

Systematic Detection of Familial Hypercholesterolaemia in Primary Health Care: A Community Based Prospective Study of Three Methods



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Background

Familial hypercholesterolaemia (FH), a co-dominantly inherited disease of cholesterol that markedly increases risk of premature coronary artery disease (CAD), is significantly under-diagnosed. Primary health care is increasingly seen as a setting in which to increase the detection rate of index cases. We report a prospective study of three methods of case detection using pre-existing primary health care services in one community.

Methods

Three methods of case detection were tested: pathology laboratory database search, workplace health checks and general practice database search. People identified at risk by each of the three screening methods were offered detailed assessment for FH using the Dutch Lipid Clinic Network Criteria score (DLCNCS).

Results

1316 participants underwent detailed assessment for FH. The proportion of at risk people identified for further assessment was in decreasing order: GP (659 of 2494, 26.4%), workplace assessment (60 of 268, 22.4%) and pathology database (597 of 4517, 13.2%) $p < 0.001$. Eight-six (6.5%) were identified as clinical FH (DLCNCS > 5) of which 59 had genetic testing and 11 of 59, 18.6%, were confirmed to have a mutation causing FH. Pathology database detected the greatest number of clinical FH (51 of 86, 59.3%) and mutation positive participants (8 of 11, 72.7%).

Conclusion

Screening within primary health care was successful in detecting participants with FH. An integrated case detection model combining screening of pathology and GP databases is proposed.

Keywords

Familial hypercholesterolaemia • Primary health care • General practice • Screening • Case detection • Preventative cardiology

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Introduction

Familial Hypercholesterolaemia (FH) is a co-dominantly inherited disorder of cholesterol metabolism causing premature coronary artery disease (CAD). Resulting from mutations in the low density lipoprotein (LDL) receptor gene [1], FH occurs with an estimated frequency of 1 in 500 in the general population [2] and at higher rates due to founder effects in selected populations [3]. Primary Health Care (PHC) is increasingly seen as important for detection of new index cases of FH [4–7]

Individuals with FH have early atherosclerosis from childhood and the only evidence that they may be at risk may be a family history of premature CAD. Given the usual age for screening for CAD is 45 years and over [8] these individuals may have significant cardiovascular disease before they are considered for screening.

FH is a condition that is detectable, treatable and potentially cost-effective for screening [9]. Diagnosis of FH is made on clinical history, examination, biochemical findings and DNA testing. In Australia the DLCN criteria [10] are preferred for phenotypic diagnosis because they combine clinical findings, biochemical results and DNA results without relying on any one feature exclusively [11].

Cascade screening is the most cost-effective means of screening for FH [12]. However, detection of new cases is limited by identification of index cases. Estimates of the percentage of diagnosed FH within the community range from 10% [11] to 25% [13], meaning that the majority of cases remain undiagnosed. In Australia there may be as many as 45,000 undiagnosed cases of FH [14].

The role of PHC and in particular general practice in screening for FH has been recognised by a number of authors [5,6,11,13,15–17]. In Australia 83% of the population sees the general practitioner GP at least once a year [18]. Up to 92% of all cholesterol tests may be requested by GPs [19]. However,

low awareness and gaps in GP knowledge on FH [20] reflect inadequate diagnosis and identification of index cases.

To date there are limited numbers of studies of the best screening strategies for FH in PHC. We report a case detection study using three different screening strategies based in PHC.

Methods

This study was a prospective comparison of three screening methods for the detection of FH. The study comprised three phases: Phase 1 initial screening in PHC settings, Phase 2 case detection in a primary care setting by a research nurse and general practitioner, and Phase 3 specialist clinical follow up of high-risk cases. Research participants were recruited between January 2010 and December 2012. Clinical follow-up of high-risk cases continued until June 2013.

Three PHC settings were used in screening for possible risk of FH: community pathology laboratory databases (PLD), work place based occupational health assessment (WPA) and general practice patient databases (GPD).

PLD screening method involved three community pathology providers who performed a data extraction of records of all patients 18 to 60 years with total cholesterol > 7.5 mmol/l or LDL-C > 4.5 mmol/L over the previous five years from South West Australian postcodes (6200-6299). The pathology laboratories contacted patients by mail and they were recruited when they contacted the research office for a primary care assessment.

WPA screening method involved the workforce at a large local mineral processing operation. Workers were offered a short five-question questionnaire on CAD risk (Figure 1), administered as part of their annual health assessment. Information about the condition and the consequences of a positive response to the questionnaire and of the diagnosis of FH were given and informed consent taken prior to the

	Questions
1	Have you ever had any of the following: Heart Attack, Stroke, By-pass Artery Operation, Blocked Arteries or Bad Circulation
2	Have you ever been told that your blood cholesterol is high (over 7)?
3	Have you ever been advised to take medicine to lower your blood cholesterol?
4	Has any BLOOD relative (grandparent, brother, sister, or child) aged 60 years or below, had any of the following: Heart Attack, Stroke, By-pass Artery Operation, Blocked Arteries or Bad Circulation anywhere in the body?
5	Has any BLOOD relative (grandparent, brother, sister, or child) had "high" cholesterol or cholesterol over 7?

Figure 1 WPA CAD risk questionnaire.

administration of the questionnaire. Participation was voluntary. Respondents identifying two or more positive risk factors for CAD were contacted by the research nurse and offered a primary care assessment.

GPD screening method involved screening the electronic database of two private general practices using data extraction software, known as the Canning Tool [21]. For this project the Canning Tool was modified for specific FH and cardiovascular indicators and the particular practice software used in each general practice. Criteria for the FH Canning Tool were: age 18-70 years, history of cardiac event <60 years, any CAD, diagnosis of lipid disorder, TC >7.5 mmol/L, LDL >4.0 mmol/L or prescription for statins.

Children and adolescents were not included in the clinical assessment. Individuals identified as being at increased risk of CAD or elevated cholesterol from any of the three screening models were invited to participate in a face-to-face assessment by a trained nurse to screen for FH. The nurse offered subjects a 30-minute assessment, if they consented to participation. Assessment included a thorough medical and family history and a focussed examination for clinical signs of FH. Based on this assessment participants were given a Dutch Lipid Clinic Network Criteria Score (DLCNCS). DLCNCS were preferentially calculated using a pre-treatment LDL-C, although if this was not available, a pre-treatment LDL-C was estimated by adding 30% to the on-treatment LDL-C. [22]. People with a DLCNCS > 5 were identified as at high-risk of FH. The lead investigator, a GP, reviewed the nurse's clinical notes and checked and finalised the DLCNCS allocated. Participants with unclear or equivocal clinical signs such as tendon xanthomata and arcus cornealis were reviewed by the GP to corroborate the nurse's findings. The accuracy of the DLCNCS calculated by the PHC team compared with that of lipid specialists was verified in a concordance analysis performed on a subset of 153 patients as previously reported [23].

All participants identified at high risk of FH were offered further follow-up with a specialist lipid clinic via referral from their GP as part of routine care. This assessment included establishing the likelihood of FH, presence of vascular disease and other cardiovascular risk factors and optimised therapy. Participants with a DLCNCS > 5 were offered DNA testing and this required formal consent.

This project received ethics approval from University of Western Australia UWA Human Research Ethics Committee HREC (RA/4/1/4003), St John of God Health Care Ethics Committee (Ref: 417), and WA Country Health Service Board Research Ethics Committee WACHSBREC (2010:02).

Total cholesterol, triglyceride and high density lipoprotein (HDL)-cholesterol analyses were performed on fasting bloods with enzymatic, colorimetric assays using either Abbott, Siemen's or Roche analysers and reagents, depending on the community laboratory the patient presented to. All laboratories were nationally certified. LDL-C was calculated according to the Friedewald equation [24] except for those with triglycerides >4.5 mmol/L. Genetic testing involved sequencing all 18 exons of the low density lipoprotein receptor (*LDLR*), and

multiplex ligation dependent probe amplification of the *LDLR* to assess for large deletions or duplications. Exons 26 and 29 of apolipoprotein B were sequenced, as was exon 7 of proprotein convertase subtilisin kexin type 9 (*PCSK9*) as previously described [25].

Because of the application of different screening models across the same community there was a risk of overlap effect. To control for this all participants responding to the invitation into the research project were asked if they had received and/or responded to a prior invitation from another detection method in the research project.

Counts, percentages, means and standard deviations were used to summarise detection outcomes and describe participant characteristics. Differences in participant characteristics between the samples generated by the three screening methods were assessed using Chi-square and ANOVA or Fisher's Exact Test and the Kruskal-Wallis test when the parametric test assumptions could not be met. Reliability of assessment using the DLCNCS was investigated and is reported in [23]. DLCNCS was also dichotomised using a cut point of >5 and a logistic regression performed to determine the comparative odds of detecting high-risk patients amongst the three methods. Participants were classified as high risk of FH (DLCNCS > 5, which equates to a DLCN criteria for probable FH), or low risk (DLCNCS 0-5). Statistical significance was set at alpha = 0.05 and analyses were performed using Stata 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.)

Results

Summary data for the three screening methods are presented in Figure 2. The initial screening by each method is represented in the first box. Those identified at risk of CAD are represented in the second box. The third box represents those people who responded to the invitation to participate and were assessed by the research nurse. Those who had a DLCNCS > 5 and were referred for specialist review are represented in the fourth box and those completing the review are in the fifth box. The last box represents those positive for FH-causing mutations.

Table 1 summarises demographic and cardiovascular risk factors for PLD, WPA and GPD. There were significant differences among screening methods for age, gender, obesity, smoking, hypertension, diabetes, pre-existing CAD, cerebrovascular disease and whether they are on cholesterol lowering therapy. GPD participants were older, more obese and had a higher level of comorbidity and cardiovascular risk factors than PLD and WPA and they were also significantly more likely to be on cholesterol lowering therapy. WPA participants were younger and had significantly more males than PLD and GPD. PLD participants had the lowest levels of smoking and other cardiovascular risk factors and also the lowest levels of cholesterol lowering therapy.

Figure 3 shows the detection rate (%) of high-risk FH (DLCNCS > 5) for each screening method. There is a significant difference between the three methods, $p = 0.028$.

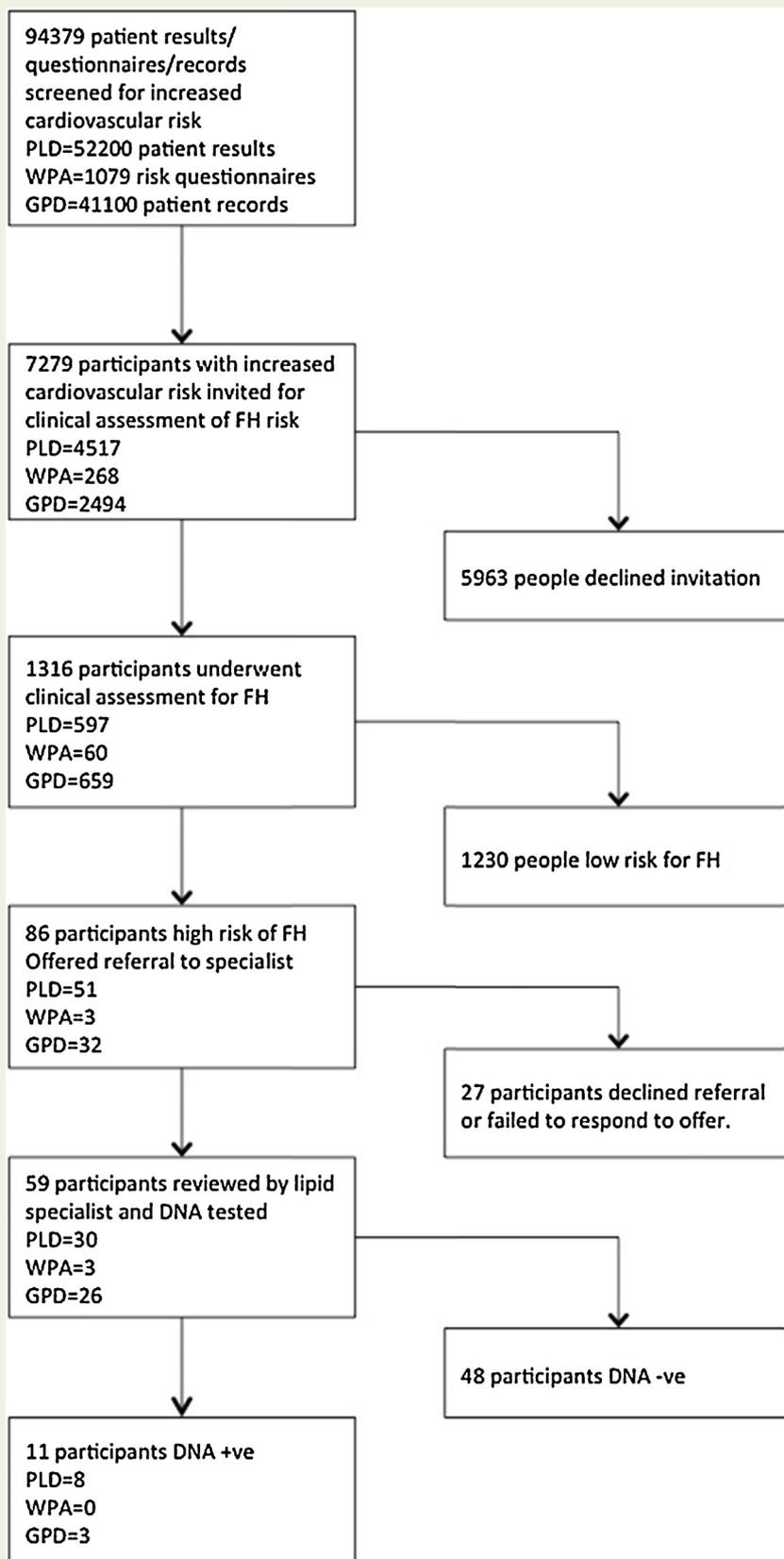


Figure 2 Flow diagram for FH case detection study
 PLD-Pathology laboratory database, WPA-work place assessment, GPD-general practice database, FH-familial hypercholesterolaemia, DNA-deoxyribonucleic acid.

Table 1 Demographic and cardiovascular risk factors by screening method. Chi-squared analysis unless otherwise indicated.

Risk factors	PLD N = 597	WPA N = 60	GPD N = 659	P-value
Age, years #	53.3 (7.6)	48.4 (10.4)	57.6 (9.1)	<0.001 [†]
BMI, kg/m ² #	29.6 (5.0)	28.9 (4.0)	30.4 (5.2)	0.007 [†]
Gender male	296 (49.6)	57 (95)	328 (50)	<0.001
Smoking				
Never	351 (58.1)	30 (50)	327 (49.7)	0.013
Ex	184 (30.8)	22 (36.7)	262 (39.8)	
Current	62 (10.4)	8 (13.3)	69 (10.5)	
Exercise >2.5 hrs/week	384 (65.0)	37 (61.7)	390 (61.4)	0.424
Hypertension	141 (23.7)	12 (20)	267 (40.5)	<0.001
Diabetes	30 (5.0)	5 (8.3)	94 (14.3)	<0.001
Coronary Artery Disease	19 (3.2)	7 (11.7)	86 (13.0)	<0.001
Peripheral Vascular Disease	2 (0.3)	0 (0.0)	7 (1.1)	0.319 [*]
Cerebrovascular disease	4 (0.7)	2 (3.3)	25 (3.8)	<0.001 [*]
Cholesterol lowering therapy	267 (46.1)	23 (39.0)	492 (74.9)	<0.001

PLD-Pathology laboratory database, WPA-work place assessment, GPD general practice database, BMI-body mass index.

Hypertension and diabetes defined as reported on patient history.

#Mean (sd), otherwise n (%).

^{*}Fisher's exact test,

[†]Kruskal-Wallis test.

Logistic regression analysis of these data showed that the odds of DLCNCS > 5 in PLD were 82% higher than for patients in GPD (OR = 1.82 95%CI 1.16,2.86).

Costs of screening, total and per case detected, for the different methods are shown in Table 2. Costs in \$AUD were calculated for Australian clinical practice in 2011/12 based on the following items: data extraction, questionnaire, mail-out, stationary, postage, appointment phone calls, travel by car to clinical sites interview and assessments and case reviews. Costs were calculated using the following hourly rate for different staff: GPs \$300/hour, nurses \$30/hour,

Office staff \$20/hour and pathology technicians \$45/hour. In addition development of the Canning tool for this project cost a one-off payment of \$3000. Costs did not include the cost of lipid testing as this was previously performed for other clinical reasons.

For high-risk FH cases (DLCNCS > 5), 28 of 86 (32.6%) were not on cholesterol lowering therapy at the time of assessment. In addition Table 1 shows the variation in lipid management between the various models with 75% of patients in the GPD being on lipid lowering medication but only 46% and 39% of the patients in the PLD and WPA model respectively.

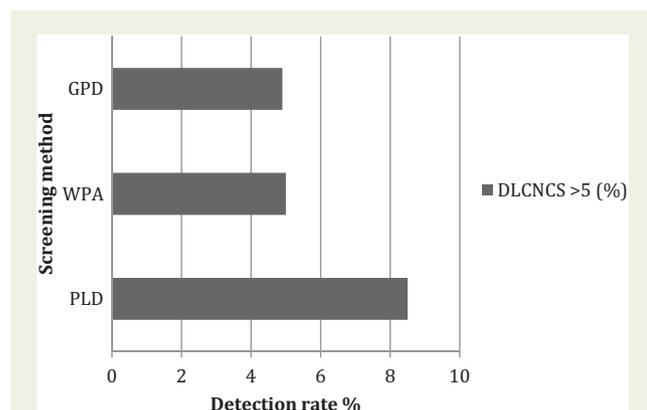


Figure 3 Detection rate of high risk FH based on DLCNCS >5 according to initial screening using the GPD, WPA and PLD methods.

Table 2 Costs of each screening model in \$AUD.

Model	Assessed for FH	DLCNCS > 5	Total Cost \$AUD	Cost per patient DLCNCS > 5, \$AUD
PLD	597	51	32086	629
WPA	60	3	14645	4882
GPD	659	32	31256	976

\$AUD- Australian dollars, PLD-Pathology database, WPA- work place assessment, GPD general practice database, DLCNCS- Dutch Lipid Clinic Network Criteria Score.

Figure 2 shows 59 high-risk cases reviewed by specialists. These reviews were either carried out face-to-face or via telehealth clinics. A pathogenic mutation causative of FH was found in 11(18.6%).

The overall overlap effect was 235 of 1316 (17.8%) participants reporting contact from different screening methods. There were 99 (16.5%) PLD, 0 (0%) WPA and 136 (20.6%) GPD participants who reported they had been contacted by two or more of the screening methods.

Discussion

This study is the first to test three different models of detecting index cases with FH using the existing medical and social infrastructure of a regional primary care setting. Two of the three methods successfully screened large numbers of participants, identified high-risk cases and subsequently yielded new index cases of DNA +ve and phenotypic FH. PLD was the most efficient method of detecting high-risk cases. It surveyed the largest number of participants and discovered cases with less pre-existing cardiovascular disease and comorbidity. This study demonstrated the odds of a DLCNCS > 5 were 82% higher in the PLD method than the GPD method. GPD had the best response rate from patients. GPs recalling patients generated twofold greater involvement in the screening process than the letter mail-out by pathology laboratories. All methods tested PLD, WPA and GPD, were part of the existing primary health care setting.

The study demonstrated that screening for FH within the community utilising existing primary care services is possible and cost of each model suggests that a community-screening program is potentially viable. Our data suggest that an integrated screening program including elements of all methods linked to centralised cascade screening combined approach will probably be more effective. Initial screening through pathology databases yielded a higher percentage and higher absolute number of high-risk patients. Engagement of the local GPs in recalling and following up these patients generated greater patient involvement in the screening process. We propose a two-stage process where at risk patients are identified from LDL results on the pathology database/interpretive commenting, and then flagged for formal assessment of FH by their GP or their primary care nurse. This study supports the argument for pathology alerts as a cost-effective measure in the initial screening for FH cases illustrated by Bell et al [26]. GP's are central to both systematic and opportunistic FH screening strategies [6]. GP's can accurately assess the likelihood of FH in a PHC setting using the DLCNC [23].

An uncomplicated algorithm for detection and management of FH is available on the Australian Atherosclerosis Society website <http://www.athero.org.au/FH/calculator>, along with educational material for clinicians and patients, <http://www.athero.org.au/FH/index>. Such tools along with alerts from community pathology laboratories will help to increase awareness and are likely to increase awareness

and are likely to improve the detection and management of FH [27].

The study identified a gap in the use of cholesterol lowering medication in high-risk patients, with 30% not being on any lipid lowering medication at initial assessment. This adds further support to the value of population screening, over and above the identification of DNA +ve cases of FH. Identification of patients on sub-optimal lipid lowering therapy is an opportunity for improving the care of all patients regardless of the cause of their high cholesterol.

An important consequence of this study was the referral of new cases of high risk FH to lipid specialists for review and assessment. Not all patients identified as high risk accepted referral. Those that were assessed were either seen face to face or via telehealth videoconference. This was a new service to the region in which the study occurred. An assessment of the provision of these telehealth services is being conducted.

This study had a number of limitations. Using existing clinical services in a research context meant that research priorities were competing with day-to-day clinical care priorities. Despite our best efforts the capture rate of patients identified as high risk in the initial screening phase remained low. We were unable to test for systematic bias in patients responding to the research project over those that failed to respond. There is evidence that FH will be found in patients with lower LDL-C levels than the thresholds we used in our study. A lower LDL-C threshold would have created a much larger sample population to be assessed and was beyond the capacity of this project. There is potential for overlap between the screening methods as the cholesterol data used in the PLD method would have been repeated in some of the patient data in the GPD method. We tested for overlap of patients between the different methods and this was found to be low. General agreement amongst GPs and specialists in DLCNC scores, reported separately [23], is encouraging. However interventions to improve relatively low FH knowledge and awareness are still required [20].

Conclusion

This study shows that finding individuals with FH within the community and utilising existing primary care services is a viable strategy for the detection of FH. This study supports the development of an integrated screening program, combining use of pathology services, for example using interpretive commenting on lipid profiles, and the engagement of primary care practitioners in detection and management. Further work and research is required to develop GP education and clinical tools for FH detection in primary care and to determine the impact on the detection and management of FH. The project successfully employed telehealth services to bring specialist review to potential new cases of FH identified in a rural region of Western Australia. Further investigation of how best to integrate index case detection by the primary methods we recommend with cascade screening for FH is also warranted.

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