Ethical challenges associated with prediction and early detection of dementia

Dr Richard Milne
<table>
<thead>
<tr>
<th>The promise of prediction</th>
<th>The problems of prediction</th>
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</thead>
<tbody>
<tr>
<td>Right to know</td>
<td>Right not to know</td>
</tr>
<tr>
<td>Support ability to plan, manage health</td>
<td>Limited predictive power</td>
</tr>
<tr>
<td>Maximise treatment possibilities,</td>
<td>Limited options for action</td>
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<tr>
<td>Obtain early access to care and support</td>
<td>Risk of harm</td>
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<tr>
<td>Right to access a diagnosis</td>
<td>Potential for overtreatment and medicalisation</td>
</tr>
<tr>
<td></td>
<td>Stigma, employment and insurance implications</td>
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<tr>
<td></td>
<td>Unequal access</td>
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Prediction in practice

Guidance on ApoE recommends against general clinical use in asymptomatic population
- limited clinical utility
- poor predictive value (Goldman et al. 2011)

Amyloid guidance similar (Johnson et al. 2013)

Challenges:
- Direct to consumer and interest (Horton et al. 2019)
- Research/clinic boundary
- Clinical trial recruitment
Ethics in EPAD and beyond

EPAD/AMYPAD workgroup on ethical, legal and social implications of move to prevention and early detection in Alzheimer’s disease

Empirical ethics study of emerging diagnostic technologies (SPACE)
EPAD involves recruitment from a cohort study to a phase II clinical trial targeting ‘high risk’ populations.

Individual research results should be returned to research participants only when clinically valid and actionable.

When research participants are invited to take part in a clinical trial, they should be informed about the reason why they were selected.
What are the consequences of risk communication
Among cognitively healthy research participants disclosure of ApoE ε4-positivity in a trial setting:

- does not lead to elevated anxiety and depression levels,
- does increase test-related distress
- some evidence of a nocebo effect (Lineweaver et al. 2014)
- results in behaviour changes concerning insurance and health (Chao et al. 2008)
- does not reliably effect individual’s baseline risk perception
- but does affect people’s perception of the benefits and drawbacks of genotype-based risk information (Christensen et al. 2011)
- Dominated by REVEAL and US context
• Studies of abnormal amyloid disclosure to cognitively normal individuals in a trial setting suggest low risk of psychological harm (cf de Wilde et al. 2018; Burns et al. 2017)

• Very few studies yet published, predominantly attached to clinical trials

• Interest in results drops when uncertainties made clear (Gooblar et al. 2016; Milne et al. 2017)

• Importance of clarity about terminology and communication
  • Not a clear binary result
The importance of communication

- Link between impact of risk and quality of communication (cf REVEAL II)
- Protocols for amyloid disclosure developed for clinical trials (A4, EARLY, EPAD) often derived from HD/genetics experience
- Involve stages of education/information, screening and informed consent, disclosure discussion, follow up
- Challenges in terms of discussing uncertainty and availability of resource

Living with risk

Zallen (2016) qualitative interview study with 26 members of the ApoE4.info community

Testing did produce adverse psychological reactions in participants who hadn’t received pre-test counselling or for whom it was unexpected

Nearly all (23/26) concluded that they had benefited in the long term although a small number continued to regret

I definitely was emotionally traumatized … The emotional impact so high, it was strong and huge; it was almost as if I was imagining I was already having a thing that really gave me comfort.

( Participant F: homozygous, tested for a different health problem)

In the end I’m glad I did it … And, yes, I’m glad I know because I think I am doing things that I might not do. But, obviously, I wish I didn’t have it.

( Participant F)

I wish I never knew about this. There’s really nothing I can do at my age. It’s like a cloud, hanging over my head. I’m basically, I think, optimistic and happy, and I pulled myself out of that really down period. But, it’s just a terrible thing hanging over me.

( Participant N: homozygous, tested for general interest)
DTC

- >26 million people have had some form of DTC
- Little data on emotional impact
- Effect on baseline risk perception greatest for Alzheimer’s disease
- Problems of false positive/false negatives

<table>
<thead>
<tr>
<th>Type of information</th>
<th>General</th>
<th>Disease-specific risks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>not interested</td>
<td>somewhat interested</td>
</tr>
<tr>
<td>Ancestry</td>
<td>3.9</td>
<td>22.5</td>
</tr>
<tr>
<td>Traits*</td>
<td>2.3</td>
<td>25.5</td>
</tr>
<tr>
<td>Disease risk</td>
<td>1.9</td>
<td>26.2</td>
</tr>
<tr>
<td>Drug response</td>
<td>9.1</td>
<td>38.8</td>
</tr>
<tr>
<td>Carrier status</td>
<td>43.0</td>
<td>26.1</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>6.8</td>
<td>26.9</td>
</tr>
<tr>
<td>Arthritis</td>
<td>16.9</td>
<td>42.0</td>
</tr>
<tr>
<td>Asthma</td>
<td>31.1</td>
<td>39.2</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>25.9</td>
<td>36.4</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>5.8</td>
<td>27.3</td>
</tr>
<tr>
<td>Colon</td>
<td>11.2</td>
<td>36.1</td>
</tr>
</tbody>
</table>

The future of prediction: DTC 2.0?

DTC 2.0

Clinical oversight vs autonomy

Specific challenges associated with data-driven detection based on ‘edge’ data

• Consent
• Transparency
• Fairness
• Accountability
• Governance
• Commercialisation
“Lumosity preyed on consumers’ fears about age-related cognitive decline, suggesting their games could stave off memory loss, dementia, and even Alzheimer’s disease,” said Jessica Rich, director of the FTC’s Bureau of Consumer Protection, in a statement. “But Lumosity simply did not have the science to back up its ads.”
Conclusions

• In absence of clear clinical benefit and accuracy, arguments in favour of communicating risk predictions rely on autonomy and personal utility
• Arguments against emphasise potential psycho-social harms
• Understanding impact can help with discussion of when it is right to return prediction results and how
  • Information about risk predictions doesn’t cause harm to the majority of people, in controlled settings - focus on what key features of communication are and how and to whom they are made available
• Wider social and economic consequences of detection and prevention less considered
• Including fair and equitable access to prevention
Thank you

EPAD ELSI workpackage
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  Maartje Schermer
  Krista Tromp
  Luc Truyen

Wellcome SPACE study
  Alessia Costa
References and further reading

The REVEAL studies https://www.genomes2people.org/research/reveal/


Smedinga M, Tromp K, Schermer M, Richard E. Ethical arguments concerning the use of Alzheimer’s Disease biomarkers in individuals with no or mild cognitive impairment – a systematic review and framework for discussion *J Alz Dis* 2018;66:1309-1322


