The emerging new paradigm in pregnancy care. Reproductive Genetic Carrier Screening: a review of 12,000 cases shows high clinical utility.

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MCRI

Not-for-profit subsidiary of Murdoch Children’s Research Institute at Royal Children’s Hospital

Comprehensive laboratory and clinical genetics service

Key role in research and development, translational research, and policy development

Service provider for public & private Non-invasive Prenatal Testing & carrier screening in New Zealand
Population screening programs

1960-70's
- Newborn screening
  - Severe childhood onset metabolic conditions
  - Interventions can result in normal/greatly improved development outcomes
  - >20 conditions screened for in Aus and NZ - government funded programs

1970’s
- Haemoglobinopathies
  - Mediterranean countries. Ad hoc reproductive screening

1980’s
- Tay-Sachs (1970’s internationally)
  - School age screening within local Ashkenazi Jewish comm.
  - 2003 nation wide program in Israel - 90% reduction in Tay-Sachs

1990-2012
- Maternal serum screening/NIPT
  - 2nd trimester, CFTs and Non-invasive prenatal testing

2005
- Cystic fibrosis
  - Population based reproductive screening

2013
- Reproductive Genetic Carrier Screening
  - Fragile X syndrome and spinal muscular atrophy

2015
- Expanded screening
  - 100’s of autosomal recessive and X-linked genetic conditions
Carrier screening - the shifting landscape

April 2015

Consensus-based recommendation: Where available, screening of low risk women for carrier status of the more common genetic conditions (e.g. cystic fibrosis, spinal muscular atrophy, fragile X syndrome) may be offered.

“Every baby is at a small risk of having a chromosomal or genetic condition. Prenatal screening for some chromosomal conditions is offered in maternity care to provide the pregnant woman with more information about her unborn baby. All such testing should be voluntary and only undertaken when the pregnant woman has been informed about the nature of the screening test, the possible result, and the option available to her.”

March 2017

All patients who are considering pregnancy or are already pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for cystic fibrosis and spinal muscular atrophy, as well as a complete blood count and screening for thalassemia's and hemoglobinopathies.
Screening guidelines
ACMG, ACOG, ECHG, RANZCOG

Disorders
- Approx. 2000 known recessive conditions
- Should be childhood onset
- Severe (cognitive disability, life shortening)
- Clinically actionable (alter pregnancy management)
- Relative high frequency

Test
- Should have high specificity
- Accurate
- Etiology of disorder well defined
- Ideally the ethnic prevalence is known

Support
- Increasing research supports population based screening
- Special interest groups support testing
- Families are strongly advocating to include information about screening prior to pregnancy
Changing expectations

"We are broken by our new reality"

Lobbying for pre-birth & newborn screening
2012 VCGS – Reproductive Genetic Carrier Screening

Laboratory
- Cystic fibrosis (CF)
- Spinal muscular atrophy (SMA)
- Fragile X syndrome (FXS)

Clinical
- Pre and post test genetic counselling
- Specialist paediatricians
- Prenatal diagnostic testing
- Education for health professionals
CF is a condition affecting breathing and digestion. Requires life long physiotherapy and hospital visits. Shortened life span (30-40).

SMA is a condition that affects nerves in the spinal cord and causes muscles to get weaker. SMA type 1 is the most severe. Babies with SMA type 1 usually do not live past 2 years of age.

FXS is the most common cause of inherited intellectual disability. People with FXS can have developmental delay, learning difficulties, anxiety, autism and epilepsy. Males are more severely affected than females. Some female carriers have early menopause.
### Carrier frequencies and detection rates

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of people who are carriers</th>
<th>No. of people with the condition</th>
<th>Detection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>1 in 25</td>
<td>1 in 2000-2500</td>
<td>90%</td>
</tr>
<tr>
<td>SMA</td>
<td>1 in 40</td>
<td>1 in 6000-10000</td>
<td>95%</td>
</tr>
<tr>
<td>FraX</td>
<td>1 in 250-350</td>
<td>1 in 4000</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

Many people are carriers of CF, FXS or SMA even though they do not have anybody in their family who has the condition.
Female partner screened

- "Low risk" result for all three conditions
  - No further action

- "carrier" result
  - Genetic counselling
    - CF and/or SMA carrier
      - Test partner
        - Partner "low risk" result
          - Option of Prenatal Diagnosis or PGD. Appointment with specialist paediatrician
        - Partner "carrier" result
          - Carrier testing for relatives
            - CF and SMA 1 in 4 FraX up to 1 in 2
  - Fragile X carrier

12,000 RGCS referrals

Carriers detected (n=605)

- 340, 56% (1 in 35)
- 233, 39% (1 in 49)
- 32, 5% (1 in 340)

Carriers detected (n=605):
- CF
- FraX
- SMA

1 in 20
Referrers

69% pregnant at time of testing

- Obstetricians: 55%
- Fertility specialists: 17%
- Obs/Fertility: 16%
- Genetics specialists: 8%
- General Practitioners: 4%

Leaders in Genetic Health
Partner Testing

CF and SMA partner testing (577)

- 537 (94.7%) tested
- 20 (3.5%) unknown
- 10 (1.8%) not tested

Reasons partners not tested:
- No partner
- Partner declined testing
- Ethnicity of partner
- Partner result would not change pregnancy plan
High risk couples & affected pregnancies

High risk couples
- CF: 35
- SMA: 1
- FraX: 1

Pregnant high risk couples
- CF: 21
- SMA: 9
- FraX: 1

Affected pregnancies
- CF: 2
- SMA: 1
- FraX: 4

1 in 240
1 in 1000
Prior known family history

The common misconception

- Carrier individuals: 88.4%
- High risk couples: 74.0%
- Affected pregnancies: 85.7%

No FH | Known FH
Clinical utility of carrier screening

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>T21 live birth frequency</th>
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<tbody>
<tr>
<td>15 - 19</td>
<td>1 / 1250</td>
</tr>
<tr>
<td>20 - 24</td>
<td>1 / 1400</td>
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<tr>
<td>25 - 29</td>
<td>1 / 1100</td>
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<tr>
<td>30 - 31</td>
<td>1 / 900</td>
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<tr>
<td>32</td>
<td>1 / 750</td>
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<tr>
<td>33</td>
<td>1 / 625</td>
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<tr>
<td>34</td>
<td>1 / 500</td>
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<td>35</td>
<td>1 / 350</td>
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<td>42</td>
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<tr>
<td>43</td>
<td>1 / 50</td>
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<tr>
<td>44</td>
<td>1 / 40</td>
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<tr>
<td>45 and older</td>
<td>1 / 25</td>
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</tbody>
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Carrier screening for CF, SMA, FraX

Expanded panels

All women offered maternal serum screening or NIPT (post 2000)

All women offered diagnostic testing (pre 2000)
A digital revolution

Next generation sequencing
Next Generation sequencing

Where to Next – personalised medicine

Screening
- NIPT
- Carrier status for a greater number of recessive diseases

Diagnostic testing for complex presentations
- Known phenotypes (many genes – cardiac)
- Undiagnosed phenotypes – cong. abnormalities
- Predictive testing for individuals with family histories

Assessment & Monitoring:
- Acquired abnormalities – liquid biopsy
- Monitoring of relapse and treatment

Assessment of human variation
- Pharmacogenomics
- Lifestyle genomics

The future:
- Replacing new born screening
- Health care on a stick – targeted analysis of stored data
Most carries, high risk couples and couples with an affected pregnancy have no known family history.

Recessive genetic conditions individually rare, but combined have risks akin to Down syndrome.

Availability of genetic counselling is an important part of any program.

Professional bodies are now recommending patients be made aware of carrier screening.

Testing for recessive conditions is likely to become a part of standard pregnancy care.
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