Ethical and Social Implications of the Shifting Landscape of Prenatal Testing

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PEGASUS
PEGASE

Université de Montréal

www.pegasus-pegase.ca

About PEGASUS project

PEGASUS acronym is for «PErsonalized 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

«The introduction of genomic blood testing as proposed in the context of this project could lead to increased detection of Down syndrome, less invasive screening

Two rationales of prenatal testing

- Public health
  - reduction in incidence (burden) of disease
  - testing to screen out certain conditions
  - (implicit expectation that diagnosis will be followed by termination)

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- Public health
  - Implicit, concealed, unspoken

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- Reproductive autonomy
  - providing information to expand women's options
  - promoting informed choice
  - voluntary, free of pressure
  - supported by non-directive counseling
  - expressed through informed consent

Two rationales of prenatal testing

- Public health
  - Implicit, concealed, unspoken
- Reproductive autonomy
  - The agreeable face of prenatal testing
  - Justifiable, convincing

The public health rationale: challenges

- Pressure on women to test
  - even to terminate (?)
  - testing as ‘search and destroy’
  - possibility of ‘penalizing’ via loss of coverage
- Impact on disability rights
  - expressivist argument
- Shares moral space with propensity toward:
  - abortion (individual)
  - eugenics (collective)

The autonomy rationale: challenges

- Great difficulties in implemenation
  - Resources
  - Not really in anyone's interest:
    - *Government:* increased uptake = success
    - *Clinicians*: fear of liability promotes routinization

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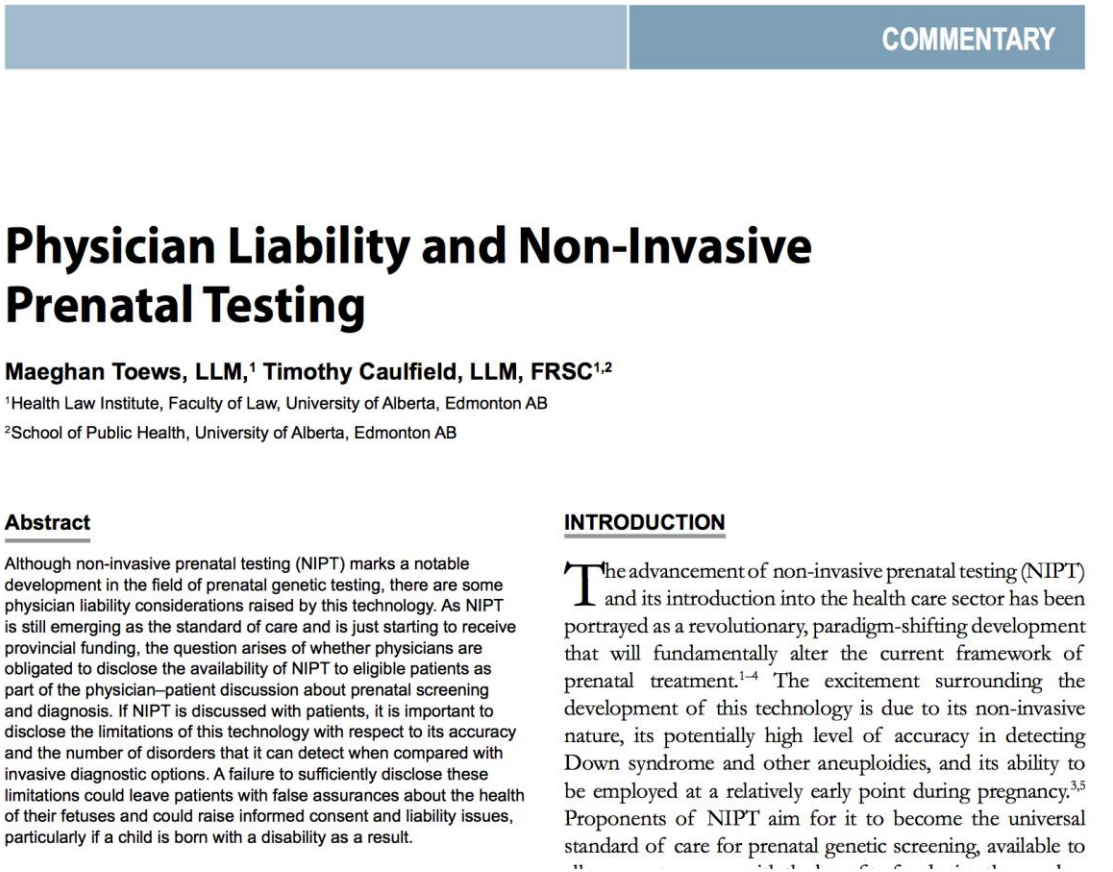

COMMENTARY

Physician Liability and Non-Invasive Prenatal Testing

Maeghan Toews, LLM,[1] Timothy Caulfield, LLM, FRSC[1,2]

[1]Health Law Institute, Faculty of Law, University of Alberta, Edmonton AB

[2]School of Public Health, University of Alberta, Edmonton AB

Abstract

Although non-invasive prenatal testing (NIPT) marks a notable development in the field of prenatal genetic testing, there are some physician liability considerations raised by this technology. As NIPT is still emerging as the standard of care and is just starting to receive provincial funding, the question arises of whether physicians are obligated to disclose the availability of NIPT to eligible patients as part of the physician–patient discussion about prenatal screening and diagnosis. If NIPT is discussed with patients, it is important to disclose the limitations of this technology with respect to its accuracy and the number of disorders that it can detect when compared with invasive diagnostic options. A failure to sufficiently disclose these limitations could leave patients with false assurances about the health of their fetuses and could raise informed consent and liability issues, particularly if a child is born with a disability as a result.

INTRODUCTION

The advancement of non-invasive prenatal testing (NIPT) and its introduction into the health care sector has been portrayed as a revolutionary, paradigm-shifting development that will fundamentally alter the current framework of prenatal treatment.[1–4] The excitement surrounding the development of this technology is due to its non-invasive nature, its potentially high level of accuracy in detecting Down syndrome and other aneuploidies, and its ability to be employed at a relatively early point during pregnancy.[3,5] Proponents of NIPT aim for it to become the universal standard of care for prenatal genetic screening, available to

Maeghan Toews and Timothy Caulfield, "**Physician Liability and Non-Invasive Prenatal Testing**". *Journal of Obstetrics & Gynaecology Canada*, 36 (10): 907–914. 2014.

The autonomy rationale: challenges

- Great difficulties in implemenation
  - Resources
  - Not really in anyone's interest:
    - *Government:* increased uptake = success
    - *Clinicians*: fear of liability promotes routinization
    - *Women*: maintaining the false narrative that testing 'ensures baby's health' ("ritual of resssurance")

The autonomy rationale: challenges

- Disability rights critique
  - The ‘parental attitude argument’
  - Shouldering individual women with responsibility for societal implications

The autonomy rationale: challenges

- Reproductive autonomy rationale as a smoke screen
  - Palatable theoretical framework that is not implemented in clinical practice (no Informed consent)
- Not innocuous
  - Allows us to absolve ourselves of facing societal issues

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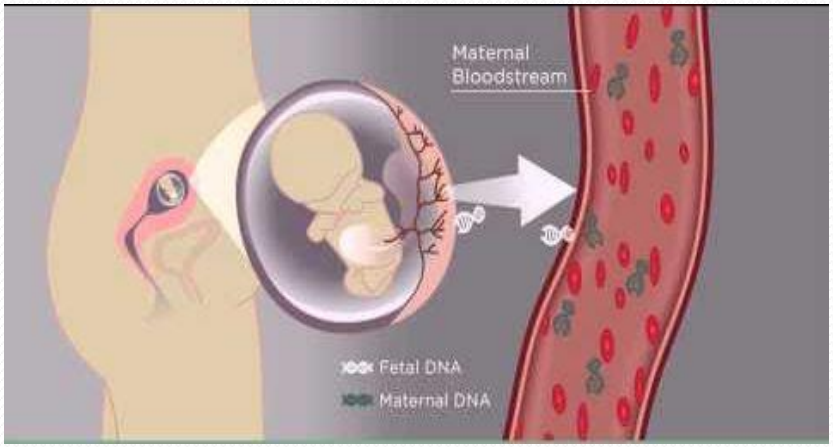
- My bottom line argument:
  - Implementing this rationale at the individual level may be a lost battle
  - so we must protect it at a societal level via policy

Enter NIPT !

(Non-Invasive Prenatal Testing)

What is Non-Invasive Prenatal Testing (NIPT)?

- Tests cell-free fetal DNA floating in maternal plasma
  - After 10 weeks of gestation, ~10-15% of cffDNA comes from the fetus



- All cffDNA clears from the woman's blood within 2 hours after birth, ensuring that any detected fetal DNA is from the *current* pregnancy

Enter NIPT !

(Non-Invasive Prenatal Testing)

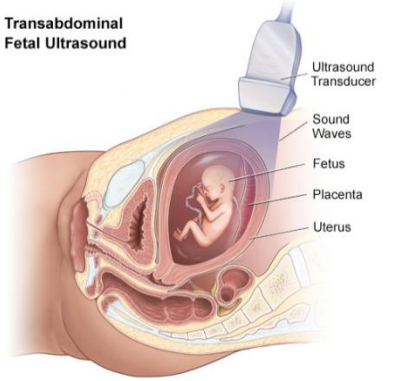
- The long awaited ‘holy grail’ of prenatal testing
  - *No increased risk of miscarriage*
  - First trimester
  - More accurate than current screening
  - Cost → decreasing
  - Conditions it can test for → increasing
- Coming soon: routinization
  - Paradoxically exacerbates the challenges of the reproductive autonomy model

Current prenatal testing (ex. Canada)

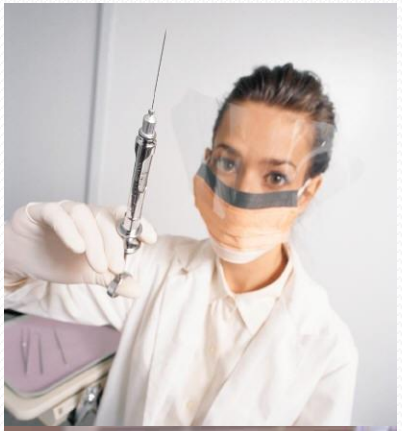
450,000 pregnancies

Biochemical tests

Trim1 Trim2



315,000 Prenatal Screening Tests (DR 85%)



10,000 amniocenteses

70 unaffected fetus lost

268 T21 detected

Weeks of gestation

11w 15w 16w 16-21w 18+w

NIPT as second-tier screening test

450,000 pregnancies

Biochemical tests

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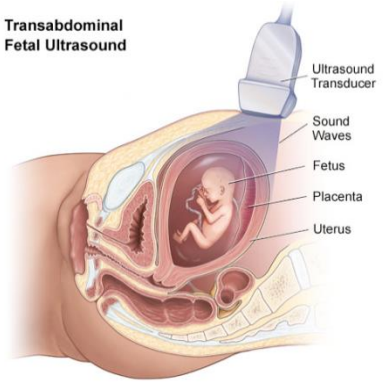

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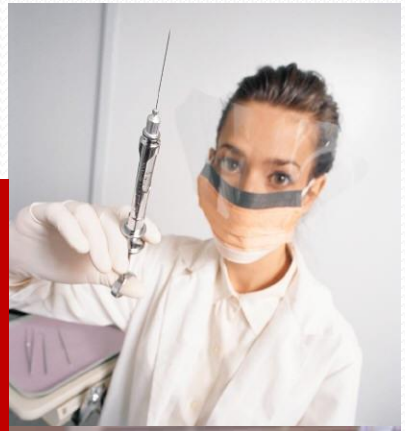
NIPT



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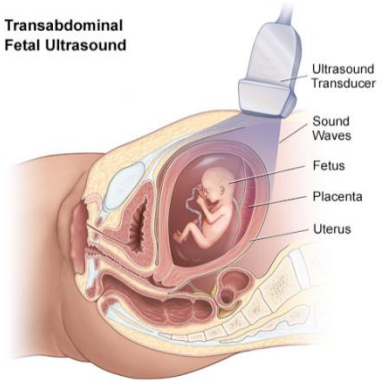

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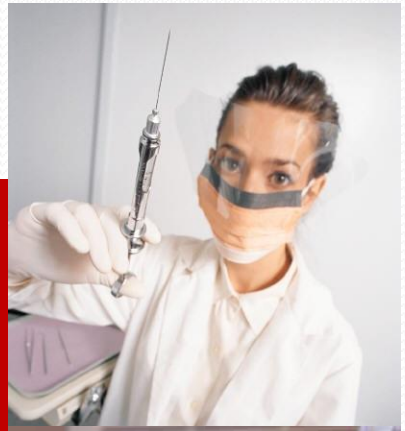


~~10,000~~ 300 amniocenteses

~~70~~ 1 unaffected fetus lost

~~268~~ 265 T21 detected

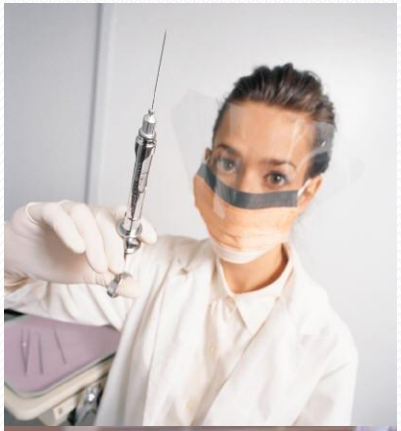
Weeks of gestation

11w 15w 16w 16-21w 18+w

NIPT as first-tier screening test

450,000 pregnancies

N I P T



~~10,000~~ amniocenteses ???

~~70~~ ? unaffected fetus lost

~~268~~ ? T21 detected

Weeks of gestation

11w 15w 16w 17-18w 18-19w

NIPT as a diagnostic test

450,000 pregnancies

NIPT

Weeks of gestation

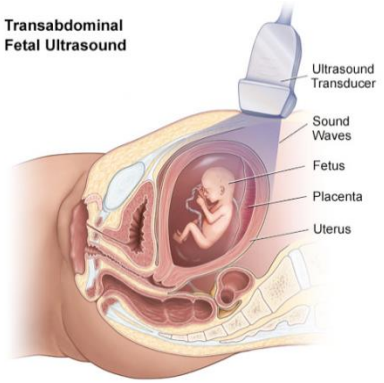
11w 15w 16w 16-21w 18+w

When does consent take place?

450,000 pregnancies

Biochemical tests

Trim1 Trim2



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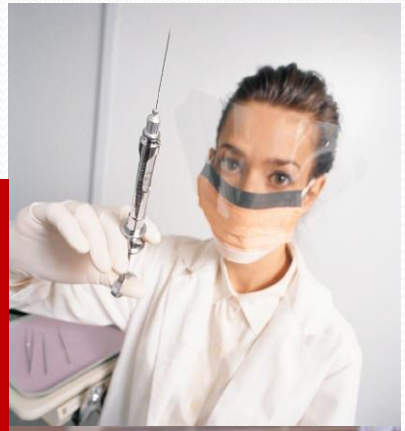

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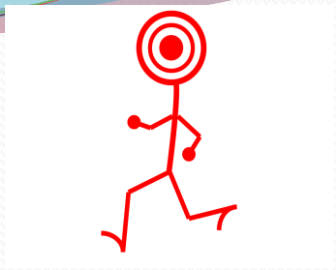
What can NIPT currently test for?



- Fetal sex (for x-linked conditions)
- Blood type
- Trisomy 21, 13, 18
- Other (more rare) trisomies
- Sex chromosome abnormalities
- Autosomal single-gene disorders
- Micro-deletion syndromes
- Technically: whole genome sequencing

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

Vardit Ravitsky, University of Montreal
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

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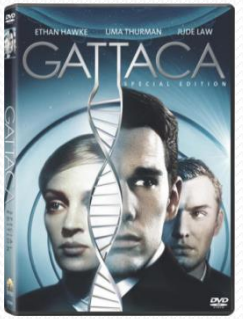
What does the future hold?

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

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



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  - voluntary, free of pressure
  - supported by non-directive counseling
  - expressed through informed consent

As NIPT enters the clinic and reshapes the landscape of prenatal testing, *which rationale should prevail* ?

- Reproductive autonomy
  - Insisting on informed consent for testing → resisting the 'nightmare scenario' of exposure to unwanted results
- Public health
  - Abandoning consent for testing (recent ex. Reflex testing)
    - (no risk to pregnancy → consent not required)
  - Accepting/addressing social implications for disability rights

My argument:

- Even if informed consent for NIPT is a lost battle at the individual level…
- …the public health rationale must be resisted at a social level
  - on moral grounds
    - protecting women/families from pressure
    - protecting disability rights
  - on pragmatic grounds
    - to avoid social backlash

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NIPT: The UK as a case study

- January 2016:
  - UK National Screening Committee recommends public funding of NIPT as part of the “National Health Service Fetal Anomaly Screening Program”
  - Only for high-risk pregnancies
  - Not deemed cost-effective for all pregnant women
  - Calculation based on impact on NIPT on
    - savings from avoided invasive tests
    - numbers of cases diagnosed

NIPT: The UK as a case study

- Decision follows a period of public consultation
- Contribution from the Royal College of Obstetricians and Gynaecologists argues that NIPT for all pregnancies may be cost effective after all…

NIPT: The UK as a case study

- Royal College of Obstetricians and Gynaecologists :

"If the decision has been made primarily on cost grounds, then a more rigorous economic analysis has to be made that **includes the lifetime costs of caring for children and adults with Down's syndrome** (bearing in mind that cfDNA testing as a primary screen test will identify approximately 289 more babies with trisomies). Such an economic analysis may (or may not) suggest that cfDNA testing for all is cost-effective."

NIPT: The UK as a case study

- September 2016:
- More than 100 healthcare professionals sign a letter attacking the Royal College for this recommendation
- The letter accuses the College of ‘advocating that women with a prenatal diagnosis of Down’s syndrome should end their pregnancy’

NIPT: The UK as a case study

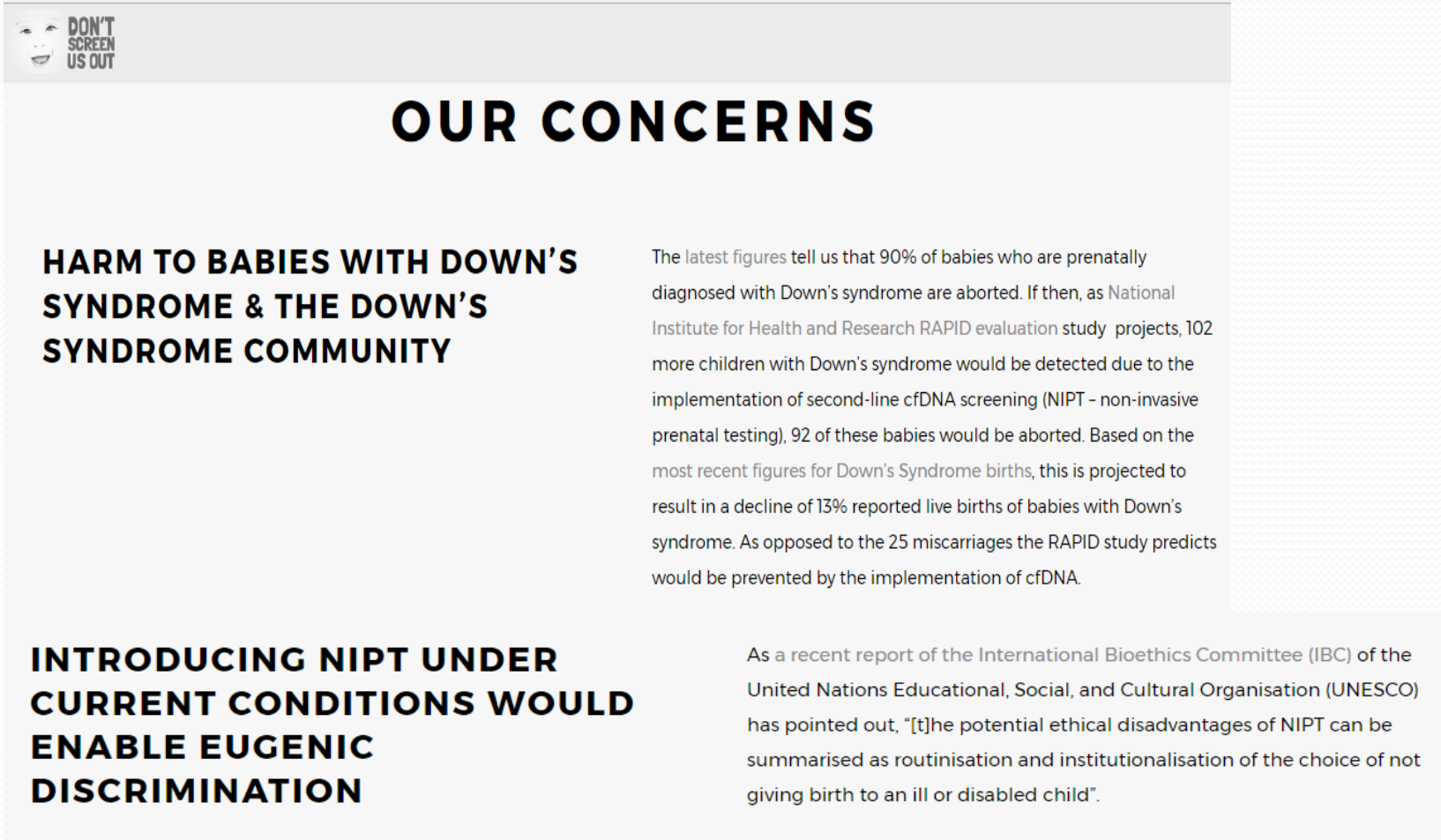
- September – October 2016:
- A public outcry follows
- Media articles condemn the College's view
- Celebrities and doctors with children who have DS say they are "shocked", "horrified", "terrified"
- Articles highlight the value of individuals with DS
- Express fear of such eugenic tendencies

NIPT: The UK as a case study

NIPT: The UK as a case study

- 28 MPs sign motion in support of a campaign titled “Don’t Screen Us Out”

NIPT: The UK as a case study



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- Even if informed consent for NIPT is a lost battle at the individual level
- the reproductive autonomy rationale must be protected/promoted at a societal level via policies that – at least at the collective level:
  - reduce pressures on women
  - allow them viable options

Required policy elements

1/ Ensure cost-effectiveness calculations *never* include the savings associated with 'prevented lives'

2/ Ensure that the objective and performance measure of any government-run prenatal screening program is to increase the *offer,* not the *uptake*, of the test

3/ Consult relevant stakeholders when designing policy, including disability rights advocates and patient groups

Required policy elements

4/ Ensure screened conditions are not considered 'pre-existing conditions' that create barriers to coverage (under the pretext that they were detectable prior to birth)

5/ Ensure and maintain social support for families raising children with the conditions screening targets

6/ Fund and support research designed to improve the health outcomes and quality of life of those living with screened conditions

7/ Ensure women have access to legal, safe and free/affordable pregnancy termination services

My argument:

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- the reproductive autonomy rationale must be protected/promoted at a societal level via policies that – at least at the collective level:
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  - allow them viable options

Some nuances:

- The bioethical tendency (legacy of principlism) to see tension as needing ‘resolution’
  - principles are specified to see if they can live in harmony
  - or balanced/weighed & to decide which would win / be sacrificed
- But tension is often inherent, productive, stimulating deeper reflection
  - requires ongoing negotiation, choreography
- How do the 2 rationales ‘speak to each other’?

How do the 2 rationales ‘speak to each other’?

At the core of both rationales is our understanding of:

- the spectrum of human difference (health, disability, disease)
- the ‘threshold of entrance’ into society, and its associated ‘costs’

How do the 2 rationales ‘speak to each other’?

- Reproductive autonomy is not an isolated exercise
- It is rather contextualized, situated, relational
  - as illustrated by the global implementation of NIPT

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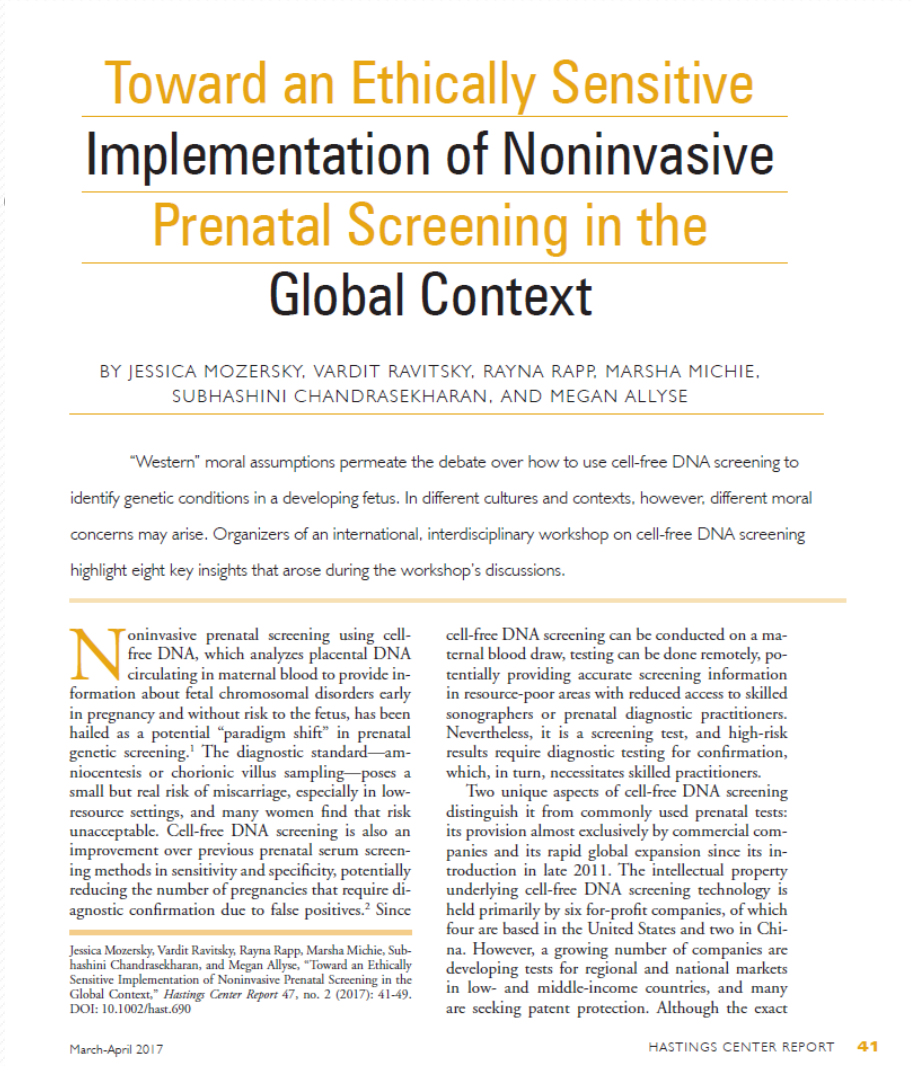

Toward an Ethically Sensitive Implementation of Noninvasive Prenatal Screening in the Global Context

BY JESSICA MOZERSKY, VARDIT RAVITSKY, RAYNA RAPP, MARSHA MICHIE, SUBHASHINI CHANDRASEKHARAN, AND MEGAN ALLYSE

"Western" moral assumptions permeate the debate over how to use cell-free DNA screening to identify genetic conditions in a developing fetus. In different cultures and contexts, however, different moral concerns may arise. Organizers of an international, interdisciplinary workshop on cell-free DNA screening highlight eight key insights that arose during the workshop's discussions.

Noninvasive prenatal screening using cell-free DNA, which analyzes placental DNA circulating in maternal blood to provide information about fetal chromosomal disorders early in pregnancy and without risk to the fetus, has been hailed as a potential "paradigm shift" in prenatal genetic screening.[1] The diagnostic standard—amniocentesis or chorionic villus sampling—poses a small but real risk of miscarriage, especially in low-resource settings, and many women find that risk unacceptable. Cell-free DNA screening is also an improvement over previous prenatal serum screening methods in sensitivity and specificity, potentially reducing the number of pregnancies that require diagnostic confirmation due to false positives.[2] Since cell-free DNA screening can be conducted on a maternal blood draw, testing can be done remotely, potentially providing accurate screening information in resource-poor areas with reduced access to skilled sonographers or prenatal diagnostic practitioners. Nevertheless, it is a screening test, and high-risk results require diagnostic testing for confirmation, which, in turn, necessitates skilled practitioners.

Two unique aspects of cell-free DNA screening distinguish it from commonly used prenatal tests: its provision almost exclusively by commercial companies and its rapid global expansion since its introduction in late 2011. The intellectual property underlying cell-free DNA screening technology is held primarily by six for-profit companies, of which four are based in the United States and two in China. However, a growing number of companies are developing tests for regional and national markets in low- and middle-income countries, and many are seeking patent protection. Although the exact

Jessica Mozersky, Vardit Ravitsky, Rayna Rapp, Marsha Michie, Subhashini Chandrasekharan, and Megan Allyse, "Toward an Ethically Sensitive Implementation of Noninvasive Prenatal Screening in the Global Context," *Hastings Center Report* 47, no. 2 (2017): 41-49. DOI: 10.1002/hast.690

How do the 2 rationales 'speak to each other'?

- Individual decisions reflect societal/cultural values, collective understandings of *the good life*

- They also reflect the pressures society constructs around these understandings (ex. 'risk' vs. 'chance')
  - in the case of NIPT – combined with commercial pressures

How do the 2 rationales 'speak to each other'?

- This makes pregnant women and their families what Rapp called 'moral pioneers'
- Their aggregate decisions both ***reflect*** and ***shape*** our cultural views of the value of human life
- These decisions feed into a public health rationale and are in turn pressured by it
- The choreography of the 2 rationales:
  - A circular dance around the threshold of

acceptable -- justified/desired -- expected testing

Thank you

謝謝

Brian Skotko's recent paper: "Out-of-pocket medical costs and third-party healthcare costs for children with Down syndrome"

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Out-of-Pocket Medical Costs and Third-Party Healthcare Costs for Children With Down Syndrome

Andrew Kageleiry,[1] David Samuelson,[1] Mei Sheng Duh,[1] Patrick Lefebvre,[2] John Campbell,[3] and Brian G. Skotko[4,5]*

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[5]Harvard Medical School, Boston, Massachusetts

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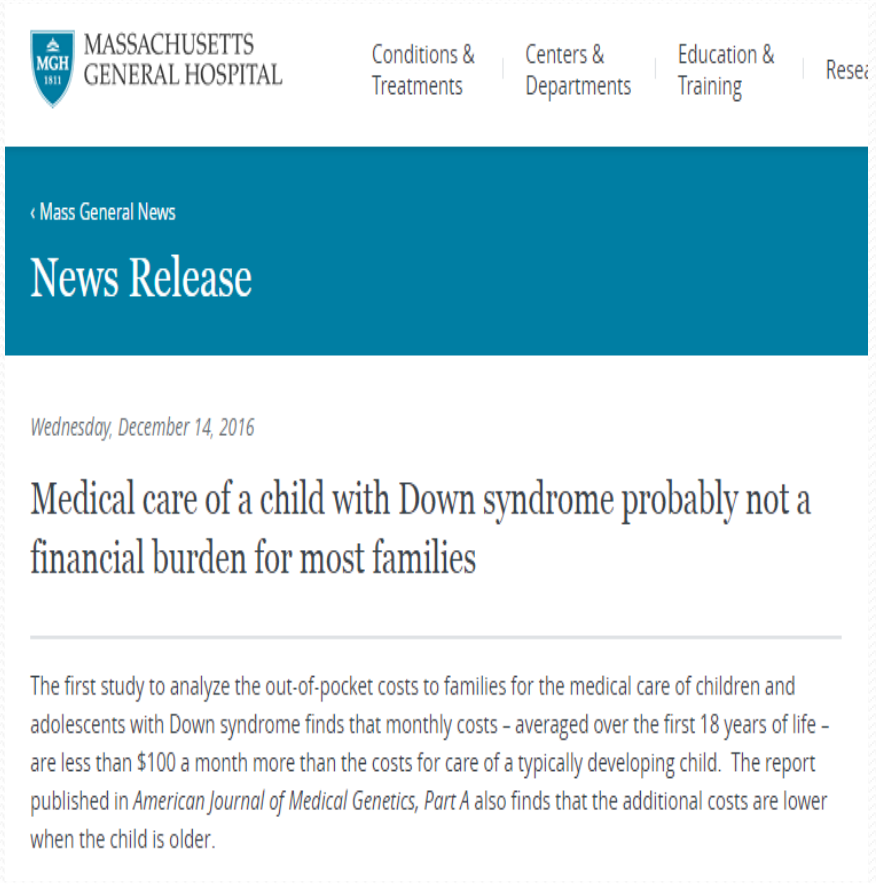
Prior analyses have estimated the lifetime total societal costs of a person with Down syndrome (DS); however, no studies capture the expected medical costs that patients with DS can expect to incur during childhood. The study utilized the OptumHealth Reporting and Insights administrative claims database from 1999 to 2013. Children with a diagnosis of DS were identified, and their time was divided into clinically relevant age categories. Patients with DS in each age category were matched to controls without chromosomal conditions. Out-of-pocket medical costs and third-party expenditures were compared between the pa-
tient-age cohorts with DS and matched controls. Patients with

How to Cite this Article:
Kageleiry A, Samuelson D, Duh MS, Lefebvre P, Campbell J, Skotko BG. 2016. Out-of-pocket medical costs and third-party healthcare costs for children with Down syndrome.
Am J Med Genet Part A 9999A:1–11.



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‹ Mass General News

News Release

Wednesday, December 14, 2016

Medical care of a child with Down syndrome probably not a financial burden for most families

The first study to analyze the out-of-pocket costs to families for the medical care of children and adolescents with Down syndrome finds that monthly costs – averaged over the first 18 years of life – are less than $100 a month more than the costs for care of a typically developing child. The report published in *American Journal of Medical Genetics, Part A* also finds that the additional costs are lower when the child is older.