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Gemphire Therapeutics

Quest Diagnostics
Implementation Science for Health Impact

FH Case Identification & Cascade Testing

Risk Assessment & Follow-up

Optimizing Treatment & Lifelong Management

Health Disparities & Access
Familial Hypercholesterolemia

Report of a second WHO Consultation
Geneva, 4 September 1998
As inherited lipid disorders are diagnosable and treatable in the primary health care context, treatment should be available on a fair basis of risk when compared to other chronic disorders.
Governments and national institutes of health should be made aware of the existence of this health hazard.
Awareness among the general public and the medical community should be promoted. The support of education about these disorders at the public, school, paramedical, and medical level is required.
WHO should issue **guidelines** for identification, diagnosis, and medical management of inherited lipid disorders.
Specific education about these disorders should be provided at all levels, especially in medical training. There should be skills in primary health care to counsel about the risk of the disease, the dietary modifications, and knowledge about statins so that on-going care can be given.
A focus should be made on *the family* and the impact that bereavement could have on children. The plight of children with homozygous FH may need special budgetary consideration.
Constraints for **treating risk**. If plasmapheresis is not available, statins with proven efficacy in homozygous FH should be considered.
Patients must have unrestricted access to treatment and to cholesterol-lowering medication at low or no cost.
Long-term follow-up and drug compliance should be assured.
Research into the genetic and environmental factors influencing the expression of inherited lipid disorders, the development of atherosclerosis and the pharmacology and efficacy of lipid-lowering drugs should be stimulated. An indication is needed for ongoing research into the factors influencing heart disease, and how to intervene in the pathogenesis of the atherosclerotic process.
Specific attention may need to be given to the management of children of this disorder and here careful research is called for the establishment of active patient organizations, focused on the implementation of the above mentioned recommendations, is of utmost importance.
History & Hope around FH

David Marais
University of Cape Town & National Health Laboratory Service
South Africa

FH GLOBAL SUMMIT
THE FH FOUNDATION

2018.10.01
Marina del Rey
CA USA
FAMILIAL
HYPERCHOLESTEROLAEMIA
(FH)

Report of a second
WHO Consultation
Geneva, 4 September 1998

This report is dedicated to the memory of
Professor Roger R. Williams, founder and first chairman
of the International MED-PED FH Organization
The Hope for FH

*a common, severe, eminently treatable condition*

1. **Awareness in the public, profession, healthcare organisations**
   - Everyone with FH to be identified, all sectors in all countries
   - Individuals to know about FH (similar to other severe common disorders)
   - All doctors to recognise, inform and prescribe
   - Health care systems to embrace FH

2. **Appropriate intervention for all**
   - Life expectancy and quality of life as good as others’
   - Preventive rather than symptomatic treatment
   - Individualisation of treatment
   - Special centres to assist with problem cases

3. **Insight and Research**
   - Impact of FH on person (age, sex), families, psyche, economy
   - International cooperation for best care globally; studies, registries
   - Aetiology of dyslipoproteinaemia, includes migration of genes, history
   - Pathogenesis of atherosclerosis, includes lifestyle, inflammation
   - Risk of atherosclerosis, includes precision medicine
   - New treatment strategies, includes gene correction
Understanding FH

- **Heritable** hypercholesterolaemia (~1 in 250 persons)
- **Premature ischaemic heart disease**, now preventable
- Often clinically evident signs of dyslipidaemia  
  (Co-)dominant and recessive inheritance patterns

- Diagnosis: clinical + conventional laboratory tests  
  Genetic confirmation

<table>
<thead>
<tr>
<th>Dominant Pattern</th>
<th>LDLR, apoB_{100}, PCSK9, STAP1, ...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysbetalipoproteinaemia, Lp(a)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recessive Pattern</th>
<th>LDLRAP1, ABCG5/G8, (analbuminaemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysbetalipoproteinaemia</td>
<td></td>
</tr>
</tbody>
</table>

- Phenotypic variation: Heterozygous, Homozygous  
  Intermediate, Masked
FH in Cape Town

Heterozygous Phenotype

LDLR mutations  n=87  First 1182 genotyped, mutations 86%
                  3 mutations explain 80%  10 explain 99%

ApoB mutations  n=4  R3500Q, R3500W, R3531C, H3543Y

PCSK9 mutations n=5  S127R, R469W, R496W, G516V, H553R

STAP-1

Homozygous Phenotype

LDL  n=60

ARH  n=1

Sitosterolaemia  n=3
Streetwise with FH

Awareness

Atherosclerosis is smouldering
Controlled with statin for most
Concomitant additional medication

Crisis can be avoided

Cure may be possible
Implementation of Cascade Testing
Current and Future Practice in FH

Gerald F Watts
Cardiometabolic Service
Department of Cardiology, Royal Perth Hospital
School of Medicine, University of Western Australia
FH 2018 Global Summit, The FH Foundation
October 2nd, 2018, Marina del Rey, CA.
Barriers to FH Screening in Primary Care

• Lack of knowledge and skills in lipid management
• Lack of awareness of lipid screening guidelines
• Poor documentation of lipid and family history data
• Lack of knowledge and skills in genetics
• Lack of knowledge of FH and skills in family screening
• Cascade testing not suitable for population screening

Zimmerman et al J Community Genetics 2018 August.
Cascade Testing: into the Future

- Review policies on disclosure of health and genetic information
- Training and credentialing of providers in risk notification
- Research on risk notification: direct, assisted, context specific
- Greater involvement of genetic services: web based technology
- Priority to detection of at-risk children; patient & advocacy groups
- Public health strategies: mandatory registration, centralized services
- **Integrated detection strategies:** universal, systematic, opportunistic

Strategies to Improve Implementation

- Enable policy making, secure public financing
- Improve performance of provider organizations
- Strengthen capabilities of providers and consumers
- Empower communities and multiple stakeholders

Stakeholder Acceptability Study of Universal Screening of Children for FH

Health professionals

Surveyed 150 General Practitioners, 25 Practice and 25 Immunisation Nurses

➢ Over 90% considered it acceptable to screen children for FH
➢ Preference was to screen before attending school

General public

Deliberative public forum
Diverse representation (n=17)

➢ 16/17 considered that benefits > harm
➢ 15/17 screening best at immunization
➢ Voluntary, parental assent, test cholesterol, referral to specialist in FH
➢ Follow genetic testing guidelines

Bowman, Martin, Watts et al 2018 (in preparation)
Population-Level Identification and Management of Familial Hypercholesterolemia in Kaiser Permanente
Richard Birnbaum, MD, FACC- Department of Cardiology KP San Leandro
### Screening KPNCAL EMR to Find Patients with a High Likelihood of FH

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Members with LDL</th>
<th>% With Test</th>
<th>Members with FH</th>
<th>% Probable (&gt;80%)</th>
<th>% Certain (&gt;99.5%)</th>
<th>% with FH (Prob. + Cert.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-20</td>
<td>98,085</td>
<td>10.17</td>
<td>368</td>
<td>0.20</td>
<td>0.17</td>
<td>0.38 (1:263)</td>
</tr>
<tr>
<td>20-29</td>
<td>205,360</td>
<td>34.44</td>
<td>846</td>
<td>0.26</td>
<td>0.15</td>
<td>0.41 (1:244)</td>
</tr>
<tr>
<td>30-39</td>
<td>355,100</td>
<td>55.40</td>
<td>1,459</td>
<td>0.28</td>
<td>0.13</td>
<td>0.41 (1:244)</td>
</tr>
<tr>
<td>40-60</td>
<td>944,972</td>
<td>81.11</td>
<td>4,472</td>
<td>0.33</td>
<td>0.14</td>
<td>0.47 (1:213)</td>
</tr>
<tr>
<td>All</td>
<td>1,603,517</td>
<td>47.62</td>
<td>7,145</td>
<td>0.30</td>
<td>0.14</td>
<td>0.45 (1:222)</td>
</tr>
</tbody>
</table>

1 Of tested members on 7/1/2017
TPMG Familial Hypercholesterolemia Program
Clinical Workflow – 5y Strategy

FH Algorithm Applied to EMR → Automatic Referral to FH clinic → Cardiology FH Clinic
- Diagnosis
- Treatment
- Genetic testing

Cascade testing for KP relatives
- Affected children referred to Pediatric Lipid Program

Pediatric Care:
- Genetics
- Pediatric Endocrinology

Pharmacy Care Manager

Precision Tracking
- Monitoring and outreach

Research Practice Improvement

Adult Primary Care

Division of Research
The FIND FH® Initiative

Michael D. Shapiro
Associate Professor of Medicine and Radiology
Center for Preventive Cardiology
Knight Cardiovascular Institute
Oregon Health & Science University
The Promise of Precision Screening

FIND FH® is an innovative big data initiative to identify the estimated 90 percent of undiagnosed FH patients.

SCREEN 10 TO FIND 8
INSTEAD OF SCREENING 1,760
FIND FH Algorithm has Produced Comparable Results at National & Health System Levels

National HCP Outreach Pilot Results

Chart Reviews of Initial Probable FH Individuals

45 Total Individuals, 39 (86.7%) Identified by One or More Method

103 Total Individuals, 79 (76.7%) Identified by One or More Method

All 11 individuals identified with Simon Broome were also flagged with DLCL and/or MEDPED

All 29 individuals identified with Simon Broome were also flagged with DLCL and/or MEDPED
• FIND FH flagged 64/103 (62%) subjects that would not have been captured by conventional LDL-C screening criteria
  – # of subjects not on LLT with LDL-C >190 mg/dL = 25
  – # of subjects on LLT with LDL-C >130 mg/dL = 14
Implementation

PCPs with flagged patients are contacted

Flagged patients referred by PCPs

Appointment set

Physician assessment, recommendation, and follow-up

HCP f/u regarding care plan, lab results, & recs

- FH Education for PCP’s
- FHF Website

- Flag as FIND FH Research Patients

- E78.01
- Encourage family screening
- FHF Education and Patient Resources
- Enroll in CASCADE FH

= FH Foundation Resources

#FHCantWait | #FHSummit18
Implementation Science for Health Impact

Raising Awareness. Saving Lives

#FHCantWait | #FHSummit18

Implementation and Sustainability Infrastructure

Risk Assessment & Follow-up

FH Case Identification & Cascade Testing

Optimizing Treatment & Lifelong Management

Health Disparities & Access
Predictors of cholesterol screening and treatment in FH

Sarah de Ferranti, MD MPH
Dir. Preventive Cardiology
Boston Children’s Hospital
Associate Professor of Pediatrics
Harvard University Medical School
AWARENESS OF HYPERCHOLESTEROLEMIA

87% 82%

Previously Told Had Elevated Cholesterol
- Definite/Probable FH
- Severe Dyslipidemia

Percentage (%)

0 10 20 30 40 50 60 70 80 90 100
PREDICTORS OF DOCUMENTED STATIN USE

- Age
  - 20-39 years
  - 40-55 years
  - 60+ years

- Insurance status
  - Uninsured
  - Intermittently insured
  - Fully insured

- Usual source of care
  - None
  - Hospital/Emergency Department
  - Clinic

- Glucose tolerance
  - Normal GT
  - Pre-diabetic
  - Diabetic

- Blood pressure
  - Normal BP
  - Pre-hypertensive
  - Hypertensive

- History of ASCVD

Odds Ratio (95% CI)

- OLDER AGE
- FULLY INSURED
- HAVING A USUAL SOURCE OF CARE
- DIABETES
- HYPERTENSION
- PERSONAL HISTORY OF ASCVD
PROVIDER KNOWLEDGE: Pediatrician familiarity with guidelines and attitude towards screening

NHLBI (2011) Guidelines

Only ~25% of pediatricians were knowledgeable about the 2011 NHLBI Guidelines
PROVIDERS: BARRIERS TO SCREENING

- Obtaining an accurate family history
- Interpreting pediatric cholesterol profile
- Patients not returning for fasting test

Graph showing the percentage of providers who consider these factors as barriers. The categories are Not a Barrier, Minor Barrier, and Major Barrier.
PROVIDERS: BARRIERS TO TREATMENT

- Lack of comfort providing dietary counseling
- Patients' inability to afford visit copays
- Lack of pediatric lipid specialists in my area
- Lack of comfort using statins

- Lack of access to affordable healthy food
- Lack of access to appropriate physical activity
- Inability to adhere to lifestyle recommendations

de Ferranti et al. Pediatrics 2017
Implications of Health Literacy on Familial Hypercholesterolemia

Brian Tomlinson
Specialist in Internal Medicine & Clinical Pharmacology
Past President, Asian Pacific Society of Atherosclerosis & Vascular Diseases
Adjunct Professor, Department of Medicine and Therapeutics
The Chinese University of Hong Kong
Hong Kong SAR, China
Health literacy in familial hypercholesterolemia

Q1: How confident are you filling out medical forms by yourself?
Q2: How often do you have someone help you read hospital materials?
Q3: How often do you have problems learning about your medical condition because of difficulty understanding written information?

How to improve health literacy in familial hypercholesterolemia?

Education

• General
• Specific
  • FH websites such as The FH Foundation and other area and country websites
Implications of Health Literacy on Familial Hypercholesterolemia

• Inadequate health literacy is common in patients with familial hypercholesterolemia in many Asian countries.

• Increased age was associated with inadequate health literacy

• Inadequate general health literacy was related to lower income

• Patients with familial hypercholesterolemia need more education on their condition and general health literacy in many countries
Negative perceptions of statins: lost opportunity for prevention

Børge G Nordestgaard
Professor, Chief Physician, MD, DMSc

Conflict of Interest Disclosure
The Danish tax payer paid my education, my personal wages, my research funding
Do you recognize this scenario?

Once upon a time.....

- You believe in evidence-based medicine
- Statins reduce heart attack, stroke, and early death
- Nothing has ever been shown more convincingly
- Patients rarely experience side effects from statins
- Double-blind: 1:1000 have statin-related muscle symptoms

Suddenly.....

- A TV program reports negative news about statins
- Many stop taking their statins
- Doctor’s consultations discuss whether statins are good or bad
- This is very frustrating!

Even you start thinking.....

- Maybe statins do have many side effects?
- Indeed my muscles ache
- Just like that reported on TV
- Perhaps you cannot trust the medical literature?
- I stop taking my statin!
Myocardial infarction

HR=1.26 (95% CI, 1.21-1.30)
P=2 × 10^{-27} by log-rank test

Cumulative incidence (%)

Early statin discontinuation
Continued statin use

Years from initiation of statin therapy

Nielsen & Nordestgaard Eur Heart J 2016; 37: 908-916
Death from cardiovascular disease

HR = 1.18 (95% CI, 1.14-1.23)

P = $3 \times 10^{-15}$ by log-rank test

Cumulative incidence (%)

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>Continued statin use</th>
<th>Early statin discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nielsen & Nordestgaard Eur Heart J 2016; 37: 908-916
Fraction of individuals >40 years on statins in Denmark

Fraction of early statin discontinuation

Statin related Danish news stories in Danish media

Nielsen & Nordestgaard Eur Heart J 2016; 37: 908-916
Summary

• Statin discontinuation: $\uparrow$ CVD & $\uparrow$ mortality
• Negative news: $\uparrow$ statin discontinuation
• Positive news: $\downarrow$ statin discontinuation

Perspective

• The Media makes money reporting on statins
• The Media will not go away
• Discuss "news and fake news" with your patient
• Use the Media to report positive news on statin
Million Hearts 2022: Actions + Actors => Lower Cholesterol => Longer Healthier Lives

2018 FH Global Summit
October 2, 2018

Janet S. Wright MD, FACC
Executive Director, Million Hearts
Cholesterol: A Major Contributor to “the Million”

Estimated events prevented during 2017-2021

- Aspirin When Appropriate
- Blood Pressure Control
- Cholesterol Management
- Smoking Cessation
- Physical Inactivity
- Sodium Reduction
- Cardiac Rehab

Notes: Describes the estimated number of events prevented if Million Hearts objectives are gradually achieved during 2017-2021. The events included closely aligns with those outlined in Ritchey et al. JAMA. 2017;6(5). The total no. of expected events prevented does not equal the sum of events prevented by risk factor type as those totals are not mutually exclusive. The “aspirin when appropriate” intervention reflects aspirin use for secondary prevention only.

<table>
<thead>
<tr>
<th>Priority Population</th>
<th>Objectives</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blacks/African Americans</td>
<td>• Improving hypertension control</td>
<td>• Deliver guideline-congruent treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Problem-solve in med adherence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Advance practice of out-of-office readings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increase access to and participation in community-based activity programs</td>
</tr>
<tr>
<td>35-64 year olds</td>
<td>• Improving BPC &amp; statin use</td>
<td>• Implement treatment protocols/SMBP</td>
</tr>
<tr>
<td></td>
<td>• Decreasing physical inactivity</td>
<td>• Increase access to and participation in community-based activity programs</td>
</tr>
<tr>
<td>People who have had a heart attack or stroke</td>
<td>• Increasing cardiac rehab referral and participation</td>
<td>• Use opt-out referral and CR liaison visits at discharge; ensure timely enrollment</td>
</tr>
<tr>
<td></td>
<td>• Avoiding exposure to particulates</td>
<td>• Increase use of Air Quality Index</td>
</tr>
<tr>
<td>People with mental and/or substance abuse disorders who smoke</td>
<td>• Reducing tobacco use</td>
<td>• Integrate tobacco cessation into behavioral health treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Institute tobacco-free policy at treatment facilities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tailored quitline protocols</td>
</tr>
</tbody>
</table>
What Works—and What Do We Do?

• Improve Prescribing
  o Encourage the use of a risk calculator and guideline-based protocol
  o Spread best practices in cholesterol management
    ▪ Deliver content and experts—both patients and clinicians---to relevant audiences
    ▪ Develop and launch cholesterol webpage on Million Hearts website
  o Increase reporting on statin therapy performance measures

• Problem-solve in medication adherence
  o Develop/disseminate lay-friendly translation of risk/benefit of statins
  o Share adherence best practices: 90 day supply, med synchronization, home pharmacy, pillboxes, reminders, mail order
What Works—and What Do We Do?

• Reward high-performance in teams, practices, systems
  o Identify high performers and spread their lessons

• Communities can increase safe, accessible, and affordable places to be active and provide peer support, training in healthy eating & cooking
  o Funding of State and local health departments
  o Y’s Healthy Heart Ambassadors, Faith-based orgs, Community Health Workers
  o Walk with a Doc, Walk with a Mayor; Girl Trek; Mall walking programs
  o CMS Community Coalitions
Advocacy Driving Research

2018 FH Global Summit
Samuel S. Gidding MD
The Dartmouth Institute Model for Disease-Based Registries

Learning Health System

- **Patient & Family**
- **Provider & Care Team**
- **Shared Information Environment**
  - Personal Health Records
  - Patient Facilitated Networks
  - Registries: Research & Improvement
  - Electronic Health Records
    - Collaborative Improvement Networks

**Optimal Health and High Value Care for Patients and Populations**
Data from the CASCADE FH Registry: Uptake of Genetic testing

- **N=4965 Registry Patients**
- **6.8%**

**338 Genetic Testing**

- **215** Confirmed mutation (64%):
  - **73%** LDL-Receptor mutation
  - **8.8%** APO-B mutation
  - **0.9%** PCSK mutation
Diversity and Outcomes

Race (N=4335)

- White: 79%
- Hispanic: 6%
- Black/African American: 8%
- Asian: 3%
- Other: 5%

Gender (N=4325)

- Male: 41%
- Female: 59%

Children (N=477)

- HeFH (n=462)
- HoFH (n=15)

Adults (N=3853)

- HeFH (n=3801)
- HoFH (n=52)
Patients in the registry have significantly lower LDL-C, by ~25 mg/dl, on follow-up. Even greater effects seen in HoFH patients (i.e. 90 mg/dl decrease in HoFH children).
Provider & Care Team
EHR; Collaborative Improvement Networks

Raising Awareness. Saving Lives

#FHCantWait | #FHSummit18

Provider & Care Team

EHR; Collaborative Improvement Networks

Pre-Treatment
LDL-C, mg/dL

231
134
102

Study Entry
LDL-C, mg/dL

230
141
120 *

Follow-up
LDL-C, mg/dL

235
85 *

All subjects (N=1900)
No CHD at entry (N=1196)
CHD at entry (N=704)
### CASCADE REGISTRY

#### CVD Event rates/100 patient years

<table>
<thead>
<tr>
<th></th>
<th>Without Event (1196)</th>
<th>With New Event (84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rate/ 100 Patient Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Prior CAD; N = 41/1196</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event Rate/ 100 Patient Years</td>
<td>0</td>
<td>2.21</td>
</tr>
<tr>
<td>Prior CAD; N = 43/704</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event Rate/ 100 Patient Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment LDL</td>
<td>231 mg/dl</td>
<td>247 mg/dl</td>
</tr>
<tr>
<td>Treated LDL</td>
<td>103 mg/dl</td>
<td>79 mg/dl</td>
</tr>
<tr>
<td>% on &gt; 2 meds</td>
<td>77%</td>
<td>83%</td>
</tr>
</tbody>
</table>
Diagnoses of E78.01

Cumulative Number Of FH Coded Individuals (E78.01)

- Oct 2016: 16,985
- Nov 2016: 34,279
- Dec 2016: 50,522
- Jan 2017: 66,768
- Feb 2017: 81,672
- Mar 2017: 97,855
- Apr 2017: 110,577
- May 2017: 123,402
- Jun 2017: 135,454
- Jul 2017: 145,246
- Aug 2017: 155,778
- Sep 2017: 165,068
- Oct 2017: 174,907
- Nov 2017: 183,747
- Dec 2017: 191,264

~10% ~1%
Disease genes and modifier genes in FH

Marianne Abi Fadel
Dean of the School of Pharmacy,
Professor of Biochemistry and Molecular Biology,
Saint Joseph University of Beirut

Catherine Boileau
Chair of the Department of Medical Genetics,
Professor of Genetics,
Paris Diderot University
FH: many genes but a missing heritability

**Dutch Lipid Clinic Score for FH**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Score</td>
<td></td>
</tr>
<tr>
<td>Definite Familial Hypercholesterolemia</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Probable Familial Hypercholesterolemia</td>
<td>6-8</td>
</tr>
<tr>
<td>Possible Familial Hypercholesterolemia</td>
<td>3-5</td>
</tr>
<tr>
<td>Unlikely Familial Hypercholesterolemia</td>
<td>&lt;3</td>
</tr>
</tbody>
</table>

**FH molecular diagnosis in the French National Registry**

- LDLR: 52.34%
- APOB: 44.01%
- PCSK9: 2.63%
- Other: 1.02%

- 342 ADH families (1972 subjects)
- LDLR: 67%
- APOB: 14%
- non-LDLR/non-APOB: 19%

*Rabès et al., Curr Opin Lipidol 2018*

*Saint-Jore et al., Eur J Hum Genet 2000/ Varret et al., Clin Genet 2008*
FH: where is the missing heritability?

HeFH-M⁻: mutation negative FH probands

- Proper gene and missed variant
- Proper gene and unrecognized variant
- Variant in an untested gene

Ex: the case of the APOE gene

APOE p.[(Leu167del)]¹

Found in 1.3% of French FH²

¹Marduel et al., Hum Mutat 2013/
²Wintjens et al., J Lipid Res 2016
HeFH-M\(^{-}\): mutation negative FH probands

- Proper gene and missed variant
- Proper gene and unrecognized variant
- Variant in an untested gene
- New still unknown disease gene

- FH4 at 16q22.1 \(^{1}\)
- FH6 at 8q24.22 \(^{2}\)
- FH7 at 21q22.3 (and 3q25-26) \(^{3}\)
- ....
- ARH2 at 15q25-q26 \(^{4}\)
- ARH3 at 1p36.1-p35 and 13q22-32 \(^{5}\)

\(^{1}\) Marques-Pinheiro et al., Eur J Hum Genet 2010
\(^{2}\) Cenarro et al., Clin Genet 2011
\(^{3}\) Wang et al., Plos One 2011
\(^{4}\) Ciccarese et al., Am J Hum Genet 2000
\(^{5}\) El-Kateb et al., Circ Res 2002
Monogenic FH: where is the missing heritability?

- **HeFH-M⁺**: mutation positive FH probands
  - Proper gene and missed variant
  - Proper gene and unrecognized variant
  - Variant in an untested gene
  - New still unknown disease gene

- **HeFH-M⁻**: mutation negative FH probands

  → A polygenic mechanism for disease initiation that mimics a monogenic disease transmission
The two first GOFs* in FH

- **S127R**
  - Patient HC92-II-7: GATGAGGCGGACCTGCTG
  - T→A at position 625 (Ser127Arg)

- **F216L**
  - Patient HC60 patient II-2: GGGACCGGCTCCACAGACA
  - T→C at position 890 (Phe216Leu)

GOF* = Gain Of Function mutation

NARC1 / PCSK9 is the third gene in FH

Mutations in PCSK9 cause autosomal dominant hypercholesterolemia

Marianne Abifadel, Mathilde Varret, Jean-Pierre Rabès, Delphine Allard, Khadija Ouggerram, Martine Devillers, Corinne Craudd, Suzanne Benjamett, Louise Wickham, Danièle Erlich, Aurélie Derré, Ludovic Villéger, Michel Farnier, Isabel Beucher, Eric Buczkrt, Jean Chambaz, Bernard Chanul, Jean-Michel Lecerfer, Gerald Luc, Philippe Moulin, Jean Weissenbach, Annick Prat, Michel Krempf, Claudine Junien, Nabil G Seidah and Catherine Boileau.

Name agreed upon with HGNC
Human Genome Organisation Nomenclature Committee
The current molecular picture of PCSK9

Abifadel et al., 2003/ Timms et al., 2004/ Allard et al., 2005/ Chen et al., 2005/ Naoumova et al., 2005/ Pisciotta et al., 2006/ Cohen et al., 2005&2006/ Kotowski et al., 2006/ Yue et al., 2006/ Cameron et al., 2006/ Berge et al., 2006/ Nassoury et al., 2007/ Fasano et al., 2007/ Homer et al., 2008/ Miyake et al., 2008/ Mayne et al., 2011/ Abifadel et al., 2012/ Hopkins et al., 2015/ El Bitar et al., 2018
Genetic architecture of human disease…

…initiation and variability

…disease genes and modifiers
The Rationale for Genetic Testing

Amy Curry Sturm, MS, LGC
Professor, Genomic Medicine Institute
Director, Cardiovascular Genomic Counseling
Co-Director, MyCode Genomic Screening and Counseling
Geisinger
The Power of Genetic Testing

An example from MyCode

- 62 year old woman
- Struggled to control high cholesterol for years
- Learned she has LDLR pathogenic variant (c.1775G>A, p.Gly592Glu) via MyCode
- Prompted her to pay attention to her chest pain
- Sought medical attention, diagnosed with CAD, underwent triple CABG
- Several relatives now tested and confirmed to also have FH

“If I had not taken that test I might be dead by now.”

October 3, 2017
THE PRESENT AND FUTURE

JACC SCIENTIFIC EXPERT PANEL

Clinical Genetic Testing for Familial Hypercholesterolemia

JACC Scientific Expert Panel

Amy C. Sturm, MS, Joshua W. Knowles, MD, PhD, Samuel S. Gidding, MD, Zahid S. Ahmad, MD, Catherine D. Ahmed, MBA, Christie M. Ballantyne, MD, Seth J. Baum, MD, Mafalda Bourbon, PhD, Alain Carrié, MD, PhD, Marina Cuchel, MD, PhD, Sarah D. de Ferranti, MD, MPH, Joep C. Defesche, PhD, Tomas Freiberger, MD, PhD, Ray E. Hershberger, MD, G. Kees Hovingh, MD, PhD, Lala Karayan, MPH, Johannes Jacob Pieter Kastelein, MD, PhD, Iris Kindt, MD, MPH, Stacey R. Lane, JD, MBE, Sarah E. Leigh, MSc, PhD, MacRae F. Linton, MD, Pedro Mata, MD, PhD, William A. Neal, MD, Borge G. Nordestgaard, MD, DMSc, Raul D. Santos, MD, PhD, Mariko Harada-Shiba, MD, PhD, Eric J. Sijbrands, MD, PhD, Nathan O. Sitziel, MD, PhD, Shizuya Yamashita, MD, PhD, Katherine A. Wilemon, BS, David H. Ledbetter, PhD, Daniel J. Rader, MD,

Convened by the Familial Hypercholesterolemia Foundation
Familial hypercholesterolemia (FH) includes multiple clinical phenotypes due to different underlying molecular etiologies and additional genetic background. Low-density lipoprotein cholesterol (LDL-C) level, number of mutations, and additional pathogenic and/or protective genetic variation determines coronary artery disease (CAD) risk level. \textit{APOB} = gene encoding apolipoprotein B; \textit{HeFH} = heterozygous familial hypercholesterolemia; \textit{HoFH} = homozygous familial hypercholesterolemia; \textit{LDLR} = gene encoding low-density lipoprotein receptor; \text{Lp(a)} = lipoprotein a; \textit{PCSK9} = gene encoding proprotein convertase subtilisin/kexin 9; \textit{SNP} = single nucleotide polymorphism.
Who should we offer genetic testing to?

Should be **offered**

Very intentional wording
Additional Considerations for Probands

Genetic testing for FH may be considered in the following clinical scenarios:

1. Children with persistent* LDL-C levels $\geq 160$ mg/dl (without an apparent secondary cause of hypercholesterolemia†) with an LDL-C level $\geq 190$ mg/dl in at least 1 parent or a family history of hypercholesterolemia and premature CAD‡

2. Adults with no pre-treatment LDL-C levels available but with a personal history of premature CAD‡ and family history of both hypercholesterolemia and premature CAD‡

3. Adults with persistent* LDL-C levels $\geq 160$ mg/dl (without an apparent secondary cause of hypercholesterolemia†) in the setting of a family history of hypercholesterolemia and either a personal history or a family history of premature CAD‡

Evidence Grade: Class of Recommendation IIb, Strength of Evidence C-EO
Recommendations for At-risk Relatives

B. At-risk relatives

1. Cascade genetic testing for the specific variant(s) identified in the FH proband (known familial variant testing) should be offered to all first-degree relatives. If first-degree relatives are unavailable, or do not wish to undergo testing, known familial variant testing should be offered to second-degree relatives. Cascade genetic testing should commence throughout the entire extended family until all at-risk individuals have been tested and all known relatives with FH have been identified.

Evidence Grade: Class of Recommendation I, Strength of Evidence B-R
Different Categories of Patients May Undergo FH Genetic Testing

Patient at risk due to family history of FH

- Cascade genetic testing
- Consider alternative molecular etiologies:
  - Polygenic
  - High Lp(a)
  - APOE
  - As yet undiscovered FH genes
  - Autosomal recessive FH (biallelic LDLRAP1 pathogenic variants)
  - Phenocopies
    - Sitosterolemia (autosomal recessive pathogenic variants in ABCG5 or ABCG8)
    - Lysosomal acid lipase deficiency (autosomal recessive pathogenic variants in LIPA)

Patient with FH phenotype

- LDLR, APOB, PCSK9 genetic testing
- Positive
- Negative

Genotype + Phenotype -
- Monitor LDL-C

Genotype + Phenotype +
- Treat LDL-C

Genotype - Phenotype +
- Treat LDL-C and/or phenocopy condition with specific treatment recommendations

Abbreviations: the same as in Figure 1.
CENTRAL ILLUSTRATION: The Genetic Testing Process in an Index Patient (Proband) and Family

Identify index patients who should be offered familial hypercholesterolemia (FH) genetic testing

Provide genetic counseling or refer for genetic counseling

Patient decides not to undergo genetic testing

Management based on current cardiovascular risk reduction guidelines

Recommend cascade screening via lipid testing for at-risk relatives

Negative or variant of uncertain significance (VUS) genetic testing results:
Management based on current cardiovascular risk reduction guidelines

Recommend cascade screening via lipid testing for at-risk relatives

Additional genetic testing may be warranted as sensitivity improves over time

If VUS classification changes, provide updated information to patient

Positive genetic testing results:
Pathogenic variant(s) identified; FH diagnosis confirmed

Recommend cascade genetic testing and genetic counseling for at-risk relatives

Relative does not undergo genetic testing: recommend clinical screening and care since could have pathogenic variant(s)

Relative tests negative: relative and their children not at risk and do not require clinical screening and care unless indicated by cardiovascular risk factors

Relative tests positive: recommend clinical screening and care; recommend genetic testing to additional at-risk relatives in cascade fashion

Genetic testing was a wake up call for me – it helped to motivate me to take my medication and give me confidence in my diagnosis.

Kari

*FH Advocate for Awareness*
Elevated Lp(a) in FH

Anne Tybjærg-Hansen MD DMSc
Professor, Chief Physician
Copenhagen University Hospital and Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

FH Global Summit October 2018
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Reduction in Lp(a)</th>
<th>Mechanism/problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>0 to ↑ 7%</td>
<td>No effect</td>
</tr>
<tr>
<td>Niacin</td>
<td>↓ 25%</td>
<td>Side effects</td>
</tr>
<tr>
<td>CETP inhibitor</td>
<td>↓ 0-50%</td>
<td>Attenuation of apoB lipidation</td>
</tr>
<tr>
<td>ApoB antisense</td>
<td>↓ 25%</td>
<td>Decreased hepatic apoB synthesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>PCSK9 inhibitor</td>
<td>↓ 25%</td>
<td>Decreased Lp(a) formation?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Increased catabolism?)</td>
</tr>
<tr>
<td>Apheresis</td>
<td>↓ 35%</td>
<td>Removal of apoB lipoproteins</td>
</tr>
<tr>
<td>Apo(a) antisense</td>
<td>↓ 90%</td>
<td>Decreased hepatic apo(a) synthesis</td>
</tr>
</tbody>
</table>
Lipoprotein(a): key points

• Lp(a) cholesterol is co-measured in LDL-C
Adjusted LDL-C: P=0.46

Dutch Lipid Clinic Network

Unlikely Possible Probable/definite

Lipoprotein(a), mg/dL

Unadjusted LDL-C: P<0.0001

Adjusted LDL-C = LDL-C minus (Lp(a)*0.30)

Copenhagen General Population Study

High lipoprotein(a) as a cause of clinical familial hypercholesterolemia (FH)

Copenhagen General Population Study
N=46,200

Ranked causes of clinical FH
1. LDLR
2. Lp(a) (25%)
3. APOB
4. PCSK9

Whom to screen for Lp(a)↑

- Premature CVD
- Familial hypercholesterolemia
- Family history premature CVD or Lp(a)↑
- Recurrent CVD despite statins
- ≥3% 10-year risk of fatal CVD - Europe
- ≥5% 10-year risk of fatal/nonfatal CHD - US
- Aortic valve calcification or stenosis
- Desirable level Lp(a)<50mg/dL (<100 nmol/L)

Nordestgård et al. EAS Consensus Panel. Eur Heart J 2010;31:2844-2853 - updated
Understanding U.S. Reimbursement: 
*Follow the Incentives*

The FH Global Summit  
October 2, 2018  
Marina del Rey, CA
The fragmented reimbursement system: different payers, different incentives…but increasing power to industrialized buyers

**Employers:** minimize employee complaints, maximize savings

**Commercial insurers:** minimize financial risk

**Medicare payers (less flexibility than commercial insurers):**
- Part D Plans (PDPs): minimize drug expense (and avoid really sick patients)
- Advantage: focus on savings, with a longer-term view

**PBMs:** restrict choice for greater rebate, fee income

**Health systems (for hospital-focused drugs):** minimize drug expense

**Patients:** Maximize therapeutic impact, minimize cost (both when paying attention)
Payers interpret labels subjectively: the PCSK9i experience

Label: HeFH or ASCVD “in patients on max tolerated statins who require additional lowering of LDL-C”

Some definitions from selected plans/PBMs

• What’s the criteria for “additional lowering”? LDL-C > or = to 130

• What’s the definition of “max tolerated statin”?
  – Statin intolerance proven by rhabdomyolysis &/or elevated CK, creatinine, myoglobin
  – Documented adherence to statins before prescription and for re-authorization

• How do you document diagnosis of HeFH patients?
  – Documented untreated LDL-C > 190
Regeneron/ICER: the challenge of value-based pricing when two sides don’t see value in the same way

• Summer 2015: prices PRALUENT® at $14.6K
• Launches DUPIXENT®, first new effective drug for atopic dermatitis
  – Works with ICER & arrives at $37k WAC/$30K net...
  – Disappointing sales – 50% below consensus expectation
• Following release of ODYSSEY: a new ICER-related pricing deal...with teeth
  – ~$4500...if payers eliminate UM requirements for high-risk patients
  – Express Scripts signs on...but Amgen appears to meet price

SOURCE: IMS; Salim Syed, Mizuho Securities
Not all new drugs will face the same level of access restrictions

For example: 2018 pharmacy-benefit launches

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Government-Driven Advantages</th>
<th>Economic</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>larotrectinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ivosidenib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidiolex (cannabinol)</td>
<td></td>
<td></td>
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<tr>
<td>brexanolone</td>
<td></td>
<td></td>
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<tr>
<td>luspatercept</td>
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<td></td>
<td></td>
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<tr>
<td>patisiran</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Palynziq (pegvaliase-ppz)</td>
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<td></td>
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<tr>
<td>inotersen</td>
<td></td>
<td></td>
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<tr>
<td>Waylivra (volanesorsen)</td>
<td></td>
<td></td>
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<tr>
<td>selumetinib</td>
<td></td>
<td></td>
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<tr>
<td>lanadelumab</td>
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<tr>
<td>Galafold (migalastat)</td>
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<tr>
<td>Calquence (acalabrutinib)</td>
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<tr>
<td>ALIS (amikacin liposome inhalation)</td>
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<tr>
<td>Biktarvy (bictegravir/entricitabine)</td>
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<tr>
<td>Mavenclad ( cladribine)</td>
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<tr>
<td>Sympazan PharmFilm (clobazam)</td>
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<td>Ajovy (fremanezumab)</td>
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<td>Aimovig (erenumab)</td>
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<td>Emgality (galcanezumab)</td>
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<tr>
<td>ozanimod</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>samidorphan/buprenorphine</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>fevipiprant</td>
<td></td>
<td></td>
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<tr>
<td>Dupixent (asthma)</td>
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<tr>
<td>elagolix</td>
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<td></td>
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<td>risankizumab</td>
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<tr>
<td>Olumiant</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ilumya</td>
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</tbody>
</table>

The chart shows the access score for various drugs, with fewer access hurdles indicating easier access and more access hurdles indicating harder access.
Case Study: brexanolone vs. samidorphan/buprenorphine

Both drugs represent significant innovations in psychiatric treatments

<table>
<thead>
<tr>
<th>Brexanolone: Postpartum depression</th>
<th>Samidorphan/buprenorphine: Persistent and resistant depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Access Advantages</strong></td>
<td></td>
</tr>
<tr>
<td>• Treats high unmet need</td>
<td>• Protected class</td>
</tr>
<tr>
<td>• Limited therapy duration</td>
<td>• Novel, opioid-targeting mechanism</td>
</tr>
<tr>
<td>• FDA breakthrough status</td>
<td>• FDA fast track status</td>
</tr>
<tr>
<td>• Medical benefit drug</td>
<td>• Effective patient advocacy organizations</td>
</tr>
<tr>
<td>• Effective patient advocacy organizations</td>
<td></td>
</tr>
<tr>
<td><strong>Access Challenges</strong></td>
<td></td>
</tr>
<tr>
<td>• New payer-expense category</td>
<td>• High prevalence</td>
</tr>
<tr>
<td>• Undefined volume of use</td>
<td>• Highly genericized market</td>
</tr>
<tr>
<td>• Off-label potential</td>
<td>• Limited bundling capabilities</td>
</tr>
<tr>
<td>• Durability of effect</td>
<td>• Significant MD advocacy pressure?</td>
</tr>
<tr>
<td></td>
<td>• Somewhat equivocal P3 data</td>
</tr>
</tbody>
</table>

```
<table>
<thead>
<tr>
<th>More Access Hurdles</th>
<th>Fewer Access Hurdles</th>
</tr>
</thead>
<tbody>
<tr>
<td>brexanolone</td>
<td></td>
</tr>
<tr>
<td>samidorphan/buprenorphine</td>
<td></td>
</tr>
<tr>
<td>neurology</td>
<td></td>
</tr>
<tr>
<td>All Drug Average</td>
<td></td>
</tr>
</tbody>
</table>
```

- Green: Government-Driven Advantages
- Orange: Economic
- Blue: Clinical

- Graph shows the comparison of access hurdles between brexanolone and samidorphan/buprenorphine.
New models of care and health economics

Dimensions of value and how to assess them

Care and Economics: A Sometimes Messy Intersection – Panel Session
FH Foundation Global Summit, Marina del Rey, USA
October 2, 2018

Finn Børlum Kristensen, MD, PhD
Science and Policy
Professor, University of Southern Denmark
What is Health Technology Assessment?

ISPOR HTA CENTRAL (web resource) explains HTA this way:

“an evidence-based, multidisciplinary process intended to support healthcare decision making by assessing properties and effects of one or more new or existing health technologies in comparison with a current standard. Aiming at determining added value, HTA uses explicit analytical frameworks based on research and the scientific method in a systematic, transparent, unbiased way”

Source: ISPOR HTA Central
www.ispor.org/strategic-initiatives/hta-central
Components of HTA within the healthcare decision-making process

**Decision-making steps**
- Request for HTA Support
- Health care technology decision problem
- Policy analysis
- Recommendation
- Decision

**Questions**
- What level of support does the decision maker need?
- What is the problem and what research is needed?
- How should research be conducted?
- What does the research say?
  - What do we know?
  - What can we infer?
  - What don’t we know?
- How should the results of the research be put into context?
- What should the decision be?

**HTA Process**
- Defining the HTA process
  - Structure and governance / organizational aspects (e.g., government/health insurance based)
  - Underlying principles (e.g., accountability for reasonableness; formal agreement with decision maker)
  - Priority setting process (e.g., application process for new medicines)
  - Framing and scoping
  - What is the role of this HTA?
  - What are the key questions to answer?
  - What output from HTA is required?
- Repeat until clearly defined

**Assessment**
- How should research be identified and interpreted?
  - Guidance for identification and interpretation of research
  - Standards / checklists for researchers
  - Peer review of HTA research
  - Use of experts or expert panels / grading systems
  - Reporting

**Contextualization**
- What considerations should be made explicit?
  - Deliberative processes; committee work
  - Stakeholder engagement; value frameworks
  - Voting rules; weighted / nominal group techniques
  - Qualitative research; thresholds
  - How can HTA from other jurisdictions be adapted?
  - How should budget impact be considered?

**Implementation and Monitoring**
- Communicating the output of HTA (e.g., recommendation)
- Defining involvement of HTA process with decision (e.g., arms length); transparency; evaluating impact of HTA

Source: *Value in Health*, accepted for publication (January 2019)
“Identifying the need for good practices in HTA: Summary of the ISPOR HTA Council Working Group Report”
Value in healthcare is multi-dimensional

<table>
<thead>
<tr>
<th>Clinical added value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health problem and current interventions</td>
</tr>
<tr>
<td>Technical characteristics of interventions</td>
</tr>
<tr>
<td>Clinical efficacy / effectiveness</td>
</tr>
<tr>
<td>Safety</td>
</tr>
<tr>
<td>Organizational aspects</td>
</tr>
<tr>
<td>Costs and economic aspects</td>
</tr>
<tr>
<td>Patient and social aspects</td>
</tr>
<tr>
<td>Ethical aspects</td>
</tr>
<tr>
<td>Legal aspects</td>
</tr>
</tbody>
</table>

Source: European Network for Health Technology Assessment, EUnetHTA
www.eunethta.eu
Paths in decision-making in Europe based on HTA

HTA

Clinical benefit

Cost effectiveness

Reimbursement / procurement decision – may be augmented by health economics Budget impact, cost-effectiveness

Reimbursement / procurement decision based on cost-effectiveness

e.g. Germany, France, Denmark

e.g. UK
Cost-Effectiveness of Screening and Management Strategies for Familial Hypercholesterolemia in the United States: A Markov Model Update

Joel W. Hay, PhD

2018 FH GLOBAL SUMMIT, Marina Del Rey CA, USA
Tuesday, October 2, 2018
Familial Hypercholesterolemia (FH)

“If untreated, approximately 50% of men and 30% of women with FH will develop CHD [coronary heart disease] by age 60 years and around 50% of men will die before the age of 60 years.”

Nordestgaard BG et al. Eur Heart J 2013; 34:3478-3490a
Methods and Data

Modeling

- 1,000 adult males in high risk initial cohort, per arm
- Decision tree for screening disease detection probabilities
- Markov model to estimate QALYs\(^\text{a}\) & costs, per arm
- ICER\(^\text{b}\) results in costs/QALY between arms

Data sources

- DNA and lipid test sensitivities:
  - Sharma (2012), literature review
- CHD\(^\text{a}\) risk adjustments:
  - Framingham Heart Study, Lee (2002), literature review
- QALYs:
- Costs:
  - 2013 VA Federal Supply Schedule, Ambry Genetics, Medicare Physician Fee Schedule, literature review

\(^\text{a}\)Quality adjusted life-years
\(^\text{b}\)Incremental cost-effectiveness ratio

Coronary heart disease
Results

Markov Model Results

<table>
<thead>
<tr>
<th></th>
<th>Total Costs</th>
<th>Total QALYs</th>
<th>Incremental Costs</th>
<th>Incremental QALYs</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Screening (reference case)</td>
<td>$10,396</td>
<td>18.34</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Genetic Screening</td>
<td>$10,559</td>
<td>18.35</td>
<td>$163</td>
<td>0.01</td>
<td>$16,292</td>
</tr>
<tr>
<td>Statin Plus PCSK-9 Inhibitor</td>
<td>$28,082</td>
<td>18.91</td>
<td>$17,523</td>
<td>0.56</td>
<td>$31,291</td>
</tr>
</tbody>
</table>

• Genetic Screening is cost-effective at a US willingness-to-pay threshold of $150,000/QALY

• Although Lipid Screening + PCSK9 Inhibitor incurs more lifetime costs than Lipid Screening alone or Genetic Screening in FH, it provides the most incremental benefits within the willingness-to-pay threshold
Discussion

• Because of falling screening costs, genetic cascade screening for FH is now generally cost-effective in the US.

• Aggressive LDL lowering with statin + PCSK-9 inhibitors in FH patients is a cost-effective way to improve health outcomes for high cholesterol patients.

• However, much additional information is needed in order to suggest policy implications, including
  • more thorough FH registries in the US,
  • large sample genetic testing for FH in the US, and
  • long term, randomized studies of adherence and outcomes.
Conclusion

• This analysis found that the benefits of genetic cascade screening for FH exceed the costs in the US for genetic screening cost < $1,500.
  • Genetic mutations for FH in the US population are not fully identified.
  • Intensive therapy (statin + PCSK-9) programs are cost effective in the FH population.
• Because FH patients face a lifetime of elevated LDL-C levels, efforts and resources can be directed towards increased screening and improved, sustained adherence to statin, PCSK-9 and other lipid treatment to help improve health outcomes for these individuals.
Clinical Implications of Delayed Care

Kelly D Myers
Chief Technology Officer
The FH Foundation
Contributors to Delayed Care

1. ~90% of individuals with FH are undiagnosed
2. Lack of first-line statin therapy early in life
3. Family screening
4. Low prescribing rates for combination therapy for those who cannot reach recommended treatment thresholds
5. Access to therapy
Beyond Lack of Diagnosis The Lack Of Prescribing for **ALL LLTs** Creates Challenges

Source: *FOCUS Data as of Dec 2017* - 133,440 Individuals with ICD-10 for FH (E78.01) vs 2,151 CASCADE FH Registry Individuals
## Delayed Care

<table>
<thead>
<tr>
<th>ICD-10 FH by Age Group</th>
<th>Any Statin in Last 5 YR</th>
<th>No Therapy in Last 5 YR</th>
<th>Any Statin Mean LDL-C</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>16.0%</td>
<td>84.0%</td>
<td>240.0</td>
<td>66.4</td>
</tr>
<tr>
<td>18-49</td>
<td>46.5%</td>
<td>53.5%</td>
<td>141.1</td>
<td>65.7</td>
</tr>
<tr>
<td>50-60</td>
<td>64.0%</td>
<td>36.0%</td>
<td>121.1</td>
<td>62.0</td>
</tr>
<tr>
<td>61-70</td>
<td>69.9%</td>
<td>30.1%</td>
<td>109.0</td>
<td>48.7</td>
</tr>
<tr>
<td>71+</td>
<td>72.3%</td>
<td>27.7%</td>
<td>95.4</td>
<td>42.6</td>
</tr>
</tbody>
</table>

132,144 Individuals with ICD-10 for FH (E78.01)
Presumptive FH Cohort:
LDL-C > 190 While on Moderate Intensity Statin + ezetimibe OR High Intensity Statin

ASCVD Cohort:
LDL-C > 100 While on Moderate Intensity Statin + ezetimibe OR High Intensity Statin

The Importance of Adherence to Therapy

**LDL-C Levels**

- **0 - 6 Months of Therapy within 12 Months**: Mean LDL-C = 123, Standard Deviation = 67
- **6 - 12 Months of Therapy within 12 Months**: Mean LDL-C = 80, Standard Deviation = 49
- **12 Months of Therapy within 12 Months**: Mean LDL-C = 73, Standard Deviation = 39
- **Rejected**: Mean LDL-C = 128, Standard Deviation = 64
- **Abandoned**: Mean LDL-C = 120, Standard Deviation = 51

2,422 Individuals prescribed a PCSK9i with LDL-C results
FH Foundation Guidance: Prior Authorization Criteria for PCSK9 inhibitors for Familial Hypercholesterolemia Treatment in Adults

Diagnostic Criteria for FH

FH Diagnosis: ICD-10 E78.01

Heterozygous FH: LDL ≥ 190 at baseline, not due to secondary causes, and a 1st degree relative similarly affected or with premature Coronary Artery Disease OR a positive genetic test result. Do not require genetic testing.

Homozygous FH: Untreated LDL-C ≥ 400 mg/dL and 1 or both parents having clinically diagnosed familial hypercholesterolemia, positive genetic testing for an LDL-C-raising (LDL receptor, apoB, or PCSK9) gene defect, or autosomal recessive FH. Do not require genetic testing. If LDL-C ≥ 560 mg/dL or LDL-C ≥ 400 mg/dL with aortic valve disease or xanthomata at < 20 years of age, homozygous FH highly likely.

Statin Use
High intensity statin (atorvastatin 40-80mg or rosuvastatin 20-40mg²) or maximally tolerated statin or statin intolerant.

Statin Trial
4 weeks³.

Statin Intolerance
Tried 2 statins (one high intensity, one at lowest recommended dose)⁴.

Ezetimibe Trial

Describes FH Foundation’s Recommendations for:
• Diagnostic criteria for FH
• Prior authorization criteria for PCSK9 inhibitors
  • Statin Use
  • Statin Intolerance
  • Ezetimibe
  • LDL-C thresholds
• Documentation
• Re-authorization
These Cholesterol-Reducers May Save Lives. So Why Aren’t Heart Patients Getting Them?

Powerful PCSK9 inhibitors were supposed to revolutionize care for cardiac patients. But insurers and other payers balked at sky-high prices.

8h ago - By GINA KOLATA
Translating a Trillion Points of Data into Diagnostics, Therapies and New Insights in Health and Disease

Atul Butte, MD, PhD
Director, Bakar Computational Health Sciences Institute
University of California, San Francisco
The data deluge
AND HOW TO HANDLE IT: A 14-PAGE SPECIAL REPORT

Kilo
Mega
Giga
Tera
Peta
Exa
Zetta
Public big data = retroactive crowd-sourcing
Yes, even a high-school student can use public data to design a new diagnostic test!

Teen develops algorithm to diagnose leukaemia

May 22, 2013 - 8:44AM

Vignesh Ramachandran

A high school junior has created a computer brain that can diagnose breast cancer with 99 percent sensitivity.

Seventeen-year-old Brittany Wenger of Sarasota, Fla., wrote a breast cancer-diagnosing app based on an artificial neural network, basically a computer program whose structure is inspired by the way brain cells connect with one another. She won grand prize at the Google Science Fair for her invention in ceremony held in Palo Alto, Calif. last night (July 23).

Like other artificial intelligence programs, artificial neural networks "learn" what to do by analyzing examples they're given and they perform better if they get more training. But since this was a high school project, she had to find a compromise.

"I wanted to prove that the infrastructure I built could work with multiple diseases": Brittany Wenger. Photo: Intel

Brittany Wenger isn't your average high-school student: she taught a computer how to diagnose leukaemia.

"The most amazing part about science is you can answer questions and really revolutionise the world and our knowledge base."
The University of California and UnitedHealth Group are teaming up to form a new accountable care organization (ACO) and clinically integrated network. As part of the 10-year strategic relationship, UC Health’s five academic medical centers will expand use of Optum’s clinically integrated network services and advanced data analytics services.
UC has an unprecedented view of the medical system

• Combined data from UCSF, UCLA, UC Irvine, UC Davis, UC San Diego, and UC Riverside

• Central database built using OMOP (not Epic) as a data backend
  – Structured data from 2012 to the present day: 4.7 million patients with “modern” data, total 15 million with an MRN
  – 101M encounters, 307M procedures, 283M med orders, 684M vital signs, 453M lab test results, 422M diagnosis codes
  – Claims data from our self-funded plans now included
  – Continually harmonizing elements

• Quality and performance dashboards
Thank You!
FH Global Summit
2019
October 20 & 21, 2019
Atlanta, GA