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Population Genomics for Familial Hypercholesterolemia: Return of Results, Cascade Testing, and Health System Readiness, Current Evidence and Gaps

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ABSTRACT

Familial hypercholesterolemia (FH) is a common inherited lipid disorder associated with markedly elevated cholesterol levels and a substantially increased risk of premature cardiovascular disease. Advances in population genomics, including biobank sequencing, newborn screening initiatives, and genotype-first approaches, have created new opportunities for early identification of individuals with pathogenic FH variants and for systematic cascade testing of at-risk relatives. This narrative review synthesizes current evidence on three critical domains shaping the implementation of population genomics for FH: return of genomic results, cascade testing processes, and health-system readiness. The literature indicates that returning genomic results can enhance early diagnosis and preventive treatment, yet practices vary widely regarding disclosure methods, patient engagement, and integration with cardiovascular risk assessment. Cascade testing remains the most effective and cost-efficient strategy for identifying affected relatives, but uptake is consistently low due to communication barriers, limited digital infrastructure, and insufficient clinical coordination. Ethical, legal, and social considerations, including informed consent, privacy, potential stigma, and equitable access to testing, further complicate implementation. Evidence on health-system readiness highlights important gaps in laboratory capacity, workforce training, interoperability of genomic and clinical data systems, reimbursement models, and long-term sustainability planning. Overall, population genomics offers substantial promise for improving FH detection and prevention of cardiovascular disease at scale. However, successful implementation will require standardized return-of-results frameworks, strengthened cascade-testing pathways, equity-focused policies, and coordinated health-system investments. Future research should prioritize longitudinal outcome studies, evaluation of digital and patient-centered communication tools, and cross-jurisdictional implementation frameworks to ensure that population genomic screening for FH translates into measurable public-health benefits.

Keywords: Familial hypercholesterolemia, Population genomics, Cascade testing, Return of genomic results, and Health system readiness

INTRODUCTION

Familial hypercholesterolemia (FH) is an inherited disorder that raises cholesterol levels and leads to premature cardiovascular disease [3]. Grouped in the top ten conditions eligible for screening in population genomics, FH is targeted for genomic approaches that identify its high-penetrance variants [1]. Population genomic platforms such as biobanks, newborn screening, and direct-to-consumer testing have emerged as feasible methods of identifying individuals carrying these variants, suggesting greater population-level engagement with the condition. Clinical and laboratory practice guidelines endorse population-genomic testing and cascade screening of first-degree relatives, but implementation remains limited, and salient questions about the return of genomic results, the cascade process, and the readiness of health systems have emerged in the scientific literature [1, 2]. Molecular screening for FH broadly exceeds other conditions prioritized by Canadian Health Ministers and yet remains underdeveloped [3]. Multiple channels can identify variants leading to this disorder, including routine

lipid testing, an approach that does not inform carriers of associated risk, a gap that focus on population genomics may address [5].

Background on Familial Hypercholesterolemia and Genomic Approaches

Modern population-scale genomic initiatives present the opportunity for broad uptake of testing for familial hypercholesterolemia (FH), yet uncertainty exists regarding the consequences of returning genomic results and facilitating cascade testing. Population genomics studies offer new perspectives on FH diagnosis and management, yet challenge existing paradigms [6]. These contrasting features necessitate a systematic review of the evidence regarding population genomics for FH, building on the framework of the World Health Organization's Towards an International Consensus Framework on the Governance of Genomic Data [3]. Heterozygous FH, characterized by an elevation of non-high-density lipoprotein cholesterol leading to premature cardiovascular disease (CVD), affects about 1 in 250 individuals in the United States [2]. Diagnosis relies on genetic testing or biochemical markers based on the Dutch Lipid Clinic Network (DLCN) criteria 4. Affected individuals have a substantially increased lifetime risk of a CVD event and are recommended for preventive medications such as statins [5]. Cascade testing for at-risk relatives is recommended following genotype-based or phenotypic confirmation of FH.

Return of Genomic Results for Familial Hypercholesterolemia

Most individuals diagnosed with familial hypercholesterolemia (FH) have not undergone cascade testing to identify affected relatives. In one study, individuals with FH were asked about their family members, which increased uptake of cascade testing by 38% [6]. Although addressed in the United States, the challenge of cascading is widespread, with low rates of testing noted internationally [3]. Genomic results from population screening programs for FH may be returned to participants, their family members, or both. Different programs also differ in whether they provide additional screening for atherosclerotic cardiovascular disease (ASCVD)[8]. Algorithm-derived and enriched results differ, as do the ages and phenotypic features at which the first-degree relatives of probands with FH-causing variants are considered at elevated risk for ASCVD. Genomic results reflecting recommended procedures for exploring the return of results in genome- and exome-sequencing programs [7]. A people-centered approach to the return of results emphasizes the importance of a two-way dialogue on preferences, values, and options [2]. Research indicates that patients may not prefer to receive test results themselves. Another genomic testing initiative for the early detection of childhood diseases solicited feedback before the return of results and collaborated closely with potential participants to develop effective strategies for communicating results [3]. Desirable adjuncts and alternatives to one-on-one disclosure meetings may be relevant as complementary approaches [6].

Ethical, Legal, and Social Implications

Pathways for returning genomic results for familial hypercholesterolemia (FH) within population genomics programs [8]. Genomic screening for FH raises ethical, legal, and social issues related to the return of results, the relatively high number of diverse conditions associated with FH-related genes, and policies surrounding the granting of consent to share genomic data [2]. These considerations build upon those raised in the return of results literature, which was developed in conventional genetic testing and the return of incidental findings literature and subsequent guidance on related matters [4]. Five ethical principles guide the provision of genomic results: respect for autonomy, prevention of harm, promotion of beneficence, advocacy for justice, and the expansion of capability through information and support. Respect for autonomy encompasses the right to access and act upon personal genomic information [8]. Harm occurs through the removal of the individual's capacity for self-authorship regarding the meaning of the information, whether at the individual or population level [7]. Programs for familial risk cascade screening raise additional questions around the minimization of harm and the distribution of costs and benefits, particularly in relation to health inequalities and the potential to misconstrue or mislabel genetic information. Furthermore, strategies for the return of results should consider the potential stigma of inheritance patterns characteristic of familial conditions, particularly on knowledge related to nature, nurture, capability, and self-authorship [3,7,8].

Communication Strategies and Patient-Centered Reporting

Providing clear, tailored communication of genomic results is intrinsically challenging. FH is a genetically heterogeneous condition caused mostly by mutations in the LDLR, APOB, and PCSK9 genes [6], with many variants of uncertain significance reported in clinical practice. The expected outcome after return of FHG results varies according to the meaning of the genomic variant(s) identified, and when test results are positive, patients must understand the risk of familial transmission when discussing these results with relatives [5]. Tests based on cell-free DNA or multiplex panels can also target additional actionable conditions, complicating message framing. Further, overlapping clinical features and the expected time from test request to result communication at the individual genetics centre limit effective pre-test information [8]. Therefore, the need for a dedicated theme to communicate the possible outcomes of population screening for FH was identified [7].

Equity and Access Considerations

Policy decisions regarding the use of population genomics for Familial Hypercholesterolemia (FH) in Canada could lead to unintended negative consequences for equity and access to health services [3]. Public health policies rooted in principles of equity and social justice also need to give specific attention to the potential for systematic disadvantage [3]. The overrepresentation of people of French-Canadian descent among carriers of FH in Quebec, and the underrepresentation of certain languages and ethnic groups in the clinical genomic databases commonly used in Canada, underscore the importance of addressing access and equity issues [1].

Cascade Testing in Familial Hypercholesterolemia

Cascade testing, genetic testing of at-risk relatives of an individual with a pathogenic variant, is the most effective way to identify individuals with familial hypercholesterolemia (FH) [9]. Cascade testing leads to timely diagnosis and treatment of FH, substantially reducing morbidity and mortality. Recommendations for cascade testing that can be implemented at the time of result disclosure have been published in numerous clinical guidelines [5]. Despite these recommendations, cascade testing remains underutilized in the United States [6]. Digital resources are expected to improve the uptake of cascade testing by facilitating communication between probands and relatives and thereby promoting the sharing of FH risk information [1]. Beyond its clinical importance, the cascade-testing process has significant economic and public health implications. Cascade testing for FH probands is estimated to be cost-effective; however, the underlying model does not account for the ongoing economic and health effects of successful diagnosis, warranted treatment, and consequently reduced cardiovascular disease risk among identified relatives [11]. Population-level adoption of genomic population screening for FH through initiatives such as biobank studies and screening for conditions amenable to preventive interventions provides opportunities to assess new forms of cascade testing at an unprecedented scale. Multi-institutional alliances and data-sharing approaches that incorporate the economics of the entire population while providing clarity regarding the fundamental uncertainties surrounding population screening offer further avenues to explore the public health implications of genomic population screening at an unprecedented scale[10].

Process Models and Optimization

Familial hypercholesterolemia (FH) management guidelines advocate for cascade testing of first-degree relatives, with research indicating an average uptake of only 29% for patients being tested and 19% for relatives [3]. Developing and evaluating a web-based tool, FH Family Share, aims to increase uptake of cascade testing by facilitating communication between probands and relatives, leveraging the prevalence of electronic health records, smartphones, and the Internet in genomic medicine [6]. Evaluated through usability testing with genetic counsellors and patients, the tool's design employs a simple user interface, a publicly accessible web link for relatives, tailored resources to facilitate prioritization of first-degree relatives, and an option for probands to send electronic letters identifying a family physician. Systematic reviews and observational studies support the cost-effectiveness of identifying a proband followed by cascade testing of first-degree relatives [7].

Uptake, Barriers, and Facilitators

Cascade testing for familial hypercholesterolemia (FH) is the practice of encouraging diagnosed individuals (probands) to share their FH status with at-risk first-degree relatives [10]. Cascade testing is recommended by the 2018 American College of Medical Genetics and Genomics guide for pharmacogenomics testing and by the 2017 National Heart, Lung, and Blood Institute FH framework. Undergeneralized cascade screening for FH has been reported in the United States and beyond. Digital tools supporting communication between probands and relatives can drive broader, expedited cascade testing [7]. Web-based systems (e.g., FH Family Share) that guide probands through the process can mitigate barriers. The tool generates personalized messages explaining the rationale for sharing FH information and offers suggested next steps. Family members receive links to FH resources. Such systems can reduce the burden of contacting multiple relatives while maintaining the personal touch necessary to elicit action [6].

Economic and Public Health Implications

Epidemiology estimates that 1,300,000 Canadians suffer from familial hypercholesterolemia (FH), a heritable cholesterol disorder [3]. The undiagnosed prevalence of FH exceeds 90% [9]. Significant health gains, including reduced premature coronary artery disease, will result from cascade screening informed by genomic sequencing 1. Costs of biobank sequencing plus analysis range from $200 to $800 per patient; these services are now becoming routine within provincial health coverage [2].

Health System Readiness for Population Genomics

Evaluating health-system readiness across jurisdictions is crucial to determining the sustainable implementation of genomic testing (various authors)[6]. This involves assessing the adequacy of infrastructure, data governance, including assortment and utilization [1], interoperability linking consumers with their families, and workforce competencies. Investigating existing policy frameworks, reimbursement schemes, and initiatives across sectors is likewise essential for patterning training programs, stakeholder engagement strategies, and sustainability assessments [3]. Identification of relevant metrics governing population, system, intervention, and individual

levels can additionally streamline evaluations by embedding population-based genomic screening into broader public health frameworks [8].

Infrastructure, Data Governance, and Interoperability

Advances in genomic technologies and data science have led to the emergence of population genomics, integrating genomic information with a wide range of social, demographic, and health data across entire populations and an increasing number of population genome programs targeting a variety of health conditions [5]. Population genomics holds the potential to improve health outcomes through earlier detection, risk prediction, tailored interventions, and more effective deployment of health system resources, while minimising health inequities. Recent provincial and national strategies have positioned population-level genomic screening as a priority area for action in Canada [5]. Population genomics for FH raises specific ethical, social, economic, and system readiness considerations, and addresses both FH diagnosis and cascade testing for relatives. Among population genomics initiatives, a screening focus on FH, either as a prototype or as part of a larger spectrum of complementary conditions, increasingly appears attractive [3]. The current health system readiness for population genomics for FH within Canada is delineated along six domains identified in the genomic readiness literature [3]. For each domain, the contemporary state and outstanding knowledge gaps are summarised, with an emphasis on available country-specific evidence that may inform decisions within a Canadian context. The health system, encompassing laboratory infrastructure, data governance, interoperability, and coverage, is the starting focus [1]. The requisite workforce expertise to operationalise population genomics initiatives for FH is highlighted subsequently. The pivotal role of policies covering health system use, reimbursement, and sustainability is emphasised throughout [2].

Workforce Competencies and Training

With the declining costs of sequencing and the growing collection of high-quality genomic data, population-scale biobanks with extensive health records have begun to emerge, offering new opportunities in large-scale epidemiological studies and facilitating the digitization of cohorts for genotype-first approaches[5]. These approaches promise to improve understanding of biological heterogeneity and the stratification of patients into subtype-specific cohorts for better-depth study and management. Familial hypercholesterolemia (FH), a common single-gene disorder due to mutations in LDLR, APOB, or PCSK9, which leads to severely elevated LDL cholesterol levels and substantially increased risk of coronary heart disease (CHD), demonstrates considerable heterogeneity, both genetically and phenotypically[2]. Recipients of FH variants exhibit widely varying levels of LDL-C, and the risk of CHD is still substantial across all these levels [1].

Policy, Reimbursement, and Sustainability

Familial hypercholesterolemia (FH) is a common genetic condition that leads to premature cardiovascular diseases and associated deaths. Condition prevalence is estimated at 1 case in 250 individuals, which warrants universal screening by cholesterol measurement, followed by cascade testing and genetic analysis for unequivocal cases [3]. The FH health impact becomes considerably higher when analyzed with a population genomic approach involving whole-exome or genome sequencing, thus creating the opportunity to make it a lower-tier test widely applicable for large-scale epidemiological studies [3]. The cost-effectiveness of one such screening programme, already conducted in Estonia, showed expected suboptimal detection rates when implemented outside clinical settings and without patient involvement [5]. On the basis of ELSI factors only, cascade screening was nevertheless judged essential [3]. Cascade screening offers a model for population genomics implementation due to the multifactorial, late-onset nature of the disease; extensive experience relating to various clinical settings; and established monitoring data supporting the efficacy of interventions in high cholesterol patients. Missing national strategies or supportive environments remain significant obstacles in most countries [3].

Evidence Synthesis: Current State and Knowledge Gaps

The emergence of genomics as a tool for population screening to identify and address familial hypercholesterolemia (FH) is gathering momentum [7]. FH is characterized by the coexistence of high cholesterol levels in childhood and accelerated coronary heart disease later in life. Recent systematic reviews show that population-wide genomic screening of newborns to identify those with genetic predisposition for FH can lead to timely tracing, diagnosis, and treatment [6]. Experience with such screening in established health care systems suggests the need for a comprehensive assessment to inform planning and operational decisions. Many gaps remain, particularly with respect to diagnostics and intervention strategies, their implications for a fragmented health care system, and the challenge of equitable access to screening and treatment [3, 6, 1].

Diagnostic Yield and Penetrance in Population Genomics for Familial Hypercholesterolemia

Population-based preventive health programs are increasingly enabled by sequencing studies and related biobanking initiatives [1]. These approaches lead to the identification of medically actionable genetic variation in otherwise healthy individuals. Programs often develop so-called "recall-by-genotype" strategies [6]. The penetrance of pathogenic and likely pathogenic (P/LP) variants and the clinical outcomes associated with these variants are profoundly relevant to cascade screening for familial hypercholesterolemia (FH), genetically

influenced disorders, and other medically actionable conditions [10]. Population screening approaches for FH rely on the identification of individuals with P/LP variants in genes associated with FH (APOB, FH, LDLRAP1, LDLR)[2]. While genetic screening of the general population is well-positioned to enhance risk evaluation and stratification for myriad conditions, including FH and associated comorbidities, the empirical evidence concerning clinical consequences and course remains insufficient. In a population-based setting, the incorporated data focuses on FH-related variants among unaffected individuals in Estonia with related health records [1]. The estimated penetrance for FH-related P/LP variants approximated 92 percent, although this figure likely exaggerates the actual estimate due to the predominant recruitment of participants [3].

Long-Term Health Outcomes and Intervention Efficacy

Familial hypercholesterolemia (FH) substantially increases the proliferation of cardiovascular diseases (CVDs) due to hypercholesterolemia commencing from childhood and progressing steadily thereafter [2]. Epidemiological studies have shown that untreated FH increases the lifetime risk of CVD significantly [3]. The efficacy of lifestyle and preventive interventions (e.g., dietary advice, physical activity, executive check-ups) relying primarily on health education decreases with age. Information on the state of an individual's genetic risk would help maintain the motivation for lifestyle measures [9]. Nevertheless, FH-carrier status does not alter the type of public health recommendation and preventive advice an individual receives. Nonetheless, lifestyle and other preventive recommendations are available for every CVD risk, regardless of genetic disposition. All public health recommendations, including screening and genetic counselling, can still apply long after the genomic information is received [3]. Individuals screened in an FH population screening program discontinued lipid-lowering treatments after excessive time-lag following screening; many single gene mutation screenings still have consumer critical skips due to various reasons; even after receiving public health screening, the population would still enrich CVD prevention strategies later by receiving rescreening offered in a more forward manner[7]. Thus, further patient risk stratification via other methods would be beneficial after a genomic evaluation dedicated to FH screening. Evaluation of lifetime risk or screening-offer exemption selection towards onset time and residual lifetime risk still remains an open path equally valid after population genomics screening. Availability of CVD risk information acquired from coronary artery imaging would also be informative to guide decision-making [4].

Patient Experience and Psychosocial Impact

A framework informed by an ecological view of health-related quality of life can be applied to investigate the psychosocial consequences in response to intervention strategies for familial hypercholesterolemia [3]. Shortly after disclosure of genomic results via an online platform, one-third of participant parents with hypertrophic cardiomyopathy notice positive changes in their family perspectives [6].

Health System Performance Metrics

Population genomics for familial hypercholesterolemia (FH) offers considerable population health potential. FH represents a common, serious genetic condition associated with critical long-term health outcomes [2]. Cascade testing of at-risk relatives of individuals diagnosed through genome-wide sequencing is feasible and results in clinically relevant genetic information [2]. Unfortunately, Canada's health system appears inadequately prepared to perform population genomics for FH. Evidence addressing specific components of health system readiness is limited but salient [3]. A synthesis of findings regarding the diagnostic yield and penetrance of FH, long-term health outcomes, and other dimensions of the patient experience has been conducted [8]. Additional insights are also available concerning the communication of genomic results, cascade testing, and related economic considerations [11]. The distribution and focus of existing knowledge remain uneven. Consequently, FH population genomic programs may benefit from further empirical investigation and the establishment of systematic evidence collection strategies [4]. Measurement of both system-level and individual-level performance remains an unresolved challenge [3]. Examples of high-level system metrics relevant to FH population genomics include the diagnostic yield of other, non-FH-related genomic tests; participation in health-behaviour change programs; and health-related quality of life. Individual-level measures include the number of at-risk relatives tested following the proband; family communication of genomic information; and the uptake of health-behaviour change programs [7].

Methodological Considerations for Future Research

Population-screening programs for the familial hypercholesterolemia (FH) phenotype are increasingly developed to identify undiagnosed cases, facilitate early intervention for individuals at higher cardiovascular risk, and improve the effectiveness of cascade testing in several countries [3]. Population genomics provides an opportunity to amend the strategic public health approach to FH. Genetic ascertainment may increase the number of screened individuals to be contacted and motivate relatives to access closely connected clinical services [1]. Additional visits to the clinic, long-distance travel, time consumption, overall inconvenient arrangement, and lack of pedigree to understand genetic linkage discourage cascade screening after lipid screening. Biobank with genetic data and an established care pathway exerts a positive influence on upstream cascade screening and builds a stable ground for downstream laboratory access and follow-up [7].

Study Designs and Analytical Frameworks

Population-based biobanks combine health records and genomic profiles to identify individuals carrying pathogenic variants for various diseases, including familial hypercholesterolemia (FH) [1]. National genomic initiatives and biobanks have engaged in return-of-results projects wherein probands with FH variants are recalled, cascade screening of first-degree relatives is offered, and health outcomes are monitored [3]. A return-of-results accelerator program utilizes a similar approach to determine the trajectory of the genome and health relationship for probands carrying pathogenic variants in three health-related genes. Furthermore, exploring the intersection of population genomics and FH screening through the lens of a single laboratory has facilitated international discussions on study design, analysis, and the design of patient-facing tools [6].

Stakeholder Engagement and Value Assessment

Stakeholder engagement and value assessment are critical components of initiatives to improve care for individuals affected by familial hypercholesterolemia (FH). A study investigating stakeholder views on cascade screening for FH, conducted in the Netherlands, identified the role of clinical genetics in producing pedigrees, providing counseling, offering emotional support, and tracing relatives as especially valuable[6]. Participants highlighted the need for broader government involvement [4]. Publicly organized screening programs, with established standard operating procedures, are believed to deliver better support and facilitate a more equitable distribution of care than approaches relying on general practitioners [2]. Cascade screening of relatives remains essential for timely diagnosis and effective treatment of FH. Consequently, efforts directed toward enhancing the cost-effectiveness of cascade screening are deemed vital in the ongoing pursuit of improved FH management [7]. A cohort study in Estonia evaluating genotype-guided reevaluation of probands and corresponding cascade screening supported these findings, reporting a similar range of benefits [1].

Equity-Focused Evaluation

Population genomics for familial hypercholesterolemia aims to identify affected individuals before the onset of premature cardiovascular disease (CVD) [7]. In Canada, returning genomic results through population screening schemes has the potential to improve health equity. Such initiatives are often conducted in tandem with cascade-testing frameworks to facilitate the identification of FM-affected family members [5]. Even when targeted sequencing for familial-expansion mutations in the gene LDLR is a low-cost and high-yield approach, population-genomic screening of FH represents a shift in the paradigm. Although widespread, documentary and mentoring efforts with stakeholders indicate considerable hesitations regarding FH screening on both fronts [3]. Some health authorities principally recommend the familial-variant strategy, while others consider hurdles regarding the closure of equity gaps and health-system readiness on return and cascade testing. Systematic longitudinal and interdisciplinary evaluations can guide population-genomic and return-of-results practices for FH to benefit Canadians by ensuring that potential improvements do not exacerbate existing inequities [6].

Policy and Practice Implications

Health systems worldwide are prioritizing genomic testing and treatment in both policy and practice. Nonetheless, in addition to evidence generation, careful consideration of implementation testing, reporting, information sharing, genomic data governance, supports for informed decision-making, and intervention delivery is necessary to enhance health outcomes [2]. The ability to test, interpret, and respond to genotypes; the rapidity of scientific evidence generation concerning various indicators for action; and the importance of tracking health consequences and defining efficiency in health systems all represent urgent concerns. Informed decision-making depends on familiarity with testing results, awareness of effective interventions, and predictions of population-scale outages and health effects over decades [4]. Health systems are gradually, but incompletely, prepared to undertake population testing for familial hypercholesterolemia [3]. Policies and practices to implement population genomics merit attention at local, regional, and national levels. Specific population settings may warrant bespoke policy considerations, while policy coherence across jurisdictions may improve funding sustainability and limit regulatory confusion [7]. Carrying early interventions from out-of-scope health programs into broader portfolios needs a continuum-of-care perspective not currently obtained for familial hypercholesterolemia or concomitant population programs. Multiple health-system-level determinants and mechanisms influence practice readiness and compliance comprehensively [11]. With such preparations, increasing testing rates and disseminating information may ameliorate anticipated health-system pressures on population genomics to enable greater public exploration of previously-contested therapeutic domains [11-14].

CONCLUSION

Population genomics represents a transformative opportunity to improve the detection and management of familial hypercholesterolemia by enabling earlier identification of affected individuals and systematic tracing of at-risk relatives. Evidence reviewed in this study shows that genomic screening programs can enhance diagnostic yield and support preventive treatment, particularly when combined with effective cascade-testing strategies. Nevertheless, the translation of these advances into routine practice remains uneven, with persistent challenges in result communication, patient engagement, ethical governance, and equitable service delivery. Cascade testing

continues to be the most efficient public-health strategy for expanding FH diagnosis, yet its implementation is hindered by low participation rates, fragmented communication pathways, and limited integration of digital tools within clinical workflows. At the same time, health-system readiness varies considerably across jurisdictions, reflecting gaps in infrastructure, workforce competencies, reimbursement structures, interoperability, and policy coordination. Without addressing these systemic constraints, the potential benefits of population genomics for FH may not be fully realized. Future efforts should therefore focus on developing standardized and patient-centered approaches to the return of genomic results, strengthening digital and clinical systems that facilitate family-based cascade testing, and embedding population genomic initiatives within sustainable public-health and healthcare frameworks. Longitudinal research assessing clinical outcomes, cost-effectiveness, and equity impacts will be essential to guide evidence-based policy and implementation. By aligning scientific innovation with ethical oversight, health-system preparedness, and inclusive access strategies, population genomics for familial hypercholesterolemia can contribute meaningfully to reducing the burden of premature cardiovascular disease and advancing precision public health.

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