Familial Hypercholesterolaemia in the Precision Medicine Era: Epidemiology, Genetics, Risk Stratification, and Therapeutic Innovations

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Familial hypercholesterolaemia is a common autosomal dominant inherited lipid disorder marked by persistently elevated plasma LDL-C levels from birth, resulting in a substantially increased risk of premature ASCVD, particularly coronary artery disease (Nordestgaard et al., 2013). The heterozygous form (HeFH) affects about 1 in 250 individuals worldwide, while the more severe homozygous form (HoFH) affects approximately 1 in 300,000 (Defesche et al., 2017). Untreated FH confers a 10- to 20-fold greater risk of early coronary events, with many patients developing symptoms before age 55 (Khera et al., 2016). Despite this prevalence and risk, FH remains underdiagnosed and undertreated: large registry data show that fewer than 10% of individuals with genetically confirmed FH are aware of their diagnosis, and a much smaller proportion achieve LDL-C goals (Simon Broome Register Group, 2008; Harada-Shiba et al., 2024).

Historically, FH diagnosis relied heavily on clinical criteria, family history, and lipid levels, with genetic testing gradually integrated into practice. However, variable phenotypic expression and genetic heterogeneity complicate diagnosis (Marks et al., 2019). Traditional therapies focused on statins and ezetimibe, reducing LDL-C and ASCVD risk but often insufficient to normalize LDL-C, especially in HoFH cases (Sabatine et al., 2017).

Recent advances have revolutionized the field: next-generation sequencing enables rapid and comprehensive mutation identification; cascade and universal pediatric screening programs improve early detection; and a burgeoning pipeline of novel therapeutics—PCSK9 inhibitors, inclisiran, ANGPTL3 inhibitors, and emerging gene-editing therapies—promise unprecedented LDL-C lowering and event reduction (Ray et al., 2020; Rosenson et al., 2023). Furthermore, precision risk stratification incorporating polygenic risk scores, imaging, and biomarkers guides individualized therapy intensity and timing.

This review covers epidemiology, genetic diagnostics, screening strategies, risk assessment, therapeutic innovations, and models of care, emphasizing current challenges and future opportunities. The goal is to inform clinicians and researchers on the evolving standards to transform FH from a largely undiagnosed killer to a manageable or potentially curable condition.

Epidemiology and Natural History

Recent large-scale population studies and international registries confirm that HeFH affects approximately 1 in 250 individuals globally, a prevalence much higher than historically believed (Harada-Shiba et al., 2024). Founder populations experience even higher rates, as do some specific ethnic groups influenced by genetic bottlenecks (Goldstein et al., 2021). Untreated individuals with HeFH have up to 20-fold enhanced risk of ASCVD, including myocardial infarction, stroke, and peripheral arterial disease, while HoFH presents with clinical manifestations often in childhood and a near-certain risk of early mortality if untreated (Cuchel et al., 2013; Khera et al., 2016).

Subclinical atherosclerosis is detectable early by carotid intima-media thickness and coronary calcium scoring, underscoring the need for early identification and intervention (Gidding et al., 2015). Phenotypic presentation and risk vary by genetic mutation severity, polygenic risk burden, sex, and environmental factors such as smoking and diet (Tada et al., 2020). Early and sustained LDL-C lowering profoundly modifies natural history, supporting lifetime risk reduction.

Genetic Architecture and Diagnosis

FH is predominantly caused by mutations in LDLR, APOB, or PCSK9 genes, with LDLR variants comprising the majority of pathogenic mutations (>1500 reported) (Defesche et al., 2017). Advances in next-generation sequencing now enable comprehensive mutation detection—even in atypical presentations—and facilitate family cascade screening and personalized care (Khera et al., 2016).

Polygenic hypercholesterolaemia—due to multiple common LDL-C-raising loci—mimics FH phenotypically but differs in risk and inheritance patterns. Polygenic risk scores aid in distinguishing these forms, improving prognostication (Tada et al., 2020). Where genetic testing is unavailable, phenotypic diagnostic tools such as Dutch Lipid Clinic Network and Simon Broome criteria remain essential and have been refined for pediatric and diverse populations (Marks et al., 2019).

Cascade Screening and Population Policies

Cascade testing of relatives represents the most cost-effective method for FH identification, leveraging autosomal dominant inheritance (Weng et al., 2016). Universal pediatric lipid screening supplements cascade approaches, especially in populations with small families or unclear histories, detecting cases early (Ramaswami et al., 2017). Reverse cascade screening from affected children enhances family-wide detection.

Barriers include limited awareness, resource variability, lack of genetic counsellors, and inconsistent reimbursement (Harada-Shiba et al., 2024). Successful programs benefit from centralized registries and integrated electronic health records.

Risk Stratification Beyond LDL-C

Risk stratification now integrates traditional LDL-C with biomarkers (lipoprotein(a), hsCRP), polygenic scores, and imaging (CAC, carotid IMT) to personalize risk and treatment intensity (Gidding et al., 2015). CAC scoring, in particular, refines risk categorization, influencing treatment escalation decisions.

Therapeutic Innovations

- **Statins** reduce LDL-C 20–50% and lower ASCVD risk, remaining first-line in adults and children (Sabatine et al., 2017).
- **Ezetimibe and bile acid sequestrants** augment LDL-C lowering, suitable in statin-intolerant or pediatric use (Ramaswami et al., 2017).
- **PCSK9 monoclonal antibodies** (evolocumab, alirocumab) cut LDL-C by ~60%, improving outcomes and approved for adults and pediatrics (Raal et al., 2020).

- **Inclisiran**, an siRNA silencing PCSK9 hepatic synthesis, offers durable LDL-C lowering with biannual dosing (Ray et al., 2020).
- **ANGPTL3 inhibitors** (evinacumab, zodasiran) benefit HoFH and severe cases by LDLR-independent pathways (Rosenson et al., 2023).
- **Lomitapide and mipomersen** are last-resort options, limited by safety concerns (Cuchel et al., 2013).
- **Emerging agents** include oral PCSK9 inhibitors, apolipoprotein(a) antisense oligonucleotides, and lipid nanoparticle–delivered gene therapies (Rosenson et al., 2023).

Gene Therapy and Editing

Gene therapies harness CRISPR/Cas9 and base editing for permanent gene modification to silence PCSK9 or ANGPTL3, offering potential lifelong LDL lowering (CRISPR Clinical Trials Update, 2024). Early human trials show promising LDL-C reductions with acceptable safety, though long-term outcomes and ethical considerations remain focal points (Cuchel et al., 2013).

Psychosocial and Equity Issues

Adherence depends on health literacy, family support, and socioeconomic factors. Stigma and misconceptions affect engagement. Disparities in access to diagnostics and novel therapies persist, especially in low- and middle-income countries, gender, and ethnic minorities (Harada-Shiba et al., 2024).

GLP-1 Receptor Agonists in Gout, Axial Spondyloarthritis, and Arthritis

Gout prevalence is rising globally, particularly in obese and cardiometabolic risk patients (Cross et al., 2024). GLP-1 receptor agonists (GLP-1RAs), while not urate-lowering agents, may reduce gout flare severity and frequency by promoting weight loss and improving metabolic and renal comorbidities (Karacabeyli et al., 2025; Steinmetz et al., 2023). Real-world data hint at cardiovascular benefit in gout patients on GLP-1RAs (MedCentral, 2025).

In axial spondyloarthritis (axSpA), GLP-1RAs show promise in reducing systemic inflammation in preclinical models, with potential for cardiovascular risk mitigation, though clinical data remain limited (Karacabeyli et al., 2025).

Mechanistic studies show GLP-1RAs modulate immune responses, suppress pro-inflammatory cytokines, promote regulatory T-cell activity, and protect cartilage via autophagy enhancement (Liu et al., 2017; Chen et al., 2018). Their safety profile is favorable; gastrointestinal side effects are the most common concern.

GLP-1RAs are thus adjunctive in arthritis management, particularly for patients with obesity or metabolic syndrome, with ongoing trials needed to define precise disease-modifying effects.

Conclusion:

Familial hypercholesterolaemia (FH) continues to be a significant global health concern due to its

high prevalence, genetic complexity, and association with accelerated atherosclerotic cardiovascular disease (ASCVD). Despite advances, FH remains underdiagnosed and undertreated, necessitating urgent improvements in all aspects of care from diagnosis to treatment. Recent genetic, molecular, and therapeutic breakthroughs—including precision screening, powerful lipid-lowering agents like PCSK9 inhibitors, and emerging gene therapies—have transformed the landscape. As implementation science and societal efforts evolve, the future of FH management promises more equitable, effective, and potentially curative strategies. This expanded conclusion synthesizes the current state and outlines critical future directions.

Advancements in the understanding of FH genetics have revolutionized diagnosis and risk stratification. Comprehensive next-generation sequencing panels and polygenic risk scores complement traditional clinical criteria by improving detection accuracy, especially in atypical or borderline cases. The growing use of universal pediatric lipid screening and family cascade approaches worldwide enhances early case identification when preventative intervention yields maximal benefit (Harada-Shiba et al., 2024; Weng et al., 2016). Nevertheless, barriers remain, such as limited awareness, lack of infrastructure for genetic counselling, and inconsistent reimbursement policies—factors that create pronounced inequities in diagnosis and care access (Nordestgaard et al., 2013).

On the therapeutic front, the armamentarium has expanded beyond statins and ezetimibe, the longstanding foundation of LDL-C lowering. PCSK9 monoclonal antibodies markedly reduce LDL-C further, with robust cardiovascular efficacy also demonstrated in children and statin-intolerant patients (Raal et al., 2020; Sabatine et al., 2017). Inclisiran's twice-yearly dosing regimen improves adherence, while ANGPTL3 inhibitors offer LDL receptor–independent mechanisms, critical for homozygous cases and therapy-resistant patients (Ray et al., 2020; Rosenson et al., 2023). Lomitapide and mipomersen, though more limited by adverse effects, complement management in the most severe phenotypes (Cuchel et al., 2013).

The frontier of gene therapy introduces exciting possibilities for durable and potentially curative treatment. RNA-targeted therapies such as siRNAs and antisense oligonucleotides offer potent, reversible gene silencing, exemplified by inclisiran and investigational ANGPTL3-targeted agents. Concurrently, genome editing technologies (CRISPR/Cas9, base editors) are advancing rapidly, with several early human trials reporting substantial LDL-C reduction following in vivo gene modification while demonstrating acceptable short-term safety profiles (CRISPR Clinical Trials Update, 2024). Despite enthusiasm, long-term safety, off-target mutation risks, patient selection, and ethical governance remain paramount considerations before clinical integration can be broadly endorsed.

Important psychosocial and systemic challenges must be redressed. Patient adherence depends heavily on education, cultural competence, and family dynamics, while substantial disparities persist in health literacy, socioeconomic status, and healthcare access (Harada-Shiba et al., 2024). Women, ethnic minorities, and patients in low- and middle-income countries remain disproportionately underdiagnosed and undertreated. Achieving equity requires integrated public health efforts, subsidized genetic testing, accessible multidisciplinary care, and innovative digital health solutions (Simon Broome Register Group, 2008).

Risk stratification has evolved to integrate imaging (coronary calcium scoring, carotid ultrasounds), biomarkers (lipoprotein(a), inflammatory markers), and genetics, allowing personalized LDL-C targets and therapy intensity aligned with individual ASCVD risk. This multi-dimensional approach enhances resource prioritization and disease management (Gidding et al., 2015; Tada et al., 2020).

Looking forward, critical research gaps include expanding trial evidence across diverse populations (including pediatrics and ethnic minorities), refining gene therapy protocols, evaluating long-term safety and cost-effectiveness of emerging therapies, and developing accessible models of care

adaptable to varied healthcare settings. Iterative integration of digital health and artificial intelligence promises to enhance identification, adherence monitoring, and risk prediction for FH patients, accelerating precision in both diagnosis and treatment (Topol, 2019).

In conclusion, FH exemplifies the triumphs and challenges of translating molecular insight into clinical and public health impact. The condition remains underdetected and undertreated but no longer incurable or unmanageable. Advances in genomic diagnostics, therapeutic innovation, and risk stratification now provide the tools to transform lives. The imperative is to close global gaps in diagnosis and care, tailor treatments with precision, and deliver equitable access. As gene editing and precision medicine mature, FH stands on the cusp of a new era where personalized, possibly lifelong cures become feasible. By sustaining research, improving implementation, and prioritizing patient-centered care, cardiovascular medicine can realize FH's potential as a preventable cause of premature ASCVD worldwide.

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