Canadian Familial Hypercholesterolemia Registry
2016 Annual Progress Report

UPDATE, December 15th, 2016

FH Canada registry sites

Over 110 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 December 2016. Several FH Canada sites in Canada have been approved or are in the process of having the FH Canada registry project accepted by their Research Ethic Board (REB) (Saint Boniface Hospital's Lipid Clinic in Winnipeg, St. Paul's Hospital Lipid Clinic in Vancouver, McGill University Health Centre in Montreal, Institut de recherches cliniques de Montreal, Robarts Research Institute in London, the Sick Children's Hospital in Toronto, Regina General Hospital in Regina, Centre Hospitalier Universitaire de Québec - Université Laval). 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.

In the province of Québec, the FH Canada registry project was recently converted to a multicentric study (MSSS) with the McGill University Health Centre as the evaluating REB so other sites in Québec will benefit from expedited REB approval. Peripheral sites in Québec: Gatineau, Joliette, Laval, Ste-Justine, Trois-Rivières, Sherbrooke, Rimouski.

Database 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. 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 Simon-Broome, Dutch Lipid Clinic Network criteria, and the new Canadian definition being validated (see New Canadian definition of FH and New "app" for a Canadian diagnosis of FH sections below), 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.

As of now, more than 2900 patients have been included in the database. Bulk upload of already existing databases is also ongoing: the iCAPTURE IT team 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.

Algorithm for imputed LDL-C

A new algorithm is now available to impute baseline LDL-C from values obtained while on lipid-lowering therapy. This algorithm is now part of the new "app" for the diagnosis of FH (FH Calculator) created in collaboration with UBC/Sanofi; it is very useful for assessing the degree of severity of FH for new patients and helps facilitate FH diagnosis. It is already available to all health care professionals across Canada through the new app for the Canadian definition (see "New "app" for a Canadian diagnosis of FH" section below). It will soon be translated to French and available on mobile/tablets. Contact Dr Isabelle Ruel if you would like a copy of the conversion factors used to impute the LDL-C from various lipid-lowering drugs and doses.

New Canadian definition of FH – Validation

Agreement from members of FH Canada and lipid experts across Canada was reached on the new Canadian FH definition, based on the Simon-Broome criteria. It is being validated in Canadian datasets and will soon be validated in International datasets. In large datasets including normal control patients, specificity and sensitivity analyses are being done to compare the new Canadian definition with the existing Simon-Broome and Dutch Lipid Clinic Network. For datasets with FH patients only, we prepared a specific concordance analysis algorithm to measure the concordance of the new definition with the two existing criteria. Please contact us if you have such a dataset and would like to be part of the on-going validation. Once published, the new definition of FH will make easier and will standardize the diagnosis of FH across Canada (it will also provide FH patients with better access to care, and family cascade screening). The plan is to publish the new Canadian definition in the *Canadian Medical Association Journal* or the *Canadian Journal of Cardiology.*

New "app" for a Canadian diagnosis of FH: The FH Calculator

An "app" for the diagnosis of FH based on the newly developed Canadian definition but also on the known FH criteria (DLCN and Simon-Broome) is now available to all health care professionals, an initiative lead by Dr John Mancini, UBC, in collaboration with Sanofi. It incorporates the principles of management and recommendations of the recently published Canadian Consensus Working Group Statin Intolerance and Adverse Effects Consensus Statement (2016), the imminent 2016 Canadian Cardiovascular Society Guidelines for Management of Dyslipidemia and the Canadian Cardiovascular Society Position Statement on the Management of Familial Hypercholesterolemia (2014). The tool has been validated and 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. Please try and give us your comments. As described earlier, the FH Calculator is incorporating the algorithm for imputing baseline LDL-C and the diagnosis of FH according to the new Canadian definition and the two already existing criteria, and also generates a report to be saved and added to patient's file. A version downloadable onto any smartphone or tablets will also be soon available (Apple and Android) and translation to French is planned.

FH Canada Network MEETING 2016

We held the FH Canada Network 2016 on October 21st, 2016, prior to CCC2016 in Montreal. The event was accredited by the Royal College of Physicians & Surgeons of Canada and the College of Family Physicians of Canada, and was intended primarily for GPs and physicians involved in prevention. We had 4 excellent presentations on familial hypercholesterolemia, which included the following topics: Definition of FH, Genetics of FH, FH Canada registry, 2016 Canadian Guidelines on CVD Prevention and Treatment of FH, and Treatment of FH. We hosted a very successful event with over 100 participants attending; the attendees rated the event positively, and felt that the learning objectives were met and that the activity improved their knowledge on FH. A similar event is planned for 2017 in Vancouver (see below).

FH Canada booth during CCC 2016

FH Canada had an exhibit space at the Canadian Cardiovascular Congress last October (CCC 2016, 22-25 October 2016 in Montreal). We met with attending physicians and members of the biopharma industry. This event was a good opportunity to evaluate the knowledge on FH of specialists and all health care professionals in cardiology in Canada, and to improve the knowledge on the definition of FH, its prevalence in Canada and how to treat patients with FH.

ON-GOING INITIATIVES

DNA diagnosis strategy is being discussed

A new molecular diagnosis of FH causing genes (*LDLR*, *APOB* and *PCSK9*) has been proposed and is being discussed. The algorithm includes 1-testing of the familial variant when known; 2-when no

known family variant: sequencing of the *LDLR*, *APOB* and *PCSK9* genes (MiSeq); 3-when no molecular defect found: proceed with deletion/duplication analysis of the genes (MLPA). If nothing is found in the studied genes, DNA samples will be submitted to targeted exome sequencing (LipidSeq). Once validated, the proposal will be submitted to the Ministry of Health and Social Services of Québec.

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. We recently added downloadable pdf presentations you might find useful: How to draw a family pedigree using the free CeGaT Pedigree Chart Designer tool, History of familial hypercholesterolemia, a presentation on other lipoprotein disorders (SMASH), etc (down the list, on following webpage http://www.fhcanada.net/?page_id=451). Contact us if you would like to have the Powerpoint slides. 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)). As a starting point, 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.

MOVING FORWARD TO 2017

Public Forum

A public forum on FH will be held some time in spring in Montreal. We will keep you informed as more details become available for this event, organized by the Institut de recherches cliniques de Montréal and the Regroupement Québécois sur les Maladies Orphelines.

FH Canada Network ANNUAL MEETING 2017

The annual FH Canada Network meeting will be held in October 2017, in Vancouver, BC, prior to CCC 2017 (date to be determined), under the leadership of Dr Liam Brunham, scientific committee chair. 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.

New Educational Resources

In 2017, efforts will be focused toward the creation of new educational resources on FH. We plan to: create an accredited teaching material on FH (slide kit) and to revise the core curriculum in lipoprotein disorders (downloadable); both educational resources will be bilingual and freely available online. They will include the latest knowledge on FH, the revised Canadian diagnostic criteria, the imputed LDL-C algorithm, the available treatments in Canada, the results from the latest clinical trials and details on the on-going trials, including the use of PCSK9 and CETP inhibitors, the update of the fourth edition of the book "Dyslipoproteinemias: The Clinical Approach" (Drs Claude Gagné et Daniel Gaudet), and a section on understanding the genetic basis of FH in Canada including the unique LipidSeq and MLPA techniques.

FH Canada Timeline 2014-2019

Dec 2014 — 2015 — 2016 — 2017 — 2018 — 2019

OBJECTIVE 1: CANADIAN FH AND SMASH REGISTRY

- Governance Structure
- Obtain agreement from collaborators
- Database (iCapture)
- Phase I 6,000 FH Patients
- Phase II Canadian FH Cascade Screening

OBJECTIVE 2: BIOMEDICAL AND GENETICS

- DNA sequencing for molecular basis of FH
- DNA sequencing for SMASH

OBJECTIVE 3: CLINICAL NETWORK

- Establishment of the Specialized Clinics Network
- Proposed CCS diagnostic FH criteria-

OBJECTIVE 4: HEALTH SYSTEMS SERVICES, OUTCOMES AND ECONOMICS

- Investigator- Industry- Governement- initiated Research Proposals

OBJECTIVE 5: GE^{3}LS AND KNOWLEDGE TRANSLATION

- Creation of a Canadian FH Registry website
- Implications of genomic research (GE^{3}LS)
- CCS Position Statement on FH
- Establishment of a National Lipid Association certification in Canada
- Dissemination and KT across Canada

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