LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to answer the following questions:

- What is (genetic) screening?
- Why genetic screening?
- Genetic screening: whom to screen?
- What to screen for?
- Pros and cons of genetic screening (in ART)

DISCLOSURE

- I am an academic
  - Therefore my salary is paid by the Belgian tax payer
- I am an MD but I do not practice medicine
  - Therefore I have no contacts with industry
- I have no commercial interests in assisted reproduction or genetic testing
  - I head a research lab separated from CRM
  - IVF and genetic testing is covered by Belgian health insurance
- I have no conflicts of interest
What is (genetic) screening?

- 24–30 variants per genome are implicated in rare disease
- Current estimate: 10,000 monogenic human diseases
- Global prevalence of single gene disorders is 10/1000 – 1%
- Monogenic diseases may account for up to 40% of hospital-based paediatric practice
- US lifetime direct medical costs
  - Hemophilia A: 12 million $
  - Cystic Fibrosis: 1.8 million $
  - Sickle cell anemia: 750,000$

Wilson and Jungner, 1968

What is (genetic) screening?

1. The condition sought should be an important health problem
2. Accepted treatment for patients available
3. Facilities for diagnosis and treatment should be available
4. There should be a recognisable symptomatic stage
5. There should be a suitable test or examination
6. The test should be acceptable to the population
7. The natural history of the condition should be understood
8. There should be an agreed policy on whom to treat
9. The cost should be economically balanced
10. Case-finding should be a continuing process

Wilson and Jungner, 1968

What is (genetic) screening?

- Newborn screening well developed, eg PKU
- Genetic carrier screening expands definition of screening:
  - a medical investigation to detect carrier status (not disease status) for a recessive disorder in a couple or a person
  - It determines a couple's risk of having a child with a recessive inherited disorder, thereby facilitating reproductive choices
- Genetic carrier screening previously, eg ACOG and ACMG panels
  - Focused on one disease
  - Focused on ethnic groups with high prevalence
  - Premarital, preconception or prenatal

World health organization, ACOG panel
Tay-Sachs disease

- Mutations in HEXA
- Autosomal recessive
- Lysosomal storage disorder, affects neurons
- Infants appear normal until 3 to 6 months, when their development slows, and progressively regress
- Life expectancy: early childhood

Thalassaemia and sickle cell anemia

- Mutations in hemoglobin
- Autosomal recessive
- Anemia results in fatigue, weakness, abdominal swelling, joint and bone pain
- Regular blood transfusion and iron chelation therapy, bone marrow transplant

Cystic fibrosis

- Mutations in CFTR
- Autosomal recessive
- Thick mucus, affects lungs and digestive track: infections, failure to thrive
- Life expectancy: 37 years
Fragile X syndrome

- Mutations in FMR1
- X-linked dominant
- FMRP is involved in synapse formation
- Causes mild to severe intellectual disability: delay in talking, anxiety and hyperactive behaviour
- Normal life span

Differences across populations

Ashkenazi Jews: bottleneck of 350 individuals, 600-800 years ago

Hemoglobin disorders and malaria

Carrier screening programs

Ashkenazi Jews

11 disorders, 20-25% chance of being carrier for at least one
They do not provide carrier status, but compatibility testing

Thalassemia testing is mandatory in
- Cyprus
- Iran
- Palestine
- Turkey (33 provinces)
- Saudi Arabia
Impact of such programs

Why Expanded Carrier Screening?

- Inaccurate knowledge of ancestry in an increasing multiethnic society
- Limits amount of genetic information available for participants
- Genetic conditions are not limited to specific ethnic groups

Edwards et al., 2015

Why Expanded Carrier Screening?

- Modelling using 346,790 screenings, 94 single-gene disorders
- 0.94-3.92% of conceptions would be affected
- Screening using ACOG and ACMG guidelines only, misses between 55 and 94% of affected pregnancies

JAMA. 2016;316(7):734-742; figure courtesy of A. Veiga
Why expanded carrier screening?

1:550 pregnancies will be affected by one of these 94 diseases.

- Down syndrome: 1:700 births
- Neural tube defects: 1:1000 births
- Cystic fibrosis: 1:3500 births

Residual risk

Cystic Fibrosis Detection and Carrier Rates Before and After Testing

<table>
<thead>
<tr>
<th>Racial or Ethnic Group</th>
<th>Detection Rate* (%</th>
<th>Individual Carrier Risk Before Testing</th>
<th>Approximate Individual Carrier Risk After Negative Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>94</td>
<td>1/59</td>
<td>1/290</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>88</td>
<td>1/56</td>
<td>1/290</td>
</tr>
<tr>
<td>Hispanic white</td>
<td>72</td>
<td>1/58</td>
<td>1/290</td>
</tr>
<tr>
<td>African American</td>
<td>84</td>
<td>1/61</td>
<td>1/170</td>
</tr>
<tr>
<td>Asian American</td>
<td>49</td>
<td>1/64</td>
<td>1/140</td>
</tr>
</tbody>
</table>

*Detection rate data based on use of a 23 mutation panel.

Why expanded carrier screening?

- To increase reproductive autonomy
  - creating awareness of carrier status
  - creating awareness of the reproductive options available
  - ‘maximising meaningful choices’
  → preferably preconception
- Reproductive options available:
  - Refrain from having children
  - Adoption
  - “Take the chance”
  - Prenatal diagnosis
  - Use of gamete donors
  - Preimplantation genetic diagnosis

www.acog.org
ACOG Recommendation 690 (2017)

- ECS does not replace risk-based screening recommendations!
- ECS is acceptable for preconception and prenatal carrier screening
- After counselling, a patient may decline any or all carrier screening
- Minimal screening: CF, SMA, hemoglobinopathies
- FRAXA and additional screening if indicated
- Patient counselling re. residual risk
- Genetic counselling re. reproductive options indicated in carrier couples

Disorders to be selected:
- A carrier frequency of ≥ 1/100
- A well-defined phenotype
- A detrimental effect on quality of life: cause cognitive or physical impairment, require surgical or medical intervention, have an early onset
- Be able to be detected prenatally, possible antenatal intervention, changes in delivery management, parents’ education
- Panel should NOT include conditions with adult onset

ESHG Recommendations (2016)

1. For couples or individuals without a known risk of recessive disorder to inform them of genetic risk and reproductive options
2. For a comprehensive set of severe childhood-onset disorders with high clinical validity and clinical utility, reporting sequence variants with affected function (clinical significance)
3. Acceptable evidence base on significance, sensitivity and specificity, costs, impact, types of interventions, public acceptability
4. Ideally preconception to maximise reproductive options
5. Assessment of effect on informed choice and reproductive decision making rather than reduced disease prevalence
ESHG Recommendations (2016)

6. Counselling pre-test if requested, post-test in carrier couples. Should include discussion of residual risk, reproductive option, consequences for relatives
7. “Generic” informed consent – to be evaluated
8. Voluntary participation knowing benefits, disadvantages, limitations and with equity of access
9. Provided by accredited genetic services and trained professionals
10. Guarantee of continued care regardless of reproductive choice
11. Professionals and public education and dialogue
12. Governance: implementation plan, quality control, systematic evaluation and oversight

Why expanded carrier screening in an ART population?

- ECS based on coding region or targeted NGS complemented with specific tests
- According to ACOG recommendations: 368 disorders (54 AD)
- Including pre- and post-test genetic counselling
- 1301 individuals
  - 483 oocyte donor candidates and 635 male partners of recipients
  - 105 women undergoing IVF with donated sperm
  - 39 couples in preconceptual context
- Oocyte donors carriers of X-linked disease were excluded
- Oocyte donors carriers of AR were matched to non-carriers

Abuli et al., 2016

- 733/1301 (56.3%) carriers of at least one pathogenic mutation
- 8/483 oocyte donors excluded as X-linked disease carrier
- 19/635 (3%) donor-recipient matches carrier of severe ARD
  - birth of affected child avoided in 0.75% of tested population
  - 532 couples need to be tested to avoid 1 affected birth

Abuli et al., 2016
Why expanded carrier screening in an ART population?

- ECD based on ACOG/ACMG recommendations: 623 diseases including AD
- All coding exons and flanking sequences of 548 genes complemented with specific tests
- 2570 individuals
  - 1170 gamete donors: 926 females, 244 males
  - 1124 partners of gamete recipients
  - 276 in 138 couples for ART
- 2161/2570 (84%) positive for at least one pathogenic variant
- 7/138 (5%) of couples with high risk – 2/7 X-linked

Martin et al., 2015

Why expanded carrier screening in an ART population?

- 4232 infertility patients self-reporting ethnicity
  - 2880 ♀, 1352 ♂
  - Comparing 3 panels:
    1. ACOG ethnicity-based guidelines
    2. ACOG 23 diseases list for ECS
    3. Counsyl 100 genetic diseases: 400 variants, 102 genes
- Plus Fragile X and SMA screening

Peyser et al., 2018

Why expanded carrier screening in an ART population?

- Carriers identified:
  - 359 (8.5%) with test 1 <
  - 659 (15.6%) with test 2 <
  - 1243 (29.4%) with test 3
- Same trend visible in all ethnic groups, except 3 groups with either small numbers or underrepresentation in test panel
- 15/1206 (1.2%) at risk couples identified through ECS (test 3)
  - 8/1206 would have been identified through test 1
  - All 15 couples went to PGT-M
- 73 women identified as FRAXA carrier

Peyser et al., 2018
Pros and Cons of expanded universal genetic screening

Three main arguments in favour:

1. ECS maximises autonomous reproductive choice
   a. Meaningful top-down implementation without sense of urgency in the population
   b. Informed choice complex nature of ECS
   c. Free choice reproductive responsibility ie pressure to undergo carrier screening and pressure to avoid birth of affected child
2. ECS means equity of access for whole population
   But may disadvantage ethnic groups with higher specific risks
3. ECS will reduce risk of stigmatisation
   But other possibilities such as information about carriership New stigma: AR = preventable disease

Van der Hout et al., 2019

Pros and Cons of expanded universal genetic screening

Pros

The ultimate aim of (ECS) is to increase the reproductive autonomy of individuals and couples...this autonomy paradigm is being increasingly challenged by the consideration of cost effectiveness

The individual and societal costs associated with caring for affected individuals outweigh the costs of ECS and PGT-M for these families

For PCS to be cost effective, a sufficiently high number of future parents should participate (...), and (... ) at risk couples identified (... ) need to alter their reproductive plans

Physicians who do not adopt PCS open themselves up to liability when it comes to (wrongful birth) lawsuits

Given that the merits and the limitations (... ) are (... ) debated, and in the absence of systematic screening offers (... ) we cannot say that medical professionals have an obligation to routinely offer PCS to their patients

Fertility Battle, F&S 2019

Pros and Cons of expanded universal genetic screening

Pros

PCS results have led to measurable changes in reproductive decision making...lower cost of ECS and higher cost of care) will (... ) increase the cost effectiveness of PCS for long-term healthcare policies aimed at reducing societal medical costs

Many people (... ) will not have this (PGT-M) option (... ) because of legal (...) or financial limitations. The benefits of PCS for people who have no access to PGD are rather limited

Implementation of PCS on a population level has the potential to significantly decrease infant mortality and morbidity

(...) the industry fosters this notion, even if the detection frequencies of added mutations are declining and clinical relevance is thus decreasing

(...) PCS has the potential to significantly decrease individual and societal costs by identifying couples at risk, who could then choose to avoid having affected offspring

For centuries the concept of eugenics has proposed exclusion of unfavourable human traits

Fertility Battle, F&S 2019
Thank you!