Outline of this presentation

- Introduction on FH
  - FH Canada registry
    - Goals
    - Inclusion criteria
    - iCapture database

- Increase awareness on FH
  - Opening new sites
  - Cascade screening strategy
  - FH Canada website
  - Update on Position Statement on FH
  - Educational resources
Familial Hypercholesterolemia

FH is One of the Most Common of Inherited Diseases

- Heterozygous FH
- Dominant ostosclerosis
- Adult polycystic kidney disease
- Huntington’s disease
- Cystic fibrosis
- Marfans syndrome
- Duchenne muscular dystrophy
- Sickle cell anemia
- Phenylketonuria
- Haemophilia

Frequency per 1,000 births

Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490

- Heritable, autosomal co-dominant disorder
- Usually due to mutations in LDL receptor gene
  - > 1700 mutations
  - LDLR mutation 1 in 250 - 500; 1/270 in Quebec
  - ~ 84,000 patients in Canada: ~ 29,000 in Qc; ~ 55,000 ROC; with less than 5% of patients diagnosed

Prevalence has been recently revised to 1 in 250 so in Canada = over 140,000 pts.

Pathophysiology of HeFH

Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490
Clinical manifestations

- Bilateral xanthelasma
- Arcus Cornae
- Xanthomas within the Achilles tendons
- Xanthoma within extensor tendon of the hand

The aim of the FH registry is to improve the detection and management of individuals and families with FH in Canada. Rare diseases of lipoprotein metabolism are also included (SMASH initiative).

Initiated at University of British Columbia and became national in 2014.

Over 90 clinicians and scientists in 18 academic centers across Canada form the “hubs” of FH Canada.

Clinicaltrials.gov: NCT02009345
The MISSION of the Canadian FH Registry is to bring together a multi-disciplinary group of physicians, basic and clinical researchers to improve the delivery of care to patients with severe lipoprotein disorders, especially FH, and to foster collaborative research.

Our VISION is to create a Canada-wide network of academic clinics, integrating lipid specialists, endocrinologists and cardiologists to treat patients with the highest standard of care and to create a collaborative research environment. Using a “hub and spoke” model, the registry will be extended in various communities to link primary care physicians with provincial academic centers.

The GOALS are to improve care to patients with FH and to reduce cardiovascular disease in this population at high risk.
FH Canada: Governance Structure

Objectives:

Objective 1: FH and SMASH Registry

Objective 2: Biomedical; Genetics
- R. Hegele
- D. Gaudet
- J. Genest
- J. Engert
- G. Pare

Objective 3: Clinical Network
- D. Gaudet,
- J. Frohlich
- J. Mancini
- J. Bergeron
- P. Couture
- and other clinicians

Objective 4: Health Systems Services Outcomes and Economics
- J. Brophy
- M. Henderson

Objective 5: GE3LS; Knowledge Translation
- Patient Rep.
- D. Bewick
- M. Gupta

Advisory Boards:

National Advisory Board:
- Ethics Rep.
- MD Rep.
- Patient Reps:
  - Legal Rep.
  - Nursing Rep.
  - Pharma Rep.

Scientific Board:
- J. Genest
- J. Frohlich
- D. Gaudet
- R. Hegele
- J. Brophy
- B. McCrindle

International Advisory Board:
- Dr. J. Knowles (US)
- Dr. GK. Hovingh (Netherlands)
- Dr. M. Farnier (France)
- Dr. F. Civeira (Spain)
- Dr. R Cramb (UK)

Coordinator: I. Ruel

Data Management

iCAPTURE Manager
Inclusion criteria: Canadian Definition

**Definite FH**
- *Known FH causing DNA Mutation in proband* or 1st-degree relative
  - OR Tendinous xanthomas
  - OR LDL-C ≥ 8.5 mmol/L

**Probable FH (Consider DNA testing)**
- 1st-degree relative with ↑ LDL-C
  - OR 1st-degree relative with early onset ASCVD
  - (<55 yr Men; <65 yr women)

**Hypercholesterolemia (Consider DNA testing)**

* Secondary causes ruled out (nephrotic syndrome, obstructive jaundice, hypothyroidism, drugs, other).
**Mutation in LDL-r, ApoB or PCSK9; Presence of a DNA causing mutation in a proband is sufficient for a diagnosis of FH. Treatment decision should be at the discretion of the treating physician.
The James Hogg Research Centre at St-Paul’s Hospital, UBC, Vancouver is providing the **iCAPTURE platform** used to capture the data from the FH Canada Registry.

Data entry at each site (local) is performed using nominative information and coded specific to the institution (hospital ID number).

**Local site:** all users receive secure login credentials (full access to all local data for investigator and study coordinator; data entry only for clerk).

In addition, a unique identifier is randomly assigned to each patient (0 to 999999) and only this number is used in the **de-identified National registry**, which will be used for health outcomes and health economic studies.
The database has built-in algorithms to generate a score for the most common FH criteria (Simon-Broome, Dutch Lipid Clinic Network (DLCN), Canadian definition).

**TABLE 1**
Simon Broome criteria for diagnostics of familial hypercholesterolemia

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Total cholesterol concentration above 7.5 mmol/L in adults or a total cholesterol concentration above 6.7 mmol/L in children aged less than 16 years, or low-density lipoprotein cholesterol concentration above 4.9 mmol/L in adults or above 4.0 mmol/L in children</td>
</tr>
<tr>
<td>b</td>
<td>Tendinous xanthomata in the patient or a first-degree relative</td>
</tr>
<tr>
<td>c</td>
<td>DNA-based evidence of mutation in the LDLR or APOB gene</td>
</tr>
<tr>
<td>d</td>
<td>Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative</td>
</tr>
<tr>
<td>e</td>
<td>Family history of raised total cholesterol concentration above 7.5 mmol/L in a first- or second-degree relative</td>
</tr>
</tbody>
</table>

**Diagnosis**

A 'definite' FH diagnosis requires either criteria a and b or criterion c. A 'probable' FH diagnosis requires criteria a and d or criteria a and e.

**TABLE 2**
Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family History</strong></td>
<td></td>
</tr>
<tr>
<td>First-degree relative with known premature (men: &lt;55 years; women: &lt;60 years) coronary and vascular disease, or</td>
<td>1</td>
</tr>
<tr>
<td>First-degree relative with known LDLC* above the 95th percentile</td>
<td></td>
</tr>
<tr>
<td>First-degree relative with tendinous xanthomata and/or arcus cornæalis, or Children aged less than 18 years with LDLC above the 95th percentile</td>
<td>2</td>
</tr>
<tr>
<td><strong>Clinical History</strong></td>
<td></td>
</tr>
<tr>
<td>Patient with premature (men: &lt;55 years; women: &lt;60 years) coronary artery disease</td>
<td>2</td>
</tr>
<tr>
<td>Patient with premature (men: &lt;55 years; women: &lt;60 years) cerebral or peripheral vascular disease</td>
<td>1</td>
</tr>
<tr>
<td><strong>Physical Examination</strong></td>
<td></td>
</tr>
<tr>
<td>Tendinous xanthomata</td>
<td>6</td>
</tr>
<tr>
<td>Arcus cornæalis prior to age 45 years</td>
<td>4</td>
</tr>
<tr>
<td><strong>Cholesterol Levels (mmol/liter)</strong></td>
<td></td>
</tr>
<tr>
<td>LDLC, ≥8.5</td>
<td>8</td>
</tr>
<tr>
<td>LDLC, 6.5-8.4</td>
<td>5</td>
</tr>
<tr>
<td>LDLC, 5.0-6.4</td>
<td>3</td>
</tr>
<tr>
<td>LDLC, 4.0-4.9</td>
<td>1</td>
</tr>
<tr>
<td><strong>DNA Analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Functional mutation in the LDLR gene</td>
<td>8</td>
</tr>
<tr>
<td><strong>Diagnosis (diagnosis is based on the total number of points obtained)</strong></td>
<td></td>
</tr>
<tr>
<td>A 'definite' FH diagnosis requires more than 8 points</td>
<td></td>
</tr>
<tr>
<td>A 'probable' FH diagnosis requires 6-8 points</td>
<td></td>
</tr>
<tr>
<td>A 'possible' FH diagnosis requires 3-5 points</td>
<td></td>
</tr>
</tbody>
</table>


When baseline LDL-C values are unknown, the database has an algorithm that can impute a LDL-C value from the LDL-C on treatment:

**Typical LDL-C reductions (% change from baseline) by statin dose.**

To get an imputed baseline LDL-C, divide the Friedewald "on-treatment" LDL-C by the factor in parentheses in the following table:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean Reduction by Dose: % change from baseline (divide LDL-C by this factor)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 mg</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>-40 (0.60)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>-</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>-26 (0.74)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>-</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>-</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>-</td>
</tr>
<tr>
<td>Ezetimibe alone</td>
<td>-</td>
</tr>
<tr>
<td>Ezetimibe 10 mg added on any other statin***</td>
<td>add -20 (0.80)</td>
</tr>
<tr>
<td>Bile acid sequestrants (Cholestyramine, Colestipol, Colesevelam): add a mean 15% decrease (divide LDL-C by 0.85)</td>
<td></td>
</tr>
</tbody>
</table>

**PCS**K9 inhibitors: Approx. 60% decrease in LDL-C on any statin +/- Ezetimibe treatment (divide LDL-C by 0.4)**

Increase awareness of FH: opening new sites

The registry is now being extended to various communities radiating from the academic centers (“hub and spoke” model).
Increase awareness of FH: Cascade screening strategy

1- The first patients to be recruited will be those with a high LDL-C already followed at the site clinic.

2- Then, family members and other undiagnosed patients (ex. siblings and cousins) are recruited from cascade screening and are referred to the nearest FH Canada participating site (www.fhcanada.net).

3- New patients will be recruited with the help of the FH Canada website and the increasing awareness of FH in Canada.
Increase awareness of FH: Website www.fhcanada.net

- Participating sites
- Database access link
- Apps (Canadian FH diagnosis, Imputed LDL-C)
- Brochures
- FH resources for patients and HCPs
- ...
Increase awareness of FH: Position Statement on FH

Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia

Primary Panel: Jacques Genest, MD,a Robert A. Hegele, MD,b Jean Bergeron, MD, MSc,c James Brophy, MD, PhD,a Andre Carpenter, MD,d Patrick Couture, MD, PhD,b Jean Davignon, MD,e Robert Dufour, MD, MSc,e Jiri Frohlich, MD,f Daniel Gaudet, MD, PhD,e Milan Gupta, MD,b Preetha Krishnamoorthy, MD,a John Mancini, MD,g Brian McCrindle, MD,h Paolo Raggi, MD,i Isabelle Ruel, PhD,a and Julie St-Pierre, MD, PhDd,k

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RECOMMENDATION

2. We suggest that the diagnosis of FH should rely on the Simon Broome Registry or Dutch Lipid Clinic Network criteria (Conditional Recommendation, Moderate-Quality Evidence).

Values and Preferences. Because there is no “gold standard” to diagnose FH, further clarification of specific criteria to facilitate diagnosis is required—especially to increase diagnostic sensitivity in the primary care setting.
Increase awareness of FH: Position Statement on FH (2)

Will be updated because:

• New Canadian definition of FH
• New information on cardiovascular risk in FH patients
• New Canadian Cholesterol guidelines 2016
• Novel therapeutic approaches
New information on cardiovascular risk in FH patients

Amit V. Khera, Hong-Hee Won, Gina M. Peloso, Sekar Kathiresan, on behalf of investigators from the Myocardial Infarction Genetics and CHARGE Consortia
Clinical Importance: For a Given Observed LDL, FH Mutation Carriers are at Increased Coronary Risk

Khera et al.
Increase awareness of FH: Educational resources

- Create an accredited teaching material on FH (slide kit)
- Revise the core curriculum in lipoprotein disorders (downloadable)

- Both educational resources will be bilingual and freely available online, and will include:
  - latest knowledge on FH
  - revised Canadian diagnostic criteria
  - imputed LDL-C tool (useful for assessing the degree of severity of FH for new patients)
  - available treatments in Canada
  - results from the latest clinical trials and details on the on-going trials, including the use of PCSK9 and CETP inhibitors
  - update of the fourth edition of the book “Dyslipoproteinemias: The Clinical Approach” (Dr D. Gaudet)
  - summary of the CCS position statement on FH
  - a section on understanding the genetic basis of FH in Canada including the unique LipidSeq and MLPA techniques

- Educational material will be assessed and updated yearly, and will be downloadable for tablets, iPods and iPhones.
FH Canada registry is a unique network of more than 150 basic researchers, clinicians specializing in lipidology, endocrinology, pediatric endocrinology, obesity and cardiology, clinic coordinators and industry partners.

If you have any questions about the registry, you may visit our website at www.fhcanada.net

You may also contact the national coordinator:
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Thank you

FH Canada sponsors: