UK - Steve Humphries
Market access and Precision medicine for FH

Portugal
João Lavinha
E.L.S.I

Netherlands - Eric Sijbrands
Clinical Studies and Health system implementation

FH Map

No of variants
- >200
- 101 – 200
- 51 – 100
- 26 – 50
- 11 – 25
- 1 – 10
- No variants?

FH Europe

Portugal
Mafalda Bourbon
Mechanism of disease and research effort

Austria –
Gaby Hanauer
Patient benefit
Translational medicine in Familial Hypercholesterolemic – from phenotype, to genotype to treatment

Mechanism of disease and research effort

Mafalda Bourbon, PhD
Head of R&D Unit and Head of Cardiovascular Research Group, Department of Health Promotion, INSA
Invited Professor, BioISI, FCUL
Familial hypercholesterolemia (FH)

FH is the most common monogenic lipid disorder

- Autosomal dominant disorder
- Heterozygote prevalence: 1/250 – 1/500
- Homozygous is more rare: 1/300 000 – 1/1,000 000
- >90% cases are due to LDLR mutations; 5-10% APOB; 1-3% PCSK9
- Patients present very high LDL values from birth
- Under-diagnosed and under-treated although there are established clinical criteria

Due to long life exposure to high LDL cholesterol levels patients develop premature coronary heart disease

It is possible to have an accurate diagnosis and treatment that will reduce cardiovascular risk
LDLR cycle

- LDL
- Endoplasmatic reticulum
- Lysosome
- Endosome
- Recycling vesicle
- Clathrin coated pit
- Golgi apparatus
- PCSK9
- Núcleo SREBP
- LDLR
- APOB
- coated pit vesicle
- Recycling vesicle
**LDLR cycle**

- LDL
- APOB
- Clathrin coated pit
- Coated pit vesicle
- Recycling vesicle
- Endosome
- Lysosome
- Golgi apparatus
- PCSK9
- Endoplasmatic reticulum
- Núcleo SREBP
### Genetics of Familial Hypercholesterolemia

Now - More than 2800 variants associated to FH in ClinVar

<table>
<thead>
<tr>
<th></th>
<th>LDLR</th>
<th>APOB</th>
<th>PCSK9</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All variants submitted to ClinVar</td>
<td>5174</td>
<td>1003</td>
<td>474</td>
<td>6651</td>
</tr>
<tr>
<td>Variants detected in FH patients</td>
<td>4973</td>
<td>580</td>
<td>355</td>
<td>5908</td>
</tr>
<tr>
<td>Unique variants detected in FH patients</td>
<td><strong>2314</strong></td>
<td><strong>353</strong></td>
<td><strong>216</strong></td>
<td><strong>2883</strong></td>
</tr>
</tbody>
</table>

Iacocca & Chora et al, 2018
Clinical Genome (ClinGen) Resource

An NIH funded consortium in collaboration with ClinVar coordinated by Stanford, Harvard and North Carolina Universities

ClinGen is dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research

FH variant curation expert panel

(chairs: Mafalda Bourbon, INSA, Portugal; Josh Knowles, Stanford, USA)

• Promote FH associated variants submission to ClinVar ✔

• Develop an FH specific algorithm on going

• Curate all FH variants in ClinVar 2019
**LDLR cycle**

- **Expression**: LDLR is expressed from the endoplasmic reticulum (ER) to the Golgi apparatus.
- **Binding**: LDLR binds LDL in the extracellular space.
- **Uptake**: LDL is internalized into the cell via clathrin-coated pits.
- **Recycling vesicle**: LDL is delivered to the lysosome for degradation.
- **LDL receptor (LDLR)**
- **Proprotein convertase subtilisin/kexin type 9 (PCSK9)**
- **Apolipoprotein B (APOB)**
- **Nucleo SREBP**
- **Endoplasmatic reticulum (ER)**
- **Golgi apparatus**
- **Clathrin coated pit**
- **Coated pit vesicle**
- **Endosome**
- **Lysosome**
Levels of expression, binding and uptake

**Expression, Binding and Uptake levels**

**Normal**
- Variants: P.Arg91Cys, P.Gly8Arg, P.Cys109Phe, P.Cys143Arg, P.Glu267Lys, P.Cys332Ser
- Protein retain some activity - milder to severe phenotype; treat accordingly

**Def. binding/uptake**
- Variants: P.Ile451Thr, P.His485Gln, P.Val690Asn, P.Gly529Arg, P.Gly622Glu, P.Glu626Lys
- Protein retain some activity - milder to severe phenotype; treat accordingly

**Null**
- Variants: P.Arg81Cys, P.Gly8Arg, P.Cys109Phe, P.Cys143Arg, P.Glu267Lys, P.Cys332Ser
- Protein retain some activity - milder to severe phenotype; treat accordingly

**Def. expression/recycling?**
- Variants: P.Arg81Cys, P.Gly8Arg, P.Cys109Phe, P.Cys143Arg, P.Glu267Lys, P.Cys332Ser
- Protein retain some activity - milder to severe phenotype; treat accordingly

**Phenotype due to others genetic/environmental causes; treat accordingly**

**Protein retain some activity - milder to severe phenotype;**
- Statin + inhibitor of intestinal cholesterol absorption

**Residual or no protein - severe phenotype;**
- Potent statin + inhibitor of intestinal cholesterol absorption + iPCSK9

From phenotype to functional genotype to treatment – personalized medicine

 FH phenotype positive, genotype negative

– Worldwide about 50% of clinical FH cases do not have a putative pathogenic mutation in one of the three genes:
  • Familial combined hyperlipidemia (if apoB>120mg/dl)
  • Environmental dyslipidemia
  • Polygenic hypercholesterolemia (LDL score)
  • Other monogenic lipid disorders (FH phenocopies, up to 5%)
  • New FH genes (up to 5%)
FH recommendations

consensus paper

Clinical Genetic Testing for Familial Hypercholesterolemia
JACC Scientific Expert Panel
Convened by the Familial Hypercholesterolemia Foundation

Patient at risk due to family history of FH

- Cascade genetic testing

Patient with FH phenotype

- LDLR, APOB, PCSK9 genetic testing

Positive

- Genotype + Phenotype -
  - Monitor LDL-C

- Genotype + Phenotype +
  - Treat LDL-C

Negative

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

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)

Sturm et al, 2018 JACC
Portuguese FH study

835 index cases from the Portuguese FH study

360 Children

- 154 FH (known mutation in either LDLR, APOB, or PCSK9)
- 54 Polygenic
- 5 Other monogenic causes

59%

465 Adults

- 166 FH (known mutation in either LDLR, APOB, or PCSK9)
- 63 Polygenic
- 1 Other monogenic causes

49%

Mariano C, et al. Manuscript under preparation
Overall causes of monogenic dyslipidemia

Overall, monogenic dyslipidemia is responsible for 39% (n=326/835) of all index cases with an FH phenotype

LDLR, 92%

APOB, 5%

PCSK9, 1%

Other Monogenic Causes, 2%
(3% in children)

Other monogenic causes (LIPA, ABCG8, APOE) are more common than PCSK9 mutations

New NGS FH test – FH panel 8 genes: LDLR, APOB, PCSK9, APOE, LIPA, LDLRAP1, ABCG5/8 + polygenic score

Mariano C, et al. Manuscript under preparation
## From phenotype to genotype

<table>
<thead>
<tr>
<th>FH phenotype</th>
<th>Disorder based on the genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children (&lt;16 years)</strong>&lt;br&gt;Total cholesterol &gt;260 mg/dL or LDL-C &gt;155 mg/dL&lt;br&gt;+ family history of hypercholesterolemia</td>
<td><strong>FH (LDLR, APOB, PCSK9)</strong></td>
</tr>
<tr>
<td><strong>Adults</strong>&lt;br&gt;Total cholesterol &gt;290 mg/dL or LDL &gt;190 mg/dL&lt;br&gt;+ family history of hypercholesterolemia</td>
<td><strong>LAL-D (LIPA)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Sitosterolemia (ABCG5/8)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Dysbetalipoproteinemia (APOE)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Autosomal-recessive hypercholesterolemia (LDLRAP1)</strong></td>
</tr>
</tbody>
</table>
From genotype to treatment

<table>
<thead>
<tr>
<th>Familial hypercholesterolemia (htFH)</th>
<th>All FH patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR, APOB, PCSK9</td>
<td>2nd generation statins and selective inhibitor of cholesterol absorption (combined therapeutic)</td>
</tr>
<tr>
<td></td>
<td>Severe heterozygous patients add new PCSK9 inhibitors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Homozygous FH (true homozygotes)</th>
<th>Statins + iPCSK9 and/or LDL apheresis and/or MTTP inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR, APOB, PCSK9</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Autosomal recessive hypercholesterolemia</th>
<th>LDL apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLRAP1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dysbetalipoproteinemia</th>
<th>Statins + fibrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LAL-D</th>
<th>LAL replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIPA</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sitosterolemia</th>
<th>Diet poor on vegetal fat Inhibitor of cholesterol absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCG5, ABCG8</td>
<td></td>
</tr>
</tbody>
</table>
Familial hypercholesterolemia (FH)

The identification and characterization of the gene defect/pathway is important to establish a precise and personalized diagnosis and treatment.
Acknowledgments

The Portuguese FH Study clinical investigators

Dra. Ana Cristina Ferreira, Pediatria, H D. Estefânia, Lisboa
Dra. Ana Gaspar, Pediatria, CH Lisboa Norte, EPE - H Sta. Maria, Lisboa
Dra. Ana Margarida Marques, Pediatria, CH Tondela, Viseu
Dra. Ana Maria Garabal, Genética Médica, H Ped. Carmona da Mota, Coimbra
Dra. Ana Rita Godinho, Cardiologia, H S. João, EPE, Porto
Dra. Ana Sofia Correia, Cardiologia, H S. João, EPE, Porto
Dr. António Cruz, Pediatria, CH Leiria Pombal, EPE - H Sto André, Leiria
Dr. António Furtado, Medicina Interna, H Pedro Hispano, Setsarela da Hora
Dr. António Guerra, Pediatria, H S. João, EPE, Porto
Dr. António Trindade, Pediatria, CH Trás-os-Montes e Alto Douro, EPE, Vila Real
Dra. Carla Laranjeira, Pediatria, CH do Alto Ave, EPE, Guimarães
Dr. Carlos Vasconcelos, Endocrinologia, H Egas Moniz, Lisboa
Dra. Cecília Frutuoso, Cardiologia, H S. João, EPE, Porto
Dra. Cláudia Costa, Pediatria, CH Lisboa Norte, EPE - H Sta. Maria, Lisboa
Dra. Clementina Fernandes, Medicina Geral e Familiar, C S Bragança, Bragança
Dra. Conceição Ferreira, Medicina Interna, H Sta Maria Maior, EPE, Bragança
Dr. Daniel Ferreira, Cardiologia, H da Luz, Lisboa
Dr. Diogo Cruz, Medicina Interna, CH Lisboa Norte, EPE - H Sta. Maria, Lisboa
Dr. Duarte Gouveia, Cardiologia, H de Santiago, Setúbal
Porf. Elisabete Martins, Cardiologia, H S. João, EPE, Porto
Dr. Fernando Simões, Pediatria, H Litoral Alentejano, Santiago do Cacém
Dra. Filipa Paramés, Cardiologia Pediátrica, H Sta Marta, Lisboa
Dra. Filipea Silva, Pediatria, CH do Porto, EPE, Porto
Dra. Gareti Lobrinhas, Pediatria, H Sta Maria Maior, EPE, Barcelos
Dra. Helena Mansilha, Pediatria, CH do Porto, EPE, Porto
Prof. Héloisa Santos, Genética Médica, Inst. Nacional de Cardiologia Preventiva
Professor Fernando de Pádua, Lisboa
Prof. Henedina Antunes, Pediatria, H de Braga, Braga
Dra. Isabel Azevedo, Medicina Interna, H Funchal, Funchal
Dra. Isabel Gaspar, Genética Médica, H Egas Moniz, Lisboa
Dra. Isabel Mangas Palma, Endocrinologia, C H Porto, EPE - H Sto António, Porto
Dr. João Anselmo, Endocrinologia, H Divino Espírito Santo, Ponte Delgada
Dr. João Porto, Medicina Interna, CH e Univ. de Coimbra, EPE, Coimbra
Dr. João Sequeira Duarte, Endocrinologia, H Egas Moniz, Lisboa
Dr. Jorge Pintado Alves, Medicina Geral e Familiar, C S Proença-a-Nova, Proença-a-Nova
Dra. José Eduardo Aguiar, Cardiologia, H Sta Luzia De Elvas, Elvas
Dra. José Manuel Feliz, Medicina Geral e Familiar, CS do Seixal, Seixal
Dra. José Manuel Moura, Medicina Interna, CH e Univ. de Coimbra, EPE, Coimbra
Dra. Leonor Sassetti, Pediatria, H D. Estefânia, Lisboa
Dra. Lina Cardoso Ramos, Genética Médica, H Ped. Carmona da Mota, Coimbra
Dra. Luísa Diogo Matos, Pediatria, H Pediátrico Carmona da Mota, Coimbra
Dra. Már Rosário Barroso, Medicina Interna, CH Leiria Pombal, EPE, H S André, Leiria
Dra. Margarida Bruges, Nefrologia, H Sta Cruz, Carnaxide
Dr. Mário Amaro, Medicina Interna, H Garcia da Orta, EPE, Almada
Dr. Mário Martins Oliveira, Cardiologia, H Sta Marta, Lisboa
Dr. Miguel Costa, Pediatria, CH de Entre o Douro e Vouga, EPE, Sta Maria da Feira
Dr. Miguel Mendes, Cardiologia, H Sta Cruz, Carnaxide
Dr. Miguel Toscano Rico, Medicina Interna, H Sta Marta, Lisboa
Dra. Natalina Miguel, Pediatria, CH Trás-os-Montes e Alto Douro, EPE, Vila Real
Dra. Oana Moldovan, Genética Médica, C H Lisboa Norte, EPE - H Sta. Maria, Lisboa
Dra. Olga Azevedo, Cardiologia, H Guimarães, Guimarães
Dr. Pascoal Moleiro, Pediatria, CH Leiria Pombal, EPE - H Sto André, Leiria
Dra. Patrícia Janzê, Pediatria, CH Lisboa Norte, EPE - H Sta. Maria, Lisboa
Dra. Patricia Pais, Pediatria, H Dia de Pediatria - CH Barreiro Montijo, EPE, Barreiro
Dra Patricia Vasconcelos, Medicina Interna, H Prof. Doutor Fernando Fonseca EPE, Amadora
Dra. Paula Garcia, Pediatria, H Pediátrico Carmona da Mota, Coimbra
Prof. Paula Martins, Cardiologia Pediátrica, H Ped Carmona da Mota, Coimbra
Dr. Pedro Marques Silva, Medicina Interna, H Sta Marta, Lisboa
Dra. Piedad Lemos, Pediatria, H Prof. Doutor Fernando Fonseca EPE, Amadora
Dra. Quitéria Rato, Cardiologia, H S. Bernardo, Setúbal
Dra. Raquel Coelho, Pediatria, H Prof. Doutor Fernando Fonseca EPE, Amadora
Dra. Raquel Ribeiro, Med Geral e Familiar, Clinica Missão-Saúde, Alverca do Ribatejo
Dra. Renata Rossi, Pediatria, H Sta Cruz, Carnaxide
Dr. Sérgio Matoso Laranjo, Cardiologia Pediátrica, H Sta Marta, Lisboa
Dra. Silva Sequeira, Pediatria, H D. Estefânia, Lisboa
Dra. Susana Correia, Pediatria, H Dia de Pediatria, CH Barreiro-Montijo, EPE, Barreiro
Grupo de Investigação Cardiovascular
(UID – DPSPDNT)

Ana Catarina Alves
(pos-doc)

Ana Margarida Medeiros
(PhD student)

Cibelle Mariano
(PhD student)

Niccolò Rossi
(PhD student)

Joana Chora
(PhD student)

Marta Correia
(PhD student)

Rafael Graça
(PhD student)

Leonor Abrantes
(lab assistant)
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

2006B190
2006T102
Nederlandse Zorgautoriteit

funded by the Netherlands Heart Foundation
ICPerMed – FH program: Clinical Approach and Health System Implementation

Eric Sijbrands

Section of pharmacology, vascular & metabolic diseases
Dept. of vascular genetics
Secret of successful national screening

John Kastelein

Joep Defesche

Peter Lansberg

Iris Kind
1. clinical presentation of FH
2. nation-wide FH screening program:
   • Why?
   • Who?
   • How?
3. any improvements?
When is the diagnosis FH considered?

premature coronary artery diseases

or

asymptomatic with severe hypercholesterolemia

- cholesterol > 8.0 mmol/l (309 mg/dL)
- LDL-cholesterol > 4.9 mmol/l (90 mg/dL)

no secondary hypercholesterolemia
Clinical diagnosis
Clinical diagnosis
untreated
OR 8.5-13
large variation!
Adult index patient

Clinical diagnosis in proband

family history
• First degree relative with premature CVD 1
• First degree relative with LDL > 95e percentile and / or 2
• xanthomas or arcus
• kids < 18 jr. with LDL > 95e perc.

personal history
• premature CVD (men < 55, women < 60) 2
• premature CVA or peripheral vasc. disease < 60 1

physical examination
• tendon xanthomas 6
• arcus (< 45 jr) 4

LDL cholesterol
• > 8.5 mmol/l ( > 330 mg/dl) 8
• 6.5-8.4 mmol/l (251-329 mg/dl) 5
• 5.0-6.4 mmol/l (196-250 mg/dl) 3
• 4.0-4.9 mmol/l (155-195 mg/dl) 1

DNA analysis
• functional mutation in LDL receptor gene 8

DNA diagnostics

screening of family

diagnosis proband:
certainly FH >8
probably FH 6-8
possibly FH 3-5
Child index with hypercholesterolemia

LDL-C in age + sex specific 95th percentile + lean + normal TSH + dominant inheritance

post-test probability = 0.95 (95% CI: 0.96-0.99)

Circulation 2011; 123:1167-73.
Genetic epidemiology

Mutations in the following genes:

1. LDLR
2. APOB
3. PCSK9
4. APOE
5. BCG5/ABCG8 (sitosterolemia)
6. LDLRAP1 (autosomal recessive)
7. Polygenic SNP-score
Statin treatment

early diagnosis

lifelong
## CHD reduction in statin-treated FH

<table>
<thead>
<tr>
<th></th>
<th>Model I</th>
<th></th>
<th>Model II</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1950</td>
<td>0.24 (0.18-0.30)</td>
<td>0.18 (0.13-0.25)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>924</td>
<td>0.20 (0.15-0.28)</td>
<td>0.17 (0.11-0.26)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1026</td>
<td>0.30 (0.20-0.43)</td>
<td>0.21 (0.13-0.34)</td>
<td></td>
</tr>
</tbody>
</table>

Model I: adjusted for sex and year of birth
Model II: + smoking, hypertension, diabetes, HDL-C and LDL-C

BMJ 2008;337:a2423.
Rotterdam study vs untreated and treated FH

HR 1.44; n.s.

HR 8.69; p<0.001
# Cost-effectiveness of cascade screening

<table>
<thead>
<tr>
<th>Country</th>
<th>Sequencing Index</th>
<th>relative</th>
<th>Costs per patient</th>
<th>Costs/life year saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL2002</td>
<td>700</td>
<td>107</td>
<td>1200</td>
<td>8700</td>
</tr>
<tr>
<td>Spain</td>
<td>600</td>
<td>100</td>
<td>n.a.</td>
<td>26000</td>
</tr>
<tr>
<td>UK-EHR of GP</td>
<td>450</td>
<td>135</td>
<td>n.a.</td>
<td>7750</td>
</tr>
<tr>
<td>UK-cascade</td>
<td>450</td>
<td>135</td>
<td>n.a.</td>
<td>7690</td>
</tr>
</tbody>
</table>

Atherosclerosis 2018;275:80e87.
Screening

enough info for a molecular diagnostic screening program?
Why shouldn’t you screen for FH?

1. severe premature complications
2. no prodromes
3. treatment available
4. good cost-effectiveness
5. whose responsibility…?
6. insurance companies guarantee insurability
7. patient support group
Cascade screening
History of Dutch FH screening

<table>
<thead>
<tr>
<th>reimbursement foundation</th>
<th>DNA Method</th>
<th>Ministry of Health, Welfare and Sport</th>
<th>Health insurers</th>
</tr>
</thead>
<tbody>
<tr>
<td>StOEH</td>
<td>high-throughput sequencing</td>
<td>LEEFH</td>
<td></td>
</tr>
</tbody>
</table>

550 patients/year

>2000 patients/year

>30,000 patients with mutation identified
% identified (prevalence 1:240)
How to improve?

- Large variation of risk in untreated FH
- Residual risk in treated FH
- Better risk prediction
- New drugs
- Personalized approaches
Genomic Risk Score (GRS)

Genomic Risk Score (GRS)

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

↓

compensate for high GRS

Proteomics

Conclusions

improve screening by adding GRS

monitor effect of treatment with functional tests like the signals from healthy vessels
Future: tailored life course health and care

smart data storage  lifestyle apps  cardiac rehabilitation support

hearth rythm monitoring  hearth failure empowerment

compliance modules

EIT Health: SkyCare; PPP’s
FH - The key issues

Steve Humphries. : Emeritus Professor Cardiovascular Genetics UCL. Medical Director StoreGene

- It is Common - Frequency FH ~1/270
  Predict > 200,000 in UK, ~2,000,000 in EU

- It is underdiagnosed - < 10% of predicted UK known in most of EU
  particularly in the < 35 years group

- It runs in Families - autosomal dominant trait so 50% of children of an FH parent will have FH
  Cascade testing → find more FH patients

- 50% of men will have MI by age 50 years, and 60% of women by age 60 years
  Early treatment with Statins reduces CHD risk

- Statin treatment very safe and cost effective
  Many identified patients are under treated

FH is a disorder of LDL-Clearance from the blood
FH Diagnostic criteria

Simon Broome FH Register criteria:
• Cholesterol > 7.5mmol/l or LDL > 4.9mmol/l in adult
• Cholesterol > 6.7mmol/l or LDL > 4.0mmol/l if < 16 yrs
• PLUS family history of high cholesterol or MI (<55yrs M)
• OR PLUS Tendon Xanthoma
• OR FH-causing mutation

Corneal Arcus  Xanthelasma  Tendon Xanthoma

Also Dutch Lipid Clinic Criteria scoring system & US system MEDPED

<table>
<thead>
<tr>
<th>Dutch Lipid Clinic Network Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history</strong></td>
<td>Points</td>
</tr>
<tr>
<td>1st-degree relative with known CVD (M &lt;55yrs/F&lt;60yrs).....</td>
<td>1</td>
</tr>
<tr>
<td>1st-degree relative with TX and/or arcus cornealis,.....</td>
<td>2</td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td>Points</td>
</tr>
<tr>
<td>Patient with premature CHD</td>
<td>2</td>
</tr>
<tr>
<td>Patient with premature stroke or PVD</td>
<td>1</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td>Points</td>
</tr>
<tr>
<td>Tendon xanthomata</td>
<td>6</td>
</tr>
<tr>
<td>Arcus cornealis prior to age 45 years</td>
<td>4</td>
</tr>
<tr>
<td><strong>LDL-C levels</strong></td>
<td>Points</td>
</tr>
<tr>
<td>LDL-C &gt;=8.5</td>
<td>8</td>
</tr>
<tr>
<td>LDL-C 6.5-8.4</td>
<td>5</td>
</tr>
<tr>
<td>LDL-C 5.0-6.4</td>
<td>3</td>
</tr>
<tr>
<td>LDL-C 4.0-4.9</td>
<td>1</td>
</tr>
<tr>
<td><strong>DNA analysis</strong></td>
<td>Points</td>
</tr>
<tr>
<td>Functional mutation in the LDLR gene</td>
<td>8</td>
</tr>
</tbody>
</table>

>8 points = Definite FH
6 - 8 = Probable FH
3 - 5 = Possible FH

Welsh include –ve points for high TG – Haralambos et al 2014
DNA tests for FH - Offered by all 7 UK NHS Diagnostic Genomic Hub Labs

- Use NGS to capture and sequence exons of all genes in one run
- 96 samples can be handled in one run
- Costs now ~£250 for an index case, single mutation in relative ~ £70.
- Time taken to report now 4-6 weeks
- Costs of tests covered by NHS England from April 2019
What is overall mutation detection rate?

100 patients with a clinical diagnosis of FH (DFH+PFH or DLCN score > 3)

66 with PFH (DLCN score > 3)
- Detection rate 20-30%
- Mutation in 13-20

34 with DFH (DLCN score > 8)
- Detection rate 70-80%
- Mutation in 24-27

Overall find a monogenic molecular cause in 35-47% of patients

Taylor et al Clin Genet 2010
**Polygenic Cause of no mutation FH**

**Hypothesis:** Having large number of common genetic variants that each raise LDL-C by small amount could mimic Monogenic FH

Talmud et al Lancet 2013

- Used 12 common LDL-Raising DNA variants (SNPs) to make an “LDL-Gene Score”
- Compared score in mutation -ve FH patients, vs 3000 healthy subjects
- **Results:** Significantly higher mean score in M-ve FH vs Controls
- **Conclusion:** In at least 80% of M-ve patients a “polygenic” cause of their elevated LDL-C is most likely explanation
- Results confirmed in samples from 9 other countries

**Only those with a detectable mutation should → a diagnosis of “FH”**
- others “Polygenic Hypercholesterolaemia”
Why is the polygenic explanation important?

- **Research**: Searching for a new gene causing FH in high score patients will not be successful!!!

  500 no mutation/low score FH patients in 100,000 Genome project

  https://www.genomicsengland.co.uk/the-100000-genomes-project/

- **Money**: Cascade testing in monogenic FH → 50% first degree relatives will be FH. BUT in polygenic hypercholesterolemia → fewer than 30% “affected” relatives - ie much less cost effective

- **Treatment**: Monogenic FH have high CHD risk and need to be managed by lipid clinics, BUT polygenic FH patients have less severe CHD and can be managed by statin treatment by GPs (not expensive tertiary referral centres)

What is evidence for higher CHD in monogenic FH?
Among 20,485 CAD-free control and prospective cohort participants, 1,386 (6.7%) had LDL-cholesterol ≥ 5.0mmol/l. Of these, 24 (1.7%) carried an FH mutation.

Mechanism: FH mutation = lifelong exposure to elevated LDL-C. → higher CAD risk than in those with a polygenic “late rising” of LDL-C

Within any stratum of LDL-C, risk of CAD was 2-4 fold higher among FH mutation carriers than non-carriers.
Guidelines → “Consider statin by age 8/10yrs..” to reduce premature CHD burden

LDL “Burden” = \sum \text{measured LDL-C} \times \text{age}

Graph showing cumulative LDL-C (mmol) over years of age for different treatment scenarios: Untreated, Treat at 10yrs, Non FH, and Treat at 18yrs. Key points include:
- Threshold for clinical CHD
- Start low dose statin
- Start high dose statin
- 35yrs, 48yrs, 53yrs, 55yr non-FH
You can be above diagnostic threshold because of:

1. having a pathogenic mutation in a single gene or by
2. the combination of > average number of common variants

Monogenic & Polygenic causes of high Cholesterol

Paradigm example of Genomic information → Precision Medicine
Commercial availability for FH DNA tests

Test must include:
- NGS for whole of LDLR/APOB/PCSK9/APOE/LDLRAP1
- Plus 12 LDL-C Score SNPs
- Plus ACMG criteria for Variant calling
- Report in 4 weeks from sample receipt

Bristol NHS lab charges £400 |

DNA/Blood or Saliva. Only accept from HCP NOT DTC. NGS of exons of all genes. Price ??

http://www.color.com

http://www.progenika.com/

Hereditary High Cholesterol Test
Learn if you have the hereditary high cholesterol disorder, Familial Hypercholesterolemia (FH), and what you can do about it.

Buy Color $99

Saliva Sample. Sent by HCP or DTC. NGS of exons of LDLR/APOB/PCSK9. Only ACMG 4/5 variants reported
Genetic counsellor by phone

SEQPRO LIPO IS FOR ILLUMINA® MISEQ FEATURES
- Simultaneous detection of all possible FH mutations.
- 6 FH related genes analyzed: LDLR, APOB, PCSK9, APOE, STAP1 (ADH) and LDLRAP1 (ARH).
- Simplicity & latest Technology: analysis of DNA from Blood or saliva samples.
- This new product complements Progenika’s portfolio for FH, including our Lab Services: CLIA & CAP Accredited Laboratory at Progenika Inc. in San Marcos, TX (USA), and Clinical Diagnosis Laboratory at Progenika’ Headquarters in Derio (SPAIN).
Commercial availability for FH DNA tests

**Quest Diagnostics**
- Genetic testing for FH, from Quest, examines 3 actionable^2-6 FH genes: LDLR, APOB, and PCSK9, to enable an early, definitive diagnosis of FH. Early testing, both in adults and in family members, through cascade screening, can lead to early
- HCP and DTC Costs, turnaround and coverage unclear

**Invitae**
- Primary panel (4 genes)
  - APOB, LDLR, LDLRAP1, PCSK9
- Panel details and technical assay limitations
- $250
- 3mls Blood or Saliva
- 2-3 weeks

**Centogene**
- NGS Panel + CNV
  - LDLR/APOB/GHR/PCSK9
- Turnaround Time: 25 business days
- Coverage: ~98-99% covered >20x
- Required Material: ≥1ml EDTA Blood or ≥1 Filter Card
- Cost unknown
- Blood spots on card and post or blood
- 2-3 weeks

Summary: Plenty of testing companies around the world. Many websites unclear about Methods, Cost, Turnaround, and after test counselling. No company currently offers 12 SNP score
Third best practice example:
Translational medicine in familial hypercholesterolemia – from phenotype to genotype to treatment

What is the PATIENT BENEFIT?

Gabriele Hanauer-Mader
President Patient Organization FHchol Austria
Vienna
Familial Hypercholesterolemia

Genetic Disease with more than 2,000 identified pathogenic mutations

It is:
UNDERESTIMATED
UNDERDIAGNOSED
UNDERTREATED

despite potent & effective therapies and a Nobel Prize in 1985 describing the genetic mechanisms of the condition that leads to heart attacks & strokes if not treated
From personal suffering to the collective mission
2004: First FH patient advocacy group in the German-speaking countries

2011: Kick-off for two individual patient organizations in Austria and Germany that cooperate very closely
Personalized medicine – what is it?

• **It is not:** a more personalized relationship between physician & patient – as much as needed at times. Patients sometimes misunderstand this.

• Focus of personalized medicine lies on the **consideration of patients’ individual properties** – in diagnosis, therapy, and prevention

• In particular: **patients’ molecular biological properties** that can be determined by biomarkers
Patient benefit through personal medicine

Biomarkers are invaluable

• when it comes to deciding which therapy the patient needs or responds to
• when it comes to reduce or avoid therapies’ side effects – in FH patients e.g. statin intolerance
• Up-to-date molecular data analysis may even lead to the development of new therapies for currently not treatable rare diseases
Personalized Medicine & Prevention

• There is great hope that personalized medicine will in the long run usher in a new era in the PREVENTION of diseases and secondary diseases – in the case of familial hypercholesterolemia cardiovascular diseases like heart attacks and strokes
Personalized medicine & patient organizations

• Interdisciplinary cooperation between scientists, clinicians and patients is pivotal and fruitful = POWERFUL TEAM

• Especially on ethical issues – e.g. protection of sensitive (genetic) data in line with strict data protection laws – patient organization can add valuable advice

• It’s the patients that can best claim patients‘ rights vis-a-vis stakeholders and public health authorities
Empowered patients raise **awareness** of their conditions

Patients do have an **important voice** – they are the faces of their conditions

Through **national and international registries** patient data can be evaluated in favor of patients’ optimal treatment according to their genetic profile – „the right drug to the right person“
Austrian FH Registry currently stores data of approx. 400 patients.
Patient Organizations and the Medical & Science Community: Perfect Team in Personalized Medicine
What can patients do?
Liaise closely with media via press conferences, awareness events, etc.
Patient Testimonials are pivotal
Liaise with health politicians

FH Awareness Day 2015: Supported by the Viennese City Counsellor for Health
FH Awareness Week 2016

Supported by 2 Tyrolean health politicians
Austrian Women’s Run 2018

Supported by the Viennese Mayor and an Austrian MP and former minister
2nd FH Symposium, Nov. 6, 18 Vienna

• Active participation of 8 FH patient testimonials
• Participation of an Austrian health politician
• Presentation of latest Austrian FH Registry data
• Excellent speech on Personalized Medicine
International cooperation

FH Europe: European FH Patient Network

https://fheurope.org/
The Austrian Platform for Personalized Medicine

A national networking platform aims to sustainably connect all relevant stakeholders
Implementation of the Objectives of the Austrian Platform for Personalized Medicine

- **Conference**: one annual conference
  - Inaugural Event and Scientific Symposium (October 2017)
  - 2nd Annual Meeting: ÖPPM – Joining Forces for Personalized Medicine (October 2018)

- **Working Groups**
  - Basic and Translational Research
  - Infrastructure and Technology
  - Society and Ethics
  - Clinical Applications

- **Website**
  - Create and operate a webpage dedicated to PM (launch December 2018)
Members / the Expert Network
of the Austrian Platform for Personalized Medicine

- **116 personal members** (university clinicians, basic scientists, patient advocates, social scientists, non-university researchers, industrial representatives…)
- **12 member organizations**
- The platform is open to all individuals and organizations that would like to contribute to the future of personalized medicine in Austria and beyond.

### Members by Organization

<table>
<thead>
<tr>
<th>Organization</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MedUni Vienna</td>
<td>42</td>
<td>36</td>
</tr>
<tr>
<td>AIT</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Med Uni Graz</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>MedUni Innsbruck</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Open Science</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>CeMM</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>116</td>
<td>100</td>
</tr>
</tbody>
</table>
Thank you for your kind attention
Translational medicine in FH: Ethical Legal and Social Issues

João Lavinha
Human Genetics Department
Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA)
Lisboa, Portugal
joao.lavinha@insa.min-saude.pt
Traditional vs. “Precision” Medicine?

Traditional Medicine

- Same Therapy
- Benefit
- No Benefit
- Adverse Effects

Precision Medicine

- DNA Testing
- Tailored Therapy
- Each Patient Benefits
What determines health? (A fuzzy pie chart)

- Genetics: 10-25%
- Risk Factors: 20-40%
- Health Services: 15-30%
- Environment & Place: 5-15%
- Opportunities/Socioeconomic Status: 20-30%

Modifiable and non-modifiable health determinants?

Source: http://www.slideshare.net/benharrissorxas/what-is-health-impact-assessment
Issues versus practice

• Worldwide, less than 1% of FH patients have been identified, although the disease meets the WHO criteria for large-scale screening.

• In Portugal,
  • a genetic test (LDLR, APOB, PCSK9) is performed in symptomatic FH children and asymptomatic relatives of FH patients: identification and earlier treatment of ~4% of expected cases; to be further improved by NGS of a wider candidate gene panel; interpretation and communication of incidental findings;
  • the affected pathway is determined and characterised: patient stratification for a (more precise) mechanism-based therapy;
  • a patient registry (as part of ongoing international initiatives) is being set up.
Lessons learned

• Beyond the individual’s genetic make-up, “the protection or restoration of individual health results from structural transformations affecting the population as a whole” (Chowkwanyun et al. NEJM. 2018;379:1398-1400):
  • Life styles (social class, ethnic background, gender and sexual identity), physical environment.
  • Dyslipidaemia control, including in FH, is particularly susceptible to the structural factors above.
  • Genomics: a tool in an expanding arsenal not to be used in isolation.
  • Epigenetics as part of gene x environment interactions.

• Although genetic services and screening programs aim to improve the health of the population, there is growing concern that the increasing number of genetic tests becoming available at lower costs could compromise the viability of the health care system.
  • Clinical utility assessment mandatory before the test is reimbursed.

• In spite of the Portuguese NHS being universal, general and virtually free at the point of care, many health inequities remain to be solved by improving other policies (food, city planning, housing, education,...).