Cascade Screening for FH: the U.S. experience

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Disclosures

• Consultant
  — Genzyme, Amgen, Regeneron

• Research funding
  — Regeneron, Merck
A striking family history

- Roger was shocked as a teenager when his neighbor died from MI on the golf course at age 42.
- And more shocked to learn the family had expected it!
- Several generations of males in this family had died from MIs before meeting their grandchildren.

Roger R. Williams, MD
Aug 11, 1944 – Sep 2, 1998
Initial efforts in Utah

• “Characterization of Coronary Prone Pedigrees”
  – Roger R. Williams, MD, principal investigator
  – NIH grant 1977-1992
  – Goal:
    “to understand the genetics and epidemiology of different types of early familial coronary disease ...”
Syndromes in 97 Utah Multiplex Families (2+ cases with early CAD and risk factor)

- Cigarette Smoking: 37%
  - Hypertension: 24%
  - FDH (MetS): 12%
  - Diabetes: 8%
  - Homocysteine: 12%

- High Lp(a): 23%
- FCHL: 12-60%
- High TG: 14%
- High TG, Low HDL: 7%
- All Low HDL: 23%
- Type III: 3%
- High LDL: 5%
- FH: 4%

Familial dyslipidemias in premature CHD kindreds (n = 102)

- No identifiable familial abnormality 43%
- Familial apo A-1 deficiency 1.0%
- Familial high TG 1.0%
- FH 3.0%
- Familial hyperapobeta 5.0%
- Familial hypoalpha 4.0%
- Familial dyslipidemia 14.7%
- FCHL 13.7%
- L(a) excess 18.6%

## Familial Syndromes of Early CAD in Seattle, Boston, and Utah

<table>
<thead>
<tr>
<th></th>
<th>Seattle (N = 366)</th>
<th>Boston (N = 102)</th>
<th>Utah (N = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diagnosis</td>
<td>60%</td>
<td>35%</td>
<td>25%</td>
</tr>
<tr>
<td>Familial combined hyperlipidemia</td>
<td>13%</td>
<td>18%</td>
<td>36%</td>
</tr>
<tr>
<td>Familial hypertriglyceridemia</td>
<td>6%</td>
<td>18%</td>
<td>21%</td>
</tr>
<tr>
<td>Isolated low HDL</td>
<td>--</td>
<td>4%</td>
<td>15%</td>
</tr>
<tr>
<td>all low HDL</td>
<td>--</td>
<td>35%</td>
<td>20%</td>
</tr>
<tr>
<td>Elevated Lp(a)</td>
<td>--</td>
<td>19%</td>
<td>23%</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>4%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Type III hyperlipoproteinemia</td>
<td>2-3%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>--</td>
<td>--</td>
<td>24%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>--</td>
<td>--</td>
<td>8%</td>
</tr>
<tr>
<td>Smoking</td>
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<td>37%</td>
</tr>
</tbody>
</table>

MEDPED

A humanitarian project to find and help persons with familial hypercholesterolemia
Brief Historical Review of MEDPED

• MEDPED was “officially” started at the University of Utah by Roger Williams in 1989

• First 5 years
  – funding from the CDC
  – established MEDPED methods
  – refined ascertainment methods since then
“Documented Need for More Effective Diagnosis and Treatment of Familial Hypercholesterolemia According to Data from 502 Heterozygotes in Utah”

- 101 FH probands with 502 identified relatives
- 50% had been told they had very high cholesterol
  - 31% of those had been told they had FH
- 42% taking a cholesterol-lowering medication
  - 23% had total-C or LDL-C below the 90th percentile
- Cascade screening most cost-effective way to find new probands

Williams RR, Am J Cardiol 1993; 72:18D
First degree relatives

1993 LDL cholesterol levels

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>SD</th>
<th>(OLD)</th>
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</thead>
<tbody>
<tr>
<td>FH</td>
<td>289</td>
<td>63.0</td>
<td></td>
</tr>
<tr>
<td>Non-FH</td>
<td>130</td>
<td>31.4</td>
<td></td>
</tr>
</tbody>
</table>

Hopkins PN. Clin Lipidol 2010; 5:339
1993 “MEDPED” Criteria for Diagnosing Heterozygous FH in U.S. Population

- Cut points chosen for 80% probability that an individual is affected.
- **ADDITIONAL CRITERIA** were applied to Dx a newly identified family.
- Shown are total-C (LDL-C) in mg/dl

<table>
<thead>
<tr>
<th>Age</th>
<th>Degree of Relation to Closest FH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
</tr>
<tr>
<td>&lt;20</td>
<td>220 (155)</td>
</tr>
<tr>
<td>20-29</td>
<td>240 (170)</td>
</tr>
<tr>
<td>30-39</td>
<td>270 (190)</td>
</tr>
<tr>
<td>40+</td>
<td>290 (205)</td>
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</tbody>
</table>

• FH is a dominantly (or co-dominant) transmitted disease.
• To provide a “clinically definite” diagnosis of FH, there should be evidence of dominant transmission in the family.
• LDL-C levels in family members besides proband were used to diagnose FH using “additional criteria” or rules.
• **NOTE:** other diagnostic approaches do not explicitly utilize actual LDL levels in the family for diagnosis.
Examples of “additional criteria” to diagnose new FH probands/families

- For “DEFINITE HETEROZYGOTE”
  - diagnosis by gene testing (rare)
- For “CLINICALLY DEFINITE HETEROZYGOTE”
  - Tendon xanthoma present and LDL-C meets at least first degree relative criteria.
  - Isolated pediatric case (<20 years old) with LDL cholesterol ≥240 mg/dl (>99.9 percentile).
  - Two first degree relatives meet “general population” criteria for LDL cholesterol.
  - ETC !! (including rules for “probable”, etc.

WHO Consultation on FH
Industry funding begins in 1994

- 5 centers added
  - Cincinnati (Stein)
  - Baltimore (Kwiterovich/Kafonek)
  - Boston (Lees)
  - Portland (Illingworth)
  - San Francisco (Kane/Malloy)
U.S. MEDPED Registry Growth

- **Number of Cases Found**
  - **Utah**
  - **USA + Utah**

- **Year**
  - 1989
  - 1991
  - 1993
  - 1995
  - 1997
  - 1999
  - 2001

- **Graph**
  - The graph shows the growth in the number of cases found from 1989 to 2001 for both Utah and the USA combined.
MEDPED Case Finding (FH Only) by Center

Number registered

- Coord. Center
- Utah
- Cincinnati
- Portland
- San Francisco
- Lipid Clinics
- Baltimore
- Cambridge

Legend:
- relatives
- probands
Total-C Levels in the Treatment Support Program

Year (number)  | Baseline | Final (by 2000)
---|---|---
<1993 (14) |  | 220 - 240
1993 (21) | 320 - 340 | 220 - 240
1994 (43) | 360 - 380 | 220 - 240
1995 (75) | 400 - 420 | 220 - 240
1996 (176) | 420 - 440 | 220 - 240
1997 (56) | 440 - 460 | 220 - 240

Multiple lipid phenotypes in a Utah FH kindred with a novel LDLR mutation (D92K)

Utah FH Pedigree
What are some of the challenges of FH screening?

- Identifying FH patients
  - DNA (gold standard only if found) versus clinical?
  - Who pays for DNA diagnosis?
  - How can clinical Dx be made available to anyone?

- There is urgency to finding FH
  - Previously, the Dx usually came after MI
  - Earlier, aggressive Rx → better outcomes
    - Universal screening of teenagers cost-effective for CAD prevention
Additional challenges in the U.S.

- No current data on:
  - How many FH are currently diagnosed
  - What percent are treated (any Rx)
  - How well FH are treated (current LDL-C)
  - CURRENT CAD RISKS OR OUTCOMES
Rethinking practical aspects of MEDPED

- Prior approach to diagnosis was labor intensive and relatively costly.
  - telephone contacting and data collection
  - diagnosis by MEDPED physician
- Diagnostic rules for initial FH pedigree or proband diagnosis lacked theoretical rigor, generalizability, or specific probabilities.
- MEDPED cutpoints had low sensitivity generally.
- Both general population and FH total-C and LDL-C mean ± SD needed updating.
Diagnostic approach using complex segregation analysis and likelihood theory

\[ \sum_{g_1=1}^{G} \sum_{g_2=1}^{G} \ldots \sum_{g_N=1}^{G} \prod_{i=1}^{F} f(g_i) \prod_{j=F+1}^{N} t(g_j \mid g_{jf}, g_{jm}) \prod_{n=1}^{N} p(x_n \mid g_n) \]

Indices comprising all combinations of genotypes. Each combination defines a “string”.

Likelihood products for probability of given set of genotypes. Separated into “founders” (prior probabilities) and “offspring” (transmission probabilities).

Penetrance function(s). Probability of an observed phenotype given the genotype.

MEDPED patent pending
Diagnostic approach using complex segregation analysis and likelihood theory

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0.998 or 0.002

Mendelian transmission probabilities

MEDPED patent pending
Diagnostic approach using complex segregation analysis and likelihood theory

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0.998 or 0.002

Mendelian transmission probabilities

updated means, SD

penetrance functions

MEDPED patent pending
Diagnostic approach using complex segregation analysis and likelihood theory

Actual family with LDL-C values known

MI death age 39, smoked prior LDL-C 216 age 24

age 11
LDL-C 198 (treated)

<table>
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<tr>
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<td>1</td>
</tr>
</tbody>
</table>

2 most informative product “strings”

\[
\begin{align*}
(0.998)(0.998)(1.0)(2.34E-06)(3.04E-05) \\
(0.998)(0.002)(0.5)(7.19E-03)(4.25E-03)
\end{align*}
\]

\[
\frac{\sum \text{strings with child}}{\sum \text{all possible strings}} = 99.3\% \text{ child has FH}
\]

MEDPED patent pending
What if ......... ?

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>FH Dx %</th>
</tr>
</thead>
<tbody>
<tr>
<td>... we only knew daughter’s LDL-C</td>
<td>58.9%</td>
</tr>
<tr>
<td>... her untreated LDL-C was 220</td>
<td>98.6%</td>
</tr>
<tr>
<td>... we only knew dad had MI age 39</td>
<td>93.3%</td>
</tr>
<tr>
<td>... the dad had a tendon xanthoma (almost regardless of dad’s LDL-C)</td>
<td>99.8%</td>
</tr>
</tbody>
</table>

MEDPED patent pending
Accurate Dx of FH using this method will depend on good underlying data

• “Prior” probability of FH in “founders”
  – Limited US data may need to be re-assessed
• LDL-C mean ± SD for FH and non-FH
  – general population LDL-C has dropped
  – old mean for FH was too high (ascertainment bias)
• CAD risk in FH and non-FH
  – some reasonable estimates exist
• Xanthoma by age in FH (available)
  – almost unheard of in non-FH

MEDPED patent pending
Cumulative Probability of Fatal and Non-Fatal CAD in 116 FH Pedigrees

Cumulative Probability of Non-Fatal CAD in Utah FH vs a Random U.S. Population

Hopkins PN. Clin Lipidol 2010; 5:339
Cumulative probability of CAD

FH men
FH women
non-FH men
non-FH women
Prevalence (%) in 346 Utah FH Heterozygotes

- Xanthoma
- Full Arcus

Age (years):
- <30
- 30-39
- 40-49
- 50-59
- 60+

Hopkins PN. Current Treatment Options in Cardiovascular Medicine 2002; 4:121
Tendon xanthoma prevalence by age in Utah FH

Prevalence of xanthoma expected to be 0 at age 2.2

\[ y = 0.8205x - 1.8113 \]

\[ R^2 = 0.9936 \]
Conclusions

• By 2004, about 8,000 FH had been diagnosed in the MEDPED registry
  — about 1.3% of US FH
• We have a long way to go!
• New automated approach will help!