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Reducing the Clinical and Public Health Burden of Familial Hypercholesterolemia
A Global Call to Action

Representatives of the Global Familial Hypercholesterolemia Community

IMPORTANCE Familial hypercholesterolemia (FH) is an underdiagnosed and undertreated genetic disorder that leads to premature morbidity and mortality due to atherosclerotic cardiovascular disease. Familial hypercholesterolemia affects 1 in 200 to 250 people around the world of every race and ethnicity. The lack of general awareness of FH among the public and medical community has resulted in only 10% of the FH population being diagnosed and adequately treated. The World Health Organization recognized FH as a public health priority in 1998 during a consultation meeting in Geneva, Switzerland. The World Health Organization report highlighted 11 recommendations to address FH worldwide, from diagnosis and treatment to family screening and education. Research since the 1998 report has increased understanding and awareness of FH, particularly in specialty areas, such as cardiology and lipidology. However, in the past 20 years, there has been little progress in implementing the 11 recommendations to prevent premature atherosclerotic cardiovascular disease in an entire generation of families with FH.

OBSERVATIONS In 2018, the Familial Hypercholesterolemia Foundation and the World Heart Federation convened the international FH community to update the 11 recommendations. Two meetings were held: one at the 2018 FH Foundation Global Summit and the other during the 2018 World Congress of Cardiology and Cardiovascular Health. Each meeting served as a platform for the FH community to examine the original recommendations, assess the gaps, and provide commentary on the revised recommendations. The Global Call to Action on Familial Hypercholesterolemia thus represents individuals with FH, advocacy leaders, scientific experts, policy makers, and the original authors of the 1998 World Health Organization report. Attendees from 40 countries brought perspectives on FH from low-, middle-, and high-income regions. Tables listing country-specific government support for FH care, existing country-specific and international FH scientific statements and guidelines, country-specific and international FH registries, and known FH advocacy organizations around the world were created.

CONCLUSIONS AND RELEVANCE By adopting the 9 updated public policy recommendations created for this document, covering awareness; advocacy; screening, testing, and diagnosis; treatment; family-based care; registries; research; and cost and value, individual countries have the opportunity to prevent atherosclerotic heart disease in their citizens carrying a gene associated with FH and, likely, all those with severe hypercholesterolemia as well.

Supplemental content

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Familial hypercholesterolemia (FH) is an underdiagnosed and undertreated genetic disorder that leads to premature morbidity and mortality due to atherosclerotic cardiovascular disease (ASCVD).[1,2] Carriers of a gene variant in any of the FH-related genes (ie, *LDL-R*, *APOB*, *PCSK9*, and *LDLRAP*) have a considerably greater risk of cardiovascular disease because of lifelong exposure to elevated cholesterol levels.[3,4] When left untreated, FH is the most common life-threatening genetic condition and is found around the world in all races and ethnic groups, with a prevalence of about 1:200-250 and, in some cases, higher owing to founder effects.[1,2] The first symptom of FH may be a myocardial infarction or sudden death at a young age.

Although the science related to FH has advanced rapidly since the 1998 World Health Organization (WHO) recommendations were published,[5] public awareness and implementation of the original recommendations regarding FH care have lagged substantially. The number 1 barrier to care for the 34 million people worldwide born with FH is lack of diagnosis. Health care clinicians across high-, middle-, and low-income countries underestimate the prevalence, high level of risk for morbidity and mortality due to premature ASCVD, importance of treatment initiation within the first 2 decades of life, and the inheritance pattern necessitating family screening. Additional issues, such as variation in guidelines, understanding by affected individuals of their condition, economic ramifications of living with and affording lifelong care, and pragmatic concerns surrounding possible genetic discrimination, pose additional barriers to care in the minority of people who are able to receive an accurate diagnosis.[1,2]

This Global Call to Action is intended to refocus attention on FH as a global health priority. Substantial gains to global health could be achieved by optimally diagnosing and treating FH (**Figure**).

Familial hypercholesterolemia meets current WHO criteria for screening: there is a defined target population, it causes premature morbidity, it is common, it is diagnosable, it is treatable, evidence-based guidelines exist for care, and examples of successful implementation of screening programs exist in many different settings.[1,2] In 1998, given both the need and the means available to identify and treat this population, the WHO and many members of the international FH community published the 1998 WHO Report on Familial Hypercholesterolemia[5] (**Box 1** and **Box 2**). Examples of successful implementation of FH care in the more than 20 years since that report exist globally (**Table 1**). Some countries have government-supported FH programs that have led to substantial improvements in recognition and treatment, with as much as a 76% reduction in premature cardiovascular disease rates for those identified.[25]

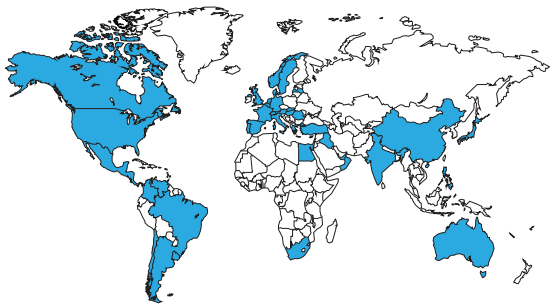
For most of the world's countries, few of the 11 WHO recommendations have been widely implemented, and today 9 of 10 people born with FH remain undiagnosed and therefore are not properly treated.[2,6] This lack of care leaves them and their families at high risk for ASCVD. The WHO report suggests the need for an interdisciplinary FH model of care that integrates primary and specialty therapy and includes lifelong care, emotional support (dealing with a genetic diagnosis, stress related to ASCVD, and lifelong need for medication), genetic counseling, and medication adherence strategies.[5,8] Advances in the understanding of FH, including basic science, epidemiologic factors, genetics, and drug development, have improved the prognosis for FH since the 1998 report. However, failure to implement the original recommendations has led to a lack of achievement of ASCVD prevention for most of the worldwide FH population, despite the presence of low-cost generic medications to lower cholesterol levels and guidelines for direct care (Box 1 and Box 2).[12,26,27]

The lack of awareness regarding FH among the general population, health care professionals, health care systems, and the public health community has created many health disparities. These disparities range from age- and sex-based differences for ASCVD prevention to the lack of access to preventive care and medications. Homozygous FH, as an especially severe form of FH affecting younger persons, requires additional resources with care guaranteed by government programs. Concerns about genetic discrimination have created barriers to FH recognition and early treatment. A need to provide new public policy recommendations following the WHO framework was perceived by the global FH community.

Developing the Global Call to Action

In 2018, the Familial Hypercholesterolemia Foundation and the World Heart Federation partnered to convene the international FH community of individuals with FH, advocacy leaders, scientific experts, and policy makers. The Call to Action was initiated at the FH Foundation Global Summit in Marina Del Rey, California, at a meeting held on October 3, 2018. Representatives from 23 countries agreed to attend and participated in the meeting, including members of advocacy groups and international societies dedicated to improving care

Figure. The Global Call to Action for Familial Hypercholesterolemia (FH)



Recommendations
- Raise awareness
- Advocate
- Screen, test, and diagnose
- Treat FH
- Guarantee care for severe and homozygous FH
- Develop family-based care plans
- Research and implement
- Fund FH registries
- Understand value and cost

There are 34 million people affected by FH of every sex, race, and ethnicity; 90% are undiagnosed. The participating countries are Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, Czech Republic, Denmark, Egypt, France, Germany, Greece, Hungary, India, Iraq, Italy, Japan, Latvia, Malta, Mexico, the Netherlands, Norway, Oman, Philippines, Portugal, Romania, Slovenia, South Africa, Spain, Sweden, Switzerland, Turkey, United Arab Emirates, United Kingdom, United States, Uruguay, and Venezuela.

Box 1. The 1998 WHO FH Recommendations, Gaps, and Scientific Progress, and the 2019 FH Public Policy Recommendations, Presented by Topic for the 2019 Recommendations: Awareness; Advocacy; Screening, Testing, and Diagnosis; and Treatment

Awareness

1998 WHO Recommendations[a]

1. Governments and national institutes of health should be made aware of the existence of this health hazard.
2. Awareness among the general public and the medical community should be promoted. The support of education about these disorders at the public, school, paramedical and medical level is required.
3. Specific education about these disorders should be provided at all levels, especially in medical training. There should be skills in primary health care to counsel about the risk of the disease, the dietary modifications, and knowledge about statins so that ongoing care can be given.

Gaps in Recommendations

- <10% of patients worldwide with FH are diagnosed; clinicians have limited knowledge of FH[2,6]
- Patients with FH require education regarding the condition.
- FH care remains in specialty care, not primary care
- Most countries do not have FH care programs
- Popular press and media often have incorrect information about statin safety and other lipid-lowering treatments[7]

Scientific Progress and Implementation of Recommendations

- Models of care and funding for FH care exist in some countries (Table 2)[8]
- Tier 1 genomic application for FH screening[4]
- General awareness about the high cardiovascular risk entailed by high cholesterol levels is widespread, although not specifically about FH
- Guidelines and scientific statements regarding FH care have been published worldwide (Table 2)

2019 FH Public Policy Recommendations[b]

Awareness should be enhanced regarding the importance of severe hypercholesterolemia and FH as a global public health issue; awareness should be raised in a broad range with the general public, educational institutions (both public and medical), the general medical community, and health care delivery systems.

Advocacy

1998 WHO Recommendations[a]

1. Specific attention may need to be given to the management of children with FH and careful research is called for the establishment of active patient organizations, focused on the implementation of the above-mentioned recommendations, is of utmost importance.

Gaps in Recommendations

- Very low general and medical FH awareness persists over the world.[2,6]
- Children remain underrecognized and undertreated worldwide.[2]

Scientific Progress and Implementation of Recommendations

- Advocacy organizations exist in several countries (eTable 1 in the Supplement)[9]
- Guidelines for pediatric care of FH developed (Table 2)

2019 FH Public Policy Recommendations[b]

Establishment of country/region specific advocacy organizations, focused on the implementation of the recommendations herein, is of utmost importance. Organizations should be a partnership of patients, physicians, and other health care professionals needed for FH care.

Screening, Testing, and Diagnosis

1998 WHO Recommendations[a]

1. As inherited lipid disorders are diagnosable and treatable in the primary health care context, treatment should be available on a fair basis of risk vs other chronic disorders.

Gaps in Recommendations

- FH care remains predominantly with specialists
- FH screening programs do not exist in most countries around the globe; genetic testing not available in many countries
- Discrimination surrounding genetic testing remains pervasive[10,11]

Scientific Progress and Implementation of Recommendations

- Diagnostic criteria have been developed based on genetic testing[1,2,12]
- Consensus phenotypic criteria have been developed[1]
- Genetic testing now exists for FH and cost is declining
- Cascade and universal screening programs now exist in a few countries around the world[4,13-18]

2019 FH Public Policy Recommendations[b]

Screening for FH should be performed according to country-specific conditions and guidelines. Screening, testing, and diagnosis may be based on cholesterol levels (with cutoff levels adapted to the country/target population) or positive genetic tests for an LDL cholesterol receptor function defect.

Treatment

1998 WHO Recommendations[a]

1. Patients must have unrestricted access to treatment and to cholesterol-lowering medication at no or low cost.
2. Long-term follow-up and drug adherence should be ensured.

Gaps in Recommendations

- Newer medications are not available everywhere in the world (PCSK9 inhibitors, lomitapide)[6]
- Limited studies on statin adherence for FH

Scientific Progress and Implementation of Recommendations

- Highly effective generic medications now exist (statins, ezetimibe)[1]
- FH care is cost-effective with statins and ezetimibe[16-18]
- Scientific rationale for early intervention established[19]
- Integration of health care clinicians other than physicians and social media present new opportunities for organizing care

2019 FH Public Policy Recommendations[b]

Screening for FH should be performed according to country-specific conditions and guidelines. Screening, testing, and diagnosis may be based on cholesterol levels (with cutoff levels adapted to the country/target population) or positive genetic tests for an LDL cholesterol receptor function defect.

Abbreviations: FH, familial hypercholesterolemia; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin kexin type 9; WHO, World Health Organization.

[a] The order of the 11 WHO recommendations has been modified to align with 2019 recommendations and many of the 1998 recommendations overlap with more than 1 of the new recommendations.

[b] See article body for full recommendations; text in the Box has been shortened for space considerations.

Box 2. The 1998 WHO FH Recommendations, Gaps, and Scientific Progress, and the 2019 FH Public Policy Recommendations, Presented by Topic for the 2019 Recommendations: Severe and Homozygous FH, Family-Based Care, Registries, Research, and Cost and Value

Severe and Homozygous FH

1998 WHO Recommendations[a]

1. Constraints for treating risk. If plasmapheresis is not available, statins with proven efficacy in homozygous FH should be considered.

Gaps in Recommendations

- Patients with homozygous FH remain difficult to treat and have reduced life expectancy[20]

Scientific Progress and Implementation of Recommendations

- High risk for atherosclerotic heart disease exists for those with very high LDL cholesterol regardless of heterozygous FH or homozygous FH status, presence of additional risk factors including lipoprotein(a) add risk[1,3,12,20,21]
- New therapies for homozygous FH are available and more are in development; liver transplant used in children[20]
- Life expectancy for those with homozygous FH has increased[20]

2019 FH Public Policy Recommendations[b]

Create, as a special case, separate guidelines for severe and homozygous FH, defined as either the presence of LDL cholesterol level ≥400 mg/dL or a pathogenic gene variant in any of the FH-related genes on 2 different alleles.

Family-Based Care

1998 WHO Recommendations[a]

1. A focus should be made on the family and the effect that bereavement could have on children. The plight of children with homozygous FH may need special consideration within budgetary.

Gaps in Recommendations

- Integrated care across the lifespan remains underdeveloped worldwide
- Protection against genetic discrimination needed

Scientific Progress and Implementation of Recommendations

- Improved understanding of the importance of family-based care for FH demonstrated[8,19]

2019 FH Public Policy Recommendations[b]

Develop a family-based care plan with opportunities for patient involvement and shared decision-making over the continuum of the life span.

Registries

1998 WHO Recommendations[a]

None.

Gaps in Recommendations

- Registries require sustained funding

Scientific Progress and Implementation of Recommendations

- FH registries exist worldwide and are providing important data on the state of FH care around the globe (eTable 1 in the Supplement).[22-24]

2019 FH Public Policy Recommendations[b]

Fund national and international FH registries for research to quantify current practices and identify the gaps between guidelines and health care delivery, to publish outcome metrics for monitoring and standardizing care, identify areas for future resource deployment, dissemination and defining best practices, as well as facilitating FH awareness and screening.

Research

1998 WHO Recommendations[a]

1. Research into the genetic and environmental factors influencing the expression of inherited lipid disorders, the development of atherosclerosis, and the pharmacologic characteristics and efficacy of lipid-lowering drugs should be stimulated. An indication is needed for ongoing research into the factors influencing heart disease, and how to intervene in the pathogenesis of the atherosclerotic process.

Gaps in Recommendations

- FH research underfunded internationally vs other conditions with similar or lower morbidity and mortality
- A research agenda for FH, identifying gaps, has been published and gained international acceptance[1]

Scientific Progress and Implementation of Recommendations

- Existing scientific statements, reviews, and guidelines continuously update FH research and progress (Table 2)
- Improved understanding of the genetic causes of FH, including mutations in *LDL-R*, *APOB*, *PCSK9*, *LDLRAP1*, and *LPA*

2019 FH Public Policy Recommendations[b]

Conduct basic science, genetic, epidemiologic, clinical, and implementation science research to improve FH care.

Cost and Value

1998 WHO Recommendations[a]

1. WHO should issue guidelines for identification, diagnosis, and medical management of inherited lipid disorders.

Gaps in Recommendations

- Cost of therapies for new medications remains high

Scientific Progress and Implementation of Recommendations

- Cost-effectiveness and value analyses of FH care exist and are being updated[4,13-18]
- An international guideline has been developed; European scientific statements have been published. Many country-specific guidelines exist (Table 2)[2,12]

2019 FH Public Policy Recommendations[b]

Understand value in FH care, both for the family and for society, including gained years of life expectancy, gained years of life without disability, and lost productivity.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin kexin type 9; WHO, World Health Organization.

SI conversion factor: To convert LDL cholesterol to millimoles per liter, multiply by 0.0259.

[a] The order of the 11 WHO recommendations has been modified to align with 2019 recommendations and many of the 1998 recommendations overlap with more than 1 of the new recommendations.

[b] See article body for full recommendations; text in the Box has been shortened for space considerations.

Table 1. Examples of Government Funding for FH Care, Research, Regulation of Payer Structure, and Support for Education

Country	Examples
Australia	• Subsidy for costs of seeing physicians (Medicare) • State health support for specialist services: physicians, nurses, and genetic counselors • Subsidy for PCSK9 inhibitors is for all patients with homozygous FH and patients with heterozygous FH patients with and without atherosclerotic cardiovascular disease (Pharmaceutical Benefits Scheme) • LLTs at a subsidized cost (Pharmaceutical Benefits Scheme) • Education and training programs for primary care and the testing of primary care screening throughout Australia (National Health and Medical Research Council Partnership Programme) • Translational research fellows (Medical Research Future Fund)
Austria	• Full reimbursement of the LLTs statins, ezetimibe, and PCSK9 inhibitors is provided under certain circumstances, for instance, in patients with proven statin intolerance and in secondary prevention for patients who had already had CV disease • Genetic testing is available but not automatically reimbursed in all of Austria's 9 federal states
Belgium	• Full reimbursement of LLTs based on Dutch Lipid Clinics Network score for statins, ezetimibe, and PCSK9 inhibitors • Genetic testing for FH reimbursed if Dutch Lipid Clinics Network >5 • Current multicenter studies on feasibility of cascade screening with field nurses and cholesterol assays in Belgium are being conducted • A Parliament conference was held November 20, 2015, with patients, health care professionals, payers, and policy makers to establish 10 recommendations for better management of FH in Belgium
Czech Republic	• Full reimbursement of LLTs: all statins (all doses), ezetimibe; PCSK9 inhibitors for patients with FH with LDL cholesterol level >154 mg/dL at maximum tolerated statin therapy • Genetic testing covered by national health insurance but has had to be requested from geneticists (since 2018) • Mandatory cholesterol testing in children aged 5 and 13 y in case of a premature CV event in their families by primary care pediatricians (this selective screening strategy should be a part of reimbursed care, but has not been fully implemented in practice) • Registry and lipid clinics network supported by the Czech Atherosclerosis Society, but not the government
Denmark	• No cost to patients for seeing physicians for FH or genetic testing • Nationwide quality control database to improve diagnosis, cascade screening, and treatment of patients with FH. By 2029, 15% of expected FH will be diagnosed with the aim of reaching 80% by 2029 • Statins and ezetimibe are inexpensive, while expensive therapies, such as PCSK9 inhibitors, are free to patients (ie, funded through taxes)
Germany	• Genetic testing is available if indicated by the treating physician, covered by national health insurance • PCSK9 inhibitors and lipoprotein apheresis are available, covered by private insurance • Reimbursement of lipid-lowering drugs by national health insurance, ie, statins, ezetimibe; reimbursement of PCSK9 inhibitors since 2015 • Reimbursement of lipoprotein apheresis since 1991 by national health insurance if approved by the apheresis committee of the regional association of statutory health insurance physicians, or by the individual's statutory or private health insurance fund according to German reimbursement guidelines
Hungary	• High percentage of reimbursement for LLTs: statin and ezetimibe • LDL cholesterol apheresis is reimbursed in main centers • No reimbursement for PCSK9 inhibitors (limited funding for severe FH cases) • Genetic screening available only in 1 center for limited patients
Iraq	• Iraqi lipid clinics networks for screening and management of adult and pediatric FH programs
Italy	• Pediatric and adult patients with FH are fully reimbursed by the public health care system including travel costs, physician/hospital costs, laboratory costs, and prescription medication • Establishment of lipid clinics network (treating and follow-up of families with high cholesterol levels) throughout the country in the 1980s • Guidelines on lipoprotein apheresis in homozygous and heterozygous FH available since 1990
Japan	• Reimbursement of LLTs: statins, ezetimibe, PCSK9 inhibitors, lipoprotein apheresis, lomitapide • Special reimbursement for homozygous FH and pediatric FH
The Netherlands	• Dutch government funded cascade screening; thereafter, FH screening became part of regular care and has been reimbursed by the insurance companies; government terminated funding by 2014 with decline in program efficacy • Full reimbursement of LLTs: all statins (all doses), ezetimibe, and PCSK9 inhibitors for patients with FH • Full lipid clinic network covering the entire country • Genetic testing for FH and other genetic dyslipidemias • Genetic cascade testing organization and national FH registry financed by the Department of Clinical Genetics at Amsterdam University Medical Center
Norway	• Fully reimbursed public health care system including travel costs, physician/hospital costs (eg, lipoprotein apheresis), laboratory costs (eg, genetic testing for FH), and prescription medication (eg, statins, ezetimibe, and PCSK9 inhibitors)[a] • Establishment of the lipid clinic (treating and follow-up of families with high cholesterol levels) in Oslo in 1984 • Unit for cardiac and CV genetics (genetic testing for FH and cascade screening) in 1998 • Since 2014, a yearly grant of 2.1 million NOK (approximately €220 000) to run a National Advisory Unit on FH[57]
Oman	• Oman Society for Lipid and Atherosclerosis and the International Atherosclerosis Society annually run 2 educational programs since 2015 • 2017 – educational program on the management of lipid disorders and severe FH for the physicians in the Middle East and North Africa regions • Oman cascade screening in Familial Hypercholesterolemia Index (Oryx) Registry
Portugal	• Director general of health recommended in the National Child Health Program that children between the ages 2 and 4 y with a family history of premature CV disease, sudden death, FH, and hereditary dyslipidemias be screened • Portugal has reference centers specializing in FH: metabolic unit, pediatric department, Centro Hospitalar Lisboa Norte, and cardiogenetics department, Hospitalar Lisboa Ocidental, Lisbon, and private hospitals • Portugal has variable reimbursement of therapeutics for FH, and LDL apheresis is free of charge • FH is included in the curriculum of Medical School at the University of Lisbon and specialist training programs for health care professionals

(continued)

Table 1. Examples of Government Funding for FH Care, Research, Regulation of Payer Structure, and Support for Education (continued)

Country	Examples
Slovenia	• Slovenia started universal screening for hypercholesterolemia in children aged 5 y in 1995 • Measuring total cholesterol level at the age of 5 y was formally mandated by the official leaflet of the Republic of Slovenia as an obligatory part of the blood checkup at the programmed visit of all children aged 5 y at the primary care pediatrician • Screening was gradually implemented through the whole country and only in the last few years, after investing efforts to better inform primary care pediatricians, the program now reaches approximately 20 000 children a year • In 2011, routine FH genetic testing was introduced at the University Children's Hospital Ljubljana Genetics Laboratory, which enabled more accurate diagnosis of FH and further improved implementation of universal FH screening programs • The universal FH screening program was a 2-step approach: (1) Universal hypercholesterolemia screening in preschool children (age 5-6 y) at their programmed visit at the primary care pediatrician; (2) Genetic FH screening in children referred to tertiary care level (lipid clinic at the University Children's Hospital Ljubljana) according to clinical guidelines, with additional cascade screening of family members and further clinical care as required. Universal hypercholesterolemia screening in preschool children (age 5-6 y) at their programmed visit at the primary care pediatrician. Genetic FH screening in children referred to tertiary care level (lipid clinic at the University Children's Hospital Ljubljana) according to clinical guidelines, with additional cascade screening of family members and further clinical care as required; (3) Financed by the national health insurance system of Slovenia; and (4) The genetic FH diagnostics, which is implemented into routine clinical practice, is currently still funded by hospital genetics funds and/or research projects, but in February of 2018 it was approved by the Slovenian National Council of Pediatrics, which is a precondition for obtaining regular funding by health insurance which we expect in the near future • Education about the universal FH screening program in Slovenia is part of the medical school curriculum and pediatrics residency and regularly presented to health care professionals at workshops, symposia, and on other occasions
Spain	• Reimbursement of LLTs: statins, ezetimibe, LDL apheresis, PCSK9 inhibitors • Genetic testing for FH in some Spanish regions • Some regional detection programs with participation of primary care practitioners in collaboration with the Fundación Hipercolesterolemia Familiar (Spanish FH Foundation) • National strategy for FH detection (pending approval) • SAFEHEART Registry developed by the Fundación Hipercolesterolemia Familiar • Online training for specialists and primary care practitioners
Sweden	• 2013: Strategy to manage patients with FH in the health care system • 2015: National Guidelines for Cardiac Care, cascade screening in adults and children • 2016: Swedeheart: the Cardiogenetics Register, which is a Swedish quality register for hereditary heart disease • 2017: Prescribed drugs for FH are reimbursed; PCKS9 inhibitors with some restriction; updated in 2019 to include more patients • 2018: Swedish Association of Local Authorities and Regions (21 with local governance) initiated national program areas focusing on best practice to secure same level of health care throughout Sweden. FH is 1 of 5 prioritized areas • 2019: Swedish-specific diagnostic code for FH

Turkey	• Reimbursement of LLTs: statins, ezetimibe
	• PCSK9 inhibitor (evolocumab) is reimbursed only for homozygous FH
	• LDL apheresis is widely available and fully reimbursed for FH and high lipoprotein(a)
	• Genetic testing is available for scientific purposes in academic centers
	• First lipid clinic was established in 1994 in Izmir for treatment of familial dyslipidemias
	• National FH awareness and treatment program was established in 2015 under the umbrella of the Turkish Society of Cardiology
	• National FH registries (A-HITs)
	  • A-HIT1: Registry of patients with homozygous FH undergoing lipid apheresis (88 pts, 19 centers)
	  • A-HIT2: Registry of patients with heterozygous FH (1071 pts, 30 centers; these centers are becoming a lipid network for familial dyslipidemias)
	  • A-HIT3: Registry of FH in premature myocardial infarction (2000 pts, 50 centers)
	• The universal cholesterol screening for children is not mandatory; however, Ministry of Health suggests:
	  • Screening of LDL levels in high-risk children in the first year of life
	  • For all others, LDL measurement to be done at ages 2-7 y or in puberty

United Kingdom	• Reimbursement for LLTs: statins, ezetimibe, and PCSK9 inhibitors • Reimbursement of nationally commissioned lomitapide and LDL apheresis • Genetic testing for FH in some UK regions; central national funding for genetic testing agreed from 2020 • National strategy in the 5-y forward plan to identify 25% of FH cases by 2024

(continued)

for individuals with FH, to revise the original WHO 1998 recommendations and work as an international community to drive global policy change regarding FH. On October 3, 2018, a revised set of recommendations was developed. With goals of increasing inclusion from the international community and further revising and updating the 1998 WHO recommendations, a second meeting was held during the World Congress of Cardiology and Cardiovascular Health in Dubai on December 6, 2018. The international coalition now represents 40 countries and added new advocacy organizations (Figure). Overall attendance included authors of the original 1998 WHO report on FH, patient advocacy organizations from around the world, and international scientific, medical, and public health experts.

This Global Call to Action aims to reinvigorate the WHO's interest in recognizing FH within their cardiovascular disease prevention strategies as well as advance national efforts to elevate FH as a public health priority. Final recommendations should be considered by countries around the world for implementation as new public policy initiatives regarding FH. The work herein reflects the discussion generated by these 2 meetings, which was reviewed, edited, and signed by all contributors.

Scientific Progress in the Past 20 Years

The prevalence of FH, originally thought to be about 1:500, has now been demonstrated to be approximately 1:250 worldwide, making it the most common genetic condition causing premature morbidity and mortality associated with ASCVD.[4] Improvements in FH knowledge have occurred in the past 20 years. These advances are highlighted in Boxes 1 and 2 and summarized in the FH-specific guide-

Table 1. Examples of Government Funding for FH Care, Research, Regulation of Payer Structure, and Support for Education (continued)

Country	Examples

United States	• FH designated as a tier 1 genomics application for family screening by the CDC
	• FH Foundation applied and advocated for a specific *ICD-10* code for Familial Hypercholesterolemia in the United States in 2014. In October 2016, 2 *ICD-10* codes went into effect after being approved by the *ICD-10* Coordination and Maintenance Committee of the Center for Medicare & Medicaid Services and the Centers for Disease Control and Prevention National Centers for Health Statistics:
	  • E78.01: Familial hypercholesterolemia
	  • Z83.42: Family history of familial hypercholesterolemia
	• In 2016, lomitapide received US Food and Drug Administration orphan product clinical development grant funding
	• All LLTs for FH, including apheresis and lomitapide, are covered by Medicare, Medicaid, and TriCare for patients who meet criteria
	• In November 2018, the National Heart, Lung and Blood Institute convened a workshop to develop a multidisciplinary, multilevel research agenda for late-stage translational research and implementation science in FH
	• National Heart, Lung and Blood Institute guidelines strongly recommend universal cholesterol screening:
	  • Between the ages of 9 and 11 y and again between 17 and 21 y
	  • At age 2 y if there is a positive family history of lipid and cholesterol disorders and/or premature heart disease in close family members
	• Million Hearts, a national initiative co-led by the CDC and CMS, has added cholesterol and FH as a key priority for reducing heart attacks in the United States
	• The National Academies of Sciences, Engineering, and Medicine created a Genomics and Population Health Action Collaborative and recruited a diverse group of stakeholders with an interest in integrating genomics at the population health level. The FH Foundation is leading the cascade screening working group
	• Since 2000, the West Virginia State Legislature has funded the CARDIAC Project to identify FH. This project offers free blood cholesterol level screening in West Virginia for:
	  • 20 Counties
	  • 134 Schools
	  • 15 072 students in kindergarten, 2nd grade, and 3rd grade

Uruguay	• In Uruguay, the National Program for the Early Detection and Treatment for FH is a centralized national registry that provides access for early diagnosis, genetic testing, cascade screening for patients with FH and their affected relatives. Of 347 cases analyzed so far, 202 patients are carriers of the *LDLR* gene mutations (97.6%) and 5 in the *APOB* gene (2.4%) of an expected population of between 6000 to 9000 carriers

Abbreviations: CV, cardiovascular; FH, familial hypercholesterolemia; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; LDL, low-density lipoprotein; LLTs, lipid-lowering therapies; PCSK9, proprotein convertase subtilisin kexin type 9.

SI conversion factor: To convert LDL cholesterol to millimoles per liter, multiply by 0.0259.

[a] A minor fee is charged per prescription of physician's appointment up to a maximum of 2360 NOK (approximately €240; $262 US) per patient per year in total for all health care system services, travel, expenses, and prescriptions. In FH primary prophylaxis if LDL cholesterol level is greater than 193 mg/dL maximal tolerable dose of statins and ezetimibe, or in any patient (also non-FH) in secondary prophylaxis if LFL cholesterol level is greater than 193 mg/dL.

lines, medical reviews, and scientific statements presented in **Table 2**. International and country-specific, evidence-based lipid guidelines often embed sections regarding FH care. An FH code was introduced in the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, in 2016.[1]

Successful screening programs, using cascade testing of first-degree relatives of identified adults and cascade testing of first-degree relatives of affected infants, have been reported.[13-15] These programs identify large numbers of previously unrecognized and untreated individuals with FH and are cost-effective.[16-18] Scoring systems to identify probands have been used successfully in many programs, including MEDPED, Simon Broome Registry, and Dutch Lipid clinics.[51] Probands identified are often younger than the index cases, have not experienced any ASCVD event, and are untreated.[4] An approach to genetic testing, including a definition of index cases for whom genetic testing should be considered, has been published.[4]

Beyond underdiagnosis, important barriers to FH care exist.[10,11] Cost of care, knowledge levels of health care clinicians and patients, guideline variation, competing health issues, understanding of risk, perceptions regarding personal control over health outcomes, and family influence all affect decision-making for this condition, because it is lifelong and puts different demands on families at different times of life. There appears to be clear value to families in establishing a diagnosis of FH that explains high cholesterol levels independent of lifestyle; however, in many countries, there is a personal cost to having this information, such as difficulty in obtaining life insurance or other forms of genetic discrimination.

Research on risk stratification, including the influence of lipoprotein(a), conventional cardiovascular risk factors, subclinical atherosclerosis imaging, and genetics is ongoing.[22] Effective lipid-lowering therapies, including statins and ezetimibe, are now available as generic medications for children and adults. In addition, there have been major advances in drug development for the treatment of FH.[12,26,27] Potent lipid-lowering therapies, such as inhibitors of proprotein convertase subtilisin kexin type 9 (PCSK9), have been shown to be safe and effective in large clinical trials and are available for patients who do not meet recommended lipid goals during statin and ezetimibe treatment. New therapies, such as lomitapide, are available in some jurisdictions for patients with homozygous FH, and a variety of other investigational agents are currently in development or being evaluated in clinical trials.[1,20]

Future research must address current gaps in knowledge. While observational data suggest that FH outcomes improve significantly with treatment earlier in life and carrying an FH gene triples the risk for ASCVD at any given level of low-density lipoprotein (LDL) cholesterol, therapeutic inertia exists.[10,11] Consensus has not been achieved on the exact timing of treatment initiation, FH-specific LDL cholesterol level goals related to early treatment, and the value of universal screening to identify FH.[2,19] Implementation research strategies to increase physician knowledge about FH and improve treatment adherence are needed and should be specific to individual countries.

Table 2. FH Scientific Statements and Guidelines

Country	Source
Argentina	Elikir et al,[28] 2018
Australia	The Cardiac Society of Australia and New Zealand,[29] 2016
Belgium	Descamps et al,[30] 2011
Brazil	Santos et al,[31] 2012
Canada	Brunham et al,[32] 2018
China	Atherosclerosis and Coronary Heart Disease Group of the Chinese Society of Cardiology of Chinese Medical Association, Editorial Board of *Chinese Journal of Cardiology*,[33] 2018
Colombia	Múñoz et al,[34] 2014
	Merchán et al,[35] 2016
Czech Republic	Vrablik et al,[36] 2015
France	Farnier et al,[37] 2013
Hong Kong	Tomlinson et al,[38] 2018
Italy	Cuchel et al,[20] 2014
	Stefanutti,[39] 2017
Japan	Harada-Shiba et al,[40] 2018
	Harada-Shiba M et al,[41] 2018
The Netherlands	Walma et al,[42] 2006
Poland	Myśiliwiac et al,[43] 2014
Spain	Mata et al,[44] 2015
Switzerland	Battegay et al,[45] 2004
Taiwan	Li et al,[46] 2017
United Kingdom	National Institute for Health and Care Excellence,[47] 2008
	France et al,[48] 2016
United States	Goldberg et al,[49] 2011
International reviews	Cuchel et al,[20] 2014
	Defesche et al,[50] 2017
	Vallejo-Vaz et al,[6] 2018
	Gidding et al,[1] 2015
	Nordestgaard et al,[2] 2013
	Santos et al,[21] 2016
	Sturm et al,[4] 2018
	Watts et al,[12] 2014
	Wiegman et al,[19] 2015

Abbreviation: FH, familial hypercholesterolemia.

Registry Documentation of FH Care Needs

National and international registries for FH were called for in the 1998 report and have been developed in many countries. Cystic fibrosis registries provide an example for how registries can facilitate improved care and outcomes.[52] A list of FH registries is presented in eTable 1 in the Supplement. The registries have provided information regarding the natural history of FH, documenting the harm of late recognition of FH, including the failure to prevent premature ASCVD, and care disparities for women and the underserved population. Registries also document the success of family-based FH screening in identifying previously untreated and unrecognized cases.[6,22-25,53] Registries have the potential to serve as resources of information spanning medical, scientific, and social aspects of care; repositories of data showing regional/geographic differences in care; a platform for patients enabling them to be participants in clinical trials; and vehicles for quality improvement and implementation of FH care, including transition of care from childhood to adulthood. International experience demonstrates that registries require governmental funding and support for sustainability. Components of a successful registry have been published.[23,24,53]

Patient Advocacy Organizations

Recognized in the 1998 report as key factors in better individual outcomes, patient advocacy organizations for FH have been established by individuals with FH in many countries.[9] A list of these organizations and components is presented in eTable 2 in the Supplement. Components of a successful advocacy organization have been published.[9] Advocacy organizations maintain registries, cultivate community support, connect stakeholders with disparate backgrounds, lead in enhancing patient-centered care, and provide a bridge between science and policy.

Advocacy organizations create an FH community that provides peer support. Such organizations help navigate long-term care and facilitate family screening, especially for homozygous FH, the most severe form. The organizations identify high-quality lipid treatment programs in individual countries and often facilitate the referral of patients from generalists to lipid specialists for advanced care, as well as provide education for patients and health care professionals, advocacy for government programs, funding and initiation of research, and awareness-raising campaigns.

Importance of Government Support

Screening and care for FH have been demonstrated to be cost-effective as has use of traditional cholesterol management guidelines on treating people with lower risk than those with FH.[16-18,54,55] Care for individuals with FH results in potential freedom from myocardial infarction, increased life expectancy, increased productivity, and absence of the strain placed on families owing to the occurrence of premature ASCVD or sudden death in a young mother or father.

All successful FH care programs around the world have benefited from government support to a multifactorial approach, including medical, nursing, pharmacologic, genetic counseling, nutrition, and psychology resources. Government support helps mandate and optimize medical care in parallel with the work of advocacy organizations' efforts to improve FH care, but a country-specific approach is needed. Although treatment strategies are clear, best practices to deliver guideline-based care in diverse settings need to be evaluated. Because resources and social structure vary by region and country, health care must be scalable for high-, middle-, and low-income countries.[6,56] How governments have created successful programs, raised awareness, educated health care professionals, addressed disparities, and monitored population outcomes is presented in Table 1. The final recommendations of this report should be considered for adoption as health policy around the world, as government support is necessary to guarantee care for the patients with FH who are the most severely affected and prevent genetic discrimination.

Recommendations of the Global Call to Action

Awareness

Awareness should be enhanced regarding the importance of severe hypercholesterolemia and FH as a global public health issue. Without general awareness of the need for detection and treatment beginning early in life, risk of ASCVD cannot be reduced in the estimated 34 million individuals affected worldwide. Awareness should be raised in a broad range of constituencies, including the general public, educational institutions (both public and medical), the general medical community (including primary and specialty care), and health care delivery systems. The annual worldwide FH Awareness Day is September 24.

Advocacy

Establishment of country/region-specific advocacy organizations, focused on the implementation of the recommendations presented herein, is important. Organizations should be a partnership of patients, physicians, and other health care professionals needed for FH care. Organizations should provide education and patient support for obtaining medical care. A country-specific toolkit should be developed to facilitate a basic understanding of how to create an advocacy organization, such as understanding the determinants of government health care policy, the health technology assessment process, regulations for lobbying governments, advocacy (including against genetic discrimination), communications, dissemination of information, and other basic fundamentals, regardless of income levels.

Screening, Testing, and Diagnosis

Screening for FH should be performed according to country-specific conditions and guidelines. Screening may be based on cholesterol levels (with cutoff levels adapted to the country/target population) or positive genetic tests for an LDL receptor function defect. A combination of universal child-parent screening and cascade testing of first- and second-degree relatives of index cases is more useful. Because many individuals with FH meet phenotypic criteria, these criteria could be used as a first step for wide screening programs and to identify those who may benefit the most from undergoing genetic testing where resources are limited. Resources for screening and diagnosis throughout the life course and risk stratification beginning in childhood should be available on a fair basis, respecting the best interests of the child, similar to other genetic conditions.

Treatment

Treatment for FH to prevent premature ASCVD should be person centered, available, and affordable. Ideally, treatment should begin in childhood and continue over the life course.

Severe and Homozygous FH

As a special case, separate guidelines should be created for severe and homozygous FH, defined as either the presence of LDL cholesterol levels 400 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0259) or a pathogenic gene variant in any of the FH-related genes on 2 different alleles. Guidelines should include strategies for FH identification, genetic diagnosis, differential diagnosis, and medical management of both secondary ASCVD and aortic valve disease. Specialized centers for diagnosis and management for these individuals are a requirement for optimal care. Care of individuals with severe and homozygous FH should be guaranteed by government.

Family-Based Care

A family-based care plan should be developed with opportunities for patient involvement and shared decision-making over the continuum of the life span. The model of care is best served via integration of primary and specialty care, screening of family members, genetic counseling, social support, community health workers, and developmentally specific resources (eg, childhood, pregnancy, adulthood, management of morbidities, grief counseling).

Registries

National and international FH registries for research should be funded to quantify current practices and identify the gaps between guidelines and health care delivery, publish outcome metrics for monitoring and standardizing care, identify areas for future resource deployment, disseminate and define best practices, and facilitate FH awareness and screening. If feasible, patient-centered approaches should be considered, such as a patient platform for data entry and education. Privacy and confidentiality should be ensured by health care professionals, patient advocacy organizations, data processors, and data handlers.

Research

Funding should be provided for research on the genetic and environmental factors influencing the expression of inherited lipid disorders, their natural history, the development of atherosclerosis, interventions to halt the progression of atherosclerosis, risk stratification, and the pharmacologic characteristics, safety, and efficacy of new and existing lipid-lowering drugs. Implementation science should be funded to determine optimal, affordable, and acceptable integrated health care delivery systems applicable to the regional structure. Implementation science has to address health care delivery using existing evidence-based guidelines at multiple levels: government, society as a whole, health care infrastructure, and health care encounters.

Cost and Value

Understanding the value of FH care, both for the family and society, including gained years of life expectancy, gained years of life without disability, and lost productivity, is necessary. If FH-specific health economic models (health technology assessment tool) to assess the value of intervention are considered, they must be flexible enough to allow each country to use them according to local circumstances. Ideally, models would be used to calculate value in quality-adjusted life-years or other acceptable metrics. The models should accommodate changes in characteristics (eg, cost of medication and testing) over time. Model components should include prevalence; screening approach (type of testing); cost of treatments, including events; and payers. The models should allow delineation of cost savings from preventive care and identification of previously untreated individuals from cascade testing if applicable.

Implications for Public Policy

Historically, FH has served as a paradigm for the cholesterol hypothesis with regard to ASCVD and translational medicine (discovery of the LDL receptor and PCSK9). Given the recent technological advances in both computing and genomics, in the future, FH may serve as a paradigm for bringing together the strengths of both public health and precision medicine approaches to care. The policies advocated herein may help to achieve long-term prevention goals for millions of people in a cost-effective manner.

By developing health systems to manage FH, the perfect model case to evaluate both the strengths and limitations of family-centered lifelong prevention will be created. Evaluating the implementation of programs that initiate simple population screening at young ages and then evolve in complexity to identify individuals who may benefit from new low-cost screening, genetic screening, and then more precise evaluation of family members through targeted cascading of first-degree relatives is both prudent and encompassing. Public awareness of efficient screening paired with providing generic medications for all individuals and improving access to more advanced therapies to those at high risk will serve as a model for how we evaluate the full spectrum of risk for atherosclerotic disease. Tailoring specific and life-saving therapies to those who can benefit most from them is the ultimate goal.

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