Pathology (February 2019) **51(2)**, pp. 213–221

LIPIDS AND CARDIOVASCULAR DISEASE

Improving the detection of familial hypercholesterolaemia

Nick S. R. Lan[1], Andrew C. Martin[2], Tom Brett[3], Gerald F. Watts[4,5], Damon A. Bell[4,5,6,7]

[1]*Department of Endocrinology and Diabetes, Fiona Stanley Hospital, Murdoch, WA, Australia;* [2]*Department of General Paediatrics, Perth Children's Hospital, Nedlands, WA, Australia;* [3]*Department of General Practice and Primary Health Care Research, School of Medicine, The University of Notre Dame Australia, Fremantle, WA, Australia;* [4]*Faculty of Health and Medical Sciences, School of Medicine, The University of Western Australia, Crawley, WA, Australia;* [5]*Department of Cardiology, Lipid Disorders Clinic, Cardiometabolic Service, Royal Perth Hospital, Perth, WA, Australia;* [6]*Department of Clinical Biochemistry, PathWest Laboratory Medicine, Royal Perth Hospital, Perth, WA, Australia;* [7]*Department of Clinical Biochemistry, Australian Clinical Laboratories, Perth, WA, Australia*

Summary

Familial hypercholesterolaemia (FH) is a dominantly inherited disorder of low-density lipoprotein (LDL) catabolism, which if untreated causes lifelong elevated LDL-cholesterol (LDL-c), accelerated atherosclerosis and premature cardiovascular disease. Recent evidence suggests the prevalence of heterozygous FH is ~1:220, making FH the most common autosomal dominant condition. Lowering LDL-c with statin and lifestyle therapy reduces the risk of cardiovascular events. Furthermore, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors significantly lower LDL-c in addition to statin therapy, and early outcome data suggest improved vascular outcomes with these agents in FH patients in addition to statins. However, the vast majority of people with FH still remain undiagnosed. The onus is on clinicians to identify kindreds with FH, as PCSK9 inhibitors, although expensive, are funded for patients with FH in Australia. Multiple strategies for detecting FH have been proposed. The detection of index cases can be achieved through applying electronic screening tools to general practice databases, universal screening of children during immunisation, and targeted screening of patients with premature cardiovascular disease. Advances in genomic technology have decreased costs of genetic testing, improved the understanding of the pathogenesis of FH and facilitated cascade screening. However, awareness of FH amongst clinicians and the general public still requires optimisation. This review outlines recent advances in FH detection, including emerging strategies and challenges for the next decade.

Key words: Familial hypercholesterolaemia; detection; diagnosis; genetic testing; screening; dyslipidaemia.

Received 7 September, revised 15 October, accepted 15 October 2018
Available online 19 December 2018

INTRODUCTION

Familial hypercholesterolaemia (FH) is the most common autosomal dominant condition.[1] It is characterised by markedly elevated low-density lipoprotein cholesterol (LDL-c) concentrations from birth secondary to reduced LDL catabolism, leading to accelerated atherosclerosis and premature cardiovascular disease if left untreated.[2,3] Recent evidence suggests the prevalence of heterozygous FH in the general population is ~1:220, as opposed to 1:500 previously quoted.[4–12] In certain ethnic groups and founder populations the prevalence is higher.[2] Homozygous or compound heterozygous FH manifests with severely elevated LDL-c (often >13 mmol/L) with vascular events often occurring in the late teens or early twenties.[13] It affects approximately 1:300,000 in the Netherlands.[7]

Individuals with untreated heterozygous FH have a prevalence of coronary heart disease of approximately 50% in men by age 50 years and 30% in women by age 60 years.[14,15] Recent Norwegian data found that the incidence of coronary heart disease was more than four times higher in people with FH.[16] However, lowering LDL-c with statin and lifestyle therapy effectively reduces cardiovascular risk in FH patients.[15,17–19] Furthermore, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can significantly lower LDL-c in addition to statin therapy, and can reduce cardiovascular events, thus adding a new dimension to FH management.[20]

Despite the importance of FH detection, the majority of people with FH remain undiagnosed worldwide.[4,21,22] Numerous international guidelines have been published to address this gap.[4,21,23–25] FH fulfils the World Health Organization (WHO) criteria for systematic screening and in the current era of genomic medicine, is recognised as a tier 1 genetic disorder by the Centers for Disease Control and Prevention (CDC).[26,27] A variety of strategies have been proposed for universal, targeted and opportunistic screening. However, the systematic detection of index cases (first individuals diagnosed with FH in a kindred) remains a major challenge. Furthermore, despite the autosomal dominant

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: https://doi.org/10.1016/j.pathol.2018.10.015

inheritance, cascade screening alone is not the sole solution for FH detection, as it has been estimated that to achieve detection rates in excess of 80% for FH, between 17% and 47% of cases need to be identified independent of cascade screening.[28] The purpose of this review is to build on the review published in *Pathology* in 2012 and describe recent advancements in the detection of FH.[29]

CLINICAL DIAGNOSIS

The diagnosis of FH can be made using criteria combining clinical features such as tendon xanthomata, arcus cornealis and xanthelasma, personal and family history of hypercholesterolaemia or premature cardiovascular disease, and LDL-c concentration. However, clinical signs are becoming less prevalent in FH patients as they have often been partially treated before the diagnosis is made.[30–32] Whilst physical stigmata are highly suggestive of FH, their absence does not exclude the diagnosis.[33] Features such as early tendon xanthomata can be subtle, and in Japan, ultrasonography has been used to detect Achilles tendon xanthomas.[34] In addition, there is a significant overlap in the LDL-c between people with and without FH, as depicted in Fig. 1.[35]

Commonly used tools for diagnosing FH include the Dutch Lipid Clinic Network Criteria (DLCNC), the Simon Broome Register criteria, the Make Early Diagnosis – Prevent Early Death (MED-PED) criteria, the Japanese criteria and the Canadian criteria.[4,36–38] However, there are no internationally agreed criteria for FH diagnosis, nor consensus on which criteria are superior, perhaps due to geographical differences in phenotype, care and service delivery.[12,39] As such, considerable heterogeneity exists in the application and performance of these criteria.[9,40–42] Even within the United States, the CASCADE-FH registry found a lack of uniformity in the use of criteria.[22] Chan *et al.* found only moderate concordance amongst the criteria, thus suggesting a need for standardisation.[43] Furthermore, there are issues with self-reported family history, and family history being unavailable.[44,45] The American Heart Association has proposed a simpler set of criteria to combat this.[46]

The DLCNC is currently the preferred tool in Australia.[47] The DLCNC assigns numerical values to each diagnostic criterion and the total score is stratified as 'definite', 'probable', 'possible' or 'unlikely' FH. This tool is not valid in children.

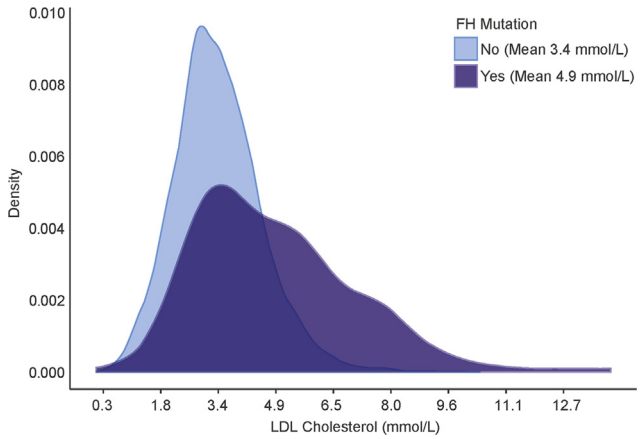

Fig. 1 The distribution of LDL-c values according to FH mutation status among the Myocardial Infarction Genetics Consortium studies, adapted from Khera *et al.*[35] and used with permission.

When FH is suspected, a fasting lipid profile should be performed and secondary causes of hypercholesterolaemia such as nephrotic syndrome, hypothyroidism, cholestasis and medications must be excluded. In addition, elevated lipoprotein(a) [Lp(a)], a genetically determined LDL-like particle, may mimic FH, as it is estimated in the LDL-c fraction by the Friedewald equation and is independently associated with cardiovascular events.[48,49] The presence of elevated Lp(a) in FH significantly increases the risk of cardiovascular disease and its measurement should be considered, as elevated Lp(a) is a biochemical mimic of FH, but without the physical stigmata.[48,50,51]

GENETIC TESTING

Genetic confirmation may be regarded as the gold standard for FH diagnosis, although there has been debate over the utility of FH genetic testing. A recent international consensus panel has endorsed FH genetic testing as the standard of care for patients with probable/definite FH.[12] Owing to the heterogeneous nature of the clinical phenotype, and difficulties classifying some genetic variants, it is paramount that genetic testing occurs alongside clinical/phenotypic assessment.[12] Genetic testing can confirm the diagnosis of FH, facilitate cascade screening, aid cardiovascular risk assessment, guide treatment and may improve medication compliance.[12,35,44,52–54] It is acceptable to patients, does not cause anxiety and is cost-effective.[55–59] The results of genetic testing and subsequent risk must be communicated to patients to improve understanding and management of hypercholesterolaemia.[60] However, it is important to consider both the clinical and genetic heterogeneity and other coexisting variables when treating a person with FH, as depicted in Fig. 2.[12]

Genetic mutations

FH is most commonly caused by mutations in the LDL receptor (*LDLR*) gene, resulting in defective LDLR function and thereby reducing the clearance of LDL-c particles from plasma.[3] Over 90% of pathogenic variants are in the *LDLR* gene, with over 2000 pathogenic or likely pathogenic variants reported in ClinVar.[2,3,61] Less commonly seen are variants in the apolipoprotein B-100 (*APOB*) and *PCSK9* genes, and other very rare mutations (e.g., *STAP1*).[2,3,62] Moreover, a very rare recessive form of FH is caused by mutations in the low-density lipoprotein adaptor protein 1 (*LDLRAP1*) gene.[3]

Advancements in genetic testing have led to the identification of novel gene mutations in FH, and have improved the diagnosis of other genetic causes of hypercholesterolaemia.[63–66] Next generation sequencing can rapidly sequence the entire genome, exomes and/or targeted genes.[63,67] It is more sensitive, specific and cheaper than conventional sequencing techniques for FH detection.[68–70] Furthermore, copy number variants can be detected by next generation sequencing and many laboratories are now using this powerful tool.[65,71] Raising public awareness of genomics is important, as genetic testing remains under-used in FH.[12,22]

However, pathogenic variants are only found in 60–80% of phenotypically definite FH and 20–30% of probable FH, which is likely multifactorial, but significantly affected by the lack of specificity of the clinical diagnostic criteria.[72–74] Importantly, the presence of a pathogenic variant is independently predictive of cardiovascular disease and is associated with a higher cumulative exposure to LDL-c.[35] To

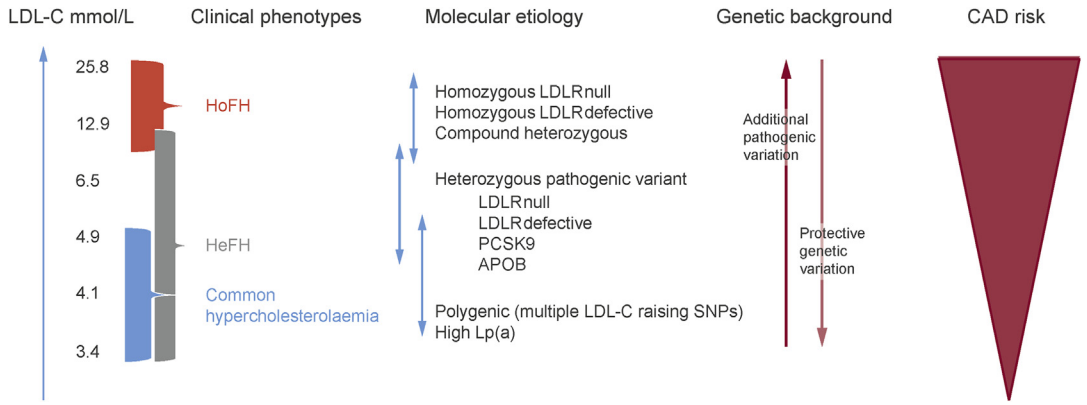

Fig. 2 The phenotypic spectrum and molecular aetiology of FH, adapted from Sturm *et al.*[12] and used with permission.

improve cost-effectiveness of FH genetic cascade screening, methods identifying individuals at highest risk of having a mutation have been developed. For example, Besseling *et al.* developed an online model using data from the Dutch FH cascade screening service, whilst Haralambos *et al.* developed a modified DLCNC in Wales.[75,76] In addition, coronary artery calcium score or carotid intima-media thickness may be useful in deciding whether cases of possible FH require genetic testing.[41] Furthermore, an apolipoprotein B/apolipoprotein AI ratio >0.82 may be predictive of an FH mutation in children.[77] However, these methods require further validation in different clinical settings.

Polygenic hypercholesterolaemia

Polygenic hypercholesterolaemia is a common cause of phenotypic FH, where no mutation is identified, and is increasingly being recognised as an FH mimic.[78,79] Polygenic hypercholesterolaemia is caused by multiple LDL-c raising single nucleotide polymorphisms (SNPs), with each causing incremental increases in LDL-c.[72,79] This condition is associated with less preclinical atherosclerosis compared to treated FH, as demonstrated by Sharifi *et al.* using non-invasive imaging.[80]

LDL-c specific genetic risk scores based on the number of SNPs have been used to distinguish between polygenic and monogenic hypercholesterolaemia.[78,79,81] Futema *et al.* demonstrated discriminatory ability using a 6 SNP score whilst Sjouke *et al.* demonstrated that use of such scores in children appears limited.[78,81] Future research should aim to determine the utility of genetic risk scores in FH detection and address issues relating to communication of risk based on genetic information to patients.[82] The impact of concomitant polygenic hypercholesterolaemia and elevated Lp(a) in a patient with monogenic FH remains to be elucidated.

Interpretation of variants

An on-going challenge in genomics is the identification of variants that may not have functional consequences.[65] The wide range of LDL-c concentrations in FH and the lack of standardised diagnostic criteria complicate the assessment.[35,83,84] Guidelines can aid in interpreting whether genetic variants are 'pathogenic', 'likely pathogenic', 'uncertain significance', 'likely benign' or 'benign'.[85] Chora *et al.* classified all known FH variants and found approximately 40% require functional evidence to be considered disease-causing mutations.[86] However, Bourbon *et al.* demonstrated that 88% of variants in people with a genetic diagnosis of FH are pathogenic or likely pathogenic.[87] Interpretation of pathogenicity will evolve as laboratories worldwide contribute to online genomic databases such as ClinVar.

SCREENING IN PRIMARY CARE

Primary care is an area with unique, un-tapped potential to help improve FH detection and management.[4,88] FH detection rates remain low in primary care, despite evidence that FH is more prevalent than once thought.[5,8] For a practice population of 15,000, approximately 60 would have FH. Unfortunately, only five or six are diagnosed and are often suboptimally managed.[89–91]

Public awareness of FH and its inherited nature remains low despite FH being as common as type 1 diabetes and ten times more common than cystic fibrosis.[89,92] However, education of the general public at a community event in the United States found that people are generally receptive towards testing.[93] After cholesterol screening in almost 1,000 people at the event, five cases of possible FH were found.[93] Difficulties surrounding communication of genetic testing to relatives was the main concern identified. Thus, educational resources for the public are important, and in Australia, the FH Australasian Network has resources available.

Whilst primary care is ideal for early recognition of FH, this regrettably has not occurred.[94] Awareness and knowledge of FH remain suboptimal even amongst physicians.[95,96] Multi-morbidity is common and time is often spent managing complex, undifferentiated presentations.[97,98] Serious hereditary conditions such as FH occur infrequently compared to tertiary care.[90] However, primary care physicians request over 90% of LDL-c measurements, highlighting the need for FH recognition.[99]

Recent initiatives in the United Kingdom and Australia have improved primary care contribution.[89,100–102] The National Institute for Health and Clinical Excellence (NICE) guidelines were updated in 2017 to address this need.[33] Physicians are advised to suspect FH in adults with total cholesterol >7.5 mmol/L, especially if there is family or personal history of premature coronary heart disease.[33] Weng *et al.* showed that simple interventions delivered in primary care practices, such as educational sessions on the NICE guidelines and computer-based messages when total cholesterol is >7.5 mmol/L, improve FH detection.[103]

Opportunistic screening for FH can potentially be incorporated into wellness checks, unrelated presentations or workplace screening. Chronic disease care plans offer incentive of financial reward to practices to optimise management of life-long conditions.[104] The sustainability of this approach should be enhanced due to funding.

Electronic screening tools can detect FH by searching patient databases and registries.[88,105] The recent approval of International Classification of Diseases (ICD) diagnostic codes for FH may improve case-detection in electronic records. FH diagnostic criteria can be applied to patient records and its prevalence can be estimated, as demonstrated by Casula *et al.*[88] Other examples of screening tools for detecting FH include FAMCAT and TARB-Ex.[100,101]

FAMCAT is a case ascertainment tool that identifies patients using coded variables to enhance the discriminatory information contained in medical records.[100] TARB-Ex extracts information from electronic records using the DLCNC.[101] TARB-Ex minimises extraction costs because of its high sensitivity, specificity and negative predictive power.[101] However, success is dependent on the quality of information in databases, where family histories are often poorly recorded.[89,90,92]

A sustainable early detection approach embedded in primary care is essential. FAMCAT and TARB-Ex build on earlier, less time-efficient electronic screening approaches.[106,107] Both approaches have shown potential, with TARB-Ex's 10 minutes for electronic data extraction showing much greater efficiency compared to 60 hours or more using a manual approach.[101] However, FAMCAT and TARB-Ex rely on clinical expertise once high-risk patients are identified. Patients not meeting phenotypic diagnosis are then excluded from further testing.

A close relationship with cardio-metabolic or lipid specialists is ideal to augment a shared-care approach. The potential role for specialist nurses and pharmacists to detect FH in the community requires further research.[108,109] Multidisciplinary collaboration is emphasised in several published models of FH care, in which primary care plays a crucial role.[4,21,23,24,110]

SCREENING IN PAEDIATRIC CARE

A consensus paper that seeks to encourage earlier detection and management of FH has called for a paradigm shift in how the condition is perceived in children and adolescents.[24] The diagnosis of FH in children usually follows cascade testing.[110,111] Children over 5 years of age should be offered testing when a parent or close relative in absence of a parent is diagnosed with FH.[24] A non-fasting lipid profile is sufficient as a first screening test. However, fasting LDL-c should be measured at least twice over 3 months to establish the diagnosis of FH in children.[110]

Total cholesterol or LDL-c measured between 1 and 9 years of age provides optimal phenotypic discrimination between children with and without FH.[112] However, the detection of a pathogenic mutation remains the gold standard for FH diagnosis in children. Early treatment with statins is recommended from 8–10 years of age to reduce the lifetime burden of LDL-c and the progressive development of atherosclerosis.[24] Individuals with FH who are treated from a young age can expect a normal life expectancy.[24] However, the safety of long-term lipid-lowering treatment from childhood remains unknown.[113]

The efficacy of FH screening in paediatric settings has been of increasing interest. Universal screening of children aged 5 years in Slovenia between 2009 and 2013 identified 272 children at high-risk of FH based on total cholesterol and family history.[114] Subsequent genetic testing found that 57% had FH-causing mutations.[114] The authors postulated that combined with cascade screening, universal screening of children would become a powerful approach for FH detection.[114]

The efficacy and feasibility of child-parent screening has been demonstrated by Wald *et al.*[10,115] More than 10,000 children aged 1–2 years had a total cholesterol level measured using point-of-care heel-prick blood testing during immunisation, with subsequent genetic testing.[10] For each child identified with FH using this opportunistic, universal screening strategy, the affected parent was identified using a systematic, selective screening strategy so-called 'reverse cascade testing'. Using the 95th percentile for total cholesterol plus an FH mutation, or two cholesterol levels $\geq$99th percentile, 40 children and 40 parents with FH were identified.[10] However, this is likely to be an underestimate, as only a dedicated panel of 48 genetic mutations was tested for.[10]

Futema *et al.* evaluated Wald's child-parent screening strategy in the Avon Longitudinal Study of Parents and Children.[116] A two-stage model was used which included total cholesterol followed by next generation sequencing of FH genes for all screen positive samples.[116] A total cholesterol cut-off using the 99th percentile resulted in a similar FH detection rate of 83% and a false-positive rate of 0.8%.[116] The authors proposed that including a next generation sequencing step for all screen positive samples would eliminate false positive cases.[116]

Identifying FH in parents and relatives significantly improves the cost-effectiveness of childhood screening programs. The ability to identify eight new individuals with FH for every 1,000 children screened is favourable compared with other commonly screened conditions in the newborn period such as congenital hypothyroidism (1:3,500) and cystic fibrosis (1:2,500). Furthermore, by undertaking screening at the time of scheduled immunisation, costs are reduced and the acceptability by families is greater compared to stand-alone screening programs.

The cost-effectiveness of universal FH screening in children has been assessed by McKay *et al.*[117] The study utilised decision analytic modelling to compare costs and consequences of seven cholesterol and/or mutation based universal screening ± reverse cascade testing alternatives against no universal screening.[117] It was assumed that two mutation-positive individuals would be identified via reverse cascade screening for every mutation-positive individual identified in universal screening.[117] Applying cholesterol screening followed by diagnostic genetic testing plus reverse cascade screening was the most cost-effective alternative compared to no universal screening.[117]

Wald *et al.* have established that childhood universal screening for FH with reverse cascade testing appears feasible.[10] This approach appears to be acceptable to the general population and cost-effective.[117,118] However, additional research needs to be undertaken, including replication

studies, studies of where services should be embedded (e.g., primary care, cardiology or paediatrics), the logistics of follow-up and management of caseloads. Nevertheless, child-parent screening has the potential to change the natural history of FH, where all members of a given population can be identified and offered treatment before suffering adverse health outcomes.

SCREENING IN CORONARY CARE

Current guidelines recommend patients presenting with premature cardiovascular disease, primarily coronary heart disease, should be routinely screened for FH.[21] Cardiologists can play a crucial role in the detection and management of FH, as many patients are unaware of their condition and may present with an acute coronary syndrome or with recurrent events.[47,119] Estimates of FH prevalence in cardiology units vary considerably.[120–125] In patients with premature coronary heart disease, studies have quoted up to a 14.3–15.4% prevalence of probable/definite FH in coronary care units.[124,126] A more recent study in patients aged less than 65 years with LDL-c $\geq$4.1 mmol/L quoted a 27.2% prevalence of probable/definite FH and a 9% prevalence of genetically confirmed FH.[127] Nonetheless, FH appears to be relatively common amongst this cohort and targeted screening would be of higher yield.

However, there are currently no systematic screening strategies for FH that are widely employed in coronary care. There is also a relative paucity of studies examining methods aimed at improving FH detection in this cohort. Screening should be encouraged as it can be easily performed during hospital admission, cardiac catheterisation procedures or cardiac rehabilitation.[47,121]

Targeted screening may be extended to patients with premature cardiovascular disease in stroke, vascular surgery and cardiothoracic surgery units. A recent study found that 3.1% of patients admitted with premature ischaemic stroke or transient ischaemic attack had probable/definite FH.[128] The SAFEHEART registry found an increased prevalence of peripheral arterial disease in people with FH, and in a separate study, the odds of peripheral arterial disease in FH were 5.6 times that of normo-lipidaemic controls.[129,130] Similar to primary care, databases of patients can be used for screening. Application of an algorithm to a cardiac catheterisation database by Zafrir *et al.* identified 54 people with severe FH, as well as 161 relatives.[131]

However, in tertiary care FH remains under-recognised and poorly understood.[119,120] A survey in cardiologists performed by the American College of Cardiology suggests a need for increased awareness.[119] Multiple studies have found that FH is frequently not considered in patients with premature cardiovascular disease, with as many as 28–54% in cardiology units not having cholesterol recorded.[120,132,133] Documentation of family history and/or the presence/absence of physical stigmata is often scarce.[120,133] Simplified tools based on FH diagnostic criteria for use in the hospital setting have been proposed.[124,133] Hospital-based screening programs may also be useful.[134] Furthermore, widespread education to increase awareness will likely reduce the number of missed cases.[119,135]

The occurrence of a coronary event in a young family member may increase willingness of relatives to be tested for FH.[21] Cardiologists are in an ideal position to refer patients and relatives for genetic testing.[47] Furthermore, cardiologists are well placed in integrating care and improving multidisciplinary awareness of cardiovascular disease prevention by collaborating with primary care physicians, geneticists, pathologists and lipid specialists.[47] Incorporating preventative cardiology and cardiovascular genetics into training programs may enable future cardiologists to close the gap.[136]

SCREENING BY CLINICAL BIOCHEMISTRY LABORATORIES

Clinical biochemistry laboratories are ideally placed to augment the opportunistic detection of FH.[99] Primary care physicians request the majority of lipid profiles in community laboratories and prefer interpretative comments on lipid profiles to highlight if a patient is at risk of FH.[95] Research has shown that interpretative comments, especially with specific recommendations, can significantly improve the detection of people with FH.[137,138] These were the first controlled studies to demonstrate the effectiveness of interpretative commenting from the laboratory, and open the field for further optimisation of laboratory to clinician interactions in other disorders. Collaborations between the laboratory, primary care and hospital specialists recommend appending interpretative comments to augment FH detection, although these have not yet been universally applied in Australia.[94]

Furthermore, if a laboratory has access to an expert computer system this may further optimise detection of FH by incorporating information provided on request forms and previous laboratory results.[139] Closer interaction between primary care and laboratory software may further optimise this. Currently, the FH Network of the Australasian Atherosclerosis Society has a website with an interactive DLCNC calculator which provides recommendations based on the DLCNC score and a list of clinicians with expertise in FH management to assist primary care clinicians in detecting FH (https://www.athero.org.au/fh/calculator/). However, research is required to determine the impact that interaction with websites has in practice. Furthermore, the impact of the hospital laboratory in augmenting FH detection for inpatients also requires investigation, as does the potential interaction with electronic health records held by the patients themselves.

CASCADE SCREENING

Cascade screening is the systematic process of identifying, contacting and screening close relatives of individuals affected by a genetic condition.[140] Once FH is confirmed in an index case, cascade screening should be offered using phenotypic plus genotypic approaches where available.[4,23,33] The identification of a pathogenic mutation facilitates genetic cascade screening.[141] Many ethical factors need to be considered and consent must be obtained. All individuals involved must be adequately informed on the implications of undergoing testing.

An index case's siblings, children and parents will have a 50% chance of having FH, as it is autosomal dominantly inherited.[2,3] For every index case, 2–8 new cases are identified using cascade screening, many of whom are younger with less cardiovascular disease, thus providing an opportunity for primary prevention.[54,55,142] Cascade screening programs utilising genetic testing have consistently been shown to be feasible and cost-effective in many

countries.[54,56,59,142–146] This is reinforced by the decreasing costs of genetic testing and off-patent statins.[145]

However, despite aspirations to screen relatives, rates of cascade screening are low, and only in countries with systematic approaches to cascade screening has this approach met high levels of success.[12,54,147] Once dedicated funding to achieve high levels of FH detection is withdrawn, success rates rapidly fall to much lower levels.[148] To sustain cascade screening, the implementation of infrastructure and support will need to be family-centric and coordinated by existing lipid clinics and genetic services. Furthermore, advocacy for raising awareness of cascade screening methodology amongst clinicians and patients, and to identify strategies that target systematic barriers is needed.[149] The optimisation of family notification and risk communication is also required.[150]

The implementation of cascade screening at a population level requires significant resources.[94] Although, cascade screening will be a fundamental component of all methods that detect FH index cases.[10,115]

CONCLUSION

FH is the most common autosomal dominant disorder, with strong evidence that early detection and treatment effectively reduces cardiovascular events. However, the vast majority of people with FH remain undiagnosed, and there is an urgent global need for increased awareness and recognition of FH, perhaps aided through standardised diagnostic criteria. Furthermore, the onus is on clinicians to identify kindreds with FH, as they will likely benefit from PCSK9 inhibitors, and while expensive, are funded for FH patients. Advances in genomics have increased both the specificity and cost-effectiveness of FH diagnosis, and have culminated in a very recent international consensus on the central role of genetic testing in the diagnosis and management of FH. However, despite these advances, strategies to improve the detection of index cases, even in high-risk settings, remain suboptimal. Formulation and implementation of multiple strategies to improve the detection of FH are likely to be required to optimise the care of kindreds with FH.

Conflicts of interest and sources of funding: Nick S. R. Lan is supported by a Sanofi Clinical Fellowship in Endocrinology and Diabetes. Sanofi did not have any role in writing this manuscript or the decision to submit it for publication. Andrew Martin is supported by a Raine Foundation Clinician Research Fellowship. The authors state that there are no conflicts of interest to disclose.

Address for correspondence: Damon A. Bell, Department of Clinical Biochemistry, PathWest Laboratory Medicine, Royal Perth Hospital, Perth, WA, Australia. E-mail: Damon.Bell@health.wa.gov.au

References

1. Vallejo-Vaz AJ, Kondapally Seshasai SR, Cole D, *et al*. Familial hypercholesterolaemia: a global call to arms. *Atherosclerosis* 2015; 243: 257–9.
2. Austin MA, Hutter CM, Zimmern RL, *et al*. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *Am J Epidemiol* 2004; 160: 407–20.
3. Soutar AK, Naoumova RP. Mechanisms of disease: genetic causes of familial hypercholesterolemia. *Nat Clin Pract Cardiovasc Med* 2007; 4: 214–25.
4. Nordestgaard BG, Chapman MJ, Humphries SE, *et al*. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013; 34: 3478–3490a.
5. Watts GF, Shaw JE, Pang J, *et al*. Prevalence and treatment of familial hypercholesterolaemia in Australian communities. *Int J Cardiol* 2015; 185: 69–71.
6. de Ferranti SD, Rodday AM, Mendelson MM, *et al*. Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation* 2016; 133: 1067–72.
7. Sjouke B, Kusters DM, Kindt I, *et al*. Homozygous autosomal dominant hypercholesterolaemia in The Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. *Eur Heart J* 2015; 36: 560–5.
8. Benn M, Watts GF, Tybjaerg-Hansen A, *et al*. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. *J Clin Endocrinol Metab* 2012; 97: 3956–64.
9. Benn M, Watts GF, Tybjaerg-Hansen A, *et al*. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. *Eur Heart J* 2016; 37: 1384–94.
10. Wald DS, Bestwick JP, Morris JK, *et al*. Child-parent familial hypercholesterolemia screening in primary care. *N Engl J Med* 2016; 375: 1628–37.
11. Abul-Husn NS, Manickam K, Jones LK, *et al*. Genetic identification of familial hypercholesterolemia within a single US health care system. *Science* 2016; 354.
12. Sturm AC, Knowles JW, Gidding SS, *et al*. Clinical genetic testing for familial hypercholesterolemia: JACC Scientific Expert Panel. *J Am Coll Cardiol* 2018; 72: 662–80.
13. Raal FJ, Sjouke B, Hovingh GK, *et al*. Phenotype diversity among patients with homozygous familial hypercholesterolemia: a cohort study. *Atherosclerosis* 2016; 248: 238–44.
14. Neil HA, Seagroatt V, Betteridge DJ, *et al*. Established and emerging coronary risk factors in patients with heterozygous familial hypercholesterolaemia. *Heart* 2004; 90: 1431–7.
15. Marks D, Thorogood M, Neil HA, *et al*. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis* 2003; 168: 1–14.
16. Mundal LJ, Igland J, Veierod MB, *et al*. Impact of age on excess risk of coronary heart disease in patients with familial hypercholesterolaemia. *Heart* 2018; 104: 1600–7.
17. Versmissen J, Oosterveer DM, Yazdanpanah M, *et al*. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* 2008; 337: a2423.
18. 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: 2625–33.
19. Vallejo-Vaz AJ, Robertson M, Catapano AL, *et al*. Low-density lipoprotein cholesterol lowering for the primary prevention of cardiovascular disease among men with primary elevations of low-density lipoprotein cholesterol levels of 190 mg/dl or above: analyses from the WOSCOPS (West of Scotland Coronary Prevention Study) 5-year randomized trial and 20-year observational follow-up. *Circulation* 2017; 136: 1878–91.
20. Ridker PM, Rose LM, Kastelein JJP, *et al*. Cardiovascular event reduction with PCSK9 inhibition among 1578 patients with familial hypercholesterolemia: results from the SPIRE randomized trials of bococizumab. *J Clin Lipidol* 2018; 12: 958–65.
21. Watts GF, Gidding S, Wierzbicki AS, *et al*. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. *Int J Cardiol* 2014; 171: 309–25.
22. deGoma EM, Ahmad ZS, O'Brien EC, *et al*. Treatment gaps in adults with heterozygous familial hypercholesterolemia in the United States: data from the CASCADE-FH registry. *Circ Cardiovasc Genet* 2016; 9: 240–9.
23. 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: S1–8.
24. Wiegman A, Gidding SS, Watts GF, *et al*. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J* 2015; 36: 2425–37.
25. Harada-Shiba M, Arai H, Ishigaki Y, *et al*. Guidelines for diagnosis and treatment of familial hypercholesterolemia 2017. *J Atheroscler Thromb* 2018; 25: 751–70.

26. Andermann A, Blancquaert I, Beauchamp S, *et al*. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull World Health Organ* 2008; 86: 317–9.
27. CDC Office of Public Health Genomics. Genomic tests by level of evidence. 15 Apr 2013; cited 18 Aug 2018. https://www.cdc.gov/genomics/gtesting/file/print/tier.pdf
28. Morris JK, Wald DS, Wald NJ. The evaluation of cascade testing for familial hypercholesterolemia. *Am J Med Genet A* 2012; 158a: 78–84.
29. Bender R, Bell DA, Hooper AJ, *et al*. Screening for familial hypercholesterolaemia. *Pathology* 2012; 44: 122–8.
30. Kindt I, Mata P, Knowles JW. The role of registries and genetic databases in familial hypercholesterolemia. *Curr Opin Lipidol* 2017; 28: 152–60.
31. Perez de Isla L, Alonso R, Watts GF, *et al*. Attainment of LDL-cholesterol treatment goals in patients with familial hypercholesterolemia: 5-year SAFEHEART registry follow-up. *J Am Coll Cardiol* 2016; 67: 1278–85.
32. Perez de Isla L, Alonso R, Mata N, *et al*. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation* 2017; 135: 2133–44.
33. National Institute for Health and Care Excellence (NICE). *Identification and Management of Familial Hypercholesterolaemia. NICE Clinical Guideline Addendum CG71*. London: NICE, 2017.
34. Michikura M, Ogura M, Yamamoto M, *et al*. Achilles tendon ultrasonography for diagnosis of familial hypercholesterolemia among Japanese subjects. *Circ J* 2017; 81: 1879–85.
35. Khera AV, Won HH, Peloso GM, *et al*. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol* 2016; 67: 2578–89.
36. Wierzbicki AS, Humphries SE, Minhas R. Familial hypercholesterolaemia: summary of NICE guidance. *BMJ* 2008; 337: a1095.
37. 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: 171–6.
38. Ruel I, Brisson D, Aljenedil S, *et al*. Simplified Canadian definition for familial hypercholesterolemia. *Can J Cardiol* 2018; 34: 1210–4.
39. Bell DA, Watts GF. Progress in the care of familial hypercholesterolaemia: 2016. *Med J Aust* 2016; 205: 232–6.
40. Ahmad ZS, Andersen RL, Andersen LH, *et al*. US physician practices for diagnosing familial hypercholesterolemia: data from the CASCADE-FH registry. *J Clin Lipidol* 2016; 10: 1223–9.
41. Clarke RE, Padayachee ST, Preston R, *et al*. Effectiveness of alternative strategies to define index case phenotypes to aid genetic diagnosis of familial hypercholesterolaemia. *Heart* 2013; 99: 175–80.
42. 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: 155–60.
43. Chan DC, Pang J, Hooper AJ, *et al*. A comparative analysis of phenotypic predictors of mutations in familial hypercholesterolemia. *J Clin Endocrinol Metab* 2018; 103: 1704–14.
44. Leren TP, Finborud TH, Manshaus TE, *et al*. Diagnosis of familial hypercholesterolemia in general practice using clinical diagnostic criteria or genetic testing as part of cascade genetic screening. *Commun Genet* 2008; 11: 26–35.
45. Neal WA, Knowles J, Wilemon K. Underutilization of cascade screening for familial hypercholesterolemia. *Clin Lipidol* 2014; 9: 291–3.
46. Gidding SS, Champagne MA, de Ferranti SD, *et al*. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation* 2015; 132: 2167–92.
47. Watts GF, Sullivan DR, van Bockxmeer FM, *et al*. A new model of care for familial hypercholesterolaemia: what is the role of cardiology? *Heart Lung Circ* 2012; 21: 543–50.
48. Langsted A, Kamstrup PR, Benn M, *et al*. High lipoprotein(a) as a possible cause of clinical familial hypercholesterolaemia: a prospective cohort study. *Lancet Diabetes Endocrinol* 2016; 4: 577–87.
49. Ellis KL, Pang J, Chan DC, *et al*. Familial combined hyperlipidemia and hyperlipoprotein(a) as phenotypic mimics of familial hypercholesterolemia: frequencies, associations and predictions. *J Clin Lipidol* 2016; 10. 1329–1337.e3.
50. Li S, Wu NQ, Zhu CG, *et al*. Significance of lipoprotein(a) levels in familial hypercholesterolemia and coronary artery disease. *Atherosclerosis* 2017; 260: 67–74.
51. Alonso R, Andres E, Mata N, *et al*. Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation. *J Am Coll Cardiol* 2014; 63: 1982–9.
52. Tada H, Kawashiri MA, Nohara A, *et al*. Impact of clinical signs and genetic diagnosis of familial hypercholesterolaemia on the prevalence of coronary artery disease in patients with severe hypercholesterolaemia. *Eur Heart J* 2017; 38: 1573–9.
53. Ahmad Z, Li X, Wosik J, *et al*. Premature coronary heart disease and autosomal dominant hypercholesterolemia: increased risk in women with LDLR mutations. *J Clin Lipidol* 2016; 10. 101–8.e1-3.
54. 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: 165–8.
55. 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.
56. Nherera L, Marks D, Minhas R, *et al*. Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. *Heart* 2011; 97: 1175–81.
57. Jenkins N, Lawton J, Douglas M, *et al*. How do index patients participating in genetic screening programmes for familial hypercholesterolemia (FH) interpret their DNA results? A UK-based qualitative interview study. *Patient Educ Couns* 2013; 90: 372–7.
58. Hallowell N, Jenkins N, Douglas M, *et al*. A qualitative study of patients' perceptions of the value of molecular diagnosis for familial hypercholesterolemia (FH). *J Commun Genet* 2017; 8: 45–52.
59. Ademi Z, Watts GF, Juniper A, *et al*. A systematic review of economic evaluations of the detection and treatment of familial hypercholesterolemia. *Int J Cardiol* 2013; 167: 2391–6.
60. Jones LK, Rahm AK, Manickam K, *et al*. Healthcare utilization and patients' perspectives after receiving a positive genetic test for familial hypercholesterolemia: a pilot study. *Circ Genom Precis Med* 2018; 11: e002146.
61. Leigh S, Futema M, Whittall R, *et al*. The UCL low-density lipoprotein receptor gene variant database: pathogenicity update. *J Med Genet* 2017; 54: 217–23.
62. Fouchier SW, Dallinga-Thie GM, Meijers JC, *et al*. Mutations in STAP1 are associated with autosomal dominant hypercholesterolemia. *Circ Res* 2014; 115: 552–5.
63. Motazacker MM, Pirruccello J, Huijgen R, *et al*. Advances in genetics show the need for extending screening strategies for autosomal dominant hypercholesterolaemia. *Eur Heart J* 2012; 33: 1360–6.
64. Maglio C, Mancina RM, Motta BM, *et al*. Genetic diagnosis of familial hypercholesterolaemia by targeted next-generation sequencing. *J Intern Med* 2014; 276: 396–403.
65. Hooper AJ, Burnett JR, Bell DA, *et al*. The present and the future of genetic testing in familial hypercholesterolemia: opportunities and caveats. *Curr Atheroscler Rep* 2018; 20: 31.
66. Elbitar S, Susan-Resiga D, Ghaleb Y, *et al*. New sequencing technologies help revealing unexpected mutations in autosomal dominant hypercholesterolemia. *Sci Rep* 2018; 8: 1943.
67. Hegele RA, Ban MR, Cao H, *et al*. Targeted next-generation sequencing in monogenic dyslipidemias. *Curr Opin Lipidol* 2015; 26: 103–13.
68. Hinchcliffe M, Le H, Fimmel A, *et al*. Diagnostic validation of a familial hypercholesterolaemia cohort provides a model for using targeted next generation DNA sequencing in the clinical setting. *Pathology* 2014; 46: 60–8.
69. Vandrovcova J, Thomas ER, Atanur SS, *et al*. The use of next-generation sequencing in clinical diagnosis of familial hypercholesterolemia. *Genet Med* 2013; 15: 948–57.
70. Norsworthy PJ, Vandrovcova J, Thomas ER, *et al*. Targeted genetic testing for familial hypercholesterolaemia using next generation sequencing: a population-based study. *BMC Med Genet* 2014; 15: 70.
71. Iacocca MA, Hegele RA. Role of DNA copy number variation in dyslipidemias. *Curr Opin Lipidol* 2018; 29: 125–32.
72. Futema M, Whittall RA, Kiley A, *et al*. Analysis of the frequency and spectrum of mutations recognised to cause familial hypercholesterolaemia in routine clinical practice in a UK specialist hospital lipid clinic. *Atherosclerosis* 2013; 229: 161–8.
73. Hooper AJ, Nguyen LT, Burnett JR, *et al*. Genetic analysis of familial hypercholesterolaemia in Western Australia. *Atherosclerosis* 2012; 224: 430–4.
74. 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: 572–80.
75. Besseling J, Reitsma JB, Gaudet D, *et al*. Selection of individuals for genetic testing for familial hypercholesterolaemia: development and external validation of a prediction model for the presence of a mutation causing familial hypercholesterolaemia. *Eur Heart J* 2017; 38: 565–73.
76. Haralambos K, Whatley SD, Edwards R, *et al*. Clinical experience of scoring criteria for Familial Hypercholesterolaemia (FH) genetic testing in Wales. *Atherosclerosis* 2015; 240: 190–6.
77. Plana N, Rodriguez-Borjabad C, Ibarretxe D, *et al*. Lipid and lipoprotein parameters for detection of familial hypercholesterolemia in

childhood. The DECOPIN Project. *Clin Investig Arterioscler* 2018; 30: 170–8.
78. Futema M, Shah S, Cooper JA, *et al*. Refinement of variant selection for the LDL cholesterol genetic risk score in the diagnosis of the polygenic form of clinical familial hypercholesterolemia and replication in samples from 6 countries. *Clin Chem* 2015; 61: 231–8.
79. 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: 1293–301.
80. Sharifi M, Higginson E, Bos S, *et al*. Greater preclinical atherosclerosis in treated monogenic familial hypercholesterolemia vs. polygenic hypercholesterolemia. *Atherosclerosis* 2017; 263: 405–11.
81. Sjouke B, Tanck MWT, Fouchier SW, *et al*. Children with hypercholesterolemia of unknown cause: value of genetic risk scores. *J Clin Lipidol* 2016; 10: 851–9.
82. Khera AV, Chaffin M, Aragam KG, *et al*. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* 2018; 50: 1219–24.
83. Haralambos K, Ashfield-Watt P, McDowell IF. Diagnostic scoring for familial hypercholesterolaemia in practice. *Curr Opin Lipidol* 2016; 27: 367–74.
84. Huijgen R, Hutten BA, Kindt I, *et al*. Discriminative ability of LDL-cholesterol to identify patients with familial hypercholesterolemia: a cross-sectional study in 26,406 individuals tested for genetic FH. *Circ Cardiovasc Genet* 2012; 5: 354–9.
85. Richards S, Aziz N, Bale S, *et al*. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; 17: 405–24.
86. Chora JR, Medeiros AM, Alves AC, *et al*. Analysis of publicly available LDLR, APOB, and PCSK9 variants associated with familial hypercholesterolemia: application of ACMG guidelines and implications for familial hypercholesterolemia diagnosis. *Genet Med* 2018; 20: 591–8.
87. Bourbon M, Alves AC, Alonso R, *et al*. Mutational analysis and genotype-phenotype relation in familial hypercholesterolemia: the SAFEHEART registry. *Atherosclerosis* 2017; 262: 8–13.
88. Casula M, Catapano AL, Rossi Bernardi L, *et al*. Detection of familial hypercholesterolemia in patients from a general practice database. *Atheroscler Suppl* 2017; 29: 25–30.
89. Qureshi N, Humphries SE, Seed M, *et al*. Identification and management of familial hypercholesterolaemia: what does it mean to primary care? *Br J Gen Pract* 2009; 59: 773–6.
90. Brett T, Watts GF, Arnold-Reed DE, *et al*. Challenges in the care of familial hypercholesterolemia: a community care perspective. *Expert Rev Cardiovasc Ther* 2015; 13: 1091–100.
91. Hollman G, Olsson AG, Ek AC. Disease knowledge and adherence to treatment in patients with familial hypercholesterolemia. *J Cardiovasc Nurs* 2006; 21: 103–8.
92. Watts GF, Sullivan DR, Poplawski N, *et al*. Familial hypercholesterolaemia: a model of care for Australasia. *Atheroscler Suppl* 2011; 12: 221–63.
93. Campbell M, Humanki J, Zierhut H. A novel approach to screening for familial hypercholesterolemia in a large public venue. *J Community Genet* 2017; 8: 35–44.
94. Vickery AW, Bell D, Garton-Smith J, *et al*. Optimising the detection and management of familial hypercholesterolaemia: central role of primary care and its integration with specialist services. *Heart Lung Circ* 2014; 23: 1158–64.
95. Bell DA, Garton-Smith J, Vickery A, *et al*. Familial hypercholesterolaemia in primary care: knowledge and practices among general practitioners in Western Australia. *Heart Lung Circ* 2014; 23: 309–13.
96. Pang J, Sullivan DR, Harada-Shiba M, *et al*. Significant gaps in awareness of familial hypercholesterolemia among physicians in selected Asia-Pacific countries: a pilot study. *J Clin Lipidol* 2015; 9: 42–8.
97. Brett T, Arnold-Reed DE, Popescu A, *et al*. Multimorbidity in patients attending 2 Australian primary care practices. *Ann Fam Med* 2013; 11: 535–42.
98. Valderas JM, Mercer SW, Fortin M. Research on patients with multiple health conditions: different constructs, different views, one voice. *J Comorb* 2011; 1: 1–3.
99. Bell DA, Hooper AJ, Bender R, *et al*. Opportunistic screening for familial hypercholesterolaemia via a community laboratory. *Ann Clin Biochem* 2012; 49: 534–7.
100. Weng SF, Kai J, Andrew Neil H, *et al*. Improving identification of familial hypercholesterolaemia in primary care: derivation and validation of the familial hypercholesterolaemia case ascertainment tool (FAMCAT). *Atherosclerosis* 2015; 238: 336–43.
101. Troeung L, Arnold-Reed D, Chan She Ping-Delfos W, *et al*. A new electronic screening tool for identifying risk of familial hypercholesterolaemia in general practice. *Heart* 2016; 102: 855–61.
102. Arnold-Reed DE, Brett T, Troeung L, *et al*. Detection and management of familial hypercholesterolaemia in primary care in Australia: protocol for a pragmatic cluster intervention study with pre-post intervention comparisons. *BMJ Open* 2017; 7: e017539.
103. Weng S, Kai J, Tranter J, *et al*. Improving identification and management of familial hypercholesterolaemia in primary care: pre- and post-intervention study. *Atherosclerosis* 2018; 274: 54–60.
104. Harris MF, Zwar NA. Care of patients with chronic disease: the challenge for general practice. *Med J Aust* 2007; 187: 104–7.
105. Safarova MS, Liu H, Kullo IJ. Rapid identification of familial hypercholesterolemia from electronic health records: the SEARCH study. *J Clin Lipidol* 2016; 10: 1230–9.
106. Gray J, Jaiyeola A, Whiting M, *et al*. Identifying patients with familial hypercholesterolaemia in primary care: an informatics-based approach in one primary care centre. *Heart* 2008; 94: 754–8.
107. Kirke AB, Barbour RA, Burrows S, *et al*. Systematic detection of familial hypercholesterolaemia in primary health care: a community based prospective study of three methods. *Heart Lung Circ* 2015; 24: 250–6.
108. Green P, Neely D, Humphries SE. Improving detection of familial hypercholesterolaemia in primary care using electronic audit and nurse-led clinics. *J Eval Clin Pract* 2016; 22: 341–8.
109. Krass I, Walker AT, Watts GF. Detection and care of familial hypercholesterolaemia in the community: is there a role for the pharmacist? *Int J Clin Pharm* 2012; 34: 501–5.
110. Martin AC, Coakley J, Forbes DA, *et al*. Familial hypercholesterolaemia in children and adolescents: a new paediatric model of care. *J Paediatr Child Health* 2013; 49: E263–72.
111. Pang J, Martin AC, Bates TR, *et al*. Parent-child genetic testing for familial hypercholesterolaemia in an Australian context. *J Paediatr Child Health* 2018; 54: 741–7.
112. Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. *BMJ* 2007; 335: 599.
113. Lozano P, Henrikson NB, Dunn J, *et al*. Lipid screening in childhood and adolescence for detection of familial hypercholesterolemia: evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2016; 316: 645–55.
114. Klancar G, Groselj U, Kovac J, *et al*. Universal screening for familial hypercholesterolemia in children. *J Am Coll Cardiol* 2015; 66: 1250–7.
115. Wald DS, Kasturiratne A, Godoy A, *et al*. Child-parent screening for familial hypercholesterolemia. *J Pediatr* 2011; 159: 865–7.
116. Futema M, Cooper JA, Charakida M, *et al*. Screening for familial hypercholesterolaemia in childhood: Avon Longitudinal Study of Parents and Children (ALSPAC). *Atherosclerosis* 2017; 260: 47–55.
117. McKay AJ, Hogan H, Humphries SE, *et al*. Universal screening at age 1-2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: a cost-utility analysis. *Atherosclerosis* 2018; 275: 434–43.
118. Lister K, Molster C, Martin AC, et al. Screening for familial hypercholestrolaemia: engaging the public in policy direction (abstract) World Congress of Public Health, 3–7 April 2017, Melbourne, Australia.
119. Foody JM. Familial hypercholesterolemia: an under-recognized but significant concern in cardiology practice. *Clin Cardiol* 2014; 37: 119–25.
120. Bates TR, Burnett JR, van Bockxmeer FM, *et al*. Detection of familial hypercholesterolaemia: a major treatment gap in preventative cardiology. *Heart Lung Circ* 2008; 17: 411–3.
121. Faggiano P, Pirillo A, Griffo R, *et al*. Prevalence and management of familial hypercholesterolemia in patients with coronary artery disease: the heredity survey. *Int J Cardiol* 2018; 252: 193–8.
122. Mortensen MB, Kulenovic I, Klausen IC, *et al*. Familial hypercholesterolemia among unselected contemporary patients presenting with first myocardial infarction: prevalence, risk factor burden, and impact on age at presentation. *J Clin Lipidol* 2016; 10: 1145–11452.e1.
123. Nanchen D, Gencer B, Auer R, *et al*. Prevalence and management of familial hypercholesterolaemia in patients with acute coronary syndromes. *Eur Heart J* 2015; 36: 2438–45.
124. Pang J, Poulter EB, Bell DA, *et al*. Frequency of familial hypercholesterolemia in patients with early-onset coronary artery disease admitted to a coronary care unit. *J Clin Lipidol* 2015; 9: 703–8.
125. Rallidis LS, Triantafyllis AS, Tsirebolos G, *et al*. Prevalence of heterozygous familial hypercholesterolaemia and its impact on long-term prognosis in patients with very early ST-segment elevation myocardial infarction in the era of statins. *Atherosclerosis* 2016; 249: 17–21.
126. De Backer G, Besseling J, Chapman J, *et al*. Prevalence and management of familial hypercholesterolaemia in coronary patients: an analysis of EUROASPIRE IV, a study of the European Society of Cardiology. *Atherosclerosis* 2015; 241: 169–75.

127. Amor-Salamanca A, Castillo S, Gonzalez-Vioque E, *et al*. Genetically confirmed familial hypercholesterolemia in patients with acute coronary syndrome. *J Am Coll Cardiol* 2017; 70: 1732–40.
128. Toell T, Mayer L, Pechlaner R, *et al*. Familial hypercholesterolaemia in patients with ischaemic stroke or transient ischaemic attack. *Eur J Neurol* 2018; 25: 260–7.
129. Pereira C, Miname MH, Makdisse MR, *et al*. Peripheral arterial disease in heterozygous familial hypercholesterolemia. *Atherosclerosis* 2015; 242: 174–8.
130. Perez de Isla L, Alonso R, Mata N, *et al*. Coronary heart disease, peripheral arterial disease, and stroke in familial hypercholesterolaemia: insights from the SAFEHEART registry (Spanish Familial Hypercholesterolaemia Cohort Study). *Arterioscler Thromb Vasc Biol* 2016; 36: 2004–10.
131. Zafrir B, Shapira C, Lavie G, *et al*. Identification and characterization of severe familial hypercholesterolemia in patients presenting for cardiac catheterization. *J Clin Lipidol* 2016; 10: 1338–43.
132. Dorsch MF, Lawrance RA, Durham NP, *et al*. Familial hypercholesterolaemia is underdiagnosed after AMI. *BMJ* 2001; 322: 111.
133. Yudi M, Omera L, McCubbery N, *et al*. Suboptimal consideration and management of potential familial hypercholesterolaemia in patients with suspected premature coronary artery disease. *Singapore Med J* 2012; 53: 174–8.
134. Scicali R, Di Pino A, Platania R, *et al*. Detecting familial hypercholesterolemia by serum lipid profile screening in a hospital setting: clinical, genetic and atherosclerotic burden profile. *Nutr Metab Cardiovasc Dis* 2018; 28: 35–43.
135. Rangarajan N, Balasubramanian S, Pang J, *et al*. Knowledge and awareness of familial hypercholesterolaemia among registered medical practitioners in Tamil Nadu: are they suboptimal? *J Clin Diagn Res* 2016; 10: OC52–6.
136. Bairey Merz CN, Alberts MJ, Balady GJ, *et al*. ACCF/AHA/ACP 2009 competence and training statement: a curriculum on prevention of cardiovascular disease: a report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Competence and Training (Writing Committee to Develop a Competence and Training Statement on Prevention of Cardiovascular Disease): developed in collaboration with the American Academy of Neurology; American Association of Cardiovascular and Pulmonary Rehabilitation; American College of Preventive Medicine; American College of Sports Medicine; American Diabetes Association; American Society of Hypertension; Association of Black Cardiologists; Centers for Disease Control and Prevention; National Heart, Lung, and Blood Institute; National Lipid Association; and Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol* 2009; 54: 1336–63.
137. Bell DA, Bender R, Hooper AJ, *et al*. Impact of interpretative commenting on lipid profiles in people at high risk of familial hypercholesterolaemia. *Clin Chim Acta* 2013; 422: 21–5.
138. Bender R, Edwards G, McMahon J, *et al*. Interpretative comments specifically suggesting specialist referral increase the detection of familial hypercholesterolaemia. *Pathology* 2016; 48: 463–6.
139. Bell DA, Edwards G, Hooper AJ, *et al*. The potential role of an expert computer system to augment the opportunistic detection of individuals with familial hypercholesterolaemia from a community laboratory. *Clin Chim Acta* 2015; 448: 18–21.
140. Datta BN, McDowell IF, Rees A. Integrating provision of specialist lipid services with cascade testing for familial hypercholesterolaemia. *Curr Opin Lipidol* 2010; 21: 366–71.
141. Knowles JW, Rader DJ, Khoury MJ. Cascade screening for familial hypercholesterolemia and the use of genetic testing. *JAMA* 2017; 318: 381–2.
142. Bell DA, Pang J, Burrows S, *et al*. Effectiveness of genetic cascade screening for familial hypercholesterolaemia using a centrally coordinated clinical service: an Australian experience. *Atherosclerosis* 2015; 239: 93–100.
143. Kerr M, Pears R, Miedzybrodzka Z, *et al*. Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK. *Eur Heart J* 2017; 38: 1832–9.
144. Ademi Z, Watts GF, Pang J, *et al*. Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolemia. *J Clin Lipidol* 2014; 8: 390–400.
145. Lazaro P, Perez de Isla L, Watts GF, *et al*. Cost-effectiveness of a cascade screening program for the early detection of familial hypercholesterolemia. *J Clin Lipidol* 2017; 11: 260–71.
146. Jannes CE, Santos RD, de Souza Silva PR, *et al*. Familial hypercholesterolemia in Brazil: cascade screening program, clinical and genetic aspects. *Atherosclerosis* 2015; 238: 101–7.
147. Leren TP, Manshaus T, Skovholt U, *et al*. Application of molecular genetics for diagnosing familial hypercholesterolemia in Norway: results from a family-based screening program. *Semin Vasc Med* 2004; 4: 75–85.
148. Louter L, Defesche J, Roeters van Lennep J. Cascade screening for familial hypercholesterolemia: practical consequences. *Atheroscler Suppl* 2017; 30: 77–85.
149. George R, Kovak K, Cox SL. Aligning policy to promote cascade genetic screening for prevention and early diagnosis of heritable diseases. *J Genet Couns* 2015; 24: 388–99.
150. Wurtmann E, Steinberger J, Veach PM, *et al*. Risk communication in families of children with familial hypercholesterolemia: identifying motivators and barriers to cascade screening to improve diagnosis at a single medical center. *J Genet Couns* 2018; Aug 14: (Epub ahead of print).