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# Familial Hypercholesterolemia in India: Current Challenges in Diagnosis and Management

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**ABSTRACT**

**Background:** Familial hypercholesterolemia (FH) is a genetic lipid disorder with an autosomal dominant inheritance, characterized by lifelong elevations of low-density lipoprotein cholesterol (LDL-C) levels from early childhood. This lifelong exposure to high LDL-C markedly increases the risk of premature atherosclerotic cardiovascular disease (ASCVD)**.** Although globally affecting approximately 1 in 250 individuals, FH remains significantly under-recognized in India, where millions are likely affected but remain undiagnosed.

**Review:** This narrative review summarizes current evidence regarding the epidemiology, genetic basis, diagnostic approaches, clinical manifestations, and management strategies of FH in the Indian population. Existing challenges, including limited physician awareness, inadequate access to genetic testing, lack of nationwide screening programs, and financial barriers to advanced lipid-lowering therapies, are also discussed. Recent advances in therapeutic options and the importance of cascade screening and national registries are highlighted.

**Conclusion:** India faces a critical gap in the identification and management of FH. Immediate priorities include physician education, implementing cascade screening, expanding affordable genetic testing, and establishing a nationwide FH registry. Recent lipid-lowering therapies such as PCSK9 inhibitors, inclisiran, bempedoic acid, and evinacumab have shown considerable benefit in managing resistant cases; however, their widespread use is limited by high treatment costs.

**Keywords:** Familial hypercholesterolemia, LDL receptor, LDLR mutations, PCSK9, cascade screening, premature coronary artery disease, lipid-lowering therapy, genetic testing, cardiovascular risk

## 1. INTRODUCTION

Cardiovascular disease (CVD) is the top killer in India, representing a large proportion of premature mortality and increasing economic burden on the health system. In this context, familial hypercholesterolemia (FH) is one of the most important inherited metabolic diseases that cause early-onset atherosclerotic disease.

FH is characterized by lifelong elevation of LDL cholesterol beginning at birth, leading to accelerated atherosclerotic plaque formation over decades. In untreated individuals, this sustained lipid burden can increase the risk of coronary artery disease by more than 10–20 times compared with the general population, significantly reducing life expectancy. [1,2]

Globally, heterozygous FH (HeFH) is believed to affect roughly 1 in 250-350 individuals, translating to approximately 30–40 million affected individuals worldwide.[3] In India, with a population exceeding 1.4

billion, this prevalence implies that at least 5 million individuals may harbor FH-causing mutations—yet the vast majority remain undiagnosed and untreated.[4]

India faces a dual epidemiological challenge: a high burden of premature CAD (occurring 5–10 years earlier than in Western counterparts) combined with a grossly underdeveloped infrastructure for hereditary cardiovascular disease management. Despite these alarming statistics, FH has not received the clinical and public health attention it warrants. The proportion of diagnosed cases in India is thought to remain extremely low, though no formal national diagnostic audit exists.[5]

This narrative review summarizes current evidence on FH in India, examining epidemiology, genetic spectrum, diagnostic tools, clinical management, and emerging therapies, and identifies systemic, educational, and infrastructural barriers that continue to impede progress in this domain.

## 2. EPIDEMIOLOGY AND BURDEN OF FH IN INDIA

### 2.1 Global Context

Familial hypercholesterolemia (FH) is a relatively common monogenic disorder of lipid metabolism with heterozygous forms estimated at 1 in 250–300 individuals worldwide. Homozygous FH is much less common, with a reported prevalence of 1 in 160,000 to 1 in 1,000,000. On a global scale, FH represents a major but underdiagnosed contributor to premature cardiovascular disease, particularly in populations with limited access to genetic screening and lipid specialist services.

The Asia–Pacific region is believed to carry a substantial share of the global FH burden, reflecting both population size and increasing prevalence of premature coronary artery disease. However, diagnosis rates remain low across most low- and middle-income countries, where systematic screening programs are largely absent.[8]

### 2.2 Indian Prevalence Data

Epidemiological data on FH specifically from India remain sparse. The most comprehensive prevalence estimate from India comes from a study by Sawhney et al. (2019), which assessed 635 patients with premature coronary artery disease (PCAD) attending a tertiary care hospital in North India, and found an FH prevalence of 15% as per the Dutch Lipid Clinic Network (DLCN) criteria.[9] This figure is substantially higher than population estimates, reflecting the enrichment of FH in premature CAD cohorts.

A subsequent study conducted in Ranchi, Jharkhand, by Prajapati et al. (2022), involving 200 patients with angiographically confirmed premature CAD, detected FH in 23.5% of cases using DLCN criteria, with LDL-C concentration being highest in definite FH (250.39 mg/dl), followed by probable FH (184.32 mg/dl) and possible FH (136.11 mg/dl). Notably, corneal arcus was found in 55.31% of potential FH patients in this cohort.[10]

Barde et al. (2022), applying DLCN criteria to LDL-C values>155 mg/dL, observed definite, probable, and possible FH in 90 patients at Max Hospital, further corroborating the notion that true FH prevalence in the Indian population is likely underestimated.[11]

A community-based opportunistic screening study conducted across outpatient departments of two hospitals in Rajasthan by Gupta et al. (2022) demonstrated the feasibility of health-worker-led screening. Among 2,549 statin-naive participants evaluated with DLCN criteria, a meaningful proportion met criteria for possible or probable HeFH, and the study demonstrated that non-physician health workers could screen 25–30 individuals per day with high concordance with clinician assessments.[12]

Severe hypercholesterolemia (LDL-C > 190 mg/dL) was reported in nearly 1 in 300 individuals in a multisite study, with a similar prevalence observed in a Delhi school-based study, suggesting that FH may

be as common as 1 in 300 in urban Indian populations.[13]

## 3. PATHOPHYSIOLOGY AND GENETICS

### 3.1 Molecular Basis of FH

Genetic defects in the clearance of low-density lipoprotein cholesterol from the circulation are the main cause of familial hypercholesterolemia. The gene most implicated is LDLR, which encodes the LDL receptor responsible for the hepatic uptake and degradation of circulating LDL particles. Loss-of-function mutations in LDLR reduce receptor activity, leading to impaired LDL clearance and a persistent increase in plasma LDL-C from birth. These mutations explain most cases of FH worldwide.[14]

Other genetic contributors include gain-of-function mutations in PCSK9, which increase LDL receptor degradation, and mutations in APOB, which impair LDL particle binding to its receptor. Together, these mechanisms converge on reduced hepatic clearance of LDL cholesterol. Rare forms of FH are associated with mutations in genes such as LDLRAP1, leading to autosomal recessive hypercholesterolemia. In addition, several modifier genes, including APOE, LIPA, STAP1, CETP, APOA5, EPHX2, and SREBP2, have been implicated in patients with FH-like phenotypes but without classical mutations.[15]

Clinically, disease severity correlates with the functional impact of the mutation. Null mutations in LDLR, which completely abolish receptor function, are associated with markedly elevated LDL-C levels and early-onset cardiovascular disease. In contrast, defective mutations that retain partial receptor activity generally result in a milder phenotype.[16]

### 3.2 Genetic Landscape of FH in India

Genetic data on familial hypercholesterolemia (FH) in India are extremely limited, with only six formal genetic studies published as of 2022.[5.] Across these studies, involving a total of 245 FH patients, LDLR mutations account for approximately 32% of identified mutations, APOB mutations for 4%, and PCSK9 mutations for 2%. Critically, the mutational spectrum remains unknown in approximately 37% of patients, highlighting Considerable gaps exist in current knowledge of FH molecular epidemiology within the Indian population.

In the largest single-center genetic analysis of familial hypercholesterolemia (FH) in Asian Indians, Setia et al. (2020) used Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) of the LDLR, APOB, PCSK9, and APOE genes in 100 unrelated probands. We identified 38 pathogenic variants in 47 individuals, including 33 in LDLR, 3 in APOB, and 2 in PCSK9, of which 10 were novel. A probable founder mutation in intron 10 of LDLR (c.1587-1G>A) was identified in six North Indian families. Interestingly, common pathogenic variants commonly observed in Western populations were mostly absent in this cohort, indicating considerable genetic heterogeneity.[17]

Reddy et al. (2021) performed targeted exome sequencing of a 23-gene lipid panel in 54 South Indian FH patients and identified 19 mutations in 28 (52%) subjects, including a novel LDLR frameshift mutation. Importantly, ~73% of clinically identified FH patients did not have mutations in major FH genes, including LDLR, APOB, and PCSK9, strongly implicating polygenic inheritance and non-classical FH-associated genes, including CETP, APOA5, EPHX2, and SREBP2, which were identified for the first time in Indian FH patients.[18]

Screening of PCSK9 and LDLR by Reddy et al. (2021) in western Indian FH patients identified three previously reported pathogenic variants, along with one benign variant, in the hotspot exons of LDLR. No pathogenic PCSK9 variants were detected, suggesting PCSK9 mutations may be clinically less relevant in the western Indian population.[19]

A recent study from Telangana by Bhatt et al. (2025) further expanded the genetic landscape, confirming novel mutations and reinforcing the notion that Indian FH patients harbor distinct, population-specific mutations that differ from those described in European or North American cohorts.[20]

Ashavaid et al. (2000), the earliest genetic study from India, further characterized LDLR heterogeneity in North and South Indian cohorts, highlighting geographic variation in the mutation spectrum across Indian subpopulations. In addition, mutations in LDLR exons 3 and 4 have been reported in 25 FH patients across multiple studies (Kulkarni et al., 2011; Aruljothi et al., 2016; Setia et al., 2016, 2018) [5]

These findings collectively underscore three critical points: (1) genetic heterogeneity is greater in India than in most Western populations; (2) conventional mutation panels designed for European FH may miss a substantial proportion of Indian FH cases; and (3) next-generation sequencing (NGS) approaches with broader gene panels are essential for comprehensive genetic characterization of FH in India.

**Table 1: Summary of Published Genetic Studies on FH in India**

| Study / Year | Region / Center | N Probands | Genes Studied | Key Findings |
|---|---|---|---|---|
| Ashavaid et al., 2000 | Mumbai | 25 | LDLR (Exons 3, 4) | First Indian genetic study; mutations in LDLR exons 3 and 4 |
| Kulkarni et al., 2011 | Karnataka | Not specified | LDLR | Demonstrated LDLR gene heterogeneity in Indian families |
| Aruljothi et al., 2016 | South India | Not specified | LDLR | Molecular analysis of LDLR in CAD patients: population-specific variants |
| Setia et al., 2016 | Delhi/North India | Not specified | LDLR, APOB, PCSK9 | 4 novel mutations in HoFH; spectrum of mutations in homozygous FH |
| Setia et al., 2020 | Delhi (AIIMS) | 100 | LDLR, APOB, PCSK9, APOE (NGS + Sanger) | 47 of 100 had pathogenic variants; founder mutation in LDLR intron 10; 10 novel variants |
| Reddy et al., 2021 | Mumbai / South India | 54 | 23-gene lipid panel (NGS) | 52% had mutations; 73% lacked classical gene variants; CETP, APOA5, EPHX2 novel in India |
| Reddy et al., 2021 (PCSK9/LDLR) | Western India | 50 | PCSK9 (all 12 exons), LDLR (Exons 3,4,9) | 3 pathogenic LDLR variants; no pathogenic PCSK9 variants; PCSK9 may be less relevant in western India |

## 4. CLINICAL PRESENTATION

### 4.1 Heterozygous FH (HeFH)

Heterozygous familial hypercholesterolemia (HeFH) is the more frequently encountered form of the disease and affects nearly 1 in 250–300 individuals globally. Patients typically exhibit markedly elevated total cholesterol and LDL-C concentrations from early life, usually with LDL-C levels above 190 mg/dL in the absence of secondary causes of hypercholesterolemia.

Clinical manifestations may include tendon xanthomas involving the Achilles tendon or extensor tendons of the hands, xanthelasma, and premature corneal arcus, particularly in younger individuals. However, many patients do not display obvious physical findings, making lipid profiling and family history crucial for diagnosis. .[21]

If left untreated, HeFH substantially increases the lifetime risk of premature atherosclerotic cardiovascular disease. Coronary artery disease may develop decades earlier than in the general population, and myocardial infarction frequently occurs before the age of 50 years in affected men and before 60 years in affected women. .[22]

In Indian cohorts, premature CAD occurs 5–10 years earlier than in Western patients, compounding the urgency of early FH detection. CVD prevalence in urban India is 6.5–13.2% and in rural India 1.6–7.4%, with both figures rising steadily.[23]

### 4.2 Homozygous FH (HoFH)

HoFH is a rare but devastating condition, occurring in approximately 1 in 160,000 to 1 in 1,000,000 individuals, with LDL-C levels typically between 500 and 1,000 mg/dL. Clinical manifestations include prominent cutaneous xanthomas, tuberous xanthomas, and aortic root stenosis, often manifesting in the first decade of life. Without treatment, the mean age of the first major CV event is as young as 20 years.[24]

The HICC (Homozygous International Clinical Collaboration) Registry has demonstrated that HoFH patients on maximal pharmacological therapy still frequently require lipoprotein apheresis to achieve adequate LDL-C reduction. India currently lacks formal lipoprotein apheresis centers integrated into routine FH care pathways, representing a critical gap in management infrastructure.[25]

## 5. DIAGNOSTIC APPROACHES AND CURRENT CHALLENGES

### 5.1 Clinical Diagnostic Criteria

Three validated clinical criteria are currently employed for FH diagnosis: (1) the Dutch Lipid Clinic Network Criteria (DLCN), (2) the Simon Broome (SB) criteria, and (3) the MEDPED (Make Early Diagnosis to Prevent Early Deaths) program criteria.[26]

The DLCN criteria use a point-based scoring system integrating family history, personal history of premature ASCVD, physical examination findings, and LDL-C levels to classify patients as definite (>8 points), probable (6–8 points), possible (3–5 points), or unlikely (<3 points) FH. The DLCN has been the most widely used tool in Indian studies and is considered optimal for lipid clinic settings. [26,27]

The Simon Broome criteria classify FH as definite (tendon xanthoma plus TC >290 mg/dL or LDL-C >190 mg/dL; or positive DNA test) or possible (TC >290 mg/dL or LDL-C >190 mg/dL plus family history of premature CHD or high cholesterol). While easier to apply in primary care settings, the Simon Broome criteria may miss cases without physical signs, a limitation particularly relevant in Indian patients, where physical examination is often cursory.[28]

Neither the DLCN nor Simon Broome criteria have been formally validated in Indian populations. This represents a significant concern: the LDL-C thresholds used in these European-developed tools may need

recalibration for Indian ethnic groups, which exhibit distinct lipid profiles, body mass indices, and dietary patterns. No India-specific diagnostic scoring tool has yet been developed or validated.[29]

### 5.2 Genetic Testing: Status and Challenges

Genetic testing remains the gold standard for FH diagnosis, enabling definitive confirmation, risk stratification, and cascade screening. In India, however, genetic testing for FH is in its infancy. The major challenges include the high cost of next-generation sequencing panels (typically INR 15,000–50,000 per test in private laboratories), limited insurance coverage, limited availability outside metropolitan cities, and the absence of standardized laboratory reporting for FH-causing variants. [5,18]

Given the distinct mutational spectrum of FH in India compared to Western populations, commercially available FH mutation panels (designed for Dutch, French-Canadian, or South African founder mutations) are likely to have low sensitivity in Indian patients. Whole-gene or whole-exome sequencing approaches are preferable but remain prohibitively expensive for widespread clinical implementation. [17,18]

Indian studies have demonstrated that even among definite FH cases (DLCN score >8), only 91.4% harbored a detectable pathogenic variant, implying that a significant proportion of clinically evident FH cases may be genetically unresolved with current testing strategies. This likely reflects polygenic contributions, uncharacterized variants, or mutations in non-classical FH genes not included in standard panels.[17]

### 5.3 Underdiagnosis: Key Contributing Factors

The pervasive underdiagnosis of FH in India can be attributed to multiple interacting factors:

- **Low physician awareness:** Most primary care physicians and general practitioners lack awareness of FH diagnostic criteria, the significance of family history of premature CAD, and appropriate referral pathways. A study from Saudi Arabia (with likely parallels to India) found substantial deficits in physician knowledge of FH, cascade screening, and statin alternatives.
- **Absence of systematic screening programs:** India has no national or state-level FH screening program. Identification relies predominantly on incidental detection during lipid profiling or after a cardiovascular reactive rather than proactive approach.
- **Lack of lipid specialist services:** Dedicated lipid clinics are confined to a small number of tertiary centers, primarily in major metropolitan cities. The vast majority of FH patients in tier 2 and tier 3 cities, as well as in rural areas, have no access to specialist care.
- **Delayed presentation:** FH is asymptomatic until ASCVD events occur. Without routine lipid screening, most Indian patients first present after a heart attack or stroke, by which time significant irreversible atherosclerotic damage has occurred.
- **Ethnic-specific challenges:** The higher average LDL-C thresholds used in Western diagnostic criteria may lead to under-referral of Indian FH patients who have LDL-C levels that are elevated for their ethnic group but fall below Western cut-offs.
- **Limited registry infrastructure:** Only 215 Indian patient records had been entered into the EAS-FHSC global registry as of 2022, from just three contributing centers (Mumbai, Delhi, Chennai)—a grossly inadequate representation of a population of 1.4 billion.

## 6. MANAGEMENT OF FH IN INDIA

### 6.1 Lifestyle Modification

Lifestyle interventions form the cornerstone of FH management but are insufficient as monotherapy. Non-pharmacological interventions—including a low–saturated fat, high-fiber diet, regular aerobic activity,

avoidance of smoking, and correction of secondary hypercholesterolemia causes such as hypothyroidism, nephrotic syndrome, and obesity—are essential alongside drug therapy. In HoFH, dietary changes have negligible effects on LDL-C as there are no functional LDL receptors to upregulate.[29]

### 6.2 Pharmacological Therapy

#### 6.2.1 Statins

High-intensity statins constitute the first-line pharmacological treatment for familial hypercholesterolemia. Agents such as atorvastatin and rosuvastatin significantly reduce LDL-C concentrations by enhancing hepatic LDL receptor expression and increasing LDL clearance.

Early initiation of statin therapy is strongly recommended, particularly in children and young adults with FH, as prolonged LDL-C exposure is directly associated with cumulative cardiovascular risk.

In India, generic statins are widely available and comparatively affordable. Nevertheless, long-term adherence remains suboptimal because of poor awareness, fear of adverse effects, irregular follow-up, and lack of structured counseling.[31]

Despite maximal statin therapy, many high-risk FH patients fail to achieve recommended LDL-C targets, necessitating combination treatment with additional lipid-lowering agents.[32]

#### 6.2.2 Ezetimibe

Ezetimibe (10 mg/day) reduces LDL-C by an additional 15–25% when added to statin therapy by inhibiting intestinal cholesterol absorption. It is recommended as second-line therapy in FH. In India, ezetimibe is widely available as a generic and is moderately affordable, though its prescription rates in FH patients remain low due to insufficient physician awareness.[19]

#### 6.2.3 PCSK9 Inhibitors

Monoclonal antibodies against PCSK9—evolocumab (Repatha®) and alirocumab (Praluent®)—represent a major therapeutic advance. When added to maximally tolerated statin therapy, PCSK9 inhibitors reduce LDL-C by 50–60% in HeFH and are FDA- and EMA-approved for both HeFH and HoFH (evolocumab is approved only for HoFH).[33] Both agents are administered as subcutaneous injections every 2–4 weeks and have demonstrated favorable safety profiles in pivotal trials.

Despite regulatory approval in India, PCSK9 inhibitors are prohibitively expensive (approximately INR 15,000–30,000 per injection, with no current insurance coverage for most patients), effectively limiting their use to a small minority of affluent patients. This represents one of the most critical access barriers to optimal FH management in India.[4]

#### 6.2.4 Inclisiran

Inclisiran, a first-in-class small interfering RNA (siRNA) targeting hepatic PCSK9 mRNA, offers the advantage of twice-yearly subcutaneous dosing. The ORION-9 trial demonstrated an approximately 45% reduction in LDL-C in HeFH patients already on maximally tolerated statins.[35] Its twice-yearly dosing may address adherence challenges in resource-constrained settings, but it is not yet approved or available in India.

#### 6.2.5 Bempedoic Acid

As an oral ATP-citrate lyase inhibitor, bempedoic acid reduces LDL-C levels by approximately 15–18% as monotherapy. It has a favorable safety profile, particularly because it lacks statin-related muscle toxicity. It serves as adjunct therapy in statin-intolerant FH patients or those with inadequate lipid control. Despite regulatory approval in the USA and Europe, it remains unavailable in the Indian market.[35]

#### 6.2.6 Evinacumab

Evinacumab is a monoclonal antibody against angiopoietin-like 3 (ANGPTL3), an LDL-receptor-indepe-

ndent mechanism that can reduce LDL-C by more than 50% even in patients with null LDLR mutations—making it uniquely valuable for HoFH. The FDA currently approves it for HoFH. Given its LDLR-independent mechanism, it is the only therapy likely to benefit patients with a complete absence of LDL receptor function.[36]

### 6.2.7 Lipoprotein Apheresis

Lipoprotein apheresis—extracorporeal removal of ApoB-containing lipoproteins—is the standard of care for HoFH patients who fail to achieve adequate LDL-C reduction on combined pharmacotherapy. Weekly or biweekly apheresis can achieve LDL-C reductions of 50–70% per session, with additional benefits of reducing lipoprotein(a) levels.[37]

Unfortunately, lipoprotein apheresis is virtually unavailable in the routine clinical setting in India. The few centers capable of performing the procedure lack the necessary equipment and trained personnel, and no public or private insurance scheme covers the procedure. This represents a catastrophic gap in care for HoFH patients in India, who currently have no viable rescue therapy when pharmacological options are exhausted.

### 6.2.8 Lomitapide

Lomitapide, a microsomal triglyceride transfer protein (MTP) inhibitor, is approved as an adjunct to a low-fat diet and other lipid-lowering treatments in adults with HoFH. It reduces LDL-C by approximately 40–50% but is associated with hepatotoxicity and gastrointestinal side effects. It is neither approved nor available in India.

**Table 2: Lipid-Lowering Therapies for FH – Efficacy and Availability in India**

| Drug | Mechanism | LDL-C Reduction | FH Indication | India Availability | Affordability |
|---|---|---|---|---|---|
| High-intensity statins | HMG-CoA reductase inhibition | 50–60% | HeFH, HoFH | Available | Affordable (generic) |
| Ezetimibe | Intestinal cholesterol absorption inhibitor | 15–25% (add-on) | HeFH, HoFH | Available | Moderately affordable |
| Evolocumab / Alirocumab | PCSK9 monoclonal antibody | 50–60% | HeFH, HoFH (evolocumab) | Approved, limited access | Very expensive; no insurance coverage |
| Inclisiran | PCSK9 siRNA | ~45% | HeFH | Not approved in India | N/A |
| Bempedoic acid | ATP-citrate lyase inhibitor | ~18% | HeFH (statin-intolerant) | Not approved in India | N/A |

| | | | | | |
|---|---|---|---|---|---|
| Evinacumab | ANGPTL3 inhibitor | >50% | HoFH | Not approved in India | N/A |
| Lomitapide | MTP inhibitor | 40–50% | HoFH (adults) | Not approved in India | N/A |
| Lipoprotein apheresis | Extracorporeal LDL removal | 50–70% per session | HoFH; refractory HeFH | Virtually unavailable | No infrastructure; no coverage |

### 6.3 Pediatric Management

Early diagnosis and treatment of FH in childhood is critical, as atherosclerosis begins in youth and lifelong LDL-C exposure drives cumulative cardiovascular risk. Carotid intima-media thickness (CIMT) is measurably elevated in FH children as young as 8 years old.[38]

Current guidelines recommend initiating statin therapy in children with FH aged 8–10 years (or earlier in HoFH), with an LDL-C target of <130 mg/dL in the absence of other risk factors. A study by Setia et al. (2018) on cascade screening in Indian FH children demonstrated that of 133 family members tested from 31 probands, 88 (66.1%) carried the family mutation, including 12 children below 18 years.[39]

In India, statins are not routinely prescribed to children with FH due to regulatory concerns, lack of pediatric lipid specialists, and low awareness among pediatricians. No dedicated pediatric FH clinic exists in India outside a few academic centers, leaving an entire generation of FH children without appropriate treatment.

## 7. SCREENING STRATEGIES: GLOBAL MODELS AND APPLICABILITY IN INDIA

### 7.1 Cascade Screening

Cascade screening involves targeted testing of biological relatives of diagnosed FH patients and is regarded as the most efficient and evidence-based method for case detection. Since FH follows an autosomal dominant inheritance pattern, first-degree relatives have a one-in-two risk of inheriting the condition.[40]

DNA-based cascade screening is superior to cholesterol-based cascade screening in specificity and sensitivity. The Setia et al. (2018) Indian study demonstrated that molecular testing of family members identified 66% of relatives as mutation carriers, a yield that justifies the investment in genetic testing.[39]

International studies confirm that cascade screening is cost-effective, with a cost per life-year gained comparable to other accepted preventive healthcare interventions.

In India, cascade screening is in its infancy. Barriers include the cost of genetic testing, cultural reluctance to disclose hereditary disease within families, lack of structured family communication protocols, absence of government mandates, and privacy concerns. The EAS-FHSC global registry has highlighted that cascade screening is one of the most underprioritized components of FH care in developing nations.[8]

### 7.2 Opportunistic Screening

The feasibility study by Gupta et al. (2022) in Rajasthan demonstrated that health-worker-led opportunistic screening at hospital biochemistry laboratories, using DLCN criteria, is a practical, scalable, and cost-

effective approach to FH detection in low-resource settings.[12] This model, which requires only a trained non-physician health worker, a fasting lipid profile, and a structured questionnaire, could be replicated across India's large district hospital and primary health center network.

### 7.3 Universal Childhood Lipid Screening

The NHLBI Expert Panel has recommended universal cholesterol screening in children aged 9–11 years to enable early detection of familial hypercholesterolemia (FH). Similarly, the EAS-FHSC global registry has emphasized universal childhood lipid screening as an effective strategy for identifying FH prior to the development of atherosclerotic cardiovascular disease (ASCVD).[41] In India, there is no national childhood cholesterol screening program. A school-based pilot study in Delhi reported FH-equivalent hypercholesterolemia in approximately 1 in 300 children, suggesting the potential yield of such a program would be substantial.

## 8. KEY CHALLENGES AND BARRIERS IN INDIA

### 8.1 Healthcare System Barriers

India's healthcare infrastructure faces structural challenges that compound the FH burden: (1) a predominantly outpatient-focused primary care system without systematic chronic disease management programs; (2) a large, unorganized private sector with highly variable standards; (3) inadequate health insurance coverage for preventive care and genetic testing; and (4) limited electronic health records, making family history documentation inconsistent.

### 8.2 Physician Education Gaps

FH remains absent from most undergraduate and postgraduate medical curricula in India. The concept of familial hypercholesterolemia as a distinct, actionable genetic diagnosis—rather than 'high cholesterol'—is not widely appreciated by physicians, general practitioners, or cardiologists outside academic centers. National guidelines from the Cardiological Society of India (CSI) have increasingly emphasized FH, but dissemination remains inadequate.

### 8.3 Financial and Access Barriers

The high cost of PCSK9 inhibitors (INR 15,000–30,000 per injection), genetic testing (INR 15,000–50,000 for comprehensive panels), and lipoprotein apheresis sessions places definitive FH management beyond the reach of the vast majority of Indian patients. India's out-of-pocket health expenditure remains among the highest globally, and FH patients requiring complex management are particularly vulnerable to catastrophic health expenditure.

### 8.4 Absence of a National FH Registry

A national FH registry is an essential prerequisite for understanding disease burden, monitoring treatment outcomes, facilitating cascade screening, and guiding health policy. As of 2022, only three Indian centers (Mumbai, Delhi, Chennai) contribute data to the EAS-FHSC global registry, with a total of 215 patient records—representing a fraction of 1% of the estimated 5 million affected Indians. Establishing an all-India FH registry, as proposed by Reddy et al. (2022), is an urgent national priority.[5]

### 8.5 Cultural and Societal Factors

Cultural factors unique to the Indian context further complicate FH management. Consanguineous marriages in several communities increase the risk of HoFH. Reluctance to disclose hereditary disease information within families impedes cascade screening. Dietary practices (high ghee and coconut oil intake, and high carbohydrate intake) in many populations exacerbate LDL-C elevations. Moreover, deeply held beliefs about medication use and natural remedies may reduce statin adherence.

## 9. RECOMMENDATIONS AND WAY FORWARD

**Table 3: Priority Recommendations for FH Management in India**

| Domain | Recommendation | Priority | Implementers |
|---|---|---|---|
| Registry | Establish a national Indian FH Registry integrated with the EAS-FHSC, covering all major states and population groups. | Immediate | Govt., CSI, ICMR |
| Screening | Implement routine lipid screening at ages 9–11 in schools and opportunistic screening at primary healthcare facilities. | High | Ministry of Health, State Govts. |
| Cascade Screening | Develop structured, funded cascade screening programs with family tracing for confirmed FH index cases. | High | Lipid specialists, Genetics departments. |
| Physician Education | Integrate FH education into UG/PG curricula; mandatory CME for cardiologists, physicians, and GPs | High | MCI/NMC, CSI, API |
| Genetic Testing | Develop affordable, India-specific FH gene panels; subsidize NGS testing through PMJAY or state health schemes. | Medium-High | ICMR, Private Diagnostics |
| Drug Access | Negotiate price caps for PCSK9 inhibitors; pursue inclusion in the National Essential Medicines List; expedite approval of inclisiran and bempedoic acid. | High | CDSCO, Ministry of Health |
| Apheresis | Establish at least one lipoprotein apheresis center per major state; develop insurance coverage protocols. | Medium | Govt. medical colleges, AIIMS |
| Guidelines | Develop India-specific FH diagnostic criteria validated in the Indian population; revise CSI lipid guidelines with a dedicated FH section. | Medium | CSI, Endocrine Society of India |

## 10. CONCLUSION

Familial hypercholesterolemia represents an enormous but largely invisible cardiovascular disease burden in India. The convergence of a high-risk ethnic background for premature CAD, a genetic predisposition to severe hypercholesterolemia, and a healthcare system unprepared to diagnose and manage FH creates a perfect storm of preventable cardiovascular mortality.

Published evidence clearly demonstrates that FH affects approximately 15–23% of premature CAD cohorts in India, the genetic spectrum is distinct from Western populations with significant unexplained

heterogeneity, clinical diagnostic tools are underutilized, cascade screening is nearly nonexistent, newer evidence-based therapies are financially inaccessible, and a coherent national strategy is absent.

The imperative is clear: India must treat FH as a national public health priority. A coordinated response involving physician education, national screening programs, affordable genetic testing, equitable drug access, lipoprotein apheresis infrastructure, and a comprehensive national FH registry is urgently needed. The potential gain from early identification and treatment of the estimated 5 million Indians living with FH—in life-years saved, ASCVD events prevented, and healthcare costs avoided—would be enormous. The technology, guidelines, and evidence base exist. What is needed is the political will and healthcare investment to translate them into action.

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