CS 68: BIOINFORMATICS

Prof. Sara Mathieson
Swarthmore College
Spring 2018

Outline: Apr 30

- Overview of Non-invasive Prenatal Testing (NIPT)
- Small group discussion of papers
- Regroup as a class

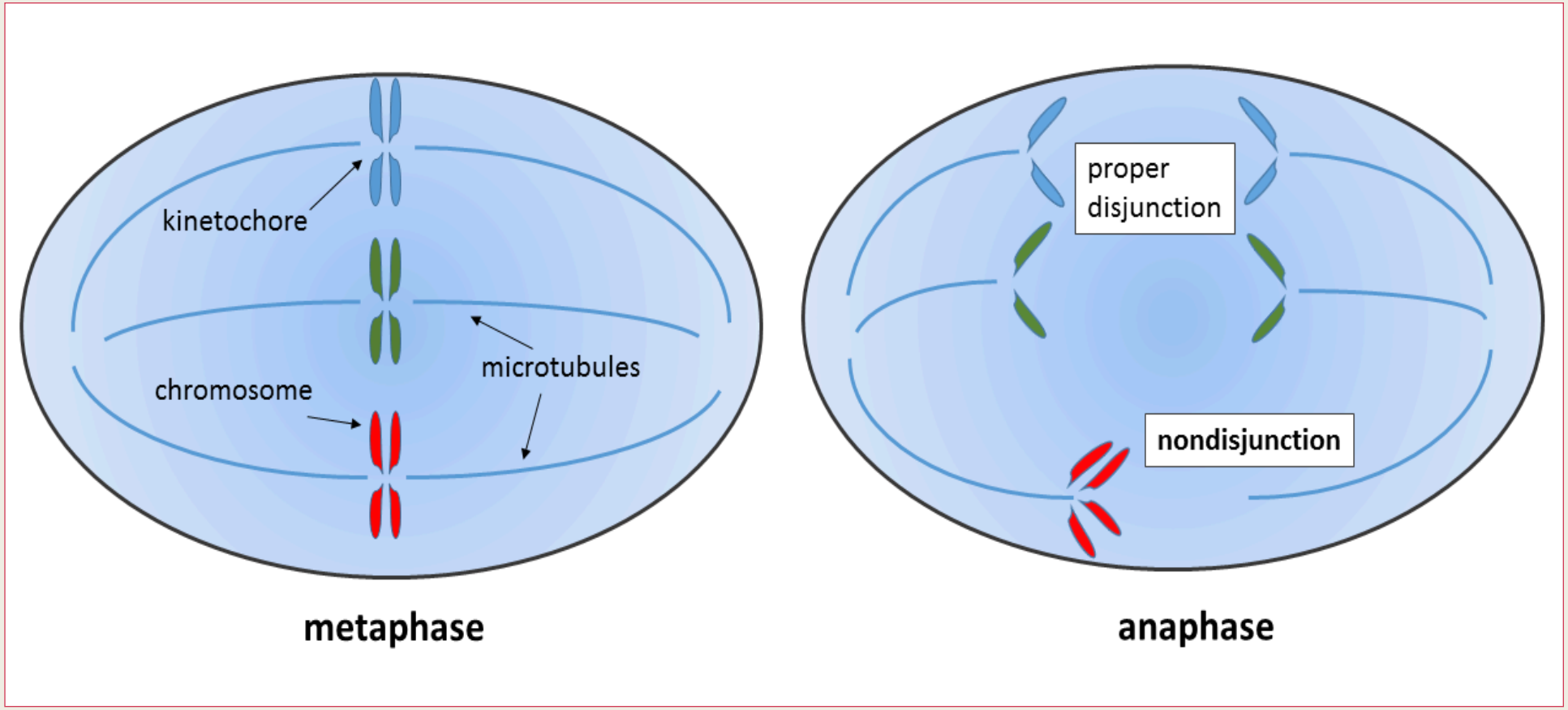
Notes:

-Office hours TODAY 3:15-5pm
-Project meetings in lab on Thursday

Prenatal Testing Background

Causes of aneuploidy

abnormal number of chromosomes (usually 1 or 3 instead of 2)



"Mitotic nondisjunction" by Wpeissner - https://commons.wikimedia.org

Motivation: aneuploidy testing

Autosomal chromosomes:

- Trisomy 13: Patau syndrome
- Trisomy 18: Edwards syndrome
- Trisomy 21: Down syndrome

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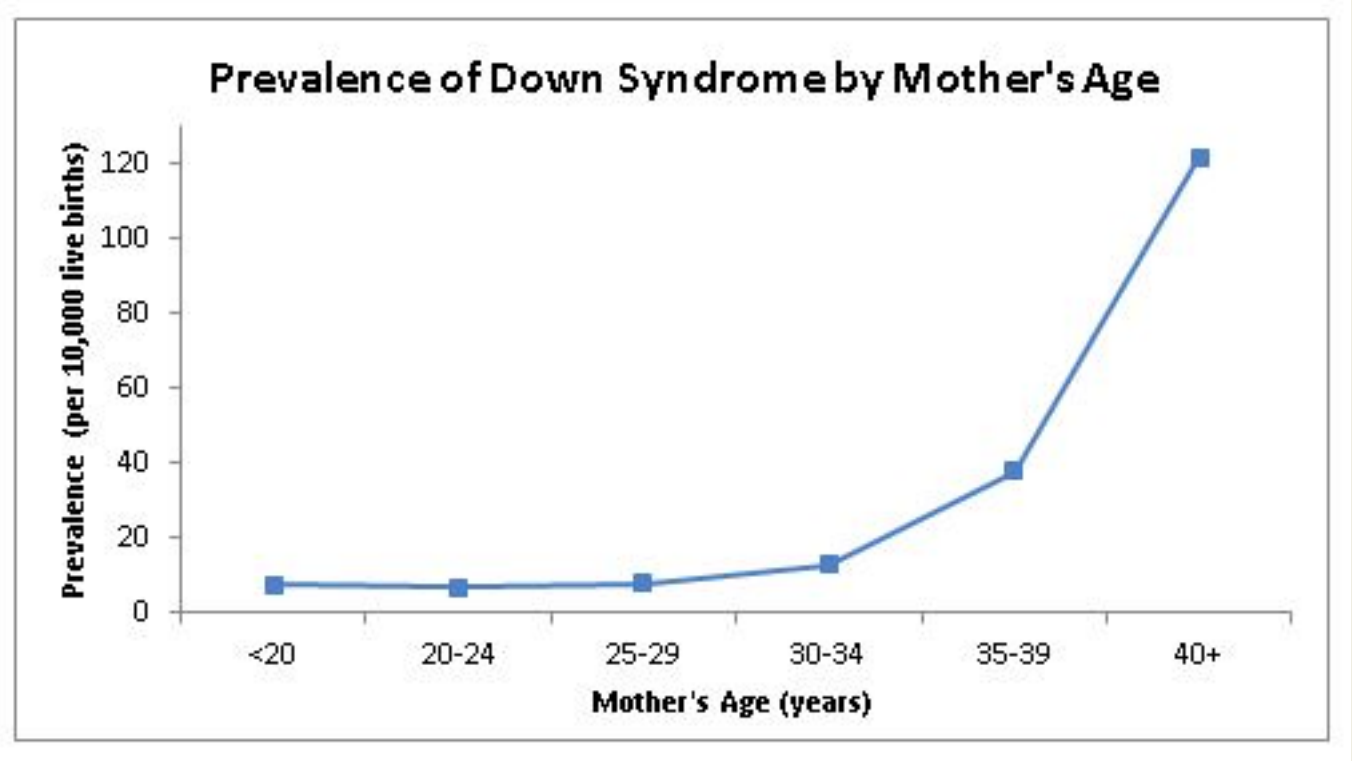
Sex chromosomes:

- X0 (one X chromosome): Turner's syndrome
- XYY or XXX: normal male or female phenotype
- XXY: Klinefelter Syndrome

Older women are more at risk



Current testing procedures

- cFTS (combined First-Trimester Screening), 12-14 weeks
  - *Looks at biomarkers and other data*

- Amniocentesis (invasive)
  - *16-22 weeks, uses karyotyping to determine anueploidy*

- 1997: proof of fetal DNA in maternal blood (Y-chromosome)

- ≈2011: companies offer Non-Invasive Prenatal Testing (NIPT)
  - *Verinata, Harmony, NIFTY*
  - *All using next-generation sequencing*

Basic Procedure

1) Sample maternal blood

- contains cell-free fetal DNA (cffDNA)

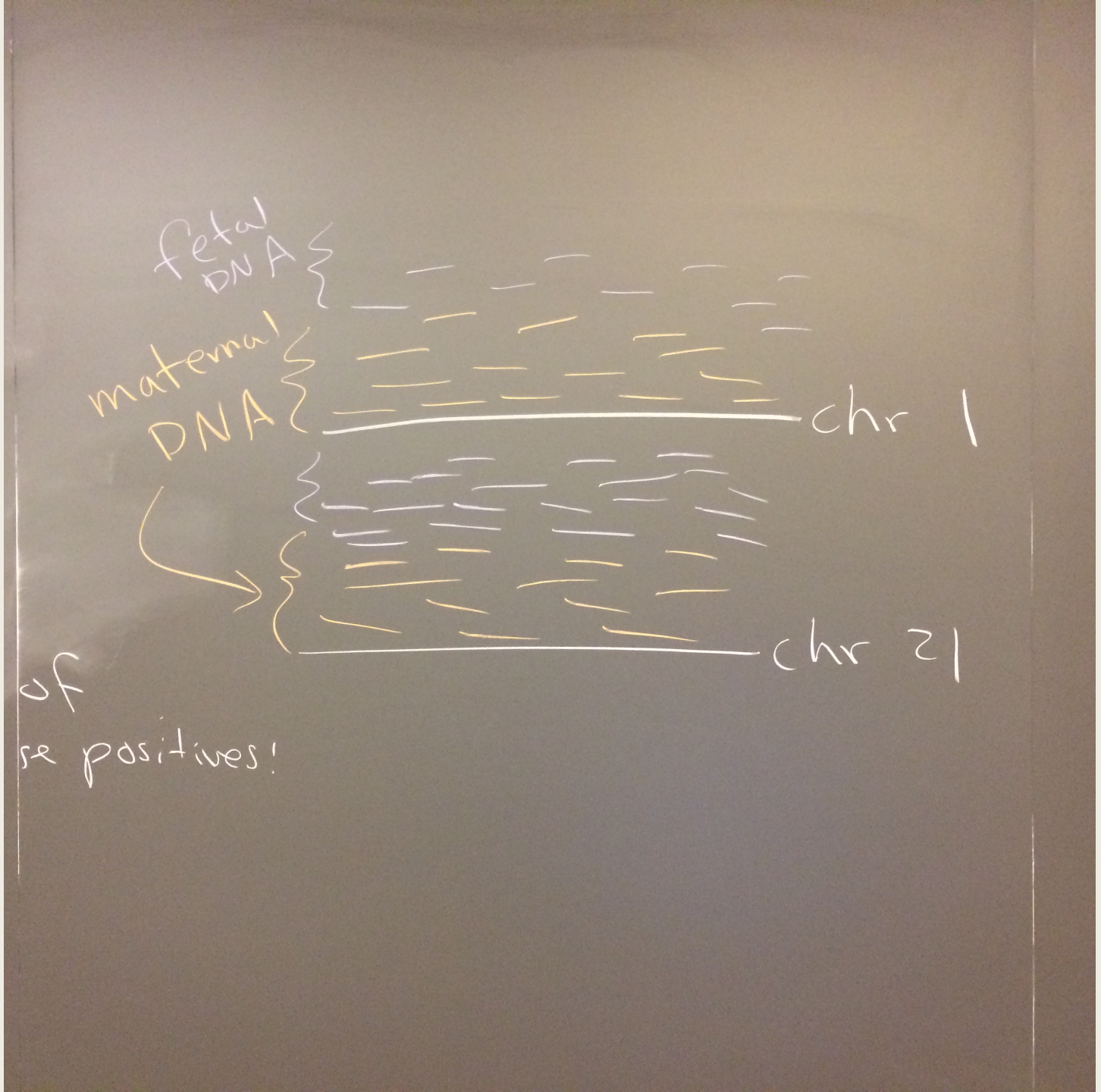
2) Low-coverage sequencing (0.1x - 4x)

3) Read alignment/mapping to human genome (using BWA or similar)

- save reads that map uniquely

4) Compute coverage for each chromosome

5) *t*-test for aneuploidy (coverage differences)


fetal DNA
maternal DNA
chr 1
chr 21
of
se positives!

Direct to Consumer (DTC) testing

verinata

Continuous innovation

Increased safety and peace of mind for your patients

Swift acceptance of the verifi® prenatal test has made a world of difference to high-risk patients across the country:

- SAFE—Routine blood draw, **just one tube** (7-10 ml)
- ACCURATE—Directly analyzes cell-free fetal DNA with our proprietary SAFeR™ algorithm
- EASY—Test as early as 10 weeks, no limitations in reference to patient ethnicity, BMI, ART, or egg donor cases
- FAST—Results reported in 3-6 business days after sample receipt

The basic verifi® test detects:

- T21 (Down syndrome)
- T18 (Edwards syndrome)
- T13 (Patau syndrome)

Trisomy 21, 18, 13

Now a wider option is available for sex chromosomes at no extra charge:

- Monosomy X (MX; Turner syndrome)
- XXX (Triple X)
- XXY (Klinefelter syndrome)
- XYY (Jacobs syndrome)
- Fetal sex (XX or XY)—aids in stratifying the risk for X-linked disorders such as hemophilia, Duchenne muscular dystrophy, or cases of ambiguous genitalia, such as congenital adrenal hyperplasia

verinata

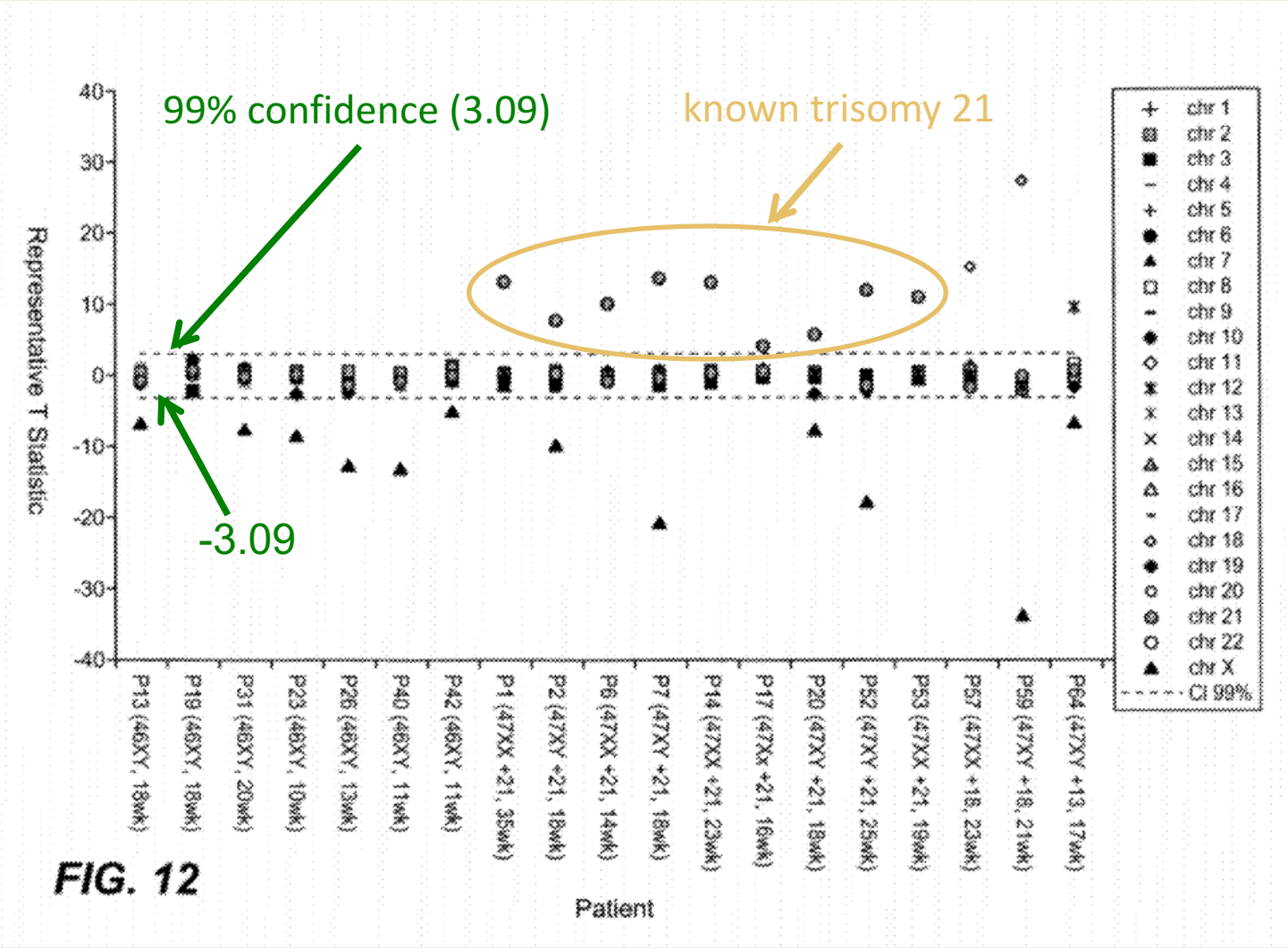


FIG. 12

DNA Sequencing versus Standard Prenatal Aneuploidy Screening

Diana W. Bianchi, M.D., R. Lamar Parker, M.D., Jeffrey Wentworth, M.D., Rajeevi Madankumar, M.D., Craig Saffer, M.D., Anita F. Das, Ph.D., Joseph A. Craig, M.D., Darya I. Chudova, Ph.D., Patricia L. Devers, M.S., C.G.C., Keith W. Jones, Ph.D., Kelly Oliver, B.S., Richard P. Rava, Ph.D., and Amy J. Sehnert, M.D. for the CARE Study Group

N Engl J Med 2014; 370:799-808 | February 27, 2014 | DOI: 10.1056/NEJMoa1311037

	false positive (sequencing)	false positive (standard)	false negative (sequencing)	num positives	PPV (sequencing)	PPV (standard)
T21	0.30%	3.60%	0	5	45.50%	4.20%
T18	0.20%	0.60%	0	2	40.00%	8.30%
T13			0	1		

Probability Considerations

Clinical Trials Example

- Disease affects 1/100 people: *P*(disease) = 0.01
- Test for the disease with 90% accuracy
  - *P(positive|disease) = 0.9*
  - *P(negative|healthy) = 0.9*

Clinical Trials Example

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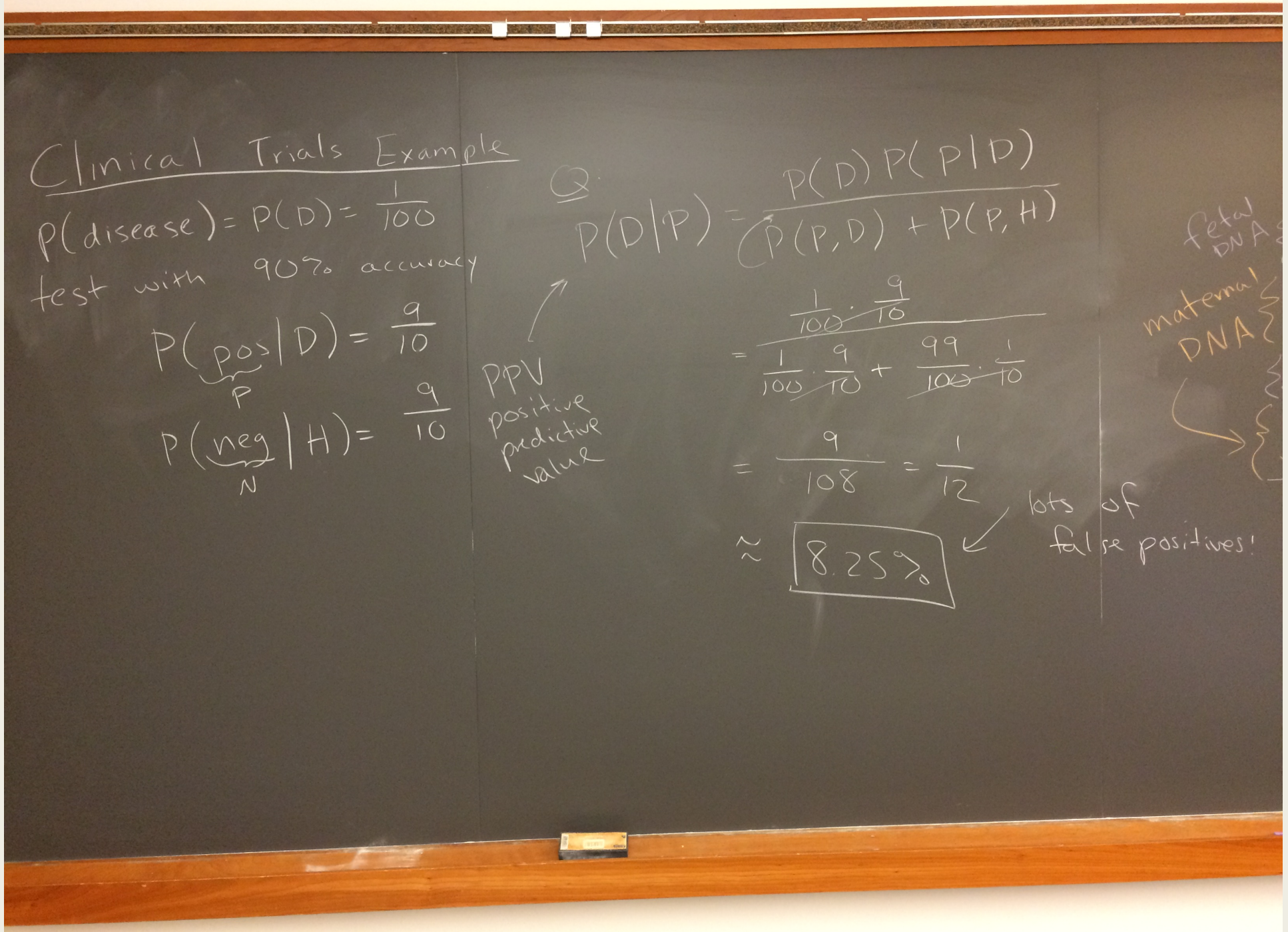
$$\approx 8.3\%$$


Clinical Trials Example
P(disease) = P(D) = 1/100
test with 90% accuracy
P(pos | D) = 9/10
P
P(neg | H) = 9/10
N
PPV
positive
predictive
value
Q.
P(D|P) = P(D) P(P|D) / (P(P,D) + P(P,H))
= (1/100 · 9/10) / (1/100 · 9/10 + 99/100 · 1/10)
= 9/108 = 1/12
≈ 8.25%
lots of
false positives!
fetal DNA
maternal DNA

Bayesian Model

Input data are read counts for each chromosome (1,2,…,n):

$$q_1, q_2, \cdots, q_n = \vec{q}$$

$$\sum_{i=1}^{n} q_i = N$$

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Goal:

$$\mathbb{P}(T_{21}|\vec{q}\,) = \frac{\mathbb{P}(\vec{q}\,|T_{21}) \cdot \mathbb{P}(T_{21})}{\mathbb{P}(\vec{q}\,)}$$

$$= \frac{\mathbb{P}(\vec{q}\,|T_{21}) \cdot \mathbb{P}(T_{21})}{\mathbb{P}(\vec{q}\,|T_{21}) \cdot \mathbb{P}(T_{21}) + \mathbb{P}(\vec{q}\,|T_{21}^{C}) \cdot \mathbb{P}(T_{21}^{C})}$$

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Prior:

$P(T_{21})$

Maternal Age	Trisomy 21	All Trisomies
20	1 in 1,667	1 in 526
21	1 in 1,429	1 in 526
22	1 in 1,429	1 in 500
23	1 in 1,429	1 in 500
24	1 in 1,250	1 in 476
25	1 in 1,250	1 in 476
26	1 in 1,176	1 in 476
27	1 in 1,111	1 in 455
28	1 in 1,053	1 in 435
29	1 in 1,000	1 in 417
30	1 in 952	1 in 384
31	1 in 909	1 in 384
32	1 in 769	1 in 323
33	1 in 625	1 in 286
34	1 in 500	1 in 238
35	1 in 385	1 in 192
36	1 in 294	1 in 156
37	1 in 227	1 in 127
38	1 in 175	1 in 102
39	1 in 137	1 in 83
40	1 in 106	1 in 66
41	1 in 82	1 in 53
42	1 in 64	1 in 42
43	1 in 50	1 in 33
44	1 in 38	1 in 26
45	1 in 30	1 in 21
46	1 in 23	1 in 16
47	1 in 18	1 in 13
48	1 in 14	1 in 10
49	1 in 11	1 in 8

Second paper

Refusing to provide a prenatal test: can it ever be ethical?

Rony E Duncan, research officer,[1] Bennett Foddy, PhD candidate,[2] and Martin B Delatycki, director[3]

"A couple in which the man carries the mutation for Huntington's disease request prenatal testing during their first pregnancy. Though they would not terminate an affected pregnancy, they would like the information. There is no treatment available that can change the course of the disease so the diagnosis will not result in medical benefit for the child."

Viewpoint 1: not to test
Viewpoint 2: to test

Discussion Questions

- Form small groups (3-4 people)
- Discuss questions below (or anything else you find interesting/relevant about this topic)
- Choose a representative to mention an interesting part of your discussion to the class

1) Which side of the second article (about Huntington's Disease) do you find most compelling?

2) Considering the potential of NIPT to resolve the entire fetal genome, what would be your recommendation about how to use this technology?