Background behind the genetic sonogram

- The genetic sonogram started with an observation by Benacerraf and Bromley that there was a relationship between nuchal skin fold (NSFT) and Down syndrome.
- From there, other markers surfaced that could be used together to better adjust the risk for DS than by age alone.
- Initially it was used for patients of advanced maternal age with or without other screening tests but then evolved as an often used adjunctive test for T21 and T18.

Three parts of the genetic sonogram

1. The size of the fetus and long bones
2. A search for major anomalies
3. Assessment of soft markers
Most common markers

- Nuchal skin fold thickness
- Nasal bone length
- Echogenic inta-cardiac focus (EIF)
- Bilateral pyelectasis
- Femur and humeral lengths
- Ventriculomegaly

Second tier markers

- Ear length and configuration
- Frontal lobe length
- Right heart predominance
- Tricuspid regurgitation
- Middle bone of the fifth digit
Isolated Findings that Produce Heartburn

Nasal bone

Lateral ventricles

Echogenic intra-cardiac focus
Echogenic bowel

Bilateral pyelectasis

Fetal profile/frontal lobe
The genetic sonogram

- What does one do with the information?

- The sensitivity of the method is dependent upon the center. The goal is to drop the pre-scan risk by at least 50%. In some centers by 80-90%. 

## FaSTER: Genetic Sonogram

<table>
<thead>
<tr>
<th>Down Syndrome Preganacies</th>
<th>Unaffected Preganacies</th>
<th>LR +</th>
<th>LR -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Malformation</td>
<td>6/59 (8.5%)</td>
<td>38/7783 (0.49%)</td>
<td>17</td>
</tr>
<tr>
<td>Nuchal Fold (≥6 mm)</td>
<td>6/31 (18%)</td>
<td>24/6473 (0.37%)</td>
<td>49</td>
</tr>
<tr>
<td>Femur Length (&lt;0.91 MoM)</td>
<td>16/56 (28%)</td>
<td>514/7761</td>
<td>4.6</td>
</tr>
<tr>
<td>Humrene Length (&lt;0.89 MoM)</td>
<td>8/26 (31%)</td>
<td>346/7725</td>
<td>5.0</td>
</tr>
<tr>
<td>Echogenic Intacardiac Focus</td>
<td>15/53 (28%)</td>
<td>346/7725</td>
<td>6.3</td>
</tr>
<tr>
<td>Pyelectasis (&gt;3 mm)</td>
<td>4/55 (7.3%)</td>
<td>99/7771</td>
<td>5.5</td>
</tr>
<tr>
<td>Marked Echogenic Bowel</td>
<td>2/55 (3.6%)</td>
<td>12/7777</td>
<td>24</td>
</tr>
<tr>
<td>Moderate Echogenic Bowel</td>
<td>4/55 (11%)</td>
<td>28/7777</td>
<td>30</td>
</tr>
<tr>
<td>Ventriculomegaly (&gt;10 mm)</td>
<td>3/54 (5.6%)</td>
<td>15/7767</td>
<td>25</td>
</tr>
<tr>
<td>None *</td>
<td>21/59 (36%)</td>
<td>6786/7783 (85%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Excluding humerus length

Agaard-Tillery, in press

### A reassuring genetic sonogram

- Example: using a likelihood ratio of 0.50
- A 37 y/o woman has an AAR of 1 in 190.
- After combined screening (NT and/or biochemistry), her risk drops, let's say, to 1 in 500 for DS.
- A reassuring genetic sonogram will then drop her risk below 1 in 1000.

### The genetic sonogram

- The greatest controversy involves how to counsel when an isolated marker is found, but a lot depends upon WHICH marker is in question.
Choroid plexus cysts (CPCs)

- Although they clearly are not markers of Trisomy 21, they can be markers for trisomy 18.

- However, their presence needs to be put in proper perspective.
Choroid Plexus Cysts

- If found, every effort must be made to rule out other markers for trisomy 18.
- There are a gazillion of them

Here is just one
John C. Hobbins, MD
Isolated Findings that Produce Heartburn

Ultrasound Stigmata of Trisomy 18

- CPC's (40%)
- Cerebellar hypoplasia
- Large cisterna magna
- Strawberry-shaped calvarium
- Micrognathia
- Small ears
- Cardiac defects (~90%)
- Early IUGR
- Single umbilical artery
- Echogenic bowel
- Clubbed hands and feet
- Overlapping fingers
- Rocker bottom feet

Summary of studies regarding CPCs and aneuploidy

- 1. There is no relationship to trisomy 21 or any other form of aneuploidy other than trisomy 18
- 2. About 40% of fetuses with Trisomy 18 will have them
- But, if truly isolated, there is no increased risk for trisomy 18 and, therefore, not a reason, as such, for amniocentesis!

Echogenic Intra-cardiac Focus (EIF)
Echogenic Intra-Cardiac Focus

EIF Background

- First report by Bromley et al. She noted a relationship between EIF and Down syndrome.
- Obstet Gynecol 1995; 86: 998-1001
- 1,374 patients evaluated with a genetic sonogram
  - 69 (5%) had EIF
  - 4 of 22 (18%) fetuses with Down syndrome had EIF
  - 65 of 1,374 (4.8%) normal fetuses had EIF

Echogenic intra-cardiac focus

- Since the original paper surfaced, the EIF was immediately blown way out of proportion, especially in lay publications.
- After a few years of heartburn, its meaning was put in proper perspective.
Echogenic Intra-cardiac Focus

Here is what we know now

- EIF more commonly noted in papillary muscles in the left ventricle compared with the right (4:1) relationship irrespective of any correlation with Down syndrome
- Finding is dependent upon the angle of insonation, i.e., apical scans results in 2x as many EIFs as a cross-sectional view at the level of the 4-chamber view of the heart
- It is seen in 15% of Asian fetuses
- It is not associated with structural cardiac anomalies

Echogenic Intracardiac Focus

- Likelihood ratios of an isolated EIF in mixed, but presumably, high-risk group
  - Bromley 1.4
  - Nyberg 1.8
  - Nicolaides 1.0

Echogenic focus

- Take home message:
  - If isolated in a patient with other normal screening tests (combined screen or NIPT), then the patient’s risk for DS is the same as her pre-ultrasound risk.
  - The greatest risk to a fetus with an isolated EIF is the mis-information on the internet
Echogenic Bowel

- Fetal swallowing of blood following amniocentesis or abruption
- Cystic fibrosis
- Down syndrome
- Infection, such as CMV or parvo virus

Hyperechoic Bowel

- Watch out for later emergence of IUGR
- Especially if elevated HCG, inhibin, or AFP
Bilateral Pyelectasis

- Some markers have a very high false positive rate
- Example: this one

Most common threshold is 4 mm in the AP dimension
Bottom line on isolated markers

- Is the effect of an isolated finding neutralized by not finding other markers? It depends upon the LR of the marker.
- If an EIF, short long bones, or mild pyelectasis is found, we neither increase or decrease the risk for DS from the pre-scan risk.
- All bets are off with increased NSFT, small nasal bone, ventriculomegaly, or EB, where LR is quite high.

The worth of the genetic sonogram

- How much does the genetic sonogram add to the accuracy of the standard screening modalities that have been in place over the last 5 years?
- Let's look at FASTER trial data

### FASTER Trial data

<table>
<thead>
<tr>
<th></th>
<th>STANDARD</th>
<th>AFER SONOGRAM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Detection Rate</td>
<td>FPR</td>
</tr>
<tr>
<td>Combined</td>
<td>88%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Quadruple</td>
<td>86%</td>
<td>12%</td>
</tr>
<tr>
<td>Integrated</td>
<td>93%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Step-Wise</td>
<td>97%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Contingent</td>
<td>95%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Step-Wise Sonogram**</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Contingent Sonogram**</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Non invasive prenatal testing (NIPT)

- Enter cell free DNA
- This method has the capability to rule out Trisomies 21, 18, and 13 with detection rates of 100%, 92% and 87%, respectively.
- So before even thinking of where the genetic sonogram will fit in, let’s first figure out where cfDNA has a role.

Cell free DNA. The yin and yang

- The good news: It is the most accurate non invasive test we have for the more common aneuploidies.
- The bad news: It is very expensive at the moment. However, the cost will drop as the demand increases and it has been difficult to do analyses of the cost effectiveness of the test because different companies have different deals.
- Another problem is that there is much variability between tests regarding the nature of their “indeterminate” or “inconclusive” (waffle) zones. About 1 in 5 fetuses in this category have aneuploidy, generally T 18 and 13.

Different first trimester screening options for DS

<table>
<thead>
<tr>
<th>PPV (%)</th>
<th>Cost/case</th>
<th>DR (%)</th>
<th>DR (%)</th>
<th>FPR (%) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Combined</td>
<td>220K</td>
<td>81.7</td>
<td>2.4</td>
<td>4.3</td>
</tr>
<tr>
<td>2. Contingent</td>
<td>199K</td>
<td>89.2</td>
<td>1.6</td>
<td>6.7</td>
</tr>
<tr>
<td>3. Combined and NB</td>
<td>190K</td>
<td>90.2</td>
<td>1.3</td>
<td>8.2</td>
</tr>
</tbody>
</table>

- Cell free DNA
- 1. Routine (everybody) | 770K | 99.3 | 0.11 | 54 |
- 2. Contingent | 300K | 94.5 | 0.09 | 58 |
- 3. AMA plus contingent | 320K | 94.8 | 0.06 | 68 |

Ultrasound Obstet Gynecol 2014;44: 621-30
Hobbins’ take on NIPT

- Now the cost/benefit data strongly favor the combined/contingency approach in low risk populations with cfDNA being used as a first line in high risk patients.

- However, because of the incredible financial attraction of 40 million potential customers, the companies will lower their prices to make it economically feasible to screen all patients.

So where does the genetic sonogram fit in?

- Possibilities:
  - 1. In those with “indeterminate” results who do not wish invasive testing but have a 16% chance of aneuploidy
  - 2. In those having an amniocentesis while waiting for the results
  - 3. In those rare patients who shun any screening test but who will accept an ultrasound exam for reassurance.

The fate of the genetic sonogram

- Based on the small amount of patients who would either benefit or even want it, the marker search may go the way of the: Ford Pinto or rabbit ears antennas.

However, nothing will replace the (new) standard second trimester anatomy scan.