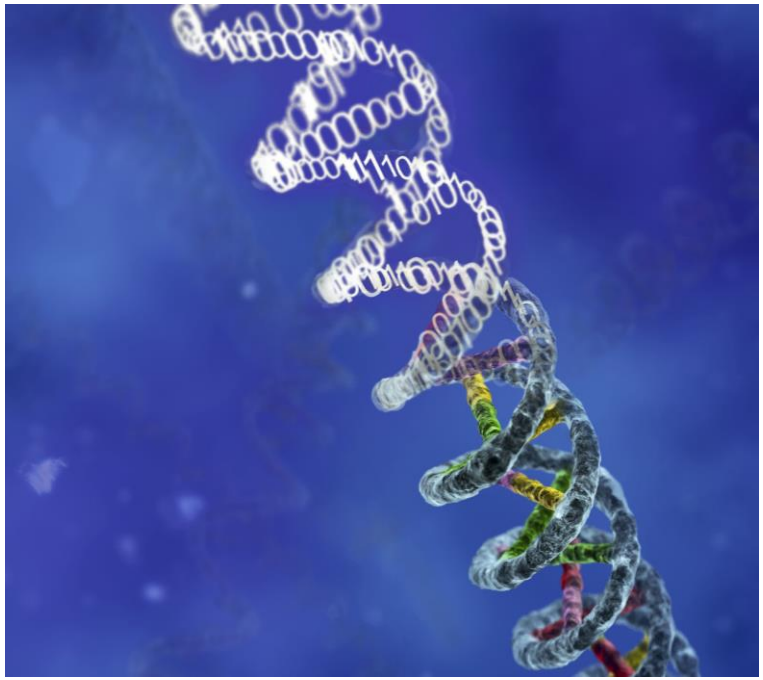
Cell Free DNA Screening for Aneuploidy



Mary E Norton MD

Professor, Obstetrics, Gynecology and Reproductive Sciences

Vice Chair of Clinical and Translational Genetics

David E. Thorburn, M.D. and Kate McKee Thorburn Endowed Chair in Perinatal Medicine and Genetics

Disclosures

- Principal Investigator of clinical trials of cfDNA screening supported by Ariosa Diagnostics and by Natera
- No personal financial involvement in any of the cfDNA companies

Objectives

- Elucidate options for accelerating pace of implementation and evidence generation in genomic medicine
- Highlight strategies for reaching diverse populations
- Explore challenges, successes, and best practices to facilitate rapid and appropriate translation of genomic medicine into population health

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Cell free DNA screening

- Clinical testing was developed over decade from 2000-2010
- Introduced as clinical test in October 2011
- High sensitivity, specificity, PPV, NPV in carefully pre-selected populations

Cell free DNA screening*: A Cautionary Tale*

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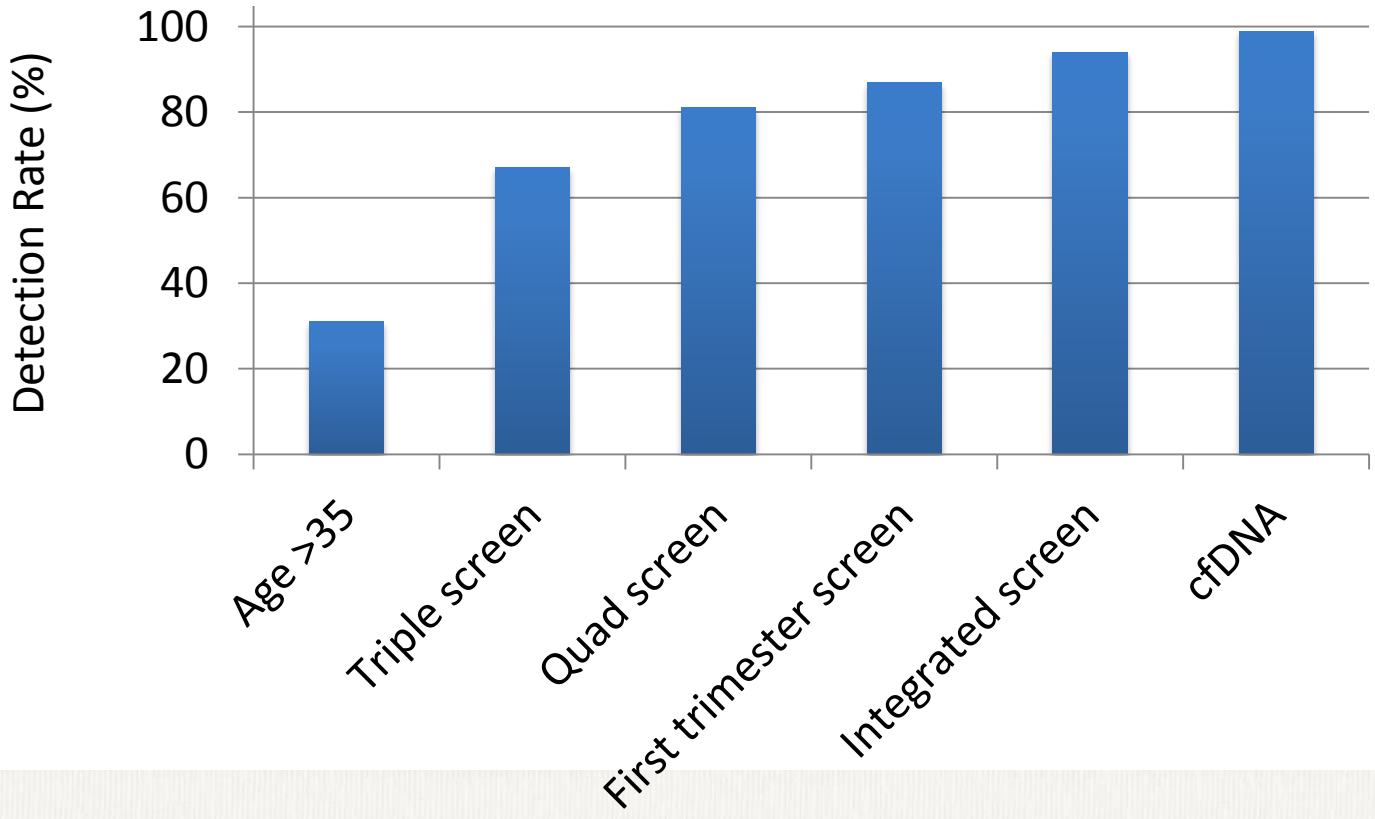
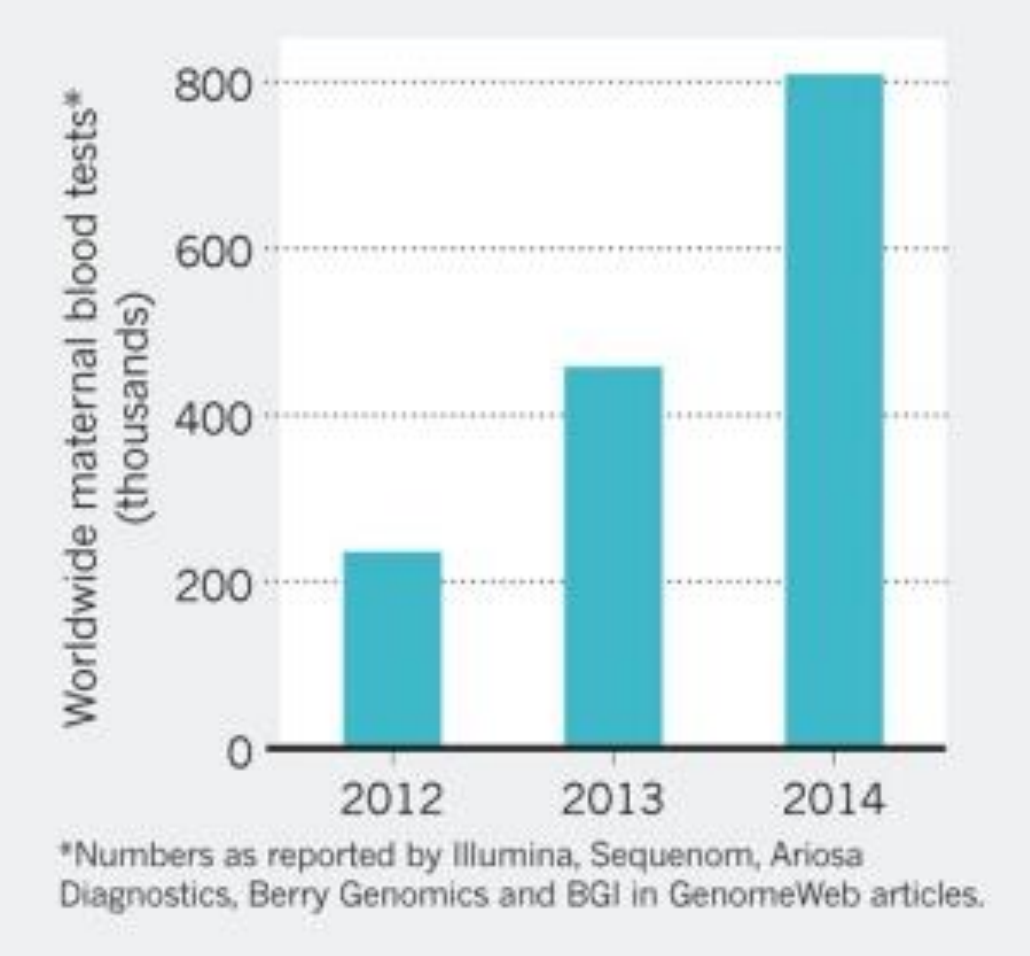
  - Broad, inexpensive screening for many conditions
- Diagnostic testing with chorionic villus sampling, amniocentesis
  - Low risk of complications, ~1/500-1000

Detection rate of prenatal screening for Down syndrome has improved over time

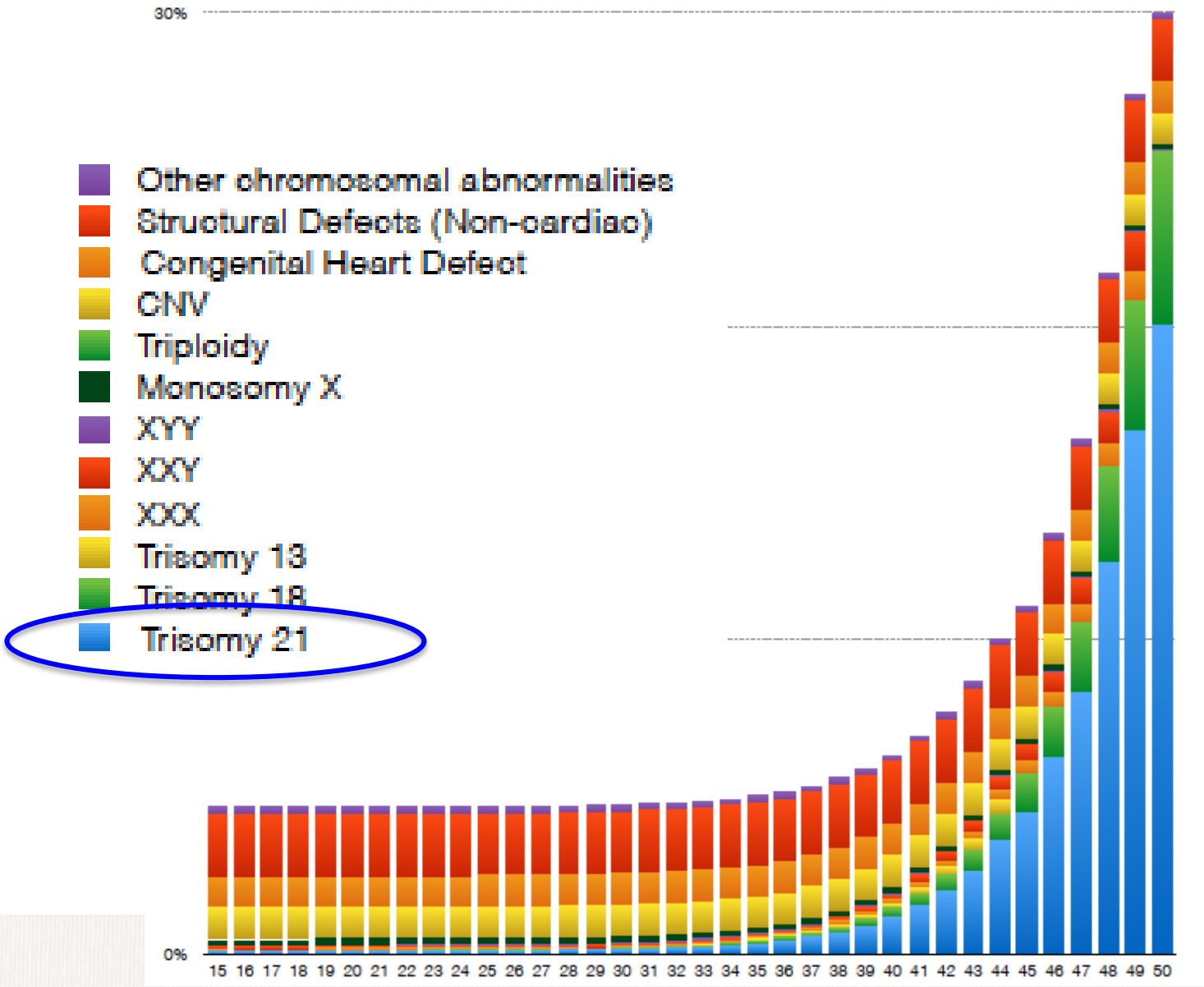


Uptake of cfDNA screens (in thousands)

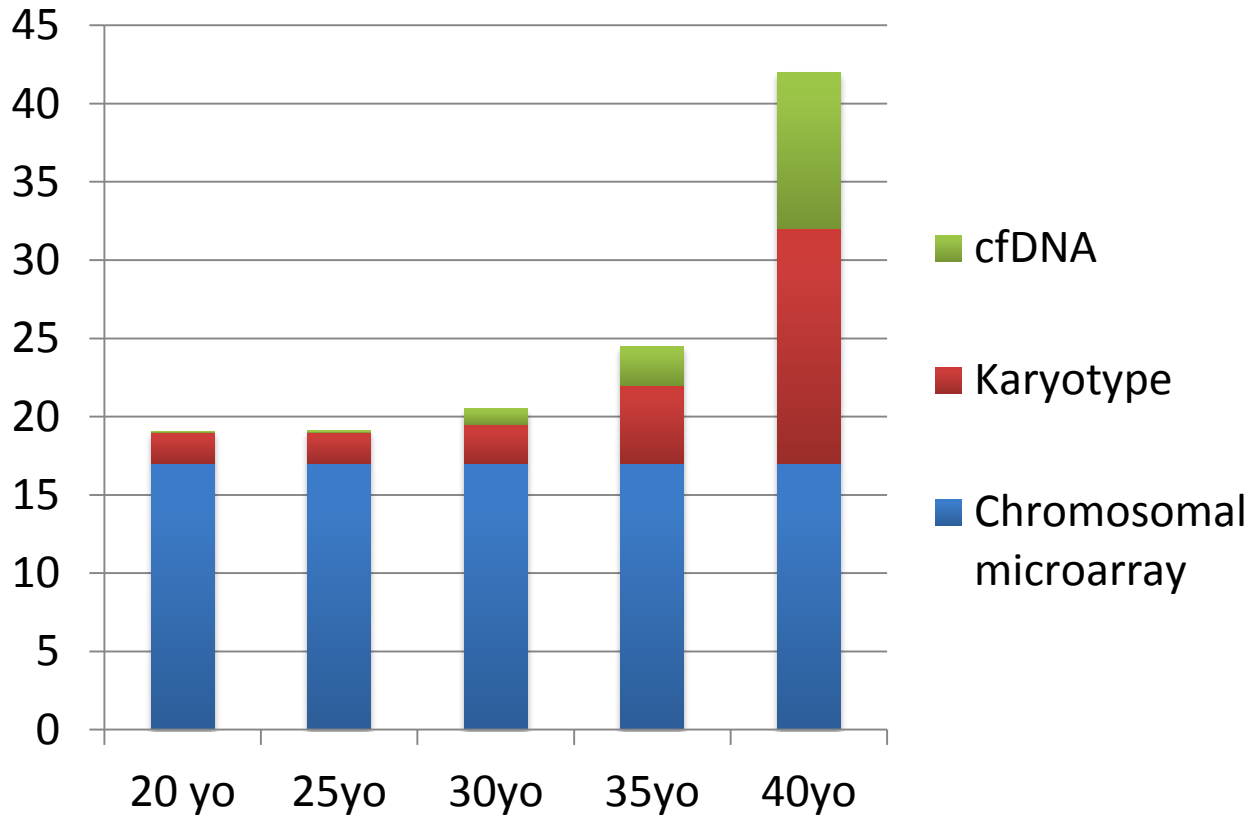


Bianchi DW. Nature 2015;52:;29 -3.

Rate of abnormalities by maternal age



Abnormalities detected per 1000 births



Wapner et al 2012; Hook 1983

Cell free DNA screening

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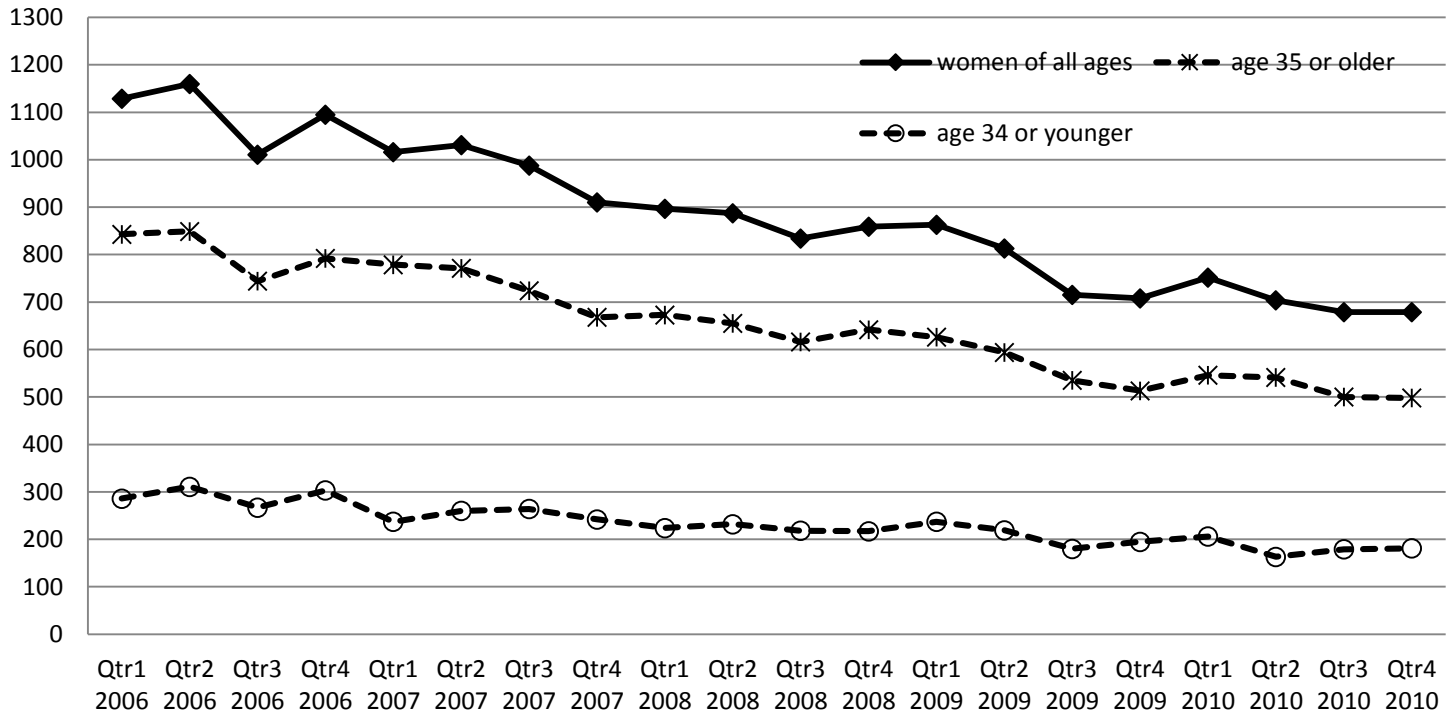
  - Broad, inexpensive screening for many conditions
- Diagnostic testing with chorionic villus sampling, amniocentesis
  - Low risk of complications, ~1/500-1000
- cfDNA screens for *fewer conditions* at *higher cost*

Volume of Prenatal Diagnosis Procedures 2006-2010 at Kaiser Northern California



Norton et al, 2012

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal-Fetal Medicine

(Published Electronically Ahead of Print on June 26, 2015)

COMMITTEE OPINION

Number 640 • September 2015

(This Committee Opinion Replaces Committee Opinion Number 545)

Committee on Genetics
Society for Maternal–Fetal Medicine

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Cell-free DNA Screening for Fetal Aneuploidy

ACOG/SMFM September 2015

- Conventional screening is most appropriate first line screen for most patients
- Ethically, any patient may choose cfDNA screening, but should be counseled regarding limitations and benefits
- Diagnostic testing is required to confirm abnormal results before irreversible decisions
- Testing for microdeletions and in twins should not be performed

Challenges of appropriate implementation

- Inadequate provider knowledge
- Lack of standardized patient education/information
- Misunderstanding of the test
  - “non-invasive amniocentesis”
- Misunderstanding of results (PPV)

BRIEF REPORT | Genetics in Medicine

Discordant noninvasive prenatal testing and cytogenetic results: a study of 109 consecutive cases

Jia-Chi Wang, MD, PhD[1], Trilochan Sahoo, MD[1,2], Steven Schonberg, PhD[3], Kimberly A. Kopita, MS[1], Leslie Ross, MS[1], Kyla Patek, MS[3] and Charles M. Strom, MD, PhD[1]

Genet Med 2015

Wang et al, *Genetics in Medicine,* 2015

Aneuploidy	No. of positives	No (%) confirmed
T21	41	38/41 (93%)
T18	25	16/25 (64%)
T13	16	7/16 (44%)
45X	16	6/16 (38%)
Total	**98**	**67 (67%)**

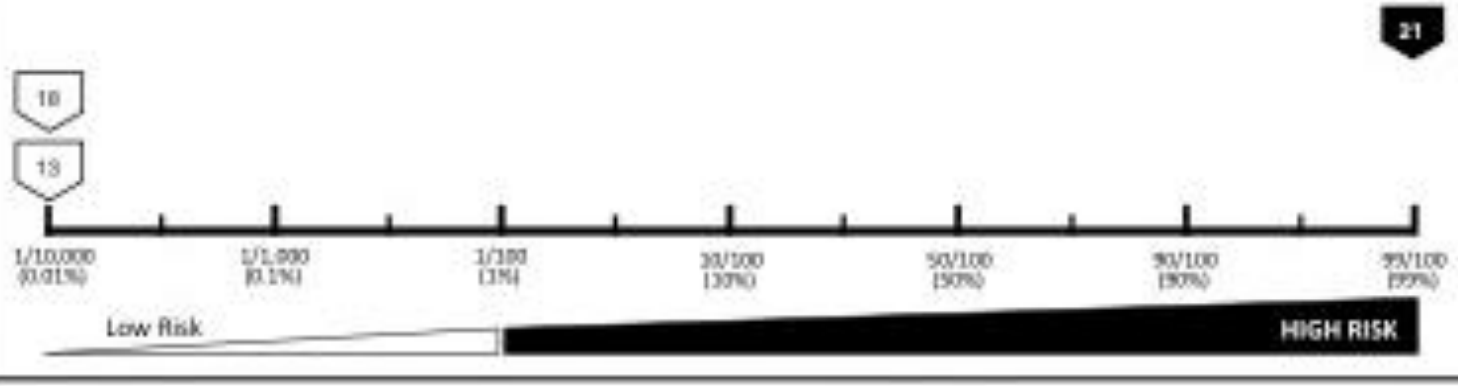
Questions
(800) 848 - 4436

COLLECTION DATE: 01/01/2012
RECEIVED DATE: 01/02/2012

OTHER PROVIDER FAX #: 987-654-3210
REPORT DATE: 01/12/2012

Test Results

CHROMOSOME	RESULT	RISK SCORE	RECOMMENDATION
Trisomy 21 (T21)	**HIGH RISK**	**Greater than 99/100 (99%)**	**Genetic counseling and additional testing**
Trisomy 18 (T18)	Low Risk	Less than 1/10,000 (0.01%)	Review results with patient
Trisomy 13 (T13)	Low Risk	Less than 1/10,000 (0.01%)	Review results with patient



TEST DESCRIPTION

CLINICAL DATA

The poorly understood PPV

Oversold prenatal tests spur some to choose abortions

“Disruptive technology”

- “A good disruptive technology can succeed in creating a market that didn’t exist before by meeting a need that people didn’t know they needed.”

What has contributed to very rapid uptake?

- Valid, legitimate evidence?
  - All industry sponsored, not true cohorts
  - As presented, evidence is compelling**
- Clinician/staff knowledge/skill
  - History of Down syndrome screening**
  - Deceptively simple**
- Supportive professional norms
  - Long history of DS screening**
  - Traditional screening continues to be recommended
- External expectations
  - Competitive industry, attractive $6b market**

What has contributed to very rapid uptake?

- Patient acceptance
  - History of DS screening, simple blood draw**
  - “Noninvasive Prenatal Testing”
- Evidence of quality gaps
  - Test was not developed to fill a gap
- Feasible methods, systems
  - Simple test to administer**

How will outcomes be assessed?

- Analytic, clinical validity largely in industry sponsored trials
- Clinical utility varies by author/investigator
  - Industry sponsored cost-effectiveness vs academic
  - Outcomes assessed
- Incidental/unexpected findings

Preliminary Communication

Noninvasive Prenatal Testing and Incidental Detection of Occult Maternal Malignancies

Diana W. Bianchi, MD; Darya Chudova, PhD; Amy J. Sehnert, MD; Sucheta Bhatt, MD; Kathryn Murray, MS; Tracy L. Prosen, MD; Judy E. Garber, MD; Louise Wilkins-Haug, MD, PhD; Neeta L. Vora, MD; Stephen Warsof, MD; James Goldberg, MD; Tina Ziainia, MD; Meredith Halks-Miller, MD

JAMA. 2015;314(2):162-169. doi:10.1001/jama.2015.7120
Published online July 13, 2015.

Pregnancy: Prepare for unexpected prenatal test results

Diana W. Bianchi

Women are learning about their own health problems through fetal screening. Revise consent forms and raise awareness, urges Diana W. Bianchi.

Models to collect high quality evidence:

- Large integrated health systems
  - Kaiser Permanente
- Integrated programs
  - California Prenatal Screening Program
- Patient/provider registries
  - Perinatal Quality Foundation

Obstet Gynecol, October 2015

Current Commentary

Current Status of Testing for Microdeletion Syndromes and Rare Autosomal Trisomies Using Cell-Free DNA Technology

Yuval Yaron, MD, Jacques Jani, MD, Maximilian Schmid, MD, and Dick Oepkes, MD

- "cell-free DNA testing for microdeletion syndromes and rare autosomal trisomies is currently unsupported by sufficient clinical evidence."

- "…health policy needs to be primarily based on good evidence, but also involves much broader political as well as socioeconomic consideration. The conversation on which conditions deserve prenatal screening and what standards to accept in doing so cannot be left to commercial companies alone."

The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies

Office of Public Health Strategy and Analysis
Office of the Commissioner
Food and Drug Administration

November 16, 2015

The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies

"…these products may have caused or have caused actual harm to patients."

Office of Public Health Strategy and Analysis
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November 16, 2015

C. Tests with the Potential to Yield both Many False-Positive and False-Negative Results

i. Noninvasive Prenatal Testing (A.K.A. cell-free DNA testing)

Category	LDT Characteristics
LDT Name	Noninvasive prenatal cell-free DNA testing (NIPT, or cfDNA)
Description	Blood test to identify traces of fetal chromosomes in maternal blood
Purpose	To detect a range of fetal chromosomal abnormalities
Target Population	Pregnant women concerned about a fetal chromosomal abnormality
Alternatives	Invasive testing, including amniocentesis and chorionic villi sampling; "quad testing" of multiple substances combined with ultrasound imaging
LDT Problem 1	Lack of clinical validation that tests detect and predict fetal abnormalities at an appropriate rate
LDT Problem 2	Many false-positive results when used in the general population
Clinical Consequence	Women with false-positive results may abort a normal pregnancy; women with false-negative results may deliver a child with an unanticipated genetic syndrome
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims
Cost Impact of Inaccuracy	Not estimated

Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening

EJHG Open

Wybo Dondorp[1], Guido de Wert[1], Yvonne Bombard[2], Diana W Bianchi[3], Carsten Bergmann[4,5], Pascal Borry[6], Lyn S Chitty[7], Florence Fellmann[8], Francesca Forzano[9], Alison Hall[10], Lidewij Henneman[11], Heidi C Howard[12], Anneke Lucassen[13], Kelly Ormond[14], Borut Peterlin[15], Dragica Radojkovic[16], Wolf Rogowski[17], Maria Soller[18], Aad Tibben[19], Lisbeth Tranebjærg[20,21,22], Carla G van El[11] and Martina C Cornel[11] on behalf of the European Society of Human Genetics (ESHG) and the American Society of Human Genetics (ASHG)

- **Crucial elements are the quality of the screening process as a whole (including non-laboratory aspects such as information and counseling), education of professionals, systematic evaluation of all aspects of prenatal screening, development of better evaluation tools in the light of the aim of the practice, accountability to all stakeholders including children born from screened pregnancies and persons living with the conditions targeted in prenatal screening and promotion of equity of access.**

Summary

- cfDNA has had a tremendously rapid uptake
- Very limited clinical data was available prior to implementation
- Some complexities of test are only coming to light subsequent to clinical introduction
- Test options are rapidly expanding with even less validation
- Powerful tool when appropriately implemented