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Heart, Lung and Circulation

Familial hypercholesterolaemia in 2020: a leading tier 1 genomic application

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Abstract

Familial hypercholesterolemia (FH) is caused by a major genetic defect in the low-density lipoprotein (LDL) clearance pathway. Characterised by LDL-cholesterol elevation from birth, FH confers a significant risk for premature coronary artery disease (CAD) if overlooked and untreated. With risk exposure beginning at birth, early detection and intervention is crucial for the prevention of CAD. Lowering LDL-cholesterol with lifestyle and statin therapy can reduce the risk of CAD. However, most individuals with FH will not reach guideline recommended LDL-cholesterol targets. FH has an estimated prevalence of approximately 1:250 in the community. Multiple strategies are required for screening, diagnosing and treating FH. Recent publications on FH provide new data for developing models of care, including new therapies. This review provides an overview of FH and outlines some recent advances in the care of FH for the prevention of CAD in affected families. The future care of FH in Australia should be developed within the context of the National Health Genomics Policy Framework.

Introduction

Familial hypercholesterolemia (FH), characterised by high plasma low-density lipoprotein (LDL)-cholesterol levels and a strong risk of premature coronary artery disease (CAD), is the most common autosomal dominantly inherited genetic disorder (**Figure 1**) [1, 2]. FH is classified by the Centers for Disease Control and Prevention as a tier 1 genomic application [3]. A tier 1 genomic application is considered as a preventable cause of premature disease and death, with significant potential for positive impact on public health based on available evidence-based guidelines and recommendations [3]. FH is more common than other tier 1 genomic applications, such as hereditary breast and ovarian cancer syndrome and Lynch syndrome [4].

Since FH is an inherited condition with risk exposure beginning at birth, early detection and intervention is crucial for the prevention of CAD. With an estimated prevalence of approximately 1:250 [5] in the general population, FH represents a major gap in preventative medicine and is clearly a public health problem. Reflecting the public health challenges that FH poses, gaps in care are currently being addressed by clinicians and researchers around the world [6, 7].

The purpose of this review is to provide a contemporary overview of core information and advances that may be employed to improve healthcare and therapy to prevent premature CAD in patients and families with FH.

Molecular pathophysiology

LDL-cholesterol is cleared from circulation via LDL-receptors (LDLR) in the liver. In FH, there is a disturbance to this clearance pathway and subsequently, an increase in the plasma concentration of LDL-cholesterol [8]. Genetic defects that impair the LDLR pathway include variants in the *LDLR* gene itself, variants in the *APOB* (apolipoprotein B, the receptor ligand) gene and/or variants in the *PCSK9* (proprotein convertase subtilisin/kexin type 9; an enzyme that regulates cell surface receptors that degrades LDLR) gene. The inheritance of FH is autosomal dominant; individuals with heterozygous FH (heFH) have 50% chance of transmitting the mutation to each offspring. If both parents have heFH, there is a chance of an offspring inheriting two FH variants, resulting in homozygous, compound or double heterozygous FH (hoFH) [9].

In FH, plasma LDL-cholesterol concentrations are markedly elevated from birth and if untreated can lead to an acceleration of foam cell formation and atherosclerotic plaques in the arterial wall, principally in proximal coronary arteries and the aorta. Atherogenesis is proportional to the LDL-cholesterol burden over time and hence, development of atherosclerosis is much more severe in hoFH than in heFH. If undiagnosed and untreated, the risk of CAD in heFH is more than 50% by the age of 50 in men and at least 30% by the age of 60 in women [10]. HoFH patients tend to exhibit an aggressive coronary atherosclerosis before the age of 20 [9].

Prevalence

The theoretical prevalence of heFH was commonly considered to be 1:500 [11], more extensive and contemporary studies, some based on genetic testing, have now suggested that the prevalence of heFH in the community is approximately 1:250 [12-14]. The prevalence of hoFH is considered to be between 1:160,000 and 1:300,000 [9, 15], and higher in some populations owing to a founder-effect [16], such as in the Afrikaners (1:70) and Lithuanian Jewish (1:70) populations [10]. Knowledge of the prevalence of FH allows the extent of under-diagnosis to be estimated, and perhaps with the exception of the Netherlands and Norway, FH is globally under-diagnosed [17, 18].

The prevalence of heFH in younger hypercholesterolaemic patients with premature CAD can be as high as 1:10 [19]. Therefore, major efforts should be made to screen for FH in these patients and to initiate cascade testing of close family members for primary as well as secondary prevention.

Screening and Detection

Cases of FH may be detected using selective (eg. selective screening of high-risk coronary patient), systematic (eg. systematic screening of family members from a known index case), opportunistic (eg. opportunistic alerts on pathology reports and in primary care) and universal (eg. screening of all newborns or children at immunisation) screening strategies. However, the feasibility and cost-effectiveness of implementing and integrating these approaches remains to be demonstrated [20, 21], and are highly dependent on the existing health system.

Selective screening of patients with premature CAD offers a high yield but does not allow for the primary prevention of CAD in the index case. This is important, given that the first clinical presentation of CAD can actually be sudden death [22]. Selective screening of school children is another option but a recent study demonstrated a low rate of uptake [23]. Screening employing genetic testing in biobanks [24] and blood donors [25] are recent opportunistic approaches. Cascade screening remains the classical systematic method for detecting new cases but relies *a priori* on identifying an index case. A proposed method of cascade screening is depicted in **Figure 2**. A centralised service approach for cascade screening has been demonstrated to be cost-effective in Australia and the UK [26, 27].

Population modelling has suggested that to detect the majority of FH cases in the community requires more than just cascade testing [28]. Hence, universal screening now needs serious consideration, especially in children [29]. Universal screening of children combined with child-parent “reverse” cascade testing is potentially the most effective method for detecting most cases of FH in the community and prior to the development of CAD [30]; this approach appears to be acceptable [31] and cost-effective [32]. However, this strategy has only been implemented in Slovenia [33] (which has a population of approximately 2 million) and requires adaptation and evaluation in countries with different healthcare systems, larger populations and geographical areas, as well as addressing concerns related to logistics and anxiety amongst parents.

From a community perspective, there is great potential for primary care physicians to play a much greater role in the detection and management of FH [34]. In Australia, over 87% of the population consult a general practitioner (GP) at least once a year [35] and over 90% of LDL-cholesterol tests undertaken through a community-based pathology laboratory are requested by GPs [36]. It is increasingly recognised that this ease of access could be harnessed to encourage greater awareness and use of opportunistic screening for the condition as part of regular surgery consultations, with a potential for cascade testing of relatives within the same practice. Additionally, community screening in general practice can be supported by digital technology for searching electronic health records for potential cases of FH [37-40].

Clinical Diagnosis

An elevated untreated LDL-cholesterol is the major phenotypic criterion for diagnosing FH. However, a wide overlap exists in plasma LDL-cholesterol levels between patients with and without heFH or hoFH [41] (**Figure 3**). The Dutch Lipid Clinic Network Score (DLCNS) (**Figure 4**) is the most widely used phenotypic method for diagnosing adult index cases with heFH [6] and is based on several key criteria including the patient's family history of premature CAD, personal history of premature CAD, their untreated LDL-cholesterol level and physical stigmata such as tendon xanthomata and/or arcus cornealis. Recent US guidelines have defined FH in adults using simply a family history of premature CAD and an elevated plasma LDL-cholesterol level >4.9 mmol/L [21, 42]. However, concordance with the genetic diagnosis of FH can be low [43]. As familial elevation of lipoprotein(a) [Lp(a); an LDL-like particle] can be a common phenotypic mimic of FH, adjustments for the cholesterol content of Lp(a) in LDL-cholesterol could improve diagnosis in some cases [44], but this is not widely appreciated nor practiced. Paediatric index cases of FH may be diagnosed phenotypically as an LDL-cholesterol of >5 mmol/L (on two separate occasions) or as an LDL-cholesterol >4 mmol/L with high cholesterol in one parent [2].

LDL-cholesterol alone is also the major phenotypic criterion for diagnosing FH in first-degree family members of an index case. The detection of FH in first-degree relatives should not be made using DLCNS, which was designed for making the diagnosis of FH in index cases. There is obviously a much higher probability of first-degree relatives of a definite FH proband having FH (50% vs. 1 in 250 in the community). LDL-cholesterol thresholds, with adjustments for age and gender, for use in cascade testing of relatives of index cases are shown in (**Figure 5**) [45].

Given the ambiguities in making a contemporary diagnosis of heFH and hoFH, a phenotypic definition of "severe FH" was proposed by an international consensus panel. Severe FH was defined as a plasma LDL-cholesterol level >10.0 mmol/L alone, >8.0 mmol/L plus one high cardiovascular risk, or >5.0 mmol/L plus two high cardiovascular risk [46]. This definition has recently been shown to predict an adverse cardiovascular outcome [47]. Although the definition is pragmatic and has clinical appeal, the definition undermines the merits of precision offered by genetic testing.

Genetic Testing

Cost-effective deployment of lipid-lowering therapies and the decision to cascade test family members is reliant on an accurate diagnosis of heFH. The use of genetic testing allows an accurate diagnosis of heFH and hoFH and is also important for risk stratification [12]. The extent of cholesterol elevation and atherogenesis in FH is dependent on the severity of the genetic variant [48], whether the variant affects receptor synthesis, transport, binding, internalisation and/or recycling. Genetic testing has a role in pre-conception genetic counselling and a special role in the care of hoFH [41], in the prediction of responsiveness to certain therapies for those with null mutations (no LDLR activity) [49].

Although the detection of a pathogenic variant for FH is the gold standard for diagnosis [41], genetic testing also has several barriers, such as cost implications, issues with variant interpretation [50], restrictions on life insurance and under-availability of genetic counselling services [51]. Genetic testing is not at present widely available, although this could change rapidly in the new era of widespread next-generation sequencing (massively parallel sequencing) [52]. Frameworks for genetic counselling of families with FH are fundamental to clinical practice and has been emphasised in recent guidelines [41].

Genetic testing for FH has been proposed by the Medical Services Advisory Committee as an item that should be listed on the Medicare Benefits Schedule (MBS). As with other genetic conditions, all testing and reporting in Australia must comply with the requirements of the National Pathology Accreditation Advisory Council [53]. A National Health Genomics Policy Framework has also been developed to co-ordinate a strategic approach to incorporate genomics into the health system [54]. This has the general aim of employing genomics to improve health outcomes and quality of life for the Australian population and this has implications for people with FH. Success of implementation will be underpinned by effective digital health technology [55]. The strategic priority areas and their relevance to FH are highlighted in **Table 1**.

Risk Assessment

There is wide variation in the risk of CAD among FH. Severity of FH is proportional to severity of the mutation and the total burden of LDL-cholesterol (heFH and hoFH). At every level of LDL-cholesterol, presence of a mutation predicts risk [12].

Traditional risk factors are well recognised to increase cardiovascular disease (CVD) risk in FH [56]. Estimating risk is important to guide therapy, particularly in those at the pre-symptomatic stage. Risk prediction algorithms employing CVD risk factors have been developed specifically in genetically defined FH cohorts in Canada and Spain [57, 58]. However, these models require further validation in other sample populations.

Genetic risk factors, such as an elevation in plasma Lp(a) concentration [59, 60], a high genetic CAD risk score or high polygenic cholesterol score [61-63], can predict adverse CVD risk, particularly in genetically defined FH. Variants in the 9p21.3 loci and ABO blood group have also been associated with higher risk of CVD in FH [62, 64]. Of these genetic risk factors, recent data demonstrates value in assessing Lp(a) concentration in FH and during cascade testing of family members [65, 66]. However, the extent to which the genetic risk scores extend to different ethnic groups remains to be determined [67, 68]; their clinical use also requires further evaluation.

Imaging of pre-clinical atherosclerosis may currently be the most valuable tool for assessing risk in FH. Coronary artery calcium (CAC) measurements can be done quickly and cheaply. CAC scores are independently associated with subsequent coronary events in patients with FH receiving standard lipid-lowering therapy [69]. Compared with CAC, coronary computed tomography angiography (CCTA) takes more time, involves radiation exposure and requires a controlled heart rates with a venous injection of contrast. However, it can more accurately assess the burden of both soft and calcified plaque burden. CCTA has been demonstrated to identify the very early development of coronary atherosclerosis in heFH subjects and the magnitude of coronary plaque burden can predict future coronary events [70]. CCTA and CAC can be undertaken together for more accurate delineation of disease burden and prospective risk stratification of asymptomatic heFH subjects [71]. However, the precise economic and patient-level impact of coronary imaging remains to be demonstrated. Recent European guidelines have recommended that asymptomatic individuals with a strong family history of premature CAD, such as FH, be considered for CCTA [72]. Additionally, it has been recommended that unequivocal evidence of CVD on imaging in FH should be considered at very-high cardiovascular risk [73].

Carotid-intima media thickness (CIMT) on ultrasonography may be useful to detect early atherosclerosis in FH [2, 74]. CIMT has been shown to be responsive to LDL-cholesterol

reduction with statin therapy and has recently been shown to be associated with reductions in cardiovascular outcomes in children over 20 years [75, 76]. Measurement of carotid plaque burden with 3D ultrasound may be more valid than CIMT for estimating atherosclerosis burden in adult patients, but its role in clinical management remains to be established [77-79].

Management

Treatment of elevated LDL-cholesterol in FH involves dietary, lifestyle management and pharmacotherapy. Statins are the mainstay pharmacotherapy and is supported by new evidence from cohort and registry data [80-82], long-term follow-up data from relevant clinical-endpoint trials [83] and surrogate-endpoint studies [75, 84]. However, a significant proportion of patients do not reach LDL-cholesterol targets on high-intensity statins [85, 86] and additional therapy with ezetimibe and/or bile-acid sequestrants may be required [87-90]. Supported by clinical trial data in non-FH populations, PCSK9 inhibitors are recommended as third-line therapy to treat FH [42, 73, 91-97] (**Figure 6**). Drug interactions and toxicity needs to be monitored in FH given that the majority of adult patients will be on two or more drugs, with appropriate investigations of renal, liver and glucose biochemistry [20, 21].

Adults

The recommended initial treatment target for FH has been a 50% reduction in plasma LDL-cholesterol concentration [42], followed by an LDL-cholesterol <2.6 mmol/L (no CVD or major risk factors) and <1.8 mmol/L (CVD or major risk factors)[20, 98, 99]. However, recent guidelines from the American Association of Clinical Endocrinologists (AACE) and the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) have recommended an LDL-cholesterol of <1.8 mmol/L for primary prevention and <1.4 mmol/L for secondary prevention (or very-high risk) [73, 100]. Recent data suggest that the use of these treatment targets are probably unrealistic for FH patients [101].

The two PCSK9 inhibitors registered in Australia are Repatha (evolocumab) and Praluent (alirocumab). The Pharmaceutical Benefits Scheme (PBS) allows a PCSK9 inhibitor be offered to hoFH and heFH patients meeting the sets of eligibility criteria detailed in **Table 2**.

Dietary (eg. heart healthy diet) and lifestyle (eg. exercise and avoidance of smoking) management is adjunctive to pharmacotherapy and may be the only treatment option for certain groups, such as pregnant women, younger children and individuals with a pathogenic FH-causing mutation that has yet to express as hypercholesterolemia [12, 102]. Although statins are contra-indicated in pregnancy and during breastfeeding [103, 104], no association has been reported in cohort studies for birth defects, preterm delivery or lower birth weights [105, 106]. In a recent study, the use of statins in hoFH women during pregnancy was reported to be safe for both mother and foetus [107], particularly when taken in the second and third trimester. PCSK9 inhibitors cross the placenta and should not be used in pregnancy [99]. PCSK9 inhibitors are also not licenced for use in children.

Children

Mendelian randomisation [108, 109] and observational studies [76] provide evidence that FH patients should receive aggressive, life-long lifestyle management and initiate lipid-lowering therapy from an early age. A recent study from the Netherlands comparing cumulative incidence of cardiovascular events in FH patients who commenced statin therapy during childhood (8-18 years) to their affected parents who commenced on statin therapy later in life (20-51 years) was 1% vs 26% (**Figure 7**). Expert recommendations are that statins should be initiated in children with heFH between the ages of 5 and 10 years [2, 42, 73, 110], or earlier according to shared decision making with parents [2, 21, 99]; children with hoFH should be treated with statins and additional therapies at diagnosis. Guideline recommended targets are a 50% reduction in plasma LDL-cholesterol concentration [110] or LDL-cholesterol <3.5 mmol/l for heFH [2], and <2.6 mmol/L [111] and <1.8 mmol/L for hoFH children without and with symptomatic ASCVD, respectively [9, 111]. However, these targets may not be achievable in clinical practice with contemporary treatments approved for use in children.

Apheresis

All contemporary guidelines recommend lipoprotein apheresis (LA) for hoFH and severe heFH patients, who remain above LDL-cholesterol treatment targets despite being on maximal drug therapy [20, 46, 112, 113]. Recent studies confirm that the cardiovascular benefits of LA are related to the degree of reduction in the cumulative exposure to LDL-

cholesterol [114-116], but pleiotropic effects may play a role, particularly reduction in arterial inflammation [117]. However, apheresis is not widely available or practiced [112]. PCSK9 inhibitors reduce the need for LA in heFH [118] and can further lower LDL-cholesterol in hoFH patients on LA [119]. As a final option, liver transplantation may be an effective therapy for younger patients with hoFH and rapidly progressive atherosclerosis [120, 121].

New therapies

Several new therapies for lowering LDL-cholesterol are in development or in the early phases of clinical trials [95, 122, 123]. These agents could have indications for FH patients who cannot tolerate maximal doses of currently available pharmacotherapies or who have refractory hoFH. Beyond monoclonal antibodies, PCSK9 may be targeted with small interfering RNA (Inclisiran) [124], which is undergoing testing in cardiovascular outcomes trials, and with gene-editing approaches, which are at an early experimental stage [122, 123]. For hoFH patients, therapies that act independent of the LDL receptor pathway, such as inhibitors of ANGPTL3 (evinacumab) [125] offer new opportunities for further lowering of LDL-cholesterol [122].

Adherence

Poor adherence to treatment is associated with increased risk of CVD [126, 127]. Hence, it is vital to carefully address patient concerns and beliefs about medication [128], as well as the impact of media reports on the adverse perceptions of statins [129, 130]. In an era of personalised and participatory medicine [42], the care of FH must be patient-centred to improve the quality of decision making process [131, 132], and this may be facilitated by the use of decision aids [133]. As with other chronic disorders, health literacy issues in FH must be addressed to ensure adherence to therapies [134].

Organisation of Care

The optimal care of FH requires a systems approach to the provision of services [1]. Organisational aspects of FH healthcare need to be designed according to available resources and contexts and be integrated across a continuum to deliver a life-long management plan. A multi-disciplinary approach is fundamental; key disciplines include general practice [135], cardiology, paediatrics, genetics, imaging and transfusion medicine,

with support from allied health professionals experienced in nursing, dietetics, psychology and pharmacy [136]. Design and implementation of models of care also should involve government policy makers, patients and families, as well as patient advocates and the wider public [137, 138].

From a community perspective, it has been recommended that most individuals diagnosed with FH should be treated in primary care and preferably in a family context, with more complex cases including children referred to specialised lipid or FH clinics [98]. The potential to optimise a “shared care” model between primary care and specialist services is attractive and is well recognised [98, 139]. The UK has established specialist regional lipid clinics to support GPs and practices which has resulted in greater detection of FH in the community [140].

Patient support groups and networks are essential for advocating improvement in care and are a vital component of modern-day participatory medicine, being also well aligned with a central theme of the National Health Genomics Policy Framework [54]. Beyond providing awareness raising through social media [141], general education and counselling, international achievements to date are evidenced by government run screening programs, inception and growth of national registries, support for new screening strategies and improvements in access to effective therapies [142]. The last is particularly relevant at a time of access barriers to new therapies [143]. The value of patient support networks are classically exemplified by the activities of the US FH Foundation and the European FH Patient Network [142].

Clinical Registries

The primary function of quality clinical registries is the collection of data on patients in a systemic and standardised way that reflects “real world” clinical practice. Clinical registries on FH meet a key requirement of the 1998 World Health Organisation Report [144] and have now been promulgated in several countries [145, 146]. Registries are important not only to raise overall awareness of FH, but also to collect information for clinical trials and for healthcare policy and planning as a means for improving the quality of patient care and outcomes [147]. In Australia, a web-based registry for FH has been established since 2015 with over 40 clinical sites nationally [148] (**Figure 8**); preliminary analysis of the extant data

confirms that in Australia the shortfalls in the detection and care of FH reflect that of other countries [6].

In order to capture a large global FH dataset, the Familial Hypercholesterolemia Studies Collaboration (FHSC) initiative aims to collect data from FH investigators worldwide [7, 145]. To improve the precision of data acquisition and analyses, a more specific ICD-10 code for FH has been introduced in the US [21], but requires consistent application at an international level [149].

Research

A scientific statement from the American Heart Association has identified a number of key research needs in FH [21]. An agenda has been proposed that serves as a useful template for developing context-specific research programs. The main themes are basic science, life course, clinical research, patient-centric research, models of care and population science [20]. Healthcare gaps need to be closed through adequately funded research that addresses these themes [20, 21]. The value of implementation research in effectively translating evidence into practice has been more recently emphasised [4, 150].

Educational and Training Needs

The National Health Genomics Policy Framework emphasises a core need to upskill health care professionals in genomics [54], and this clearly extends to FH noting the potentially imminent incorporation of genetic testing into the clinical care of FH in Australia [151].

Several surveys have shown that healthcare professionals, including primary care physicians and cardiologists, lack awareness, knowledge and skills relating to the epidemiological, genetic, clinical and therapeutic aspects of FH [152-156]. Strategies are required to ensure the inclusion of adequate skills within professional development programs. General practitioners, cardiologists, pharmacists and nurses are ideally placed to identify and manage individuals with FH. Education and training of these healthcare professionals is important for improving and maintaining quality care [20]. Physicians and nurses managing patients with FH should ideally have certified training in clinical lipidology and competencies in preventative cardiology and clinical genetics [1, 157].

From a primary care perspective, beyond gaps in fundamental knowledge of FH, there is a major need to train and upskill staff in basic genetic counselling methods [158] and the effective implementation of cascade testing of first- and second-degree relatives of index cases. The effective integration of primary care within comprehensive screening strategies for FH is dependent on increasing the capabilities, opportunities and motivation of GPs.

Conclusions

As a leading tier 1 genomic application [3], FH has great potential to prevent premature disease and death. The key major advances in FH have been in genetics, imaging, registries and therapies. Despite exponential advances in knowledge, there is a significant shortfall in the detection and treatment of this relatively common inherited cause of premature CAD. This relates to a shortfall in patient, provider, organisational, policy and community awareness factors. A major challenge is translating new evidence into health policy and high quality care and implementation research is a core function [137] for improving outcomes of FH patients over their life-span. Updating the World Health Organisation Report from 20 years ago is a critical first step for effectively implementing improved care of FH [159], which is now a global health priority [160]. Developments in genomics and digital health now need to be embedded into the evolving model of care of FH in Australia and beyond.

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Figure 1. The prevalence of familial hypercholesterolaemia is more common than other genetic diseases, adapted from Wiegman et al 2015 [2]. FH is a leading tier 1 genomic application [3].

Figure 2. This is a scheme for approaching and risk notification of family members during cascade testing of families for FH. Adapted from Bell et al 2015 [161] and Kullo et al 2018 [162].

Figure 3. The phenotypic and genetic spectrum of familial hypercholesterolemia and the estimated risk of coronary artery disease, adapted from Sturm et al 2018 [41].

Figure 4. The Dutch Lipid Clinic Network criteria for making a diagnosis of familial hypercholesterolaemia in adult index cases, adapted from the World Health Organisation [144].

Criteria*		Score
Section 1: Family history		
First degree relative with known premature coronary and/or vascular disease (men aged <55 years, women aged <60 years) OR First degree relative with known LDL-cholesterol above the 95 th percentile for age and gender		1
First degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged <18 years with LDL-cholesterol above the 95 th percentile for age and gender		2
Section 2: Clinical history		
Patients with premature coronary artery disease (men aged <55 years, women aged <60 years)		2
Patients with premature cerebral or peripheral vascular disease (men aged <55 years, women aged <60 years)		1
Section 3: Physical examination		
Tendinous xanthomata		6
Arcus cornealis before 45 years of age		4
Section 3: Biochemical results		
LDL-cholesterol (mmol/L)	LDL-cholesterol ≥ 8.5	8
	LDL-cholesterol 6.5–8.4	5
	LDL-cholesterol 5.0–6.4	3
	LDL-cholesterol 4.0–4.9	1

*Note that only the highest score in each section is chosen to add up to the total score, to a maximum of 18.

Diagnosis	Total Score
Definite FH	>8
Probable FH	6-8
Possible FH	3-5
Unlikely FH	<3

Figure 5. LDL-cholesterol cut-offs for the diagnosis of FH in cascade testing, based on age and gender, in first-degree relatives of FH patients: (A) for females and (B) for males. Adapted from Starr et al 2008 [45].

Colour	Likelihood of FH
Red	Likely
Grey	Uncertain
Green	Unlikely

Figure 6. Simplified treatment scheme for adults with familial hypercholesterolemia. Shared-decisions should be practice at each step of treatment. Adapted from Gidding et al 2015 [21].

*Guideline recommended threshold based on primary or secondary prevention; patient should be on at least 3 months of therapy, is adherent and treatment is tolerable.

Figure 7. Kaplan-Meier curves of cardiovascular event-free survival in patients with familial hypercholesterolaemia who commenced statin therapy during childhood (8-18 years) and their affected parents who commenced on statin therapy later in life (20-51 years) [76].

Figure 8. Clinical sites of the Australian FH registry, which includes the public and private sector. Data from all sites are entered onto a secure web-based registry platform [148].

Table 1. Five key priorities of the National Health Genomics Policy Framework [54] and examples of their application to the diagnosis and management of familial hypercholesterolaemia. Successful implementation of the framework is underpinned by digital innovation and technology [55].

Strategic priority areas				
Person-centred approach	Workforce	Financing	Services	Data
Provide support for FH individuals and their families to make informed choices in genetic testing; support patient advocacy groups and the public to promote awareness for FH	Build capacity for improving skills and literacy of health care professionals in genomics, employing evidence-based education and training programs for managing FH	Ensure sustainable and strategic investment in cost-effective use of genetic testing in the diagnosis and management of FH patients; support for evidenced-based models of care	Promote evidence-based and nationally consistent best practice in genetic testing and counselling services for FH and their incorporation into models of care integrated across primary and specialist care	Develop a high quality national register to enable screening, data collection, storage, sharing, analysis and reporting

Table 2. Pharmaceutical Benefits Scheme eligibility criteria for Repatha (evolocumab) for homozygous and heterozygous familial hypercholesterolaemia in Australia. Praluent (alirocumab) has been recommend for heterozygous familial hypercholesterolaemia.

Criteria	HoFH	HeFH
Diagnosis	DLCNS ≥ 7 OR Confirmed by genetic testing	DLCNS ≥ 6 OR Confirmed by genetic testing
LDL cholesterol	>3.3 mmol/L	>5 mmol/L OR >3.3 mmol/L plus symptomatic atherosclerotic cardiovascular disease
Treatment	Maximum recommended dose of Atorvastatin or Rosuvastatin for ≥ 3 months OR Statin contraindicated as defined by the TGA-approved Product Information	
	OR Clinically important product- related adverse event necessitating a withdrawal of statin treatment	OR Clinically important product-related adverse event necessitating withdrawal of statin treatment to trials of each Atorvastatin and Rosuvastatin
	AND In conjunction with dietary therapy and exercise for ≥ 3 months	
		AND On ezetimibe ≥ 3 months

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