal (h.r.) questions

Unborn child:

- Right to private life
  - Incl. personal autonomy (control over personal data – right not to know)
- Right to health and life
- Right not to be discriminated against
  - On genetic, health or other status

Legal (h.r.) questions

Rights of other persons:

- father/partner pregnant woman
  - Also autonomy/family life?
- people with same genetic make-up as unborn
  - Protection against discrimination
  - Different levels of protection?
- providers NIPD-based prenatal screening techniques
  - Property / Commercial interests

Legal (h.r.) questions

Do rights concur or conflict?

In case of conflict – how to resolve?

Legal (h.r.) questions

Main problems: rights pregnant woman and rights unborn child

But: is an unborn a person/Does an inborn have rights?

The same standards everywhere?

Applicable standards

Rights (pregnant) women

- (Procreational) autonomy;
- Access to health care services;
- Right to life;
- Right to (protection of) health.

Applicable standards

- Universal Declaration Human Rights
- Convention Discrimination Against Women (CEDAW)
- European Convention Human Rights (ECHR)
- EU-Charter of Fundamental Rights

Applicable standards

Case-law ECtHR

Ternovszky v. Hungary (14.12.10)

- Procreational rights

A., B. & C. v. Ireland (16.12.10)

- Restricting access to abortion
- Balancing with right to life (*Vo v. France*)

Applicable standards

Rights unborn child

- 'Best interest child' primary consideration;
- Right to life – also for disabled children;
- Special support disabled children;
- Right to (protection of) health;
- Non-discrimination and equal protection of law;…

Applicable standards

Rights unborn child

- Respect for dignity regardless of genetic characteristics;
- Private life –control over personal data;
- Predictive test only for health purposes;
- Non-selection of sex;
- Prohibition eugenic practices.

Applicable standards

- Convention on the Rights of Child
- Convention Rights Persons with Disabilities (CRPD)
- UNESCO Declaration Human Genome and Human Rights
- European Convention Human Rights (ECHR)
- Biomedine Convention
- EU-Charter of Fundamental Rights

Applicable standards

Case-law ECtHR

Vo v. France (08.06.04)

- Procreational rights

Biomedicine Convention > No answers.

Why no international norm?

- Legal status unborn child?
- Meaning
  - Person
  - Human dignity
  - Procreational autonomy
  - Best interests child
  - Discrimination (v. justified differentiation)
  - Eugenic practices

Why no international norm?

- How to balance (potentially) conflicting rights/interests?
- Should we distinguish between monogenetic, multifactorial and non-health factors?

Why no international norms?

ECtHR on margin of appreciation

Narrow: Important aspect individual's existence of identity
Particularly vulnerable group

Wide: No European consensus
Sensitive moral and ethical issues

Why no international norms?

What is the normative question?

Future

- Identify the normative problems
e.g. urge for 'healthy' babies?
Lack of protection unborn child?
Restrictions on women's autonomy?

- Analyse normative principles

- Try to formulate legal norms

Conclusions

- As yet, no clear international norms;
- No consensus on the problems / questions;
- (Human rights) law can not function in a vacuum when it comes to sensitive moral and ethical issues.

Post scriptum

Judgment ECtHR of 26 May 2011

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Mark your calendar for the upcoming ESHRE campus workshops!

- Early pregnancy disorders: integrating clinical, immunological and epidemiological aspects
  23-26 August 2011 - Copenhagen, Denmark
- The management of infertility – training workshop for junior doctors, paramedicals and embryologists
  7-8 September 2011 - St. Petersburg, Russia
- Basic genetics for ART practitioners
  9 September 2011 - Bucharest, Romania
- The whole man
  22-23 September 2011 - Sevilla, Spain
- Accreditation of a Preimplantation Genetic Diagnosis Laboratory
  3-4 October 2011 - Athens, Greece
- Human reproductive tissues, gametes and embryos: Innovations by science-driven culture and preservation systems
  9 October 2011 - Cairns, Australia
- Comprehensive preimplantation screening: dynamics and ethics
  13-14 October 2011 - Maastricht, The Netherlands
- Endometriosis and IVF
  28-29 October 2011 - Rome, Italy
- Endoscopy in reproductive medicine
  23-25 November 2011 - Leuven, Belgium
- What you always wanted to know about polycystic ovary syndrome
  8-10 December 2011 - Sofia, Bulgaria

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