Canadian Familial Hypercholesterolemia Registry
JULY 2018 Bi-Annual Progress Report

Bi-annual report for year 2018, 16 JULY 2018

FH Canada registry

Over 120 clinicians and scientists in 19 academic centers across Canada (the "hubs") and 7 peripheral sites (the "spokes") composed the FH Canada network (Clinicaltrials.gov: NCT02009345) as of June 2018. Including clinical coordinators and members of the biopharma industry, it is more than 200 individuals working together to increase awareness of FH in Canada.
Sites ready to submit the project to their institutional REB need to contact us for updated versions of the project proposal, consent form and patient questionnaire, and to get help in answering REB letters. Contact info: www.fhcanada.net.

Database iCAPTURE

As mentioned in the previous reports, 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. Individual secure access to the database is given once the project is approved locally. Data captured include familial history of elevated cholesterol levels and CVD, the patient's medical and surgical history, the physical signs of FH, and the patient's medication profile. It has built-it algorithms to generate a FH diagnosis score using the Canadian definition, Simon-Broome, and Dutch Lipid Clinic Network criteria, as well as one to impute a baseline LDL-C value for patients on lipid-lowering medication for which the untreated LDL-C is unknown[1].

Bulk upload of already existing databases is possible: the iCAPTURE IT team can re-format and upload the data onto the database and grant access to users. Funds granted by the industry for the initialization of the registry are available for site data entry stipend if needed.

As of June 2018, 3195 patients have been included in the database, including 63 patients with other lipoprotein disorders (*ABCA1, SMPD1, APOAI, CPT2, LCAT* mutations). Preliminary results from the FH Canada registry will soon be published in Atherosclerosis:
Brunham LR, Ruel I, Khoury E, Hegele RA, Couture P, Bergeron J, Baass A, Dufour R, Francis GA, Cermakova L, Mancini GBJ, Brophy JM, Brisson D, Gaudet D, Genest J. Familial Hypercholesterolemia in Canada: Initial Results from the FH Canada National Registry. *Atherosclerosis, In Press.*

Algorithm for imputed baseline LDL-C: paper published in the Clinical Chemistry journal

The paper on the imputation of baseline LDL-C paper from values obtained while on lipid-lowering therapy is now available online. With this paper, we provide a validated estimation of baseline LDL-C for patients with FH that will help clinicians in making a diagnosis. Please do not hesitate to contact us if you would like a pdf copy of the final paper.

The full reference is:
Ruel I, Aljenedil S, Sadri I, de Varennes É, Hegele RA, Couture P, Bergeron J, Wanneh E, Baass A, Dufour R, Gaudet D, Brisson D, Brunham LR, Francis GA, Cermakova L, Brophy JM,

Ryomoto A, Mancini GBJ, Genest J. Imputation of Baseline LDL Cholesterol Concentration in Patients with Familial Hypercholesterolemia on Statins or Ezetimibe. *Clinical Chemistry* 2018. 64(2):355-362.
PMID: 29038147
https://www.ncbi.nlm.nih.gov/pubmed/29038147

The FH Calculator: an "app" for a diagnosis of FH

The FH Calculator is constantly being updated so please make sure you are using the most recent version. Current version is 1.3.3. The app provides the imputed baseline LDL-C but also leads to a clinical diagnosis of FH based on the Canadian definition as well as the known FH criteria (DLCN and Simon-Broome). The tool is now freely available to all health care professionals; it generates a report to be saved and added to patient's file.

The version downloadable on PC or MAC is currently available at http://www.circl.ubc.ca/. Click on CardioRisk Calculator™ and install on your computer, or download the "app" directly onto your smartphone or tablet. Both Android and iPhone/iOS versions are now available, in French or in English). Please try and give us your comments.

New Canadian definition of FH – Validation and publication

We are pleased to report that the paper on the Canadian definition of FH (**Figure 1**) was accepted for publication by the Canadian Journal of Cardiology and is available online on the Canadian Journal of Cardiology website (not on Pubmed yet). In this manuscript, we show that the simplified and practical Canadian FH definition has diagnostic performance comparable to existing algorithms, but adapted to the Canadian population. The Canadian FH definition is available on the FH Calculator web-based and downloadable application.

Link to the application:
http://www.circl.ubc.ca/cardiorisk-calculator.html

Link to the paper:
https://www.sciencedirect.com/science/article/pii/S0828282X18303830?via%3Dihub

Ruel I, Brisson D, Aljenedil S, Awan Z, Baass A, Bélanger A, Bergeron J, Bewick D, Brophy JM, Brunham LR, Couture P, Dufour R, Francis GA, Frohlich J, Gagné C, Gaudet D, Grégoire JC, Gupta M, Hegele RA, Mancini GBJ, McCrindle BW, Pang J, Raggi P, Tu JV, Watts GF, Genest J. *Canadian Journal of Cardiology. In Press.*

Impact of a genetic diagnosis of FH: systematic review

We have been working closely with the late Dr. Jack V. Tu from ICES and his student, Leo Akioyamen on the impact of a DNA diagnosis on specific outcomes. We plan to publish this work.

FH Canada registry: collaboration with the EAS-FHSC

The EAS-FH Studies Collaboration (FHSC) is a global initiative led by Prof Kausik Ray (Imperial College London, UK) and an international steering committee (http://www.eas-society.org/?page=fhsc_registry). The mission of the EAS-FHSC is to empower the medical and global community to seek change in their respective countries or organizations regarding how FH is detected and managed, with a view to promoting early diagnosis and more effective treatment of this condition. Through international collaboration of stakeholders, the EAS-FHSC aim to generate large scale robust data on how FH is detected, managed and the clinical consequences of current practice on outcomes[2].

The FHSC currently involves lead investigators from over 60 countries. We were invited to present the FH Canada registry status at their annual meeting in Lisbon, Portugal last May 2018. The FH Canada network participates in the preparation of a manuscript, which should be submitted soon: “Overview of the current status of and initiatives related to FH in over 60 countries participating in the EAS Familial Hypercholesterolemia Studies Collaboration (FHSC)”.

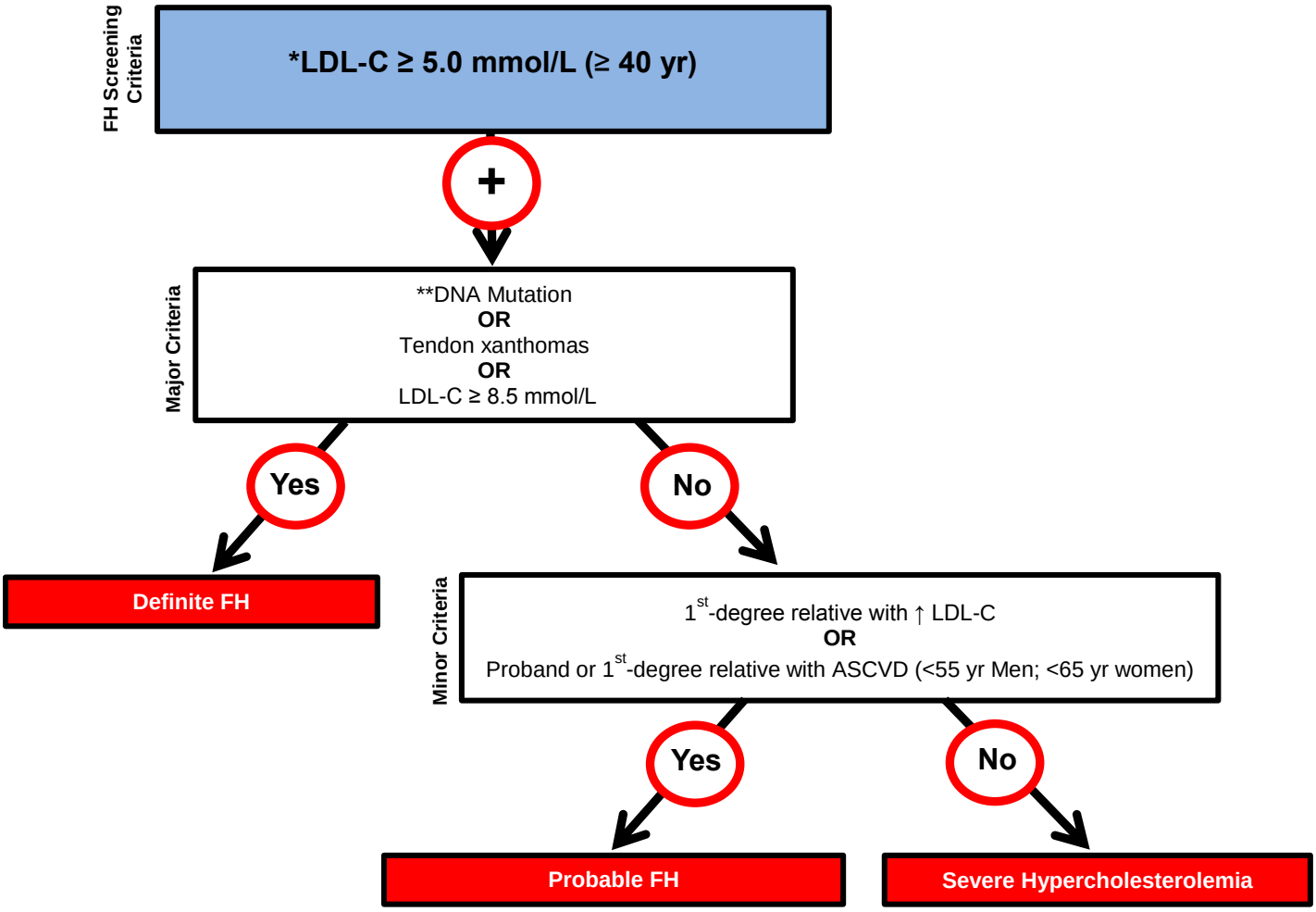

Figure 1. Canadian definition for the clinical diagnosis of FH.
* Secondary causes of high LDL-C should be ruled out (severe or untreated hypothyroidism, nephrotic syndrome, hepatic disease (biliary cirrhosis), medication especially antiretroviral agents);
LDL-C ≥ 4.0 mmol/L for age < 18 yr;
LDL-C ≥ 4.5 mmol/L for age ≥ 18 yr and < 40 yr.
** Causal DNA mutation refers to the presence of a known FH-causing variant in the *LDLR*, *APOB* or *PCSK9* gene based on presence of the variant in ClinVar, HGMD or WDLV databases, in the proband or a first-degree relative. FH diagnosis in a patient with a DNA mutation but normal LDL-C levels is unclear. Yearly follow-up of the proband is suggested and cascade screening of family members should be initiated. Note: In any case, cascade screening should be implemented; treatment decision should be at the discretion of the treating physician.

CCS position statement on FH: an update for 2018

The Canadian Cardiovascular Society has requested an update of the 2014 position statement on FH[3]. Specific changes took place since then and both a primary and secondary panel have worked together to review this important document. The update includes, for instance, new data on the prevalence of FH worldwide, suggesting that the frequency is greater than previously thought, the new information on the risk estimates for atherosclerotic cardiovascular disease in the presence of a mutation causing FH, the new Canadian definition of FH, and the availability in Canada of new drugs available to treat FH. The revised position statement guidelines will be published in the *Canadian Journal of Cardiology* (paper expected for October 2018).

A CCS FH Position Statement Workshop is scheduled for Monday, October 22 during the CCC 2018 congress in Toronto (pending CCS Council approval).

A strategy for a molecular diagnosis of FH is being discussed

A new genetic assay for the molecular diagnosis of FH (NGS sequencing of known causing genes - *LDLR*, *APOB* and *PCSK9*) has been validated at the McGill University Health Centre (MUHC). The algorithm includes 1) testing of the familial variant when known; 2) when no known family variant: NGS sequencing of the *LDLR*, *APOB* and *PCSK9* genes (MiSeq); 3) when no molecular defect found: proceed with deletion/duplication analysis of the LDLR gene by MLPA. If nothing is found in the studied genes, DNA samples will be submitted to targeted exome sequencing (LipidSeq).

At the MUHC, the Core Molecular Diagnostic Laboratory is CLIA-approved (CLIA #99D1042152) and will soon be offering the genetic testing of FH from a clinically-certified laboratory. We are preparing the forms (requisition, procedure for shipment of samples, consent form) and will let you know as soon as it is available. The assay will be submitted to the Ministry of Health and Social Services of Québec at the end of the summer. Similar initiatives are ongoing in Ontario and BC.

FH Canada Network MEETING 2018: SAVE THE DATE

The next annual FH Canada Network meeting will be held on October 20th, 2018, at the Li Ka Shing Knowledge Institute in Toronto, ON, prior to CCC 2018. Like for the previous meetings, the event will be accredited by the Royal College of Physicians & Surgeons of Canada and the College of Family Physicians of Canada, and will be intended primarily for GPs and physicians involved in prevention with the primary goal of increasing awareness of FH in Canada. More details to come.

www.FHCanada.net website

The FH Canada registry website is www.fhcanada.net. Please contact us if you would like to be listed on our list of lipid specialists so patients with FH or other lipoprotein disorders can be referred to your clinic. Contact us if you would like to have specific Powerpoint slides (only pdfs files were uploaded). Do not hesitate to send us reference papers and new accomplishments in the field of FH: we will be happy to add them on the website.

Homozygous FH patient registry

There is a global effort to raise awareness on FH and our colleagues in Europe have initiated an important international registry on FH (Familial Hypercholesterolemia Studies Collaboration (FHSC)). We have agreed to capture data on all Canadians with homozygous FH (HoFH). We can help format the patient data for physicians with HoFH patients willing to participate.

References

[1] Ruel I, Aljenedil S, Sadri I, *et al*. Imputation of Baseline LDL Cholesterol Concentration in Patients with Familial Hypercholesterolemia on Statins or Ezetimibe. *Clin Chem* 2018. 64(2):355-362.

[2] Vallejo-Vaz AJ, Kondapally Seshasai SR, Cole D, et al. Familial hypercholesterolaemia: A global call to arms. Atherosclerosis. 2015 243(1):257-9.

[3] Genest J, Hegele RA, Bergeron J, Brophy J, Carpentier A, Couture P, Davignon J, Dufour R, Frohlich J, Gaudet D, Gupta M, Krisnamoorthy P, Mancini J, McCrindle B, Raggi P, Ruel I, St-Pierre J. Canadian Cardiovascular Society position statement on familial hypercholesterolemia. Can J Cardiol. 2014 30(12):1471-81.