The Role of Genetic Testing in Family Planning & Pregnancy

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The pathway for genetic testing in family planning and pregnancy

- **Family history of genetic disease**
  - Understanding your risk of an affected child.
  - Options for prevention

- **No known family history of genetic disease**

  Genetic testing **before** becoming pregnant:
  - Reproductive carrier screening

  Genetic testing **during** pregnancy:
  - First trimester screening
  - Diagnostic tests

All types of genetic testing for family planning or during pregnancy are optional.
Tom and Sandra are planning to start a family, however Tom is nervous because he has recently been diagnosed with retinitis pigmentosa, a condition which is causing him to gradually lose his vision.
Meet Tom and Sandra

No known family history of genetic disease

Understanding your risk of an affected child.

Options for prevention

Genetic testing before becoming pregnant:
- Preconception carrier screening

Genetic testing during pregnancy:
- First trimester screening
- Diagnostic tests

Retinitis pigmentosa is a complicated condition because it can also be inherited in different ways.
Autosomal Recessive Inheritance Pattern

DAD IS AFFECTED
MUM IS NOT A CARRIER

WORKING GENE
NON-WORKING GENE

ALL CHILDREN WILL BE UNAFFECTED, BUT CARRIERS OF THE CONDITION
Autosomal Recessive Inheritance Pattern

DAD IS AFFECTED
MUM IS A CARRIER (not affected)

WORKING GENE
NON-WORKING GENE

CHILDREN DO NOT HAVE THE CONDITION
CHILDREN HAVE THE CONDITION
50% OF CHILDREN DO NOT HAVE THE CONDITION
50% OF CHILDREN HAVE THE CONDITION

Common Inheritance Patterns

Autosomal Dominant

Autosomal Recessive
X-Linked Recessive Inheritance
Father has the Condition

DAD HAS THE CONDITION
MOM DOES NOT HAVE THE CONDITION

X CHROMOSOME WITH WORKING GENE
X CHROMOSOME WITH NON-WORKING GENE

ALL SONS DO NOT HAVE THE CONDITION
ALL DAUGHTERS ARE CARRIERS BUT DO NOT HAVE THE CONDITION

*There are exceptions to this. Some female carriers of X-linked recessive conditions may have symptoms. One example of this is fragile X syndrome.

Common Inheritance Patterns

Autosomal Dominant
Autosomal Recessive
X-Linked Recessive
Tom books in to see a genetics team, meeting with a genetic counsellor and clinical geneticist to discuss his options for genetic testing and family planning. They first ask about his family history:

![Family Tree Diagram]

- **Tom's Grandad**: Diagonal square indicating a genetic condition
- **Tom's Dad**: Square indicating a genetic condition
- **Tom**: Male
- **Sandra**: Female
Next the genetics team discusses what options are available for Tom to try to identify the genetic variant that has caused his Retinitis Pigmentosa.
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Each pair of books represents a pair of chromosomes.
Next the genetics team discusses what options are available for Tom to try to identify the genetic variant that has caused his Retinitis Pigmentosa.

Each chapter represents one gene. A gene is a set of instructions for one thing that our body needs.

Chapter 1: RHO Rhodopsin
Forms part of the light sensing cells at the back of the eye

Single Gene Test
Next the genetics team discusses what options are available for Tom to try to identify the genetic variant that has caused his Retinitis Pigmentosa.

Many chapters often work together to ensure that our body is functioning correctly.

**Chapter 1: RHO Rhodopsin**
- Forms part of the light sensing cells at the back of the eye

**Chapter 2: USH2A Usherin**
- Helps support and maintain the light sensing cells

**Multi-Gene (Panel) Test**
Next the genetics team discusses what options are available for Tom to try to identify the genetic variant that has caused his Retinitis Pigmentosa.

Sometimes when a condition is not well understood or very rare, we might need to look at all the chapters to find an answer.

Whole Exome/Genome Sequencing
There are different types of results that Tom can expect from his testing:

- **We find the genetic variant that is causing Tom’s condition.** This result can be used to help estimate risk for a future pregnancy.
- **We find a variant of uncertain significance.** We don’t have enough information to know if this variant might be causing Tom’s condition and therefore this result does not provide information to help us understand risk for a future pregnancy.
- **We do not find the genetic variant that is causing Tom’s condition.** This result does not provide information to help us understand risk for a future pregnancy.

**How likely is it that we’ll find out what’s causing my condition?**

50-80% chance
Reproductive Carrier Screening

While at the clinic, Tom and Sandra talk about wanting to start a family and the team explain that they might want to also think about reproductive carrier screening.

Autosomal Recessive
- Both parents need to be carriers
- 25% chance of an affected child

X-Linked
- Only the mother needs to be a carrier
- Sons have a 50% chance of being affected
While at the clinic, Tom and Sandra talk about wanting to start a family and the team explain that they might want to also think about reproductive carrier screening.

A recent guideline from the Royal Australian & New Zealand College of Obstetricians and Gynaecologists (RANZCOG) recommends that reproductive carrier screening be offered to all women planning a pregnancy or in their first trimester.

- Because X-linked conditions are carried by the female partner, testing is usually started in her to look for both X-linked and recessive conditions.
- If she is found to be a carrier of a recessive condition, her male partner will be tested to see if he is a carrier of the same condition.
- Alternatively, couples can be tested at the same time.
While at the clinic, Tom and Sandra talk about wanting to start a family and the team explain that they might want to also think about reproductive carrier screening.

Target Screening:

Only looks at conditions that are common in those of particular ethnic backgrounds:

- For those of a Caucasian background, often three conditions (cystic fibrosis, spinal muscular atrophy, and fragile X) are tested
- For those of an Ashkenazi Jewish background more than 200 conditions that have an increased prevalence in their community may be tested.
While at the clinic, Tom and Sandra talk about wanting to start a family and the team explain that they might want to also think about reproductive carrier screening.

**Expanded Screening:**

Takes a much broader approach and looks at many hundreds of conditions in a single test:

- Applicable for an increasing pan-ethnic (diverse) population
- Covers many severe or life-limiting conditions
- Also includes some more variable conditions, where the outcome for a child may be difficult to predict.
- Some conditions may have implications for carriers
Making a Decision

Tom and Sandra discuss all their options and decide what testing they want to have.

- Multi-Gene Diagnostic Test
- Reproductive Carrier Screening
Sandra’s results are available first, let’s see what they are.

Reproductive Carrier Screening

Sandra’s result comes back with a negative result.

A negative result means there is only a small residual risk that Sandra is a carrier.

About 75% of patients are expected to receive a normal result like Sandra.

About 25% are expected to be identified as carriers of one condition. Some people will be identified as carriers of multiple conditions.

Of those identified as carriers, <1% of those are expected to have a partner that is a carrier of the same condition.
RHO is the most common cause of autosomal dominant RP. The chance that Tom will pass this onto his children is 50%.

Tom is found to have a pathogenic variant in RHO.

RHO is the most common cause of autosomal dominant RP.

The chance that Tom will pass this onto his children is 50%.

Tom’s results are now available first, let’s see what they are.
Tom has a 50% of passing Retinitis Pigmentosa onto his children. Let’s think about what Tom and Sandra need to know next...

What are our options?

- Natural conception without further testing
- Natural conception with testing during pregnancy
- IVF with preimplantation genetic diagnosis
- Sperm donor
- Adoption
Tom has a 50% of passing Retinitis Pigmentosa onto his children. Let’s think about what Tom and Sandra need to know next...

Retinitis pigmentosa is a condition that varies in severity, even within family members that have the same causative variant.

Therefore if a child does inherit Tom’s variant, there is no way to know how severely they may be affected.

Tom and Sandra need to make a personal decision about whether they think the condition is severe enough to consider their options for prevention.

Let’s explore what these options are...

- **Natural conception without further testing**

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**Natural conception with testing during pregnancy**

Testing during pregnancy serves two purposes.

1. Early diagnosis
   - Early intervention
   - Preparation for the birth of a child with special needs

2. Option for terminated an affected pregnancy

Differences in perspective may exist amongst medical professionals and within families regarding the termination of a pregnancy based on the diagnosis of retinitis pigmentosa.
Family Planning Options

If they decided to test during pregnancy they have two options to consider:

**Chorionic Villus Sampling (CVS)**
- Between 11-13 weeks

**Amniocentesis**
- From 15 weeks
Tom has a 50% of passing Retinitis Pigmentosa onto his children. Let’s think about what Tom and Sandra need to know next...

What are our options?

- **IVF with preimplantation genetic diagnosis**
  
  Pre-implantation genetic diagnosis involves testing a small number of cells from an embryo during the IVF process. Any affected embryos are not implanted.

  IVF, even if there are no existing fertility problems is still not guaranteed to succeed.

  Likely to be expensive
Tom has a 50% of passing Retinitis Pigmentosa onto his children. Let’s think about what Tom and Sandra need to know next…

What are our options?

- **Use a donor sperm**
  
  For many genetic conditions using a donor egg or sperm is an option.
  
  In particular, if the causative genetic variant isn’t known, would be the alternative to PGD.

- **Adoption**
  
  Couples that are at risk can consider alternative ways of forming a family, such as adoption.
From 12-14 weeks it is recommended to have a first trimester ultrasound to check early development.

Sandra is pregnant!
Sandra is pregnant!

First Trimester Screening

Accuracy 80-90%

Trisomy 21 Down Syndrome
Trisomy 18 Edward Syndrome
Trisomy 13 Patau Syndrome
Sandra is pregnant!

Non-Invasive Prenatal Screening (NIPS)

Sex chromosome variations include XXY, XXX, and XYY

Accuracy 99%
Diagnostic Testing

If there were any high risk results or concerns as the pregnancy progresses, invasive testing may be used as a diagnostic test.

Chorionic Villus Sampling (CVS)
- Between 11-13 weeks

Amniocentesis
- From 15 weeks

Microarray Panel Test
WGS

Figure 11.17a Genetics and Genomics in Medicine (© Garland Science 2015)
There is no test that gives a 100% guarantee of a healthy baby

Summary

- **No known family history of genetic disease**
  - Genetic testing before becoming pregnant:
    - Reproductive carrier screening
  - Genetic testing during pregnancy:
    - Nuchal translucency
    - NIPS
    - CVS
    - Amniocentesis

- **Family history of genetic disease**
  - Understanding your risk of an affected child:
    - Single gene test
    - Multi-gene panel
    - Whole genome sequencing
  - Options for prevention:
    - IVF with PGD
    - Prenatal diagnosis
Resources are available on www.genetics.edu.au or by contacting:

The Centre for Genetics Education NSW Health
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Thank you!