Centre for Bioethics
The Chinese University of Hong Kong
香港中文大學生命倫理學中心

Current and Emerging prenatal testing technologies: Bioethical implications

Vardit Ravitsky, PhD

The Hastings Center

Harvard Medical School

THE HASTINGS CENTER

CENTER FOR BIOETHICS
HARVARD MEDICAL SCHOOL

https://magazine.hms.harvard.edu/articles/ethics-prenatal-genetic-testing

HARVARD medicine
THE MAGAZINE OF HARVARD MEDICAL SCHOOL

← All Articles

August 2024

The Ethics of Prenatal Genetic Testing

Is more information better when it comes to prenatal screening?

Summer 2024

by Molly McDonough

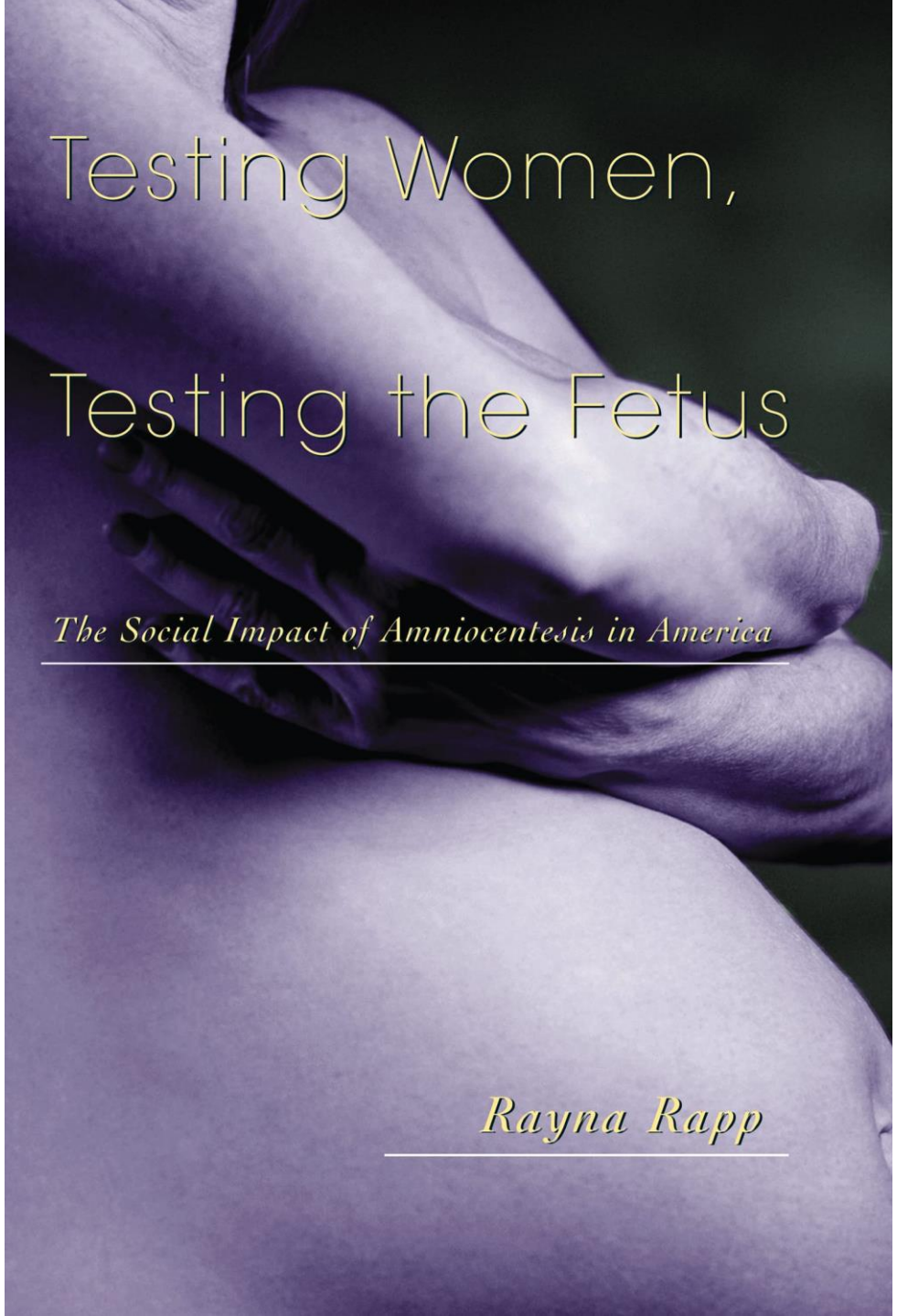
7 min read

Interview

Vardit Ravitsky

When Vardit Ravitsky was pregnant at age forty, a routine screening test revealed a 1-in-40 chance her child could be born with Down syndrome. Suddenly Ravitsky, senior lecturer on global health and social medicine, part-time, at HMS, faced a dilemma: Was it worth undergoing further invasive testing, risking miscarriage, to find out for certain?

Rayna Rapp:
Women as ‘moral pioneers’ (1999)



(1999)

The Disability Rights Critique of Prenatal Genetic Testing

Reflections and Recommendations

The international project to sequence the human genome was undertaken in the expectation that knowing the sequence will offer new ways to understand and treat disease and disability. If researchers can identify the sequences of genes that code for the body's building blocks, then, it is hoped, they can identify and correct the sequences associated with disease and disability.

So far, researchers have enjoyed only minimal success in using gene therapy to correct such conditions, and no researcher has yet even attempted to use gene therapy to correct genetic impairments in a fetus. Rather, the discovery of abnormal or incorrect sequences has led primarily to the development of genetic tests that can reveal whether a person, embryo, or (in the usual case) a fetus carries an abnormality or "mutation" associated with disease or disability. It is now possible to test for gene mutations associated with some 400 conditions, from those universally viewed as severe, such as Tay Sachs, to those that many might describe as relatively minor, such as polydactyly (a trait involving an extra little finger). The number and variety of conditions for which tests are available grows almost daily.[1]

Today we test for one trait at a time. In the future, however, with advances in biochip technology, it will be possible to test simultaneously for as many traits as one would like. In principle, we will be able to test for any trait we wish that has been associated with any given allele. Not only will the cost of such testing likely decrease as the diagnostic technology advances, but advances in the technology will make it possible to do the testing earlier in the pregnancy. One such technology will isolate the very small number of fetal cells that circulate in the maternal blood. Insofar as these earlier tests will be performed on fetal cells obtained from the mother's blood (rather than from the amniotic sac or chorionic villi) they will be noninvasive. Thus it will be possible to do many more tests, at once, and with less cost to the pregnant woman in time, inconvenience, risk, or dollars, than is now the case.[2]

As the ease of testing increases, so does the perception within both the medical and broader communities that prenatal testing is a logical extension of good prenatal care: the idea is that prenatal testing helps prospective parents have healthy babies. On the one hand, this perception is quite reasonable. Though no researcher has yet even attempted to correct a genetic impairment with in-utero gene therapy, increasingly there are nongenetic approaches to such impairments. At the time of this writing, more than fifty fetuses have undergone in-utero surgery to repair neural tube impairments (myleomeningoceles).[3] Moreover, negative (or reassuring) prenatal test results will reduce the anxiety felt by many prospective parents, and this in itself can be construed as part of good prenatal care. On the other hand, as long as in-utero interventions remain relatively rare, and as long as the number of people seeking prenatal genetic information to prepare for the birth of a child with a disability remains small, prospective parents will use positive prenatal test results primarily as the basis of a decision to abort fetuses that carry mutations associated with disease and/or disability. Thus there is a sense in which prenatal testing is not simply a logical extension of the idea of good prenatal care.

Logical extension or no, using prenatal tests to prevent the birth of babies with disabilities seems to be self-evidently good to many people. Even if the testing will not help bring a healthy baby to term this time, it gives prospective parents a chance to try again to conceive. To others, however, prenatal testing looks rather different. If one thinks for even a moment about the history of our society's treatment of people with disabilities, it is not difficult to appreciate why people identified with the disability rights movement might regard such testing as dangerous. For the members of this movement, including people with and without disabilities and both issue-focused and disability-focused groups, living with disabling traits need not be detrimental either to an individual's prospects of leading a worthwhile life, or to the families in which they grow up, or to society at large. Although the movement has no one position on prenatal diagnosis, many adherents of

Erik Parens and Adrienne Asch, "The Disability Rights Critique of Prenatal Testing: Reflections and Recommendations," Special Supplement, *Hastings Center Report* 29, no. 5 (1999): S1-S22.

5

The Down Syndrome Information Act and "Mere Difference": Redefining the Scope of Prenatal Testing Conversations?

Marie-Eve Lemoine and Vardit Ravitsky[1]

Since the very introduction of amniocentesis, prenatal testing for Down syndrome (DS) has raised objections from disability rights scholars and activists. The most well-known objection, the expressivist argument, claims that prenatal testing and selective terminations send a hurtful message to people living with the conditions tested for. Another claim is that selective abortion is a discriminatory practice because it lets one trait stand for the whole in justifying terminating an otherwise wanted pregnancy.[2]

Disability rights advocates have also raised consequentialist concerns, such as the potential effects of an expected reduction in the populations living with the tested conditions, including a reduction in the perceived need for providing support to families and research directed at improving care and quality of life.[3] They also include the idea of a loss of social and moral benefits that society gains from diversity and from dealing with vulnerability of various forms.[4] In Chapter 2 of this volume, Ani Satz refers to pregnancy termination for DS as an act of normalization that obscures the need and possibility of raising awareness and maximizing function in ways that are considered "atypical."

Based on these concerns, disability rights literature and activism, coupled with feminist literature and activism, have strongly contributed to a shift away from a public health narrative for prenatal testing to a reproductive autonomy narrative. This means that prenatal testing is no longer presented as a means to reduce the incidence of DS. Rather, it is now based on a desire to provide pregnant women and expecting couples with more information to promote informed choice.[5] In this

[1] The authors would like to thank Professors Arthur Caplan, Diane Paul, and Govind Persad for their helpful comments on earlier versions of this chapter.

[2] See Erik Parens & Adrienne Asch, *Special Supplement: The Disability Rights Critique of Prenatal Genetic Testing Reflections and Recommendations*, 29 Hastings Center Report S1 (1999).

[3] See, for example, Deborah Kaplan, *Prenatal Screening and Its Impact on Persons with Disabilities*, 8S Fetal Diagnosis & Therapy 64 (1993).

[4] See generally Rosemarie Garland-Thomson, *The Case for Conserving Disability*, 9 J. Bioethical Inquiry 339 (2012).

[5] See, for example, Mianna Meskus, *Personalized Ethics: The Emergence and the Effects in Prenatal Testing*, 7 BioSocieties 373, 381 (2012).

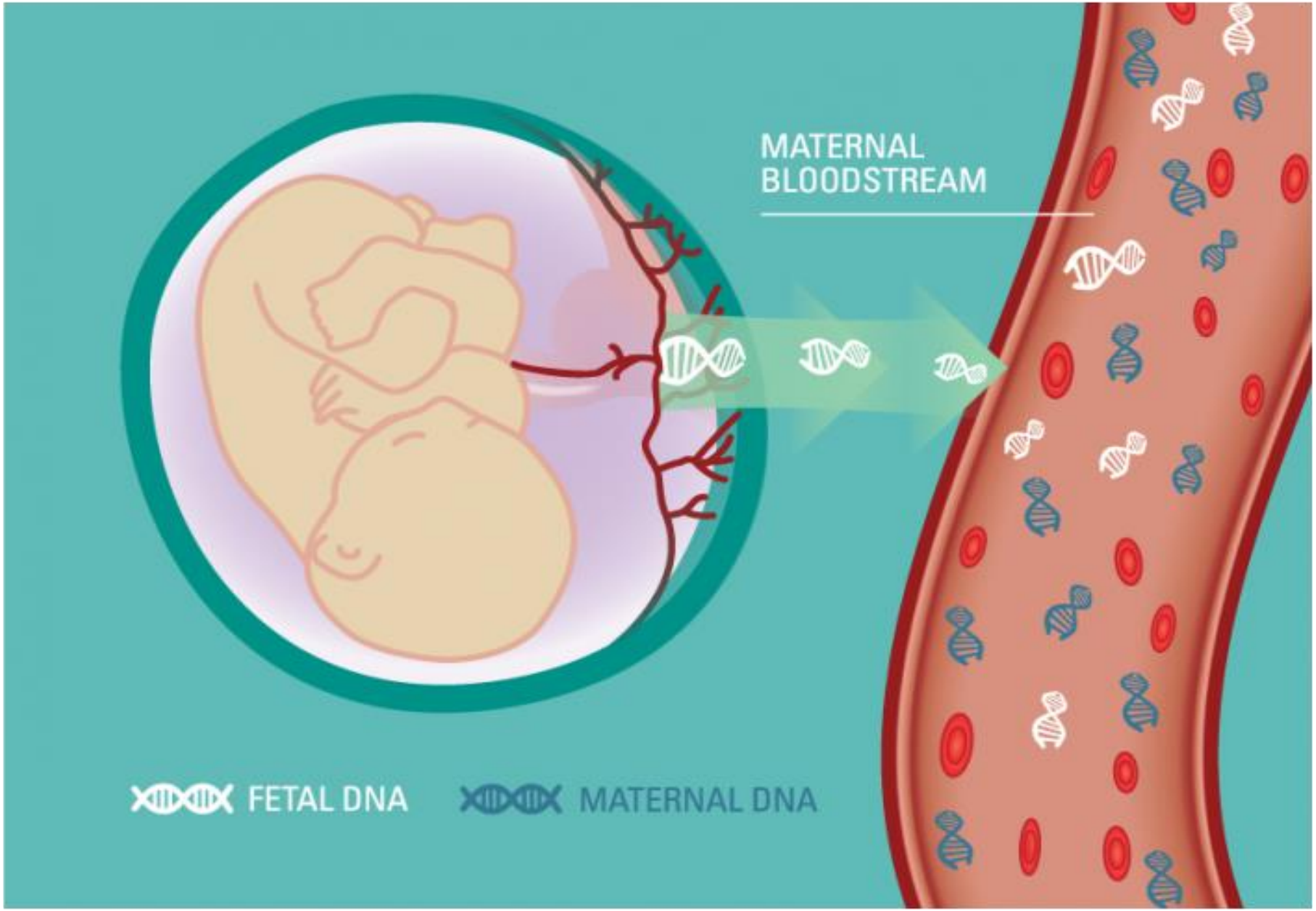
Balanced and neutral?

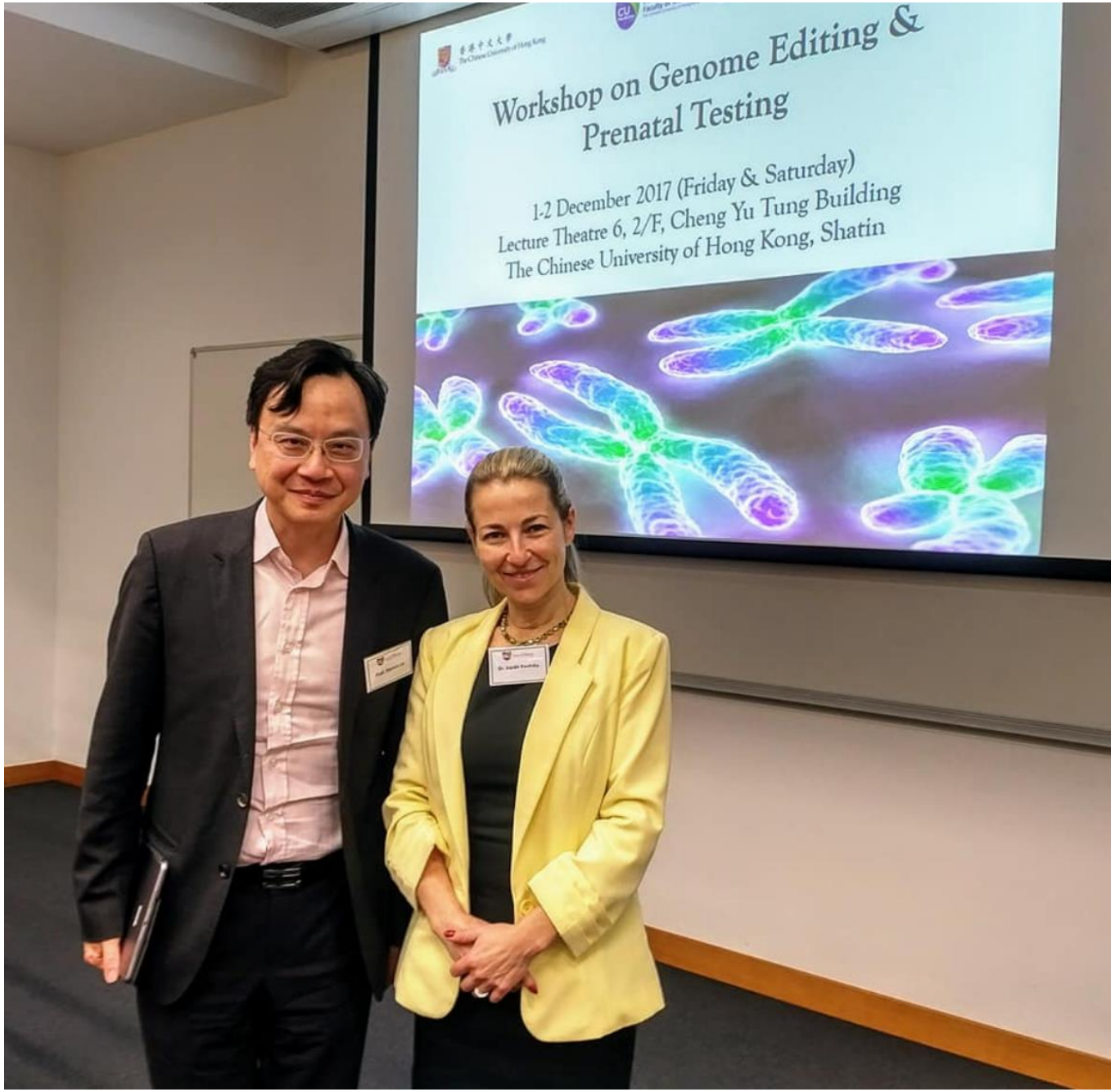
- DS Information Acts aim to ensure that health professionals who offer prenatal care provide complete information about DS, including its positive aspects

- But what does it *mean* to provide complete, balanced, and neutral information?

2011 - NIPT enters the scene
Non-Invasive Prenatal Testing

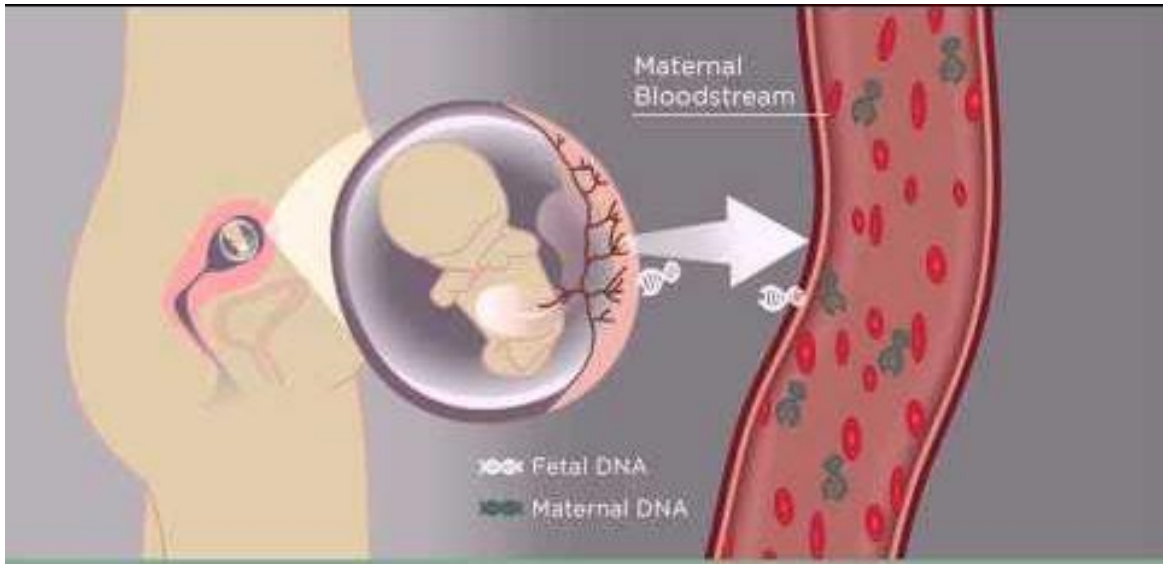
1997




Workshop on Genome Editing &
Prenatal Testing
1-2 December 2017 (Friday & Saturday)
Lecture Theatre 6, 2/F, Cheng Yu Tung Building
The Chinese University of Hong Kong, Shatin

What is NIPT?

- Tests cell-free fetal DNA floating in maternal plasma
  - At ~9 weeks gestation, ~10-15% of cffDNA comes from the placenta (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

Non-invasive prenatal diagnosis: an ethical imperative

(2009)

Vardit Ravitsky

In their Ethics watch article (An offer you can't refuse? Ethical implications of non-invasive prenatal diagnosis. *Nature Rev. Genet.* **10**, 515 (2009))[1], Schmitz *et al.* argue that the implementation of non-invasive prenatal diagnosis (NIPD) for fetal aneuploidies would pose a threat to the reproductive autonomy of women by impeding the provision of adequate pre-test counselling. I argue that the introduction of NIPD would in fact increase reproductive autonomy by allowing women to access information without subjecting their pregnancy to the risk posed by amniocentesis or chorionic villus sampling (CVS).

benefit and should therefore be available as soon as it is ready to be clinically implemented, even if the demand for it is initially so high as to prevent comprehensive pre-test counselling.

Second, because NIPD eliminates the risk of pregnancy loss, genetic counsellors would be able to focus on discussing the possible results of the test — and the alternatives open to women and their families — rather than spend a substantial amount of time and effort discussing the risk inherent in the test. Non-invasive prenatal diagnosis would therefore change the context of counselling in a way that would promote

nature reviews genetics

www.pegasus-pegase.ca

About PEGASUS project

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

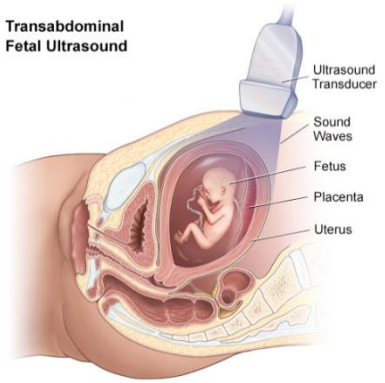
Each year, 450,000 Canadian women become pregnant and, as a result of their participation in prenatal screening for Down syndrome, approximately 10,000 of

«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

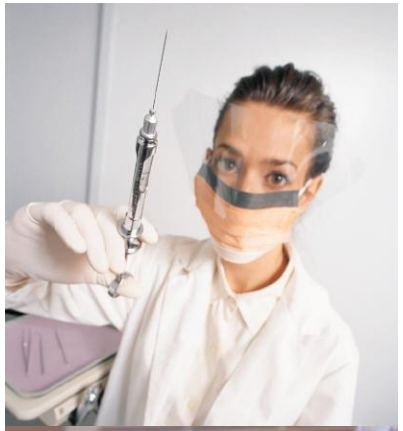
Pre-NIPT (ex. Canada)

450,000
pregnancies

Biochemical tests
Trim1 Trim2



315,000
Prenatal
Screening
Tests (DR 85%)



10,000
amniocenteses

70
fetuses lost

268
T21 detected

Weeks of
gestation

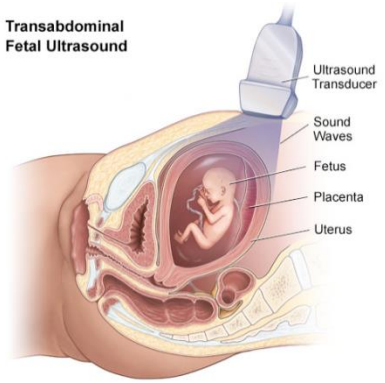
11w 15w 16w 16-21w 18+w

NIPT as second-tier screening test

PEGASUS
PEGASE

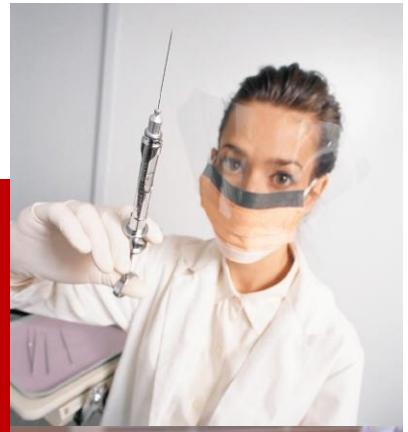
450,000 pregnancies

Biochemical tests
Trim1 Trim2



315,000 Prenatal Screening Tests (DR 85%)

NIPT



~~10,000~~ 300 amniocenteses

~~70~~ 1 fetus lost

~~268~~ 265 T21 detected

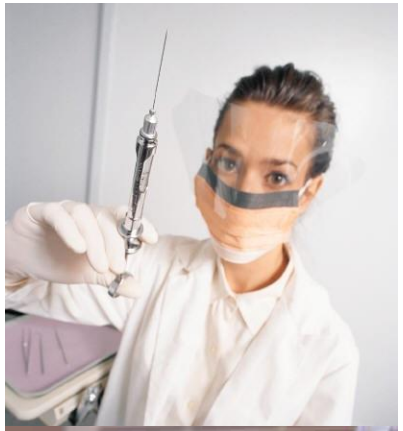
Weeks of gestation

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

NIPT as first-tier screening test

450,000
pregnancies

NIPT



~~10,000~~ ??
amniocenteses

~~70~~ ??
fetus lost

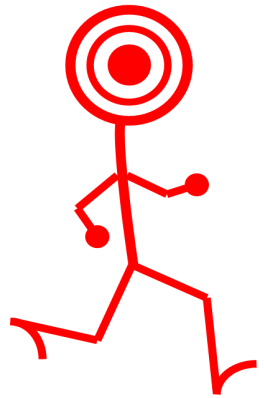
~~268~~ ??
T21 detected

Weeks of gestation

11w 15w 16w — 16-21w — 18+w

NIPT today

- NIPT is performed using next-generation sequencing
  - Different platforms
  - Different types of bio-informatic analysis
  - Different interpretation methods
- The technology's performance is rapidly evolving
  - What conditions are tested
  - In what populations
- NIPT implementation is rapidly evolving
  - Challenges of implementing a moving target into clinical practice



What can NIPT currently test ?

- 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

Threshold for appropriate testing

- Invasive testing is only carried out for conditions that are considered ‘serious enough’ to justify the risk of miscarriage
- Risk-free nature of NIPT + ability to test earlier in the pregnancy, can *lower the threshold* for ‘appropriate testing’

- Individuals may wish to / be pressured to test for -
  - less severe / treatable conditions
  - late-onset conditions
  - non-medical information such as sex and paternity
  - physical or even behavioral / personality traits

Routinization and 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 → to reproductive autonomy
- Need to ensure women are *offered* NIPT and feel free to decline

Global & cross-cultural analysis

ANNUAL REVIEWS

(2021)

Annual Review of Genomics and Human Genetics

The Emergence and Global Spread of Noninvasive Prenatal Testing

Vardit Ravitsky,[1,*] Marie-Christine Roy,[1,*] Hazar Haidar,[2] Lidewij Henneman,[3] John Marshall,[4] Ainsley J. Newson,[5] Olivia M.Y. Ngan,[6] and Tamar Nov-Klaiman[7]

[1]Department of Social and Preventive Medicine, School of Public Health, University of Montreal, Quebec H3C 3J7, Canada; email: vardit.ravitsky@umontreal.ca

[2]Institute for Health and Social Policy, McGill University, Montreal, Quebec H3A 1A3, Canada; email: hazarhaidar@hotmail.com

[3]Department of Clinical Genetics, Amsterdam Reproduction and Development Research Institute, Amsterdam UMC, Vrije Universiteit Amsterdam, 1081 BT Amsterdam, The Netherlands; email: l.henneman@amsterdamumc.nl

[4]United Kingdom National Screening Committee, London SE1 8UG, United Kingdom; email: john.marshall@phe.gov.uk

[5]Sydney Health Ethics, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales 2006, Australia; email: ainsley.newson@sydney.edu.au

[6]Centre for Bioethics, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong SAR, China; email: oliviangan@cuhk.edu.hk

[7]Department of Sociology and Anthropology, Ben-Gurion University of the Negev, Beer-Sheva 8410501, Israel; email: tamarnk@gmail.com

Global comparative analysis

Describes the implementation of NIPT in 9 countries:

- Australia, Canada, China and Hong Kong, India, Israel, Lebanon, Netherlands, UK, US

Addresses:

- structure of the healthcare system
- how NIPT is offered
- counseling needs and resources
- cultural and legal context regarding
  - disability
  - pregnancy termination

Similarities between countries

Cost as a barrier to equitable access:

- Cost is perceived as a barrier in countries that do not offer public funding, raising concerns about justice and inequitable access

Similarities between countries

Cost as a barrier to equitable access:

- However, public funding can send a message that the government
  - strongly supports prenatal testing
  - expects the prevention of certain births

- Importance of framing NIPT in terms of preparation for birth, not just a focus on termination

Similarities between countries

Public funding and cost-effectiveness:

- Public funding of NIPT is endorsed by users
- Is key to promoting equitable access and reducing use of invasive tests
- However, in some countries, funding is challenging due to limited resources
- Decisions surrounding cost-effectiveness can be complex
- Esp. ethical challenge of considering reduction in costs of caring for individuals with the conditions tested by NIPT (savings to society through the prevention of certain births)

"Quantifying the cost of care of individuals with disabilities can translate into an evaluation of the value of their lives, raising acute ethical concerns regarding disability rights and eugenic social attitudes."

Similarities between countries

Public funding and co

- Public funding c
- Is key to promot
- However, in son
- Decisions surrou
- Esp. ethical chal with the conditi of certain births

"Quantifying the c evaluation of the v disability rights an

invasive tests

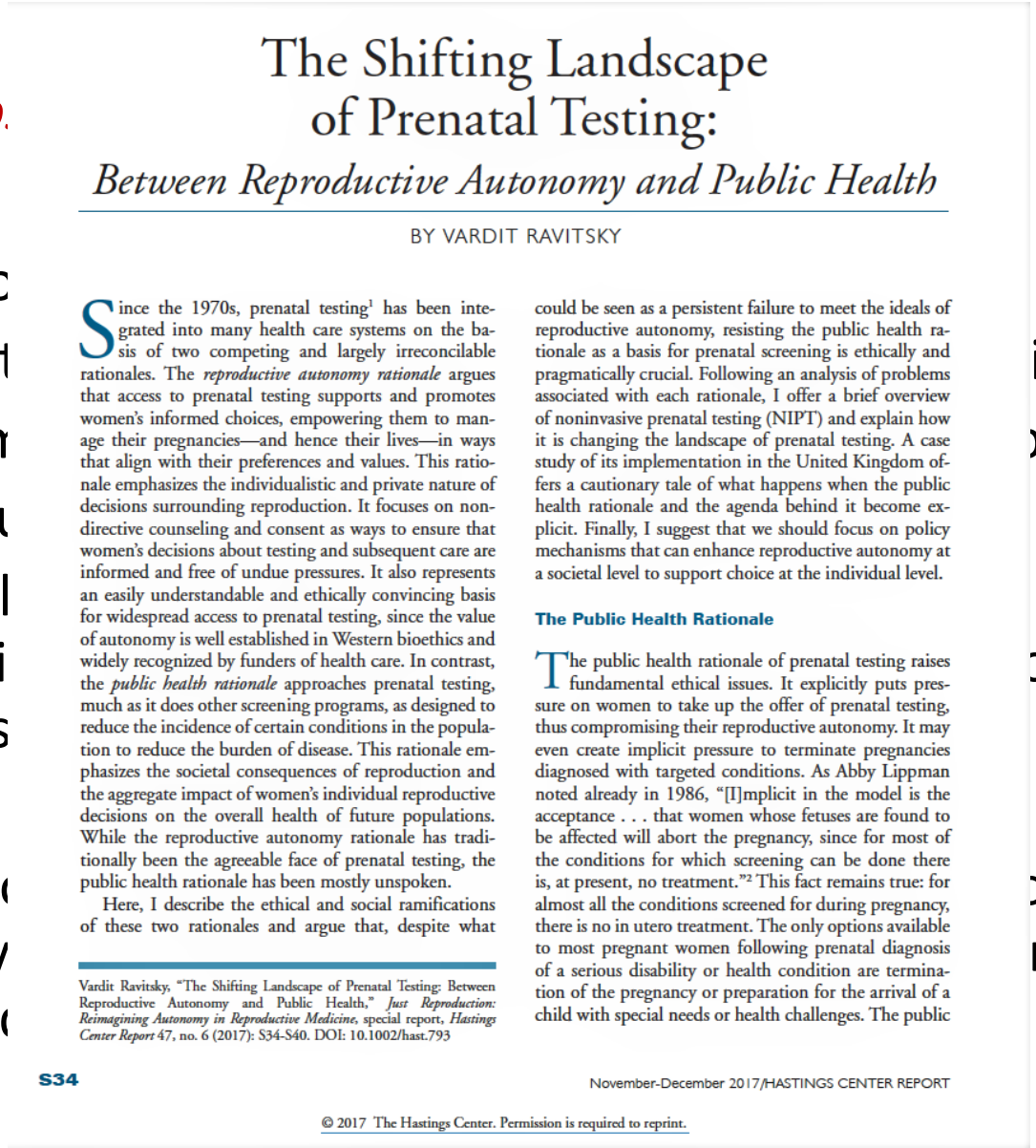
limited resources

caring for individuals

ough the prevention

can translate into an

ncerns regarding



The Shifting Landscape of Prenatal Testing:

Between Reproductive Autonomy and Public Health

BY VARDIT RAVITSKY

Since the 1970s, prenatal testing[1] has been integrated into many health care systems on the basis of two competing and largely irreconcilable rationales. The *reproductive autonomy rationale* argues that access to prenatal testing supports and promotes women's informed choices, empowering them to manage their pregnancies—and hence their lives—in ways that align with their preferences and values. This rationale emphasizes the individualistic and private nature of decisions surrounding reproduction. It focuses on nondirective counseling and consent as ways to ensure that women's decisions about testing and subsequent care are informed and free of undue pressures. It also represents an easily understandable and ethically convincing basis for widespread access to prenatal testing, since the value of autonomy is well established in Western bioethics and widely recognized by funders of health care. In contrast, the *public health rationale* approaches prenatal testing, much as it does other screening programs, as designed to reduce the incidence of certain conditions in the population to reduce the burden of disease. This rationale emphasizes the societal consequences of reproduction and the aggregate impact of women's individual reproductive decisions on the overall health of future populations. While the reproductive autonomy rationale has traditionally been the agreeable face of prenatal testing, the public health rationale has been mostly unspoken.

Here, I describe the ethical and social ramifications of these two rationales and argue that, despite what could be seen as a persistent failure to meet the ideals of reproductive autonomy, resisting the public health rationale as a basis for prenatal screening is ethically and pragmatically crucial. Following an analysis of problems associated with each rationale, I offer a brief overview of noninvasive prenatal testing (NIPT) and explain how it is changing the landscape of prenatal testing. A case study of its implementation in the United Kingdom offers a cautionary tale of what happens when the public health rationale and the agenda behind it become explicit. Finally, I suggest that we should focus on policy mechanisms that can enhance reproductive autonomy at a societal level to support choice at the individual level.

The Public Health Rationale

The public health rationale of prenatal testing raises fundamental ethical issues. It explicitly puts pressure on women to take up the offer of prenatal testing, thus compromising their reproductive autonomy. It may even create implicit pressure to terminate pregnancies diagnosed with targeted conditions. As Abby Lippman noted already in 1986, "[I]mplicit in the model is the acceptance . . . that women whose fetuses are found to be affected will abort the pregnancy, since for most of the conditions for which screening can be done there is, at present, no treatment."[2] This fact remains true: for almost all the conditions screened for during pregnancy, there is no in utero treatment. The only options available to most pregnant women following prenatal diagnosis of a serious disability or health condition are termination of the pregnancy or preparation for the arrival of a child with special needs or health challenges. The public

Vardit Ravitsky, "The Shifting Landscape of Prenatal Testing: Between Reproductive Autonomy and Public Health," *Just Reproduction: Reimagining Autonomy in Reproductive Medicine*, special report, *Hastings Center Report* 47, no. 6 (2017): S34-S40. DOI: 10.1002/hast.793

Similarities between countries

Shortage of appropriate resources that promote informed choice:

- Need for appropriate counselling regarding NIPT
- Shortage of trained professionals
- Shortage of comprehensive, balanced, neutral informational materials

- As the number of conditions NIPT can test increases, creative and innovative counseling mechanisms will be required
- Concerns regarding harms of informational overload

Similarities between countries

Shortage of app *choice*:

- Need for app
- Shortage of t
- Shortage of c onal materials
- As the numb ative and innovative cc
- Concerns reg

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

Address correspondence to Vardit Ravitsky, University of Montreal, C.P. 6128, succ. Centre-ville, Montreal, Quebec, H3C 3J7, Canada. E-mail: vardit.ravitsky@umontreal.ca

Differences between countries

Attitudes toward disability:

- Attitudes toward disability vary greatly across countries
- Not necessarily associated with the status of NIPT implementation

- In some countries with advanced implementation of NIPT (e.g. Netherlands & UK) implementation provoked strong reactions
- In some countries where NIPT is only partially covered or not covered at all (e.g. Israel & China) NIPT has raised no disability rights concerns

Differences between countries

Attitudes toward pregnancy termination:

- Political context surrounding abortion varies greatly across countries
- Availability of legal and safe abortion is relevant to the implementation of NIPT for those who might consider terminating the pregnancy based on a diagnosed condition in the fetus


Thank you NIPTeam