Expanding access to prenatal genetic information: ethical, legal and social issues

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No conflicts of interest.

All human subject research was supervised by the Institutional Review Board of Stanford University and/or Duke University.

Prenatal Information Research Consortium

Acronym	Name	Location	Lead	Study Population
PEAPS	Parental Attitudes and Experiences in Prenatal Testing	SHC	Erin	Pregnant Women
KEAPS	Kaiser Attitudes and Experiences in Prenatal Testing	Kaiser San Diego	Cherie	Pregnant Women
PIPS	Provider Insights on Prenatal Testing	National	Stephanie	Providers
MUPPETS	MUltisite Prenatal Providers' Experiences with Testing and Screening	National	Stephanie	Providers
STEAPS	STanford Experiences and Attitudes in Prenatal Testing	Stanford PDCs	Marsha	Pregnant Women
QUIPS	Q-Sort on Understandings and Ideals in Prenatal Testing	Varies	Melissa	Stakeholders
InVEST	Integrating Values and Ethics in Science and Technology: NIPT	Online	Megan	National Sample
Bass Connections	Commercialization of NIPT in the Developing World (Hong Kong)	Duke	Megan	Hong Kong
	Commercialization of NIPT in the Developing World (Argentina)	Duke	Elisa	Argentina
	Commercialization of NIPT in the Developing World (India)	Duke	Shuba	India
LITTLE SURVEY	National Survey on Public Attitudes Towards Non-Invasive Prenatal Testing	Online	Megan	National Sample
BIG SURVEY	National Survey on Public Attitudes Towards Prenatal Testing for Complex Traits	Online	Megan/Laure	National Sample
OB PILOT	Pilot Study of Obstetric Provider Attitudes Towards Prenatal Testing	UCSF	Closed	Providers
CLASP	Community Leaders, Advocates, and Stakeholders Perspectives	Stanford/Duke	Marsha/Shut	Stakeholders

Prenatal Testing

Prenatal Screening & Diagnostic Testing Options

	Serum Integrated Screening (SIPS)	Integrated Prenatal Screening (IPS)	First Trimester Screening (FTS)	Non-Invasive Prenatal Testing (NIPT)	Amniocentesis
What it Detects	Trisomy 21, 18, ONTDs*	Trisomy 21, 18, ONTDs*	Trisomy 21, 18, 13	Trisomy 21, 18, 13, X, XXX, XXY, XYY	All major chromosome problems
How Done	2 blood draws	2 blood draws 1 ultrasound	1 blood draw 1 ultrasound	1 blood draw	Transabdominal amniotic fluid aspiration
When Done	10-14 weeks 15-21 weeks [a]	10-14 weeks 15-21 weeks [a]	11-14 weeks [b]	≥ 10 weeks [c]	>15 weeks [a]
Detection Rate for T21	85% [b]	87% [b]	83% [b]	>99.9% [d]	100% [c]
False Positive Rate	4.4%[b]	1.9%[b]	5.0%[b]	0.2% [d]	0%[c]
Risk	None	None	None	None	1 in 200[a] pregnancy loss
Cost	MSP covered [a]	MSP covered if >35 years old [a]	Fee varies by institution (not MSP covered)	$1,100	MSP covered if high risk or >40 years old [a]

*ONTDs = Open Neural Tube Defects

a: http://www.perinatalservicesbc.ca/NR/rdonlyres/91324196-D8AF-4CE2-978E-41ED290F9FB1/0/GuidelineMarch.pdf

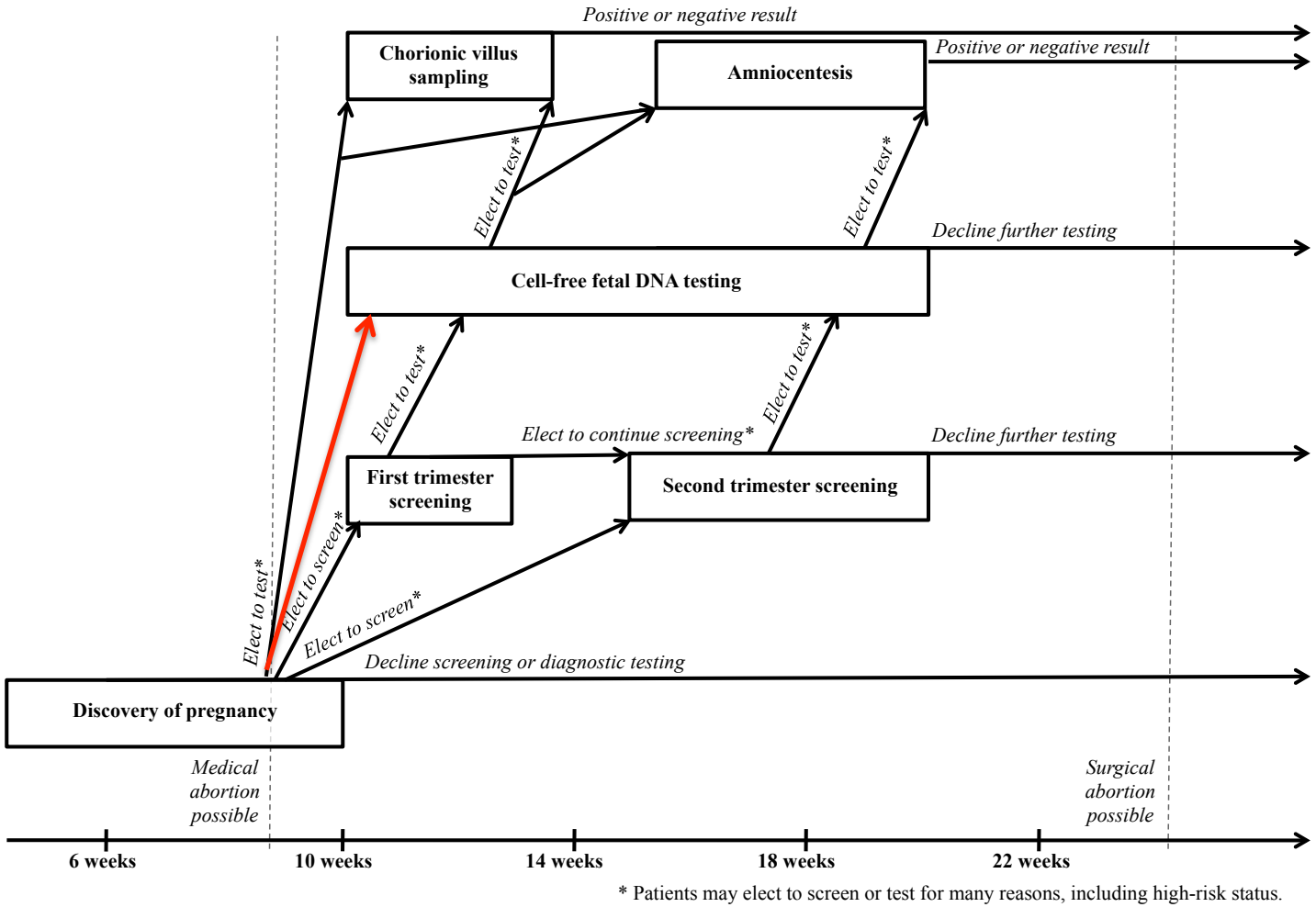
b: http://sogc.org/guidelines/prenatal-screening-for-fetal-aneuploidy-in-singleton-pregnancies-replaces-187-february-2007/

c: http://www.perinatalservicesbc.ca/NR/rdonlyres/F6663D9C-8089-4C72-89BD-7F5618973036/0/ComparisonofamniocentesisandNIPTrevised01Sept2013.pdf

d: http://www.verinata.com/

Prenatal Testing

Figure 1. Prenatal screening and testing schematic incorporating cell-free fetal DNA testing for aneuploidy



* Patients may elect to screen or test for many reasons, including high-risk status.

Allyse M, Sayres C, King S, Norton E, Cho K. Cell-free fetal DNA testing for fetal aneuploidy and beyond: Clinical integration challenges in the US context. *Human Reproduction* 2012, Aug 3;27(11):3123 - 3131.

Advantages

Photo: Daily Mirror, UK

- No procedure related risk.
- Earlier use.
- No clinical skill required.
- Can be done remotely.
- Lower false positive rate. High sensitivity.
- Can be used to reassure women who are carriers of X linked diseases that the fetus is female.

NIPT in the US

	Natera's *Panorama*	Verinata's *verifi*	Sequenom's *MaterniT21 PLUS*	Ariosa's *Harmony*
Trisomies tested	13, 18, 21	13, 18, 21, sex chromosomes	13, 18, 21, sex chromosomes	13, 18, 21
Monosomy tested	X	X	X	
Genetic testing method	Single nucleotide polymorphism	Massively parallel sequencing	Massively parallel sequencing	Chromosome-selective sequencing
Sensitivity	92-99%	87-99%	92%-99%	80-99%
Accuracy	100%	100%	>99%	>99%
Earliest gestational age	9 weeks	10 weeks	10 weeks	10 weeks
Price	$1,495	$1,500	$2,762	$795

Source: Nature Medicine

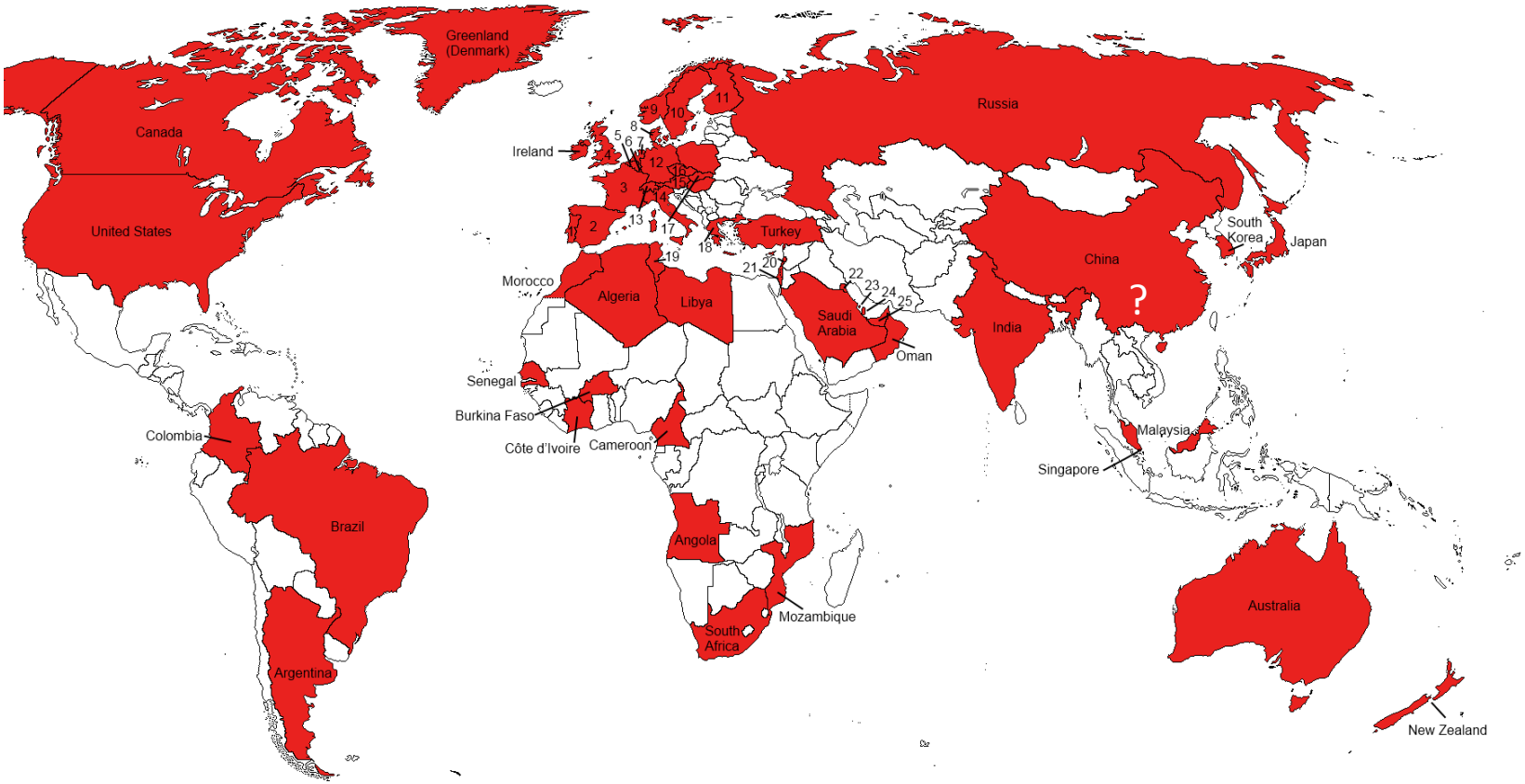
MATERNIT21™ PLUS

Harmony™ PRENATAL TEST

panorama™ prenatal test

verifi®

NIPT Internationally



BerryGenomics

华大基因 BGI

Chandrasekharan S, Minnear M, Allyse M. Noninvasive prenatal testing goes global: Making sure all women benefit. *Science Translational Medicine*, 2013. (Manuscript Submitted).

Expanding Panels

- 22q deletion syndrome (DiGeorge)
- 5p (Cri-du-chat)
- 15q (Prader-Willi/Angelman)
- 1p (1p36 deletion)
- Trisomy 16
- Trisomy 22

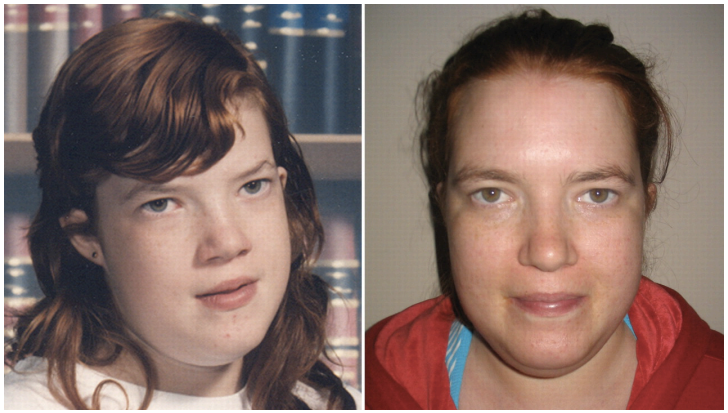


Photo: CMAJ

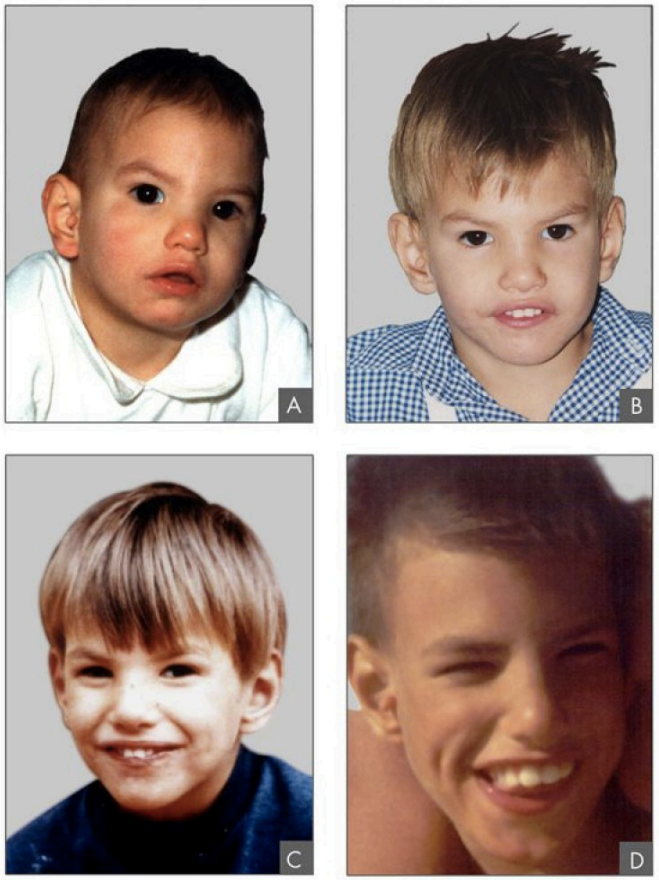


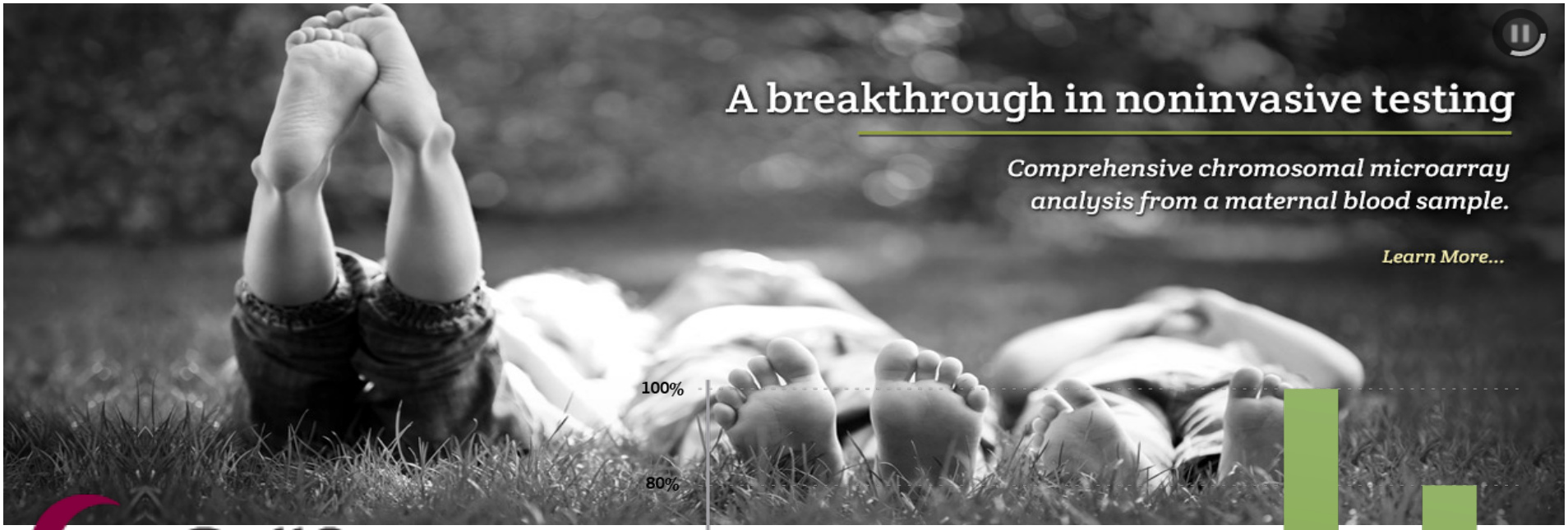
Photo: Wikipedia

Expanding Panels

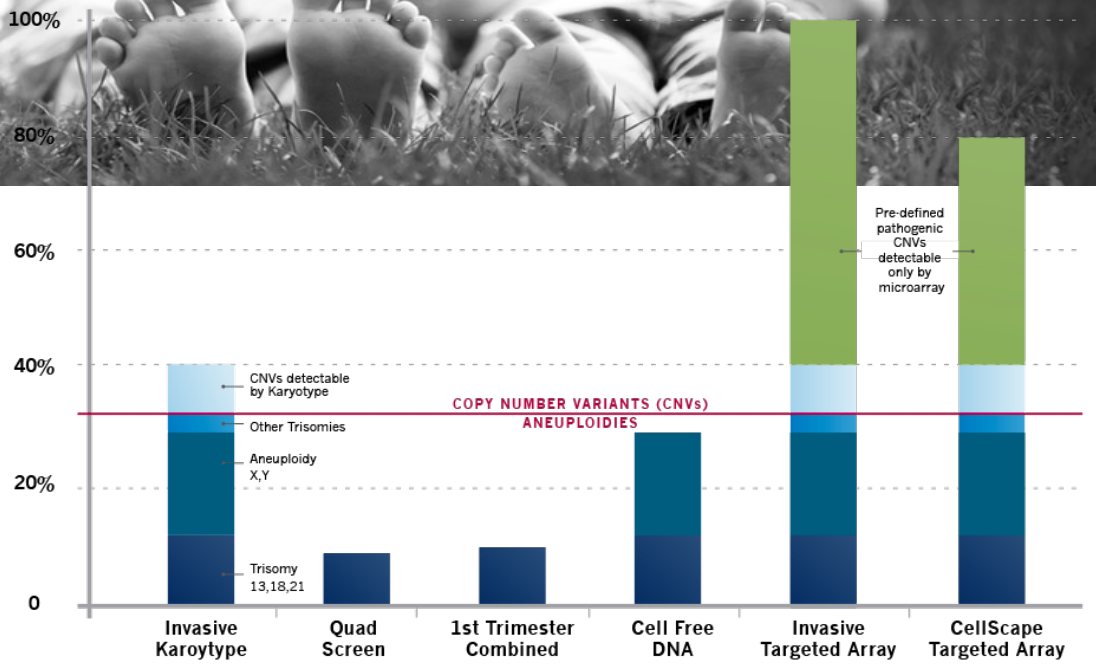
- Single gene disorders:
  - Sickle Cell Disease
  - Achondroplasia
  - Cystic Fibrosis
  - Thalessemia

Photo: Facebook.com

Emerging Technologies



CellScape



Whole Genome Sequencing

Noninvasive Whole-Genome Sequencing of a Human Fetus
Jacob O. Kitzman *et al.*
Sci Transl Med **4**, 137ra76 (2012);
DOI: 10.1126/scitranslmed.3004323

Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetic and Mutational Profile of the Fetus
Y. M. Dennis Lo *et al.*
Sci Transl Med **2**, 61ra91 (2010);
DOI: 10.1126/scitranslmed.3001720

"Although these methods must be refined and their costs driven down, this study hints that comprehensive, noninvasive prenatal screening for Mendelian disorders may be clinically feasible in the near future."

"The analysis of cell-free fetal DNA in maternal circulation for fetal aneuploidy screening is likely the first of major steps toward the eventual application of whole fetal genome/whole fetal exome sequencing" - ACMG Policy Statement

Ethical and Clinical Challenges

- Informed Consent and Autonomy
- Regulation and Validation
- Commercial Model
- Intellectual Property and Access
- Interpretation and Counseling
- Broader Social Issues

Informed Consent

"The failure to give an IC is significantly higher among women who elected to have the Quad screen (72.6%) than women who declined (50%)… A significantly higher proportion of women who elected to have the Quad screen demonstrated insufficient understanding of the Quad (64.5%) than women who did not accept the screen (36.6%)."[1]

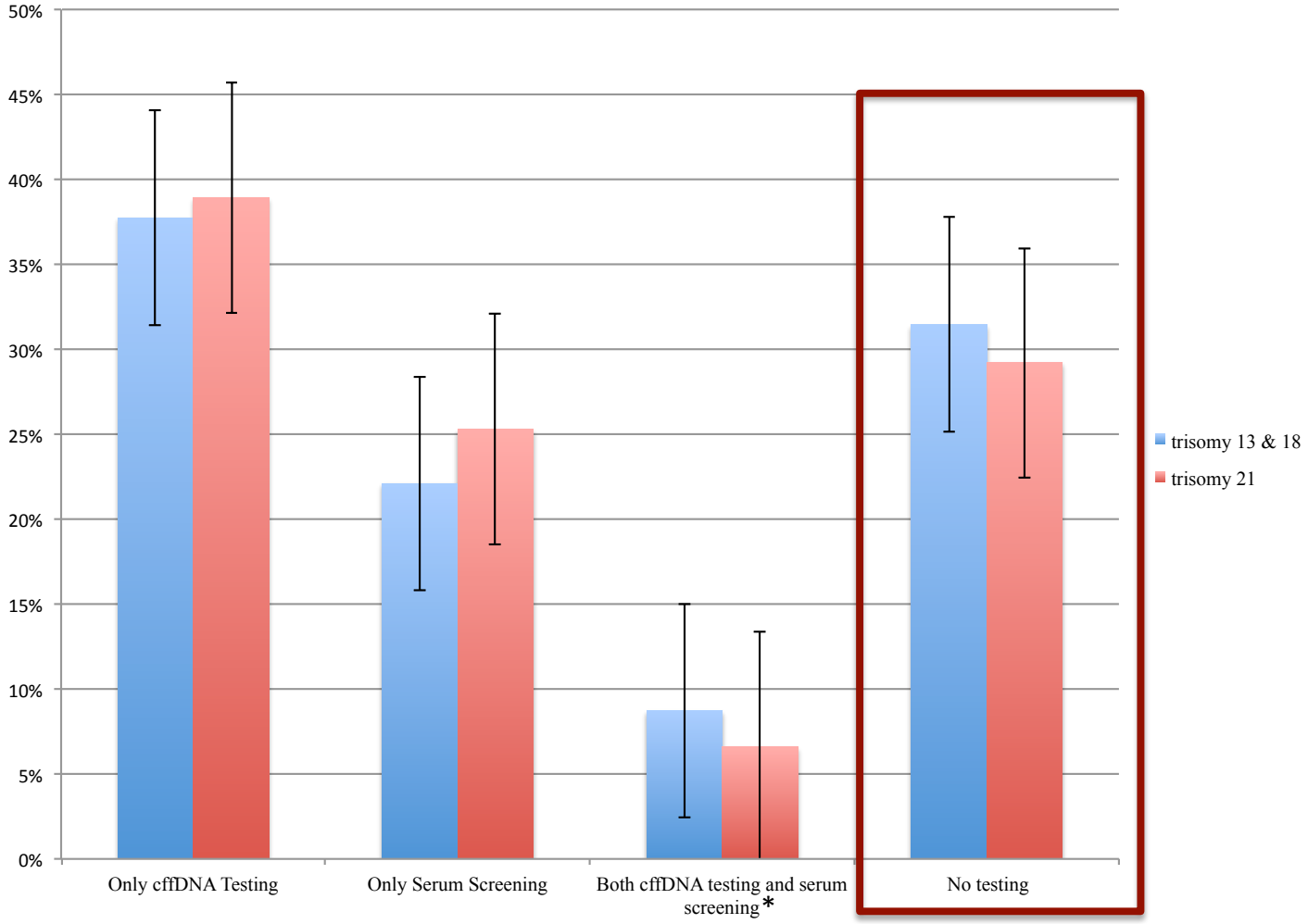
"I mean on a daily basis… we see patients all the time who had no idea [the] quad screen was being drawn. They have no idea what their results mean. The concept of a false positive is just way too high for them to understand."

"When you are told you might lose your baby if you have this test, you really, really concentrate on whether you need to go through this test or not.… Whereas if you don't have to think about that it's quite easy for you to stick out your arm and say OK fine take another blood test."[2]

1. Constantine M, Allyse M, Rockwood T, Wall M, De Vries R. (In press) Imperfect informed consent for prenatal screening: Lessons from the quad screen. *Clinical Ethics* .

2. Hill M, Karunaratna M, Lewis C, Forya F, Chitty L. Views and preferences for the implementation of non-invasive prenatal diagnosis for single gene disorders from health professionals in the United Kingdom. Am J Med Genet A 2013, Jul;161A(7):1612-8.

Informed Consent



* Statistically significant difference between trisomy 13& 18 and trisomy 21

Allyse M, Sayres LC, Goodspeed T and Cho MK (In Press) Attitudes Towards Non-Invasive Prenatal Testing for Aneuploidy Among United States Adults of Reproductive Age. *Journal of Perinatology*.

Declining Testing

"I would want the child to be expected with happiness regardless of the outcome, I would not want to worry about something like this during pregnancy." [Female, 25–34 years] [1]

"It honestly is up to the mother to decide. My thoughts were that no matter what the test says I am going to keep this child and love this child no matter what, so I thought it was pointless to get checked." [Female, 23] [2]

1. Allyse M, Sayres LC, Goodspeed T and Cho MK. "Don't want no risk and don't want no problems": Public understandings of the risks and benefits of novel prenatal genetic technologies in the United States. *AJOB Empirical Bioethics* (Manuscript Submitted).
2. R.J. Steinbach, M.A. Allyse, M. Michie, E.Y. Liu, M.K. Cho (In Prep) Public Narratives of Disability and Prenatal Genetic Testing

Regulation and Validation

- cffDNA tests are considered 'laboratory developed tests' and are thus not regulated by the US FDA to establish safety and efficacy.
  - The clinical validation studies performed by current providers are unlikely to be eligible for US FDA approval.
  - Expanded panels have not even been clinically validated in broad studies.
- The FDA is reconsidering its enforcement discretion for cffDNA tests because these tests involve complex software and non-transparent automation and their clinical validity is not well understood.
- They are broadly advertised at a national level and aggressively marketed with direct-to-consumer advertising despite their lack of comprehensive validation.

Chinese FDA

- The Chinese FDA has frozen NIPT in China in order to regulate clinical validity.
  - Multiple companies claiming to offer NIPT.
  - No clinical integration between testing companies and medical providers.
  - Only one company has published clinical trial data on their test.
- International companies cannot offer NIPT in China.
- Ban has no effect on testing outside of China by Chinese companies.

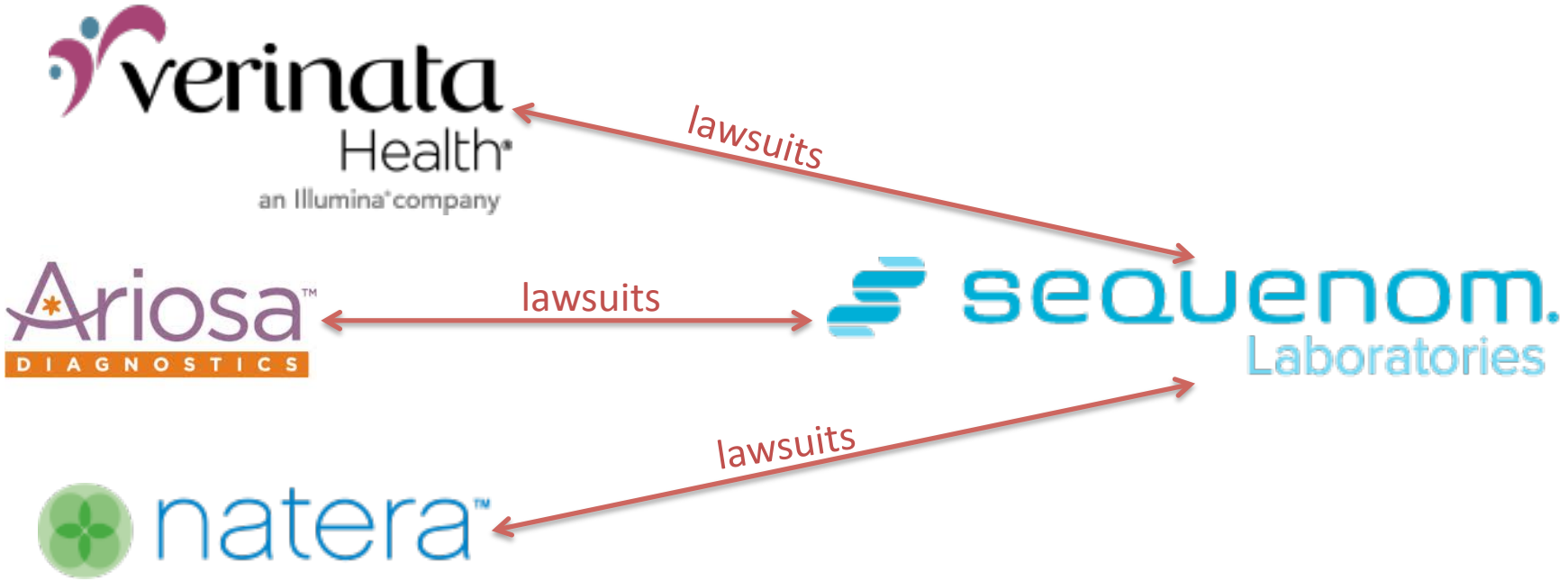
Risks of Non-validation

- Harder for health care practitioners to explain the complexities of prenatal risk factors and testing characteristics
- Clinicians may find themselves in the position of bearing fiduciary responsibility for inaccurate or misleading results.
- Given that pregnancy termination is an option in the setting of a positive test for fetal abnormality clinicians bear a heavy burden to ensure the analytic and clinical validity of tests they refer.

Commercial Model

- What is driving clinical implementation?
  - "They ... the reps have approached us. All four of these labs have very aggressive sales representatives…I can only imagine what a general OB ... I don't know how they're dealing with this… [this is] not the first time, but definitely the most aggressive onslaught."
- Cost
  - HK$4500 - $8000
  - No insurance coverage
  - Serum Screening:
    - Available at HA
    - Out of pocket $2500

Intellectual Property



"With a dominant and growing IP estate, we expect that Sequenom, to the exclusion of others, may have the freedom to decide which of many technologies to employ in the commercialization of noninvasive prenatal genetic testing."

Sayres L, Goodspeed T, Allyse M, Cho MK. In the public interest? *Science Translational Medicine* 2012, Jul;4(144):144fs23

Diagnostic Monopoly

Monopolies can preclude:

- Basic clinical research,
- Using methods or patented material in a different manner,
- Acquiring a second opinion,
- Testing for those insured by non-covering insurers,
- Research and development to improve quality or reduce cost,
- Competitive head-to-head testing to establish relative efficiency and effectiveness.

Diagnostic monopolies can:

- Set the cost of testing arbitrarily high,
- Hold proprietary data on allele frequency, aggregate results, ect.
- Not contribute to public databanks regarding known variants or mutations,
- Refuse to license patented material to non-profits or academic research institutions.

Cook-Deegan R, Chandrasekharan S, Angrist M. The dangers of diagnostic monopolies. *Nature* 2009. 26;458(7237):405-6.

Interpretation and Counseling

"Comprehensive patient pretest and post-test genetic counseling from qualified personnel such as a genetic counselor or geneticist regarding the benefits, limitations, and results of chromosomal microarray analysis is essential."

- ACOG Committee Opinion 581

Photo: Kaiser Permanente

Interpretation

- "There is no single database currently available that represents an accurately curated compendium of known pathogenic variants, nor is there an automated algorithm to identify all novel variants meeting criteria for pathogenicity… evaluation and reporting of positive findings in these genes may require significant manual curation."[1]
- "Any result of uncertain clinical significance was reviewed along with clinical information by a clinical advisory committee composed of genetic specialists, physicians, and genetic counselors. The committee decided if the finding was potentially clinically relevant and hence reported to the patient."[2]

1. Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 2013, 15(7):565-74.
2. Bernhardt BA *et al. Genet Med* 2012, Sep 6.

Counseling

- "of 48 patients evaluated for the program, 17 have been accepted, and their families have gone through six hours or more of genetic counseling before sequencing."[1]
- "To respect preferences in the same manner as with targeted testing, the patient whose exome or genome is sequences would have to undergo an extensive and possibly overwhelming amount of genetic counseling for numerous conditions unrelated to the primary indication for sequencing. This will become impractical as clinical sequencing becomes more common."

1. Karow, J *GenomeWeb* 2013. December 18.
2. Green RC *et al. Genet Med* 2013, 15(7):565-74.

Broader Social Issues

- Sex testing
  - There is no law about reporting fetal sex in Hong Kong.
    - "It is a human right to know the sex of your baby."
  - "We don't do sex pre-selection, but we do do fetal sexing."
  - HK$3000-$4000 for fetal sex test using NIPT (if used independently from T21 testing.)

Broader Social Issues

NEWS • CHINA • CRIME

Zhejiang man arrested for arranging sex tests in Hong Kong for pregnant mainland women

Suspect allegedly sent blood from fetuses to clinics in city, where sex testing is legal

"The pregnant women would receive the test results three to four days later. They paid up to 7,500 yuan (HK$9,400) in the seventh week of pregnancy, or 6,000 yuan in the eighth week. Chen allegedly made 800 yuan for each blood sample he took.

A woman who worked as a receptionist for such a service in Shenzhen yesterday said the service was very much in demand. The blood samples received in Shenzhen would be sent across the border to Hong Kong within an hour, she said.

"We are a big medical company. There are many such requests and we send at least a dozen blood tests … across the border a day," she said."

Broader Social Issues

- "Nobody wants a defective child."
  - 99% or higher termination of T21 affected fetus in Hong Kong.
  - Expanding number of conditions testable but many results may not have clear penetrance.
  - Many conditions vary widely in severity.

Thank You!

Thank you to my collaborators: The Prenatal Information Research Consortium (PIRC)

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