Familial hypercholesterolemia, PCSK9 inhibition, and other lipid biomarkers of cardiovascular risk

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Genomic and Precision Medicine in Prevention

Preventive and therapeutic interventions
Linking genomic and phenomic data at scale

Genotyping and sequencing

Electronic health records
Deep phenotyping
Familial hypercholesterolemia: mutations in genes that impair LDL receptor function

FH Genes
- LDLR
- APOB
- *PCSK9

Diagram showing the LDLR and apoB with a cross indicating impaired function. VLDL and LDL are also shown with arrows indicating the pathway.
FH is grossly underdiagnosed in the US and most of the world.
A ‘Genome-first’ approach to finding undiagnosed patients with Familial Hypercholesterolemia

FH prevalence:
~ 1 in 250
FH is a CDC-designated ‘Tier 1’ genetic health condition

CDC has designated three ‘Tier 1’ genetic health conditions for application of genomic medicine to public health:

1. Hereditary Breast and Ovarian Cancer (HBOC) Syndrome
2. Lynch Syndrome (colon cancer and other cancers)
3. Familial Hypercholesterolemia (FH)

- Significant public health concerns
- Effective preventive therapies
- Autosomal dominant conditions

Family screening for FH saves lives
Figure. Process From Case Identification to Cascade Screening

Case identification

Ways to identify possible proband
Health care visit
Lipid screening
Database search (electronic health record, laboratory results, billing record)*

Possible FH

Confirm diagnosis
Repeat lipid testing
Genotyping
Family history
Physical examination

Diagnosis

Proband

Cascade screening

I

II

III

Proband

IV

Location
Oregon (OR)
Virginia (VA)
Texas (TX)

Cascade cycle (cumulative no. of identified cases)

Potential barriers to cascade screening
Family structure and dynamics
Geographic dispersion
Health care literacy
Access to care
Privacy concerns

Early onset of ASCVD
(men, age <50 y; women, age <60 y)

High cholesterol (LDL >190 mg/dL)

Proband

Deceased
Divorced
Addressing barriers to care in FH

• Increase awareness of prevalence and severity
• New ICD10 code (E78.01)
• Promote systematic approach to cascade screening and genetic testing
• First FH disease registry
• Find all the undiagnosed cases
FH: Call to action

Make the diagnosis: FH Diagnosis app, ICD 10 E78.01

Educate the patient: thefhfoundation.org

Consider genetic testing

Actively promote family-based cascade screening

Evaluate other risk factors [ie Lp(a)]

Aggressively treat LDL, including combination therapies

Refer for clinical trials where appropriate
Inherited Syndromes of Extremes of LDL-C: Story of PCSK9

- Gain of function mutations in PCSK9
- Loss of function mutations in PCSK9

Frequency (%)
The Role of PCSK9 in the Regulation of LDL Receptor Expression
Impact of an PCSK9 mAb on LDL Receptor Expression
PCSK9 Inhibitors

- Alirocumab and Evolocumab
- SQ injection biweekly or monthly
- Indications:
  - Patients with heterozygous familial hypercholesterolemia on maximally tolerated statin therapy with inadequate plasma LDL levels
  - Patients with a history of CHD with inadequate plasma LDL levels
- Reduce cardiovascular outcomes (FOURIER)
**Placebo**

59% mean reduction (95%CI 58-60), P<0.00001

Absolute reduction: 56 mg/dl (95%CI 55-57)

**Evolocumab**

(median 30 mg/dl, IQR 19-46 mg/dl)
Primary Endpoint

Hazard ratio 0.85 (95% CI, 0.79-0.92) P<0.0001

CV Death, MI, Stroke, Hosp for UA, or Cor Revasc

0 6 12 18 24 30 36

Evolocumab

Placebo

12.6% 14.6%
Substantial residual risk of CV events remains even in patients treated to very low levels of LDL-C
Lipoproteins and Coronary Disease

Remaining opportunities for reducing residual risk through lipid modulation
ApoB-lipoproteins are biomarkers of CAD risk

Clinical trait | Association with CAD | Lipoprotein class
--- | --- | ---
LDL cholesterol | Upward arrow | Lipoprotein class
Triglycerides | Upward arrow | Lipoprotein class
Lipoprotein(a) | Upward arrow | Lipoprotein class
TG-rich lipoproteins are causally related to coronary disease
Lipoprotein lipase is a critical regulator of TG-rich lipoprotein metabolism.
ApoC3 inhibits metabolism of TG-rich lipoproteins and is a genetically validated therapeutic target.

[Diagram showing the metabolism of TG-rich lipoproteins (TRLs) with ApoC-III and LPL enzyme.]
Volanesorsen (ASO to APOC3) reduces apoC-III and TGs
Other proteins influencing the LPL pathway are genetically validated targets.
Blood biomarkers that predict risk of and are causal for cardiovascular disease

- Lipoprotein(a) [Lp(a)]
An ASO to APO(a) reduces Lp(a) levels in humans

HDL-C is a strong inverse predictor of CAD risk but is NOT causally associated with CAD.
ApoA-I promotes macrophage cholesterol efflux and reverse cholesterol transport

“Cholesterol efflux capacity” of HDL is predictive of cardiovascular events
Will apoA-I/reconstituted HDL remove cholesterol from plaque and reduce CV events after ACS?
Lipid management in high-risk patients

- **LDL, TG-rich lipoproteins, Lp(a)**
  - High-intensity statin therapy
  - Target LDL-C aggressively, using combinations as needed
  - Non-HDL-C and possibly TG-rich lipoproteins as secondary targets
  - Enroll in clinical trials of new lipid-lowering therapies

If HDL-C is low:
- Lifestyle intervention
- High-intensity statin therapy
- Consider TG reduction if TGs are elevated