LDL polygenic risk scores in practice

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FH Global Summit, Atlanta 211019
Outline

• Introduction to polygenic risk score

• Polygenic risk scores for LDL cholesterol and FH

• Polygenic risk scores for CAD and FH – polygenic versus omnigenic scores

• Take home message
Introduction to polygenic risk score
Genome-wide association study of LDL cholesterol (from GLGC)

Willer CJ et al. Nat Genet 2013
Creating a polygenic score

GWAS SNPs
Individually: tiny effects
Combined: larger effect

Effect of gene score on trait level
Genome-wide association study of LDL cholesterol

Polygenic risk score

Willer CJ et al. Nat Genet 2013
Genome-wide association studies (GWAS') for lipids

In sufficiently large samples, many previously non-significant loci would become nominally significant, although effect sizes are close to zero.

~ 100,000
European ancestry
95 loci

~ 200,000
7,898 non-Europeans
62 novel loci

~ 600,000
~85,000 non-Europeans
>118 novel loci
(~268 known loci)
30.4 mill SNPs

2010
2013
2018
Polygenic risk scores for LDL cholesterol and Familial Hypercholesterolemia
# Diagnostic criteria for FH

<table>
<thead>
<tr>
<th>Group 1: family history</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) First-degree relative with known premature (&lt; 55 years, men &lt; 60 years, women) coronary heart disease (CHD) OR</td>
<td>1</td>
</tr>
<tr>
<td>(ii) First-degree relative with tendon xanthoma and/or corneal arcus OR</td>
<td>2</td>
</tr>
<tr>
<td>(iv) Child(ren) &lt; 18 years with LDL cholesterol &gt; 95th percentile by age and gender for country</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2: clinical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Subject has premature (&lt; 55 years, men &lt; 60 years, women) CHD</td>
</tr>
<tr>
<td>(i) Subject has premature (&lt; 55 years, men, &lt; 60 years, women) cerebral or peripheral vascular disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 3: physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Tendon xanthoma</td>
</tr>
<tr>
<td>(i) Corneal arcus in a person &lt; 45 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 4: biochemical results (LDL cholesterol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 8.5 mmol/L (≥ 325 mg/dL)</td>
</tr>
<tr>
<td>6.5 - 8.4 mmol/L (251 - 325 mg/dL)</td>
</tr>
<tr>
<td>5.0 - 6.4 mmol/L (191 - 250 mg/dL)</td>
</tr>
<tr>
<td>4.0 - 4.9 mmol/L (155 - 190 mg/dL)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 5: molecular genetic testing (DNA analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Causative mutation shown in the LDLR, APOB, or PCSK9 genes</td>
</tr>
</tbody>
</table>

### 1/220 individuals

- **Definite FH**: > 8 points
- **Probable FH**: 6-8 points
- **Possible FH**: 3-5 points
- **Unlikely FH**: 0-2 points
Clinical vs. mutation diagnosis

Polygenic cause?
- 20-40%

High Lp(a)?
- 60-80%

Polygenic cause?

Modified from Eur Heart J. 2013, 34:3478-3490 EAS Consensus
Previous work on polygenic risk scores in FH

Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study

Philippe J Taamoult, Sonia Shah, Ros Whittall, Marta Futema, Philip Howard, Jackie A Cooper, Seamus C Harrison, KaWah Li, Fotios Dromos, Frederik Karpe, II Andrew W Neil, Olivier S Descamps, Claudia Langenberg, Nicholas Lench, Mika Kivimäki, John Whittaker, Arun D Hingorani, Meena Kumari, Steve E Humphries

Lancet, 2013
Deep-coverage whole genome sequences and blood lipids among 16,324 individuals

- Genomewide polygenic risk score on LDL
  - 2 million SNPs (MAF>0.01)

- Monogenic causes: LDLR, APOB, PCSK9, ABCG5/8 and LDLRAP1

### (a). Effect of monogenic mutation or polygenic score on odds for extremely high or low LDL-C

<table>
<thead>
<tr>
<th>Ancestry</th>
<th>$N_{total}$</th>
<th>$N_{extreme}$</th>
<th>Monogenic carrier ($N_{extreme}$)</th>
<th>High polygenic score ($N_{extreme}$)</th>
<th>Monogenic carrier OR (95% CI)</th>
<th>Monogenic carrier p-value</th>
<th>Monogenic carrier PAF</th>
<th>High polygenic score OR (95% CI)</th>
<th>High polygenic score p-value</th>
<th>Top 5th percentile of Polygenic score PAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA</td>
<td>5910</td>
<td>284</td>
<td>5</td>
<td>64</td>
<td>10.92 (7.31,12.14)</td>
<td>$1.4\times10^{-5}$</td>
<td>1.60</td>
<td>7.65 (5.56,10.57)</td>
<td>$1.6\times10^{-5}$</td>
<td>5.78$\times10^{-36}$</td>
</tr>
<tr>
<td>AA</td>
<td>4380</td>
<td>217</td>
<td>7</td>
<td>29</td>
<td>7.43 (3.01,18.35)</td>
<td>$1.4\times10^{-5}$</td>
<td>2.79</td>
<td>3.2 (2.1,4.89)</td>
<td>$6.7\times10^{-2}$</td>
<td>9.2</td>
</tr>
</tbody>
</table>

2% vs. 23%

### (b). Effect of monogenic mutation or polygenic score on LDL-C in mg/dl

<table>
<thead>
<tr>
<th>Ancestry</th>
<th>$N_{total}$</th>
<th>Monogenic carrier (N)</th>
<th>High Polygenic score (N)</th>
<th>Monogenic carrier Beta mg/dl</th>
<th>Monogenic carrier SE</th>
<th>Monogenic carrier p-value</th>
<th>High Polygenic score Beta mg/dl</th>
<th>High Polygenic score SE</th>
<th>High Polygenic score p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA</td>
<td>5910</td>
<td>18</td>
<td>297</td>
<td>29.98</td>
<td>8.07</td>
<td>$2.1\times10^{-4}$</td>
<td>33.07</td>
<td>2.05</td>
<td>1.7$\times10^{-37}$</td>
</tr>
<tr>
<td>AA</td>
<td>4380</td>
<td>25</td>
<td>220</td>
<td>41.05</td>
<td>7.93</td>
<td>$2.3\times10^{-7}$</td>
<td>16.96</td>
<td>2.74</td>
<td>6.4$\times10^{-10}$</td>
</tr>
</tbody>
</table>

0.8 mmol/L


LDL-C >5% percentile
Polygenic risk scores for CAD and FH – polygenic versus omnigenic scores
Extreme polygenic risk for CAD comparable to FH

8% with ≥3-fold risk
2% with ≥4-fold risk
0.5% ≥5-fold risk

FH-mutations (LDLR, APOB, PCSK9)
Prevalence: 0.5%
~3-fold CAD-risk

6.6 mill SNPs
>400,000 individuals from UK BioBank

Odds ratio versus remainder of population

Khera et al. Nat Genet 2018
Comparison with previous risk scores

1st percentile of score
Prevalence for CAD: 5.9%

1st percentile of score
Prevalence for CAD: 7.2%

1st percentile of score
Prevalence for CAD: 11.1%

Khera et al. Nat Genet 2018
Take home message

• The risk of LDL cholesterol >5th percentile is similar in monogenic carriers of FH mutations and in individuals with a high polygenic score (top 5th percentile)

• But the number of individuals with a high polygenic score for LDL cholesterol is app. 10-fold higher than for monogenic mutations

• App. 8% of the population have a polygenic risk of CAD which corresponds to the risk of monogenic mutations for FH (≥3 fold)

• But the number of individuals with a high polygenic risk of CAD is almost 20-fold higher

• Omnigenic risk scores are (probably) superior to polygenic scores at predicting CAD risk
That’s all folks!
Clinical utility and unresolved issues
Potential clinical implications and implementation

• Scores are established at birth and can be used early in life

• Practical considerations regarding type of technology used

• Risk reporting: absolute score, its percentile compared to the general population, risk evaluation

• Who would report and interpret the results?
Unresolved issues

• Which score model should be used?

• Prospective replication

• Standards for clinical validation

• Ethnic based scores?

• Sex specific scores?

• Or one size fits all?

• How will the score be integrated into an overall risk assessment?
Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults Implications for Primary Prevention

- >1.7 mill SNPs
- 22,242 CAD cases
- 460,387 controls from UKBiobank
A genomic risk score for coronary artery disease

Greater association with future coronary artery disease than any single conventional risk factor
Independent of yet complements conventional risk factors
Provides meaningful lifetime risk estimates of coronary artery disease
Quantifiable at or before birth and shows potential for risk screening in early life


The genomic score provides potential for risk screening early in life as well as complements conventional risk factors for coronary artery disease.
Figure 3. 10-Year Coronary Event Rates, According to Lifestyle and Genetic Risk in the Prospective Cohorts
UK Biobank

- N=500,000
- Recruited from 2006-2010
- 40-69 years old
- 98% White
- Extensively phenotyped
  - Baseline questionnaire
  - Clinical endpoints from electronic health records
  - Biochemistry
  - DNA (GWAS n=500,000. Exome sequencing due in 2020)
  - Imaging (n=100,000)

All data open for all researchers

- 9 mill. invited, participation rate ~5%
Modifiers of the penetrance of familial hypercholesterolemia mutations on coronary artery disease risk

Sekar Kathiresan, M.D.
CEO, Verve Therapeutics

Cardiology Division, Massachusetts General Hospital  Institute Member, Broad Institute, on leave
Professor of Medicine, Harvard Medical School, on leave

October 21, 2019
# Disclosures

<table>
<thead>
<tr>
<th>Grants</th>
<th>Equity</th>
<th>Consulting</th>
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<tbody>
<tr>
<td>Bayer, Novartis</td>
<td>Verve Therapeutics, Maze Therapeutics</td>
<td>MedGenome, Color Genomics, Novo Nordisk, Merck, Eli Lilly, Alnylam, Regeneron, Acceleron, Corvidia, Illumina</td>
</tr>
</tbody>
</table>
911 call: 42yo male with dizziness, profuse sweating

21:10
Airway
The stretcher was brought into the residence and the pt was getting ready for transfer from the chair to the stretcher when he started posturing and having a seizure. Pt was lifted from the chair to the stretcher, placed supine on the stretcher and a nasal airway was inserted and breathing was assisted with a BVM and O2. Pt was transported to the unit. Oxygen initiated at 25 lpm via BVM by personnel. Pt Response: Unchanged.

21:15
Initiate IV
Once inside the unit the pt went into cardiac arrest, ALS back-up was called, CPR was started, V-Fib was noted on the monitor, precordial thump, CPR continued. Pupils noted to be dilated and fixed. Peripheral IV initiated by [redacted] with 16ga. at LF. Attempts: 1, successful. Authorization: Via Protocol. Pt Response: Unchanged. 1000cc’s of NS wide open.
42yo male with fatal myocardial infarction (MI)

MI risk factors

**Lipid**
- Total cholesterol: 241 mg/dl
- LDL cholesterol: 167 mg/dl
- HDL cholesterol: 40 mg/dl
- Triglycerides: 170 mg/dl

**Non-lipid**
- Blood pressure: 120/80 mm/Hg
- Body mass index: 26 kg/m²
- Non-smoker
- No type 2 diabetes
Two scientific questions

Beyond LDLR, APOB, PCSK9, are there other genes that cause FH?

What might modify the penetrance of FH mutations on CAD risk?
ABCG5 or ABCG8: sterol transporters, pump plant sterols back into intestine
ABCＧ5 or ABCＧ8 homozygous deficiency:
sitosterolemia, high LDL, premature CAD

Eric Lee, slideshare

Does heterozygous ABCG5 or ABCG58 deficiency impact LDL or CAD risk?
Heterozygous ABCG5 deficiency raises plasma sitosterol, LDL and CAD risk

ABCG5 loss of function mutations: roughly 1 in 1000 are carriers

25 mg/dl higher

2-fold increased risk

LDL Cholesterol

Atherosclerosis
New Results

**Heterozygous ATP-binding Cassette Transporter G5 Gene Deficiency and Risk of Coronary Artery Disease**


doi: https://doi.org/10.1101/780734

This article is a preprint and has not been certified by peer review [what does this mean?].
Can now add ABCG5 to list of genes where coding mutations confer large effect on MI risk

<table>
<thead>
<tr>
<th>Gene</th>
<th>Carrier frequency</th>
<th>Blood biomarker</th>
<th>Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-density lipoprotein receptor (LDLR)</td>
<td>1 in 250</td>
<td>LDL</td>
<td>3-10 fold</td>
</tr>
<tr>
<td>ATP-binding cassette transporter G5 (ABCG5)</td>
<td>1 in 1000</td>
<td>LDL</td>
<td>2-fold</td>
</tr>
<tr>
<td>Lipoprotein lipase (LPL)</td>
<td>1 in 500</td>
<td>TRL</td>
<td>2-fold</td>
</tr>
<tr>
<td>Apolipoprotein A5 (APOA5)</td>
<td>1 in 3000</td>
<td>TRL</td>
<td>4-fold</td>
</tr>
<tr>
<td>Apolipoprotein(a) (LPA)</td>
<td>1 in 100</td>
<td>Lp(a)</td>
<td>3-fold</td>
</tr>
</tbody>
</table>

Khera*, Won* et al., JAMA (2017)
42yo male with fatal myocardial infarction

family carried **ABCG5 p.Arg446Ter**

**Lipid**
- Total cholesterol 241 mg/dl
- LDL cholesterol 167 mg/dl
- HDL cholesterol 40 mg/dl
- Triglycerides 170 mg/dl

**Non-lipid**
- Blood pressure 120/80 mm/Hg
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What might modify the penetrance of FH mutations on CAD risk?
What might modify penetrance of an FH mutation on risk for CAD?
What might modify penetrance of an FH mutation on risk for CAD?

\[ \text{FH Mutation} \rightarrow \text{LDL Cholesterol} \rightarrow \text{Atherosclerosis} \]

- **Inherited**
  - Specific mutation
  - Polygenic LDL score

- **Inherited**
  - Polygenic CAD score
What might modify penetrance of an FH mutation on risk for CAD?

- **Inherited**
  - Specific mutation
  - Polygenic LDL score

- **Inherited** Polygenic CAD score

**FH Mutation** ➔ **LDL Cholesterol** ➔ **Atherosclerosis**

**Non-genetic**
- Lifestyle
- LDL-lowering therapy

**Non-genetic**
- Lifestyle
- Traditional risk factors
- Therapy
What might modify penetrance of an FH mutation on risk for CAD?

**Inherited**
- Specific mutation
- Polygenic LDL score

**Inherited**
- Polygenic CAD score

**Non-genetic**
- Lifestyle
- LDL-lowering therapy

**Non-genetic**
- Lifestyle
- Traditional risk factors
- Therapy
Two genetic paths to MI risk

MI at age < 50  age-of-onset MI
Polygenic model: capture risk through 6.6M common variants, distill genomic risk into a single # Gaussian distribution in population

Cases N=60K

Controls N=120K

Klarin et al., Nature Genetics (2017)
Nikpay et al., Nature Genetics (2015)
Deloukas et al., Nature Genetics (2013)
McPherson et al., Science (2007)
Samani et al., Nature Genetics (2011)
Helgadottir et al., Science (2007)
Kathiresan et al., Nature Genetics (2009)
High polygenic CAD score identified in 17% of early MI patients

100 patients with early myocardial infarction

↑ Risk

Monogenic 3.8-fold

High polygenic 3.7-fold

Does polygenic CAD score modify penetrance of FH mutations?
UK Biobank: sequence for FH genes + calculate polygenic CAD score

Dataset 1

- CAD cases: N = 6.5K
- Controls: N = 6.5K

Dataset 2

- Population-based: N = 50K

Fahed, Wang, Khera, unpublished
Without considering polygenic background, FH mutation increases CAD risk 5.6 fold

FH mutation carrier: average risk is OR 5.6

Fahed, Wang, Khera, unpublished
Based on polygenic background, CAD risk for FH mutation can be refined: from OR ~1.0 to ~20.0

FH mutation carrier: average risk is OR 5.6

Polygenic background important

Fahed, Wang, Khera, unpublished
For an FH mutation carrier, cumulative probability of CAD (by age 75) can vary from 17% to 78% based on polygenic background.

Fahed, Wang, Khera, unpublished
Same pattern for three Tier 1 genomic conditions: CAD, breast cancer, and colorectal cancer

FH

Hereditary breast and ovarian cancer

Lynch syndrome

Fahed, Wang, Khera, unpublished
Ultimate modifier: early identification FH mutation and treatment of LDL cholesterol

- **Inherited**
  - Specific mutation
  - Polygenic LDL score

- **Inherited**
  - Polygenic CAD score

- **FH Mutation**

- **LDL Cholesterol**

- **Atherosclerosis**

- **Non-genetic**
  - Lifestyle
  - LDL-lowering therapy

- **Non-genetic**
  - Lifestyle
  - Traditional risk factors
  - Therapy
20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia

Ilse K. Luijink, M.D., Albert Wiegman, M.D., Ph.D.,
D. Meike Kusters, M.D., Ph.D., Michel H. Hof, Ph.D.,
Jaap W. Groothoff, M.D., Ph.D., Eric de Groot, M.D., Ph.D.,
John J.P. Kastelein, M.D., Ph.D., and Barbara A. Hutten, Ph.D.
184 kids with FH (mutation-defined)
Baseline LDL 237 mg/dl
Treatment initiation at mean age 14
20y follow-up
Follow-up LDL 160 mg/dl

Comparison with affected parents
(assumption no statin Rx childhood for parents)
By age 40, 26% of affected parents had CV event; in contrast, only 1% treated children with FH had CV event!!

184 kids with FH (mutation-defined)
Baseline LDL 237 mg/dl
Treatment initiation at mean age 14
20y follow-up
Follow-up LDL 160 mg/dl

Comparison with affected parents
(assumption no statin Rx childhood for parents)
Beyond LDLR, APOB, PCSK9, are there other genes that cause FH?

Heterozygous ABCG5 deficiency increases plasma LDL and CAD risk

What might modify the penetrance of FH mutations on CAD risk?

Polygenic background as well as early LDL-lowering therapy modifies penetrance
Adherence to a healthy lifestyle impacts penetrance of FH mutations on atherosclerotic CVD

Adherence to Healthy Lifestyle

Odds Ratio (95% CI) of MI

FH Mutation
- Noncarrier
- FH carrier

Healthy Lifestyle Score
- Favorable
- Intermediate
- Unfavorable
MY DISCLOSURES

Small funding: multiple companies and funding bodies
Modest funding: Astellas, Novartis, Merck, Pfizer, Erasmus MC
Large funding: Netherlands Heart Foundation, Amgen, EIT Health
Outrageous: Dutch Healthcare Authority
Hypercholesterolemia

Multiple “Omics”
Today and Tomorrow

Eric Sijbrands
TAILORED FH CARE? – CAD risk assessment

• important cause of CVD
• effective preventive measures: lifestyle, medication
• medication hardly has side effects

but

• treating averages → large residual risk → precision medicine?
WHAT DETERMINES THE SEVERITY OF FH?

• phenotype?

or

• genotype?
ANSWER

BOTH and perhaps more
**GENOTYPE = CAUSE OF FH**

Next Generation Sequencing of 29 genes

<table>
<thead>
<tr>
<th>High LDL</th>
<th>Low LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>low-density lipoprotein receptor D</td>
<td>apolipoprotein B D</td>
</tr>
<tr>
<td>apolipoprotein B D</td>
<td>proprotein convertase subtilisine/kexine 9 D</td>
</tr>
<tr>
<td>proprotein convertase subtilisine/kexine 9 D</td>
<td>angiopoietin-like 3 D</td>
</tr>
<tr>
<td>LDL-receptor associated protein 1 D</td>
<td>microsomal triglyceride transfer protein R</td>
</tr>
<tr>
<td>ATP-binding cassette G5 R</td>
<td>myosin regulatory light chain interacting protein D</td>
</tr>
<tr>
<td>ATP-binding cassette G8 R</td>
<td>Secretion related Ras associated GTPase 1B R</td>
</tr>
<tr>
<td>lipase A (lysosomal acid lipase) R</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phenocopy</th>
<th>Statin myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>cytochroom P450, family 27, subfamily A – 1 R</td>
<td>solute carrier organic anion transporter 1B1 D</td>
</tr>
</tbody>
</table>

Lp(a); Polygenetic hypercholesterolemia
HIGH CAD RISK IN MUTATION CARRIERS

MILLION VETERAN PROJECT (n=331107)

- substantial variation untreated LDL-C and CAD risk within and across genetic variants
- ethnic differences in frequencies but not in effect
- population-based info on genotype-phenotype is required to optimize the molecular diagnostics of FH

GENOMIC RISK SCORE (GRS)

**Table 2** Association of the 49K GRS with incident CHD (binary outcome in logistic regression) in the five studies, per standard deviation of the GRS

<table>
<thead>
<tr>
<th>Dataset</th>
<th># Incident CHD/Non-CHD</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WTCCC-CAD1</td>
<td>1926/2938</td>
<td>1.74 (1.63–1.86)</td>
</tr>
<tr>
<td>MiGen-Harps</td>
<td>488/531</td>
<td>1.57 (1.37–1.81)</td>
</tr>
<tr>
<td>ARGOS FH</td>
<td>248/216</td>
<td>1.49 (1.21–1.84)</td>
</tr>
<tr>
<td>FINRISK</td>
<td>757/11919</td>
<td>1.74 (1.61–1.89)</td>
</tr>
<tr>
<td>FHS</td>
<td>587/2819</td>
<td>1.28 (1.17–1.41)</td>
</tr>
</tbody>
</table>

GENOMIC RISK SCORE (GRS)

1. low RR
2. non-smoking
3. low cholesterol

↓

compensate high GRS

GENOMIC RISK SCORE (GRS) – UK

ASYMPTOMATIC, TREATED FH

how to monitor atherogenesis... ?

healthy coronary arteries

end-stage coronary disease
TREATED FH: PROTEOMICS

LRG1 = leucine-reich alpha-2-glycoprotein
ITIH3 = inter-α-trypsin inhibitor heavy chain H3
C4B = complement C4-B
C1QB = Complement C1q subunit B
CD14 = monocyte differentiation antigen
HRG = histidine-rich glycoprotein

↓ signals of healthy vessels?

METABOLIC PROFILING

- **Biocrates p180 kit**
  - chromatography + flow injected analyses
  - LC-MS/MS: amino acids & biogenic amines
  - FIA-MS: lipids, acylcarnitins & hexose

- **Sciex Lipidyzer™**

<table>
<thead>
<tr>
<th>class</th>
<th>species</th>
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<tbody>
<tr>
<td>neutral</td>
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<tr>
<td>triacylglycerols</td>
<td>502</td>
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<tr>
<td>diacylglycerols</td>
<td>67</td>
</tr>
<tr>
<td>free fatty acids</td>
<td>28</td>
</tr>
<tr>
<td>cholesteryl esters</td>
<td>34</td>
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<tr>
<td>polar</td>
<td></td>
</tr>
<tr>
<td>phospholipids</td>
<td>394</td>
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<tr>
<td>lysophospholipids</td>
<td>56</td>
</tr>
<tr>
<td>sphingomyelins</td>
<td>16</td>
</tr>
<tr>
<td>ceramides</td>
<td>56</td>
</tr>
</tbody>
</table>

(both on 5500 QTRAP®)
Biocrates: 30 most contributing metabolites

Healthy CA

Healthy CAD
METABOLIC PROFILING: Lipidyzer top 31

38% of variation explained by the 1st PCA
METABOLIC PROFILING

Single Omics

It's a fan!

It's a spear!

Multi-Omics

It's a giant animal!

It's a rope!

It's a snake!

It's a tree!
COMBINATION OF Biocrates & Lipidyzer

amino acid cluster from Biocrates
COMBINATION OF Biocrates & Lipidyzer

Example Ca vs CAD: clustering of Lipidyzer is improved by adding analytes of Biocrates:

1. kynurenine
2. 14-OH-proline
3. spermine
4. Glutamine

c-index for CAD 0.6
among FH patients risk is predicted by:
1. FH mutation carrierrship
2. GRS
3. signals of healthy vesels
4. modest clustering of metabolites
5. combining omics?
6. too small population?
**IAS FH Initiatives**

- **Guidelines**
  - Severe FH guideline (Lancet Diabetes Endocrinol 2016)
- **Cascade screening programs**
  - Screen PRO in Eastern Europe
- **Registries**
  - European pediatric FH registry
- **Research/Implementation science/Models of care**
  - 10 Country Study (focus developing regions)
- **Awareness/Advocacy**
  - FH Foundation
  - Iberoamerican FH Network
- **Education**
  - Severe FH Master Classes in MENA region
  - Joint Symposia on FH (China, Brazil)
  - Sub-Saharan Africa Initiative
Disclosure

• Honoraria received for consulting, speaker and or researcher activities: Ache, Akcea, Astra Zeneca, Amgen, Esperion, Kowa, Merck, MSD, Novo-Nordisk, Pfizer, Sanofi/Regeneron.
The Ten Countries FH Study
Lessons from an international network

Raul D. Santos MD, PhD
On Behalf of the Authors

Supported by an International Atherosclerosis Society-Pfizer Independent Grant for Learning and Change (ID: 1083951)
Countries Involved in the Study

Ten Countries Study: 5 Principal Projects

- Study 1: Prevalence of FH in communities
- Study 2: Phenotypic and genetic testing for FH
- Study 3: Knowledge and practices among GPs
- Study 4: Comparison of services and facilities
- Study 5: Patient perceptions and experiences

FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

References:
Chan DC et al. J Clin Endocrinol Metab 2018; 103:1704–1714
Over Half the World’s People with FH are found in the Asia-Pacific Region

FH, familial hypercholesterolemia.

Ten Countries Study: 5 Principal Projects

- **Study 1**: Prevalence of FH in communities
- **Study 2**: 
- **Study 3**: 
- **Study 4**: 
- **Study 5**: 

FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Chan DC et al. *J Clin Endocrinol Metab* 2018; 103:1704–1714
Study 1. Prevalence in Australian Children

n=1,602

LDL-cholesterol >4.0 mmol/L on 2 occasions with a parental history of premature CHD and/or high cholesterol

FH Prevalence of 1 in 270

Figure. Frequency histogram of LDL-cholesterol in 1602 adolescents from the Raine Study with the 95th percentile at 3.4 mmol/L.

Pang et al J Peds 2016; 170:315-6
Watts et al Int J Cardiol 2015;185:69-71
Ten Countries Study: 5 Principal Projects

Study 1

Study 2
Phenotypic and genetic testing for FH

Study 3

Study 4

Study 5

FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Chan DC et al. J Clin Endocrinol Metab 2018; 103:1704–1714
## Diagnostic Tests for FH

### Phenotypic FH and access to genetic testing

<table>
<thead>
<tr>
<th>Country</th>
<th>Phenotypic Criteria</th>
<th>Genetic Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DLCN</td>
<td>Simon Broome</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Australia</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Brazil</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>China</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>✓⁠ᵃ</td>
<td>✓</td>
</tr>
<tr>
<td>Japan</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Malaysia</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>New Zealand</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Philippines</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>South Africa</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Taiwan</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vietnam</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

- **a** Wales FH Service Scoring Criteria
- **b** Based on the National consensus statement on FH
- **c** DLCN phenotypic criteria with a lower threshold for LDL-cholesterol levels

† With research funding alone; ‡ With international assistance.

---

DLCN, Dutch Lipid Clinic Network; MEDPED, Make Early Diagnosis to Prevent Early Deaths
Diagnostic; SB, Simon Broome.

## Study 2: Discordance between phenotypic criteria

<table>
<thead>
<tr>
<th></th>
<th>Concordance rate</th>
<th>Discordance rate</th>
<th>Kappa coefficient</th>
<th>Overall agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dutch Score vs Simon Broome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For total group (n=885)</td>
<td>74%</td>
<td>26%</td>
<td>0.378</td>
<td>Fair</td>
</tr>
<tr>
<td>For positives (n=594)</td>
<td>87%</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For negatives (n=291)</td>
<td>49%</td>
<td>51%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Positives and negatives refer to outcomes by the former phenotypic diagnostic category.*

DLCN, Dutch Lipid Clinic Network; FH, familial hypercholesterolemia; SB, Simon Broome.

1: Plasma LDL-Cholesterol as a Predictor of FH Mutations

885 Index Cases

LDL-cholesterol = 7.1 mmol/L
Correctly Classified = 80%

Phenotypic DLCN score > 8
Correctly Classified = 78%

AUC_{LDL-cholesterol} = 0.835 (95%CI 0.806-0.865)
AUC_{DLCN score} = 0.816 (95%CI 0.784-0.847)

Chan DC et al. J Clin Endocrinol Metab 2018; 103:1704–1714
Evaluation of clinical and laboratory parameters used in the identification of index cases for genetic screening of familial hypercholesterolemia in Brazil

ROC curve for LDL-C 230 mg/dL (AUC: 0.730) and DLCN scores (AUC: 0.744), p=0.014
Ten Countries Study: 5 Principal Projects

Study 1

Study 2

Study 3 Knowledge and practices among GPs

Study 4

Study 5

FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Chan DC et al. J Clin Endocrinol Metab 2018; 103:1704–1714
An enquiry based on a standardised questionnaire into knowledge, awareness and preferences concerning the care of familial hypercholesterolaemia among primary care physicians in the Asia-Pacific region: the “Ten Countries Study”
# Study 3: GP Awareness - Knowledge

<table>
<thead>
<tr>
<th>Awareness</th>
<th>Australia</th>
<th>Japan</th>
<th>Malaysia</th>
<th>South Korea</th>
<th>Philippines</th>
<th>Hong Kong</th>
<th>China</th>
<th>Vietnam</th>
<th>Taiwan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familiarity with FH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid specialists</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Knowledge</th>
<th>Australia</th>
<th>Japan</th>
<th>Malaysia</th>
<th>South Korea</th>
<th>Philippines</th>
<th>Hong Kong</th>
<th>China</th>
<th>Vietnam</th>
<th>Taiwan</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH description</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lipid profile</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prevalence of FH</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission of FH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD risk</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Limitations of genetic testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins as first drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Value of statin and ezetimibe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Red* = significantly less than the United Kingdom  
*Blue* = significantly more than the United Kingdom.

FH, familial hypercholesterolemia; CVD, cardiovascular disease

Ten Countries Study: 5 Principal Projects

- Study 1
- Study 2
- Study 3
- Study 4: Comparison of services and facilities
- Study 5

FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Chan DC et al. J Clin Endocrinol Metab 2018; 103:1704–1714
# Study 4: Health Services - Treatments

Dietary, drug and apheresis treatments for patients with FH in the countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Low saturated fat diet</th>
<th>Statins Adults</th>
<th>Statins Children</th>
<th>Ezetimibe</th>
<th>Resins</th>
<th>Niacin</th>
<th>Probucol</th>
<th>Apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>✓</td>
<td>✓</td>
<td>8 years</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Australia</td>
<td>✓</td>
<td>✓</td>
<td>10 years</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Brazil</td>
<td>✓</td>
<td>✓</td>
<td>8 years</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>China</td>
<td>✓</td>
<td>✓</td>
<td>10 years</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>✓</td>
<td>✓</td>
<td>15 years</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Japan</td>
<td>✓</td>
<td>✓</td>
<td>15 years</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Malaysia</td>
<td>✓</td>
<td>✓</td>
<td>8 years</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>New Zealand</td>
<td>✓</td>
<td>✓</td>
<td>10 years</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Philippines</td>
<td>✓</td>
<td>✓</td>
<td>No</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>South Africa</td>
<td>✓</td>
<td>✓</td>
<td>8 years</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Taiwan</td>
<td>✓</td>
<td>✓</td>
<td>8 years</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vietnam</td>
<td>✓</td>
<td>✓</td>
<td>5 years</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Apheresis facilities available in these countries, but services are limited owing to lack of government support and/or reimbursement by insurers*
Getting Down to Low Targets of LDL-C is Difficult with Usual Treatments in FH

LDL-Cholesterol Targets:

< 100 mg/dL (2.6 mmol/L)  
Without ASCVD

< 70 mg/dL  (1.8 mmol/L)  
With ASCVD or multiple RFs

Registration, reimbursement and use of PCSK9 inhibitors for treating FH in different countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Registered for clinical use</th>
<th>Government reimbursement</th>
<th>% diagnosed patients with FH treated with PCSK9 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HoFH</td>
<td>HeFH</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Australia</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Brazil</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>China</td>
<td>✅ a</td>
<td>✓</td>
<td>✅</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Japan</td>
<td>✅</td>
<td>✓</td>
<td>✅</td>
</tr>
<tr>
<td>Malaysia</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>New Zealand</td>
<td>*</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Philippines</td>
<td>*</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>South Africa</td>
<td>*</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Taiwan</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Vietnam</td>
<td></td>
<td>✅</td>
<td>✅</td>
</tr>
</tbody>
</table>

*PCSK9 inhibitors only available as part of clinical trials

aRegistered but not available for use as at October 2018
Percentage of FH at LDL Targets in 12 Countries

- United Kingdom
- Australia
- Brazil
- China
- Hong Kong
- Japan
- Malaysia
- New Zealand
- Philippines
- South Africa
- Taiwan
- Vietnam

Ten Countries Study: 5 Principal Projects

FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Study 1

Study 2

Study 3

Study 4

Study 5  Patient perceptions and experiences

Chan DC et al. J Clin Endocrinol Metab 2018; 103:1704–1714
Study 5: Patient Perceptions and Beliefs

• Value of cascade screening
• Assistance in contacting relatives
• Heart disease first priority
• Drugs important, but feared side-effects
• Lifestyles changes considered less important
• Poor health literacy, especially China and Malaysia
• Specific and general beliefs of treatment affected adherence

Hagger MS et al *Atherosclerosis* 2018; 277: 493-501
Conclusions

- Frequency of FH at least 1 in 250
- No standard clinical tool for FH; value of genetic testing
- GPs have poor knowledge and awareness of FH
- Several service gaps; less economically developed countries
- Patient perceptions and literacy were a key for improved care

New Data: Primary Care Knowledge in the Americas

Rodrigo Alonso Karlezi, MD, PhD
Meeting of the Americas

September 26th, 2017
<table>
<thead>
<tr>
<th>Country</th>
<th>Leaders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>Dario Igolnikof, Laura Schreir, Pablo Corral</td>
</tr>
<tr>
<td>Brazil</td>
<td>Cristina Izar, Luz Victoria Salazar, Patricia Vieria, Raul Santos, Regina Prospero, Tana Martinez</td>
</tr>
<tr>
<td>Canada</td>
<td>Brian McCrindle, Daniel Gaudet, Durhane-Wong Rieger, Liam Brunham</td>
</tr>
<tr>
<td>Chile</td>
<td>Ada Cuevas, Rodrigo Alonso</td>
</tr>
<tr>
<td>Colombia</td>
<td>Greizy Lopez, Luz Bernal, Martha Tamayo</td>
</tr>
<tr>
<td>Mexico</td>
<td>Alejandra Vasquez, Carlos Castro, Carlos Salinas, Lucila Carreaga, Roopa Mehta</td>
</tr>
<tr>
<td>Portugal</td>
<td>Mafalda Bourbon</td>
</tr>
<tr>
<td>Spain</td>
<td>Pedro Mata</td>
</tr>
<tr>
<td>United States</td>
<td>Hatim Hanif, Jasmine Patel, Samuel Gidding, Katherine Wilemon</td>
</tr>
<tr>
<td>Uruguay</td>
<td>Nicolas Dell’ Oca, Mario Stoll, Ximena Reyes</td>
</tr>
<tr>
<td>Venezuela</td>
<td>Marcos Lima</td>
</tr>
</tbody>
</table>
Methods

1. FH Foundation convened Meeting of the Americas during 2017 FH Global Summit in Miami, Florida
2. Received permission to modify original survey by Gerald Watts
3. Translated into French, Portuguese, and Spanish and retro translated to validate
4. Digitized on Survey Monkey
5. Country leaders were responsible for dissemination
6. Target population: General Practitioner
Survey Responses per Country

N = 1,036
Medical Specialty by Country

- Argentina: 6% General Practitioners (5%-78%, Avg 42%), 38% Other Specialists (6%-82%, Avg 40%), 56% Cardiologists (2%-43%, Avg 17%)
- Brazil: 42% General Practitioners (5%-78%, Avg 42%), 15% Other Specialists (6%-82%, Avg 40%), 82% Cardiologists (2%-43%, Avg 17%)
- Canada: 13% General Practitioners (5%-78%, Avg 42%), 43% Other Specialists (6%-82%, Avg 40%), 15% Cardiologists (2%-43%, Avg 17%)
- Chile: 5% General Practitioners (5%-78%, Avg 42%), 12% Other Specialists (6%-82%, Avg 40%), 82% Cardiologists (2%-43%, Avg 17%)
- Colombia: 2% General Practitioners (5%-78%, Avg 42%), 43% Other Specialists (6%-82%, Avg 40%), 56% Cardiologists (2%-43%, Avg 17%)
- Mexico: 7% General Practitioners (5%-78%, Avg 42%), 46% Other Specialists (6%-82%, Avg 40%), 47% Cardiologists (2%-43%, Avg 17%)
- Portugal: 16% General Practitioners (5%-78%, Avg 42%), 8% Other Specialists (6%-82%, Avg 40%), 76% Cardiologists (2%-43%, Avg 17%)
- Spain: 9% General Practitioners (5%-78%, Avg 42%), 32% Other Specialists (6%-82%, Avg 40%), 59% Cardiologists (2%-43%, Avg 17%)
- United States: 10% General Practitioners (5%-78%, Avg 42%), 12% Other Specialists (6%-82%, Avg 40%), 78% Cardiologists (2%-43%, Avg 17%)
- Uruguay: 35% General Practitioners (5%-78%, Avg 42%), 37% Other Specialists (6%-82%, Avg 40%), 28% Cardiologists (2%-43%, Avg 17%)
- Venezuela: 12% General Practitioners (5%-78%, Avg 42%), 29% Other Specialists (6%-82%, Avg 40%), 60% Cardiologists (2%-43%, Avg 17%)
How familiar are you with FH?

Answer: Familiar & Very Familiar
Are you aware of the diagnostic criteria of FH?

Answer: Yes
What is the prevalence of FH around the world?

**Answer:** 1 in 250 People

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>36%</td>
</tr>
<tr>
<td>Brazil</td>
<td>43%</td>
</tr>
<tr>
<td>Canada</td>
<td>67%</td>
</tr>
<tr>
<td>Chile</td>
<td>39%</td>
</tr>
<tr>
<td>Colombia</td>
<td>22%</td>
</tr>
<tr>
<td>Mexico</td>
<td>43%</td>
</tr>
<tr>
<td>Portugal</td>
<td>59%</td>
</tr>
<tr>
<td>Spain</td>
<td>74%</td>
</tr>
<tr>
<td>Uruguay</td>
<td>61%</td>
</tr>
<tr>
<td>USA</td>
<td>51%</td>
</tr>
<tr>
<td>Venezuela</td>
<td>23%</td>
</tr>
</tbody>
</table>

Understanding of prevalence across most countries is very low, except for countries with nation-wide screening programs.
How much greater is CAD risk in untreated FH patients?
Answer: 10-20x
What age would you test young individuals for FH in a family with premature CAD?
Answer: 0-6 Years
General Practitioners, Cardiologist, and Other Specialists
Total Survey Responses

- **42% (438)**
- **17% (179)**
- **40% (419)**
Are you aware of the diagnostic criteria of FH?

Answer: Yes

<table>
<thead>
<tr>
<th></th>
<th>General Practitioners</th>
<th>Cardiologists</th>
<th>Other Specialists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>47%</td>
<td>72%</td>
<td>57%</td>
</tr>
</tbody>
</table>
Only genetic testing can make an accurate FH diagnosis?

Answer (opinion): True
If you have FH patients, do you routinely screen close relatives?

<table>
<thead>
<tr>
<th></th>
<th>Yes patients’ children and other close relatives</th>
<th>Yes patients’ children only</th>
<th>No</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Practitioners</td>
<td>48%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiologists</td>
<td>63%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Specialists</td>
<td>53%</td>
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<tr>
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<th>General Practitioners</th>
<th>Cardiologists</th>
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<td>General Practitioners</td>
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<tr>
<td>Cardiologists</td>
<td>17%</td>
<td>6%</td>
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</tr>
<tr>
<td>Other Specialists</td>
<td>27%</td>
<td>20%</td>
<td>30%</td>
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What age would you test young individuals for FH in a family with premature CAD?

Answer: 0-6 Years
Conclusions

• There are significant deficiencies in the awareness and knowledge of FH among physicians

• Although half of the physicians reported they are familiar with FH, their understanding of the prevalence, the CAD risk, and screening strategies are still very low

• Countries with screening programs have higher level of awareness and knowledge

• Based on the results, we can assess that country-specific FH guidelines increase the awareness and knowledge in the Americas

• Knowledge of FH recommendations and their implementation are essential for an early diagnosis, treatment, and prevention of CAD