Prenatal Genetic Testing in 2007

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Regional Director, Perinatal Genetic Services
Kaiser Permanente, Northern California

Significant changes in past several years:
- More available testing options
- Lower procedure related loss rates
- More advanced cost effectiveness analysis
- Emphasis on patient autonomy and decision making

Changes in approach to prenatal screening recommendations

Advances in Second Trimester Biochemical Screening

<table>
<thead>
<tr>
<th>Open NTDs</th>
<th>Trisomy 21</th>
<th>Trisomy 18</th>
<th>Inhibin A</th>
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<tr>
<td>AFP</td>
<td>uE3</td>
<td>hCG</td>
<td>(Triple screen)</td>
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Second Trimester Screening Detection Rates

<table>
<thead>
<tr>
<th>Screening Type</th>
<th>Detection Rate</th>
</tr>
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<tbody>
<tr>
<td>Triple Screen</td>
<td>69%</td>
</tr>
<tr>
<td>(All Ages)</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>69% &lt;35</td>
</tr>
<tr>
<td></td>
<td>69% ≥35</td>
</tr>
<tr>
<td>Quad Screen</td>
<td>81%</td>
</tr>
<tr>
<td>(All ages)</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>69% &lt;35</td>
</tr>
<tr>
<td></td>
<td>91% ≥35</td>
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</tbody>
</table>

First Trimester Screening

Nuchal translucency ultrasound

12 week fetus with normal nuchal translucency

12 week fetus with enlarged nuchal translucency

NT ultrasound and biochemical screening can be combined for improved detection

NT + PAPP-A and beta hCG (11-14 weeks)
- First trimester screening
- Contingent screening
  - Add 2nd trimester testing if 1st tri results borderline
- Sequential screening
  - Do both 1st and 2nd trimester tests
- Integrated screening
  - Perform 1st and 2nd, no results until all is complete
Proposed Screening Options: First Trimester Combined Screen

NT + biochemistry (11-14 wks):
- 87% detection rate
- Simple (relatively)
- Early results

Proposed Screening Options: Integrated Screening

Perform both 1st and 2nd trimester tests (NT + PAPP-A, then quad screen)
- All results are combined in single algorithm and provided to the patient when complete (2nd tri)
- Best detection rate (94%)
- Results not provided until 2nd trimester
- “Nondisclosure sequential screening”

Proposed Screening Options: Sequential Screening

Perform both 1st and 2nd trimester tests (NT + PAPP-A and hCG, then quad screen)

3 approaches:
- Independent
- Stepwise
- Contingent

Proposed Screening Options: Sequential Screening

Independent: Report 1st and 2nd separately
- If 1st tri results are not considered with calculation of 2nd trimester risk, results inaccurate
  - If 1st tri risk > age risk and that is not considered, risk estimate will be too low
  - If 1st tri risk < age risk, estimate will be too high
- Estimated DR 95%, but FPR 17%
- Least desirable
**Proposed Screening Options: Sequential Screening**

**Stepwise:** Report 1st, but 2nd trimester test is “integrated,” taking into account 1st tri results

- DR 95%, false positive rate 5%
- Results approximate integrated screen but early results available with option of early diagnostic testing

**Contingent:** 1st trimester results divide patients into 3 groups: high, med, low risk

- High risk: offered diagnostic testing
- Med risk: offered 2nd trimester screening (integrated)
- Low risk: No further testing

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>% population</th>
<th>% T21</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (1/65)</td>
<td>1%</td>
<td>70%</td>
</tr>
<tr>
<td>Med (1/65-300)</td>
<td>18%</td>
<td>25%</td>
</tr>
<tr>
<td>Low (1/300)</td>
<td>81%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Proposed Screening Options: Summary**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Pros/Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st tri screen</td>
<td>Early result, DR 87%</td>
</tr>
<tr>
<td>Integrated</td>
<td>Late result, best stats</td>
</tr>
<tr>
<td>Stepwise</td>
<td>Early results, excellent stats</td>
</tr>
<tr>
<td>Contingent</td>
<td>Early results, excellent stats, complex protocols</td>
</tr>
<tr>
<td>Independent</td>
<td>Least accurate, high FP rate</td>
</tr>
</tbody>
</table>

**ACOG PRACTICE BULLETIN**

Clinic Management Guidelines for Obstetrician-Gynecologists

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Obstetrics (CPBO) in consultation with the Maternal-Neonatal Medicine Section. Comments were solicited from the membership of the Section on Obstetrics and Gynecology of the American College of Obstetricians and Gynecologists. This practice bulletin was reviewed and approved by the Committee on Practice Bulletins—Obstetrics (CPBO). The CPBO is the policy-making body of the ACOG. Please send comments to the section on Obstetrics and Gynecology at ACOG headquarters.
ACOG Practice Bulletin, Jan 2007

• All women should be offered aneuploidy screening before 20 weeks of gestation, regardless of maternal age.
• An option that includes both first and second trimester screening should be offered to women who present for care in the first trimester.
• Invasive diagnostic testing for aneuploidy should be available to all women...regardless of maternal age.

Table 1. Down Syndrome Screening Tests and Detection Rate (95% Positive Screen Rate)

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Detection Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT measurement</td>
<td>64-70*</td>
</tr>
<tr>
<td>NT measurement + MCA</td>
<td>82-87*</td>
</tr>
<tr>
<td>First trimester</td>
<td></td>
</tr>
<tr>
<td>Nuchal translucency</td>
<td>70*</td>
</tr>
<tr>
<td>Quad screen</td>
<td>81*</td>
</tr>
<tr>
<td>Combined screening</td>
<td>94-96*</td>
</tr>
<tr>
<td>Second trimester</td>
<td></td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
</tr>
</tbody>
</table>
| Invasive diagnostic testing for aneuploidy should be available to all women...regardless of maternal age.
SB1555 passed in Sept 2006 with the following language:

- “The department shall expand prenatal screening to include all tests that meet or exceed the current standard of care....Therefore one goal of the current program expansion is to provide the Prenatal Screening Program with sufficient flexibility … so that further improvements can be added in a timely fashion.”

To comply with SB1555 and update program, CA will provide:

- Quad screening
- Serum integrated screening
- Sequential screening (for patients with access to NT)

<table>
<thead>
<tr>
<th>Second-trimester Cut-off for Quad Screening (mid-trimester risk)</th>
<th>Dating</th>
<th>False Positive Rate</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:120 U/S</td>
<td>3.71%</td>
<td>77.87%</td>
<td></td>
</tr>
<tr>
<td>1:120 LMP or Exam</td>
<td>3.92%</td>
<td>76.56%</td>
<td></td>
</tr>
<tr>
<td>1:150 U/S</td>
<td>4.50%</td>
<td>80.12%</td>
<td></td>
</tr>
<tr>
<td>1:150 LMP or Exam</td>
<td>4.79%</td>
<td>79.08%</td>
<td></td>
</tr>
<tr>
<td>1:180 U/S</td>
<td>5.22%</td>
<td>81.83%</td>
<td></td>
</tr>
<tr>
<td>1:180 LMP or Exam</td>
<td>5.60%</td>
<td>80.37%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second-trimester Cut-off for Serum Integrated Screening (mid-trimester risk)</th>
<th>Dating</th>
<th>False Positive Rate</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:160 U/S</td>
<td>3.72%</td>
<td>83.93%</td>
<td></td>
</tr>
<tr>
<td>1:160 LMP or Exam</td>
<td>4.20%</td>
<td>82.40%</td>
<td></td>
</tr>
<tr>
<td>1:200 U/S</td>
<td>4.47%</td>
<td>85.57%</td>
<td></td>
</tr>
<tr>
<td>1:200 LMP or Exam</td>
<td>5.09%</td>
<td>84.34%</td>
<td></td>
</tr>
<tr>
<td>1:240 U/S</td>
<td>5.19%</td>
<td>86.84%</td>
<td></td>
</tr>
<tr>
<td>1:240 LMP or Exam</td>
<td>5.91%</td>
<td>85.79%</td>
<td></td>
</tr>
</tbody>
</table>

- If NT not available or desired
- 1st tri: PAPP-A; 2nd tri: quad screen
- Results given in 2nd trimester
California State Program: Sequential Screening

- 1st tri: NT + PAPP-A and hCG
- Second trimester Quad screen
- Results provided in 1st and 2nd trimesters

<table>
<thead>
<tr>
<th>First-trimester Cut-off for Sequential Screening (mid-trimester risk)</th>
<th>Second-trimester Cut-off for Sequential Screening (mid-trimester risk)</th>
<th>Total (1&lt;sup&gt;st&lt;/sup&gt; + 2&lt;sup&gt;nd&lt;/sup&gt;) False Positive Rate</th>
<th>Total (1&lt;sup&gt;st&lt;/sup&gt; + 2&lt;sup&gt;nd&lt;/sup&gt;) Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:80</td>
<td>1:200</td>
<td>4.60%</td>
<td>90.40%</td>
</tr>
<tr>
<td>1:100</td>
<td>1:200</td>
<td>4.60%</td>
<td>90.00%</td>
</tr>
<tr>
<td>1:120</td>
<td>1:160</td>
<td>4.62%</td>
<td>89.82%</td>
</tr>
</tbody>
</table>

California State Program: Summary of Test Options

<table>
<thead>
<tr>
<th>Screening Modality</th>
<th>Dating Method</th>
<th>Screen Positive Rate</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential (1&lt;sup&gt;st&lt;/sup&gt; + NT + 2&lt;sup&gt;nd&lt;/sup&gt;)</td>
<td>U/S</td>
<td>4.60%</td>
<td>90.06%</td>
</tr>
<tr>
<td>Serum Integrated (1&lt;sup&gt;st&lt;/sup&gt; + 2&lt;sup&gt;nd&lt;/sup&gt;)</td>
<td>U/S</td>
<td>4.47%</td>
<td>85.57%</td>
</tr>
<tr>
<td>Quad (2&lt;sup&gt;nd&lt;/sup&gt; only)</td>
<td>LMP</td>
<td>5.09%</td>
<td>84.34%</td>
</tr>
<tr>
<td></td>
<td>U/S</td>
<td>4.50%</td>
<td>80.12%</td>
</tr>
<tr>
<td></td>
<td>LMP</td>
<td>4.75%</td>
<td>79.03%</td>
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Prenatal genetic testing

Significant changes in past several years
- More available testing options
  - Lower procedure related loss rates
- More advanced cost effectiveness analysis
- Emphasis on patient autonomy and decision making
- Changes in approach to prenatal screening recommendations

Amniocentesis Loss Rates

- 1/200 standard quoted loss rate not based on reliable data, origins obscure
- Only one large RCT, Tabor et al, 1986: 1/100 excess risk in patients who had amnio
**Amniocentesis Loss Rates**  
*Review of 29 Studies*

<table>
<thead>
<tr>
<th></th>
<th>Amnio</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>All controlled studies (n=19,979)</td>
<td>1.81%</td>
<td>1.17%</td>
</tr>
<tr>
<td>Controlled studies w/US guidance (n=11,372)</td>
<td>1.68%</td>
<td>1.08%</td>
</tr>
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- Procedure-related loss rate was 0.6% for controlled studies w/US guidance

*Seeds, AJOG, 2004*

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**Amniocentesis Loss Rates**

*Eddelman et al, 2006*

- Data from FASTER trial
- N=35,000 patients, compared those who had amnio (n=3096) with those who did not (n=31,907)
- Procedure-related loss rate estimated at 1/1600
- However, elective terminations were excluded
- Aneuploidy in spontaneous losses not considered

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**Amniocentesis Loss Rates**

*Caughey et al, 2006*

- Compared loss rates of CVS (n=9900) and amnio (n=31,000) at UCSF over 20 years
- Loss rate for both decreased, now both ~1/350

- Loss rate generally agreed to be lower than previously quoted, ~1/400

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**Recommendations from ACOG**  
*Bulletin, Jan 2007*

- All women should be offered aneuploidy screening before 20 weeks of gestation, regardless of maternal age
- An option that includes both first and second trimester screening should be offered to women who present for care in the first trimester

- Invasive diagnostic testing for aneuploidy should be available to all women … regardless of maternal age.
1979 NICHD Consensus Panel Guidelines on Amniocentesis

Access to prenatal diagnosis should be limited because of limited resources:
- Few established laboratories
- Few trained cytogeneticists
- Few trained amniocentesis providers

Down syndrome and 35 y.o. threshold

NICHD guidelines were also based on cost-benefit analysis
- Compared cost of amniocentesis vs cost of caring for individuals with Down syndrome
- Cost of amnio at >35 y.o. offset by savings accrued if all women terminated affected pregnancies
- DS risk=SAB risk made it “logical”

Importance of patient preferences

How do women weigh the risk of SAB vs risk of giving birth to a Down Syndrome child?

35 year old threshold

Cost of testing must be offset by savings accrued by averting DS births
- Much more stringent economic requirement than is currently required for medical interventions
- Most interventions improve health at increased cost
- Intervention need not save $$ to be justifiable economically

Setting the threshold for DS risk=SAB risk assumes that they are equal.
Prenatal diagnosis

The potential benefits include:

- Providing reassurance when results are normal
- Allowing preparation for birth of an affected child
- Allowing providers to prepare for care of affected infant
- Providing risk information to couples for whom termination of pregnancy is an option

NICHD Consensus Panel

“This statement is more than five years old and is provided solely for historical purposes. Due to the cumulative nature of medical research, new knowledge has inevitably accumulated in this subject area in the time since the statement was initially prepared. Thus some of the material is likely to be out of date, and at worst simply wrong.”

NIH Consensus Development Program

Patient Preferences and Prenatal Diagnosis

Three recent studies addressing whether women would rather have a procedure related miscarriage or Down syndrome birth:

- Kuppermann et al, 2000
  - 584 racially/ethnically diverse women in SF
- Grobman et al, 2002
  - 186 women receiving prenatal care at Northwestern U in Chicago
- Chan et al, 2006
  - 136 women in Hong Kong

All 3 studies demonstrated procedure-related miscarriage to be less burdensome than a DS birth
Measured preferences and utilities for prenatal diagnosis testing outcomes, including:

- Testing/normal results/unaffected birth 0.93
- No test/unaffected birth 0.918
- Testing/SAB/future unaffected birth 0.87
- Testing/TAB/future unaffected birth 0.836
- Testing/SAB/no future birth 0.70
- Testing/TAB/no future birth 0.692
- No test/delivery of DS infant 0.672

Kuppermann et al, 2000, Obstet Gynecol

Cost effectiveness of amniocentesis for women of all ages compares favorably with many commonly accepted interventions (mammography, PAP smears, etc)
- Results did not depend on maternal age or risk of Down syndrome birth
- Results were dependent on how much individual woman valued reassurance about the chromosomal status of her fetus
- The more reassurance women desire, the more cost effective is the testing

Harris et al, 2004, Lancet

Would offering invasive prenatal diagnosis to all pregnant women place undue burden on available resources?
“Should all pregnant patients be offered prenatal diagnosis regardless of age?”

1993, Druzin et al, Obstet Gynecol

- Cornell/NYH
- N=591 low risk women <35 offered amniocentesis
- Patients paid if insurance did not
- 133 (22.5%) requested amnio

How Pregnant Women Use Risk-Assessment Information

- N=30,564 consecutive, singleton pregnancies
- Pregnant women are able to use sophisticated risk assessment information to make rational decisions about invasive testing.

Will this new approach place undue burden on available resources?

- Available evidence does not indicate that this is the case.
- Even if demand increases, and rationing is required, using specious criteria for testing is not the appropriate response.

What is the appropriate response to rising costs?

- We do not know better than our patients what is best for them.
- Our challenge is to help them reach a decision that is best for them given their particular background, experience, and values.

Ethics and Prenatal Diagnosis

Autonomy

- We do not know better than our patients what is best for them.
- Our challenge is to help them reach a decision that is best for them given their particular background, experience, and values.
Autonomy

**Informed Consent**
- The patient needs to have been given accurate information in sufficient quantity and in enough depth and detail to make a good decision for herself.

**Non-Directive Counseling**
- The provider should not let his or her own beliefs affect the decision

Maternal age and chromosomal abnormalities

Prenatal Genetic Screening: Putting It All Together

Based on current analysis of data regarding amniocentesis loss rate, cost effectiveness and ethical provision of medical care, it is not longer acceptable to dichotomize prenatal genetic testing by maternal age
Prenatal Genetic Screening: Putting It All Together

- Current challenge is primarily *education* of patients and providers
- Instead of focusing on thresholds for offering or denying testing on the basis of age/risk, guidelines must emphasize ways to support informed choice