Canadian Familial Hypercholesterolemia Registry
YEAR 2019 Annual Progress Report

6 JAN 2019

Dear Colleagues,

We are pleased to present the 2019 FH Canada progress report. We would like to thank you for your commitment, your support and your many contributions! Please do not hesitate to contact us if you want to share updates in the field. Looking forward to 2020, we hope to continue to provide guidance to patients with FH and other lipoprotein disorders and advocate to access to proper diagnosis and treatments.

1. Major update of the FH Canada website

Please have a look at the new FH Canada registry website: www.fhcanada.net. Do not hesitate to contact us if you would like to be listed on our roster 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.

2. FH Canada registry – update

Over 145 clinicians and scientists in 19 academic centers across Canada composed the FH Canada network (Clinicaltrials.gov: NCT02009345). Including clinical coordinators, nurses, pharmacists and members of the biopharma industry, it is more than 250 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.

Quick description of the registry:
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.

Preliminary results from 3195 patients from the FH Canada registry were published in *Atherosclerosis* in 2018 (https://www.ncbi.nlm.nih.gov/pubmed/30270080). The registry now includes 4458 patients with FH or other lipoprotein disorders.

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.

3. Homozygous FH patient registry

We are pleased to let you know that the FH Canada network was successful in the "Knowledge Synthesis Grant: Socio-Economic Burden of Inherited Disease" competition, from the CIHR. We submitted a project called “Homozygous FH in Canada”, and we are funded for one year. Here’s a brief summary of the project:

…Most HoFH patients develop significant ASCVD in their teens and early adulthood. Data from other countries show a median survival of HoFH patients at < 40 years of age. Clinical outcomes in HoFH patients, especially ASCVD events (fatal and non-fatal myocardial infarctions, strokes and peripheral vascular disease) and severe, calcific aortic stenosis are difficult to capture, in part because of the rarity of the disorder and the lack of registry focusing on this disease. Our ***first objective*** *will be to obtain a comprehensive registry of HoFH in Canada. In our* ***second objective****, we will perform three systematic reviews and meta-analyses in HoFH patients a) examine the quality of life (QoL), b) the risk of ASCVD and deaths and c) the risk of calcific aortic stenosis and aortic valve replacement on HoFH patients. Based on the results of the first objective, we will be able to estimate the burden of disease and cost to society caused by HoFH; our* ***third objective*** *will be to estimate the life-long costs to society for HoFH patients in Canada. Lastly, we plan to use this data at provincial levels to provide HoFH patients access to care, including PCSK9 inhibitors, orphan drugs such as lomatipide and techniques, especially extracorporeal LDL filtration or apheresis. Gene therapy using adeno-associated viruses (AAV) has the potential to offer a new modality of treatment. The use of novel agents, such as Evinacumab, a fully human antibody directed against Angiopoietin-like protein 3 (ANGPTL3), and Gemcabene that lowers LDL-C in a LDLR independent fashion. Gene editing, using CRISPR/Cas9 may one day be used against PCSK9 and ANGPTL3 to treat HoFH. In* ***our forth objective****, we will use the data generated by this grant to implement change within provincial health care systems, with the Canadian Organization for Rare Diseases (CORD) and the Réseau Québecois des maladies orphelines (RQMO). This work will provide important new health-related knowledge about the determinants of ASCVD risk and phenotypic manifestations of HoFH in Canada and examine the quality of life and burden to the healthcare system.*

With this project, we would like to have an in-depth look at HoFH in Canada and for this, we need to capture the HoFH patients in a single registry. We ran a survey last summer and thanks to your cooperation, we have identified 79 unique patients with HoFH across Canada. Mean age is 36.7 ± 20.6 y; 54% males. If you follow a patient with HoFH, please contact us to discuss and do not hesitate to forward this announcement to your colleagues with HoFH patients. For the purposes of the registry, we plan to include any HoFH patient alive in 2008 so we can provide Kaplan-Meier survival curves. The required data includes mutation (if known), age at diagnosis, baseline lipids and

lipoprotein lipid levels, changes in lipids and lipoprotein lipid levels in time and medications, the effects of LDL apheresis/plasmapheresis and experimental treatments. Importantly, we would like to capture all cardiovascular events, including imaging and interventions (ACS, STEMI, NSTEMI), TAVI/AVR, CABG/PCI, arrythmias, CHF, PAD (by-pass, endarterectomy), strokes, aortic stenosis, as presented in a case-report we recently published:

The Lifelong Burden of Homozygous Familial Hypercholesterolemia.
Banerjee A, Alothman L, Couture P, Bergeron J, Bélanger AM, Ruel I, Genest J.
Can J Cardiol. 2019 Oct;35(10):1419. PMID: 31521416
https://www.ncbi.nlm.nih.gov/pubmed/31521416

Finally, while working on a Canadian HoFH patient registry, we will collaborate with the HoFH International Clinical Collaborators (HICC) registry initiative from the Netherlands, gathering info on HoFH patients worldwide. We are using a secure RedCap database, and data collected is similar to that required for the Canadian initiative. If you agree, we can submit your data under your name. Please find attached the latest data from the HICC registry, presented during the FH Global Summit in October 2019.

We hope you will join us on both the Canadian and International initiatives so we can better characterize this orphan disease! We will keep you informed on the progress of this initiative.

4. 2019 PUBLICATIONS

Here's a list of a few Canadian systematic reviews and meta-analyses in FH published in 2019. Please do not hesitate to contact us if you would like a pdf copy of these articles.

Estimating the Prevalence of Familial Hypercholesterolemia in Acute Coronary Syndrome: A Systematic Review and Meta-analysis.
Kramer AI, Trinder M, Brunham LR.
Can J Cardiol. 2019; 35(10):1322-1331.
PMID: 31500889
https://www.ncbi.nlm.nih.gov/pubmed/31500889

Risk of Ischemic Stroke and Peripheral Arterial Disease in Heterozygous Familial Hypercholesterolemia: A Meta-Analysis.
Akioyamen LE, Tu JV, Genest J, Ko DT, Coutin AJS, Shan SD, Chu A.
Angiology. 2019;70(8):726-736.
PMID: 30871330
https://www.ncbi.nlm.nih.gov/pubmed/30871330

Diagnostic accuracy of ultrasound and MRI for Achilles tendon xanthoma in people with familial hypercholesterolemia: A systematic review.
Scott A, Zahradnik TM, Squier K, Beck C, Brunham LR.
J Clin Lipidol. 2019;13(1):40-48.
PMID: 30503304
https://www.ncbi.nlm.nih.gov/pubmed/30503304

Genetic testing for familial hypercholesterolemia: Impact on diagnosis, treatment and cardiovascular risk. Lee S, Akioyamen LE, Aljenedil S, Rivière JB, Ruel I, Genest J. *Eur J Prev Cardiol.* 2019;26(12):1262-1270.
PMID: 30755017
https://www.ncbi.nlm.nih.gov/pubmed/30755017

Risk factors for cardiovascular disease in heterozygous familial hypercholesterolemia: A systematic review and meta-analysis.
Akioyamen LE, Genest J, Chu A, Inibhunu H, Ko DT, Tu JV.
J Clin Lipidol. 2019;13(1):15-30.
PMID: 30527766
https://www.ncbi.nlm.nih.gov/pubmed/30527766

ClinVar database of global familial hypercholesterolemia-associated DNA variants.
Iacocca MA, Chora JR, Carrié A, Freiberger T, Leigh SE, Defesche JC, Kurtz CL, DiStefano MT, Santos RD, Humphries SE, Mata P, Jannes CE, Hooper AJ, Wilemon KA, Benlian P, O'Connor R, Garcia J, Wand H, Tichy L, Sijbrands EJ, Hegele RA, Bourbon M, Knowles JW; ClinGen FH Variant Curation Expert Panel.
Hum Mutat. 2018;39(11):1631-1640.
PMID: 30311388
https://www.ncbi.nlm.nih.gov/pubmed/30311388

5. FH Canada registry: collaboration with the EAS-FHSC

The EAS-FHSC (FH Studies Collaboration) is a global initiative led by Prof Kausik Ray (Imperial College London, UK) with the mission 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. The FHSC spans 69 countries, includes 87 Lead Investigators and the registry now has 61,650 cases recorded across 59 countries. Please use the following link to upload the latest FHSC newletter (NOV2019), including the most recent accomplishments in FH in Canada, Germany, Egypt and Iraq.

https://cdn.ymaws.com/www.eas-society.org/resource/resmgr/fhsc/newsletters/newsletter_issue_10_nov_20.pdf

6. FH Canada Network MEETING 2019

The annual FH Canada Network meeting was held on May 30, 2019, at the Drs. Sylvia and Richard Cruess Amphitheatre at the Research Institute of the McGill University Health Centre in Montreal, Qc. This “Montreal Cholesterol Summit” event was accredited by the Royal College of Physicians & Surgeons of Canada and was intended primarily for residents and physicians involved in prevention with the primary goal of increasing awareness of FH in Canada. An International panel of speakers, including the recipient of the 2019 Lucian Award Dr Nabil Seidah for his discovery of PCSK9, presented on clinical trials of PCSK9, the new 2019 Canadian Cholesterol Guidelines, the genetics of lipoprotein disorders and the public policies of genetic diagnosis, which was followed by a discussion and a public forum.

SAVE THE DATE: the next annual meeting will be held in Vancouver, possibly in October. More details to come.

ON-GOING INITIATIVES

7. A strategy for a molecular diagnosis of FH is being discussed

Initiatives are ongoing across Canada to offer a new genetic assay for the molecular diagnosis of FH, mainly in BC, Ontario and Quebec. For instance, the Core Molecular Diagnostic Laboratory at the MUHC, in Montreal offers the genetic testing for FH from a clinically-certified laboratory (CLIA #99D1042152). In brief, 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) proceed with deletion/duplication analysis of the *LDLR* gene by MLPA. Please contact the CMDL lab director Dr Jean-Baptiste Rivière for more details: jean-baptiste.riviere@mcgill.ca.

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

Make sure you are using the most recent version of the FH Calculator has it is constantly being updated. Current version is 1.4.0. For current iPhone and Android users, your device(s) should have automatically updated the software to this new version but for PC/Windows users, you have to manually download the new version from this link: http://www.circl.ubc.ca/cardiorisk-calculator.html

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 freely available to all health care professionals; it generates a report to be saved and added to patient's file.

9. Ongoing studies on use of a PCSK9 inhibitor during pregnancy

Data on the use of a PCSK9 inhibitor during pregnancy are lacking so if one of your patients was on a PCSK9 inhibitor just before or while being pregnant (any number of days, at any dose, and at any time from the first day of the the last menstrual period up to and including the end of pregnancy), they can register to specific on-going clinical trials (registries). The registries are also looking for non-PCSK9i exposed FH or ASCVD pregnant women (disease control group) and non-PCSK9i exposed non-FH, non-ASCVD pregnant women (non-disease control group).

The experts from MotherToBaby, a non-profit organization, are in charge of collecting the data so please use the following link to get more information:
https://mothertobaby.org/ongoing-study/high-cholesterol/