Ethical Issues in Genomic Testing In Children Including Newborns
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Ethical issues in genomic testing in children

Fundamental issue

- Regulating risk
  - Who gets to assess the risks?
  - Who gets to decide if they are too great?
  - For which people/patients?
  - With what justification?

Genetic testing is perceived as dangerous!
The argument for oversight

- People need to be protected
  - From their own bad decisions
  - From decisions that harm others
- Certain practices need to be regulated
  - People will hurt themselves, and
  - Cause harm to others

Specific and non-specific fears

- Psychological consequences
- Stigmatization or discrimination
- Brave New World dystopias – cloning, designer babies, environmental disaster
- Fear of hubris – stealing fire from the Gods

The triple whammy of runaway social inequality, genetic technology and catastrophic climate change, has finally culminated in some apocalyptic event.
November, 2013

• FDA ordered 23&Me to “immediately discontinue marketing the PGS (Personal Genome Service).”
• Concern about the “potential health consequences that could result from false positive or false negative assessments for high risk conditions.”
FDA Example

- “...A false positive (BRCA) could lead a patient to undergo prophylactic surgery, chemoprevention, intensive screening, or other morbidity-inducing actions, while a false negative could result in a failure to recognize that an actual risk that may exist...”


Customer reaction

- “I think the FDA has lost their minds... Does the FDA plan to ban the entire internet? Patients make all sorts of decisions everyday, based on discussions with their doctors, internet research, magazine articles, news reports.”

  • A blog somewhere

Parallels

- Popularity may be because they are risky.
- Should we be protected from our own risk-seeking desires?
- What if Risk = Fun?
Debate about Harvard’s Personal Genome Project (HGP)

- Volunteers
- Full genome sequence
- Given all the data, and agree to make it public
- Available on website

Informed Consent

- Your posted genomic and medical information could be used to:
  - Infer paternity
  - Claim statistical evidence that could affect your employment or insurability
  - Claim your relatedness to infamous villains
  - Synthesize DNA and plant it at a crime scene
  - Reveal propensity for a disease

Three people wrote about being participants in the PGP

Richard Powers

Misha Angrist

Steven Pinker
Risks

• There are risks of misunderstandings, but there are also risks in much of the flimflam we tolerate in alternative medicine, and in the hunches and folklore that many doctors prefer to evidence-based medicine.
  – Pinker

Risks and curiosity

• I had no idea what I was blundering into. But I figured I could start learning now about privacy and public good, research and entrepreneurship, risk and susceptibility—all the dangers of knowing the full story—or I could bump up against them later, along with the rest of unwitting humanity. Curiosity may be just suspicion co-opted by endorphins.
  – Richard Powers

Risks and fun

• “Personal genomics is just too much fun.”
  – Pinker
Does genetics reveal hidden truths?

• When the connection between the ACTN3 gene and muscle type was discovered, parents and coaches started swabbing the cheeks of children so they could steer the ones with the fast-twitch variant into sprinting and football.
  – Steven Pinker

Genotype and phenotype

• Carl Foster, one of the scientists, had a better idea: “Just line them up with their classmates for a race and see which ones are the fastest.”
  – Steven Pinker

Critics of HGP echo the FDA

• “...the dangers of actively handing out data that we know are not fully reliable and can lead to misinterpretation.”
  – Dondorp et al, Science, 2014
Defenders evoke rights

- Access gives people the freedom to choose whether or not to examine their own data.
- “The central ethical principle of respect for persons demands that we give people access to their own genetic data and allow them to make their own choices.”


An underlying assumption

- On their own, people will make bad decisions
- But doctors will make good decisions
- Data is not so clear…

Screening can be dangerous
Neuroblastoma population screening

- Urine catecholamines at 6 months of age
- All children in Quebec (1989-94)
- Compared mortality with 4 unscreened populations.


Table 1. Quebec Neuroblastoma Screening Project (QNSP): selected results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>QNSP</th>
<th>Ontario</th>
<th>ONSP rate relative to Ontario rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>GNSP compliance rates, %*</td>
<td>3 wks</td>
<td>89</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>73</td>
<td>N/A</td>
</tr>
<tr>
<td>Incidence per 100,000 births, %</td>
<td>27.01</td>
<td>14.56</td>
<td>1.92</td>
</tr>
<tr>
<td>Total cases diagnosed†</td>
<td>9.02</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Detected via screening†</td>
<td>18.89</td>
<td>14.56</td>
<td>1.30</td>
</tr>
<tr>
<td>Detected clinically†</td>
<td>13.35</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Silent tumors†</td>
<td>8.18</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>False positives†</td>
<td>4.76</td>
<td>4.33</td>
<td>1.10</td>
</tr>
</tbody>
</table>

*Among children <8 years of age per 100,000 births, †
Benefits of not screening

• In total, the US and Canada avoided $574.1 million in health costs by not using neuroblastoma screening between 1989 and 2002. Furthermore, 5003 false-positive cases and 9223 silent tumors were avoided.

  • Soderson L, et al JNCI 2003
Screening smokers for lung Ca

• Lung CT to screen smokers for cancer.
  – Plausible.
  – Should allow earlier detection and treatment.
• NCI sponsored prospective study – compared screening population to known historical risks

Screening smokers for lung Ca

• 3246 asymptomatic current or former smokers
• Annual chest CT scans, evaluation and treatment of positives.
• Four year follow up.
• Main Outcome Measures:
  – new lung cancer cases,
  – lung cancer resections,
  – deaths from lung cancer

- Bach et al. JAMA. 2007

Results

• Many more diagnoses: 144 vs. 44.5  (p<.001)
Results

• Many more diagnoses: 144 vs. 44.5 (p<.001)
• Many more lung resections 109 v 11, (p<0.001)
• No change in mortality 38 v 38.8 (p = .90)


Copyright restrictions may apply.
In other words…

• Higher cost
• More surgical morbidity
• No benefit

These screening projects

• Designed by doctors
• Approved by scientists
• Thought to be beneficial
• Will ordinary people make worse decisions?

Some think the fears are overblown
What's it all about?

• Knowledge is power.
  – “Personal genomic medicine is about the gradual replacement of luck with control. Once upon a time, we were dealt a hand by Fate, God, or the Unreliable Narrator, and the task of life was to deal with that hand. Now the task is to improve the deal.”

  – Richard Powers

“I'm sick of reading about the dangers of the genome…”

Slate
It’s Time To Stop Obsessing About the Dangers of Genetic Information

People are smarter and more resilient than ethics debates give them credit for.

By Virginia Hughes
How dangerous is knowledge?

Huntington’s screening

Predictive testing for adults known to be at high risk for HD

- Autosomal dominant – if parent has HD, 50% of children likely to get HD.
Key question
• If you were at risk (because a parent had HD), would you want to know?
• Would you want to go from 50/50 to 100% one way or the other?
• 60% of “at risk” people say they want testing, but only 10% of people get tested.

Ignorance is bliss
• Knowing genetic status changes behavior
  – HD + less likely to marry or have children.
  – More likely to retire early
• Individuals who don’t know genetic status behave like like non-carriers.
  • Oster E et al NBER

Predictive testing for Huntington’s
• Concern about catastrophic psychological reactions – breakdowns, suicide.
• Canadian Collaborative Study of Predictive Testing (1988)
  – 14 genetic testing centers
  – Anyone >18 with + FH and consent
  • Wiggins et al, NEJM 1992
Protocol

• Baseline: two counseling sessions
• Standardized psychological assessments
  – Beck Depression Inventory
  – General Well-Being Scale
• With consent: neuro exam, blood draw from patients and relatives.
• 3rd counseling session to prepare for results
• Follow up psych testing

Definitive results – positive or negative - led to lower psychological distress

"Predictive testing for HD may maintain or even improve the psychological well-being of many people at risk."

"Programs of testing for Huntington’s have the potential for harm. However, they also have the potential to enhance quality of life."

» Wiggins et al. NEJM 1992
BRCA testing

- Most women with +FH say they want testing.
- Few women actually get tested.
- Most women misperceive risk:
  - Underestimate their own risk
  - Overestimate the predictive value of testing
- Women cannot predict their own responses to test results:
  - Most anticipate that positive test results would lead to anxiety and depression
    • Pasacreta, Cancer Invest 2003

Psych distress after BRCA testing

- Within the range of population norms.
- Most common in women with pre-existing psychological issues.
- Not predictably associated with + or − result.

• Pasacreta Can Invest, 2003
Bottom line

- Hard to predict the psychological effects.
- Some are relieved, some are made worse.
- Some people want to know, others don’t.
- Testing does not seem to cause psychological problems, but can exacerbate existing ones.
- Harms of uncertainty vs. certainty

Dealing with bad news

- We know what happens to people who do get the worst news. They don’t sink into despair or throw themselves off bridges; they handle it perfectly well. Most of us cope using some combination of denial, resignation and religion.
  – Steven Pinker

Can access be restricted?

- Censorship vs. “free market”
- Faith in ordinary people or faith in experts?
- Avoid risks? Or seek benefits?
- Different ideas of what counts as “healthy” and what counts as “harm.”
My view

- People should be offered testing
  - With informed consent
  - With ongoing surveillance
- Outcomes should be carefully studied.
- Communication and trust are essential.
- If there are harms, we should try to understand and avoid them.

The Catch-22

- The only way to show that it is harmful would be to study it.
- To study it, you’d have to permit it.
- To permit it is to assume that it is okay to do.

Special issues for kids
Ongoing questions

- How to “call” variants of unknown significance
- Assessing clinical utility
- Disclosure of predictors of adult-onset disease

- Disclosing information about adult-onset conditions: a major clash is coming!

Professional policies (2013)

- “Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality.”
- Ethical and Policy Issues in Genetic Testing and Screening of Children, AAP COMMITTEE ON BIOETHICS, COMMITTEE ON GENETICS, AND THE AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS SOCIAL, ETHICAL, AND LEGAL ISSUES COMMITTEE
• "We're still discouraging predictive genetic testing [for children]. Testing a two-week old for BRCA is totally unnecessary. Nothing can be done clinically, and you're not going to change anything."

What do parents want?
• Varied opinions.
• Not all parents want the same thing.
• Clearly, though, many parents want much more genetic info about their children than current policies allow.

Parents’ Preferences for Return of Results in Pediatric Genomic Research
• Mailed survey – 6874 families, child had been cared for in last year at BCH. (2010)
• 1060 responses (16%)
• 39% with more than college degree, 44% with household income over $100K
• Asked if they’d want different types of results for themselves and for their children
Would you want results about untreatable diseases?

- For yourself - 86%
- For your child – 85%

Decision results

- 30 couples, given decision aids and scenarios about the sorts of tests they wanted
- Measured preferences, and concordance

Lewis M, Bailey D, Powell C, UNC, Unpublished data, used with permission.

Mom and dad agreement

- Want traditional newborn screening - - 93%
- Childhood onset, no treatment – 90%
- Adult onset, treatment available – 83%
- Adult onset, no treatment - 53%

Lewis M, Bailey D, Powell C, UNC, Unpublished data, used with permission.
For your child, would you want results for only childhood-onset diseases?

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood onset</td>
<td>97%</td>
</tr>
<tr>
<td>Adult onset</td>
<td>95%</td>
</tr>
</tbody>
</table>

Note

- 7% of parents don't want something that is mandated
- 53% of parents want something that is prohibited.
- Whose views should prevail?

The coming storm

- There is no compromise between these positions.
- Either parents have the right to their child’s genetic information or they don’t.
- Without strong evidence that such evidence is harmful, it is hard to prohibit it.
The Future

- People who have grown up with the democratization of information will not tolerate paternalistic regulations that keep them from their own genomes.

  — Steven Pinker

Thanks!