Genetic screening in children: a complex mess

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Children’s Mercy Hospital, KCMO
Why a mess?

• Complicated history, many debacles
• Rapidly developing screening technology
• Many interest groups
• Lack of good research
  – On efficacy
  – On harms
• Different goals, different fears
Complicated history

- Newborn screening began in 1962
- “Guthrie spots” used for PKU
- Controversies arose almost immediately
  - Sensitivity/specificity issues
  - Complex treatment regimens
  - Concern about “labeling” children
  - Risks/benefits of treatment regimens
Horror stories

“A phenylalanine-restricted diet was as harmful, or more harmful, as a diet with excess of phenylalanine. Many children — we don't know how many — were made retarded by this program. Some were killed.”

• (Norm Fost, testifying to the President’s Council on Bioethics, 2008)
Horror stories may not be true

- Exhaustive historical review.
- Literature, interviews with key informants.
- Total of five or six cases.
- Harms unrelated to screening or treatment.

- Brosco et al Peds, 2006
Hard to separate myths and perceptions from realities
Myth: sickle cell screening a disaster

“The early mass screening programs for sickle cell anemia in the United States during the 1970s could be summarized by the Dickensian axiom “How Not To Do It!”

What actually went wrong?

  – Not accepted by the public
  – Physicians did not understand the results
  – No treatment/intervention available
  – Led to discrimination and no benefit
A clear eugenic philosophy

• “There should be tattooed on the forehead of every young person, a symbol showing possession of the sickle cell gene [so as to prevent] two young people carrying the same seriously defective gene in single dose from falling in love with one another.”
  – Linus Pauling, 1974
Case study - Seattle

• 1971 – routine screening begun at Odessa Brown Children’s Clinic.
• Program evaluated after 1 year.

“Sickle Cell Non-disease, Hampton et al, AJDG, 1974.”
Odessa Brown Children’s Clinic

- 1930 children tested
- 85 children had trait
- No cases of disease found
- 47 families participated in follow-up interviews; along with 100 control families

Hampton et al, AJDC, 1974
Widespread misunderstanding about carrier status among both "cases" and "controls."
Many parents reported symptoms in children with “trait.”

### Table 1.—Symptoms Reported by Families as Expected “Common Complaints” in Children With Sickle Cell Trait*

<table>
<thead>
<tr>
<th>Common Complaints</th>
<th>Carrier N = 47, %</th>
<th>Control N = 100, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of energy</td>
<td>53</td>
<td>60</td>
</tr>
<tr>
<td>Pain in limbs</td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td>Pain in abdomen</td>
<td>32</td>
<td>27</td>
</tr>
<tr>
<td>Colds</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>Headaches</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>Weakness</td>
<td>30</td>
<td>43</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>19</td>
<td>32</td>
</tr>
<tr>
<td>None</td>
<td>28</td>
<td>33</td>
</tr>
</tbody>
</table>

* Several respondents gave more than one complaint.
And treated them differently

Table 2.—Restriction of Physical Activity by Families With Children With Sickle Cell Trait

<table>
<thead>
<tr>
<th></th>
<th>Carrier N = 47</th>
<th>Control N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete restriction*</td>
<td>4%</td>
<td>27%</td>
</tr>
<tr>
<td>Moderate restriction†</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>Mild restriction‡</td>
<td>30%</td>
<td>12%</td>
</tr>
<tr>
<td>No restriction</td>
<td>51%</td>
<td>49%</td>
</tr>
</tbody>
</table>

* No participation in any sports.
† Stop playing when tired.
‡ No competitive or strenuous sports.
Screening program discontinued

- Often cited as typical example of harms that can result from screening.
  - Stigmatization.
  - Medicalization of “non-disease.”
  - Vulnerable child syndrome.
Doctors didn’t know much about genetics

- 1975 survey
- 67 obstetricians
- Only 12% knew that Down Syndrome was caused by a chromosomal aberration.
- 50% knew the recurrence risk of PKU
- 20% did not know that the gene is the basic unit of inheritance.
  - Naylor EW. Social biology, 1975
Carrier status and stigma

• Oft-cited study from Orchemenos, Greece
• Small farming village
• 23% of population were SSD carriers
• 1/100 babies had SSD
• 2/3 of marriages were arranged – health was a factor in betrothal negotiations
Screening program

• Goal – reduce marriage between carriers
• Outcomes
  – Genotype information was widely shared
  – Carrier status was stigmatized
  – No reduction in carrier-carrier marriages
“…the Orchemenos experience may not be representative of thalassemia screening or sickle-cell screening in the United States.”

Kenen and Schmidt, AJPH, 1978
Contrasting with Tay-Sachs (TS)

- Study of TS screening, Baltimore
  - 131 carriers and their non-carrier spouses
  - 149 non-carrier couples
  - 52 people with “inconclusive” tests

Childs, Am J Hum Genet 1976
<table>
<thead>
<tr>
<th></th>
<th>Upset</th>
<th>Not upset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carriers</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>Carrier spouses</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td>Non-carriers</td>
<td>0</td>
<td>438</td>
</tr>
</tbody>
</table>

Childs, Am J Hum Genet 1976
<table>
<thead>
<tr>
<th>Question</th>
<th>Carriers Only</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change attitude toward each other?</td>
<td>0</td>
<td>262</td>
<td>0</td>
<td>262</td>
<td>262</td>
</tr>
<tr>
<td>Had adverse effect on sex life?</td>
<td>2</td>
<td>259</td>
<td>1</td>
<td>262</td>
<td>262</td>
</tr>
<tr>
<td>Change attitude on birth control?</td>
<td>2</td>
<td>258</td>
<td>2</td>
<td>262</td>
<td>262</td>
</tr>
<tr>
<td>Influenced family planning?</td>
<td>0</td>
<td>262</td>
<td>0</td>
<td>262</td>
<td>262</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All Participants</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you glad you were tested?</td>
<td>690</td>
<td>2</td>
<td>18</td>
<td>710</td>
<td></td>
</tr>
<tr>
<td>Life changed?</td>
<td>77</td>
<td>626</td>
<td>7</td>
<td>710</td>
<td></td>
</tr>
<tr>
<td>Would you be screened again?</td>
<td>700</td>
<td>6</td>
<td>4</td>
<td>710</td>
<td></td>
</tr>
</tbody>
</table>
Such studies led to caution

- Geneticists and pediatricians warned about potential harms of screening.
- New tests only slowly and cautiously added to newborn screening panel.
- Wilson-Junger criteria
Wilson-Junger criteria

- Disorder must pose a serious threat to the health of the child
- Natural history must be well understood
- Timely and effective treatment must be available
- The intervention as a whole (screening, follow-up, treatment) should provide a substantial benefit to the affected child
What changed?

• New techniques
  – Tandem mass spectrometry
  – Human genome project
  – SNPs
  – genome sequencing

• New philosophies on screening
Tandem Mass Spectrometry

- Developed for newborn screening in 1990s
- Rapid, sensitive, accurate measurements of many metabolites at once
- Quicker, cheaper, and more accurate
- Challenge for state screening programs
The Massachusetts story

- In 1996 – state-mandated testing for 9 diseases
- 1997 – for-profit company offers hospitals “a deal” on testing for 27 more conditions
- “Much more comprehensive testing at a substantially lower cost…”
- MA expands state newborn screening
Newborn screens, MA, 1996

• phenylketonuria  
• galactosemia  
• homocystinuria  
• biotinidase deficiency  
• maple syrup urine disease  
• congenital adrenal hyperplasia  
• hypothyroidism  
• toxoplasmosis  
• sickle cell disease
Additions, 1998

Increase in newborn screening panels according to state: 1995-2005

Concerns about justice/equality

• 2000: call for uniform national panel
• 2002: HRSA commissions the ACMG to provide recommendations.
• 2006: ACMG recommends screening for 29 conditions – endorsed by AAP, March of Dimes, HHS
• Universal panel adopted by most states.
Support from NICHD

“Many have begun to question one standard tenet of newborn screening, ie, that it is appropriate to screen only for conditions for which an effective treatment already exists…The old dogma cannot be allowed to stand in the way of developing effective treatments for these rare genetic disorders.”

Criticism from bioethicists

• Lack of data on
  – Impact of screening
  – Treatment of conditions on the panel
  – Risks and benefits

• “Proceed with caution”

Bioethicists recommendations

• Screening programs are experimental
• Should be studied before implementation.
• National (IOM?) working group on ethical and policy issues.
• “Independent and impartial organization” should make policy.

Mandatory screening only for conditions that meet Wilson-Junger criteria.

For other conditions, voluntary screening with accompanying research.

Avoid screening “just because we can.”
Competing philosophies

• “It is appropriate to screen only for conditions for which effective treatment already exists.”

• “Screen unless there is a compelling reason not to screen.”
  • NICHD (2005), ACMG (?) (2006)
Two major ethical issues

• Research ethics: Can we actually study screening programs?
• Clinical ethics: balancing individual autonomy and public health?
Can we study screening programs?
Methods

- Prospective randomized trials
- Concurrent geographic controls
- Historical controls
Prospective RCT for CF

- Wisconsin did a controversial RCT
- 650,000 babies randomized, ’85-’94.
- Randomized by birthday
- Every baby was tested for CF
  - Only those with odd birthdays were told*
  - Those with even birthdays told at age 4
  - Followed for lung disease, nutrition, mortality
    - *There was an “opt-out” – parents could call a number and get their results. 195 parents (0.3%) did.
Cystic fibrosis

• Some newborns diagnosed at birth without screening (meconium ileus).
• Most others diagnosed in the first few years of life – FTT, pulmonary problems
• Big Question: Will earlier diagnosis improve outcomes?
Possible harms of CF screening

• False positives.
• False negatives
• Misinformation and misunderstanding
• Unwanted info on carrier status
• Toxicities of treatments
Possible benefits of CF screening

• Lower mortality, fewer hospitalizations
• Better health related quality of life
• Better lung function, growth
RESULTS

No differences seen in pulmonary function between screened and control groups.
Wisconsin

- 2 CF centers – Madison and Milwaukee
  - Madison: screened group → less lung disease.
  - Milwaukee, screened group → more lung disease.
- Overall – no diffs between groups.
- What explains the differences?
Differences seen in growth and nutrition

Weight differences – screened vs. control
Height differences – screened vs. control
In Italy, concurrent geographic controls
Veneto (screening) and Sicily (no screening)

Mastella et al, Pancreatology, 2001
In the UK, historical controls

<table>
<thead>
<tr>
<th></th>
<th>Screened (n=60)</th>
<th>Non-screened (n=57)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female</td>
<td>34:26</td>
<td>29:28</td>
<td>0.5</td>
</tr>
<tr>
<td>Meconium ileus</td>
<td>7</td>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>Age of diagnosis (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>1.8 (0.1-81.0)</td>
<td>5.7 (0.1-51.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Excluding meconium ileus</td>
<td>1.8 (0.1-81.0)</td>
<td>6.2 (1.1-51.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Excluding 3 patients missed by screening (n=57)</td>
<td>1.8 (0.1-7.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS:PI at diagnosis</td>
<td>16:44</td>
<td>6:51</td>
<td>0.03</td>
</tr>
<tr>
<td>PS becoming PI</td>
<td>10</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>Symptoms at diagnosis (including meconium ileus)</td>
<td>30</td>
<td>56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Height SDS at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined mean (SD)</td>
<td>−0.2 (1.6)</td>
<td>−1.2 (1.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Pancreatic sufficient [PS]</td>
<td>−0.4 (1.4)</td>
<td>−0.06 (0.9)</td>
<td></td>
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<tr>
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<td>−0.2 (1.7)</td>
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<td>−0.2 (1.6)</td>
<td>−1.3 (1.3)*</td>
<td></td>
</tr>
<tr>
<td>Deaths due to CF</td>
<td>1</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td>Total lost to follow up (includes deaths and transfers)</td>
<td>10</td>
<td>17</td>
<td>0.1</td>
</tr>
</tbody>
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SDS = standard deviation score; SD = standard deviation; Students t test: * p<0.01 for difference in SDS between PS and PI.
In the UK, they used historical controls

Table 1  Comparison of screened and non-screened birth cohorts

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Conclusions about CF

• Unanticipated harms, modest benefits.
• More in nutrition and growth than in pulmonary function.
• May be associated with better survival
Lessons from CF screening

- It took fifteen years to prove that screening made a difference.
- Tough to study.
- Unintended consequences along the way.
- Questions remain.
- Adopted in all 50 states, most of Europe.
Neuroblastoma screening

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

Cumulative Mortality Due to Neuroblastoma among Children Younger Than Eight Years of Age.

Neuroblastoma screening in Japan

• 1984-2003 – all infants screening
  – 1984-9: qualitative spot tests of urine for VMA

• Compared outcomes in three cohorts
  – Before any screening
  – Qualitative screening
  – Quantitative screening
Neuroblastoma screening in Japan

• 22 million children
• Overall mortality lower in screened cohorts
  – Pre-1984: 5.38/100,000
  – 1984-9: 3.90
  – 1989-2003: 2.83

Lessons from neuroblastoma

- Early detection not necessarily beneficial.
- Screening changes our understanding of disease.
- Timing, cut-offs crucial.
- May be true with other syndromes.
Screening for Krabbe disease

- Autosomal recessive lysosomal storage disease
- Variable age of onset and progression
- Incidence: 1/100,000 (with ethnic variation)
- Can be treated with stem cell transplant
Screening for Krabbe disease

• In 2006, New York started screening
• Positives are categorized, clinically, as high, medium or low risk.
• High risk → monthly neuro exams, quarterly MRI, LP, AERs.
• Point system to decide whom to transplant
New York results

• 550,000 babies tested
• 25 positive screens
  – 15 low risk
  – 6 moderate risk
  – 4 high risk
• 2 referred for transplant (others have no symptoms)
Are there harms?

• Imagine being told that your child is “at risk” for a degenerative neurologic disease, that the only treatment is a bone marrow transplant, but that, for now, the best approach is watchful waiting.

• Imagine not being told.
Not so different from cancer screening in adults

• PSA
• CAT scans for lung cancer in smokers
Lessons from PSA

• Two prospective studies.
• Conflicting results
Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

• 1993 through 2001,
• 76,693 men at 10 U.S. study centers
• Randomized to either annual PSA screening (38,343) or usual care (38,350).
Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

• Screening group
  – annual PSA testing for 6 years
  – digital rectal examination for 4 years.
  – subjects and health care providers received results and decided on the type of follow-up evaluation.

• Usual care
  – sometimes (40-52% of the time) included screening

• Outcomes: All cancers, deaths, and causes of death
More cancers diagnosed in screened arm
No difference in deaths
But…

The cumulative death rate from prostate cancer at 10 years in the two groups combined was 25% lower in those who had undergone two or more PSA tests at baseline than in those who had not been tested.
European Randomized Study of Screening for Prostate Cancer

• 182,000 men, ages 50-74 (most 55-69)
• PSA testing every 4 years
• PSA cutoffs and f/u varied across countries
Improved survival in screened group – after 12 years
In Europe, PSA screening associated with…

- Absolute reduction of 0.71 deaths/1000 men after 9 years of follow-up.
- A 20% relative reduction in deaths from prostate cancer.
- To prevent one prostate cancer death, 1400 men would have to be screened and 48 would have to be treated.
Screening for Prostate Cancer — The Controversy That Refuses to Die

Michael J. Barry, M.D.
Systematic Review: Comparative Effectiveness and Harms of Treatments for Clinically Localized Prostate Cancer

Timothy J. Wilt, MD, MPH; Roderick MacDonald, MS; Indulis Rutks, BA; Tatyana A. Shamlayan, MD, MS; Brent C. Taylor, PhD; and Robert L. Kane, MD

The paucity of clinically important information from high-quality randomized trials remains the main barrier to well-informed decision making. Few existing trials assessed between-treatment rather than within-treatment category differences. Few randomized trials were adequately powered to assess overall or disease-specific survival or metastases. The 3 RCTs comparing surgery with watchful waiting or radiation therapy were old or were conducted before prostate cancer detection with PSA testing was available.
Screening smokers for lung Ca

• Lung CT to screen smokers for cancer.
  – Plausible.
  – Should allow earlier detection and treatment.
• NCI sponsored prospective study – did not randomize, compared screening population to known historical risks
Screening smokers for lung Ca

• **Population:** 3246 asymptomatic current or former smokers screened for lung cancer

• **Intervention:** Annual CT scans, evaluation and treatment of positives.

• **Follow up:** Four years.

• **Main Outcome Measures:** new lung cancer cases, lung cancer resections, and deaths from lung cancer

Bach et al. *JAMA*. 2007
Results

- More diagnoses: 144 vs. 44.5 (p<.001)
- More lung resections 109 vs 11, (p<0.001)
- Same mortality 38 vs 38.8 (p = .90)
Can we study screening?

• Yes, but…
  – it is expensive, complicated,
  – each test is different,
  – Unexpected results are common
  – Diseases found on screening may not be the same disease
In spite of these complexities...

- Newborn screening is expanding
- Driven by doctors, parents, advocacy groups, and for-profit enterprises
- Many conditions that don’t meet Wilson-Junger criteria.
- Concern about psychosocial harms
ASHG/ACMG conclusions

“Providers who receive requests for genetic testing in children must...consider the medical, psychosocial, and reproductive issues. Such testing has the potential for great benefit and great harm...”
ASHG/ACHG recommendations

• Weigh interests of children and parents
• Consider medical, psychosocial, and reproductive issues
• Individualized decisions
What are the psychosocial risks?
Meta-analysis of psychosocial benefits and harms

• Relatively high levels of worry among those at risk.

• Children who received genetic test results, whether indicative of increased risk or not, did not experience significant changes in psychosocial wellbeing.

• Wade, Wilfond, McBride, Gen in Med, 2010
Meta-analysis of psychosocial benefits and harms

• Testing might influence children’s perspectives on future partner selection and parental roles.

• High reported satisfaction among tested children and positive emotional responses among children who tested negative.
  • Wade, Wilfond, McBride, Gen in Med, 2010
Systematic review – psychological impact of genetic testing

• 35 articles, 30 studies
• Testing for genes associated with cancer and Alzheimers
• “Overall, predispositional genetic testing has no significant impact on psychological outcomes, little effect on behavior, and did not change perceived risk.”
  – Heshka et al, Gen in Med, 2008
<table>
<thead>
<tr>
<th>General outcome</th>
<th>Specific outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>Perceived risk</td>
</tr>
<tr>
<td>Affective</td>
<td>Disorder-specific distress or worry</td>
</tr>
<tr>
<td></td>
<td>General or state anxiety</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>General distress</td>
</tr>
<tr>
<td></td>
<td>General health status</td>
</tr>
<tr>
<td></td>
<td>Psychiatric diagnosis</td>
</tr>
<tr>
<td>Behavioral</td>
<td>Surveillance behaviors</td>
</tr>
<tr>
<td></td>
<td>Prophylactic surgery</td>
</tr>
<tr>
<td></td>
<td>General preventive behaviors (i.e., diet, exercise, lifestyle)</td>
</tr>
</tbody>
</table>
Psychosocial harms

- Associated with being “at risk” rather than being tested.
- Similar to findings from TS screening in the 1970s.
Key question

• Public health model?
  – Population-based, mandatory, state-financed

• Clinical model?
  – Individualized, voluntary, covered

• Non-medical consumer good?
The Experimental Man Project

Online and Book
First Step: Visit My Internist

Prognosis after routine check-up:
- Healthy
- Borderline high cholesterol
- Heart attack risk: 4 percent risk 10 years
The Experiment

- Number of labs, companies: ~250
- Amount of blood drawn, in liters: ~2
- Hours spent in an MRI: 22
- Number of chemical toxins tested for: 320
- Gene markers tested, in millions: 7 – 10
- Gigabytes of data produced: ~100
- Cost: ~$150,000
GENES
Blood, Spit, and Swabs
## Threat Levels

- **Red:** risks over 1.5 times normal
- **Orange:** risks over 1.2 times normal
- **White:** Average or normal risk
- **Yellow:** Between .5 and .99 times normal
- **Green:** Protective SNP or risk factor below .5

### Gene / Location

<table>
<thead>
<tr>
<th>Gene / Location</th>
<th>SNP</th>
<th>Risk Variant</th>
<th>DED Result</th>
<th>Risk Factor *</th>
<th>Source</th>
<th>Lifetime Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELSR2+</td>
<td>rs599839</td>
<td>G</td>
<td>AG</td>
<td>.00</td>
<td>deCode me</td>
<td>42%</td>
</tr>
<tr>
<td>9p21</td>
<td>rs1011627</td>
<td>T</td>
<td>GT</td>
<td>1.00</td>
<td>deCode me</td>
<td>49%</td>
</tr>
<tr>
<td>9p21</td>
<td>rs1333049</td>
<td>C</td>
<td>CC</td>
<td>1.72</td>
<td>Navigenics</td>
<td>62%</td>
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<tr>
<td>MTHFD1L</td>
<td>rs6922269</td>
<td>A</td>
<td>AA</td>
<td>1.53</td>
<td>Navigenics</td>
<td>29.9%</td>
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<tr>
<td>9p21</td>
<td>rs2383207</td>
<td>G</td>
<td>GG</td>
<td>1.22</td>
<td>23andme</td>
<td>29.9%</td>
</tr>
</tbody>
</table>

### My “Lifetime” Risk

- **Heart Attack:**
  - High (Navigenics) – 62% (Ave: 42%)
  - Low (deCode me) – 42% (Ave: 49%)
  - Not Sure (23andme) – 29.9% (Ave: 17%)
### Chemical Report Card

Labs: Axyss Analytical, Quest Diagnostics

**Chemicals Tested:** 320

**Detected:** 165

**Cost:** $15,000

---

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Tested</th>
<th>Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCBs</td>
<td>209</td>
<td>97</td>
</tr>
<tr>
<td>PBDEs</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Pesticides</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>Dioxins</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Phthalates</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>PFAs</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Metals</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Bisphenols</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

---

### Results of Concern

- **BDE-47 (Tetra)**
  - Test Result: 240 ppb*
  - CDC Mean: n/a

**Health Effects (suspected)**
- Thyroid
- Neurodevelopmental

Notes: Now being phased out, this fire retardant is in many products and resists environmental degradation.

- **Dieldrin**
  - Test Result: 5.11 ppb
  - CDC Mean: n/a

**Health Effects**
- Neurological
- Kidney

Notes: A pesticide once used to kill termites and other soil insects, it still lingers in the environment.

- **p,p-DDE**
  - Test Result: 256 ppb
  - CDC Mean: 295 ppb

**Health Effects (suspected)**
- Reproductive
- Liver

Notes: A breakdown product of DDT (now banned) that lingers in the body, it has health effects similar to those of the pesticide.

- **mMeP**
  - Test Result: 34.8 ppb
  - CDC Mean: 1.15 ppb

**Health Effects (suspected)**
- Reproductive

Notes: It's a member of a class called phthalates, used to thicken lotions and make plastics flexible.

- **Mercury**
  - Test 1: 5 micrograms/liter
  - Test 2: 12 micrograms/liter

**CDC Poisoning Level:** 10

**Health Effects**
- Neurological
- Reproductive

Notes: Duncan's blood level of the toxic metal more than doubled after he ate two meals of swordfish and halibut.

*Parts per billion.
BRAIN
Getting my head examined
MRI, EEG, other brain tests
BODY
Scans: Ultrasound and CT

Carotid and Chest

(Part of a full-body scan)
Still going... more tests

My Proteomic Scan

Microbial Scan (Coming)
More Information

The Experimental Man Project

www.experimentalman.com

Center for Life Science Policy
UC Berkley

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Implications for ethics

• Population-based, public-health interventions must be safe and effective.
• Individualized clinical interventions must only have a favorable risk-benefit ratio.
• Consumer goods don’t even need that.
Next-generation sequencing

- Emerging technology
- Whole genes - quickly and cheaply
- Used in research:
  - GWAS studies
  - biobanking
- Now available for clinical use
Next-generation sequencing

• What genes should testing target?
• In which populations?
• “NGS technologies will certainly enable us to identify all the causative variants including “rare variants” within individual human subjects.”
  – Zhang et al, J Gen Genomics, 2011
The CMH-595

- Whole-gene sequencing
- Genes for 595 autosomal recessive conditions
- $250
- CLIA lab – test done with MD order
- Not GWAS, not biobanking, not research
When you come to a fork in the road, take it.
Choice of ethical models

- **Clinical ethics** – individualized, focus on autonomy. Goal: patient satisfaction
- **Public health ethics** – population-based, focused on beneficence. Goal: Population health
- **Research ethics** – risk-averse, utilitarian. Goal: generalizable knowledge
“Old” doctor-patient relationship

• Patient came to doctor only when sick
• Doctor took history, did physical exam, and ordered tests in order to find the cause of illness.
• Incidental findings were rare.
“New” doctor-patient relationship

• Healthy (and sick) patients undergo many screening tests
• Most tests find something
• Significance of finding is uncertain
• Do we disclose? Get more tests? Keep secrets?
Alternative visions of future

• Better technology will decrease the need for careful history, physical exam, trusting doctor-patient relationship.

• Technology will create need for more careful conversations in order to help patients understand implications.
Welcome to the Children’s Mercy Hospitals and Clinics Bioethics Center Website

We have developed some tools for clinicians and teachers to help analyze ethical issues that arise in pediatrics.

For each of the topic areas on the right, we offer a brief introduction to the ethical issues, a power point presentation to use in your teaching, interviews with leading figures in the field about those issues, and an annotated list of references.

We will be adding topics all the time. If you have an issue that you’d like us to address, or feedback on the materials we’ve developed, please contact us. All of the original materials can be used without permission. Please give us credit, though, and send colleagues our way.

We give links to full text reference material that is in the public domain. For other reference material, we give links to abstracts.
Thanks
REFERENCES


REFERENCES


