Population carrier screening for fragile X syndrome

Attitudes and experiences of women undergoing screening

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Arguments for population screening for FXS

• Most common known cause of inherited intellectual disability
• Significant impact on people with FXS and their families
• Molecular testing is accurate, rapid and inexpensive
• Options for prevention and interventions available

\(^1\text{Hill, M.K., Archibald, A.D., Cohen, J., Metcalfe, S.A. 2010.}\)
Carrier screening for FXS

• Reproductive risk for female carriers
  – 50% risk of passing expanded allele to child
  – Risk of expansion from PM to FM varies

• Health concerns for PM carriers
  – Primary ovarian insufficiency (FXPOI)
    • Fertility problems
    • 20% risk of early menopause (before 40 yrs)
Carrier screening - current recommendations

- **Guidelines**\(^1,^2,^3\)
  - **Carrier testing for:**
    - Family history of FXS or undiagnosed intellectual disability
    - Reproductive or fertility problems
    - Late onset tremor or cerebellar ataxia of unknown origin

- **Limitations of family history based approach**
  - Dissemination of genetic risk information in families\(^4\)
  - Relies on diagnosis of affected relative
  - Many people do not have a family history of FXS or related conditions

- **ACOG recommendations (2010)**\(^5\): offer to any woman who requests FXS carrier testing regardless of family history

>>> Is population screening for female carriers an option?

\(^1\)Sherman et al, 2005; \(^2\)McConkie-Rosell et al, 2005; \(^3\)HGSA, 2003; \(^4\)van Rijn, 1997, \(^5\)ACOG, 2010
Population carrier screening for FXS

• Support for population carrier screening for FXS

• Women offered screening may be unprepared for a carrier result (NB No preparation time)

• Families support offering carrier screening for FXS

• Development of screening programs requires the consideration of:
  • Community views about screening
  • Practicalities of offering screening

Our research to date

1. Pilot study\textsuperscript{1,2}
   • Offered FXS carrier screening to non-pregnant women
   • Study setting: a sexual and reproductive health clinic

   FINDINGS:
   - Interested in screening
   - Good knowledge
   - Few participants regretted their decision
   - Uptake of testing dependent on:
     - reproductive stage of life
     - practicalities of having the test

2. Needs assessment\textsuperscript{3}
   • Explored views of key stakeholders
     • General population
     • Health professionals
     • Families impacted by FXS

   FINDINGS:
   - Lack of awareness about FXS and the implications of genetic screening
   - Important to offer all women the \textit{choice} to have screening
   - Screening should ideally be offered to non-pregnant women
   - Screening should be offered in primary healthcare settings
   - Women should be supported to make an informed decision

\textsuperscript{1}Metcalfe et al, 2008; \textsuperscript{2}Archibald et al, 2009, \textsuperscript{3}Archibald et al, 2012 – \textit{in press}
Developing our screening protocol

1. Exploring views of staff and patients
2. Development of information materials and questionnaires
3. Pilot carrier screening study (Metcalfe et al, 2008)
4. Exploring views of key stakeholders
5. Refinement of study protocols and materials
6. Large carrier screening study (NHMRC funded)
Current project

- Carrier screening generally perceived to be acceptable
- Need to support women to make informed decisions
- Need to determine how best to offer screening with impact
- Stages of life at which screening could be offered:

<table>
<thead>
<tr>
<th>Before pregnancy</th>
<th>Pregnancy</th>
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<tbody>
<tr>
<td>Time for decision-making</td>
<td>Less time for decision-making</td>
</tr>
<tr>
<td>More reproductive options</td>
<td>Limited reproductive options</td>
</tr>
<tr>
<td>More difficult to access target population</td>
<td>Easy to access target population</td>
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The fragile X syndrome carrier screening study
NHMRC 3yr multi-site attitudinal survey

Aims:
1. To compare informed decision-making by pregnant and non-pregnant women offered carrier screening for FXS
2. To compare uptake and predictors of uptake in pregnant and non-pregnant women offered carrier screening for FXS
3. To undertake an economic appraisal involving: (i) a trial-based cost-effectiveness analysis linking costs with trial outcomes; and (ii) an assessment of the value placed on the information provided using Willingness-To-Pay methods
Screening offered in primary healthcare settings

- Victoria and Western Australia
- non-pregnant women in GP clinics
- early pregnancy in obstetric/ultrasound clinics
- take-home information pack, buccal sample, new screening test
- brochure, website (videos), questionnaires
Providing information

- Healthcare staff upskilled
- Genetic counsellor on site and per telephone
- Brochures - validated
- www.fragilexscreening.net.au
- Time to prepare between info and test
- Follow up interviews
Data collection

• Questionnaires
  – Socio-demographic
  – Informed decision-making (knowledge, attitudes, deliberation, health beliefs, decision-making process)
  – DASS (depression, anxiety, stress); STAI
  – Willingness-to-pay
  – Decision satisfaction/ regret

• Interviews
  – Informed decision-making (as above)
  – Factors influencing decision
  – Experience of program (women and clinic staff)
Preferred recruitment models can be tailored for each clinic.

**Invitation to potential participants**

- **Decline**
  - Ask reasons
- **Accept**
  - Participant speaks with research genetic counsellor

**Decide at home whether or not to have test**

- **Yes**
  - Complete Q1
  - Collect DNA sample (saliva kit) & send to lab
  - Positive result
    - Referral for genetic counselling
  - Normal result
    - Result letter posted

- **No**
  - Complete Q1
  - 1 month follow up:
    - Participants complete Q2
    - Interviews with sample of women

**Interviews with sample of women** (tested and not tested)

**Referral for genetic counselling**

**Interviews with clinic staff**
Data at end May 2012

Recruited
n = 803
(690 non-pregnant; 113 pregnant)

Awaiting return of study packs
n = 20
(all pregnant)

Made decision
n = 625
(540 non-pregnant; 85 pregnant)

Actively withdrawn
n = 52
(49 non-pregnant; 3 pregnant)

Q1 never returned
n = 106
(101 non-pregnant; 5 pregnant)

Accepted test
n = 523 ~70%
(449 non-pregnant: 70%; 74 pregnant)

Not tested
n = 102 actively declined
(91 non-pregnant; 11 pregnant)

Normal
n = 505

Grey Zone
n = 10

Premutation
n = 2

Awaiting test result
n = 6
Considerations for population carrier screening for FXS

- Most women offered screening will have limited/no knowledge or experience of FXS
  - Providing appropriate information is essential
  - Emphasise family history not necessary to be a carrier
- Women may need support in making a decision about screening
  - Providing pre-test genetic counselling is important
- Women may be unprepared for a carrier result
  - Allow appropriate time between info and test
  - Genetic counselling essential if carrier test positive
- Molecular test
  - Traditional PCR ± Southern blot
  - New screening test
Considerations for population carrier screening for FXS

• Offering carrier screening in primary healthcare settings is feasible provided:
  – Appropriate information/training for health professionals
  – Clinic staff are well informed (including practice manager)
  – There is good communication between the coordinators of the screening program and the clinics

• Challenges of carrier screening in pregnancy include:
  • Ensuring prompt test turnaround time
  • Managing anxiety
  • Limited reproductive choices
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