Canadian Familial Hypercholesterolemia Registry
Régistre Canadien d’hypercholestérolémie familiale
Aim of FH Canada registry

• 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 200 clinicians and scientists in 19 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 Registry “hub and spoke” model
Familial Hypercholesterolemia

FH is One of the Most Common of Inherited Diseases

- Heritable, autosomal co-dominant disorder
- Usually due to mutations in LDL receptor gene
  - > 1800 mutations
  - LDLR mutation 1 in 250
  - ~ 143,000 patients in Canada, with less than 10% of patients diagnosed

Pathophysiology of HeFH

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

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

Overview: What does the study involve?

Subject with high LDL-C + family history

- Explain project + consent form
  - Patient brochure
  - Consent Form

- Signature of consent form

- Fill patient questionnaire
  - Patient questionnaire (40 questions, 30 min/pt)

- Blood sampling and/or saliva collection
  - Blood analysis at clinic; Plasma + Buffy coat/Saliva collection for DNA

- Start cascade screening on relatives

- Yearly follow-up

Enter data in iCapture
Inclusion criteria: Canadian definition

Any patient with a clinical diagnostic criteria for FH:

*LDL-C ≥ 5.0 mmol/L (≥ 40 yr)
LDL-C ≥ 4.5 mmol/L (18-39 yr); ≥ 4.0 mmol/L (<18 yr)

**DNA Mutation
OR
Tendon xanthomas
OR
LDL-C ≥ 8.5 mmol/L

Definite FH

1st-degree relative with ↑ LDL-C
OR
Proband or 1st-degree relative with ASCVD (<55 yr men; <65 yr women)

Probable FH

Severe Hypercholesterolemia

* 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.
Data collected from patient questionnaire
*Mainly “Yes/No” answers, max 30 min/patient

Section 1: Patient Data
• Demographics (name, address, birth date, gender, self-reported ethnicity, consent form signed + date, preferred method of contact)
• Family doctor contact info

Section 2: Past medical Exam
• Family history (familial history of CVD and high LDL-C in 1st-degree relatives)
• Smoking status (non-, ex or smoker, nb years, nb cigarettes/day)
• Medical history (hypertension, DM, CAD as in MI, Angina, etc)
• Surgical history (PCI, CABG, arterial revascularisation)

Section 3: Physical exam
• Standard measurements (weight, height, blood pressure)
• Physical signs of FH (corneal arcus <45 years old, xanthelasma, xanthomas)
Section 4: Medication data
• Lipid-lowering medication (statin, ezetimibe, etc with dose and frequency, statin intolerance)
• Non lipid-lowering medication (prescribed or over-the-counter with dose and frequency)

Section 5: Lab data entry
• Date of analysis
• Fasting as Yes/No
• Known or self-reported baseline LDL-C (untreated)
• Blood glucose, Hemoglobin A1C, Total cholesterol, LDL-C, HDL-C, TG, CK, Creatinine, AST, ALT, Lipoprotein (a), ApoB

Section 6: Genetic
• DNA gene mutation(s) if known (DNA isolation Yes/No, gene + mutation name)
• SNP score if known
Entering data in iCapture

• 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.

• The database utilizes an Oracle backend and is firewalled and maintained in a separate non public network, and it is FDA, Health Canada, PHIA and PIPEDA compliant. All user access is logged.

• A unique identifier will be randomly assigned to each patient (0 to 999999) and only this number will be used in the de-identified national registry.

• All de-identified data from the registry will be made available for statistics on FH in Canada, for health outcomes and health economic studies which will help allow resource allocation and quality control.
Data collected include demographics, family history of high LDL-C or CVD, patient’s medical history, physical signs of FH, meds and lab data (blood glucose, HbA1C, total cholesterol, LDL-C, HDL-C, TG, CK, creatinine, AST, ALT, Lp(a), ApoB.

FH scores automatically generated

SMASH: patients with other lipoprotein disorders also included
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>
<thead>
<tr>
<th>Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of DNA mutation known to cause FH (LDLR, APOB, PCSK9 genes)</td>
<td>Definite</td>
</tr>
<tr>
<td>LDL-C &gt; 4.9 mmol/L in adults (&gt; 4.0 mmol/L in children under 16yr) or Total cholesterol &gt; 7.5 mmol/L in adults (&gt; 6.7 mmol/L in children under 16yr)</td>
<td>Definite</td>
</tr>
<tr>
<td>Tendon xanthomas or evidence of these signs in first- or second-degree relative</td>
<td></td>
</tr>
<tr>
<td>Family history of myocardial infarction before age 50 yr in a second-degree relative or before age 60 yr in a first-degree relative or Family history of raised total cholesterol concentration &gt; 7.5 mmol/L in a first- or second-degree relative or &gt; 6.7 mmol/L in children under 16 yr</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Adapted from *Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ 1991;303:893-6.*
### Dutch Lipid Clinic Network criteria for the clinical diagnosis of familial hypercholesterolemia (FH)

<table>
<thead>
<tr>
<th>Group 1: Family history</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• First-degree relative known with premature coronary and vascular disease (men under 55 yr, women under 60 yr) or • First-degree relative known with LDL-C &gt; 95th percentile</td>
<td>1 point</td>
</tr>
<tr>
<td>• First-degree relative with tendon xanthomata and/or arcus cornealis or • Children under 18 yr with LDL-C &gt; 95th percentile</td>
<td>2 points</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2: Clinical history</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient has premature (men under 55 yr, women under 60 yr) CAD or • Patient has premature (men under 55 yr, women under 60 yr) cerebral or peripheral vascular disease</td>
<td>2 points 1 point</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 3: Physical examination</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tendon xanthomata or • Corneal Arcus under 45 yr</td>
<td>6 points 4 points</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 4: Laboratory analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• LDL-C &gt; 8.5 mmol/L or • LDL-C 6.5 - 8.50 mmol/L or • LDL-C 5.0 - 6.49 mmol/L or • LDL-C 4.0 - 4.99 mmol/L</td>
<td>8 points 5 points 3 points 1 point</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 5: DNA analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Functional mutation known to cause FH</td>
<td>8 points</td>
</tr>
</tbody>
</table>

**FH DIAGNOSIS**

- **Definite** 9 or more points
- **Probable** 6-8 points
- **Possible** 3-5 points

_The highest score per group should be applied_

Increase awareness of FH: Cascade screening strategy

1- The first patients to be recruited are 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 are recruited with the help of the FH Canada website and the increasing awareness of FH in Canada.
What has been done so far:

1- Publication of a snapshot of the FH Canada registry - 2018 
2- Characterization of the prevalence of FH (Meta-analysis) 
3- Validation of a simpler definition of FH for Canadians 
4- Validation of an algorithm to impute the baseline LDL-C when patient is on treatment and baseline LDL-C is unknown 
5- Creation of a new FH Canada “App” - Apple and Android to ease the diagnosis of FH 
6- Update of the CCS Position Statement on FH 
7- Set-up the genetic testing for FH – complete DNA sequencing at MUHC.
Familial hypercholesterolemia in Canada: Initial results from the FH Canada national registry

Liam R. Brunham a,*, Isabelle Ruel b, Etienne Khoury h, Robert A. Hegele c, Patrick Couture d, Jean Bergeron d, Alexis Baass e,f, Robert Dufour g, Gordon A. Francis a, Lubomira Cermakova a, G.B. John Mancini i, James M. Brophy b,j, Dianne Brisson h, Daniel Gaudet h, Jacques Genest b,j,**
3185 patients in the database -2018:
• 3108 HeFH
• 14 HoFH
• 63 patients with other lipoprotein disorders (*ABCA1, SMPD1, APOAI, LCAT mutations*)

Table 1
Baseline characteristics of patients in the Canadian FH Registry.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HeFH</th>
<th>HoFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3108</td>
<td>14</td>
</tr>
<tr>
<td>Age, years (mean ± SD) (n = 3022)</td>
<td>43 ± 17</td>
<td>38 ± 15</td>
</tr>
<tr>
<td>DLCNCa score (mean ± SD) (n = 3108)</td>
<td>5.7 ± 5.2</td>
<td>15.2 ± 5.2</td>
</tr>
<tr>
<td>Male sex (%) (n = 3097)</td>
<td>52.5%</td>
<td>57.1%</td>
</tr>
<tr>
<td>BMIb, kg/m² (mean ± SD) (n = 2912)</td>
<td>26.0 ± 5.0</td>
<td>26.1 ± 4.0</td>
</tr>
<tr>
<td>Coronary artery disease (%) (n = 1857)</td>
<td>16.6%</td>
<td>57.1%</td>
</tr>
<tr>
<td>Systemic hypertension (%) (n = 2480)</td>
<td>21.1%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Type 2 diabetes (%) (n = 1758)</td>
<td>5.6%</td>
<td>0%</td>
</tr>
<tr>
<td>Current smoker (%) (n = 2360)</td>
<td>17.0%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L (mean ± SD) (n = 3043)</td>
<td>8.09 ± 1.83</td>
<td>13.0 ± 5.13</td>
</tr>
<tr>
<td>LDL-C, mmol/L (mean ± SD) (n = 2992)</td>
<td>6.06 ± 1.74</td>
<td>11.2 ± 5.35</td>
</tr>
<tr>
<td>HDL-C, mmol/L (mean ± SD) (n = 3037)</td>
<td>1.21 ± 0.37</td>
<td>1.03 [0.85–2.6]</td>
</tr>
<tr>
<td>Triglycerides, mmol/L (median [interquartile range]) (n = 3035)</td>
<td>1.60 [1.03–2.30]</td>
<td>1.03 [0.85–2.6]</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L (mean ± SD) (n = 1419)</td>
<td>1.48 ± 0.37</td>
<td>2.55 ± 0.83</td>
</tr>
<tr>
<td>Lipoprotein(a), mg/L (median [interquartile range]) (n = 994)</td>
<td>263 [81.0–678.0]</td>
<td>326 [97.7–1220.0]</td>
</tr>
<tr>
<td>Lipid-lowering therapyb (%) (n = 2293)</td>
<td>59.1%</td>
<td>78.6%</td>
</tr>
<tr>
<td>Any statin (%) (n = 2293)</td>
<td>51.4%</td>
<td>71.4%</td>
</tr>
<tr>
<td>High intensity statin (%) (n = 2293)</td>
<td>9.9%</td>
<td>57.1%</td>
</tr>
</tbody>
</table>

The number in parenthesis for each row indicates the number of HeFH participants for whom the data field was captured.

HeFH = heterozygous familial hypercholesterolemia. HoFH = homozygous familial hypercholesterolemia. Lipid levels were at the time of entry to registry.

a Dutch Lipid Clinic Network Criteria.
b Body mass index.
c Use of lipid lowering therapy is at time of entry into the Registry.
2- Meta-analysis of FH prevalence

BMJ Open  Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis

Leo E Akioyamen,¹,² Jacques Genest,³,⁴ Shubham D Shan,¹,² Rachel L Reel,¹ Jordan M Albaum,¹ Anna Chu,¹,² Jack V Tu¹,²,⁵
The pooled prevalence of FH from 19 studies including 2,458,456 unique individuals was 0.40% (95% CI 0.29% to 0.52%) = frequency of 1 in 250 individuals.
3- New Canadian FH definition

Training/Practice
Contemporary Issues in Cardiology Practice

Simplified Canadian Definition for Familial Hypercholesterolemia

Isabelle Ruel, PhD, Diane Brisson, PhD, Sumayah Aljenedil, MD, Zuhier Awan, MD, PhD, Alexis Baass, MD, MSc, Alexandre Bélanger, BSc, Jean Bergeron, MD, MSc, David Bewick, MD, James M. Brophy, MD, PhD, Liam R. Brunham, MD, PhD, Patrick Couture, MD, PhD, Robert Dufour, MD, MSc, Gordon A. Francis, MD, Jiri Frohlich, MD, Claude Gagné, MD, Daniel Gaudet, MD, PhD, Jean C. Grégoire, MD, Milan Gupta, MD, Robert A. Hegele, MD, G.B. John Mancini, MD, Brian W. McCrindle, MD, Jing Pang, PhD, Paolo Raggi, MD, PhD, Jack V. Tu, MD, PhD, Gerald F. Watts, DSc, MD, and Jacques Genest, MD.
3- New Canadian FH definition

- Concordance analyses in 5962 Canadians: very good agreement when compared to the Simon Broome ($\kappa=0.969$) and DLCN ($\kappa=0.966$), but adapted to the Canadian population
4- Algorithm to impute the baseline LDL-C when patient is on treatment and baseline LDL-C is unknown

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:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mean reduction by dose: percent 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>$-40%$</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>$-$</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>$-26%$</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 to a statin</td>
<td>$-20%$</td>
</tr>
</tbody>
</table>

** Data derived from Hou et al. (30).

PCSK9 inhibitors: Approx. 60 % decrease in LDL-C on any statin +/- Ezetimibe treatment (divide LDL-C by 0.4)**

5- FH Canada “App” - Apple and Android

http://www.circl.ubc.ca
or free download from app stores
Tools to facilitate the diagnosis of FH

ASSESSMENT

Imputed Baseline/Untreated LDL-C: 9.18 mmol/L (abnormal)

Current Lipid Lowering Medication(s):
- Atorvastatin 80mg
- Ezetimibe 10mg

Current Lipid Profile:
- Current LDL-C: 3.60 mmol/L (abnormal)

HeFH Diagnostic Information:
- Canadian Criteria for HeFH:
  - Definite Clinical Familial Hypercholesterolemia
    - Imputed Baseline/Untreated LDL-C ≥ 8.5 mmol/L
    - Premature ASCVD
6- Canadian Position Statement on FH

2018 Update of the Canadian Cardiovascular Society Position Statement on FH to be published in the Canadian Journal of Cardiology DEC 2018
7- Molecular Diagnosis of FH: complete DNA sequencing at MUHC

The McGill University Health Centre is the only CLIA-certified clinical molecular genetics lab in Canada

*Clinical Laboratory Improvement Amendments - CLIA certification from FDA, CMS and CDC*
7- Molecular Diagnosis of FH: complete DNA sequencing at MUHC
Other initiatives

- **FH Canada Network**: annual accredited meetings, including a patient advocacy forum
Conclusion: Opportunities and Challenges

- A better understanding of care gaps for patients with FH in Canada
- A simplified set of diagnostic criteria for the Canadian population with tools to aid in the diagnosis of FH.
- Access to molecular diagnosis
- Access to new medication

As the national registry further increases in size and scope, there will be opportunities to improve the diagnosis and care of patients with FH in Canada.
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:**
Isabelle Ruel PhD
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1001 Decarie blvd, Block E #E01.2123
Montreal, Quebec
H4A 3J1
514-934-1934, ext. 34852
info@fhcanada.net
If you have any questions about the registry, you may visit the website at www.fhcanada.net
Or e-mail Isabelle Ruel, info@fhcanada.net

FH Canada sponsors: