Familial Hypercholesterolemia: Personalized public health epitomized

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Stanford and the FH Foundation
There has been more progress in lowering deaths from heart attacks and strokes among people who qualify for Medicare than those who are younger.
Our most notable finding is an absence of significant declines in hospitalization rates among young women and men across all age subgroups from 2001 to 2010. This observation is in contrast to the Medicare population studies, in which we described a >20% decline in hospitalization rates for AMI during this time period (8). One potential explanation for
The known mechanisms causing familial hypercholesterolemia linked to low-density lipoprotein (LDL) receptor (LDLR) function.
FH is common and devastating

- Modern genetic studies support a prevalence of ~1 in 250
- 50% of untreated men will have MI by age 50
- Causes 2-4% of heart attacks before age 60
- Cost $100s of millions

Hopkins et al.  J. Clinical Lipidology. 2011
Goldberg et al.  J. Clinical Lipidology. 2011
Lifelong exposure to high LDL causes early onset coronary disease.

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273

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Diagnostic Yield of Sequencing Familial Hypercholesterolemia Genes in Patients with Severe Hypercholesterolemia

Amit V. Khera, MD, Hong-Hee Won, PhD, Gina M. Pelosi, PhD, Kim S. Lawson, MS,
The FH Foundation
CASCADE FH™ Registry
Treated LDL-C is suboptimal (HeFH)

Adult (≥18 Years)
- Untreated: 235 mg/dL
- Treated: 143 mg/dL
- n=2595

Pediatric (<18 Years)
- Untreated: 229 mg/dL
- Treated: 180 mg/dL
- n=335

**mg/dL**
CAD more much more common in HeFH

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>n=2095, 41%</td>
<td>n=1424, 59%</td>
</tr>
<tr>
<td><strong>Average Age</strong></td>
<td>57</td>
<td>52</td>
</tr>
<tr>
<td><strong>Prior CAD</strong></td>
<td>26%</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Prior PCI</strong></td>
<td>13%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>Prior CABG</strong></td>
<td>8%</td>
<td>17%</td>
</tr>
</tbody>
</table>

5-6 fold higher than general population *

* DeGoma, E et al, Circ CV Genetics, 2016
FH disproportionately affects the risk of premature CAD

https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6040a1.htm
Data from the CASCADE FH™ Registry
Late Diagnosis and Treatment

GUIDELINES FOR SCREENING

Universal screening
FH Screening
2 yrs\(^1\)
9-11 yrs\(^{1,2}\)
Adult Screening
21 yrs\(^3\)

AGE
0 10 20 30 40 50

Treatment initiation\(^4\)
8-10 yrs

GUIDELINES FOR TREATMENT

Age 39 hyperlipidemia therapy initiated
CASCADE FH™ Registry\(^5\)

\(^1\) The AAP recommends screening for high cholesterol at age 2 if child has two parents with FH or high cholesterol; universal screening ages 9-11
\(^2\) EAS Guidelines recommend universal screening for cholesterol ages 9-11
\(^3\) ACC/AHA Adult Guidelines recommend universal screening of adults at age 21
\(^4\) EAS Guidelines recommend US statin initiation for at ages 8-10 for FH
\(^5\) CASCADE FH™ Registry participants are initiating lipid-lowering therapy at age 39 and receiving an appropriate diagnosis of FH at age 47
Estimating FH risk in the pooled cohorts

• Individual pooled data from 6 large US epidemiological cohorts
  – FHS, FHS Offspring, CARDIA, ARIC, CHS, NHANES III mortality dataset
  – 68,565 individuals with 1.2 million person-years of follow-up

• 20-79 year olds, categorized by baseline LDL level
  – FH phenotype (LDL-C ≥190 mg/dL) found in 3850 (5.6%)
  – non-FH, LDL <130 mg/dL (comparison)

• 30-year hazard of fatal and non fatal CHD

• Sensitivity analyses varying the definition of FH

Perak Circulation 2016
CHD events in the FH phenotype

Perak Circulation 2016

CV aging
Men: 10-20 years
Women: 20-30 years
and <60 years of age, respectively. Comparing this number of deaths with the leading causes of death by age group in the United States is revealing: Early-onset CHD death associated with the FH phenotype would cause more deaths in adults <60 years of age than homicide and would be comparable to road accidents (≈9000 and ≈20,000 deaths per year).
Dutch national program has been spectacularly successful

- As of 2012: 5,151 index cases of genetically positive FH identified
- Resulted in screening of 60,000 family members
- In total **27,069** FH cases identified
  - 36% of the family members had a positive genetic test.
- Costs for identifying 1 FH patient: 1200 euro
  - Test almost 3 family members to identify 1 positive FH mutation
- Costs effectiveness: costs per life year saved: 8700 Euro *

From: Statins in Familial Hypercholesterolemia: Consequences for Coronary Artery Disease and All-Cause Mortality


- FH patients who were statin users had a 44% RR reduction for the CAD and all-cause mortality versus those who had never used statins.
- Translates to a number needed to treat (NNT) of 222 for 1 year of statin therapy to prevent a death in FH patients.
  - Far outstrips the NNT for 1 year for primary prevention in non-FH patients (NNT: 500)
  - indeed, it is lower than the NNT for secondary prevention in non-FH patients (NNT: 350)
Cascade testing for FH has a “Tier 1” indication

- Good evidence if FH is identified early and treated aggressively, morbidity and mortality reduced 80%
- Highly cost effective
  - “We never find an individual with FH, we only find families with FH”
I FIGhT FH: Randomized Trial

You have high cholesterol. It is important that your relatives get checked.

You have this particular gene mutation that is causing your high cholesterol. It is important that your relatives get checked.
In the US, FH is rarely diagnosed

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273
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E78.01: FAMILIAL HYPERCHOLESTEROLEMIA

Z83.42: Family history of familial hypercholesterolemia

EFFECTIVE OCTOBER 1, 2016
The FIND FH® Initiative

www.theFHFoundation.org
FIND FH®
A multiyear screening and engagement initiative to identify and encourage the diagnosis and treatment of FH

Lab & Claims Data Mining
- Healthcare Encounter Data on 89 Million Americans with Cardiovascular Disease
- Data from a significant majority of clinical practices

EHR Data Mining
- Comprehensive EHR data from two academic centers
- Expanding to key integrated health systems

HCP & Individual Engagement
- Multichannel tools to engage health systems and individual HCPs
- Tools for clinicians and individuals with FH

The FH Foundation

Lab & Claims Algorithm

EHR Algorithm

HCP & Individual Engagement
FH Foundation FIND FH® Clinical Partners

Stanford Health Care

Geisinger Health System

University of Pennsylvania Health System

The Ohio State University
Wexner Medical Center
Software that learns by example.
We show the model examples of FH and Non-FH patients.
Patients are described to the model using features (inputs):
  - Lab Results
  - Patient Age
  - ICD9-10 & CPT codes
  - Prescription Medications
The model learns correlation between certain features and FH rate.
Model can classify FH in new patients using just their features.
Identifying FH patient characteristics using orthogonal data

- Clinic notes, text mining
- Lab Results
- Rx Claims
- Procedure codes

Confirmed FH Patients
Identifying FH patient characteristics using orthogonal data

Use discovered patterns in the small number of patients with the most complete data to identify other patients in the larger data set.

Unstructured data
- Clinic notes, dictations for key words, phrases
  - Personal medical Hx: age of cardiac event, procedure
  - Disease names: FH, hyperlipidemia,
  - Family history: premature coronary disease
  - Signs: xanthoma, xanthelasma, arcus

Structured data
- Labs: LDL-C, Total-C
- Procedure codes: cardiac cath, PCI, CABG, stress test
- Drug lists: statin and non-statin agents
Striking a Balance Between Precision (PPV) & Recall (Sensitivity)

- Perfect Recall; Low Precision
- Balanced Recall and Precision
- Low Recall; Perfect Precision
Workflow for Random Forest model

- Cohort of 110 physician-labeled FH patients
- Patients with one comorbidity

**CASES:**
- 10 patients

**CONTROLS:**
- Sample of 300 patients

**Normalized & Filtered Data:**
- Terms
- ICD9/CPT codes
- Drugs
- Labs

**Train Classifier**

**Evaluate Model Performance**
Workflow for Random Forest model

Precision (PPV) = 0.90
Recall (Sensitivity) = 0.86
F1 = 0.87
Specificity = 0.96
ROC = 0.95

Now doing manual chart reviews

Thus, could identify 86% of cases in test set with false negative rate of 14% and a false positive rate of 10%.
FIND FH® Lab & Claims Database

19,149,553
Unique Patients in Lx Data

12,861,217
Unique Patients in Lx/Dx/Px Overlap

12,834,404
Unique Patients in Lx/Rx/Dx/Px Overlap

40,328,108
Unique Patients in Rx/Dx/Px Overlap

19,095,699
Unique Patients in Lx/Rx Overlap

40,422,524
Unique Patients in Dx/Px Data

89,112,339
Unique Patients in Rx Data
FIND FH® Lab & Claims Algorithm Developed by The FH Foundation
Claims Data Source: IMS Health Real World Data: LRx longitudinal prescriptions and Dx medical claims
The case for the utility of lipid and genetic testing in childhood
Child–Parent Familial Hypercholesterolemia Screening in Primary Care

- Child–parent screening was feasible in primary care practices at routine child immunization visits.

- For every 1000 children screened, 8 persons (4 children and 4 parents) were identified with FH and were consequently at high risk for CVD.

For diseases like familial hypercholesterolemia (FH), the time is now.

When one base pair change (misspelling) into this can turn this
The FIND FH® Team

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