Psychological and Behavioural Implications of genetic testing

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Overview

• Expanding scope of genetic testing

• Lessons of the past
  – Carrier testing
  – Predictive testing

• What about the future?
  – From monogenic to multifactorial
Scope for testing was

- So far: most genetic tests are **reproductive tests** which provide information about risk of disease in future offspring

  - E.g. carrier testing for cystic fibrosis, prenatal diagnostic testing
• Increasingly: **predictive tests** which give people information about their own risk developing disease

- **Presymptomatic tests** (dominantly inherited condition with complete penetrance)
  - E.g. Huntington’s disease

• **Predisposition tests** (having mutation means increased risk, but not a certainty)
  - E.g. Hereditary breast and ovarian cancer
• Genes **predisposing to common disease** (Alzheimer’s disease, diabetes, heart disease) are continuously being discovered.

  – Will these susceptibility tests become most important genetic test?

*Most likely: risk refinement rather than replacement*
Expanding scope of testing

• Scope for genetic testing is extended:
  – From reproductive tests to predictive testing
  – From reproductive decision making to personal risk reduction
  – From monogenic to multifactorial diseases
  – From families to large (sections of) healthy populations

• Shift from complaint-orientation to risk-orientation (risks individually determined in healthy individuals = > screening)

What is the effect on individuals, families and society? Way people think about illness and health? People’s self-image? (Organisation of) prevention and care?
How do individuals respond to genetic test?

- Lessons of the past
  - Carrier testing
  - Predictive testing
Carrier testing (why?)

- Tests for heterozygous status of inherited disorder in healthy individuals, who have a high risk of transmitting disorder to offspring.

- Aim: to allow **informed reproductive decisions**

*E.g. cystic fibrosis, sickle cell disease, Tay–Sachs disease, fragile X syndrome*
Carrier testing (who?)

• **In families** (medical indication):
  – individuals with family history of disorder
  – partners of carriers or individuals who have the disorder

• **Only minority** of carrier couples will be identified through families

1. Uptake for carrier testing in high-risk families low
   
   Insufficient knowledge, parental guilt, bad relationships, lay beliefs on how relatives will cope with information  
   (Clarke et al., *Eur J Hum Genet* 2005)

2. Majority (80%) of children with AR are born to couples with no previous family history
• Population based carrier screening programmes
  - E.g. Jewish populations (Tay Sachs), Cyprus (Thalassemia), USA (CF)
Carrier risk of CF and/or HbP depends on ancestry

- **CF risk areas**: Europe, North Africa, Turkey, Middle East, former Soviet Union
- 1 in 25-30 carrier

- **HbPs risk areas**: Africa, Middle East, Mediterranean Area, parts of Indian subcontinent and South-East Asia
- Carrier frequencies 5-40%
Sickle-cell screening in 1970s

- **State-sponsored mandatory screening program:**
  - No consideration of community views
  - Lack of adequate education and counseling

- **Result:**
  - Confusing healthy heterozygote carrier trait with homozygous disease
  - Widespread discrimination/stigmatization of African American carriers
Impact of carrier status information

- Carriers more distressed than non-carriers, usually within normal range.
- Other feelings: self-stigmatization, less optimistic health perceptions:

"I worry sometimes about whether being a carrier has an effect. Whether it actually has some effects of its own.... I have a lot of health problems." (Male carrier, brother has CF)

(Fanos et al., Am J Hum Genet 1995)
## Misunderstanding carrier status

Even after counseling/education:

<table>
<thead>
<tr>
<th>Response</th>
<th>Number of participants giving response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carriers (n=280)</td>
</tr>
<tr>
<td>Definitely a carrier</td>
<td>225 (80%)*</td>
</tr>
<tr>
<td>Likely to be a carrier</td>
<td>46 (16%)</td>
</tr>
<tr>
<td>Unlikely to be a carrier</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Definitely not a carrier</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Don’t know</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Did not answer</td>
<td>1 (0.4%)</td>
</tr>
</tbody>
</table>

*Correct response

- Some carriers believe they only “probably” have mutation (test 100% specific)
- Some non-carriers falsely believe that they were definitively not carriers (test not 100% sensitive)

- No predominant feelings of stigmatization/discrimination

  (Lakeman et al., *Genet Med* 2008)
More complexity

• In neonatal screening (aimed to find patients to prevent serious harm) carriers of sickle cell disease also found
  – Incidental findings

• Not for the child but enable reproductive decisions for parents
  – Very complex!
Impact of carrier (couple) status

- For most carriers **anxiety levels** return to normal (especially when their partner tests negative), although confusion may persist.

- Being both carriers, even in families, usually unexpected. (Miedzybrodzka., *BMJ* 1995)
Impact of carrier (couple) status

“The doctor called and said: “You are both carriers”. We had never, never thought about it. It was a terrible shock, I cried at home and called my husband at work, but he was in a meeting and therefore couldn’t come to the phone. It was a dreadfully unhappy situation.” (Elly, 2nd cousin with CF)

“My first reaction was: how on earth could this happen? However, we accepted it. It was unexpected, but that’s the way it is. We’re a carrier couple and that’s it.” (Sara, husband has two sibs with CF)

(Henneman et al., Am J Med Genet 1996)
“We planned to have three or four children. We’re both from a big family. For a long time, I still wanted to have more children, but my husband didn’t. Later on he wanted to get more information about having children in another way. It was difficult and it’s still difficult sometimes.”

(Carrier couple, Sib†, nephew†, 2nd cousin† with CF)
X-linked disorders

• Before testing was available, women at risk very stressful (decisions about termination male fetuses)

• E.g. Duchenne Muscular Dystrophy
  - In 1987: 214 families 929 females at risk (no testing)
  - In 2009: 320 families 308 female carriers at risk (testing available)

(G.J. van Ommen, ESHG, June 2010)

X-linked inheritance may lead to more maternal guilt and paternal blame compared to recessive disorder where both parents are carriers (James et al., Genet Med 2006)
What have we learnt?

- Importance of pre-test education and counseling
- Facilitate informed decision making (value-consistency)
- Respect autonomy
How do individuals respond to genetic test?

- Lessons of the past
  - Carrier testing
  - Predictive testing
The case of Huntington (HD)

- Degenerative, progressive disease (movement coordination, mental health)
- Rare (1 in 10,000), autosomal dominant inheritance
- Usually develops around age 40
- No cure
- Since 1980s HD testing (gene found in 1993)
- Genetic testing:
  - confirm diagnosis
  - prenatal testing
  - presymptomatic testing
Presymptomatic (predictive) HD testing

- Should testing be offered? How will people cope knowing they will get a deadly brain illness?
- “The way to go or the end”? 
- Genetic test-results also reveals information for other family members (who may not want to know)
Why have a predictive HD test?

• Uncertainty of gene status removed

• If positive:
  – make plans for the future
  – arrange surveillance/treatment if any
  – decide whether to have children/inform children

• If negative:
  – concerns about self and offspring reduced
Why **not** have a predictive HD test?

- **If positive:**
  - removes hope
  - introduces uncertainty (if and when)
  - known risk to offspring
  - impact on self/partner/family/friends
  - potential problems with insurance/mortgage.
Psychological impact of HD testing

• In practice (in NL) 1987-1997: 75% tested (752/1032).

• Lower-than-expected rate of problems (e.g. distress) in carriers (Duisterhof et al., *J Med Genet* 2001)

• Attributed to:
  - pre- and post-test psychological counselling
  - self-selection of the participants

• Subgroup long lasting problems
Psychological impact of HD testing


- Most distressed: those reporting to be distressed before testing  (Duisterhof et al., *J Med Genet* 2001)

- Overall: presymptomatic testing has *not* increased distress above levels generally found in those with HD

- Unexpectedly, **non-carriers** experienced difficulties adjusting to revised risk status:
  - Survivor guilt, mourning for lost opportunities, obligation to do something ordinary

*Test result (carrier or non-carrier) rarely predictive of distress*  (Broadstock et al., *Eur J Hum Genet* 2000)
Genetic testing guidelines

- Counseling
- Support
- Psychological Consequences of Testing
- Testing Symptomatic Individuals Vs. Non-symptomatic
- Family Issues/Communication
- Reproductive Decisions/Options
- Genetic Discrimination

Traditionally, tests have not been given without genetic counselling, although this is likely to change.
The case of Breast cancer

- BRCA1/2 mutation carriers highly increased risk (but not 100%)

<table>
<thead>
<tr>
<th></th>
<th>Lifetime risk in BRCA mutation Carriers</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer ♀</td>
<td>60 - 85%</td>
<td>10%</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>40-60%</td>
<td>1-2%</td>
</tr>
<tr>
<td>Ovarian Cancer  <em>BRCA1</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian Cancer  <em>BRCA2</em></td>
<td>10-20%</td>
<td>1-2%</td>
</tr>
</tbody>
</table>
### Why have a predictive BRCA test?

<table>
<thead>
<tr>
<th>Test Result</th>
<th>MUTATION PRESENT</th>
<th>MUTATION ABSENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Clear basis for existing clinical interventions that improve outcome</td>
<td>Avoidance of unnecessary interventions</td>
</tr>
<tr>
<td>Health Behaviour</td>
<td>Importance of positive health behaviour can be reinforced</td>
<td>Importance of positive health behaviour can be reinforced</td>
</tr>
<tr>
<td>Family</td>
<td>Others at risk can be identified</td>
<td>Children can be reassured about their risk status</td>
</tr>
<tr>
<td>Emotional</td>
<td>Relief of uncertainty, permission to take charge of affairs</td>
<td>Relief from worry about disease risk</td>
</tr>
<tr>
<td>Socio-legal</td>
<td>Higher insurance premiums should be avoided</td>
<td></td>
</tr>
</tbody>
</table>

- **Prophylactic surgery**
- **Intensive screening strategies (surveillance)**
- **Chemoprevention**
Overview

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• What about the future?
  – From monogenic to multifactorial
Common chronic disorders

- As result of **Genomics research** => from mendelian disorders to common disorders

Potential applications in health care: identify people at increased risk and offer interventions that will reduce that risk (phenotypic prevention)
Personalised medicine

• Assuming that:
  
  • *Individuals who learn about personal risk will be motivated to modify behaviour* or *comply with a medical intervention* to prevent disease (lifestyle, smoking, screening)

  • “One size fits all” approach is not always the best

  • *DNA test is better than non-genetic test to identify risk* (comparative effectiveness)

However,

• Aggressive prevention measures unacceptable for low/moderate risk

• Other behaviours (smoking, healthy diet) to reduce risk for many diseases at all levels of risk
Focus of research changes

**Monogenetic diseases**
Psychological impact, informed decision making e.g. reproductive decisions

**Multifactorial diseases**
Informed choices about lifestyle (and medication), such as smoking, diet and exercise: effectiveness on behaviour
Motivation to change behaviour

- Are people with increased genetic risk motivated to change behaviour (e.g. adhere to recommended screening guidelines)?

Genetic risk information may: (Marteau & Lerman, 2001)
- motivate
- lead to genetic determinism or fatalism
- Higher compliance with mammography screening BRCA1/2 carriers 59-92% vs. non-carriers 30-53%

Similar outcome:

- Uptake colonoscopy: carriers hereditary colorectal cancer 58-100% vs. non-carriers 0-41%

(Heska et al., Gene Med 2008)
Evidence from monogenic disorders (II)

- Familial hypercholesterolemia (FH)
  - AD, 1 op 500, mutatie LDL receptor gen

- Disease results from **interaction** between gene and environment/behavior

- Possibility to modify risk
smoking increases CVD risk 2x FH & smoking increases risk >4x (esp. > 50 yrs)

In FH patients stop smoking increases life expectancy with 12 years compared to 2-4 years on average

Evidence from monogenic disorders

• How do people respond to genetic risk information?

• Risk perceived different from non-genetic risks?

• Genetic determinism?
  – i.e.. misconception that all genes work like the gene for Huntington’s instead of predisposition
FH cascade screening

• In NL family members of clinically diagnosed patients are traced by cascade screening (STOEH-Foundation for Tracing Hereditary Hypercholesterolemia)

• Genetic field worker takes DNA sample (at home) and provides counseling

• Analyses of LDL receptor gene

• FH positives advised to consult GP and/or vascular specialist for treatment
  - Statines
  - Healthy lifestyle
Perception of genetic risk

- No evidence for fatalism
- **More confidence** in effectiveness of **medication** than lifestyle change to reduce CVD risk
- Impact highest: multiple family members affected with CVD

Evidence from multifactorial disorders

- Lack of evidence that individualized risk information is effective motivator

- No/small effects
  - *Smoking cessation* (*risk ~ 20% lung cancer with gene variants*)
  - *Diet, exercise* (*2.6-14.9 times greater risk Alzheimer*)
  - *Weight loss*
  - ...

(McBride et al., *Annu Rev Public Health* 2009)
False reassurance?

• Recent study on patients being tested for genetic predisposition to salt sensitive blood pressure:
  - higher intentions to restrict salt intake when anticipating positive (unfavourable) test-results
  - lower intentions when anticipating negative test results

=> suggesting false reassurance

E.g. thinking you won’t get the disease because the test-results were OK

(Smerecnik et al., Genet Test 2007)
Conclusion - psychological impact

- Genetic risk information seems to be associated with little distress or anxiety

- If having genetic (risk) mutation
  - Burden of knowing, particularly if no treatment is available
  - Genetic determinism: possible overestimation of likelihood of actually getting the disease

- If negative:
  - Evidence of ‘survivor guilt’ in some cases
  - Possible false reassurance

- **In the absence of harm: justified to provide information?**
Conclusion - behavioural impact

- Testing hereditary cancers associated with increased adherence to guidelines

- Difficult extrapolating from these findings to predict impact gene variants with low-risk probabilities
  - *predictive value of genetic tests is low (i.e. low penetrance)*
  - *Evidence from self-referred groups, counseling*

- Little/mixed evidence that genetic risk assessment will result in *higher* behavioural changes than traditional risk assessments

- How to convey risk information? (low health literacy)


• **Marteau** TM et al. The new genetics Psychological responses to genetic testing BMJ;316:693–6.