“In conclusion, after decades of efforts to find new genes for cardiovascular disease, exciting data from genome-wide association studies, remarkable insights from progress in molecular biology, and much talk about personalized medicine, we are still missing great opportunities to find and help people with one of the most common, serious genetic diseases known. **FH provides the only example of a genetic cause of premature CAD for which a systematic, population-based approach to find affected individuals and screen their families is clearly warranted at this time.**”

Cascade Screening: Critical for FH Families

- Process of systematic family tracing to identify at-risk relatives
- Should begin with 1st-degree relatives and then extend to 2nd and 3rd degree in a stepwise fashion
- DNA testing should be used if the pathogenic mutation has been identified
- Newly identified FH cases provide additional relatives who should be screened
- Facilitates early detection and treatment
- A cost-effective method for identifying people with FH

After FH has been diagnosed, any family member can have lipid or genetic testing, but a cascade strategy saves resources, and headaches!

Cascade Screening: The Dutch Experience

- National *lipid and genetic* cascade screening program for FH
  - Set up in 1994
  - Included home visits
  - So far identified over 25,000 FH patients

- First 5 years screened 5442 relatives of 237 FH patients and identified 2039 carriers
  - Initially only 39% were on meds
  - 2 years after molecular diagnosis 85% on meds

- Cascade genetic testing is cost-effective
  - $8700 per life year gained

Work from JJP Kastelein’s group
Leren, T et al. Comm Genetics 2008
*Slide modified from Josh Knowles, MD, PhD*
With no national program in place currently, how do we best commence with FH cascade testing?

- Pilot projects and local initiatives?¹
- One challenge is closely related family members typically do not share same HCP²
- Proband contact versus direct contact of relatives?
- Collection and assessment of an informative pedigree
  - Storage in the EMR
- Incorporation of genetic counseling
- “Dear Family Member” letter/email

## Comparison of relative contact methods

<table>
<thead>
<tr>
<th>Proband-initiated family contact</th>
<th>Direct contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard practice recommendation in clinical genetics</td>
<td>May not be possible due to privacy laws: can physicians contact individuals who are not their patients?</td>
</tr>
<tr>
<td>Protects confidentiality</td>
<td>Breach of confidentiality/loss of privacy</td>
</tr>
<tr>
<td>Relatives may be less at risk of psychological harm due to unsolicited contact</td>
<td>Potential for psychological harm (shock, anger, anxiety) – actual risk may not be large</td>
</tr>
<tr>
<td>Response rates likely to be lower</td>
<td>Takes away the right ‘not to know’ – respect for autonomy</td>
</tr>
<tr>
<td>Information from proband may have less impact than if it were from a health professional</td>
<td>Potential for actual harm (i.e. life insurance discrimination) – minimal risk?</td>
</tr>
<tr>
<td>Probands may never contact relatives</td>
<td>Detrimental impact on family dynamics – tailored approach ideal</td>
</tr>
<tr>
<td>Probands could provide incorrect information to relatives</td>
<td>Efficiency - # of relatives presenting for screening likely to be higher → greater cost-effectiveness</td>
</tr>
</tbody>
</table>
Patient Perceptions and Experiences

- Recent study performed thematic analysis of interviews of patients with a genetic diagnosis of FH*
  - Many reported that relatives were reluctant to attend screening due to ‘fatalistic’ outlook, denial, not wanting to know, low or lack of motivation, perception that FH is not that serious
  - Participants believed they had insufficient authority or control to persuade relatives to attend screening
    - Therefore, they welcomed greater hospital assistance for contact with relatives
  - Need for clinicians to provide clear information related to seriousness of FH and necessity for adherence to medication and lifestyle changes

Genetic testing
## Genetics of FH

<table>
<thead>
<tr>
<th>GENE</th>
<th>Chr</th>
<th># Causal Mutations</th>
<th>% of FH cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>LDLR</em> (LDL Receptor)</td>
<td>Chr 19</td>
<td>&gt; 1600</td>
<td>60-80%</td>
</tr>
<tr>
<td><em>APOB</em> (Apolipoprotein B)</td>
<td>Chr 2</td>
<td>Handful (esp. Arg3500Gln or R3500Q)</td>
<td>1-10%</td>
</tr>
<tr>
<td><em>PCSK9</em> (proprotein convertase subtilisin/kexin type 9)</td>
<td>Chr 1</td>
<td>Handful</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td>20-40%</td>
</tr>
</tbody>
</table>

* Yield for genetic testing is higher in “definite” FH (~80%) vs. “probable” and “possible” FH (35-60%)

*Slide modified from Josh Knowles, MD, PhD*
Broad Spectrum of Cholesterol Levels in FH
The Overlap Problem

The current landscape of FH genetic testing in the US

- While detection of pathogenic mutations in LDLR, APOB, or PCSK9 provides an unequivocal diagnosis of FH, such genetic testing has not been systematically incorporated in the US.

- Available via multiple commercial genetic testing labs with varying methodologies, gene coverage, clinical sensitivities, costs, and ability to bill health insurance.
  - NIH Genetic Testing Registry and GeneTests

- There are no US guidelines recommending genetic testing in FH, therefore it is not the “standard of care” even though it is the gold standard for diagnosis.
What DO the guidelines say about genetic testing?

- **International FH Foundation**
  - Genetic testing for FH should ideally be offered to all ‘index cases’ who have a phenotypic diagnosis of FH
  - DNA testing increases the accuracy of detecting FH and, if resources permit, should be considered to confirm the diagnosis, especially if cascade screening is planned

- **National Lipid Association Expert Panel on FH**
  - …genetic testing is not recommended as a universal screening measure and is not generally needed for clinical management or diagnosis, there are cases when genetic testing has an important role, such as when the diagnosis of FH is uncertain. The panel recommends that genetic testing should be covered by payers under those circumstances.

- **National Institute for Clinical Excellence (NICE) in the U.K.**
  - Offer a DNA test to people with a clinical diagnosis of FH.
  - If an FH gene mutation has been identified, use it to identify affected relatives, not LDL concentrations.

- **The Cardiac Society of Australia and New Zealand (CSANZ)**
  - Genetic testing can provide certainty of diagnosis where confounding factors make diagnosis unclear.
  - Patients requiring genetic tests should be offered genetic counseling prior to genetic analysis.

Genetic Counseling – FH Specific Foci

- Points discussed in detail regarding FH
  - Autosomal dominant inheritance
  - Cascade screening recommendations – including pediatric patients
  - Potential clinical utility of genetic testing
  - FH is a treatable condition
    - If family members have FH they require immediate initiation of treatment and aggressive management of other risk factors (e.g. hypertension, diabetes, smoking)
    - Urge family members not currently undergoing treatment to seek medical therapy immediately
    - Urge family members who are smokers to quit
  - Patients who do not respond adequately to, or are intolerant of, initial statin therapy should be referred to a lipid specialist
  - For children with FH, either consultation with or referral to a lipid specialist for management is recommended
  - Childbearing-age patients – discussion about reproductive options

- Review online resources
- Refer to CASCADE FH Registry
- Provide Dear Family Member Letter
Dear Family Member,

I have been diagnosed with familial hypercholesterolemia (FH). FH is a genetic disorder that causes high cholesterol levels in the blood resulting in a 20-times increase in risk for premature heart disease (including heart attack) if left untreated. Based on my diagnosis, you are at risk for FH. You could have FH without any physical signs or symptoms and may feel and look healthy. If diagnosed, FH needs to be treated through medication and lifestyle changes (not smoking, regular exercise and a healthy diet). The good news is that HEART DISEASE due to FH CAN BE PREVENTED if you TAKE ACTION and have your high cholesterol treated by a health care provider who knows about this condition. Knowing your cholesterol level gives you the power to act.

If you already have high cholesterol or heart disease, ask your health care provider if you might have FH. If you do not know whether you have high cholesterol, you can see your health care provider and have a fasting lipid profile. This is a standard blood test that provides information about cholesterol levels. Individuals with FH have high levels of low-density lipoprotein (LDL) cholesterol, also known as the “bad cholesterol”. Genetic testing for FH is available and can be useful to assist in diagnosis and identify other family members who may also have FH.

FH is passed down through families in an autosomal dominant manner and can be inherited from a parent. All first-degree relatives (parents, siblings, children) of a person with FH have a 50% chance of also having FH. FH affects people of all ages and high cholesterol levels need to be treated in children as well as adults. Diagnosis of FH in childhood allows for early intervention and treatment and improves chances to prevent heart disease. Therefore we recommend all children at risk for FH have their cholesterol levels checked for the first time between the ages of two and eight years old.

Next Steps

- Take a copy of this letter with you when you meet with your health care provider.
- Ask your health care provider to check your cholesterol.
  - A diagnosis of FH is probable in a family member of an affected individual with FH if:
    - Untreated LDL is greater than 170 mg/dL in adults 20 years of age and older.
    - Untreated LDL is greater than 155 mg/dL in children and adolescents less than 20 years of age (Williams RR et al. Am J Cardiol. 1993;72(2):171-176).
  - Initial screening of children at risk for FH should take place between 2 and 8 years of age.
- If you are diagnosed with FH, share this letter with your at-risk parents, siblings and children.
- If your cholesterol levels are normal:
Genetic counselors can help win the “FH Battle”!

“Our biology does not stop: the risk of developing CHD as a consequence of FH will still be present, even if relatives live in ignorance.”

Resources

- The FH Foundation [www.thefhfoundation.org/](http://www.thefhfoundation.org/)
  - Find an FH Specialist Map
- National Lipid Association [www.lipid.org/](http://www.lipid.org/)
  - Foundation of the NLA Find a Lipid Specialist Tool
- Preventive Cardiovascular Nurses Association [http://pcna.net/patients/familial-hypercholesterolemia](http://pcna.net/patients/familial-hypercholesterolemia)
- NSGC ([www.nsgc.org](http://www.nsgc.org))
  - Find a Genetic Counselor tool
  - CV Genetics SIG FH Working Group
    - FH Dear Family Member Letter
    - Letter of medical necessity for FH genetic testing