

# Reducing the Clinical and Public Health Burden of Familial Hypercholesterolemia

A Global Call to Action



In October 2018, the FH Foundation, at its annual Global Summit honored Roger Williams, MD, founder of cascade screening, to commemorate the twentieth anniversary of publication of the World Health Organization (WHO) Consultation on familial hypercholesterolemia (FH), the most common genetic disorder causing premature atherosclerotic cardiovascular disease, and underscore continued gaps in identification and care. <sup>1</sup> FH, with a prevalence of about 1:220-250 worldwide, causes lifelong elevated levels of low-density lipoprotein cholesterol (LDL-c).<sup>2,3</sup> Without treatment, 50% of affected men will have heart attacks by age 50 years and 30% of affected women will have heart attacks by age 60 years. FH has an autosomal dominant inheritance pattern, that is a parent with one FH-causing gene has a 50% chance of transmitting this gene to an offspring.

Since publication of the 1998 WHO consultation, tremendous scientific progress has occurred in understanding the genetics of FH, understanding atherosclerotic heart disease, and the development of medications to lower cholesterol and prevent heart attacks. However, many of the prescient recommendations of the WHO Consultation remain unfulfilled, particularly related to awareness of FH and education of the public and medical communities about FH. A major consequence of this failure has been under-diagnosis and under-treatment; about 90% of the world's estimated 34,000,000 people with FH remain undiagnosed and may of the rest are undertreated or have suffered premature heart disease or are at risk for sudden death. <sup>2,3</sup>

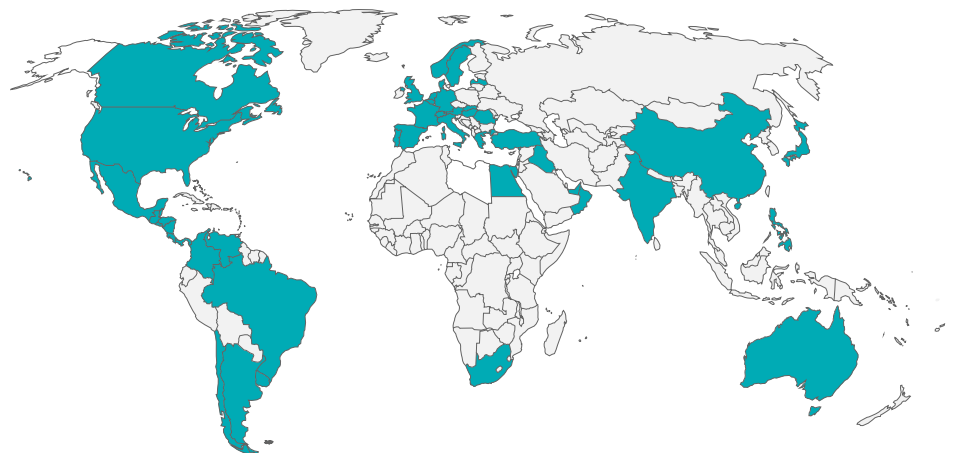
Since publication of the WHO report, several countries have developed successful FH care programs, FH medical registries have been established, and FH Advocacy groups have arisen worldwide. Critical to the most successful efforts has been government support. <sup>4</sup> Cascade genetic testing programs of affected relatives, unified models of FH care that span the life course (these include medical, nursing, pharmacologic, genetic counseling, nutrition and psychology resources), and evidence-based guidelines for FH care based on cost effectiveness research are examples of programs that can serve as generalizable models for other countries.

## Global Call to Action on Familial Hypercholesterolemia

34 million people worldwide impacted | 90% undiagnosed

### 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



Given the continued need to raise FH awareness worldwide and disseminate information regarding progress related to FH, the World Heart Federation and FH Foundation partnered to convene the original authors, the international community of FH patients, FH advocacy organizations, FH medical and scientific experts, and public health experts to develop a new set of global policy recommendations with regard to FH. The original 11 recommendations were revised into 9 new recommendations to reflect scientific progress and barriers to FH care which had occurred in the previous two decades. Forty countries participated in this effort at international meetings in 2018, the FH Global Summit and the World Conference of Cardiology, and thorough internet communication to produce the recommendations listed below. The goal was to create a document that could be used by high-, middle-, and low-income countries around the world to improve FH care. <sup>4</sup>

## RECOMMENDATIONS OF THE GLOBAL CALL TO ACTION<sup>4</sup>

### Awareness

Awareness should be enhanced regarding the importance of FH and severe hypercholesterolemia 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 affected world-wide. 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 FH Awareness Day is September 24th.

***Because FH is under-diagnosed and under-treated the first recommendation is to raise awareness.***

### Advocacy

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. 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 healthcare policy, the health technology assessment process, regulations for lobbying governments, advocacy (including against genetic discrimination), communications, and dissemination of information, and other basic fundamentals regardless of income levels.

***To improve FH care, knowledgeable champions must lead the effort. Many FH Advocacy organizations with partner patients with FH scientific content experts fulfill this role.***

### 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 cut-off 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 effective. As many with FH meet phenotypic criteria, these could be used as a first step for wide screening programs and to identify those who may benefit the most from performing 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.

***Successful models for FH identification, including screening for new cases, use of either genetic testing or clinical criteria for diagnosis, exist and can be implemented.***

## **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.

***FH treatment goals are evidence-based, and embedded in cardiovascular prevention guidelines worldwide. These can be implemented by physicians and allied health care providers.***

## **Severe and Homozygous FH**

Create, as a special case, separate guidelines for severe and homozygous FH, defined as either the presence of LDL cholesterol > 10 mmol/L (400 mg/dL) or a pathogenic gene variant in any of the FH-related genes on 2 different alleles. Guidelines should include strategies for its identification, genetic diagnosis, differential diagnosis, and medical management (both secondary ASCVD and aortic valve disease). Specialized centers for diagnosis and management for these individuals are a requirement for optimal care. Care of severe and homozygous should be guaranteed by government.

***The most severe forms of adult FH with LDL-c values > 10 mmol/L or 400 mg/dl cause morbidity and mortality early in life and create significant burdens for families. Thus care of these patients requires unique resources.***

## **Family-Based Care**

Develop a family-based care plan 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 (childhood, pregnancy, adulthood, management of morbidities, grief counseling).

***Because FH is a genetic condition affecting all generations and presents different challenges at different times of life, care should be organized across the life course.***

## **Research**

Fund research into 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 pharmacology, safety, and efficacy of new and existing lipid-lowering drugs.

Implementation science should be funded to determine optimal, affordable, and acceptable integrated healthcare 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, the health care infrastructure and, at health care encounters.

***More needs to be learned about FH, not just scientific and medical advances, but also identification of the best ways to improve FH care within the many health care delivery systems around the world.***

## Registries

Fund national and international FH registries for research to quantify current practices and identify the gaps between guidelines and healthcare 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. If feasible, patient-centered approaches should be considered such as a patient platform for data entry and education. Privacy and confidentiality should be assured by healthcare providers, patient advocacy organizations, data processors, and data handlers.

***FH registries have provided vital information on the evolving natural history of FH, including information on awareness, success of treatment, and outcomes.***

## Cost/Value

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. 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 utilized to calculate value in quality adjusted life-years (QALY) or other acceptable metrics. They should accommodate changes in model characteristics (e.g. cost of medication and testing) over time. Model components should include prevalence, screening approach (type of testing), cost of treatments including events, and payers. They should allow delineation of cost savings from preventive care and identification of previously untreated individuals from cascade testing if applicable.

***FH care must be affordable and be valuable to all stakeholders.***

## SUMMARY

The international FH community is anxious to implement the Global Call to Action within individual countries. This document can be used to develop country-specific goals and metrics to improve care and prevent heart attacks across the world. Historically, FH has served a model for understanding the causes of heart disease and developing preventive treatments so that many people do not suffer the consequences of a heart attack. If this global effort is successful, a precision medicine goal of utilizing genetic tools to save lives can be achieved.

## REFERENCES

- <sup>1</sup> Familial Hypercholesterolemia [FH]: Report of a WHO Consultation. World Health Organization, Human Genetics Programme, Division of Noncommunicable Diseases. WHO/HGN/FH/CONS/98.7. Geneva, 1998
- <sup>2</sup> Gidding SS, Champagne MA, de Ferranti SD, et al. The Agenda for Familial Hypercholesterolemia A Scientific Statement From the American Heart Association. *Circulation*. 2015;132(22):2167-92
- <sup>3</sup> Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J*. 2013;34(45):3478-90(a).
- <sup>4</sup> Representatives of the Global Familial Hypercholesterolemia Community (Gidding SS, last author). Reducing the Clinical and Public Health Burden of Familial Hypercholesterolemia. *JAMA Cardiol*. 2020: epub ahead of print

