Regional Neonatal Nursing Grand Rounds

Prenatal Diagnosis and Genetic Counseling

Bailey Brinks, RN-NIC, BSN
Kiana Siefkas, MS, CGC, LGC
May 2, 2019
Disclosures

• We do not have any conflict of interest, nor will we be discussing any off-label product use.

• This presentation has no commercial support or sponsorship, nor is it co-sponsored.
Objectives

• Describe the role and resources provided by the prenatal clinic
• State how to contact the prenatal clinic
• Understand how to access a prenatal chart in order to identify the postnatal plan of care, including genetic testing
• Describe the genetic testing done prenatally and know the next steps in pediatric evaluation
Get to know us!
Overview

• Multidisciplinary clinic that brings together obstetric and pediatric specialty care for families when a pregnancy is complicated by a known or suspected condition in the developing fetus
• Diagnostic testing, consultation and fetal intervention
  – Education
  – Birth and newborn care planning
• Screening echocardiograms
• Referring providers are Maternal-Fetal-Medicine (MFM) specialists and primary OB providers from the WAMI region.
Goals of Prenatal Diagnosis

• Improved outcomes:
  – Family logistics & support
  – Emotional preparedness
  – Health outcomes
  – Neonatal palliative care
  – DC planning
Prenatal Clinic

• Location:
  – Springbrook Professional Center (above adolescents clinic)

• Contact Us:
  – Main Line: x7-5629
  – RN Line: x7-0134
  – GC Line: x7-7973
  – Fax: x7-2962

• Regional Sites
Our Team

• Core Team:
  – Family Service Coordinators
  – Program Coordinator
  – Nursing
  – Nurse Practitioner/Clinic Manager
  – Genetic Counselor
  – Social Work
## Specialty Providers

**Templated Providers**
- Cardiology (fetal echo)
- Maternal-Fetal Medicine (OB ultrasounds)
- General Surgery
- Neurodevelopmental/Neurology
- Fetal MRI
- Nephrology
- Urology

**Non-Templated Providers**
- Medical Genetics
- Cardiac Surgery
- ENT
- Neurosurgery
- Craniofacial
- Orthopedics
Patient Volumes by Specialty

- Cardiology
- Neurodevelopmental
- General Surgery
- Other
Clinic Flow
Referral Process

• Referrals
• Triage
• Our FSCs call patient’s to schedule
• Relocation/Resource Needs, as needed
Referral Examples

Fetal Indications
• Structural anomalies
• Chromosomal anomalies
• Arrhythmias
• Unable to clear heart on routine OB scan
• Increased NT
• Hydrops

Maternal Indications
• Prior child with CHD
• Maternal CHD
• Maternal diabetes
• Maternal Lupus or like condition
• Exposures: medications, viral illness
Patient’s day lasts about 2-5 hours depending on complexity of case
Resources Provided

- Education Material
- Seattle Children’s Hospital Packet
- Group Hospital Tours
- Counseling Resources
After the Visit

- Referring provider updated
- Assist with relocation
- Coordinate appointments
- Research study
- Offer continued support and education
- Assist with delivery planning
- Forecast List
<table>
<thead>
<tr>
<th>Mother's Name / Baby's Name</th>
<th>Mother SCH MR#</th>
<th>EDC</th>
<th>Planned del date</th>
<th>Delivery Hosp</th>
<th>Home</th>
<th>Diagnosis</th>
<th>Comments</th>
<th>Most Recent Consult visits</th>
<th>Collect cord blood?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5/9</td>
<td>IOL 05/03</td>
<td>UW</td>
<td>Everett</td>
<td>IAA w/ VSD</td>
<td>NmL Microarray</td>
<td>MFM/Ma/4/22 CRD/Conwell/4/12 NEO/Maycock/4/8</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/8</td>
<td></td>
<td>Swedish</td>
<td>Seattle</td>
<td>Sacral NTD</td>
<td></td>
<td>NDV/Tully/2/21 NSR/Hauptman/2/21</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/12</td>
<td>CS 5/7</td>
<td>UW</td>
<td>Mt Vernon</td>
<td>Severe ventriculomegaly, cortical volume loss, cerebellar cleft</td>
<td>NmL microarray</td>
<td>NDV/Doherty/3/21 MFM/Ma/4/22 NEO/Maycock/4/8</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/29</td>
<td>IOL 05/22</td>
<td>UW</td>
<td>Lake Stevens</td>
<td>HLHS + microcephaly</td>
<td>Cord blood for microarray / request eval for RIGHt project</td>
<td>CRD/Arya/4/4 MFM/Oler/4/16</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/26</td>
<td>Swedish</td>
<td>Seattle</td>
<td></td>
<td>TDF, possible coarct</td>
<td>Followed by NWCHC</td>
<td>MFM/Ma/4/22 SUR/Javd/4/16 NEO/Setty/4/23</td>
<td>Y</td>
</tr>
</tbody>
</table>
Prenatal Charts
If a newborn was seen prenatally, then you can find all the prenatal information under mom’s chart.

Mom will have her own MRN in CIS.

All the diagnostic testing, prenatal records, care coordination, and genetic testing can be found there.

Postnatal genetic results should be in baby’s chart.
Prenatal Genetic Testing and Counseling
Outline

• Background

• Screening
  – Maternal Serum Screening
  – Cell Free DNA screening

• Diagnostic testing
  – Chorionic Villus Sampling and Amniocentesis
  – Karyotype and Microarray

• Overall understanding of types of prenatal testing
Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

- **Interpretation** of family and medical histories to assess the chance of disease occurrence or recurrence.
- **Education** about inheritance, testing, management, prevention, resources and research.
- **Counseling** to promote informed choices and adaptation to the risk or condition.

Chromosomes are like books

- Chromosome anomaly – an extra or missing whole book or huge portion of a book.

- Microdeletion/duplication - a few pages are extra or missing

- Single gene disorder – spelling error
Basic Brief Condition Examples

• Trisomy – an extra chromosome (extra book)
  – T21/Down – hypotonia, mild/mod ID, variety of birth defects, medical conditions
  – T18/Edwards – slow growth, heart defects, ID, multiple congenital anomalies
  – T13/Patau – heart defects, brain or spinal cord abnormalities, small or poorly developed eyes
  – T18/T13 – 5-10% live past their first year

• Microdeletion/duplication – small extra or missing piece of chromosomal material (pages)
  – 22q11 deletion – heart defects, mild/mod ID, cleft palate, low calcium

*Not comprehensive discussion of any of these conditions and more detail and nuance given to all families.
ACOG: Prenatal Genetic screening & testing

• ALL women should be offered aneuploidy screening and diagnostic testing in early pregnancy

• Wide variety of screening options
• Varying levels of information and accuracy

• No one screening method is superior to others in all test characteristics
• Relative advantages and disadvantages

• Complex counseling by providers
• Complex decision making by patients

ACOG PB 163. Screening for Fetal Aneuploidy. May 2016
Slide courtesy of Shani Delaney
Timeline of Genetic Screening and Testing

Serum screening
- Serum Integrated, Combined & Sequential screening
- Quad screen

Ultrasound
- NT sono
- Anatomy scan

Non-invasive screening
- Cell free fetal DNA screening

Invasive testing
- CVS
- Amniocentesis

1st trimester
- 10-14wks

2nd trimester
- 15-22wks

2nd and 3rd trimester

Slide courtesy of Shani Delaney
Prenatal Screening
Screening

- Definition: a test performed on a large number of people to identify those who have or are likely to develop a specified disease or condition
- Simple, generally highly sensitive to not miss potential affected persons
- False positives, hopefully few false negatives
- Indicates suspicion of condition that **warrants** confirmation through diagnostic testing
• Measure proteins/analytes produced by the fetus or placenta
• (MoM) calculated to population standards
• Compare a number of different factors: age, ethnicity, results from blood tests, gestational age, diabetes, weight, number of fetuses, etc.
• Reported as a 1 in ________ risk number
• Neural tube defects, trisomy 21, trisomy 18, trisomy 13, and more indicators
Serum Screen Results Examples

Median concentration of pregnancy-related chemicals in mother’s blood

Typical concentration of pregnancy-related chemicals in a pregnancy with Down syndrome

Typical concentration of pregnancy-related chemicals in a pregnancy with Trisomy 18
Cell Free DNA

• The entire fetal genome is represented in the maternal plasma
• Detected as early at 7 weeks GA
• Disappears rapidly from the maternal circulation after delivery
  – Undetectable 2 hours after delivery!
• Size difference:
  – Maternal 167bp
  – Fetal 147bp


Slide courtesy of Shani Delaney
Cell Free DNA = Apoptosis

~90% of cell free DNA in maternal plasma during pregnancy is maternal in origin

~10% of cell free DNA in maternal plasma during pregnancy is from *placental trophoblasts*


Slide courtesy of Shani Delaney
Cell free DNA Genetic Technique

Maternal plasma cell free DNA fragments are extracted
BOTH maternal and fetal fragments are sequenced

1. Extract and Prepare cfDNA
2. Next-Gen Sequencing

Slide courtesy of Shani Delaney
Cell free DNA Genetic Technique

Alignment of unique cell free DNA sequences

Reference Human Genome

Slide courtesy of Shani Delaney
Bin Method

Fetal cfDNA

Chromosomes:
1 2 3 ...... 21 21

Counting

VS

Trisomy 21

Slide courtesy of Shani Delaney
More than just Aneuploidy Screening!

Results are not just 5 bins!

Slide courtesy of Shani Delaney
cfDNA can provide information on genome

- Sub-chromosome deletions and duplications?
- Micro-deletions and duplications?
- Single gene disorders?
> cfDNA tells us about gains and losses of DNA
> Quantity but *not* structure, and *not* location
> Importance of diagnostic testing
Cell free DNA will **miss at least 20% of microdeletions/duplication syndromes** that are detectable by **diagnostic** prenatal testing methods

- Current resolution of cfDNA is 5Mb
- Many microdeletion/duplication syndromes are <5Mb
- Importance of diagnostic testing
Detection rates of cfDNA vs. Serum Screening (Sequential)

<table>
<thead>
<tr>
<th>Aneuploidy</th>
<th>n (%) detected by cfDNA</th>
<th>n (%) detected by SS</th>
<th>DR of SS vs cfDNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>T21</td>
<td>1265 (99.2)</td>
<td>1184 (92.9)</td>
<td>$P &lt; .0001$</td>
</tr>
<tr>
<td>T18</td>
<td>325 (96.7)</td>
<td>313 (93.2)</td>
<td>$P = .05$</td>
</tr>
<tr>
<td>T13</td>
<td>132 (92.3)</td>
<td>115 (80.4)</td>
<td>$P = .005$</td>
</tr>
<tr>
<td>45X</td>
<td>148 (91.9)</td>
<td>129 (80.1)</td>
<td>$P = .004$</td>
</tr>
<tr>
<td>Other SCA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>89 (93.7)</td>
<td>56 (58.9)</td>
<td>$P &lt; .0001$</td>
</tr>
<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26 (4.3)</td>
<td>323 (53.7)</td>
<td>$P &lt; .0001$</td>
</tr>
<tr>
<td>All</td>
<td>1985 (77.1)</td>
<td>2101 (81.6)</td>
<td>$P &lt; .0001$</td>
</tr>
</tbody>
</table>

DRs of sequential screening compared with cfDNA, assuming that “no results” cases are considered “screen positive” and referred for follow-up.

Slide courtesy of Shani Delaney
Cell free DNA and Serum testing are screening tests, both are very good.

Maternal blood used.

If a child has had SCREENING in utero suggesting a likely diagnosis then DIAGNOSTIC testing needs to happen postnatally.

Best diagnostic test depends on each situation.
Prenatal Diagnostic Testing
Diagnostic Testing

• Tests designed to establish the presence/absence of disease/condition
• May be invasive, justifiable as necessary to establish diagnosis
• Chosen towards high specificity (true negatives)
• Result provides a definite diagnosis
Diagnostic Procedures

Chorionic Villus Sampling

- Transabdominal
- Transcervical
- 11-14 weeks
- Loss rate = 0.1 - 1.1%

Amniocentesis

- ≥ 15 weeks
- Loss rate 0.2 - 0.4%

Enzensberger C. Ultraschall Med 2012; 33(7): E75-E79
Slide courtesy of Shani Delaney
Diagnostic Testing

- **iFISH from amniocentesis**
  - Fluorescent probes during interphase
  - Information only on chromosomes that you FISH for

- **Direct preparation from CVS**
  - “Low resolution karyotype” from cytotrophoblasts
  - Information about all 46 chromosomes

Slide courtesy of Shani Delaney
Diagnostic Testing

> Karyotype
  - Big picture
  - Large changes in structure or number of chromosomes
  - Resolution 5-10Mb
Microarray

- Submicroscopic level
- Resolution 50-100kb
- Duplication/deleted sections that differ in size from a reference human genome = copy number variants (CNV)
  > Benign
  > Pathogenic
  > Variants of unknown significance (VOUS)

Advantages of microarray

- Higher resolution
- Can be obtained from uncultured cells, does not require actively dividing cells (IUFD, SAB)

Limitations of microarray: quantity, not structure

- Will not detect balanced translocations
- Low-level mosaicism
33-year-old mother and unrelated father.

G2P2002

Maternal Serum Screen = increased risk for Down syndrome

Normal Harmony cfDNA testing @13w5d
  – 12.1% fetal fraction
  – <1:10,000 risk for T13, T18, T21

38 weeks 3 days gestation

Repeat cesarean section for breech

8lbs 13oz 4003 gram /OF 34cm /Length 51cm

Features of Down syndrome

She had difficulty latching for feeding & sleepy while eating.
iFISH Results

 cytogenetics

Comment:

nuc ish 21q22.13-q22.2 (D21S259x3, D21S341x3, D21S342x3)

Fluorescence in situ hybridization (FISH) analysis of peripheral blood lymphocytes, using a unique sequence DNA probe (Vysis, Inc.) for chromosome 21 at q22, revealed three hybridization signals in all 50 interphase cells analyzed.

These results are consistent with non-mosaic trisomy 21, although it does not differentiate translocation trisomy (which has recurrence risk) from free trisomy. Chromosome analysis should be ordered to determine mode of trisomy 21.

FISH results should be interpreted within the context of a full cytogenetic analysis, family history, and clinical phenotype.

This test was developed and its performance characteristics determine by Laboratory Corporation of America Holdings (LabCorp). It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. It should not be regarded as investigation or for research.

Comment:  

See Notes  

Elisabeth Keitges PhD,  
FACMG
Karyotype

**SPECIMEN TYPE**
- Comment: See Notes

**CELLS COUNTED**
- 15

**CELLS ANALYZED**
- 5

**CELLS KARYOTYPED**
- 3

**GTG BAND RES. CYTOGENETIC RESULT**
- Comment: 47,XX,+21,der(21;21)(q10;q10)x2[4]/
  46,XX,+21,der(21;21)(q10;q10)[16]

**INTERPRETATION**
- Comment: ABNORMAL FEMALE KARYOTYPE

Cytogenetic analysis of peripheral lymphocytes has revealed a female karyotype with two abnormal cell lines.

Sixteen of 20 cells show a translocation trisomy 21 with two chromosomes 21 fused (Robertsonian 21/21 translocation) in addition to one normal chromosome 21 homologue. The second population shows one normal chromosome 21 and two translocation trisomy 21's (5 copies of chromosome 21). The percentage of mosaicism can be different in varying tissues. Fluorescence in situ hybridization (FISH) can be performed on another tissue type (e.g., buccal smear) if desired to determine the level of mosaicism in that tissue.

Abnormalities seen in Down syndrome include intellectual disability, dysmorphic facial features and heart defects. Individuals with Down syndrome are also at an increased risk of developing leukemia.

Translocation trisomy 21 due to Robertsonian translocation is found in about 4% of Down syndrome cases. A balanced 21/21 translocation carrier parent has a 100% liveborn recurrence risk for Down syndrome. Parental karyotyping is recommended. Genetic counseling is recommended.

Trisomy 21 & Pentasomy 21

46,XX,+21,der(21;21)(q10;q10) in 16 cells
47,XX,+21,der(21;21)(q10;q10)x2 in 4 cells

https://christinamolin.wordpress.com/2007/01/18/translocation-trisomy-21robertsonian-trisomy-21/
Subchromosome changes and structural rearrangements

> 33 yo G3P1102 @ 25 weeks for MFM consult
> Fetal Tetrology of Fallot and brain anomalies

> cfDNA with MaterniT21 = 15Mb loss of 18p
> 18p minus phenotype
  > Hearing loss, heart defects, pituitary anomalies, seizures, cataracts, hypotonia, developmental delay

> Declined amniocentesis

Slide courtesy of Shani Delaney
> GC called Maternity T21
> “Smaller deletion also seen at the terminal end of 18q. Below reporting threshold, so not originally reported.”

> Ring chromosome 18 carries a worse prognosis than 18p-minus syndrome
Term SVD, female, weight 2832g (13% for 38 weeks)
Postnatal karyotype on cord blood confirmed a ring chromosome 18
- 15Mb loss of 18p
- 1.6Mb loss of 18q
Baby is now a ~2 year old toddler
- Has undergone repair of TOF
- Slow to meet her neurodevelopmental milestones
- But medical doing well

Slide courtesy of Shani Delaney
• We are seeing a decrease in the number of families pursuing diagnostic testing in utero even when a concern arises. This means that more diagnostic testing burden is on the pediatric care team.

• Some of this decrease is due to continued misunderstanding even with counseling that they “think they tested for everything.”
Diagnostic testing

• If a child had a diagnostic test (amniocentesis, cvs) this does not need to be repeated. **Need a copy of the result.**

• Children with **residual concerns of a genetic condition need a genetics consultation** – inpatient or outpatient is child/situation dependent.
Questions?

Contact Us:

– Main Line: x7-5629
– RN Line: x7-0134
– GC Line: x7-7973
– Fax: x7-2962
Rate of Microdeletions/duplication conditions is independent of maternal age

Rate of clinically significant microdeletions and duplications in sonographically normal fetus = 1.7%

- Among low risk women, collectively microdel/dup conditions are more common than Trisomy 21

Microdeletions are More Common Than Down Syndrome for Women Under 40

Slide courtesy of Shani Delaney