How to Judge Better Screening Tests

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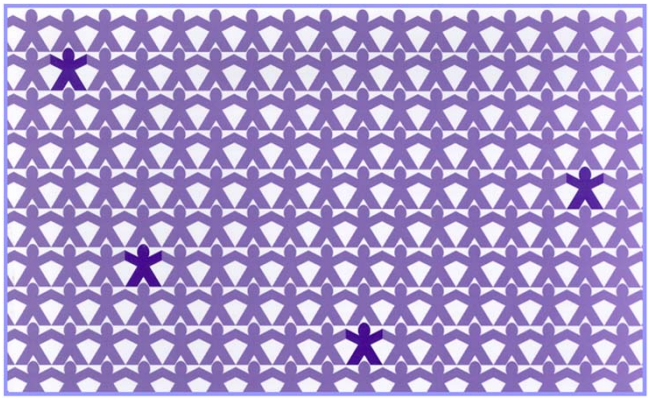
Definition of Prenatal Screening

(adapted from: Cuckle HS, Wald NJ, Principles of screening. In: *Antenatal and Neonatal Screening*. Oxford Univ Press, Oxford, 1984, pp. 1-22.

"The identification, among apparently normal pregnancies, of those at sufficient risk of a specific fetal disorder to justify subsequent invasive and/or costly prenatal diagnostic tests or procedures."



Cover of the *Journal of Medical Screening*

Requirements of a Worthwhile Screening Program

• ***Disorder***	**Well defined**
• ***Prevalence***	**Known**
• ***Natural history***	**Medically important, for which there is an effective remedy available**
• ***Financial***	**Cost effective**
• ***Facilities***	**Available or easily installed**
• ***Ethical***	**Procedures following a positive result generally agreed and accepted both to the screening authority and to the subjects**
• ***Test***	**Simple and safe**
• ***Test performance***	**Distribution of test values in affected and unaffected known; small overlap; cut-off defined**

Ref: Cuckle HS, Wald NJ, Principles of screening. In: *Antenatal and Neonatal Screening*. Oxford Univ Press, Oxford, 1984, pp. 1-22

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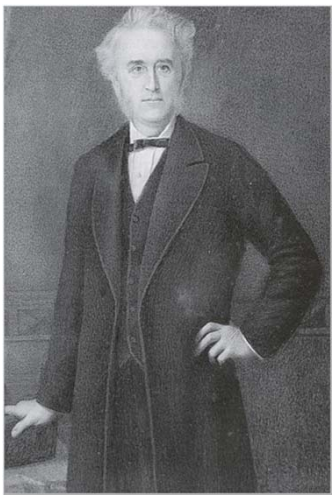
John Langdon Down (1828-1896)



Patient photographed by Langdon Down in 1865

OC Ward, *John Langdon Down, A Caring Pioneer,* Royal Soc Med Press, 1998

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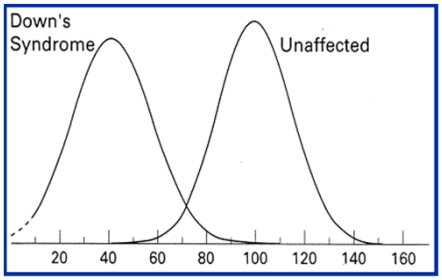
Features of Down Syndrome (Trisomy 21)

Incidence:

- ***Overall, 1 in 700 livebirths (23% higher in 2nd trimester)***
- ***Increases with advancing maternal age***

Clinical features:

- ***Mental retardation (mild to severe)***
- ***Heart malformations (40%) and medical complications***
- ***Presenile dementia after age 40***



IQ score (based on Carr, 1988)
In: J Noble, J Med Screen 1997;5:172-7

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Test Performance:

The challenge in screening is to have a test that has a high detection rate and low false positive rate.

detection rate — **percentage of *affecteds* called screen positive by the test**

The higher the better!

false positive rate — **percentage of *unaffecteds* called screen positive by the test**

The lower the better!

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Determining the Performance of a Screening Test

Need to know:

Detection Rate	***percentage of affected pregnancies called positive by the test***
False Positive Rate	***percentage of unaffected pregnancies called positive by the test***

Don't need to know, but is important in implementation:

Prevalence	***how often is the affected pregnancy found in the population being tested?***
OAPR (PPV)	***odds of affected given a positive result***
	≡ average risk amongst positives
	≡ equivalent to the positive predictive value of the test (percentage of positives that are affected)

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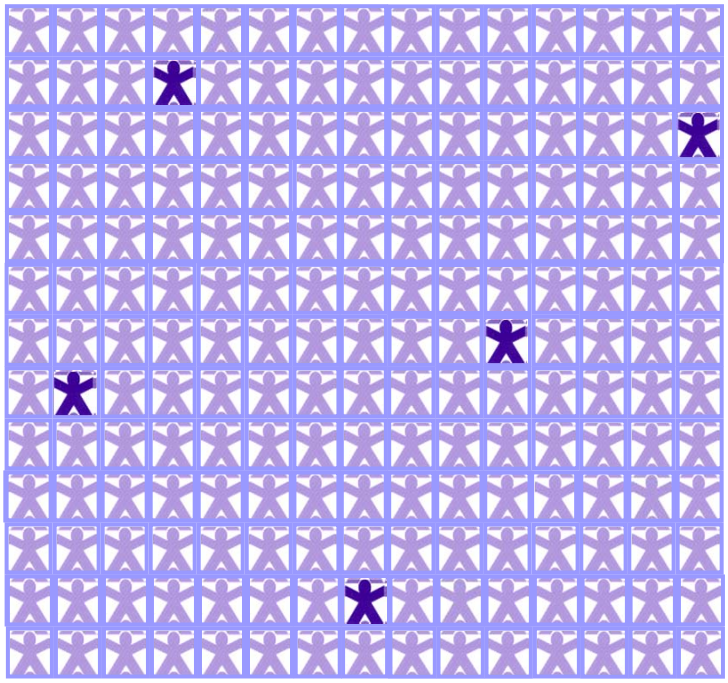
EXAMPLE

There are 195 pregnancies to be screened

5 are affected

190 are unaffected

Therefore, the prevalence is 5 in 195 or 1 in 39.



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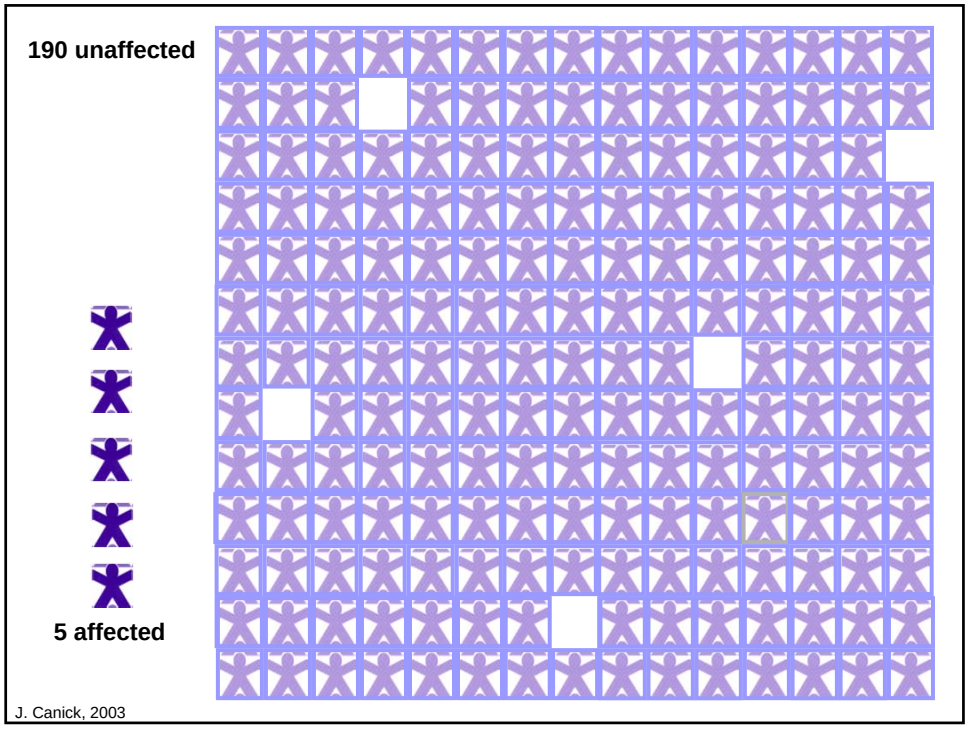
190 unaffected
5 affected
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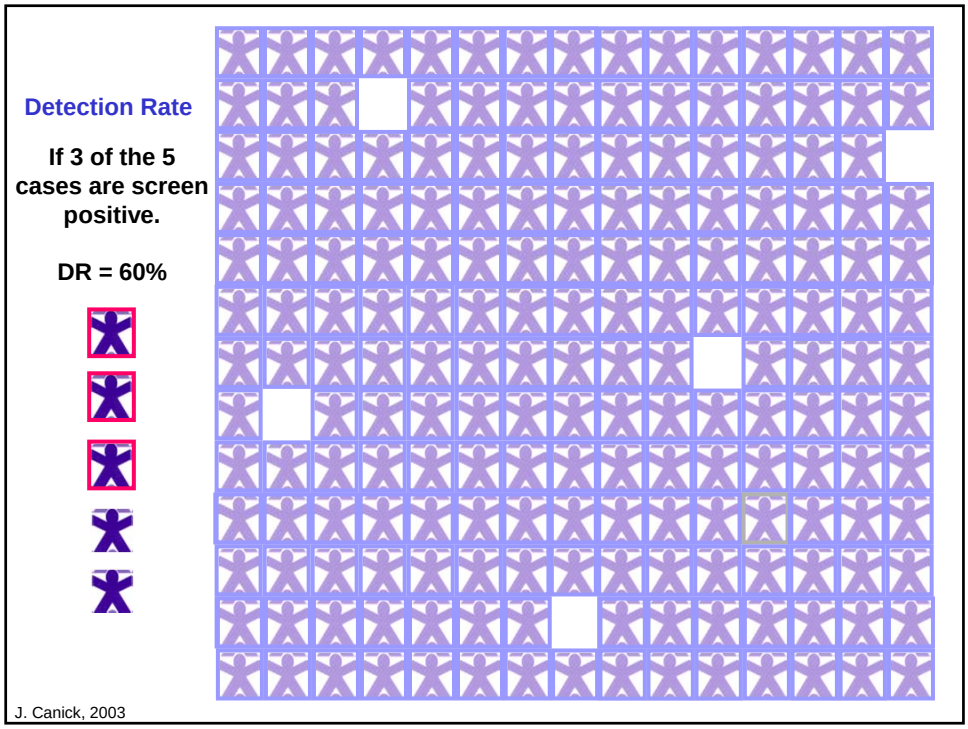
Detection Rate
If 3 of the 5 cases are screen positive.
DR = 60%
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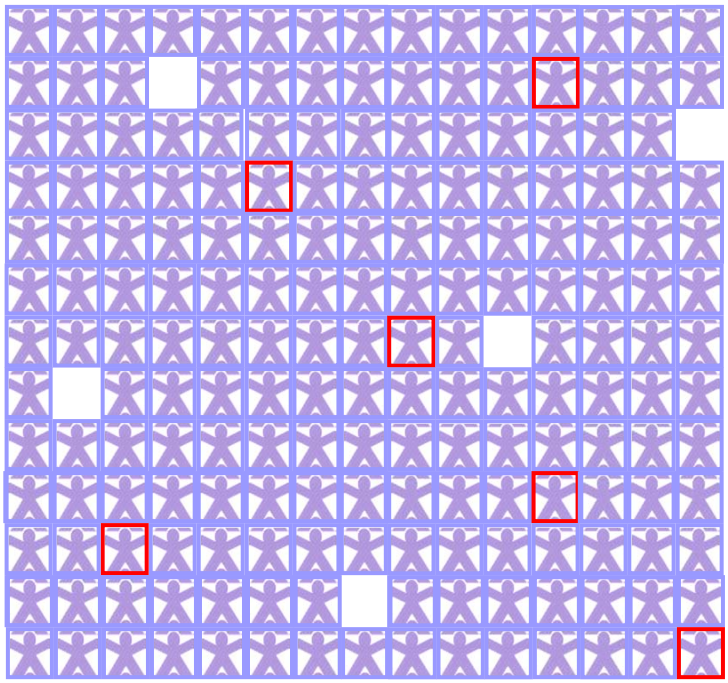
False Positive Rate

If 6 of the 190 unaffected pregnancies are screen positive

FPR = 3%



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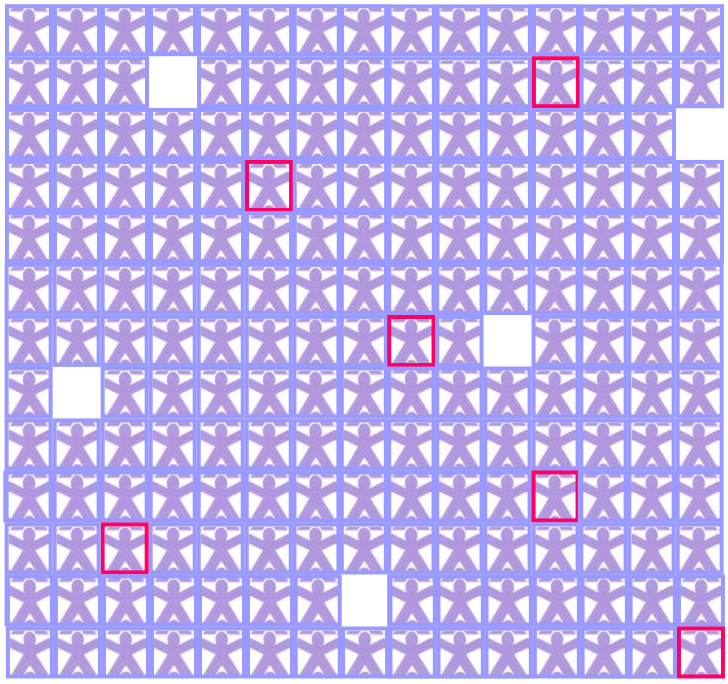
OAPR or PPV

9 pregnancies are called screen positive by the test.

3 of the 9 are affected.

OAPR = 3:6

PPV: 3/9 (33%)



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Concept of the Median and MoM

Background:

Described by N. Wald in 1976 *

Rationale:

- **maternal serum (and NT) levels are continually changing during gestation**
- **for any point in gestation, marker levels are usually log distributed (i.e., skewed to higher values)**
- **lab to lab variation in measurement markers can be large**

* Wald NJ. In: Prenatal Diagnosis, A Boue, ed., INSERM, Vol 61, pp. 227-38, 1976

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Concept of the Median and MoM

Solution:

- **the median, rather than mean, was chosen as a better estimate of the gestation-specific reference level, to account for a skewed distribution and for high outliers**
- **the multiple of the median (MoM) was chosen to normalize for the changing AFP values with gestation and between labs**

Result:

- **a simple, easy to remember number, 1 MoM, becomes the most common value for an unaffected, singleton pregnancy.**
- **the MoM has become the 'currency' used in prenatal screening throughout the world**

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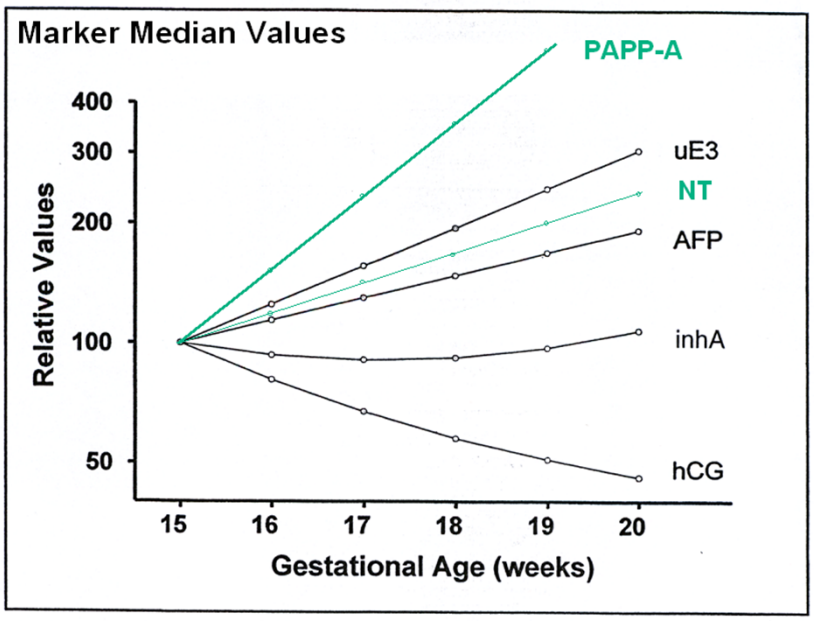

GJ Knight & GE Palomaki, personal communication

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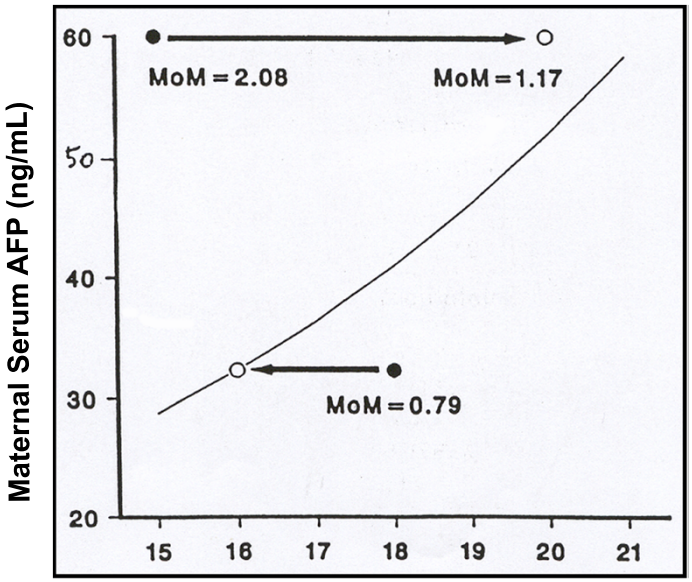
Gestational Dating and MoM



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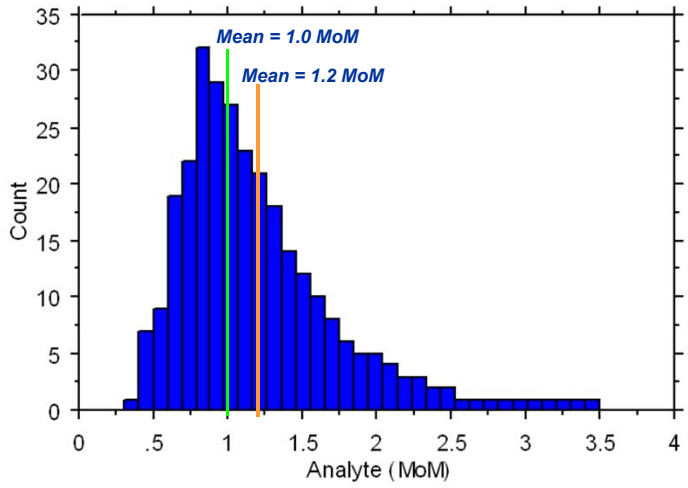
Example: MSAFP MoM Values on a Linear Scale



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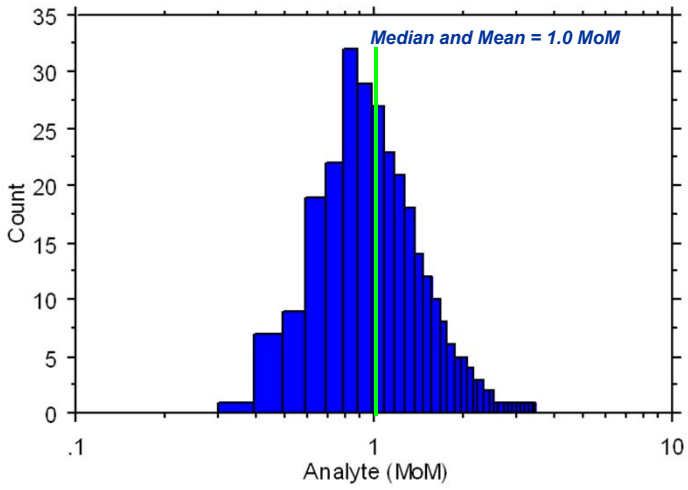
Example: MSAFP MoM Values on a Log Scale



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Calculation of Patient-Specific Risk

Patient-specific risk = patient's *a priori* risk x likelihood ratio

The *a priori* risk is given by the population risk, which is empirically derived from epidemiological studies.

For example:

- **for open spina bifida, the *a priori* risk is often a regional risk and a racial risk.**
- **for Down syndrome, the *a priori* risk is the risk based on maternal age.**

The *likelihood ratio* is the ratio of the heights of the gaussian curves at a specific analyte value.

$$LR = height_{aff} / height_{unaff}$$

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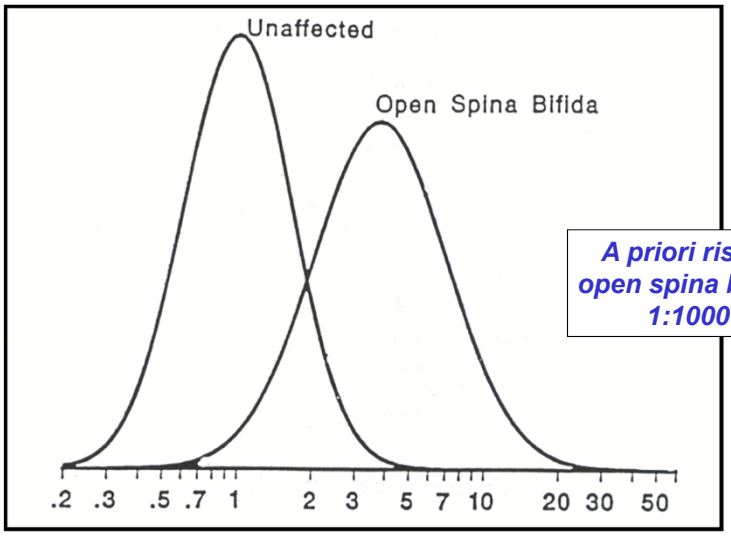

Maternal Serum AFP (MoM)

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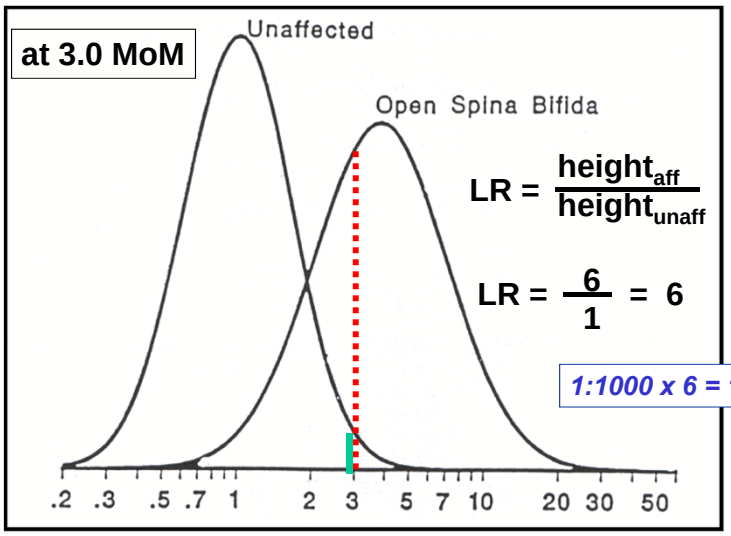

Maternal Serum AFP (MoM)

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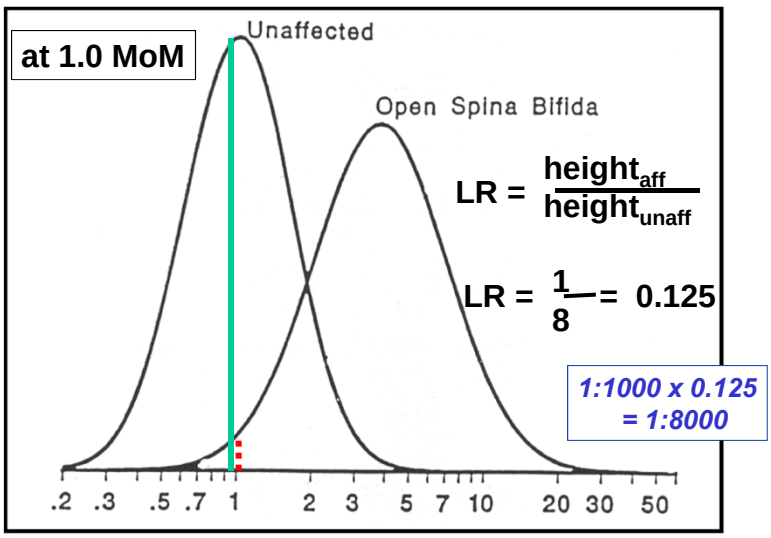

Maternal Serum AFP (MoM)

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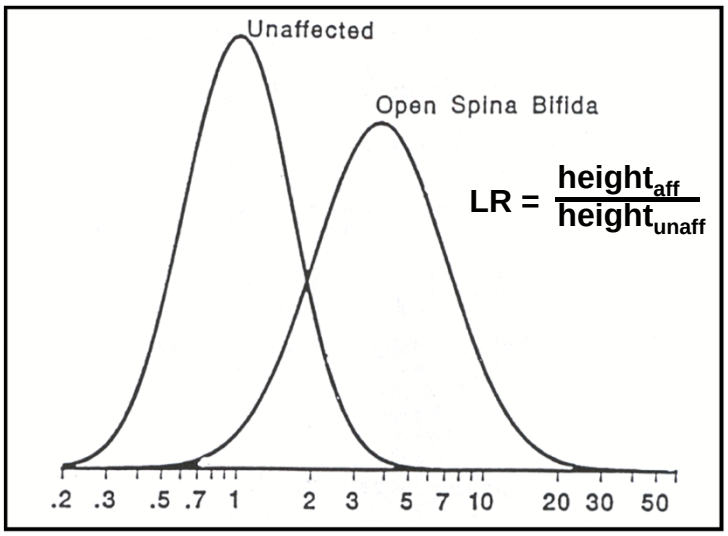
At what MoM will the risk not change?



Maternal Serum AFP (MoM)

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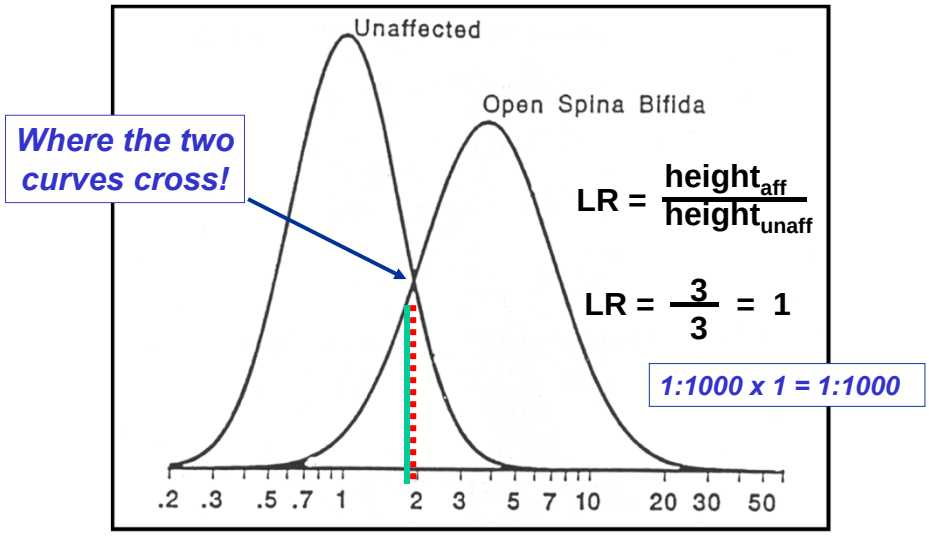
At what MoM will the risk not change?



Maternal Serum AFP (MoM)

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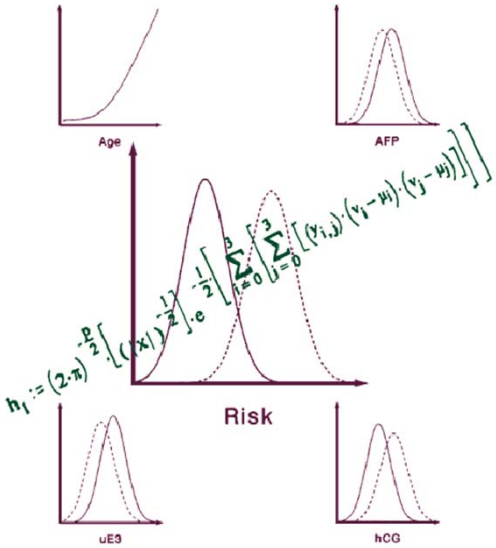
Calculation of Patient-Specific Risk Using Multiple Markers



Foundation for Blood Research website

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Prenatal Screening:
Calculation of Risk Using Multiple Markers

- **Each marker must be provide information on risk that is not provided by another marker used in that test (degree of independence).**
- **Each marker generates a likelihood ratio:**

  >1 the risk increases
  <1 the risk decreases

- **The individual likelihood ratios are multiplied to generate the overall likelihood ratio.**
- **Risk after testing = likelihood ratio$_{overall}$ x *a priori* risk**
- **The risk estimate is changed somewhat to account for small correlations between pairs of markers.**

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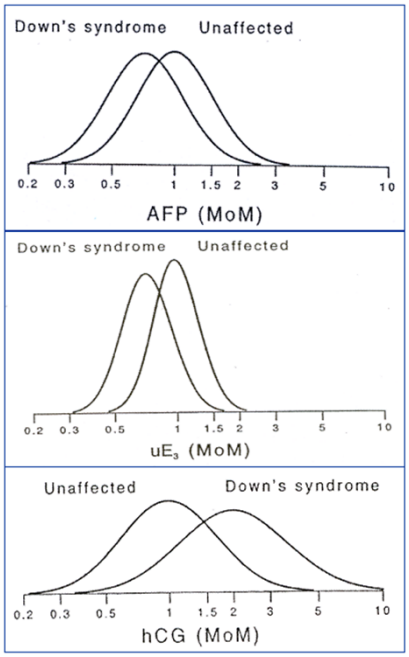

Example:

Triple marker screening

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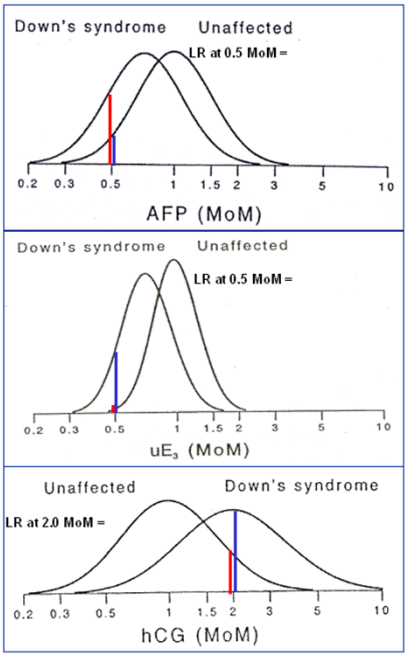

Example:

AFP = 0.5 MoM

uE3 = 0.5 MoM

hCG = 2.0 MoM

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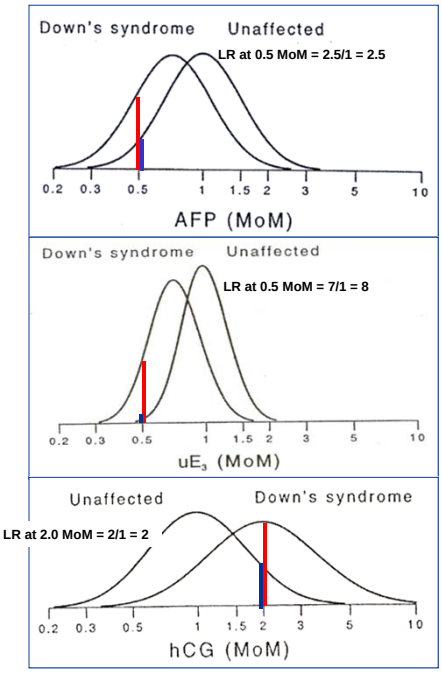

$LR_{AFP} \times LR_{uE3} \times LR_{hCG} = LR_{triple}$

2.5 x 8 x 2 = 40

40 x *a priori* risk = risk after test

40 x 1:1000 = 40:1000 = 1:25

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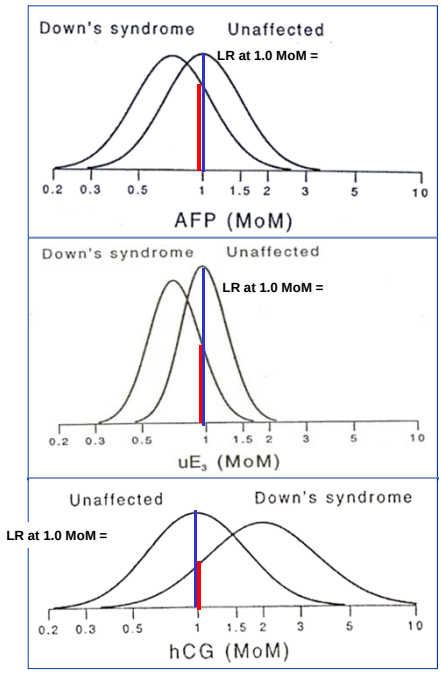

Example:

AFP = 1.0 MoM

uE3 = 1.0 MoM

hCG = 1.0 MoM

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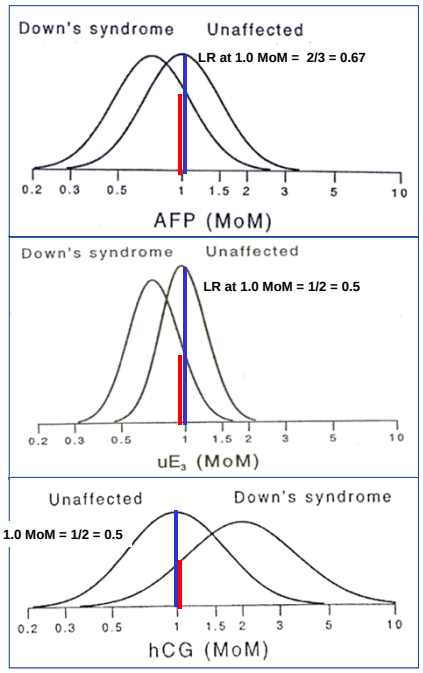

$LR_{AFP} \times LR_{uE3} \times LR_{hCG} = LR_{triple}$

0.67 x 0.5 x 0.5 = 0.18

0.18 x *a priori* risk = risk after test

0.18 x 1:1000 = 0.18:1000 = 1:6000

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How can we visualize improvements in screening performance?

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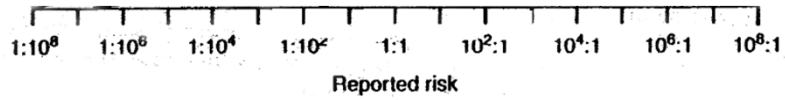
A Scale of Risks



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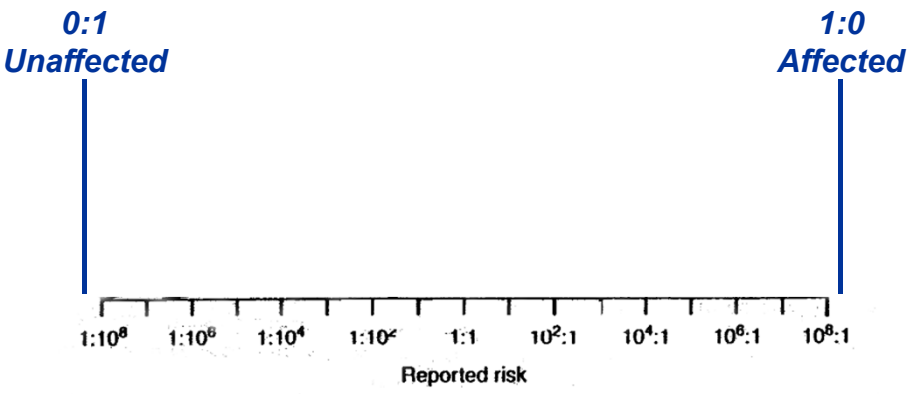
A Scale of Risks:

The pregnancy is either affected or unaffected



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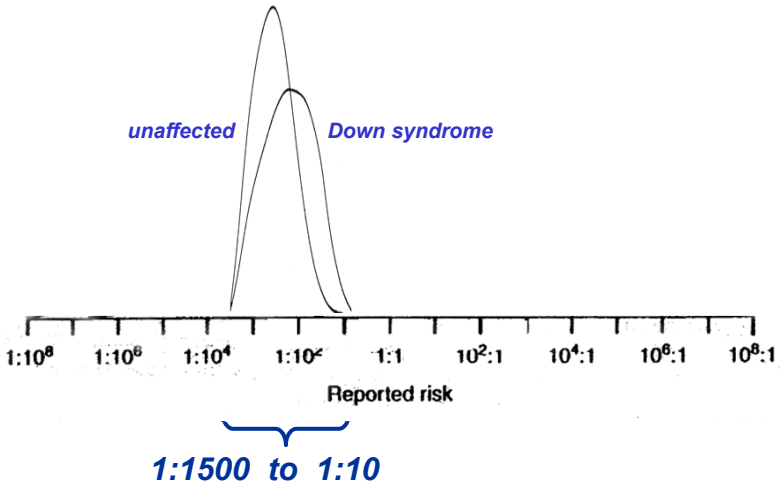
Maternal Age as a Screening Test:
Range of Risks: 150 fold



1:1500 to 1:10

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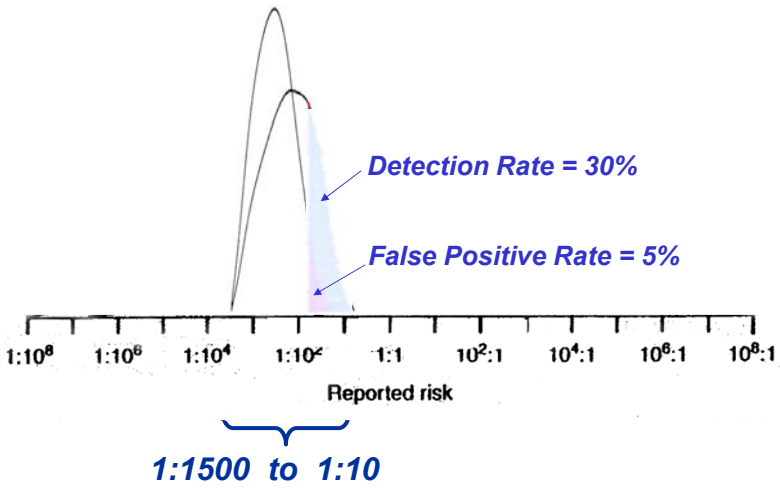
Maternal Age as a Screening Test:
Range of Risks: 150 fold



1:1500 to 1:10

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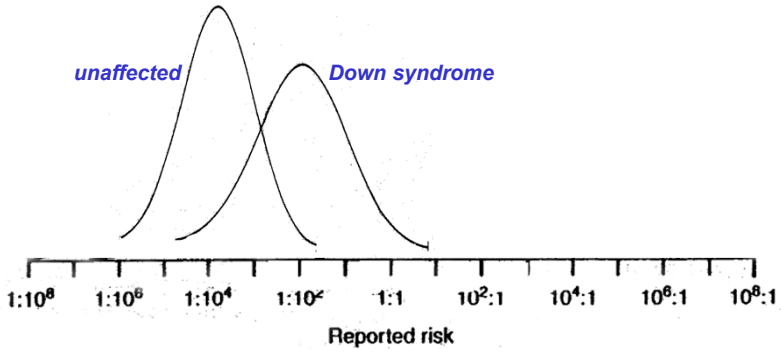
Second Trimester Triple Test:
Range of Risks: 100,000 fold



1:100,000 to 1:1

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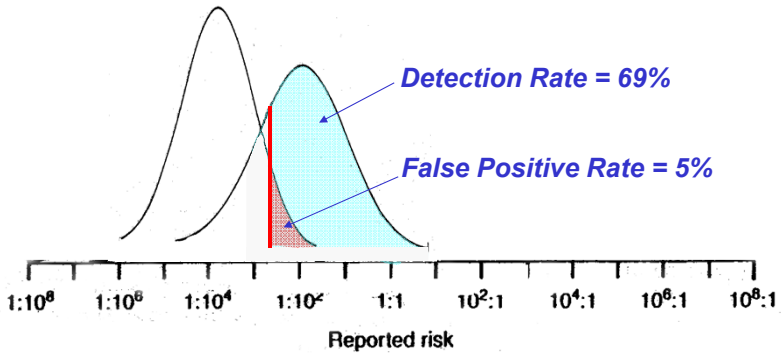
Second Trimester Triple Test:
Range of Risks: 100,000 fold



1:100,000 to 1:1

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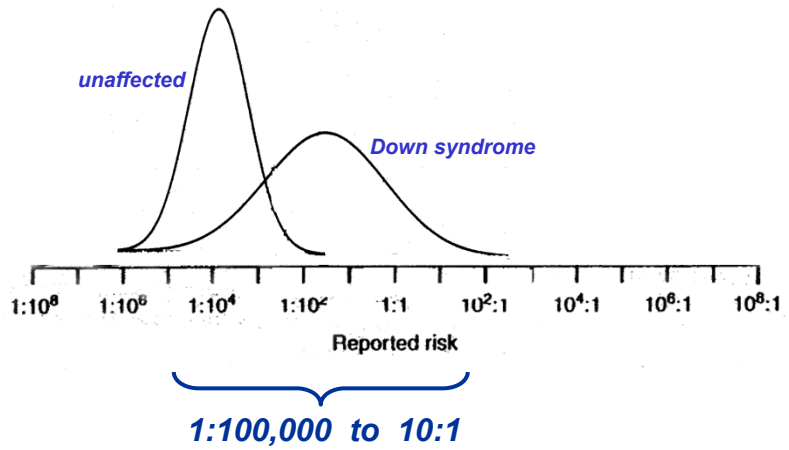
The First Trimester Combined Test:
Range of Risks: 1,000,000 fold



1:100,000 to 10:1

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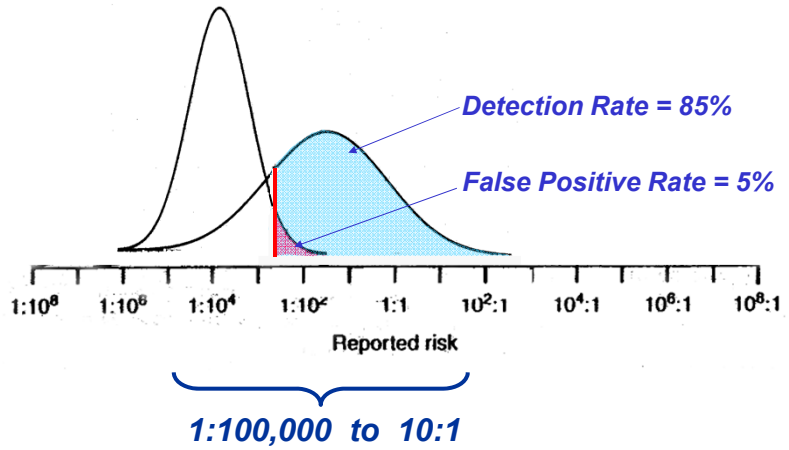
The First Trimester Combined Test:
Range of Risks: 1,000,000 fold



1:100,000 to 10:1

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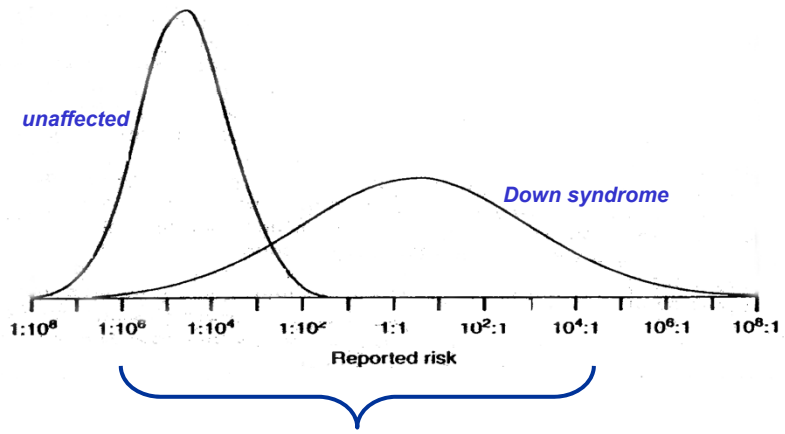
The Integrated Test:

Range of Risks: 1,000,000,000,000 (10^{12}) fold



$1:10^6$ to $10^4:1$

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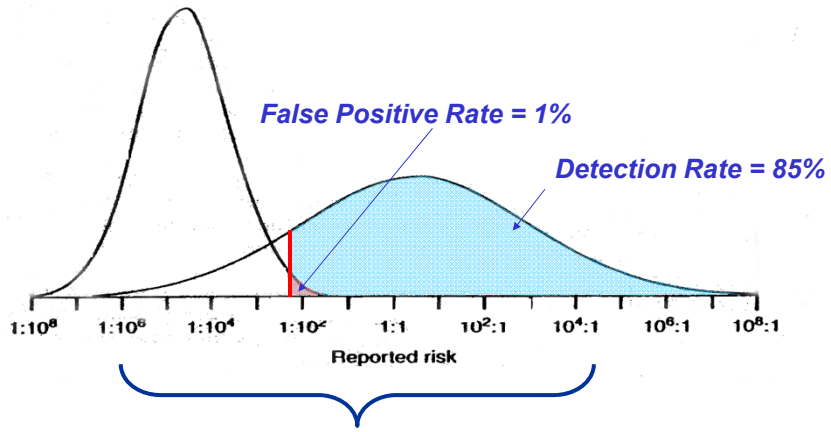
The Integrated Test:

Range of Risks: 1,000,000,000,000 (10^{12}) fold



$1:10^6$ to $10^4:1$

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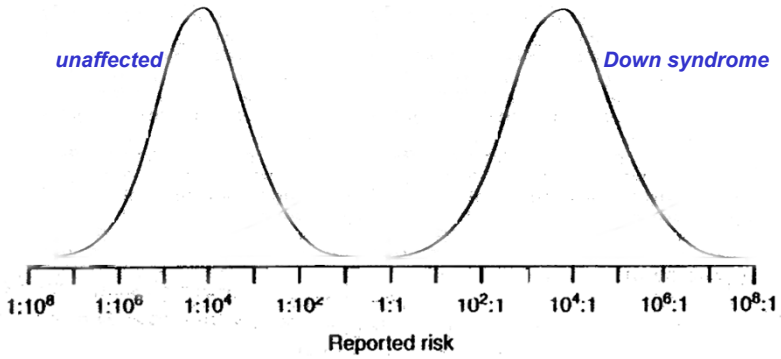
The future?



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