Genetics and Reproductive Options for SMA Families

2018 Annual SMA Conference
Dallas, Texas
Friday, June 15, 2017
Part 1: SMA and Genetics

Louise R Simard, PhD

Part 2: SMA Carrier Screening

Melissa Gibbons, MS CGC

Part 3: Reproductive Options for SMA Families

Harvey J Stern, MD, PhD
Louise R. Simard, PhD

University of Manitoba, Faculty of Medicine
Dept. Biochemistry & Medical Genetics
Winnipeg, MB, Canada R3E 0J9

Louise.Simard@umanitoba.ca

1987 - Ph.D. U Toronto – Medical Genetics.
Independent research program in SMA
DNA diagnostics Consultant, incl. SMA testing
2006-present – Professor, Department Head, U Manitoba

Questions are welcome!
Outline

• SMA
  ❖ Lower Motor Neuron Disease
  ❖ With a wide range of clinical presentation (severity)

• SMA Gene
  ❖ SMN1 and SMN2
  ❖ SMN1 Mutations
  ❖ SMA severity

• SMA Genetics
  ❖ Chromosomes as vehicles of the DNA genomic blueprint
  ❖ Autosomal Recessive Inheritance

• SMA Molecular Tests
  ❖ Diagnosis
  ❖ Carrier
SMA is a lower motor neuron disease that recurs in families (inherited).

**Type 0**
- **Prenatal SMA**
  - In utero
  - Respiratory support
  - Death before 1 month

**Type 1**
- **Werdnig-Hoffman**
  - < 6 months
  - Never sit unaided
  - Death before 2 years

**Type 2**
- **Intermediate SMA**
  - < 18 months
  - Never stand unaided
  - Decreased life expectancy

**Type 3**
- **Kugelberg-Welander**
  - 18 months
  - Stand alone but loss of mobility
  - Normal life expectancy

**Type 4**
- **Adult SMA**
  - ≥21 years of age
  - Progressive muscle weakness
  - Normal life expectancy

---

**Wide Clinical Presentation!**

**Loss of MN cells leads to Muscle Atrophy**


---

**Genetics and Reproductive Options for SMA Families**
Part 1: SMA and Genetics

Identifying the SMA gene
1 gene 5 SMA types

Gene for chronic proximal spinal muscular atrophies maps to chromosome 5q


Nature (1990) 344:767-768

Genetic homogeneity between acute and chronic forms of spinal muscular atrophy


Nature (1990) 345:823-825

Mapping of acute (type I) spinal muscular atrophy to chromosome 5q12-q14

Judith Melki, Parag Sheth, Sonia Abdelhak, Philippe Burlet, Marie-France Bachelot, Mark G. Lathrop, Jean Frezal, Arnold Munnich, and the French Spinal Muscular Atrophy Investigators


Genetic mapping of chronic childhood-onset spinal muscular atrophy to chromosome 5q11.2-13.3


Nature (1990) 540:541

Identification and Characterization of a Spinal Muscular Atrophy–Determining Gene

Genetics and Reproductive Options for SMA Families
Genetic Code = Blueprint of life
~20,000 genes in the human genome

DNA = four nucleic acids (C, G, T, A)
Different sequence of A-C-T-G = gene
C (cytosine) pairs with G (guanine)
T (thymine) pairs with A (adenine)
SMN1 vs. SMN2 gene

Chr 5q13

Mutations in SMN1 Cause 5q-SMA


DNA (a) → RNA (b) → mRNA (c) → protein

~10% Full-length transcripts
~90% Nonfunctional SMN protein

100% Full-length transcripts
Functional Wild Type SMN protein
Deletions (missing DNA) is a common mutation in SMA

Very large deletions are often associated with type I and type II SMA. Type I SMAs most often cannot make ANY SMN.

In Type II & III SMA, the mutation is often confined to SMN1 exon 7.

Part 1: SMA and Genetics

SMA locus is very variable

On average:

But...
also find:

No apparent Clinical effect

SMA causing Chromosomes
**SMN2 is a major modifier gene**

SMN2 copy number decreases with increasing severity

![Bar chart showing the distribution of SMN2 copies among patients with different SMA types.](chart.png)


- Type I: n=188
- Type II: n=110
- Type III: n=77

**Part 1: SMA and Genetics**
SMA is inherited as an Autosomal Recessive Disorder

The fundamental unit of inheritance is DNA. Each cell has over 5 feet of DNA! It must be compacted to fit inside a cell in the form of chromosomes.

We have 23 pairs of chromosomes; each set is inherited from our biological parents.

SMA → autosomal recessive mode of inheritance

There must be a mutation (error) in both copies of a gene (maternal and paternal) for the genetic disorder to be passed onto a child.
SMA is inherited as an Autosomal Recessive Disorder

- Affected individuals have mutations in both copies of a recessive gene.
- Carriers have a mutation in only one copy of a recessive gene and is asymptomatic.
- Males and females can be carriers.
- Males and females can be affected.
- If both parents are carriers, the risk of having a child with the disease is 25%.

Having an affected child is a surprise because carrier parents are asymptomatic. From this point onwards – genetic counseling becomes possible.
Part 1: SMA and Genetics

>95% of patients have deleterious mutations in the \textit{SMN1} gene (deletions, gene conversions, point mutations)

Deletion:

\textit{SMN2} \quad \text{SMN1} \quad \text{X}

Gene conversion:

\textit{SMN2} \quad \text{SMN1} \quad \text{SMN2}

Point mutation:

\text{Exon number} \quad 1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7 \quad 8

\text{Codon position} \quad 1 \quad 28 \quad 52 \quad 92 \quad 159 \quad 210 \quad 242 \quad 279 \quad 293

\text{c.834+2T>G}
Molecular Diagnostic Tests

- Detection of homozygous mutations
  - presence/absence of SMN1 Ex7 = diagnosis

- Detection of heterozygotes
  - Number of copies of exon 7 = carrier testing

- Analysis of point mutations = diagnosis
  - Not yet routine, specialized labs only
Diagnostic Tests: **SMN1 mutations**

Diagnosis of SMA patients

**All or None test!**

![DNA bands for SMN1 and SMN2](image)


Compared to EMG & muscle biopsy, the DNA test is:

- non-invasive
- sensitive, detects >95% of all SMAs
- accurate, all lacking **SMN1** exon 7 have SMA
- ideal for newborn screening

**Limitation:** Some SMA individuals have a point mutation in the **SMN1** gene. Such mutations are not detected by the deletion or quantitative PCR assay.
Diagnostic Tests: Carrier Detection

2 vs. 1 copy of \( SMN1 \) exon 7 test (dosage)

- **SMN** quantitative test

- 95% of SMA patients are lacking \( SMN1 \) exon 7
- Because SMA is an autosomal recessive disorder, most SMA carriers should have only 1 copy of \( SMN1 \) exon 7
Part 1: SMA and Genetics

Diagnostic Challenges

These tests do not detect small mutations in the \textit{SMN1} gene.

On average:

- \textbf{SMN2} \quad \textbf{SMN1}
- \textbf{SMN2} \quad \textbf{SMN1}

\textbf{But….}

- \textbf{SMN2}
- \textbf{SMN2} \quad \textbf{SMN1} \quad \textbf{SMN1}

2 to 5\% of individuals have both \textit{SMN1} genes on the same chromosome (2+0 genotype) - so are carriers.

Rarely able to give a 100\% Yes or No result.

Taken from Alias et al. (2009) Human Genetics 125:29
A Genetic Counselor is a valuable resource to help you understand the genetics of SMA, opportunities for testing (diagnosis, carrier status, prenatal) and how to interpret test results.
Part 2: SMA Carrier Screening

Melissa Gibbons, MS CGC
Certified Genetic Counselor
Neuromuscular Clinic
Children’s Hospital Colorado
Assistant Professor
University Colorado School of Medicine

Member
Cure SMA Medical Advisory Committee
Genetic Counselors are:

• Master’s-trained health care professionals who combine their knowledge of:
  — Basic science
  — Medical genetics
  — Epidemiological principles
  — Counseling theory

• With their skills in:
  — Genetic risk assessment
  — Education
  — Interpersonal communication and counseling

• To provide services to clients and their families for a diverse set of genetic or genomic indications
Genetic Counselors work in:

- Clinical Setting
  - Preconception
  - Prenatal
  - Pediatric
  - Adult
  - Cancer
- Genetic Testing Laboratory
- Pharmaceutical Companies
Genetic Counselor can:

- Explain your/your child’s results
- Discuss different genetic testing options
- Assist with coordinating carrier testing for
  - You
  - Extended Family
- Provide family education
- Discuss treatment options
- Discuss reproductive options
Understanding Your Results

(a) deletion
(b) gene conversion
(c) point mutations

Understanding Your Results

Positive Deletion Results:

<table>
<thead>
<tr>
<th>SMN1 copy number</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMN2 copy number</td>
<td>3</td>
</tr>
</tbody>
</table>

Inconclusive Deletion Results:

**Technical Results**
- SMN1: 1 copy
- SMN2: 2 copies

Sequencing Results:

**Results:** Positive for SMN (c.418-432delGATCTACTTTCCCCA) mutation

Additional Types of Sequencing Results:

- **DNA Variant 1:** 4 bp Deletion
- **Nucleotide Position:** 399-402
- **Codon:** 133-134
- **Amino Acid Change:** Frame Shift
- **Variant Type:** Disease-associated recessive mutation, heterozygous

**Results:** Positive for SMN T274I mutation
Carrier Testing

Affected Individual has 2 SMN1 Deletions

Parents and Extended Family can be tested by Deletion Studies

Affected Individual has 1 SMN1 Deletion & 1 SMN1 Point Mutation

Parents should be tested first to determine targeted testing for the extended family
Different Types of Carriers

“1 + 0”

5q

SMN1

5q

“1 + 1*”

5q

SMN1

5q

SMN1 *

“2 + 0”

5q

SMN1

5q

SMN1

“2 + 0*”

5q

SMN1

5q

SMN1 *

*Point mutation or microdeletion.
Adapted from PMCID: PMC3234503
What does negative mean?

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Carrier Frequency</th>
<th>Current Detection Rate</th>
<th>Residual risk after negative result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>1 in 41&lt;sup&gt;4&lt;/sup&gt;</td>
<td>90%&lt;sup&gt;1,4&lt;/sup&gt;</td>
<td>1 in 345&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Asian</td>
<td>1 in 53&lt;sup&gt;1&lt;/sup&gt;</td>
<td>92.6%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 in 628&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>African American</td>
<td>1 in 66&lt;sup&gt;1&lt;/sup&gt;</td>
<td>71.1%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 in 121&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 in 117&lt;sup&gt;1&lt;/sup&gt;</td>
<td>90.6%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 in 1061&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1 in 35&lt;sup&gt;1&lt;/sup&gt;</td>
<td>94.9%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 in 632&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
## What does negative mean?

### "2 + 0"

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Carrier Frequency</th>
<th>Current Detection Rate</th>
<th>Residual risk after negative result*</th>
<th>Enhanced detection rate with g.27134T&gt;G</th>
<th>Residual risk g.27134T&gt;G* negative</th>
<th>Residual risk g.27134T&gt;G* positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>1 in 41&lt;sup&gt;4&lt;/sup&gt;</td>
<td>90%&lt;sup&gt;1,4&lt;/sup&gt;</td>
<td>1 in 345&lt;sup&gt;4&lt;/sup&gt;</td>
<td>94%</td>
<td>1 in 580&lt;sup&gt;4&lt;/sup&gt;</td>
<td>^Likely Carrier&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Asian</td>
<td>1 in 53&lt;sup&gt;1&lt;/sup&gt;</td>
<td>92.6%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 in 628&lt;sup&gt;1&lt;/sup&gt;</td>
<td>93.3%</td>
<td>1 in 702&lt;sup&gt;4&lt;/sup&gt;</td>
<td>^Likely Carrier&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>African American</td>
<td>1 in 66&lt;sup&gt;1&lt;/sup&gt;</td>
<td>71.1%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 in 121&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>1 in 396&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1 in 34&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 in 117&lt;sup&gt;1&lt;/sup&gt;</td>
<td>90.6%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 in 1061&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>1 in 1762&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1 in 140&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1 in 35&lt;sup&gt;1&lt;/sup&gt;</td>
<td>94.9%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 in 632&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>1 in 769&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1 in 29&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Options for Carrier Testing

• Single gene testing
  — Testing for one condition
  — Also referred to as known familial mutation testing

• Targeted carrier screening
  — Testing based on your ethnicity or family history
  — Also referred to as ethnic-based carrier screening

• Expanded carrier screening
  — Many disorders are screened for using a single sample
  — Test selection is done without regard to race or ethnicity
  — Each company determines the genes on their panel
  — Screening panels usually focus on severe disorders that affect a person’s quality of life from an early age
ACOG Recommends Offering Additional Carrier Screening to All Women, Regardless of Ethnicity or Family History

February 27, 2017

Washington, DC – In recognition of how critical genetic testing is in preparing for and managing a successful pregnancy, The American College of Obstetricians and Gynecologists (ACOG) has expanded guidelines on carrier screening in two new Committee Opinions released today.

In the past, ACOG recommended carrier screening—genetic testing that determines whether an asymptomatic person has a genetic mutation or abnormalities associated with a particular disorder that may be passed on to children—based primarily on ethnicity. The focus was on specific ethnic populations with known increased risk for particular disorders. ACOG’s two new Committee Opinions go beyond previous guidance to broaden who should be screened and for which genetic disorders.

The new guidance recommends each provider or practice establish a standard approach for ethnic-specific, pan-ethnic—meaning all women—or expanded carrier screening. In addition to existing guidance recommending universal screening for cystic fibrosis, all women should also be offered screening for spinal muscular atrophy (SMA), as well as a complete blood count to assess risk of hemoglobinopathy.

“Genetic conditions, including SMA, are not limited to one ethnic group. And certain conditions are common enough that it’s essential offer screening for them in every patient,” said Committee Opinion author Joseph R. Biggio Jr., MD, director of the Division of Maternal Fetal Medicine at the University of Alabama at Birmingham. “A growing number of Americans are also of mixed or uncertain ethnic backgrounds, which means we may not identify some people who are at risk of passing genetic conditions to their children when we follow ethnic-based recommendations.”
Carrier Testing

• Allows for more informative preconception counseling
  - Reproductive risks for the couple
  - Discussion of preimplantation/prenatal testing options
  - Development of PGD for your family

• Provides information to family members
  - Who should be tested
  - What testing do they need
Resources

• Genetic Counselors on the Cure SMA Medical Advisory Board
  − Jin Yun (Helen) Chen, Massachusetts General Hospital
  − Khalida Liaquat, Quest Diagnostics
  − Melissa Gibbons, Children’s Hospital Colorado

• National Society of Genetic Counselors
  —NSGC.org
Part 3: Reproductive Options for SMA Families

Harvey J. Stern MD, PhD
Director, Reproductive Genetics
Genetics & IVF Institute
Workshop Goals

What are the genetic aspects of SMA especially as they relate to reproduction?

What are the reproductive choices for families at-risk for SMA?
RECESSIVE DISEASE

Unaffected
"Carrier"
Father

Unaffected
"Carrier"
Mother

Unaffected
1 in 4 chance

"CARRIER"
Unaffected
1 in 4 chance

"CARRIER"
Unaffected
1 in 4 chance

Affected
1 in 4 chance
Reproductive Options for SMA Families

Very difficult decisions about family building
Reproductive Options for SMA Families

• Decisions regarding childbearing are personal and reflect our own ethical, moral and religious views. This is not a “one size fits all” type of issue.

• Couples who are at-risk for a genetic disorder should be allowed to make up their own minds after considering all their reproductive options.
Reproductive Options for SMA Families

• Decisions are influenced by the couple’s experience with SMA. Those who have had a child or sib affected will react differently from a couple identified to be at-risk by genetic screening.

• Decisions are also influenced by couple’s attitudes towards prenatal diagnosis and assisted reproduction (“playing God”)
Reproductive Options for SMA Families

Most families do not wish to bring another child with SMA into the world.
Reproductive Options for SMA Families

- Have no or no more children (Most Common Choice)
- Adoption
- Use a gamete donor (pre-tested for SMA)
Reproductive Options for SMA Families

- Natural conception with 1\textsuperscript{st} or 2\textsuperscript{nd} trimester prenatal testing.
- Preimplantation Genetic Diagnosis
What is PGD?

- Involves the use of assisted reproduction technologies (IVF) to provide a method of prenatal diagnosis.

- Offers an alternative to traditional methods of prenatal diagnosis including chorionic villous sampling and amniocentesis, with the option of termination of affected pregnancies.
Development of PGD

• This year represents the 28th anniversary of the first application of PGD in humans.
  —(Handyside et al. Nature 244 1990)
• Since 1990, approximately 400,000 PGD cycles have been performed worldwide.
• This has resulted in over 100,000 PGD babies born after the procedure.
PGD for Genetic Disease

Transfer unaffected embryos to the patient
In-Vitro Fertilization (IVF)
Questions About PGD

Why do I need to do IVF, I have no trouble getting pregnant?
Questions About PGD

- IVF is used to increase the odds of producing a healthy child.
- There is no change in the genetic material (egg or sperm).
- By creating multiple embryos, one increases the chance that good quality embryos which are not affected with SMA will be present and available to be returned to the uterus.
IVF Procedure
IVF/PGD Procedure

Components of IVF/PGD Cycle:

1. Down-regulation (preparation)
2. Ovarian Stimulation - FSH
3. Egg Retrieval
4. Fertilization (ICSI)
5. Embryo biopsy and testing
6. Embryo transfer to uterus
Parts Of An IVF Cycle

1. Cycle Preparation
2. Ovarian Stimulation
3. Egg Retrieval
4. Fertilization and Development
5. Embryo Transfer
6. Luteal Phase Support
7. Pregnancy Surveillance

IVF Timeline

Cycle Day
Normal Ovulation
Embryo Development

Adapted from Moore and Persaud, Saunders, 1993
Natural fertilization

1. Egg maturation
   An egg matures in the ovary.

2. Ovulation
   The egg is released and starts its migration to the uterus.

3. Fertilization
   One sperm fertilizes the egg. A reaction in the egg blocks other sperm from entering.

4. Cell division
   The fertilized egg starts dividing and is now called an embryo.

5. Implantation
   The embryo attaches to the mucosa in the uterus, where it continues to develop.

IVF

1. Egg isolation
   Then: Laparoscopy, Near: Ultrasound and thin needle

2. Fertilization
   Sperm is added to fertilize the egg.

3. Implantation
   When the egg has divided a few times, it is transferred back to the uterus where the egg attaches to the mucosa.

IVF is used when sperm and egg cannot meet under normal conditions. Common causes include obstructed fallopian tubes, too few eggs or impaired production of sperm.
IVF: Monitoring Visit

Days of FSH Stimulation

Follicle measurement

Estradiol levels

Ovary
Stimulated Ovary
Egg Retrieval
Egg Aspiration
Egg Ready For Fertilization
Fertilization by Intracytoplasmic Sperm Injection

ICSI
Embryo Development

- 2 cell
- 3 cell
- 4 cell
- 8 cell

Embryo Development

Embryo Transfer
PGD for Single Gene Disorders

- Analysis involves whole genome amplification with multiplex PCR amplification of the mutation along with 3-4 linked polymorphic markers which generate a chromosomal haplotype.

- At the same time, the embryos are also tested by a chromosomal microarray for abnormalities (ie. Down syndrome) which can lead to failed implantation or pregnancy loss.
PGD for SMA

Embryo Biopsy

SMN 1 & 2 = unaffected

SMN 2 only = affected

SMN gene
<table>
<thead>
<tr>
<th>Sample File</th>
<th>Sample Name</th>
<th>Panel</th>
<th>OS</th>
<th>SQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emb4Blst1 SMN1 D02 2011-02-07.fsa</td>
<td>Emb4Blst1 SMN1</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SMN 1 & 2**

<table>
<thead>
<tr>
<th>Sample File</th>
<th>Sample Name</th>
<th>Panel</th>
<th>OS</th>
<th>SQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emb2Blst1 SMN1 H01 2011-02-07.fsa</td>
<td>Emb2Blst1 SMN1</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NO SMN1**

**Affected**
<table>
<thead>
<tr>
<th>Genomic Position</th>
<th>Mother of Wife (Normal)</th>
<th>Father of Wife (Carrier)</th>
<th>Father of Wife (Normal)</th>
<th>Father's Wife (Carrier)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D5S2019 (67.8 Mb)</td>
<td>132</td>
<td>134</td>
<td>134</td>
<td>134</td>
</tr>
<tr>
<td>D5S629 (68.4 Mb)</td>
<td>187</td>
<td>185</td>
<td>185</td>
<td>185</td>
</tr>
<tr>
<td>SMN1 5q13.2 (70.2 Mb)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>DEL</td>
</tr>
<tr>
<td>D5S610 (71.0 Mb)</td>
<td>120</td>
<td>110</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>D5S637 (71.2 Mb)</td>
<td>137</td>
<td>139</td>
<td>139</td>
<td>139</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>cent</th>
<th>Father of Husband (Carrier)</th>
<th>Father of Husband (Normal)</th>
<th>Father's Husband (Carrier)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D5S2019 (67.8 Mb)</td>
<td>149</td>
<td>151</td>
<td>138</td>
</tr>
<tr>
<td>D5S629 (68.4 Mb)</td>
<td>193</td>
<td>199</td>
<td>195</td>
</tr>
<tr>
<td>SMN1 5q13.2 (70.2 Mb)</td>
<td>N</td>
<td>N</td>
<td>DEL</td>
</tr>
<tr>
<td>D5S610 (71.0 Mb)</td>
<td>132</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>D5S637 (71.2 Mb)</td>
<td>133</td>
<td>133</td>
<td>135</td>
</tr>
</tbody>
</table>
24 Chromosome Analysis by Microarray

Performed concurrently with SMA testing to identify the embryos with the best potential to make a baby as well as being free of SMA.
Accuracy of PGD

- Using the combination of mutational analysis and linked markers the accuracy of the test 98-99%.
- Contamination with external DNA is a major concern.
- Analyses done in surgical clothing in biohazard hood.
Specific Issues with IVF/PGD

- Patient Discomfort: Medications are given by injection (subQ).

- Abdominal distention and discomfort and some nausea are common.

- Egg retrieval done under anesthesia.

- Ovarian hyperstimulation syndrome 1-2%.
Questions about IVF/PGD

• Is IVF Safe?
• What will I feel?
• Does it increase cancer risk?
• Are the babies born normal?
• What are the costs?
• What about insurance?
Questions About IVF/PGD

What is the success rate of IVF/PGD?

- Varies, particularly with maternal age, but in large series 50-60% of patients became pregnant per IVF/PGD cycle.

- Improved with concurrent testing for chromosome abnormalities.
Thank you!!!