Prenatal Screening for Open Neural Tube Defects and Aneuploidies

- LJ Perry, MD PGY-2
Disclosures

- None
Learning Objectives

1) Understand the diseases detected by prenatal screening
2) Identify the analytes, measurements, and methodology used in prenatal screening
3) Interpret the results using multiple of the median and risk analysis
Outline

- Diseases detected by prenatal screening
- Screening tests, analytes, and methodology
- Interpretation of results
- Confirmation tests for positive screens
Diseases Detected by Prenatal Screen
Diseases Detected by Prenatal Screen

- Open neural tube defects (ONTD)
- Trisomy 21 (Down Syndrome)
- Trisomy 18 (Edwards Syndrome)
- Trisomy 13 (Patau Syndrome)
Open Neural Tube Defects
Neural Tube Development

3rd - 4th week gestation

https://opentextbc.ca/anatomyandphysiology/chapter/28-2-embryonic-development/
Open Neural Tube Defects

- Pathogenesis: Failure of neural tube to close
- More superior = more severe
- Open = Defect exposed or covered by membrane
- Closed = Defect covered by skin

Williams, Dukhovny, Clarke
Open Neural Tube Defects

- Incidence: 5.5 per 10,000 births

- Risk factors
  - Folate deficiency
  - Folate antagonists
  - Diabetes
  - Obesity

Williams, Dukhovny, Clarke

https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6401a2.htm
Superior ONTD

Anencephaly
Open brain and lack of skull vault
Lethal

Encephalocele
Herniation of the meninges (and brain)
Lethal or severe neurologic damage
Inferior ONTD

- **Prognosis**
  - Ranges from healthy to neurologic damage to death
  - More superior = more severe
  - Meningomyelocele most severe (25% death rate by adulthood)
Trisomies
Trisomy

- Human cells usually have 2 copies of each chromosome
- Aneuploidy = Different number of chromosomes
- Trisomy = 3 copies of a chromosome

Trisomy Formation

1) Meiotic nondisjunction

<table>
<thead>
<tr>
<th>Normal Meiotic Division</th>
<th>Nondisjunction in Meiosis I</th>
<th>Nondisjunction in Meiosis II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meiosis I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meiosis II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gametes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Normal Meiotic Division
- Nondisjunction in Meiosis I
- Nondisjunction in Meiosis II

- Gametes: n, n, n, n
- n+1, n-1, n-1, n-1
- n+1, n-1, n, n
Trisomy Formation

1) Meiotic nondisjunction
2) Robertsonian Translocation
Down Syndrome

- Pathogenesis: Trisomy 21
- Incidence: ~1 in 800 births
  - Most common chromosomal disorder
- Risk factors:
  - Advanced maternal age
  - Prior aneuploidy pregnancy

Down Syndrome

- Intellectually disability
- Congenital heart defects
- Intestinal blockage issues
- Thyroid diseases
- Diabetes
- Leukemia
- Male infertility
- Immunodeficiencies
Down Syndrome

- Prognosis:
  - Shorter life expectancy: 56.8 years (Sweden)
  - Common causes of death
    - Pneumonia/infections
    - Congenital malformations
    - Circulatory disease
    - Dementia

---

Survival Rate (US, 1983-2003)
Edwards Syndrome

- Pathogenesis: Trisomy 18
- Incidence: 1 in 8000 births
  - 2nd most common trisomy
- Risk factor:
  - Advanced maternal age
Edwards Syndrome

- Prominent occiput
- Rocker-bottom feet
- Intellectual disability
- Nondisjunction
- Clenched fists
- Ears (low set)

Prognosis:
- Majority die in utero
- 50% die in 1-2 weeks, 95% die in first year
Patau Syndrome

- Pathogenesis: Trisomy 13
- Incidence: 1 in 15,000
- Risk factor:
  - Advanced maternal age

Pathogenesis: Trisomy 13

Incidence: 1 in 15,000

Risk factor:
  - Advanced maternal age
Patau Syndrome

- Intellectual disability
- Holoprosencephaly: Failure of left and right hemispheres to separate
- Congenital heart defects
- Intrauterine growth deficiency

Prognosis:
- Majority die in utero
- Median survival of liveborn: 7 days
- 80% die by 1 month, 91% die by 1 year
### Trisomy Risk by Maternal Age

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>Trisomy 21 Risk (1:n)</th>
<th>Trisomy 18 Risk (1:n)</th>
<th>Trisomy 13 Risk (1:n)</th>
<th>Combined Trisomy Risk (1:n)</th>
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<td>1035</td>
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<td>49</td>
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<td>150</td>
<td>570</td>
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Trisomy Risk by Maternal Age
Screening Tests and Methodology
What is a screening test?

- A screening test identifies those at increased risk of disease
- It does NOT diagnosis a disease
  - Diagnosis requires confirmation testing
- It will result in many false positives
  - Ensures patients with the disease are identified
### Overview of Screening Tests

<table>
<thead>
<tr>
<th>Timing</th>
<th>1\textsuperscript{st} Trimester Combined Screen</th>
<th>2\textsuperscript{nd} Trimester Quadruple Screen</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>9-14 weeks</td>
<td>15-23 weeks</td>
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<tr>
<td>Analytes</td>
<td>Nuchal translucency (NT)</td>
<td>Alpha fetoprotein (AFP)</td>
</tr>
<tr>
<td></td>
<td>Pregnancy associated plasma protein A (PAPP-A)</td>
<td>Beta human chorionic gonadotropin (β-hCG)</td>
</tr>
<tr>
<td></td>
<td>Beta human chorionic gonadotropin (β-hCG)</td>
<td>Unconjugated estriol (uE\textsubscript{3})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dimeric inhibin A (DIA)</td>
</tr>
</tbody>
</table>
Combining Screening Tests

<table>
<thead>
<tr>
<th>Method</th>
<th>Integrated Screen</th>
<th>Contingent Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do 1\textsuperscript{st} and 2\textsuperscript{nd} trimester screens</td>
<td>Do 1\textsuperscript{st} trimester screen</td>
<td></td>
</tr>
<tr>
<td>Don’t release results until both are done</td>
<td>If positive, offer diagnostic testing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If high to medium risk, offer 2\textsuperscript{nd} trimester screen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If low risk, stop testing</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pros</th>
<th>Integrated Screen</th>
<th>Contingent Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most sensitive</td>
<td>Fewer false positives</td>
<td></td>
</tr>
<tr>
<td>Fewer false positives</td>
<td>Fewer false positives</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No waiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can do chorionic villus sampling</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cons</th>
<th>Integrated Screen</th>
<th>Contingent Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waiting</td>
<td>Slightly less sensitive than integrated screen</td>
<td></td>
</tr>
<tr>
<td>Can’t do chorionic villus sampling</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pros
- Most sensitive
- Fewer false positives
- No waiting
- Can do chorionic villus sampling

Cons
- Waiting
- Can’t do chorionic villus sampling
- Slightly less sensitive than integrated screen
Analytes and Measurements
Nuchal Translucency (NT)

- Timing: 10w3d to 13w6d (ideal 12-13w)
- Must be done by a certified sonographer
- Measure the hypoechoic (dark) space in posterior neck by ultrasound
- Increased thickness (≥3.0 mm) = increased aneuploidy risk

Healthy

Affected

Messerlian, Clarke
Pregnancy associated plasma protein A (PAPP-A)

- Synthesized by placenta
- Increases with gestational age
- Pregnancy form: Heterotetrametric complex (htPAPP-A)
  - Two PAPP-A subunits
  - Two subunits of eosinophil major base protein (pro-MBP)
- Function: Insulin-like growth factor (IGF) protease
  - IGF is essential for fetal growth
Alpha fetoprotein (AFP)

- Binding protein similar to albumin
- Synthesized by fetal liver and yolk sac
- Peaks at 25w, then gradually declines
- ONTD: AFP in fetal circulation leaks across defect $\rightarrow$ ↑AFP in amniotic fluid $\rightarrow$ ↑AFP in maternal serum
- Also ↑AFP in yolk sac tumors, hepatocellular carcinoma, viral hepatitis, and cirrhosis
Beta human chorionic gonadotropin (β-hCG)

- 2 subunits
  - α: Shared with LH, FSH, TSH, and hCG
  - β: Unique to hCG
- Synthesized by placenta
- Detectable at 1 week, peaks at 8-10 weeks
- Pregnancy test
- Maintains corpus luteum → Estrogen and progesterone

- Also high with multiple gestations, choriocarcinoma, hydatidiform moles, and dysgerminoma

Clarke, Yarbrough, Le
Unconjugated estriol (uE₃)

- Synthesized by fetal liver, adrenals, and placenta
  - Half life of 20 minutes before maternal liver conjugates it
- Increases with gestational age

Clarke, Yarbrough
Dimeric inhibin A (DIA)

- Dimer
- Synthesized by placenta in pregnancy
- Increases with gestational age
- Inhibits follicle stimulating hormone
- Also increased in ovarian granulosa cell cancer
Analyte Concentrations & Measurements

- **NT**: Nuchal translucency (mm) vs. gestational age (weeks). The line shows an increase in NT with gestational age.
- **PAPP-A**: Placental protein A (mg/L) vs. gestational age (completed weeks). The graph shows a decrease in PAPP-A with gestational age.
- **AFP**: Alpha-fetoprotein (mg/L) vs. gestational age (weeks). The graph shows an increase in AFP with gestational age.
- **B-hCG**: Beta-human chorionic gonadotropin (IU/mL) vs. gestational age (weeks). The graph shows a decrease in B-hCG with gestational age.
- **uE3**: Free estradiol (ng/mL) vs. gestational age (weeks). The graph shows an increase in uE3 with gestational age.
- **DIA**: Dimeric inhibin A (mg/mL) vs. gestational age (weeks). The graph shows an increase in DIA with gestational age.

Yarbrough
Sandwich IA (Immunoassay) - PAPP-A
- AFP
- β-hCG
- DIA
Sandwich IA for PAPP-A, AFP, β-hCG, DIA

1) Incubate:
   - Paramagnetic particles coated with anti-PAPP-A antibodies
Sandwich IA for PAPP-A, AFP, β-hCG, DIA

1) Incubate:
   - Paramagnetic particles coated with anti-PAPP-A antibodies
   - Maternal serum (contains PAPP-A)
Sandwich IA for PAPP-A, AFP, β-hCG, DIA

1) Incubate:
   - Paramagnetic particles coated with anti-PAPP-A antibodies
   - Maternal serum (contains PAPP-A)
Sandwich IA for PAPP-A, AFP, β-hCG, DIA

2) Wash; particles held by magnetic field
Sandwich IA for PAPP-A, AFP, β-hCG, DIA

3) Add anti-PAPP-A monoclonal antibody – alkaline phosphatase conjugate
Sandwich IA for PAPP-A, AFP, β-hCG, DIA

3) Add anti-PAPP-A monoclonal antibody – alkaline phosphatase conjugate
Sandwich IA for PAPP-A, AFP, β-hCG, DIA

4) Wash
Sandwich IA for PAPP-A, AFP, β-hCG, DIA

5) Add Lumi-Phos 530
5) Add Lumi-Phos 530

6) Measure luminescence with luminometer

Sandwich IA for PAPP-A, AFP, β-hCG, DIA
Sandwich IA for PAPP-A, AFP, β-hCG, DIA

- Direct correlation: 
  \( \uparrow \) luminescence = \( \uparrow \) PAPP-A
- Quantitate by comparing to calibration curve
Competitive IA (Immunoassay) - Estriol
Competitive IA for Estriol

1) Incubate:
- Paramagnetic particles coated with anti-estriol antibodies
Competitive IA for Estriol

1) Incubate:
   - Paramagnetic particles coated with anti-estriol antibodies
   - Estriol-alkaline phosphatase conjugate
1) Incubate:
- Paramagnetic particles coated with anti-estriol antibodies
- Estriol-alkaline phosphatase conjugate
- Maternal serum (contains estriol)
Competitive IA for Estriol

1) Incubate:
   - Paramagnetic particles coated with anti-estriol antibodies
   - Estriol-alkaline phosphatase conjugate
   - Maternal serum (contains estriol)
Competitive IA for Estriol

2) Wash
Competitive IA for Estriol

3) Add Lumi-Phos 530
Competitive IA for Estriol

3) Add Lumi-Phos 530
4) Measure luminescence with luminometer
Competitive IA for Estriol

- Indirect correlation: $\uparrow$ luminescence $\Rightarrow$ $\downarrow$ Estriol
- Quantitate by comparing to calibration curve
Calibration Curves
Calibration Curve - Direct

Increasing luminescence →

Increasing analyte →
Calibration Curve - Direct

Increasing luminescence $\rightarrow$ Increasing analyte $\rightarrow$
Calibration Curve - Direct

Increasing luminescence \(\rightarrow\) Increasing analyte \(\rightarrow\)
Calibration Curve - Indirect

Increasing luminescence →

Increasing analyte →
Interpretation of Results
Multiple of the Median
Multiple of the Median (MoM)

- Analytes differ based on:
  - Gestational age (GA)
  - Maternal weight
  - Race
  - Diabetes status
  - Number of fetuses

Included in MoM calculation

Adjustment factor after MoM calculation

Clarke
Multiple of the Median (MoM)

- MoM standardizes results by gestational age

\[
\text{MoM} = \frac{\text{Patient’s analyte concentration}}{\text{Median analyte concentration for GA}}
\]
## MoM Examples

<table>
<thead>
<tr>
<th>Patient’s analyte concentration</th>
<th>Median analyte concentration</th>
<th>MoM</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>100</td>
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</table>
MoM Examples

<table>
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<tr>
<th>Patient’s analyte concentration</th>
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<th>MoM</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>100</td>
<td>[\frac{60}{100} = 0.6]</td>
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</table>
## MoM Examples

<table>
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<th>MoM</th>
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<tbody>
<tr>
<td>60</td>
<td>100</td>
<td>$\frac{60}{100} = 0.6$</td>
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<tr>
<td>110</td>
<td>100</td>
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### MoM Examples

<table>
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<tr>
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<th>MoM</th>
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<tbody>
<tr>
<td>60</td>
<td>100</td>
<td>$\frac{60}{100} = 0.6$</td>
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<tr>
<td>110</td>
<td>100</td>
<td>$\frac{110}{100} = 1.1$</td>
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### MoM Examples

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<tr>
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<th>Median analyte concentration</th>
<th>MoM</th>
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<tbody>
<tr>
<td>60</td>
<td>100</td>
<td>$\frac{60}{100} = 0.6$</td>
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<tr>
<td>110</td>
<td>100</td>
<td>$\frac{110}{100} = 1.1$</td>
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<tr>
<td>110</td>
<td>200</td>
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## MoM Examples

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<td>$\frac{60}{100} = 0.6$</td>
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<tr>
<td>110</td>
<td>100</td>
<td>$\frac{110}{100} = 1.1$</td>
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<tr>
<td>110</td>
<td>200</td>
<td>$\frac{110}{200} = 0.55$</td>
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Wrong Gestational Age?

- An incorrect gestational age will throw off MoM calculations

<table>
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<th>Patient’s analyte concentration</th>
<th>Median analyte concentration</th>
<th>MoM</th>
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<tr>
<td>15w0d</td>
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## Wrong Gestational Age?

- An incorrect gestational age will throw off MoM calculations

<table>
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<th>Gestational Age</th>
<th>Patient’s analyte concentration</th>
<th>Median analyte concentration</th>
<th>MoM</th>
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<td>15w0d</td>
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<td>18w0d</td>
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Disease Interpretation
## Disease Interpretation

### 1st Trimester

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<th></th>
<th>NT</th>
<th>PAPP-A</th>
<th>$\beta$-hCG</th>
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<tbody>
<tr>
<td>Trisomy 21</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
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### 2nd Trimester

<table>
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<tr>
<th></th>
<th>AFP</th>
<th>$\beta$-hCG</th>
<th>Estriol</th>
<th>Inhibin A</th>
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<tbody>
<tr>
<td>ONTD</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>- / ↓*</td>
</tr>
</tbody>
</table>

*Not included in risk calculation*
Relative Risk for Trisomies
Relative Risk for Trisomies

- Report a relative risk for each trisomy
- Calculated using population statistics
Relative Risk for Trisomies

1) Pre-test odds (maternal age chart)
<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>Trisomy 21 Risk (1:n)</th>
<th>Trisomy 18 Risk (1:n)</th>
<th>Trisomy 13 Risk (1:n)</th>
<th>Combined Trisomy Risk (1:n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>1495</td>
<td>9010</td>
<td>13,700</td>
<td>1175</td>
</tr>
<tr>
<td>19</td>
<td>1490</td>
<td>8985</td>
<td>13,670</td>
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<tr>
<td>20</td>
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<td>8960</td>
<td>13,635</td>
<td>1160</td>
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<tr>
<td>21</td>
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<td>13,580</td>
<td>1150</td>
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<tr>
<td>22</td>
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<td>13,510</td>
<td>1135</td>
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<td>23</td>
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<td>13,410</td>
<td>1115</td>
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<td>24</td>
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<td>13,275</td>
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<td>25</td>
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<td>13,090</td>
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<tr>
<td>26</td>
<td>1285</td>
<td>8480</td>
<td>12,840</td>
<td>1025</td>
</tr>
<tr>
<td>27</td>
<td>1220</td>
<td>8280</td>
<td>12,500</td>
<td>980</td>
</tr>
<tr>
<td>28</td>
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<td>8010</td>
<td>12,050</td>
<td>920</td>
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<td>935</td>
<td>7215</td>
<td>10,735</td>
<td>770</td>
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<tr>
<td>31</td>
<td>815</td>
<td>6655</td>
<td>9830</td>
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<td>32</td>
<td>695</td>
<td>5990</td>
<td>8770</td>
<td>580</td>
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<tr>
<td>33</td>
<td>570</td>
<td>5220</td>
<td>7585</td>
<td>480</td>
</tr>
<tr>
<td>34</td>
<td>455</td>
<td>4380</td>
<td>6345</td>
<td>385</td>
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<td>3530</td>
<td>5130</td>
<td>300</td>
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<tr>
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<td>4030</td>
<td>225</td>
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<tr>
<td>37</td>
<td>195</td>
<td>2025</td>
<td>3100</td>
<td>170</td>
</tr>
<tr>
<td>38</td>
<td>145</td>
<td>1455</td>
<td>2370</td>
<td>125</td>
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<tr>
<td>39</td>
<td>110</td>
<td>1035</td>
<td>1825</td>
<td>94</td>
</tr>
<tr>
<td>40</td>
<td>85</td>
<td>735</td>
<td>1430</td>
<td>72</td>
</tr>
<tr>
<td>41</td>
<td>66</td>
<td>530</td>
<td>1160</td>
<td>56</td>
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<tr>
<td>42</td>
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<td>395</td>
<td>970</td>
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<tr>
<td>43</td>
<td>45</td>
<td>310</td>
<td>840</td>
<td>37</td>
</tr>
<tr>
<td>44</td>
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<td>250</td>
<td>745</td>
<td>32</td>
</tr>
<tr>
<td>45</td>
<td>34</td>
<td>215</td>
<td>685</td>
<td>28</td>
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<tr>
<td>46</td>
<td>31</td>
<td>185</td>
<td>640</td>
<td>25</td>
</tr>
<tr>
<td>47</td>
<td>29</td>
<td>170</td>
<td>610</td>
<td>24</td>
</tr>
<tr>
<td>48</td>
<td>27</td>
<td>155</td>
<td>590</td>
<td>22</td>
</tr>
<tr>
<td>49</td>
<td>26</td>
<td>150</td>
<td>570</td>
<td>21</td>
</tr>
</tbody>
</table>
Relative Risk Percentage for Trisomies

1) Pre-test odds (1 in 935)
2) Calculate MoM (1.4)
Relative Risk Percentage for Trisomies

1) Pre-test odds (1 in 935)

2) Calculate MoM (1.4)

3) Calculate likelihood ratio for each analyte using the MoM
   - \[ LR = \frac{\text{Probability of affected}}{\text{Probability of unaffected}} \]
   - \[ LR = \frac{0.2}{0.5} = 0.4 \]
1) Pre-test odds (1 in 935)

2) Calculate MoM (1.4)

3) Calculate likelihood ratio for each analyte using the MoM
   - For multiple analytes, multiply the LR of each together
   - Ex: 0.4 x 1.9 x 2.3 x 3.5 = 6.1
Relative Risk Percentage for Trisomies

1) Pre-test odds (1 in 935)
2) Calculate MoM (1.4)
3) Calculate likelihood ratio for each analyte using the MoM (6.1)
4) RR = Pre-test odds x LR
   - RR = \( \frac{1}{935} \times 6.1 \approx 1 \text{ in } 153 = 0.6\% \)
Relative Risk Cutoff

- At what point is the relative risk “positive?”
- Often the risk of Down Syndrome for a 35-year-old is used as the cutoff (1:270)
- May raise or lower the cutoff to customize testing
Test Performance
## Detection Rates for ONTD

<table>
<thead>
<tr>
<th>Testing for</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONTD</td>
<td>95%</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>97%</td>
</tr>
<tr>
<td>Open spina bifida</td>
<td>99%</td>
</tr>
<tr>
<td>Abdominal wall defects</td>
<td>40-79%</td>
</tr>
</tbody>
</table>
## Detection Rates for Down Syndrome

<table>
<thead>
<tr>
<th>Test</th>
<th>Detection Rate</th>
<th>False Positive Rate</th>
<th>T21 Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined (1\textsuperscript{st})</td>
<td>85%</td>
<td>6%</td>
<td>1/230</td>
</tr>
<tr>
<td>Quad (2\textsuperscript{nd})</td>
<td>81%</td>
<td>4-5%</td>
<td>1/150</td>
</tr>
<tr>
<td>Integrated</td>
<td>87%</td>
<td>1.0%</td>
<td>1/110</td>
</tr>
<tr>
<td>Contingent</td>
<td>63% (1\textsuperscript{st})</td>
<td>0.6% (1\textsuperscript{st})</td>
<td>1/25 (1\textsuperscript{st})</td>
</tr>
<tr>
<td></td>
<td>23% (2\textsuperscript{nd})</td>
<td>1.0% (2\textsuperscript{nd})</td>
<td>1/110 (2\textsuperscript{nd})</td>
</tr>
<tr>
<td></td>
<td>86% (Total)</td>
<td>1.6% (Total)</td>
<td></td>
</tr>
</tbody>
</table>
Positive Predictive Value (Down Syndrome)

- Positive predictive values at 85% detection rate
- Good screening test

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrated</td>
<td>17%</td>
</tr>
<tr>
<td>Combined (1st)</td>
<td>3%</td>
</tr>
<tr>
<td>Quad (2nd)</td>
<td>3%</td>
</tr>
</tbody>
</table>
What Next?
Trisomy Confirmation

- Chorionic villus sampling (10-14 weeks)
  - Chromosomal analysis
  - Fetal loss rate up to 2%

[Link to Mayo Clinic's Chorionic Villus Sampling page](https://www.mayoclinic.org/tests-procedures/chorionic-villus-sampling/about/pac-20393533)

Ghidini
Trisomy Confirmation

- Chorionic villus sampling (10-14 weeks)
  - Chromosomal analysis
  - Fetal loss rate up to 2%
- Amniocentesis (>15 weeks)
  - Chromosomal analysis
  - Fetal loss rate up to 1%

https://www.madeformums.com/pregnancy/what-is-amniocentesis/
ONTD Confirmation

- Ultrasound to confirm GA and look for abnormalities
- Amniocentesis
  - Measure AFP
    - If high, also measure acetylcholinesterase (AChE)
      - If high, ONTD confirmed
  - Chromosomal analysis
    - Increased risk of chromosomal abnormalities

Baldwin, Tietz
One More Option
Non-invasive Prenatal Testing (NIPT)

- Introduced in 2011
- Offered to all pregnant women, not just high-risk patients
  - Option for those who screen positive on 1st or 2nd trimester screen, but don’t want to do invasive testing
- Detects fetal cell free DNA (cfDNA) in maternal blood
  - Rises with gestational age
  - ~11-13% of cfDNA is fetal at 1st to 2nd trimester transition
- Each chromosome makes up a certain percentage of cfDNA
  - Chromosome percentage increased = trisomy

Palomaki, Grenache, Norton
## Non-invasive Prenatal Testing (NIPT)

<table>
<thead>
<tr>
<th></th>
<th>Detection Rate</th>
<th>False Positive Rate</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>99.5%</td>
<td>0.05%</td>
<td>85%</td>
<td>&gt;99.9%</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>97.7%</td>
<td>0.04%</td>
<td>69%</td>
<td>&gt;99.9%</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>96.1%</td>
<td>0.06%</td>
<td>33%</td>
<td>&gt;99.9%</td>
</tr>
</tbody>
</table>

- High detection rate
- Low false positive rate
- Decent positive predictive value = screening test only
- High negative predictive value

Palomaki, Grenache
Non-invasive Prenatal Testing (NIPT)

- Why not replace serum screening with NIPT?
  - Cost
  - Insurance coverage
  - Availability
  - Can’t detect ONTD
- Ultimately, which (if any) screening test to do is a personal decision
Conclusion
Conclusion

- Prenatal screening detects:
  - Open neural tube defects
  - Trisomy 21
  - Trisomy 18
  - Trisomy 13

- Screening tests:
  - Combined screen (1\textsuperscript{st}): NT, PAPP-A, β-hCG
  - Quad screen (2\textsuperscript{nd}): AFP, β-hCG, uE\textsubscript{3}, DIA
  - Non-invasive prenatal testing
Conclusion

- Result reporting
  - Multiple of the Median (MoM)
  - Relative risk
- Confirmation testing
  - Chorionic villus sampling (10-14w)
  - Amniocentesis (>15w)
References