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The British Columbia Familial Hypercholesterolemia Registry

Despite having a prevalence rate similar to that of type 1 diabetes, familial cholesterolemia often goes undiagnosed—a problem now being addressed by a new provincial registry for this highly treatable disease.

ABSTRACT: With a prevalence rate of approximately 1 case in 500 people, heterozygous familial hypercholesterolemia is one of the most common genetic disorders encountered in clinical practice. Affected individuals have an impaired hepatic clearance of low-density lipoprotein particles and are thus predisposed to hypercholesterolemia, with a consequent twentyfold increased risk of premature vascular disease. Early disease modification through lifestyle changes and lipid-lowering therapy is highly effective: by treating three to four affected individuals, one premature event can be prevented. There are approximately 8000 people with heterozygous familial hypercholesterolemia in British Columbia, yet over 85% of those affected remain undiagnosed. The British Columbia Familial Hypercholesterolemia Registry has been established to address this gap in patient care. Through this registry we aim to improve identification and management of heterozygous familial hypercholesterolemia in BC, and to increase awareness of this potentially fatal yet highly treatable condition.

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Type 1 diabetes mellitus, cystic fibrosis, and congenital hypothyroidism are common terms in our medical lexicon. We are well versed in their clinical features, underlying pathophysiology, diagnostic criteria, and management approaches for these three diseases. The same, however, cannot be said for heterozygous familial hypercholesterolemia (hFH). Why is hFH—a potentially fatal disease that has a prevalence rate similar to that of type 1 diabetes and higher than that of cystic fibrosis and congenital hypothyroidism[1,2]—so often not recognized, leaving many affected individuals undiagnosed and untreated? Today, the recently established British Columbia Familial Hypercholesterolemia Registry, the first of its kind in Canada, is attempting to address this gap in patient care.

Heterozygous familial hypercholesterolemia

Heterozygous familial hypercholesterolemia is an inherited disorder of lipoprotein metabolism initially described by Müller in 1938.[3] It has since been named the most common genetic metabolic disease of consequence.[4] An autosomal condition with complete penetrance, hFH affects an estimated 13 million people worldwide;[5] however, less than 25% of these individuals have thus far been identified.[6,7] The prevalence of hFH is between 1 in 300 and 1 in 500 in most countries, although it may be as high as 1 in 100 in certain populations—

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namely those of French Canadian, Christian Lebanese, or Afrikaner (South Africans of Dutch descent) descent—due to the founder effect.[8,9] Patients with hFH have genetic alterations leading to an impaired hepatic clearance of low-density lipoprotein (LDL) particles.[10] Hypercholesterolemia is present from birth, and untreated individuals have a twentyfold increased risk of premature coronary heart disease (CHD).[8] By age 60, the cumulative risk of fatal or nonfatal CHD is over 50% in males with hFH and 30% in females with hFH.[11,12] Early treatment in the form of lipid-lowering therapy is readily available and highly effective.[10,13,14] In fact, the rate of coronary events in hFH individuals with hFH drops to that of the control population after 10 years of statin therapy.[1,14] By treating three to four patients with hFH, one premature coronary event can be prevented.[15]

The diagnosis of hFH is typically made on clinical and biochemical grounds: a personal or family history of a premature vascular event, and a low-density lipoprotein cholesterol (LDL-C) level above the 95th percentile for age and gender.[6] Tendon xanthomata, often on the Achilles tendon or on the extensor tendons of the hands (or both), are virtually pathognomonic of hFH but are not required for diagnosis.[6] Although premature arcus cornealis and xanthelasma may also be present and usually indicate an inherited lipid disorder, they are not specific for hFH.[6,8]

Several validated diagnostic criteria, such as the MED-PED (make early diagnosis—prevent early death) criteria in the United States,[16] the Simon Broome Register criteria in the United Kingdom,[17] and the Dutch Lipid Clinic Network criteria in the Netherlands,[6] stratify patients according to whether a diagnosis of hFH is "definite," "probable," "possible," or "unlikely." Demonstration of a functional mutation in the LDL receptor (*LDLR*) gene, the apolipoprotein B-100 (*APOB*) gene, or the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene allows for an unequivocal hFH diagnosis, although genetic testing is not mandatory for disease management.[8]

By treating three to four patients with hFH, one premature coronary event can be prevented.

Because patients with hFH are at considerable risk of early CHD, the 10-year Framingham cardiovascular risk score is inadequate and should not be applied to this patient population.[8,18] Dietary and lifestyle interventions are encouraged and can significantly reduce all-cause morbidity and mortality; these changes, in addition to lifelong lipid-lowering therapy, should be instituted to achieve a minimum of 50% reduction from baseline LDL-C levels.[8,19] The use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) is the cornerstone of treatment,[13,20] while ezetimibe, bile acid sequestrants, and niacin are valuable adjuncts.[8] For patients who experience medication intolerance or are unable to attain therapeutic targets, referral to a specialty lipid or cardiovascular disease prevention clinic is recommended.[8]

Benefits of disease registries

The US National Committee on Vital and Health Statistics describes disease registries as "an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects."[21] Disease registries are a powerful tool to engage physicians in the development and adoption of best practices that can lead to improved patient outcomes and reduced health care expenditures.[22] As an example, the Swedish National Hip Registry, established in 1979, led to a 50% reduction in national revision rates by identifying best practices among Swedish orthopaedic surgeons.[23] Estimated cost savings of US$140 million over a 10-year period have been attributed to this decline in revision burden.[24]

Familial hypercholesterolemia registries in other countries

Nationwide familial hypercholesterolemia registries have been successfully implemented in Spain, Wales, and the Netherlands.[25-27] Regional programs have been established in Australia, the Czech Republic, Ireland, New Zealand, Norway, the Slovak Republic, Slovenia, and Brazil.[1] In the Netherlands, 1500 to 2000 new cases of hFH are diagnosed each year through the program, with a total of 16 000 affected individuals identified

to date.[1] On average, eight new cases of hFH are detected per family, with the initiation of intervention at a mean age of 37 years.[27] The participation rate of 98.2%[27] is particularly noteworthy, and reflects a positive patient attitude toward the screening program.

Cascade, or pedigree, screening is utilized by most programs and has proven to be both economical and effective in reducing CHD and related deaths.[28-30] First-degree relatives of index patients have a 50% likelihood of inheriting hFH, while second- and third-degree relatives have a 25% and 12.5% likelihood of inheriting hFH respectively.[31] Cascade screening entails systematically contacting and identifying affected family members, and instituting therapy before the development of clinical atherosclerosis.[30,32]

The registry in British Columbia

Approximately 68 000 individuals with hFH live in Canada, with about 8000 of these people residing in British Columbia.[33] According to a 1999 World Health Organization report, only about 15% of affected Canadians have been properly diagnosed.[6] Among patients identified with the disease, many are not receiving adequate treatment.[6,27]

No hFH screening programs presently exist in Canada, although several lipid clinics have been tracking index patients and their family members. Aside from these lipid clinics, hFH screening is offered by fewer than 10% of cardiologists and family physicians.[6]

The recently established British Columbia Familial Hypercholesterolemia Registry has two primary goals: first, to diagnose, educate, and treat individuals with hFH; and second, to disseminate knowledge of this deadly heritable yet highly treatable condition to practising physicians, other health care professionals, and the general public. To identify probands currently attending the Healthy Heart Program Prevention Clinic at St. Paul's Hospital in Vancouver, we have been using the Dutch Lipid Clinic Network criteria (**Table 1** and **Table 2**).[33,34] The associated sensitivity and specificity for the criteria are outlined in **Table 3**; there is an 85% agreement between these criteria and the genetically confirmed diagnosis.[34] Not infrequently, individuals with hFH are referred to our clinic only after they experience a major premature vascular event. Once we obtain informed consent, we provide index patients with materials about the registry for their family members, who in turn are encouraged to contact the clinic for evaluation and, if necessary, proper management of hFH.

In future genetic testing will be offered to all families. This will not only allow for confirmation of hFH, but will almost certainly identify new mutations, as evident from the experiences of other screening programs.[36] Recent work has demonstrated a substantial polygenic contribution to raised LDL-C levels in hFH patients with

Table 1. Dutch Lipid Clinic Network criteria for the diagnosis of heterozygous familial hypercholesterolemia (hFH).[33,34]

Criteria		Score
Family history	First-degree adult relative with	
	• Premature coronary and/or vascular disease (male < 55 years; female < 60 years)	1
	• LDL-C > 95th percentile for age and gender	1
	• Tendon xanthomata and/or arcus cornealis	2
	First-degree relative < 18 years with LDL-C > 95th percentile for age and gender	2
Clinical history	Patient with premature IHD (ages as above)	2
	Patient with other premature vascular and/or cerebrovascular disease (ages as above)	1
Physical examination	Tendon xanthomata	6
	Arcus cornealis prior to age 45	4
Laboratory analysis	LDL-C (mmol/L)	
	• ≥8.5	8
	• 6.5–8.4	5
	• 5.0–6.4	3
	• 4.0–4.9	1
DNA analysis	Genetic test results confirming functional mutation in *LDLR*, *APOB*, or *PCSK9* gene	8

LDL-C = low-density lipoprotein cholesterol; IHD = ischemic heart disease; *LDLR* = low-density lipoprotein receptor; *APOB* = apolipoprotein B-100; *PCSK9* = proprotein convertase subtilisin/kexin9

Table 2. Dutch Lipid Clinic Network (DLCN) stratification of diagnoses based on total scores from the DLCN criteria for identifying patients with heterozygous familial hypercholesterolemia (hFH).[33,34]

Total score	Diagnosis
≥ 8	Definite hFH
6–7	Probable hFH
3–5	Possible hFH

Table 3. Sensitivity and specificity for diagnostic categories derived from the Dutch Lipid Clinic Network (DLCN) criteria for identifying patients with heterozygous familial hypercholesterolemia (hFH)[35]

Diagnosis	DLCN score	Sensitivity % (95% CI)	Specificity % (95% CI)
Definite hFH	≥ 8	41.5 (33.1-50.3)	87.9 (83.4-91.5)
Definite or probable hFH	≥ 6	66.7 (58.0-74.5)	64.5 (58.5-70.1)
Definite, probable, or possible hFH	≥ 3	99.3 (95.9-100.0)	5.9 (3.4-9.3)

Contact the BC Registry

Interested physicians and individuals may contact the BC Familial Hypercholesterolemia Registry coordinator:
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Healthy Heart Program Prevention Clinic, St. Paul's Hospital
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no known genetic defects, a category that accounts for 60% of clinical hFH cases.[37] Thus, novel causal genes may be identified in future, further improving our understanding of hFH disease mechanism and yielding new targets for therapy.

We anticipate our screening efforts will detect inherited forms of dyslipidemia other than hFH, such as familial combined hyperlipidemia (FCHL). Since individuals with FCHL, like those with hFH, have an increased risk of CHD,[38,39] they too will benefit from lipid-lowering therapy.

The British Columbia Familial Hypercholesterolemia Registry will serve as a model for the rest of Canada. Plans are already underway for similar registries in other provinces, with the ultimate goal of instituting a Canadian familial hypercholesterolemia registry unrestricted by regional boundaries. Such an endeavor will help in our goal of a future in which health care providers and the general public alike are well acquainted with heterozygous familial hypercholesterolemia.

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Competing interests

None declared.

References

1. Defesche JC. Defining the challenges of FH screening for familial hypercholesterolemia. J Clin Lipidol 2010;4:338-341.
2. Minhas R, Humphries SE, Qureshi N, et al. Controversies in familial hypercholesterolaemia: Recommendations of the NICE Guideline Development Group for the identification and management of familial hypercholesterolaemia. Heart 2009;95:584-587; discussion 587-591.
3. Müller C. Xanthomata, hypercholesterolemia, angina pectoris. Acta Med Scand 1938;89:75-84.
4. Goldstein J, Hobbs H, Brown M. Familial hypercholesterolemia. In: Scriver C, Beaudet A, Sly W, et al. (eds). The metabolic and molecular bases of inherited disease. New York, NY: McGraw-Hill; 2001.
5. Ned RM, Sijbrands EJ. Cascade screening for familial hypercholesterolemia (FH). PLoS Curr 2011;3:RRN1238.
6. World Health Organization. Familial hypercholesterolaemia (FH): Report of a Second WHO Consultation. Geneva, World Health Organization; 1999.
7. Neil HA, Hammond T, Huxley R, et al. Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: Prospective registry study. BMJ 2000; 321:148.
8. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients: Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011;5:133-140.
9. Yuan G, Wang J, Hegele RA. Heterozygous familial hypercholesterolemia: An underrecognized cause of early cardiovascular disease. CMAJ 2006;174:1124-1129.
10. Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: A prospective registry study. Eur Heart J 2008;29:2625-2633.
11. Slack J. Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. Lancet 196;2(7635):1380-1382.
12. Stone NJ, Levy RI, Fredrickson DS, et al. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. Circulation 1974;49:476-488.
13. Mortality in treated heterozygous familial hypercholesterolaemia: Implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group. Atherosclerosis 1999;142:105-112.
14. Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolaemia: A long term cohort study. BMJ 2008;337:a2423.
15. Wonderling D, Umans-Eckenhausen MA, Marks D, et al. Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands. Semin Vasc Med 2004;4:97-104.

16. Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. Am J Cardiol 1993;72:171-176.
17. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ 1991;303(6807):893-896.
18. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. Circulation 2008; 117:743-753.
19. Smilde TJ, van Wissen S, Wollersheim H, et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): A prospective, randomised, double-blind trial. Lancet 2001;357(9256):577-581.
20. Thompson GR, Maher VM, Matthews S, et al. Familial Hypercholesterolaemia Regression Study: A randomised trial of low-density-lipoprotein apheresis. Lancet 1995;345(8953):811-816.
21. National Committee on Vital and Health Statistics. United States Department of Health Services. Frequently asked questions about medical and public health registries. Accessed 4 March 2013. http://ncvhs.hhs.gov/9701138b.htm.
22. Larsson S, Lawyer P, Garellick G, et al. Use of 13 disease registries in 5 countries demonstrates the potential to use outcome data to improve health care's value. Health Aff (Millwood) 2012;31: 220-227.
23. Herberts P, Malchau H. How outcome studies have changed total hip arthroplasty practices in Sweden. Clin Orthop Relat Res 1997;344:44-60.
24. Malchau H, Herberts P, Eisler T, et al. The Swedish Total Hip Replacement Register. J Bone Joint Surg Am 2002;84-A (suppl 2):2-20.
25. Pocovi M, Civeira F, Alonso R, et al. Familial hypercholesterolemia in Spain: Case-finding program, clinical and genetic aspects. Semin Vasc Med 2004;4:67-74.
26. Datta BN, McDowell IF, Rees A. Integrating provision of specialist lipid services with cascade testing for familial hypercholesterolaemia. Curr Opin Lipidol 2010;21:366-371.
27. Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, et al. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. Lancet 2001;357(9251):165-168.
28. Marks D, Wonderling D, Thorogood M, et al. Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: A systematic review and cost-effectiveness analysis. Health Technol Assess 2000;4:1-123.
29. Marks D, Wonderling D, Thorogood M, et al. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. BMJ 2002; 324:1303.
30. DeMott K, Nherera L, Shaw EJ, et al. Clinical guidelines and evidence review for familial hypercholesterolaemia: The identification and management of adults and children with familial hypercholesterolaemia. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners; 2008.
31. Thorsson B, Sigurdsson G, Gudnason V. Systematic family screening for familial hypercholesterolemia in Iceland. Arterioscler Thromb Vasc Biol 2003;23:335-338.
32. Bhatnagar D, Morgan J, Siddiq S, et al. Outcome of case finding among relatives of patients with known heterozygous familial hypercholesterolaemia. BMJ 2000;321:1497-5000.
33. Al-Sarraf A, Allard M, Martinka M, et al. Regional and national familial hypercholesterolemia registries: Present international application, importance, and needs for Canada. Can J Cardiol 2013;29:6-9.
34. Civeira F, Ros E, Jarauta E, et al. Comparison of genetic versus clinical diagnosis in familial hypercholesterolemia. Am J Cardiol 2008;102:1187-1193.
35. Damgaard D, Larsen ML, Nissen PH, et al. The relationship of molecular genetic to clinical diagnosis of familial hypercholesterolemia in a Danish population. Atherosclerosis 2005;180:155-160.
36. Taylor A, Wang D, Patel K, et al. Mutation detection rate and spectrum in familial hypercholesterolaemia patients in the UK pilot cascade project. Clin Genet 2010;77:572-580.
37. Talmud PJ, Shah S, Whittall R, et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: A case-control study. Lancet 2013;381(9827):62127-62128.
38. Austin MA, McKnight B, Edwards KL, et al. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: A 20-year prospective study. Circulation 2000;101:2777-2782.
39. Voors-Pette C, de Bruin TW. Excess coronary heart disease in Familial Combined Hyperlipidemia, in relation to genetic factors and central obesity. Atherosclerosis 2001;157:481-489. BCMJ