Ethical and social issues in prenatal genetic testing: Challenges raised by NIPT

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About the project
If you wish to participate in this study
Investigators
Research Oversight Committee
End-User Committee

Moving towards implementing the next generation of prenatal screening

About PEGASUS project

PEGASUS acronym is for «PEnonalized Genomics for prenatal Aneuploidy Screening USing maternal blood»

Each year, 450,000 Canadian women become pregnant and, as a result of their participation in prenatal screening for Down syndrome, approximately 10,000 of...
NIPT: benefits
Current prenatal testing (ex. Canada)

Biochemical tests
Trim1  Trim2

450,000 pregnancies
315,000 Prenatal Screening Tests (DR 85%)

Weeks of gestation
11w 15w 16w

10,000 amniocenteses
16-21w

70 unaffected fetus lost
268 T21 detected

18+w
NIPT as second-tier screening test

Biochemical tests
Trim1  Trim2

Transabdominal Fetal Ultrasound

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NIPT as
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PEGASUS
PEGASE

NIPT

N
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T
NIPT as second-tier screening test

- **450,000 pregnancies**
- **315,000 Prenatal Screening Tests (DR 85%)**
- **300 amniocenteses**
- **10,000 T21 detected**
- **70 1 unaffected fetus lost**
- **268 265 T21 detected**
- **11w 15w 16w**
- **16-21w**
- **18+w**

*Biochemical tests*
- Trim1
- Trim2

*Transabdominal Fetal Ultrasound*
NIPT as first-tier screening test

450,000 pregnancies

N
I
P
T

Weeks of gestation
11w 15w 16w 17-18w 18-19w

10,000 amniocenteses

70 ? unaffected fetus lost

268 ? T21 detected
NIPT as **diagnostic test**

450,000 pregnancies

Weeks of gestation:
- 11w, 15w, 16w
- 16-21w
- 18+w
NIPT: benefits

- **Safe** – no increased risk of miscarriage
- **Accurate** – more reliable than serum/integrated screen
- As first tier test – results **earlier** in the pregnancy
- Potentially **cheaper** than current testing pathway
- Allows testing for a **growing number** of conditions

- Studies show women are very enthusiastic about NIPT
- High expected uptake
NIPT: Concerns
Ethical and social issues raised by NIPT

- Justice and equity
- Decision-making
- Disability rights and eugenics
- Threshold of testing
- Whole genome
Ethical and social issues raised by NIPT

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Justice and equity of access

- Cost of NIPT as a barrier to access
- Inequity:
  - women without resources may opt for invasive testing, that is often covered by public funding or insurance
  - subject their pregnancies to a risk of miscarriage that can be mitigated by NIPT
Justice and equity of access

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- Policy decisions about public funding should be evidence-based

- Concerns about premature implementation due to commercial pressures
Justice and equity of access

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Ethical and social issues raised by NIPT

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Decision-making:
Choice to test should be free

- *Routinization* would be the greatest success of NIPT, but…

- Routine use creates an *expectation* of uptake

- Could entail increased *pressure* on women to test, especially in the absence of risk of miscarriage

- Threat to women’s *free* choice (reproductive autonomy)

- Need to ensure women are *offered* NIPT and feel free to decline
Decision-making: Choice to test should be *informed*

- Framing of testing as “ensuring the health of the baby” is ethically problematic
  - Many women believe that: “testing somehow promotes the birth of a healthy child, such that a *caring* woman is not doing her *motherly duty* if she forgoes testing” (Seavilleklein)

- Testing is seen as a “ritual of reassurance” (Press & Browner)

- Refusing to test can therefore be perceived as ‘medically irresponsible’ and even ‘unacceptable’
Decision-making:
Choice to test should be *informed*

- But testing does not ensure a healthy baby

- Women need appropriate pre-test information to understand the meaning of the test and their options following testing

- Routine use can pose threat to *informed* choice
  - Recent reactions to proposed ‘reflex’ testing method (UK)

- Healthcare providers’ perceptions:
  - Studies show that in the absence of risk of miscarriage, many perceive consent for NIPT as *less important* than for invasive testing
Decision-making:
Choice to test should be *supported*

- As NIPT shifts to first-tier screening, volume of tests will grow substantially

- Offer of NIPT will shift from a small high-risk population to all pregnant women
  - in the US (based on current rates of screening uptake) could mean from \(~100,000\) to \(~3\) million per year

- Inability of healthcare system to counsel all women
Decision-making:
Choice to test should be *supported*

Need to:

- Rethink / reinvent current models of genetic counseling

- Support and train OB/GYNS & GPs who offer NIPT

- Create innovative educational resources for women & professionals

- Encourage shared decision-making, e.g. via decision-aid tools
Decision-making:
Choice to test should be *supported*

- Inform providers regarding possible *legal obligation* to offer NIPT
  - fear of ‘wrongful life claims’
Decision-making: Choice to test should be supported

- Inform providers regarding possible legal obligation to offer NIPT

Decision-making:
Choice to test should be *supported*

- Inform providers regarding possible *legal obligation* to offer NIPT
- Issues raised by maternal cancer discovered through NIPT
Decision-making about NIPT should be:

- Free / voluntary
- Informed
Decision-making about NIPT should be:

- Free / voluntary
- Informed

Supported:

- Women:
  - counseling
  - shared decision-making

- Clinicians:
  - training
  - addressing concerns about legal implications
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Disability rights

• The *Disability Rights Critique* of prenatal testing
  - the *expressivist* argument

  “Prenatal tests to select against disabling traits *express* a hurtful attitude about and send a hurtful message to people who live with those same traits”

  *(Parens & Asche, 1999)*
Disability rights

• Increase in testing \(\rightarrow\) in detection \(\rightarrow\) in terminations

• Decrease in the population of individuals with T21
  • in support for their families
  • in research on their conditions
Broader concerns re eugenic attitudes

• A society with less diversity can become less tolerant

• Increased expectation of ‘perfect babies’

• Stigmatization of women/couples who choose to pursue pregnancy with affected fetus

• Possibility of penalizing through loss of medical insurance for conditions that could have been detected prenatally
Ethical and social issues raised by NIPT

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Threshold for appropriate testing

• Invasive testing is only carried out for conditions that are ‘severe enough’ to justify the risk of miscarriage

• Risk-free nature of NIPT + ability to test earlier could lower the threshold for testing
Threshold for appropriate testing

- Invasive testing is only carried out for conditions that are ‘severe enough’ to justify the risk of miscarriage.
- Risk-free nature of NIPT + ability to test earlier could lower the threshold for testing.

- Individuals may wish to test for -
  - less severe / treatable conditions
  - late-onset conditions
  - physical traits (in future even behavioral/personality traits)
  - non-medical information such as paternity and fetal sex
Ethical concerns surrounding sex selection

Noninvasive Fetal Sex Determination Using Cell-Free Fetal DNA
A Systematic Review and Meta-analysis

Stephanie A. Devaney, PhD
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Joan A. Scott, MS, CGC
Diana W. Blumen, MD

Noninvasive prenatal determination of fetal sex could provide an important alternative to invasive genetic determination, which is currently the gold standard for ambiguous genitalia, X-linked conditions, and single-gene disorders such as congenital adrenal hyperplasia. Chronic villus sampling and amniocentesis have small but measurable rates of procedure-related pregnancy loss. The availability of a reliable noninvasive alternative to determine fetal sex would reduce unintended fetal losses and would presumably be welcomed by pregnant women across the United States. A much broader potential application for fetal sex determination is family balancing, which poses ethical concerns.

Fetal sex determination can be performed by sonography accurately as 11 weeks’ gestation although by 12 weeks’ gestation, performance across published studies varies significantly. According to a review by Odeh et al., fetal sex cannot be determined by ultrasound examination in 7.5% to 50% of pregnancies at 11 weeks’ gestation, and this decreases to 3% to 25% at 13 weeks. When reported, the sex determination is incorrect as often as 40% of the time at 11 weeks, although by 12 weeks, accuracy (when reported) is close to 100%.

Conclusions: Noninvasive prenatal determination of fetal sex using cell-free fetal DNA provides an alternative to invasive techniques for some heritable disorders. In some countries this testing has transitioned to clinical care, despite the absence of a formal level of performance.

Objective: To document overall test performance of noninvasive fetal sex determination using cell-free fetal DNA and to identify factors that affect performance.

Data Sources: Systematic review and meta-analysis with search of PubMed (January 1, 1997-April 17, 2011) to identify English-language human studies reporting primary data. References from review articles were also searched.

Study Selection and Data Extraction: Abstracts were independently identified to identify studies reporting primary data suitable for analysis. Countries included publications year, sample type, DNA amplification methodology, Y chromosome sequence, and gestational age. Data were independently extracted by 2 reviewers.

Results: From 57 selected studies, 80 data sets (representing 28,434 male-birth pregnancies and 27,115 female-birth pregnancies) were analyzed. Overall performance of the test to detect Y chromosome sequences had the following characteristics: sensitivity, 98.4% (95% confidence interval [CI], 97.7%–99.0%); diagnostic odds ratio (OR), 288; positive predictive value, 98.8%; negative predictive value, 98.4%; area under the curve (AUC), 0.950 (95% CI, 0.948–0.952); with significant interstudy heterogeneity. DNA methodology and gestational age had the largest effects on test performance. Methodology test characteristics were AUC, 0.988 (95% CI, 0.985–0.990) for polymerase chain reaction (PCR) and AUC, 0.956 (95% CI, 0.953–0.957) for real-time quantifiable PCR (RTQ-PCR) (P = .002). Gestational age test characteristics were AUC, 0.988 (95% CI, 0.985–0.990) (7 weeks); AUC, 0.994 (95% CI, 0.992–0.996) (9–26 weeks); AUC, 0.992 (95% CI, 0.990–0.994) (20–26 weeks); and AUC, 0.998 (95% CI, 0.990–0.999) (20 weeks) (P = .02 for comparison of diagnostic ORs across age ranges). RTQ-PCR (sensitivity, 99.0%; specificity, 99.9%) outperformed conventional PCR (sensitivity, 94.5%; specificity, 99.3%), testing at 12 weeks (sensitivity, 94.5%; specificity, 99.3%), and 13 through 20 weeks (sensitivity, 95.5%; specificity, 99.1%).

Conclusions: Despite interstudy variability, performance was high using maternal blood. Sensitivity and specificity for detection of Y chromosome sequences was greatest using RTQ-PCR after 20 weeks’ gestation. Tests using urine and tests requiring sex week’s gestation were unreliable.

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*The accuracy study was completed in 2009 with the Fair Data Women’s Health Center (FDWCH) in Pasadena, CA. Blood samples collected from the FDWCH were tested using the Consumer Genomics Inc. proprietary methodology and results were released back to the Center. A FDWCH licensed Diagnostic Medical Technologist blinded from the Pink or Blue® results conducted multiple real-time ultrasound exams. FDWCH ultrasound results and Pink or Blue® results were compared at the Center and it was determined that 97% of the results were accurate.

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First
Ethical and social issues raised by NIPT

- Justice and equity
- Decision-making
- Disability rights and eugenics
- Threshold of testing
- Whole genome
Whole genome NIPT

- ban / permit ?
- limit ?
- offer ?
- encourage ?
- cover by insurance ?
Whole genome NIPT: concerns

- Reliability of information
- Justice: equity of access concerns (if private)
- Justice: priorities in resource allocation (if public)
- Right of the child to an open future
- Counseling and consent
- Decision-making
Whole genome NIPT

‘knowledge is power’

- more information → better decision-making
- …but is information always knowledge?

‘knowledge can be vulnerability’

- Nature of information
  - reliable? actionable?
  - risk level, severity of phenotype, age of onset, treatability
- Implications of information
  - decision that is time sensitive; irreversible
  - short term - anxiety, confusion
  - long term – guilt, decisional regret

Providing Unrestricted Access to Prenatal Testing Does Not Translate to Enhanced Autonomy

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Francois Rousseau, Centre de recherche du CHU de Québec, CHU de Québec–Université Laval
Anne-Marie Laberge, CHU Sainte-Justine and University of Montreal

In “A Framework for Unrestricted Prenatal Whole-Genome Sequencing: Respecting and Enhancing the Autonomy of Prospective Parents,” Chen and Wasserman (2017) argue in favor of an unrestricted albeit well-informed prenatal testing policy for any variant of known significance. We acknowledge that prenatal genetic testing should remain focused on promoting reproductive autonomy and that we should steer clear of policies that implicitly—or explicitly—promote eugenic attitudes (Gekas et al. 2016; Ravitsky 2015). However, we disagree that the best way to achieve these objectives is through an unrestricted offer and coverage of noninvasive prenatal whole-genome sequencing (NIPW).

NIPW AND REPRODUCTIVE AUTONOMY
Public funding of any health intervention needs to meet certain criteria of evidence-based analytical and clinical validity, clinical utility (i.e., improved health outcomes), and cost-effectiveness or cost utility (Khoury et al. 2009). These criteria
Whole genome NIPT

“Burdening prospective parents with extraordinary amounts of information,

some of which has no clear clinical (or other) significance

and some of which is unreliable,

does not enhance their reproductive autonomy. If anything, it might even hinder it.”
What does the future hold?

- Ultrasound made the uterus transparent and revolutionized our perception of the fetus

- Whole genome NIPT could make the fetus itself ‘transparent’
Thank you

謝謝