Review

International Developments in the Care of Familial Hypercholesterolemia: Where Now and Where to Next?

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Several international guidelines and consensus statements have recently been published on the care of familial hypercholesterolemia (FH)¹⁻³. They agree on approaches to case detection and cascade testing, protocols in children, lifestyle and drug treatment strategies, and indications for lipoprotein apheresis. However, most countries in the world still do not have integrated, systematic FH screening programs to adequately detect and treat cases in the community. This study provides a comprehensive overview of recent and future international initiatives for closing the gaps in the care of FH.


Key words: Familial hypercholesterolemia, Models of care, Heart disease, Risk, Prevention, Screening, Treatment, Cost-effectiveness, Education, Registries

Introduction

Familial hypercholesterolemia (FH) is the most common dominantly inherited disorder. It is characterized by high plasma low-density lipoprotein (LDL) cholesterol levels and a strong risk of premature coronary artery disease (CAD). The prevalence of heterozygous FH (heFH) is estimated to be 1:200⁻¹:300⁴⁻⁹, with an estimated 30 million people worldwide. Most countries do not have a formal screening program for FH. International¹⁹ and local guidelines⁵⁻¹⁷, models of care¹⁸, and health economic evaluations¹⁹⁻²¹ have been published, but their recommendations remain to be effectively implemented. International efforts aimed at implementing models of care (Fig. 1) are a priority for closing treatment gaps and informing outcome for patients and families with FH.

Prevalence

The theoretical prevalence of heFH has been generally accepted to be 1:500²² and higher in some populations because of a founder effect²³. Recent studies from Denmark⁶, China⁵, the Netherlands⁶, Australia⁷,⁸, and United States⁹ have all estimated the prevalence of heFH to be between 1:200 and 1:400 in the general population (Table 1). The extent of under-diagnosis can therefore be estimated in countries with screening data such as the Netherlands, Norway, Iceland, Switzerland, United Kingdom and Spain²¹. Most countries do not have nationwide registries, particularly in Asia where >60% of the world population resides. For example, the reported prevalence in China is 1:359⁷, implying that there would be >4 million Chinese people with undiagnosed heFH. There are also no prevalence and screening data from India other than sporadic reports of mutations²⁴,²⁵. This strongly suggests that FH is globally under-diagnosed, as all ethnicities and racial groups are deemed to be affected.

Prevalence studies of FH in coronary care services are also informative. Recent studies from Europe²⁶ and Australia²⁷ demonstrate a prevalence of phenotypic (probable/definite) FH in individuals aged <60
years with CAD to be approximately 14% (Table 2). Therefore, the prevalence of potential FH in coronary patients is relatively high. Major efforts should be made to detect FH in these patients and to initiate cascade testing of available family members for primary and secondary prevention.

**Guidelines: Screening Strategies**

Comprehensive guidelines and models of care have been published to inform best practice in the care of FH for adults and children. The guidelines are generally congruent in their recommendations. In contrast to European and Australasian recommendations, the National Lipid Association in the United States recommends universal screening for hypercholesterolemia in the young, emphasizing the importance of early detection. This approach needs to be widely tested, but initial reports from Slovenia are encouraging.

Other recommendations suggest targeted screening of index cases in coronary care units and primary care settings, followed by cascade screening. European and Australasian approaches prefer the Dutch Lipid Clinic Network (DLCN) criteria and emphasize the value of genetic testing. Patients with tendon xanthoma, a clinical history of CAD, or imaging evidence of increased atheroma load are indicated for genetic testing. Subsequent cascade tracing to detect affected relatives provides an effective method of identifying patients with FH. This has been demonstrated in the Netherlands and reaffirmed in Wales, Brazil, and Australia, whereby first-degree relatives of index cases are cascade screened with genetic testing.

The guidance by the International FH Foundation also emphasizes the importance of integrating all screening strategies with clinical care services. Integrated screening programs are sparse in the Asia region and limited to the city states of Hong Kong and Singapore. Owing to high population densities, screening and cascade testing services may be particularly efficient and beneficial. The only guidelines and diagnostic criteria in the region are from Japan. Recent studies from South Korea have demonstrated that traditional criteria (Simon Broome, DLCN and MED-PED) have limited detection power and low specificity for mutations in their population. This mandates region- or country-specific criteria and guidelines.

US recommendations argue for cholesterol testing alone and do not see a role for genetic testing; this is mainly based on costs of genetic testing, the wide spectrum of mutations in the community and the less integrated healthcare system with difficulty of implementing cascade screening. At present, most countries in the world do not have genetic testing available. The majority of cases of FH should be detected in the community, where the use of genetic testing is at pres-
cated practice model in public health genomics that integrates primary care, clinical genetics and public health\textsuperscript{48}). Universal screening coupled with cascade testing is central to identifying most cases of FH in the community\textsuperscript{49}).

### Risk Factors and Subclinical Atherosclerosis

Studies of risk factor profiles in FH have been undertaken in several countries. Risk of CAD in FH is enhanced by hypertension, diabetes, smoking, obesity, renal insufficiency and elevated lipoprotein(a) (Lp(a))\textsuperscript{41, 50-59}. Data from Dutch\textsuperscript{53}, Japanese\textsuperscript{54}, Spanish\textsuperscript{57}, and Australian\textsuperscript{59} cohorts have shown the key role of hypertension as a CAD risk factor in patients with FH. Lp(a) is a highly polymorphic lipoprotein and a quantitative genetic trait that is inherited independent of gene variants that cause FH, and elevated plasma levels compound CAD risk in FH\textsuperscript{57}). The combination of cardiometabolic risk factors and the inherited genetic predisposition in FH contribute to increased CAD risk in FH beyond elevated plasma LDL-cholesterol levels. This underscores the need for identifying and managing modifiable risk factors that exacerbate CAD risk in FH and holistic healthcare beyond LDL-cholesterol lowering. Risk factor counting is permissible to stratify risk in FH, but absolute risk equations are not valid for assessing CAD risk in FH\textsuperscript{49}).

### Table 1. Estimated prevalence of heterozygous FH in different countries.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country</th>
<th>n</th>
<th>Age group</th>
<th>Prevalence</th>
<th>Diagnostic test</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benn, 2012\textsuperscript{4, 112}</td>
<td>Denmark</td>
<td>69,016</td>
<td>Adults</td>
<td>1 in 223</td>
<td>Clinical/cholesterol</td>
<td>Modified DLCN</td>
</tr>
<tr>
<td>Shi, 2014\textsuperscript{50}</td>
<td>China</td>
<td>9,324</td>
<td>Adults</td>
<td>1 in 359</td>
<td>Clinical/cholesterol</td>
<td>Modified DLCN</td>
</tr>
<tr>
<td>Sjouke, 2014\textsuperscript{60}</td>
<td>Netherlands</td>
<td>–</td>
<td>–</td>
<td>1 in 244</td>
<td>Derived from the Hardy-Weinberg equation applied to the prevalence of hoFH</td>
<td></td>
</tr>
<tr>
<td>Watts, 2015\textsuperscript{70}</td>
<td>Australia</td>
<td>10,904</td>
<td>Adults</td>
<td>1 in 353</td>
<td>Clinical/cholesterol</td>
<td>Modified DLCN</td>
</tr>
<tr>
<td>Miller, 2015\textsuperscript{90}</td>
<td>United States</td>
<td>1,320,581</td>
<td>Adults</td>
<td>1 in 345</td>
<td>Cholesterol</td>
<td>Age-based LDL-cholesterol threshold</td>
</tr>
<tr>
<td>Pang, 2015\textsuperscript{80}</td>
<td>Australia</td>
<td>1,602</td>
<td>Children</td>
<td>1 in 267</td>
<td>Clinical/cholesterol</td>
<td>LDL-cholesterol ≥ 4.0 mmol/L with a family history of premature CAD or HC</td>
</tr>
</tbody>
</table>

DLCN=Dutch Lipid Clinic Network Criteria, CAD=coronary artery disease, hoFH=homozygous FH, HC=hypercholesterolaemia
Table 2. Published data on the prevalence of FH in individuals with coronary artery disease. Adapted from Pang et al\textsuperscript{27}.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country/Region</th>
<th>n</th>
<th>Age</th>
<th>Prevalence</th>
<th>Diagnostic test</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patterson, 1972\textsuperscript{113}</td>
<td>United Kingdom</td>
<td>193</td>
<td>No age restriction</td>
<td>3%</td>
<td>Clinical/cholesterol</td>
<td>Type IIA phenotype plus HC\textsuperscript{<em>} and a first-degree relative with type IIA phenotype plus HC\textsuperscript{</em>}</td>
</tr>
<tr>
<td>Goldstein, 1973\textsuperscript{114}</td>
<td>United States</td>
<td>500</td>
<td>No age restriction</td>
<td>7.6%</td>
<td>Clinical/cholesterol</td>
<td>Plasma cholesterol &gt;95th percentile</td>
</tr>
<tr>
<td>Goldstein, 1973\textsuperscript{115}</td>
<td>United States</td>
<td>176</td>
<td>&lt; 60</td>
<td>4.1%</td>
<td>Clinical/cholesterol</td>
<td>Plasma cholesterol &gt;95th percentile with a first-degree relative with HC\textsuperscript{**} or premature CAD</td>
</tr>
<tr>
<td>Nikkila, 1973\textsuperscript{116}</td>
<td>Finland</td>
<td>101</td>
<td>&lt; 50</td>
<td>6%</td>
<td>Clinical/cholesterol</td>
<td>Type IIA phenotype plus HC\textsuperscript{1} and a first-degree relative with type IIA phenotype plus HC\textsuperscript{1}</td>
</tr>
<tr>
<td>Koivisto, 1993\textsuperscript{117}</td>
<td>Finland</td>
<td>150</td>
<td>&lt; 45</td>
<td>9%</td>
<td>Genetic</td>
<td>common LDLR mutations</td>
</tr>
<tr>
<td>Gaudet, 1998\textsuperscript{118}</td>
<td>French Canada</td>
<td>412</td>
<td>&lt; 45</td>
<td>16.4%</td>
<td>Genetic</td>
<td>common LDLR mutations</td>
</tr>
<tr>
<td>Dorsch, 2001\textsuperscript{119}</td>
<td>United Kingdom</td>
<td>292</td>
<td>&lt; 60</td>
<td>12%</td>
<td>Clinical/cholesterol</td>
<td>Phenotypic Simon Broome criteria</td>
</tr>
<tr>
<td>Bates, 2008\textsuperscript{120}</td>
<td>Australia</td>
<td>199</td>
<td>&lt; 60</td>
<td>2.1%</td>
<td>Clinical/cholesterol</td>
<td>Modified DLCN</td>
</tr>
<tr>
<td>Rallidis, 2008\textsuperscript{121}</td>
<td>Greece</td>
<td>135</td>
<td>&lt; 35</td>
<td>19%</td>
<td>Clinical/cholesterol</td>
<td>Phenotypic Simon Broome criteria</td>
</tr>
<tr>
<td>Wiesbauer, 2009\textsuperscript{122}</td>
<td>Austria</td>
<td>302</td>
<td>&lt; 40</td>
<td>8%</td>
<td>Clinical/cholesterol</td>
<td>Phenotypic Simon Broome criteria</td>
</tr>
<tr>
<td>Yudi, 2012\textsuperscript{123}</td>
<td>Australia</td>
<td>201</td>
<td>&lt; 60</td>
<td>1.4%</td>
<td>Clinical/cholesterol</td>
<td>Modified DLCN</td>
</tr>
<tr>
<td>Wald, 2015\textsuperscript{124}</td>
<td>United Kingdom</td>
<td>231</td>
<td>&lt; 50</td>
<td>1.3%</td>
<td>Genetic</td>
<td>common LDLR mutations</td>
</tr>
<tr>
<td>De Backer, 2015\textsuperscript{26}</td>
<td>Europe</td>
<td>7044</td>
<td>&lt; 80</td>
<td>8.3%</td>
<td>Clinical/cholesterol</td>
<td>Modified DLCN</td>
</tr>
<tr>
<td>Pang, 2015\textsuperscript{27}</td>
<td>Australia</td>
<td>175</td>
<td>&lt; 60</td>
<td>14.3%</td>
<td>Clinical/cholesterol</td>
<td>Modified DLCN</td>
</tr>
<tr>
<td>Nanchen, 2015\textsuperscript{125}</td>
<td>Switzerland</td>
<td>1451</td>
<td>&lt; 55 for men; &lt; 60 for women</td>
<td>4.8%</td>
<td>Clinical/cholesterol</td>
<td>Modified DLCN</td>
</tr>
</tbody>
</table>

HC=hypercholesterolaemia, CAD=coronary artery disease, DLCN=Dutch Lipid Clinic Network Criteria; *HC defined as age- and gender-adjusted cholesterol > 2 standard deviations above the expected level; **HC defined as cholesterol >99th percentile (age >20 years) or cholesterol >95th percentile (age ≤ 20 years); †HC defined as the 90th percentile of age- and gender-adjusted cholesterol in controls.

Imaging techniques in asymptomatic patients can be useful in assessing atherosclerosis burden. Studies from the Netherlands\textsuperscript{60, 61}, Brazil\textsuperscript{62}, and United Kingdom\textsuperscript{63} have demonstrated that patients with FH have an increased burden of coronary atherosclerosis. Cardiac computed tomography (CT) reliably ascertains coronary plaque burden and can be useful in identifying FH patients who need more intensive treatment\textsuperscript{64}. Atherosclerosis burden can, however, vary widely in FH, with hypertension and diabetes increasing the progression of disease\textsuperscript{65}. A recent Japanese study related CT coronary angiography to composite cardiovascular endpoints in treated heFH with known CAD\textsuperscript{66}. An international CT coronary angiogram consortium\textsuperscript{66} has recently been establish for FH to amalgamate data to investigate the natural history of coronary atherosclerosis and response to treatment in FH. The value of imaging in managing patients with FH needs further evaluation.

**Therapeutic Targets: Existing and New Therapies**

Treatment of elevated LDL-cholesterol in FH involves lifestyle modifications and pharmacotherapy; these are underscored by all guidelines\textsuperscript{1,3, 10-18}. Studies employing surrogate cardiovascular endpoint in FH subjects support the use of statins and cholesterol-lowering agents in reducing cardiovascular events in adults\textsuperscript{67} and children\textsuperscript{68}. Long-term observational studies also provide evidence that statin therapy lowers cardiovascular events and mortality in heFH compared
with the general population. Statins with or without ezetimibe and possibly other agents are recommended treatments for meeting all LDL-cholesterol targets. Before initiating statin therapy, safety checks on liver and muscle enzymes are required, with regular monitoring of plasma aminotransferases and plasma creatinine kinase if myalgia is reported.

A current treatment target for heFH is a 50% reduction in plasma LDL-cholesterol concentration. Drawing on the 2011 ESC/EAS guidelines, both the International guidance and EAS guidelines also suggest LDL-cholesterol targets of <2.5 mmol/L (<100 mg/dl) for patients without CHD and <1.8 mmol/L (<70 mg/dl) for those with CHD or other major risk factors. Achieving these low targets can be difficult in FH with conventional therapy and proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs) will be required in the future. Targets for children with heFH should be less intense than for adults. In contrast, the 2013 AHA/ACC guidelines have removed all LDL-cholesterol targets and focused exclusively on statin therapy and risk reduction.

The short-term safety, tolerability and efficacy of statins are well recognised in patients aged >10 years. The longest (10 year) available follow-up data of statin use in FH children from the Netherlands show that although mean carotid intima-media thickness (IMT) was greater in children with FH compared with their unaffected siblings, age at statin initiation was significantly associated with carotid IMT at follow-up.

Another study in children (aged 6–10 years) demonstrated effective lowering of LDL-cholesterol levels with ezetimibe monotherapy, and the statin-ezetimibe combination was also shown to reduce in LDL-cholesterol concentration in heFH adolescents. Initiation of statins and/or ezetimibe in children should be based on careful individualized risk estimation prior to robust long-term data in children being available.

Uniform recommendations are given for women with FH to avoid statins during (or when planning) pregnancy and lactation and to choose low estrogen or progesterone-only oral contraceptives, with barrier methods preferred. Lipoprotein apheresis should be considered in all children with severe, homozygous FH (hoFH) by the age of 5 years. Mipomersen and lomitapide are approved by the Food and Drug Administration (FDA) for adults with homozygous FH. PCSK9 mAbs have also been approved by the FDA and European Medicines Agency for primary hypercholesterolemia, such as heFH and mixed dyslipidaemia.

**“Homozygous” FH**

A new guideline for the detection, diagnosis and management of hoFH has appeared recently. The European expert panel mandates early identification of patients with hoFH and referral to a specialist center for attainment of LDL-cholesterol targets and regular follow-up by a cardiologist for progression of CAD and aortic valve disease. The therapeutic potential and indications for mipomersen, lomitapide and PCSK9 mAbs were underscored.

Recent studies have, however, shown the wide variability in the molecular bases (true homozygous and double/compound heterozygous), heritability, phenotypic penetrance and response to therapy, so called, hoFH. This suggests that the classical definition of hoFH may be clinically redundant. Establishing an accurate diagnosis of hoFH is important for risk stratification and the cost-effective deployment of high-intensity LDL-cholesterol lowering therapy. Recognizing a continuum between heFH and hoFH may be more relevant for clinical practice. A persuasive case has accordingly been made for a pragmatic definition of “severe” FH based on the response to therapies and presence and progression of CAD that accounts for such a continuum. This proposal has much clinical appeal but needs to be trialed, tested and fully evaluated.

**Knowledge, Education, and Training**

Knowledge of the prevalence, hereditability or risk, and treatment of FH are suboptimal among non-specialists. Studies on general practitioners in Australia, cardiologists in the United States, and physicians in the Asia-Pacific region all demonstrate limited awareness of prevalence and heritability as well as an underestimation of premature CAD risk associated with FH, possibly because of the lack of FH coverage in professional curriculums. A recent study of medicine and pharmacy schools in the United States found significant gaps in the coverage of FH in their courses. Strategies are required to ensure that FH instruction is sufficient within these professional programs. General practitioners and cardiologists are ideally placed to identify index individuals who have yet to be diagnosed with FH; hence, extensive education and training programs are important for improving and maintaining the total quality of FH healthcare. Physicians and nurses managing patients with FH should have specialist training in clinical lipidology and competencies in preventative cardiology and clinical genetics.

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Educational programs to increase awareness of FH among healthcare professionals are important to improve the care for FH worldwide. Recruitment of interested specialists from established centers is an important first step to create a hub that can connect with interested and participating regional or national healthcare providers. An educational program repeated at regular intervals will also help to create a network of collaborating physicians, including those in primary care, who can potentially evolve into lipid experts. There is also a need for dissemination of information beyond journals and conferences. Print, media, and social media campaigns can be initiated to raise awareness among family members, friends, and the general public to motivate individuals to get themselves screened for FH. Customization of material to address cultural, linguistic, geographic, and/or socio-economic circumstances is important for the success of these campaigns.

Role of Registries

The functions of registries are to collect data on patients with a nominated condition in a systemic and standardized way to facilitate research (including clinical trials), patient awareness and education, and improve healthcare services. Clinical registries and decision support systems can help coordinate cascade screening and increase efficiency of healthcare services. PASS clinical software has been successfully employed in Wales and the Netherlands to support FH cascade testing. Patient registries can also be instruments for clinical research and improving healthcare planning and patient care. Several national registries have been established including the Simon Broome Register in the United Kingdom, SAFE-HEART in Spain, the British-Colombian registry, the US CASCADE registry, the French registry, and the Australasia registry. Registries in the Middle East, North Africa, Mexico, and Turkey are also in development. However, these efforts are fragmented and not always accessible to FH stakeholders. Some are hospital-based electronic health registries, whereas others are web-based registries using cloud-computing resources. Coordination and harmonization in the ethical framework, links with biobanks, and the collection and use of data are key to the contribution of evidence-based enhancement in the worldwide care of FH. Interoperable registries, facilitated by application programming interfacing, can be combined to enrich datasets and answer important epidemiological questions and, hence, to strengthen evidence-based healthcare.

Patient Perspectives: Family Support Groups

The recent scientific statement from the American Heart Association (AHA) focuses on the importance of the patient perspective, as individual perceptions greatly affect behavior, and hence, adherence to lifestyle and medication interventions. Risk perception is personal and may be influenced by past experiences in the family. Face-to-face interviews with Australian patients involved in the local genetic cascade screening program aimed to determine their perceptions and experiences in relation to their health behaviors; most patients demonstrated understanding that FH was a permanent genetic condition. However, severity of risk perception was aligned with a personal or a family’s past experiences of symptomatic FH. This implies the need for clinicians to provide clear information to family members, particularly to those who are asymptomatic, in relation to the seriousness of FH and the necessity for adherence to therapies. Patients also felt that they had insufficient authority to persuade family members to attend screening and welcomed assistance from health professionals for contacting family members. Similar patient perceptions were found in an earlier Swedish study. In a Norwegian and Dutch study, FH children and their parents did not report anxiety effects. However, the children’s knowledge of the disease was poor, emphasizing the benefits of comprehensive family support.

Few studies have accessed the quality of life (QOL) of patients with FH. Even fewer are undertaken in interventional trials during treatment, and published data are limited to high-risk patients, mostly on apheresis. Further assessment of patient and families in different countries is required to ascertain patient-centric perceptions of FH disease, healthcare, and cascade screening to feedback into clinical practice.

Patient support and advocacy groups led by affected individuals have often helped to raise FH awareness in the general public. Interactions between national patient support groups to share and communicate ideas and resources would be helpful, particularly in the Asian region where advocacy activity is minimal. Activities to increase public recognition of FH have been undertaken on FH Awareness Day (September 24); this has been an annual national campaign run by the US FH Foundation since 2012. Advocacy groups in different countries have also adopted the date for FH awareness-raising activities.
levels of evidence with much reliance on a consensus view from experts. Such issues include timing and intensity of intervention, risk/benefit of cholesterol-lowering therapies in children, approaches to screening and cascade testing, practicability of universal screening, value of genetic testing, role of cardiovascular imaging in risk stratifying asymptomatic patients and plasma LDL-cholesterol concentration targets in children and adults. Further research based on high-quality international data is required to address these issues that should lead to greater global consensus. Standardized costing methods are required to support investment in programs for detecting and managing FH worldwide.

The AHA scientific statement has identified a number of key research needs in FH including models of care, population science (diagnostic criteria, screening, and registries), basic science, life course of disease, requirements for clinical research and patient-centered investigations (Table 3). Research gaps include better understanding of patient/family perspectives of living with FH, such as concerns about disease, medication, genetic testing and different aspects of care; diagnostic criteria for diverse populations (such as country-, age- and gender-specific LDL cholesterol levels); cost-effectiveness of universal and cascade screening methods; incorporation of subclinical atherosclerosis imaging into trials as risk stratifiers and decision aids for both patients and health professionals (i.e., tools to

### Health Economics

The inception and sustainability of effective healthcare of FH relies on adequate funding and resource allocation. A detailed and robust health economic evaluation of community detection, cascade screening, genetic testing, and treatment of patients identified with FH is requisite for supporting the case for funding by government bodies. Current health economic evaluations from the Netherlands, Australia, and the United Kingdom have shown that cascade screening, including genetic testing, is a cost-effective approach to detect FH. However, healthcare systems, population characteristics, and available resources in different countries require local models of care for FH detection and care. Country-specific health economic evaluations are important to drive policy change and government funding to implement and sustain screening and integrated care programs. International collaborations should aid programs of research and healthcare to fill the evidence and service gaps in FH.

### Research Agenda for FH

Despite the burgeoning number of guidelines and models of care on FH, several issues remain unresolved. These relate to the fact that healthcare recommendations regarding FH are chiefly based on diverse
help think through screening and treatment decisions)\textsuperscript{97}. Registries can facilitate all these investigations, including clinical trials\textsuperscript{89}. Meeting these recommendations requires a combined international effort.

### International Collaborations

The international drive to improve the detection and treatment of FH is underscored by several current international initiatives, such as the FH Studies Collaboration (FHSC)\textsuperscript{104} [incorporating the Homozygous autosomal dominant hypercholesterolemia (HoADH) International Clinical Collaboration (HICC)], the “10 Countries Study” based in the Asia-Pacific region\textsuperscript{38} and the “ScreenPro FH Project” based in central, southern and eastern Europe\textsuperscript{105} (Table 4). The Ibero-American FH Network and the Gulf FH Foundation are fostering collaborations with stakeholders to improve FH healthcare in their respective regions\textsuperscript{38}. Rather than fragmented attempts in respective countries, international efforts to share knowledge and expertise, initiate and develop research collaborations, and provide access to world-class infrastructure can lead efforts to address this global health challenge. The development and application of international web-based registries are forecasted to enable these collaborations.

### Conclusion

Generally, patients with FH have a very high risk of premature atherosclerotic CAD and need to be targeted for early intervention. As there is a major shortfall in the detection and treatment of FH in the world, the healthcare burden and reduced QOL of cardiovascular events are immense. Treatment for FH relies on statins and lifestyle measures and more extensive outcome data is required for combination therapy and the newer pharmacotherapy agents in both heterozygous and homozygous patients.

An integrated program of community screening, coronary care screening, and subsequent cascade screening needs to be established in most countries\textsuperscript{106, 107}. However, effective implementation of these screening programs and appropriate uptake of recommendations are challenges faced by many countries\textsuperscript{108, 109}. This requires close collaborations among clinical, bureaucratic, and political stakeholders to translate the evidence into societal-wide healthcare policy and subsequent financial support from available revenues\textsuperscript{110}. Further enhancement of existing lipid services and facilities is also warranted to optimize service models. It is also important to raise public awareness regarding the benefits of early detection of FH, and all preventative healthcare professionals should be familiar with FH. Regular auditing will allow service models to grow into a standard of excellence for the care of all patients with FH. Country-specific models of care and their implementation and sustainability are imperative to provide lifelong care for patients with FH.

The ongoing 10 Countries Study is likely to provide key data that will inform and enable the design and improvement of models of care for FH in the Asia Pacific region\textsuperscript{38}. International databases utilizing the registry framework will also play a key role\textsuperscript{111}.

### Competing Interests

Dr. Peter J Lansberg has received honoraria from...
Astrazeneca, Pfizer, and Sanofi. The other authors report no financial interests or potential conflicts of interest.

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Supplementary Table 1. Worldwide website resources for FH. Adapted from Watts et al\textsuperscript{13} and Vallejo-Vaz et al\textsuperscript{38}.

<table>
<thead>
<tr>
<th>Country</th>
<th>International FH Foundation</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Australian Heart Foundation</td>
<td><a href="http://www.heartfoundation.org.au">www.heartfoundation.org.au</a></td>
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International Developments in the Care of FH