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Original Article

Patient Perspectives Regarding Genetic Testing for Familial Hypercholesterolemia

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ABSTRACT

Background: Familial hypercholesterolemia (FH) is a common genetic disorder resulting in high levels of low-density lipoprotein cholesterol and increased risk of atherosclerotic cardiovascular disease. Genetic testing for FH is recommended but is not available in most of Canada. Consequently, there is a paucity of data regarding patient experiences with genetic testing. The objectives of this study were to investigate the attitudes and perspectives of patients with FH who underwent genetic testing.

Methods: We administered an anonymous online survey to participants in the British Columbia Familial Hypercholesterolemia Registry who had undergone research-based genetic testing for FH. The survey included 25 questions and explored patients' experiences with the genetic testing process, willingness to recommend genetic screening, and motivation to lower cholesterol levels.

Results: Among 183 respondents, 38 (20.7%) had a positive genetic test result, 27 (14.8%) had a negative result, and 118 (64.4%) were awaiting their results. Compared with individuals awaiting their test

RÉSUMÉ

Introduction : L'hypercholestérolémie familiale (HF) est une maladie génétique fréquente qui entraîne des concentrations élevées de cholestérol à lipoprotéines de faible densité et un risque accru de maladies cardiovasculaires athérosclérotiques. L'analyse génétique de l'HF est recommandée, mais n'est pas disponible dans la plupart des régions du Canada. Par conséquent, il existe peu de données sur les expériences des patients ayant subi une analyse génétique. Les objectifs de la présente étude étaient d'enquêter sur les attitudes et les points de vue des patients atteints d'HF qui avaient subi une analyse génétique.

Méthodes : Nous avons administré une enquête anonyme en ligne aux participants inscrits dans le registre British Columbia Familial Hypercholesterolemia qui avaient subi une analyse génétique fondée sur la recherche pour l'HF. L'enquête comptait 25 questions et portait sur les expériences des patients sur le processus d'analyse génétique, la volonté de recommander le dépistage génétique et la motivation à abaisser les concentrations de cholestérol.

Heterozygous familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder affecting 1/311 people worldwide.[1,2] Patients with FH have high levels of low-density lipoprotein-cholesterol and a markedly increased risk of early onset atherosclerotic cardiovascular disease (CVD), resulting in substantial morbidity and mortality.[3,4] Importantly, this risk is modifiable with the use of statins and other lipid-lowering medications.[5,6] Thus, diagnosing and treating patients with FH has been recognized as a priority in Canada[7] and internationally.[6,8]

Genetic testing is recommended in national and international guidelines to support the diagnosis of FH, enable cascade screening, and identify patients at the greatest risk of CVD.[7,9] However, genetic testing for FH is not readily available in most of Canada. In addition, relatively little is known about the experiences and perceptions of patients who undergo genetic testing for FH in Canada. The objectives of this study were to investigate the attitudes and behaviours of Canadian patients who undergo genetic testing for FH.

Methods

Patients

We included patients in the British Columbia Familial Hypercholesterolemia Registry[10] who had a clinical diagnosis

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Ethics Statement: This study was conducted in accordance with the Declaration of Helsinki and was approved by Research Ethics Board of the Providence Health Care Research Institute.

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results, participants with a positive genetic test were more likely to believe lipid-lowering therapy was highly important (74.3% vs 55.4%; $P = 0.05$). They were also more likely to strongly agree that a diagnosis of FH was important to them (71.1% vs 46.2%; $P = 0.008$), and were more likely to recommend genetic screening to their family members (85.9% vs 72.9%; $P = 0.04$).

Conclusions: To our knowledge, this is the first study in Canada to explore the perspectives of patients with FH who underwent genetic testing. These results suggest that genetic testing for FH might offer benefits in important patient-centred outcomes.

Résultats : Parmi les 183 répondants, 38 (20,7 %) avaient des résultats positifs à l'analyse génétique, 27 (14,8 %) avaient des résultats négatifs et 118 (64,4 %) attendaient leurs résultats. Comparativement aux individus qui attendaient leurs résultats d'analyse, les participants qui avaient des résultats positifs à l'analyse génétique étaient plus susceptibles de penser que le traitement hypolipémiant était très important (74,3 % *vs* 55,4 %; $P = 0,05$). Ils étaient aussi plus susceptibles d'être tout à fait d'accord sur le fait que le diagnostic d'HF était important pour eux (71,1 % *vs* 46,2 %; $P = 0,008$) et de recommander le dépistage génétique aux membres de leur famille (85,9 % *vs* 72,9 %; $P = 0,04$).

Conclusions : À notre connaissance, au Canada, c'est la première étude sur les points de vue des patients atteints d'HF qui avaient subi une analyse génétique. Ces résultats indiquent que le dépistage génétique de l'HF pourrait favoriser des résultats importants axés sur le patient.

of "possible," "probable," or "definite" FH on the basis of the Dutch Lipid Clinic Network Criteria, and who had consented to undergo research-based genetic testing of FH and subsequently receive their results.

Genetic testing

Genetic testing was performed as described previously by Trinder et al.[11] In brief, DNA was extracted from saliva or plasma samples, and targeted sequencing of the *LDLR*, *APOB*, and *PCSK9* genes was performed using the MiSeq platform (Illumina, Inc, San Diego, CA). For the purpose of this study, we considered a test "positive" if a patient had an FH-causing variant that was annotated as "pathogenic" or "likely pathogenic" in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar).[12] Results of research-based genetic testing were provided to the participants by their specialist physician managing their FH.

Survey distribution

An online questionnaire was developed by the authors, on the basis of a review of the literature of illness perception survey tools previously described.[13,14] The items explored were agreed upon by all authors, and approved by a content area expert. The questionnaire included 25 questions in a multiple choice or ranking format. Questions about ethnicity, personal history of CVD, and history of cardiac risk factors allowed more than one answer to be selected. Questions explored patients' understanding of their illness and levels of motivation to lower their cholesterol levels, take lipid-lowering therapy (LLT), and engage in healthy lifestyle behaviours on a 0-10 scale, with a high understanding/motivation level defined as a response of 10. Patients were also asked to rank the factors they believed were most important in cholesterol reduction, including LLT, diet, exercise, smoking cessation, and stress reduction. A high ranking was defined as a selection of either the first or second most important factor. Patients' perceptions of the importance of genetic testing and diagnosis of FH, willingness to recommend screening to family members, and concern regarding the effect of genetic testing on insurance and employment opportunities were evaluated on a 5-point scale. Self-reported LLT adherence was also evaluated.

The questionnaire was distributed via the Qualtrics survey platform (Qualtrics, Provo, UT) to all patients currently registered in the British Columbia Familial Hypercholesterolemia Registry who had undergone genetic testing. Implied, informed consent was provided by all participants. Participants who enrolled were entered into a draw for a chance to win a "FitBit" (FitBit Inc, San Francisco, CA). Participant responses were anonymously completed, and the results were password-protected and only accessible to the authors. Exclusion criteria included patients aged younger than 18 years and those without a valid e-mail address in the Registry's records. Invitations to participate in the study were sent via e-mail. Reminder e-mails were sent 2 and 4 weeks after the initial invitation. This study was approved by the Research Ethics Board of the Providence Health Care Research Institute.

Statistical analysis

A Pearson χ^2 test was performed to compare prespecified groups of patients, including positive vs negative, positive vs awaiting test results, and received vs awaiting test results. A subgroup analysis was performed to compare other demographic parameters in the population, including age, sex, family history of CVD, and personal history of CVD. Statistical analysis was performed using SPSS Statistics 27 software (IBM Corp, Armonk, NY).

Results

We identified 545 eligible patients with a clinical diagnosis of FH to participate in the survey. Of these, 183 (33.6%) responded to the survey. Among survey respondents, 38 (20.7%) had a positive genetic test result, 27 (14.8%) had a negative result, and 118 (64.4%) were awaiting their results at the time of the survey (Fig. 1).

Table 1 shows the demographics of the patient population, stratified according to genetic test result. Of the patients who completed the survey, 71.6% were 55 years of age or older, and 54.1% were female. There were no significant differences in age and ethnicity between the groups, and rates of CVD and cardiac risk factors were similar. There were significantly more women in the positive test group, compared with the negative test and awaiting results groups (73.7% vs 48.1% vs

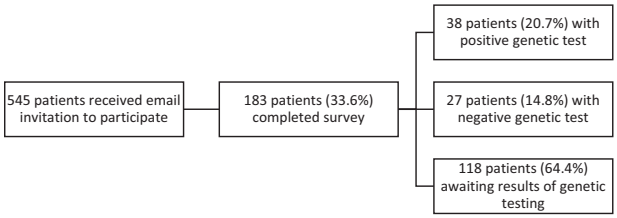

Figure 1. Flow diagram of patient population

49.2%; $P = 0.03$). Furthermore, fewer patients with a positive test were from the Lower Mainland compared with those with a negative test or awaiting their results (65.8% vs 92.6% vs 82.2%; $P = 0.03$).

Perceptions on genetic testing for FH

Patients with a positive genetic test (81.6%) were more likely to perceive genetic testing for patients with high cholesterol as "very important," compared with patients with a negative test result (59.3%; $P = 0.05$) and those still awaiting their test results (56.8%; $P = 0.006$; Fig. 2A). They also reported a better overall experience with the genetic testing process compared with those with a negative test and still awaiting their results (86.8% vs 65.4% [$P = 0.04$] and vs 52.2% [$P < 0.001$]; Fig. 2B).

Compared with patients still awaiting their test results, patients with a positive genetic test were more likely to "strongly agree" that a diagnosis of FH using genetic testing was important to them (71.1% vs 46.2%; $P = 0.008$; Fig. 2C), and were more likely to recommend genetic screening for FH in their family members (85.9% vs 72.9%; $P = 0.04$; Fig. 2D). These responses were not statistically different between the positive and negative test groups.

Patients who received a positive test result were also more likely to rank LLT as a highly important factor for cholesterol reduction compared with those awaiting their results (74.3%

Table 1. Patient characteristics

	Total		Positive test		Negative test		Awaiting results		
	n	%	n	%	n	%	n	%	*P*
Total									
Count	183	100	38	100	27	100	118	100	
Sex									0.03
Male	84	45.9	10	26.3	14	51.9	60	50.8	
Female	99	54.1	28	73.7	13	48.1	58	49.2	
Age, years									NS
18-24	2	1.1	1	2.6	0	0.0	1	0.8	
25-34	10	5.5	4	10.5	0	0.0	6	5.1	
35-44	12	6.6	5	13.2	3	11.1	4	3.4	
45-54	28	15.3	5	13.2	3	11.1	20	16.9	
55-64	56	30.6	9	23.7	10	37.0	37	31.4	
65-74	54	29.5	9	23.7	9	33.3	36	30.5	
75-84	19	10.4	4	10.5	2	7.4	13	11.0	
85 or older	2	1.1	1	2.6	0	0.0	1	0.8	
Ethnicity*									NS
African Canadian	1	0.5	0	0.0	0	0.0	1	0.8	
Asian	17	9.3	3	7.9	3	11.1	11	9.3	
Caucasian	148	80.9	31	81.6	22	81.5	95	80.5	
Hispanic/Latin	3	1.6	1	2.6	0	0.0	2	1.7	
Indigenous	3	1.6	0	0.0	1	3.7	2	1.7	
South Asian	9	4.9	1	2.6	2	7.4	6	5.1	
Other	9	4.9	3	7.9	0	0.0	6	5.1	
Location									0.03
Lower mainland	147	80.3	25	65.8	25	92.6	97	82.2	
Interior BC	12	6.6	4	10.5	2	7.4	6	5.1	
Northern BC	4	2.2	3	7.9	0	0.0	1	0.8	
Vancouver Island	11	6.0	2	5.3	0	0.0	9	7.6	
Other	8	4.4	4	10.5	0	0.0	4	3.4	
No response	1	0.5	0	0.0	0	0.0	1	0.8	
CVD history*									NS
TIA/stroke	8	4.4	1	2.6	2	7.4	5	4.2	
MI	18	9.8	2	5.3	3	11.1	13	11.0	
CAD	39	21.3	8	21.1	4	14.8	27	22.9	
PAD	4	2.2	1	2.6	0	0.0	3	2.5	
None	134	73.2	30	78.9	19	70.4	85	72.0	
Cardiac risk factors*									NS
HTN	55	30.1	6	15.8	8	29.6	41	34.7	
DM	12	6.6	1	2.6	1	3.7	10	8.5	
Family history of CVD	111	60.7	25	65.8	14	51.9	72	61.0	
Obesity	58	31.7	14	36.8	8	29.6	36	30.5	
CKD	5	2.7	0	0.0	1	3.7	4	3.4	
Smoking	3	1.6	0	0.0	1	3.7	2	1.7	
None	43	23.5	8	21.1	9	33.3	26	22.0	

BC, British Columbia; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; NS, nonsignificant; PAD, peripheral arterial disease; TIA, transient ischemic attack.

*Multiple answers were allowed for these categories.

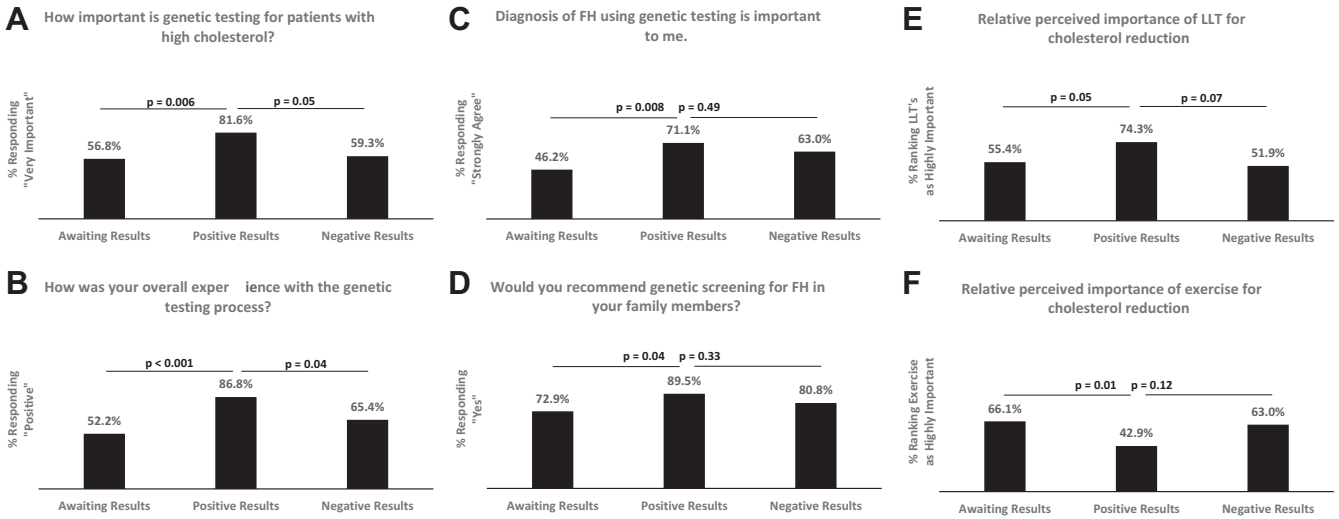

Figure 2. Comparison of survey responses on the basis of genetic test results. Comparisons are between participants with a positive test, negative test, or awaiting their test results. Results are shown for responses to questions: (**A**) How important is genetic testing for patients with high cholesterol? (**B**) How was your overall experience with the genetic testing process? (**C**) Diagnosis of FH using genetic testing is important to me. (**D**) Would you recommend genetic screening for FH in your family members? (**E**) Relative perceived importance of LLT for cholesterol reduction. (**F**) Relative perceived importance of exercise for cholesterol reduction. FH, familial hypercholesterolemia; LLT, lipid-lowering therapy.

vs 55.4%; $P = 0.05$; Fig. 2E). Furthermore, patients awaiting their results were more likely to rank exercise as a highly important factor (66.1% vs 42.9%; $P = 0.01$; Fig. 2F). These trends did not reach significance when the positive and negative group were compared.

There were several significant differences between patients who had received their results (pooled positive and negative results) compared with those who were still awaiting their results. In particular, individuals who had received their results reported that genetic testing was "very important" more often than individuals awaiting their results (72.3% vs 56.8%; $P = 0.04$), were more likely to report a positive experience with the genetic testing process (78.1% vs 52.2%; $P = 0.001$), and more frequently "strongly agreed" that a diagnosis of FH was important to them (67.7% vs 46.2%; $P = 0.005$). They were also more likely to recommend genetic testing in their family members (85.9% vs 72.9%; $P = 0.04$). These findings suggest that the experience of undergoing genetic testing, rather than the specific result, leads to more positive patient perceptions.

Motivation levels were evaluated on a scale from 0 to 10, with "high motivation" defined as a response of 10 (Fig. 3). There were nonsignificant trends suggesting the positive test group was more likely to be highly motivated to reduce cholesterol levels (54.1% vs 41.5%; $P = 0.18$), pursue healthy lifestyle behaviours (44.7% vs 36.4%; $P = 0.36$), and take LLT (71.1% vs 58.9%; $P = 0.18$) compared with those awaiting their results. Compared with the negative group, the patients in the positive group showed nonsignificant trends toward higher motivation to take LLT (71.1% vs 52.2%; $P = 0.12$) but lower motivation to engage in healthy lifestyle behaviours (44.7% vs 59.3%; $P = 0.25$). There were no differences between self-reported LLT adherence rates.

Implications of a genetic diagnosis

There were no significant differences in patients' understanding of their diagnosis between the 3 groups, although there was a trend suggesting that patients who had received their results (pooled positive and negative) more frequently reported a high understanding of their illness compared with those still awaiting their test results (19.7% vs 12.8%; $P = 0.08$). No significant differences were noted between groups regarding concerns of the effect of a genetic diagnosis on insurance and employment opportunities.

Subgroup analyses

Patients with a family history of CVD were more likely to report a high understanding of their diagnosis (19.6% vs 8.5%; $P = 0.04$; Fig. 4A). They were also more likely to believe that genetic testing was "very important" for patients with high cholesterol (68.5% vs 52.8%; $P = 0.03$; Fig. 4B), and were more likely to recommend genetic testing to their family members (82.7% vs 69.4%; $P = 0.04$; Fig. 4C).

Similarly, patients with a personal history of CVD reported a high understanding of their diagnosis more frequently than those without CVD (27.1% vs 10.8%; $P = 0.007$; Fig. 5A). They were also more likely to report high motivation to reduce cholesterol (60.4% vs 41.0%; $P = 0.007$; Fig. 5B), and were more likely to highly rank LLT as an important factor in achieving cholesterol reduction (71.7% vs 53.9%; $P = 0.04$; Fig. 5C). However, there were no significant differences in the rate of high motivation to take LLT (66.0% vs 58.6%; $P = 0.4$) or to pursue healthy lifestyle behaviours (53.1% vs 37.3%; $P = 0.06$).

Patients aged 55 years and older more frequently reported a high motivation to lower cholesterol (50.8% vs 34.6%; $P = 0.05$) and pursue healthy lifestyle behaviours (46.6% vs 28.8%; $P = 0.03$) than those younger than 55 years. They were more likely to highly rank exercise as an important factor for cholesterol reduction (66.4% vs 48.1%; $P = 0.02$). Older patients were also more likely to report never missing a dose of their LLT (66.9% vs 52.1%; $P = 0.05$).

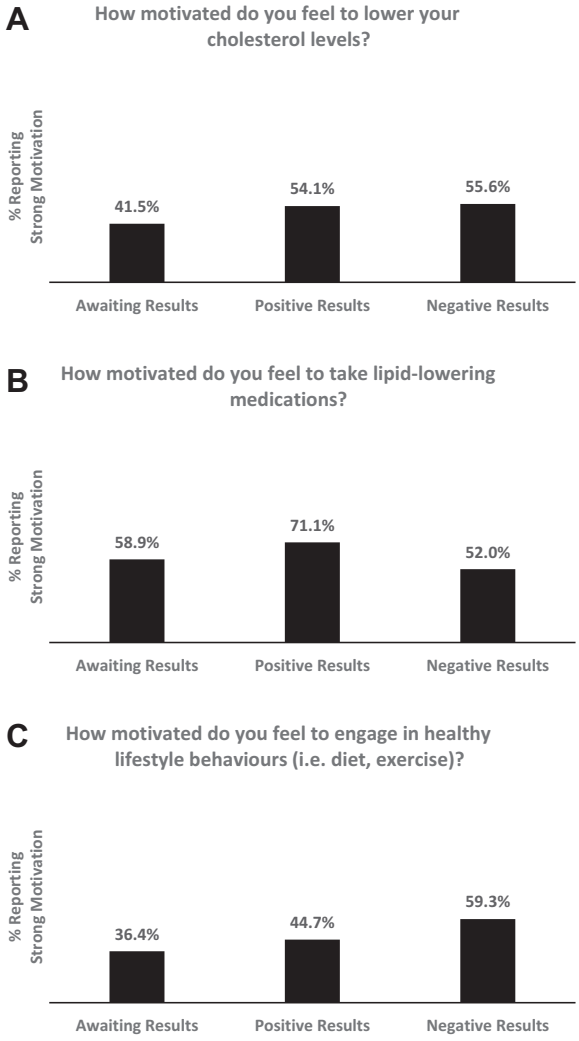

Figure 3. Comparison of motivation levels based on genetic test result. Comparisons are between participants with a positive test, negative test or awaiting their test results. Results are shown for responses to questions: (**A**) How motivated do you feel to lower your cholesterol levels? (**B**) How motivated do you feel to take lipid-lowering medications? (**C**) How motivated do you feel to engage in healthy lifestyle behaviours (ie, diet, exercise)? None of the results reached significance.

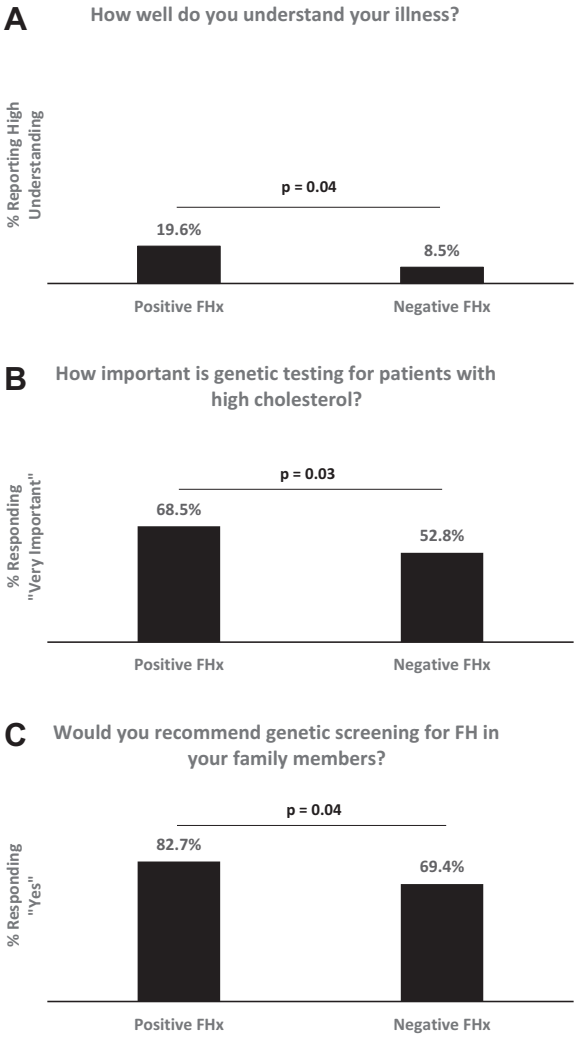

Figure 4. Comparison of survey responses on the basis of family history (FHx) of cardiovascular disease. Comparisons are between participants self-reporting a FHx of cardiovascular disease or not. Results are shown for responses to questions: (**A**) How well do you understand your illness? (**B**) How important is genetic testing for patients with high cholesterol? (**C**) Would you recommend genetic screening for FH in your family members? FH, familial hypercholesterolemia.

Men and women did not report any significant differences in motivation to lower cholesterol levels, take LLT, or engage in healthy lifestyle behaviours. However, men reported a higher concern for the implications of genetic testing on their insurance (33.3% vs 17.3%; $P = 0.01$) and statistically nonsignificant higher concern for the implications on their employment (10.8% vs 4.1%; $P = 0.08$).

Discussion

To our knowledge, this is the first study in Canada to explore the perspectives and behaviours of patients with FH who underwent genetic testing. Compared with individuals awaiting their test results, participants with a positive genetic test were more likely to believe LLT was a highly important factor to lower their cholesterol levels. They also agreed more strongly that a genetic diagnosis of FH was important and were more likely to recommend genetic screening for their family members. Importantly, most (78.1%) of the participants who had received their results reported a positive overall experience with the genetic testing process. These findings have important implications for the development of genetic testing programs for FH, because individuals with a genetic diagnosis might be more engaged with their care.

Although a number of studies have shown changes in patient behaviour after receiving genetic testing for a variety of diseases,[15,16] a meta-analysis of 17 studies performed in 2016 did not show any significant behavioural change before and after genetic testing.[17] In Norway and The Netherlands, several studies have shown increased LLT adherence and physician contact after genetic testing[18-22]; however, to our knowledge, only 1 study has ever assessed other behavioural

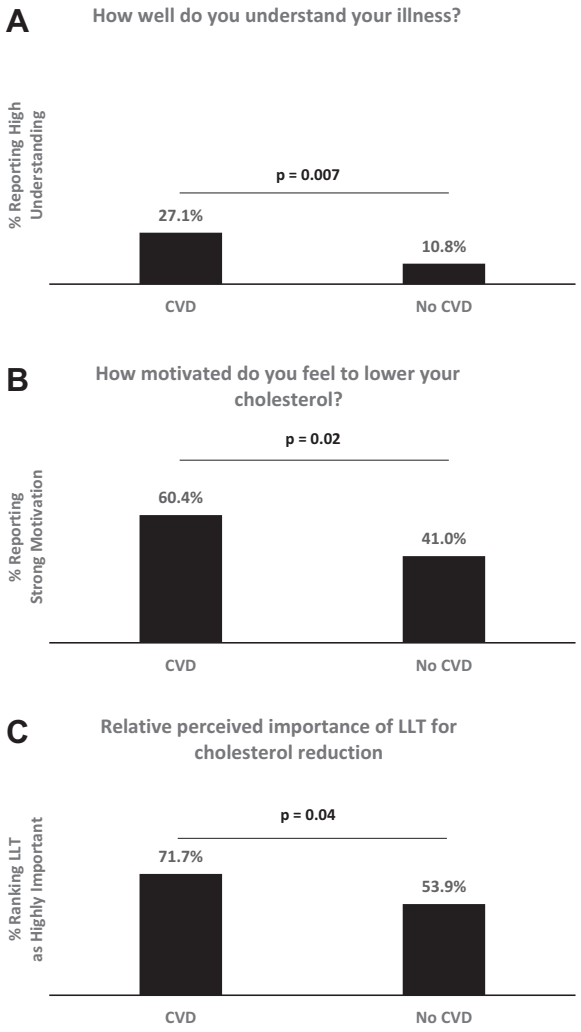

Figure 5. Comparison of survey responses on the basis of personal history of CVD. Comparisons are between participants self-reporting a personal history of CVD or not. Results are shown for responses to questions: (**A**) How well do you understand your illness? (**B**) How motivated do you feel to lower your cholesterol? (**C**) Relative perceived importance of LLT for cholesterol reduction. CVD, cardiovascular disease; LLT, lipid-lowering therapy.

changes in an FH patient population.[13] In their study in the United Kingdom, Marteau et al. did not identify any behavioural differences before and after genetic testing for FH, but participants with a genetic diagnosis believed that diet had a lesser role and LLT had a greater role in reducing cholesterol.[13] Our results corroborate this finding in a Canadian population: participants with a positive genetic test were more likely to rank LLT as a highly important factor to lower cholesterol levels, whereas individuals awaiting the results of their genetic testing were more likely to highly rank exercise. Because FH is significantly undertreated worldwide,[6,8] genetic testing might be an important tool to engage patients in their treatment and optimize medication use. Despite participants with a positive genetic test perceiving more importance of LLT, there were no differences in motivation to lower cholesterol levels, use LLT, or engage in healthy lifestyle behaviours. There were also no differences in self-reported LLT adherence after genetic diagnosis. This suggests that although patients' perceptions might change, this might not directly affect their actual motivation or behaviour. This might also reflect the fact that in our study, participants had already received a clinical diagnosis of FH, and had received physician contact and lifestyle counselling before undergoing genetic testing.

Importantly, individuals with a positive genetic test were more likely to recommend genetic screening to their family members. Because of the autosomal dominant inheritance of FH, cascade screening of family members is strongly recommended in the 2018 Canadian Cardiovascular Society's position statement on FH.[7] Cascade screening relies on index patients informing their family members of their diagnosis or providing a health care provider with their contact information. Without index patient cooperation, cascade screening is challenging, and many patients are diagnosed with FH only after suffering a major cardiovascular event. A genetic diagnosis of FH might increase rates of cascade screening, which, in turn, can allow for early diagnosis of FH and initiation of LLT and lifestyle changes, which have been proven to be effective in CVD prevention.[5,23,24] Importantly, our data suggest that genetic testing might help to engage the index patient to facilitate cascade screening of their first-degree relatives.

A genetic diagnosis did not significantly improve patients' understanding of their illness, but individuals with a personal history or family history of CVD had a significantly better understanding. Because FH is most often a clinically silent disease, patients might find it more difficult to understand unless they or a family member have developed symptomatic CVD as a result. This highlights the need for robust patient education and counselling, especially for individuals who have not experienced clinical sequelae of their diagnosis personally or in a family member. Individuals with a positive family history of CVD also believed that genetic testing was more important and were more likely to recommend genetic testing to their family members, highlighting the importance of thorough family history screening in patients with FH.

Limitations

This study included patients from a single specialized lipid clinic in Canada. Future studies will be needed to extend these observations to other jurisdictions. Because of the relatively small sample size, some of the trends we observed were not statistically significant, but might become significant in a sufficiently large sample. As a result of limited genetic testing infrastructure for FH in Canada, this study used research-based genetic testing and the tests were not performed through an accredited clinical laboratory. Results of genetic testing were returned to participants by physicians with expertise in FH, rather than by certified genetic counsellors. It is possible that patient experiences and perceptions could change on the basis of how the results are communicated. This reflects the reality in most lipid or cardiology clinics in Canada, in which genetic counselling is not readily available. Furthermore, we did not formally assess the psychometric properties of the survey instrument used, and this survey has not been validated in previous studies; however, our survey

was developed on the basis of those used in previous studies,[13,14] and in consultation with content area experts. This study was also prone to selection bias, because it relied on patients to voluntarily respond to an online questionnaire. This might have selected for individuals who were more engaged in their care and have a higher socioeconomic status. Finally, our study investigated self-reported perceptions and behaviours, but did not directly evaluate these behaviours, such as medication adherence or true rates of cascade screening, which should be areas of further study.

Conclusions

To our knowledge, this is the first study in Canada to explore the perspectives of patients with FH before and after genetic testing. Compared with individuals awaiting their test results, participants with a positive genetic test were more likely to believe LLT was a highly important factor to lower their cholesterol levels. They also agreed more strongly that a diagnosis of FH was important and were more likely to recommend screening for their family members. Overall, these results suggest that genetic testing for FH might offer benefits in important patient-centred outcomes. These results have important implications for the design and implementation of genetic screening programs for FH in Canada.

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Disclosures

The authors have no conflicts of interest to disclose.

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