

Prenatal Screening: Its History and How It Works

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DSL Presentation at AACCC 2003



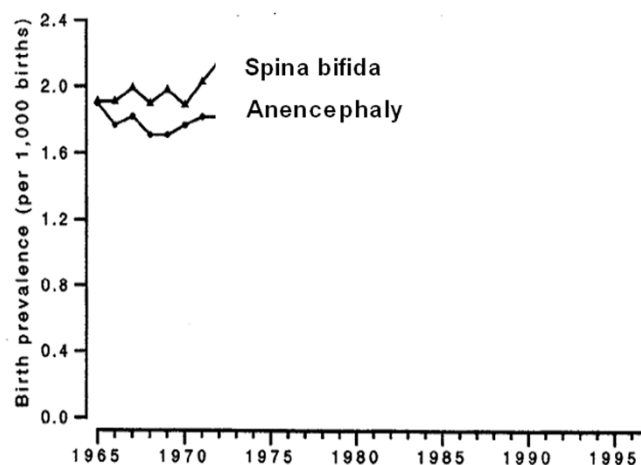
Women and Infants Hospital



Brown University

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Prevalence of NTDs at Birth in England and Wales 1965-1973



Adapted from: Wald NJ, Leck I. *Antenatal and Neonatal Screening*, Oxford, 2000

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History of Prenatal Screening: Maternal Serum Screening for Open Neural Tube Defects

Year	Milestone	Investigator(s)
1956	First description of alpha-fetoprotein	<i>Bergstrand and Czar</i>
1960s	Extremely high rates of NTD's in regions of the UK	<i>Elwood</i>
1972	Raised amniotic fluid AFP and NTDs	<i>Brock and Sutcliffe</i>
1972/3	Raised serum AFP and anencephaly	<i>Hino; Brock</i>
1974	Raised serum AFP and open spina bifida	<i>Wald ; Brock</i>
1976	The concept of the MoM	<i>Wald</i>
1977	The specification and performance of AFP screening for NTDs (the first example of a routine serum screening programme for birth defects)	<i>Wald and Cuckle</i>

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Concept of the Median and MoM

Background:

Described by N. Wald in 1976 *

Rationale:

- maternal serum 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

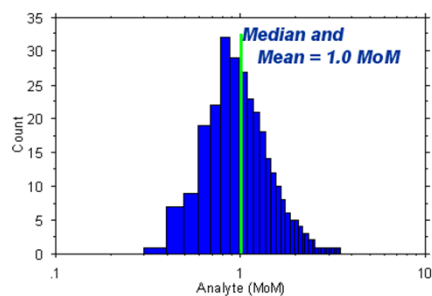
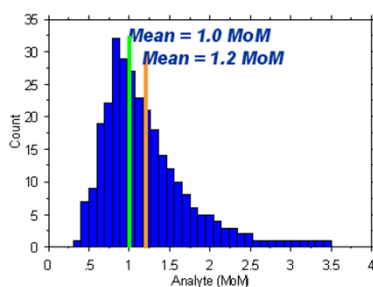
* Wald NJ. In: Prenatal Diagnosis, A Boue, ed., INSERM, Vol 61, pp. 227-38, 1976

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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



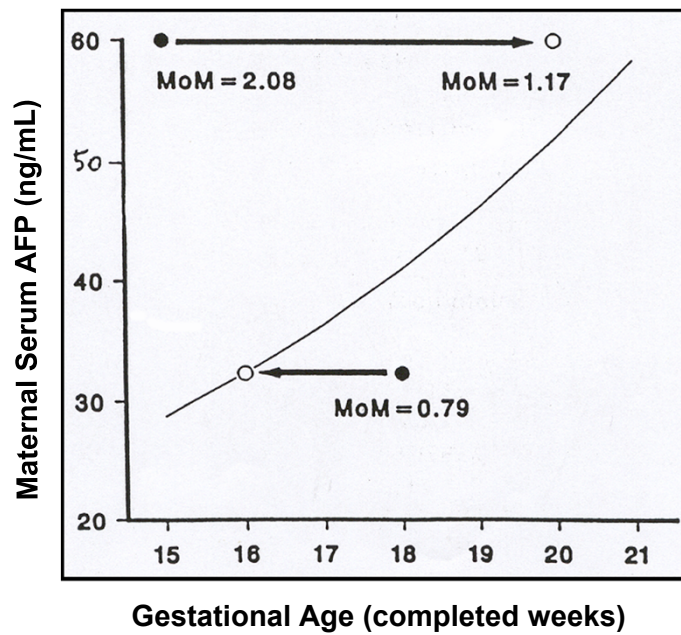
Result:

- a simple, easy to remember number, 1 MoM, becomes the most common value for an unaffected, singleton pregnancy

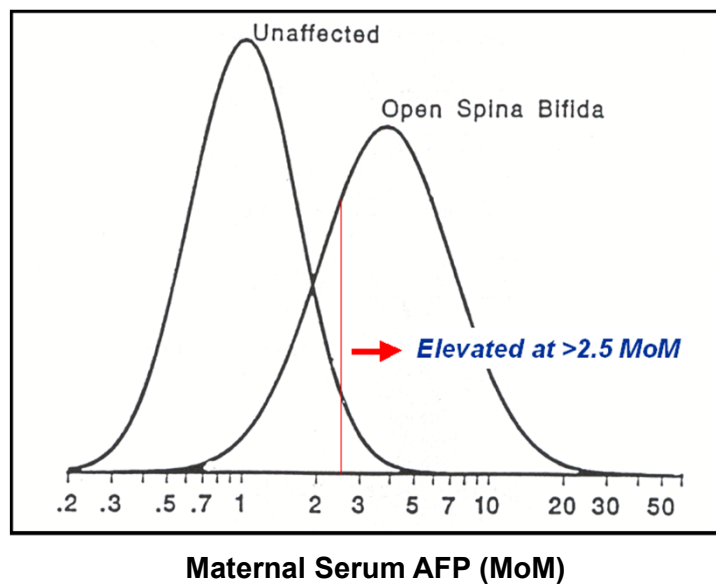
MoM = multiple of the median

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Gestational Dating and MoM

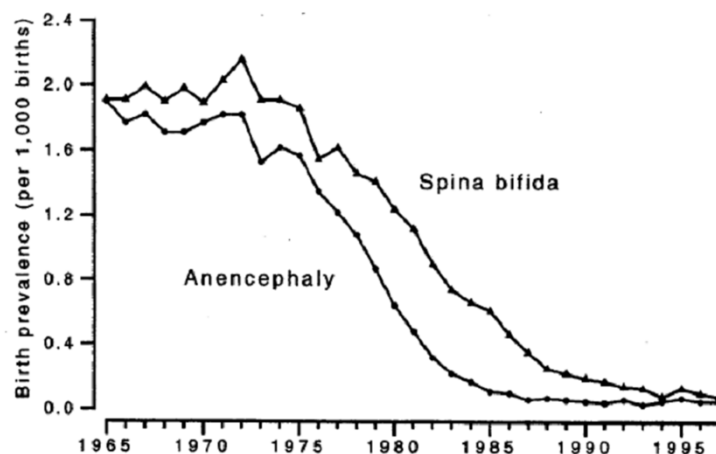


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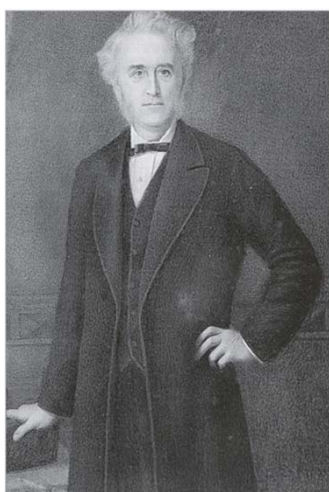
Prevalence of NTDs at Birth in England and Wales 1965-1997



Adapted from: Wald NJ, Leck I. *Antenatal and Neonatal Screening*, Oxford, 2000

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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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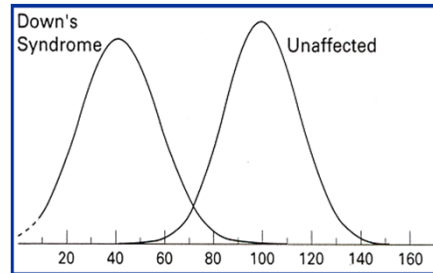
Features of Down Syndrome (Trisomy 21)

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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History of Prenatal Screening: Screening for Down's Syndrome Using Maternal Age

Year	Milestone	Investigator(s)
1933	Maternal age and risk of Down's syndrome	Penrose
1959	Discovery of trisomy 21 in Down's syndrome	Lejeune
1966	First chromosomal analysis from amniotic fluid	Steele and Breg
1968	First antenatal diagnosis of Down's syndrome	Valenti
1970s	Antenatal screening for Down's syndrome using maternal age: Amniocentesis offered to older women	

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History of Prenatal Screening: Second Trimester Serum Screening for Down's Syndrome I

Year	Milestone	Investigator(s)
1970s	Prenatal screening for open neural tube defects using maternal serum AFP	
1970s	Prenatal screening for Down's syndrome using maternal age: Amniocentesis offered to older women	
1983	Association of low serum AFP and fetal chromosomal abnormalities	<i>Merkatz</i>
1984	Low serum AFP and Down's syndrome	<i>Cuckle and Wald</i>
1987	Estimating the risk of Down's syndrome pregnancy using maternal age and serum AFP to older women	<i>Cuckle and Wald</i>

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History of Prenatal Screening: Second Trimester Serum Screening for Down's Syndrome II

Year	Milestone	Investigator(s)
1987	Elevated serum hCG & Down's syndrome	<i>Bogart</i>
1988	Low serum uE3 & Down's syndrome	<i>Canick, Haddow, Wald</i>
1988	Serum screening for Down's syndrome using the 'triple test'	<i>Wald, Haddow, Canick</i>
1992	Immunoreactive inhibin as a second trimester marker for Down's syndrome	<i>van Lith</i>
1996	Four marker serum screening with addition of inhibin A	<i>Wald</i>

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History of Prenatal Screening: *First Trimester Screening for Down's Syndrome*

Year	Milestone	Investigator(s)
1985	Abnormal skin thickening of neck in fetuses with Down's syndrome in the second trimester	<i>Benacerraf</i>
1990	Increased nuchal translucency and Down's syndrome in the first trimester	<i>Szabo</i>
1991	PAPP-A and Down's syndrome in the first trimester	<i>Brambati</i>
1992	Free beta-hCG and Down's syndrome in the first trimester	<i>Spencer</i>
1992	Nuchal translucency as a screening test for Down's syndrome	<i>Nicolaides</i>
1996	Combining ultrasound and biochemical markers in first trimester screening	<i>Wald</i>

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History of Prenatal Screening: *Integrated Screening for Down's Syndrome*

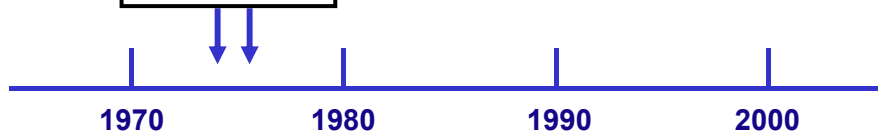
Year	Milestone	Investigator(s)
1999	Combining first and second trimester markers into a single 'integrated' screening test for Down's syndrome	<i>Wald³⁰</i>
2003	Publication of the SURUSS Trial	<i>Wald</i>

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History of Prenatal Screening: *Timeline of Discoveries*



MSAFP & NTDs
AFP screening
concept of MoM



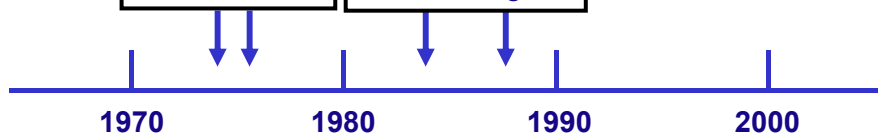
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History of Prenatal Screening: *Timeline of Discoveries*



MSAFP & NTDs
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concept of MoM

MSAFP & Down's
Down's risk estim.
Triple marker screening



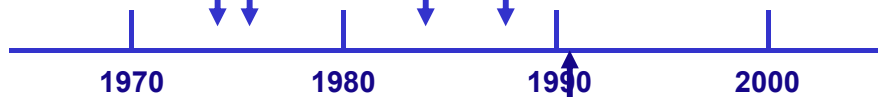
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History of Prenatal Screening: Timeline of Discoveries



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Folic acid prevention of NTDs

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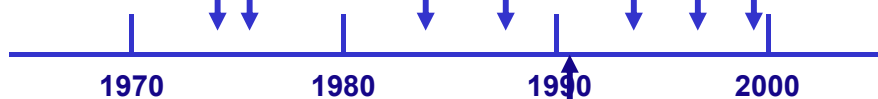
History of Prenatal Screening: Timeline of Discoveries



MSAFP & NTDs
AFP screening
concept of MoM

MSAFP & Down's
Down's risk estim.
Triple marker screening

Quad marker screening
Combined test
Integrated test



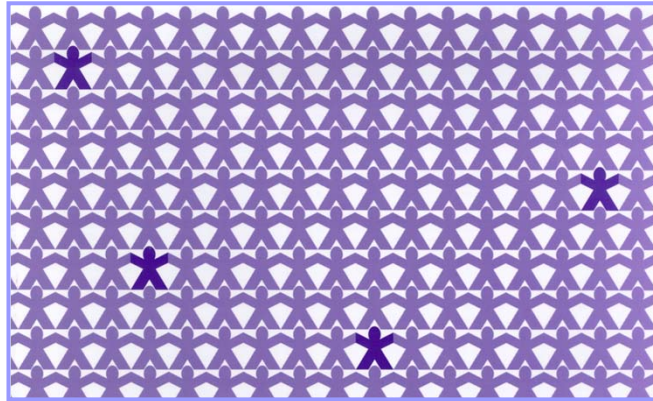
Folic acid prevention of NTDs

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Prenatal Screening: How It Works

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*

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Screening 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	<i>percentage of affected pregnancies called positive by the test</i>
False Positive Rate	<i>percentage of unaffected pregnancies called positive by the test</i>

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

Prevalence	<i>how often is the affected pregnancy found in the population being tested?</i>
OAPR (PPV)	<i>odds of affected given a positive result</i> $\equiv$ <i>average risk in positives</i> $\equiv$ <i>equivalent to the positive predictive value of the test (percentage of positives that are affected)</i>

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EXAMPLE

There are 195 pregnancies to be screened

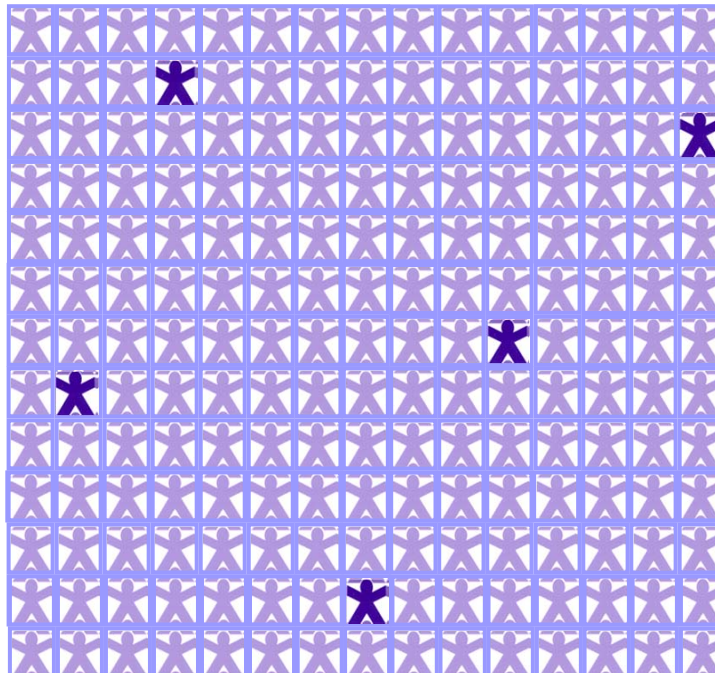
5 are affected



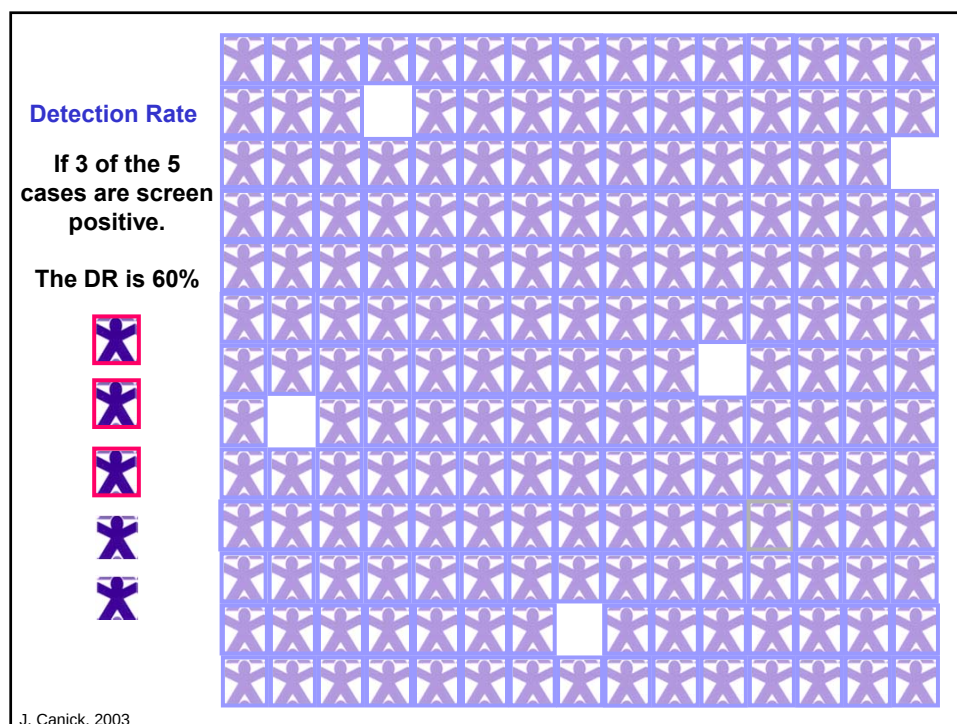
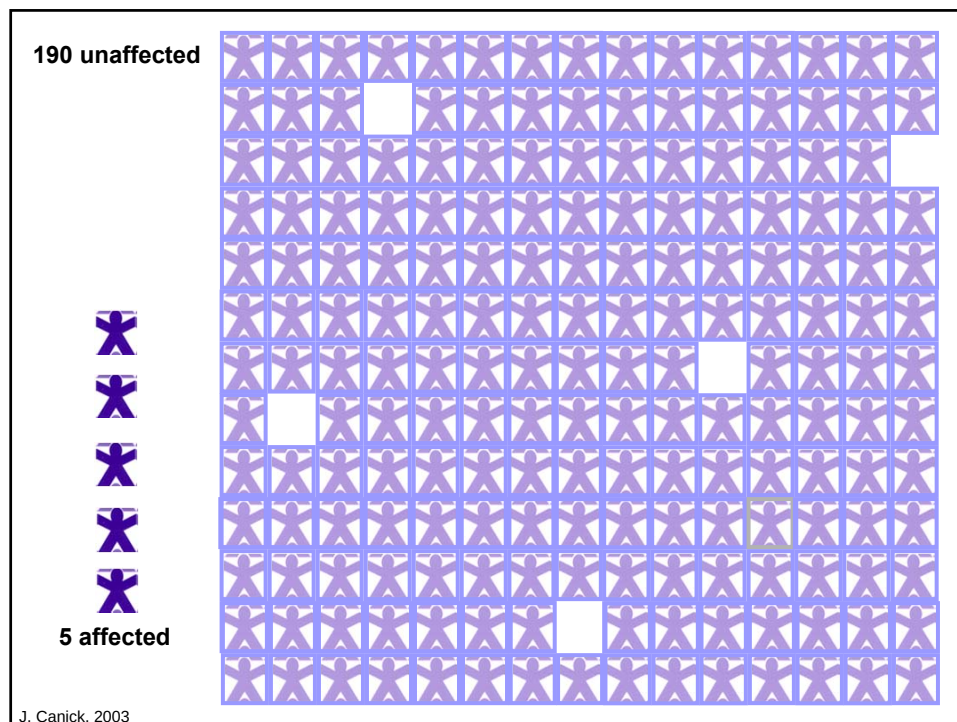
190 are unaffected

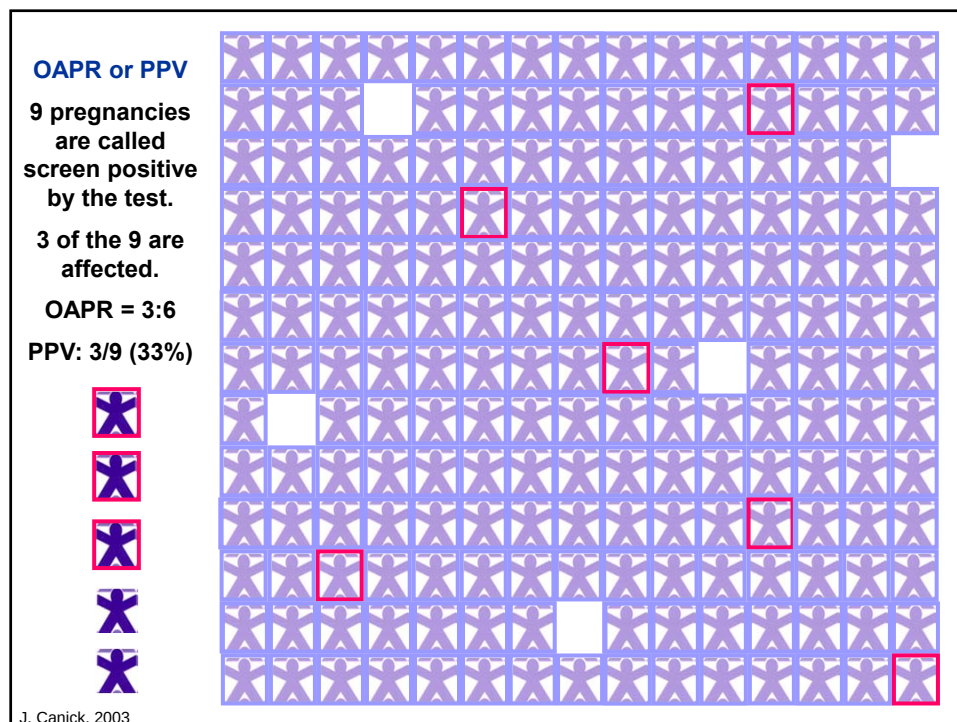
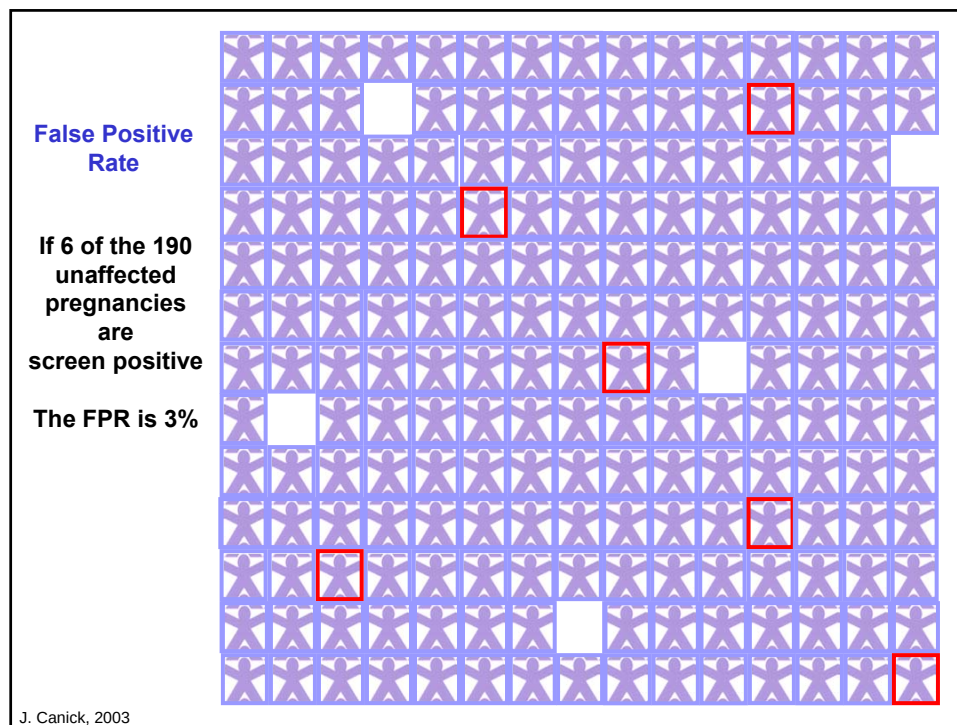


Therefore, the prevalence is 5 in 195 or 1 in 39.



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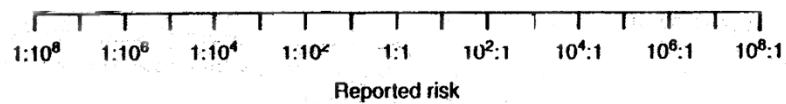


***How can we visualize improvements
in screening performance?***

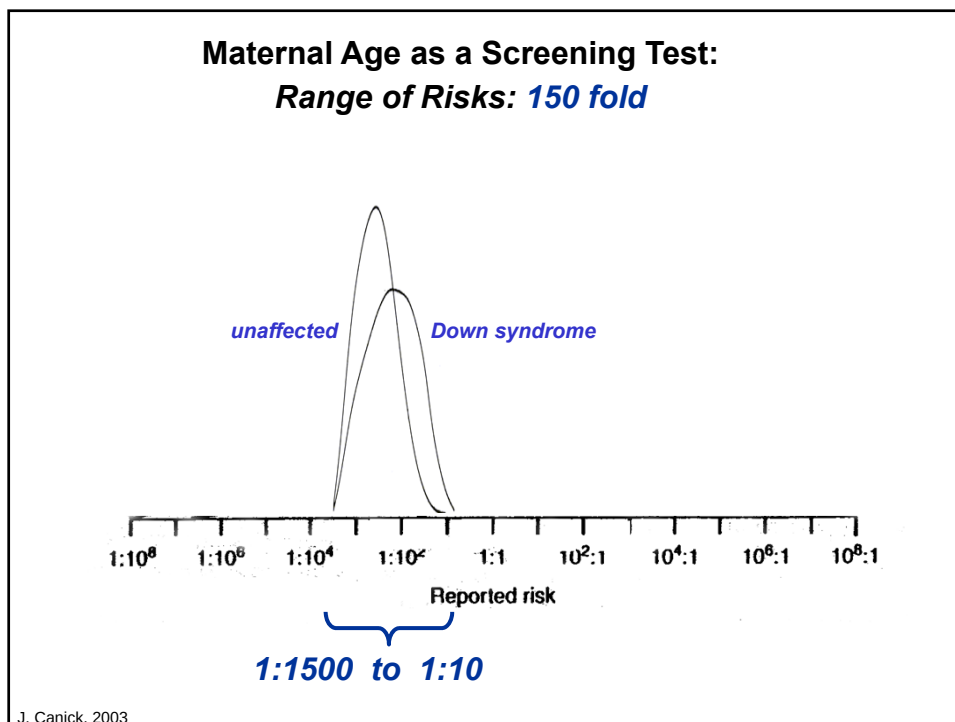
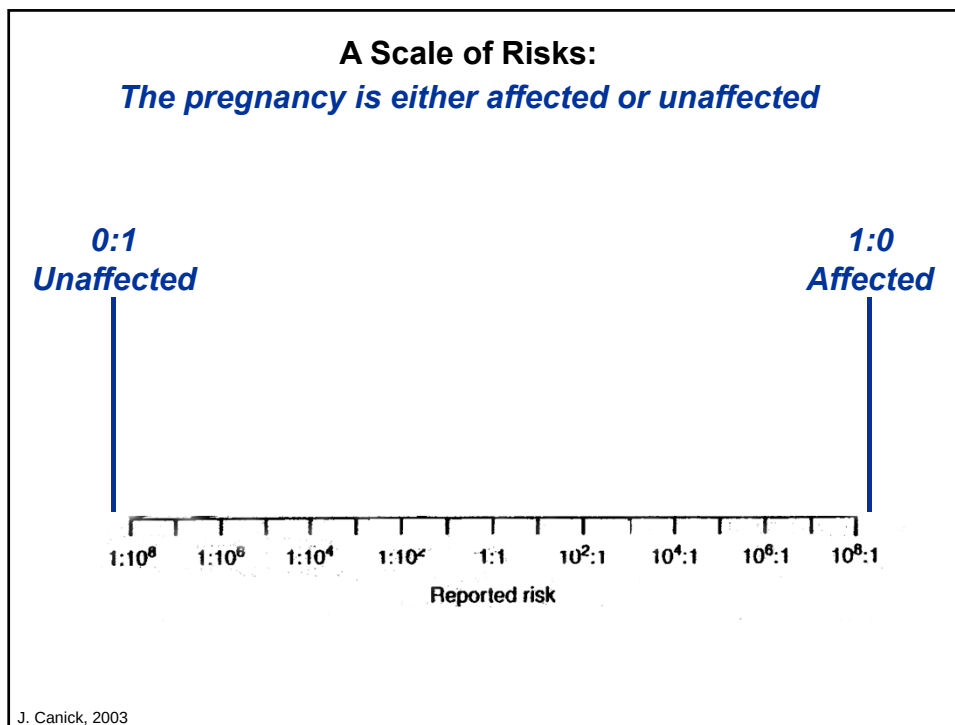


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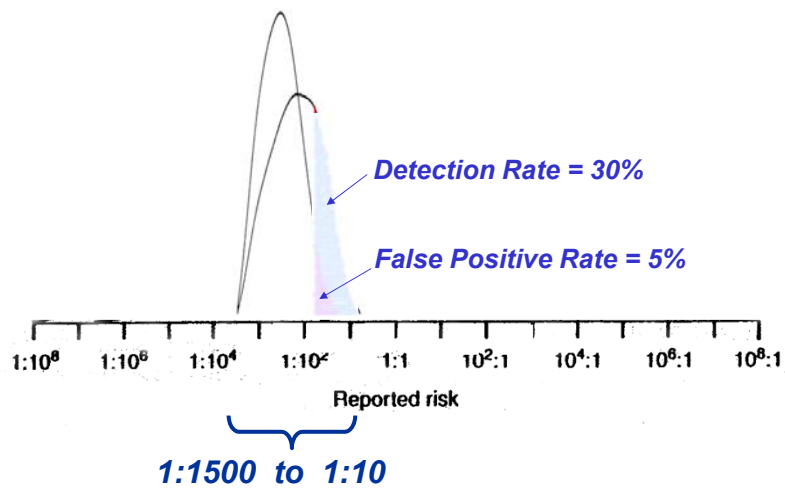
A Scale of Risks



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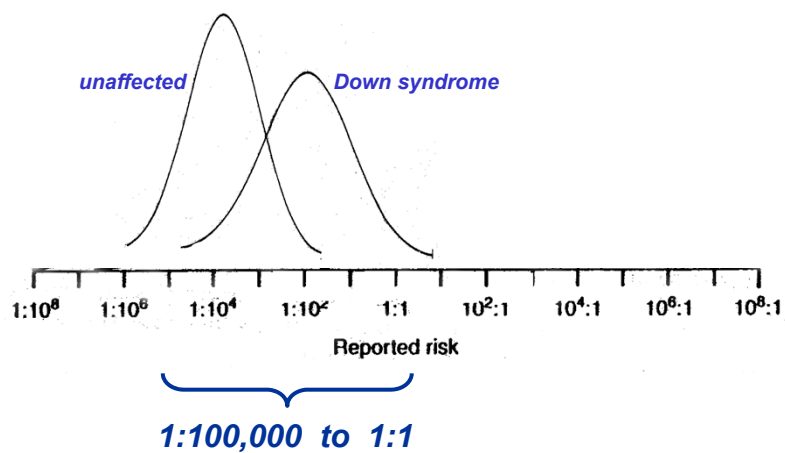


Maternal Age as a Screening Test:
Range of Risks: 150 fold



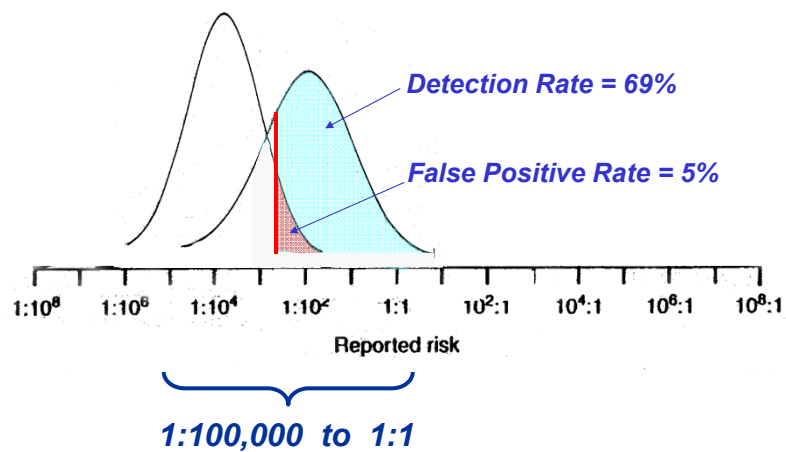
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Second Trimester Triple Test:
Range of Risks: 100,000 fold



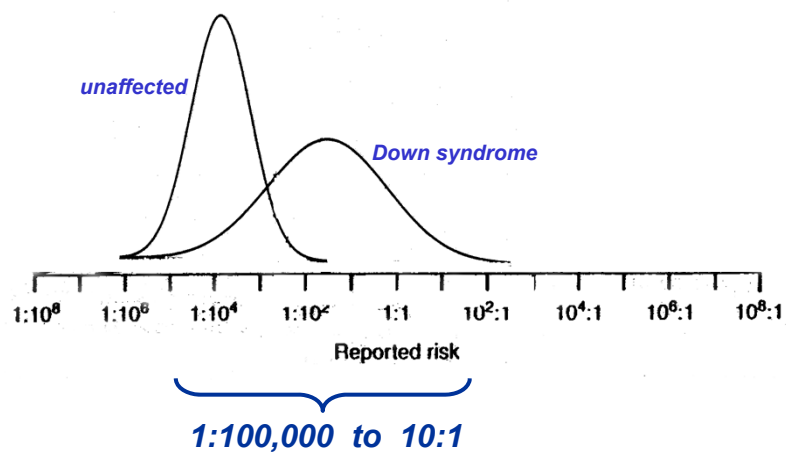
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Second Trimester Triple Test:
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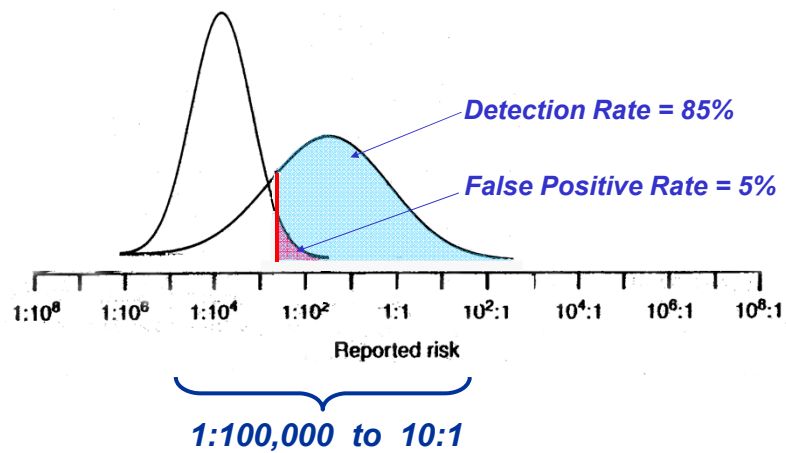
The First Trimester Combined Test:
Range of Risks: 1,000,000 fold



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The First Trimester Combined Test:

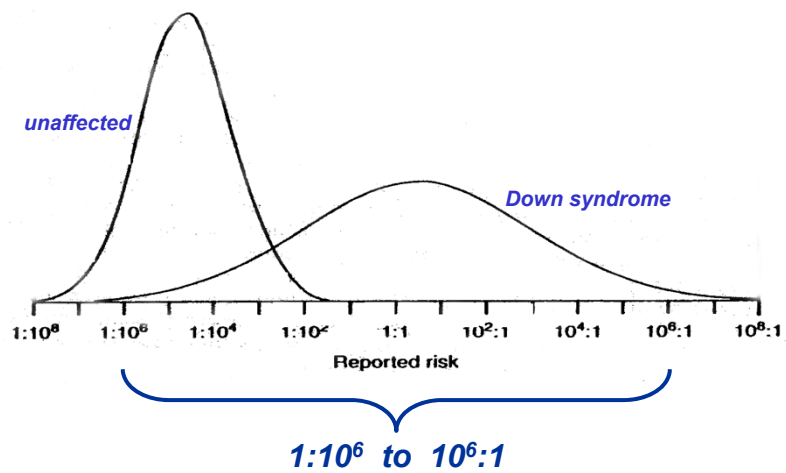
Range of Risks: **1,000,000 fold**



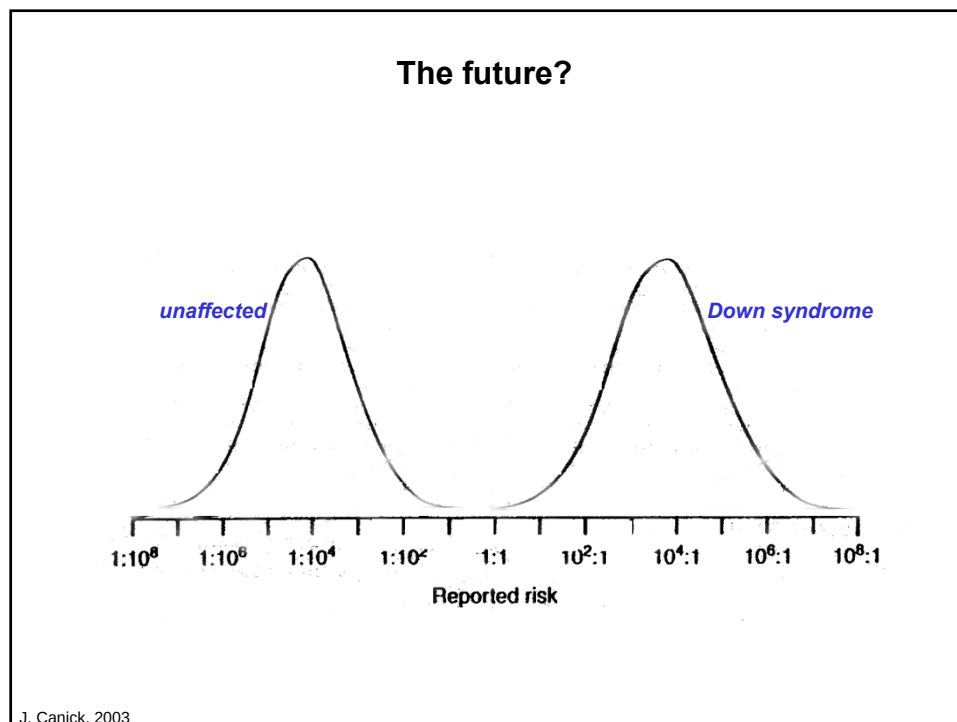
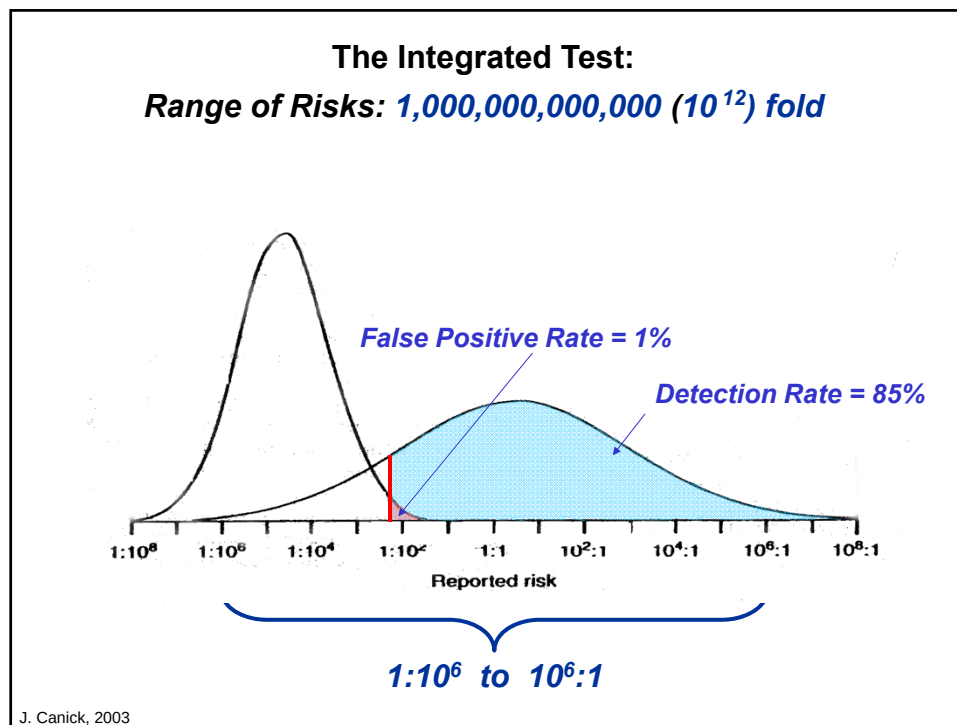
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The Integrated Test:

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



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In the year 2003, we are faced with many choices in antenatal screening :

The Screening Cafe
Menu

<i>1st trimester serum</i>	£ 10
<i>1st trimester ultrasound</i>	£ 20
<i>1st trimester combined</i>	£ 30
<i>2nd trimester serum double</i>	£ 10
<i>2nd trimester serum triple</i>	£ 20
<i>2nd trimester serum quad</i>	£ 30
<i>2nd trimester ultrasound</i>	£ 20
<i>Serum integrated</i>	£ 40
<i>Full integrated</i>	£ 50
<i>Step-wise sequential</i>	£ 2
<i>Contingent screening</i>	£ 2

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