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Implementation strategies for improving the care of familial hypercholesterolaemia from the International Atherosclerosis Society: next steps in implementation science and practice

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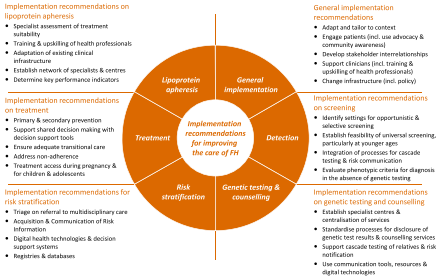
GRAPHICAL ABSTRACT



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ABSTRACT

Familial hypercholesterolaemia (FH) is the most common monogenic condition associated with premature atherosclerotic cardiovascular disease. Early detection and initiation of cholesterol lowering therapy combined with lifestyle changes improves the prognosis of patients with FH significantly. The International Atherosclerosis Society (IAS) published a new guidance for implementing best practice in the care of FH. Previous guidelines and position statements seldom provided implementation recommendations. To address this, an implementation science approach was used to generate implementation strategies for the clinical recommendations made. This process entailed the generation by consensus of strong implementation recommendations according to the Expert Recommendations for Implementing Change (ERIC) taxonomy. A total of 80 general and specific implementation recommendations were generated, addressing detection (screening, diagnosis, genetic testing and counselling) and management (risk stratification, treatment of adults or children with heterozygous or homozygous FH, therapy during pregnancy and use of apheresis) of patients with FH. We describe here the IAS guidance core implementation strategies to assist with the adoption of clinical recommendations into routine practice for at-risk patients and families worldwide. We summarise the IAS guidance core implementation strategies as operative statements.

IAS	International Atherosclerosis Society
ERIC	Expert Recommendations for Implementing Change
LDL	low-density lipoprotein
ASCVD	Atherosclerotic cardiovascular disease
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance
HoFH	homozygous FH
HeFH	heterozygous FH
CFIR	Consolidated Framework for Implementation Research

1. Introduction

Familial hypercholesterolaemia (FH) is a genetic disorder that causes markedly elevated levels of low-density lipoprotein- (LDL) cholesterol from birth [1]. If undetected and not treated, FH leads to premature atherosclerotic cardiovascular disease (ASCVD) and premature death [2–5]. FH affects approximately 1 in 300 people, equating to 35 million persons with FH worldwide [6,7]. Due to this high prevalence and potential for prevention of premature disease and death, the US Centers for Disease Control and Prevention has labelled FH a Tier 1 genomic application for substantial public health impact. However, fewer than an estimated 10 % of people with FH have been identified globally, and many of those treated do not achieve recommended LDL-cholesterol reduction targets [8,9].

The International Atherosclerosis Society (IAS) published an updated guidance for implementing best practice in the care of FH [10]. The guidance sought to address the commonly overlooked issue of implementation into routine care using implementation science [11,12]. Implementation science provides a structured approach to translating clinical guidelines into practice by identifying and addressing factors that influence proposed changes in care [13]. Different implementation science models, theories and frameworks have been developed, such as the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance), to formalise the study of research translation [14,15]. The guidance adopted a model by Sarkies and Jones et al. to embed implementation science into the guidelines development and translation processes [16]. Following this model, the guidance provided implementation recommendations to accompany the clinical recommendations promoting the development of implementation strategies to improve the outcomes of patients with FH.

Several cardiovascular disease guidelines [1,7,17–24] and position statements [6,25,26] have introduced implementation science methods to overcome gaps in translation and adoption into practice. However, these approaches remain relatively novel in the guideline development process. Therefore, we sought to describe the core implementation recommendations included in the IAS guidance and provide a platform for health systems, policy makers, organisations, health care professionals and patients to tailor and adapt them to their local contextual circumstances. The next steps in implementation science and practice require local assessment of barriers and enablers to implementation, the development and tailoring of implementation strategies, and monitoring, evaluating and sustaining implementation. This synopsis summarises the core IAS guidance implementation recommendations as operative statements. The full IAS guidance is available in Nature Reviews Cardiology at https://doi.org/10.1038/s41569–023–00892–0 [10].

2. Materials and methods

The board of the International Atherosclerosis Society selected an International Expert Working Group to develop the guidance [10]. The

development of the clinical guidance was based on previous guidelines that scored highly on an AGREE-II (Appraisal of Guidelines for Research and Evaluation) assessment [27,28]. The guidance covered the detection and management of FH, and implementation of the clinical recommendations. Previous clinical practice guideline recommendations that referred to the design, development and organisation of FH care were reviewed and categorically mapped to the Expert Recommendations for Implementing Change (ERIC) taxonomy [29] by two implementation science experts (LJ and MS). Disagreements in categorisation were resolved by discussion or consultation and consensus with the International Expert Working Group, as needed.

3. Results

Implementation statements were developed by consensus, based on this review and categorisation exercise, and were framed as strong classes of recommendations by full consensus of the International Expert Working Group contributors (see Fig. 1 for a summary of the implementation recommendations).

3.1. Core implementation strategies on screening

Central to the screening process is the coordination of efforts among various healthcare professionals supported by digital technologies for efficient detection in tertiary, secondary, and primary care settings (Table 1). Central coordination has particular importance during the cascade testing of family members, allowing for the linkage of FH cases to a clinical quality registry from a network of healthcare professionals undertaking FH screening. Adequate training and awareness of local data protection guidance amongst health care professionals is integral to the screening process. FH cases can be identified opportunistically by various healthcare professionals (medical, nursing, and allied health) and linked into centrally coordinated screening efforts using LDL-cholesterol testing, alerts and interpretive comments on laboratory reports of standard lipid profiles. If feasible and cost-effective, universal screening strategies should be integrated into routine health surveillance and prevention procedures and include other actionable Centers for Disease Control Tier 1 genetic conditions (e.g. Lynch Syndrome). Ideally, these efforts would commence in early childhood during which FH, particularly homozygous (HoFH) but also heterozygous (HeFH), can be detected early and linked into risk-reduction models of care. Diagnosis of FH in children and adolescents would preferably be confirmed by a paediatrician with expertise in lipidology and attention paid to the psychological impact of the diagnosis on the family adherence to regulations on child protection. Screening approaches are best matched with cost-effective pathways for diagnosis, which, where possible and appropriate, should include the option of genetic testing to confirm the phenotypic diagnosis of FH to facilitate cascade testing of family members. Genetic testing is best undertaken in consultation with the patient, or caregiver in case of minors, considering any local guidance about genetically confirmed diagnosis in collaboration with a genetic counsellor or other experience and trained health care professionals. The diagnosis of HoFH requires referral to specialist centers for comprehensive assessment and care planning.

3.2. Core implementation strategies on genetic testing and counselling

The core implementation strategies outlined in Table 2 highlight the need for a specialized centre to undertake genetic testing, discouraging the use of direct-to-patient genetic tests for FH diagnosis (depending on their accuracy). The recommendations emphasize a standardized process for obtaining informed consent, ensuring patient understanding, and tailoring the approach for paediatric patients with the involvement of custodial parents or guardians. Furthermore, the guidelines emphasize the need for standardized procedures in sample collection, testing, analysis, and reporting of genetic findings. Centralized testing in accredited laboratories, validated bioinformatics for result interpretation, and a uniform reporting format ensure the reliability and consistency of genetic testing outcomes.

The second set of recommendations focuses on the disclosure of genetic test results to the patient. Standardized processes should be operationalised that consider patient comprehension, attitudes, and

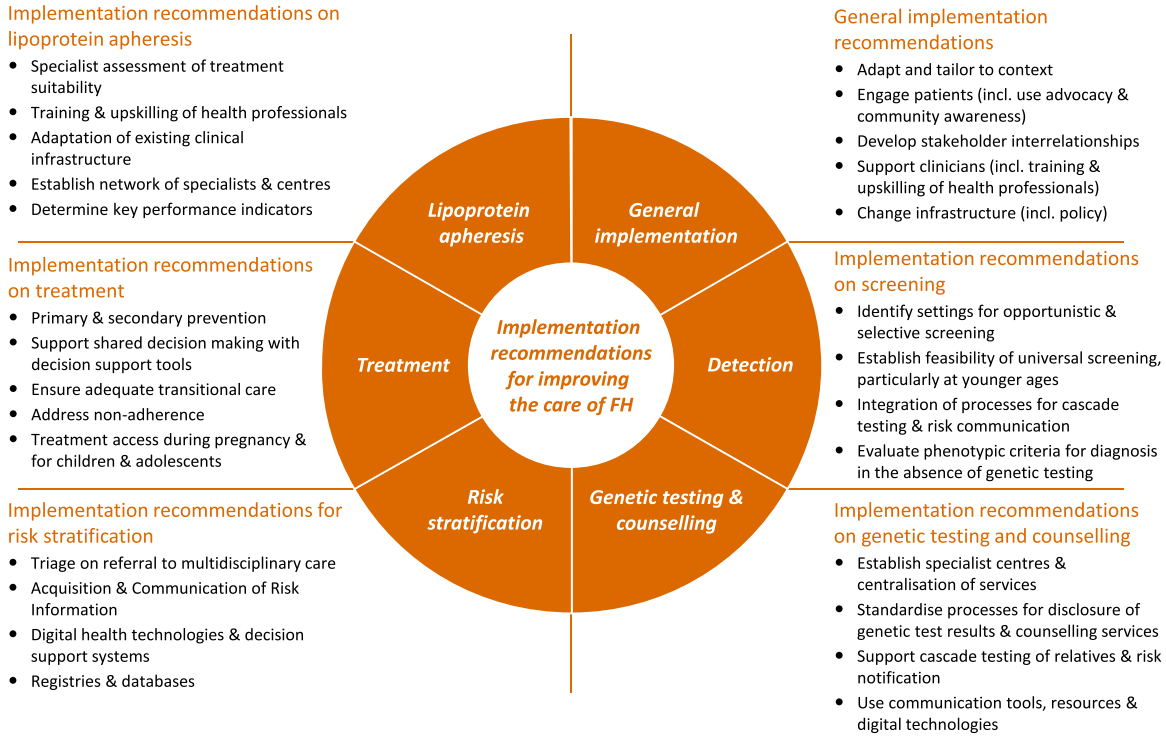

Fig. 1. Core implementation strategies for improving the care of FH.

Table 1
Core implementation strategies on screening for FH (source: modified from Watts et al. [10] Use of this content is supported by Springer Nature Rights and Permissions).

- Integrate screening strategies (selective, opportunistic and universal)
- Use a patient-centred and multidisciplinary approach, including general practice
- Use digital technologies and search of electronic health records
- Deploy alerts and comments on high LDL-cholesterol levels in laboratory reports
- Train and upskill all health-care providers on screening methods
- Identify referral pathways for expert evaluation, offering of genetic testing and risk-reduction treatment
- Develop health-care policy and funding for integrated screening strategies

Table 2
Core implementation strategies on genetic testing and counselling for FH (source: modified from Watts et al. [10] Use of this content is supported by Springer Nature Rights and Permissions).

- Establish a centre for coordinating cascade testing and a peer-support group
- Use standardized processes for consenting, testing and reporting of results
- Ensure the genetic test requestor is skilled in counselling, genomics and familial hypercholesterolaemia
- Use digital tools and practical resources to facilitate counselling and risk communication
- Align testing processes with local legislation on privacy and data protection
- Use shared decision-making and decision support tools to enable testing
- Integrate with other screening strategies and link to local or national registry

sociocultural factors. Clear communication in everyday language is advocated, with the reporting of variants restricted to those with clear pathogenic impact. Genetic counsellors or specialist clinicians are best placed to provide advice regarding variants of uncertain significance. The follow-up and re-assessment of genetic test results require a continuous dialogue between healthcare professionals and patients to address evolving concerns and changes in attitudes or behaviours related to their diagnosis. Regular performance audits and periodic reinterpretation of genetic findings in collaboration with clinicians with expertise in genetics can enhance the quality of genetic services.

The third set of recommendations delves into the diagnostic and cascade testing processes. Diagnostic genetic testing of index cases should involve specialized clinicians and referral to professional genetic counselling services whenever feasible, ensuring an optimized counselling process. Reported shortages of genetics specialists in rural areas has been thought to contribute to underutilization of genetic testing [30]. Therefore, centrally coordinated cascade testing may allow for efficiency and is best triggered through a shared decision-making process with the index case to obtain informed consent. Digital technologies can improve family communication; however, the acceptability and feasibility of novel tools and software programs for communication should be tested prior to implementation. The process of risk notification for at-risk relatives must adhere to local legislation and institutional guidelines, with direct notification without authorization by the index case only under specific legislative provisions for breach of confidentiality.

3.3. Core implementation strategies for risk stratification and treatment

The core implementation strategies described in Table 3 outline the use of risk assessment and stratification strategies as fundamental components of multidisciplinary care for FH. These strategies help to triage patients for specialized services, including apheresis, general practice support, and specialty care in paediatrics, cardiology, or diabetes, and public health programs such as for nicotine cessation. To enhance communication and accessibility, clear and culturally sensitive information should be provided in written, diagrammatic, and electronic formats, to convey the patient's risk, and overcome barriers to risk reduction management pathways such as cultural, psychological, language, and health literacy levels. The integration of digital health technologies and decision support systems is encouraged to facilitate efficient risk assessment, which could include tools like telehealth, FH risk equations, or ASCVD imaging. Furthermore, it is important for clinical quality registries, respecting prevailing confidentiality policies, to capture data on ASCVD risk, by incorporating validated risk equations and cardiovascular imaging, with a focus on linking this information to patient outcomes. These registries play a pivotal role in refining the cost-effectiveness of FH care models, fostering continuous improvement and optimization of patient outcomes.

The implementation recommendations in Table 3 address a comprehensive range of treatment approaches to optimize care across diverse scenarios for both HeFH and HoFH. The cornerstone of these recommendations is the development of personalized treatment plans, acknowledging individual and familial factors such as age, ASCVD risk, psychological considerations, sociocultural background, economic status, adherence barriers, and personal values. Providing clear and culturally sensitive information is recommended to facilitate the creation of personalized treatment plans, which can be presented in various formats. The management of well-controlled patients is well placed in general practice, while specialist centres are more suited for higher-complexity cases, including those with HoFH. Patients not receiving guideline-directed medical therapies should be identified and strategies employed to address barriers to medication adherence, including decision support aids and financial incentives.

The second set of recommendations focuses on the implementation and improvement of management pathways through regular auditing of

Table 3
Core implementation strategies on risk stratification and treatment of FH (source: modified from Watts et al. [10] Use of this content is supported by Springer Nature Rights and Permissions).

- Use risk-reduction strategies to triage patients and use cost-efective therapies and resources
- Establish networks of clinical centres to share experience and education; upskill all health-care providers
- Use iterative strategies and key performance indicators to optimize risk-reduction pathways
- Define multidisciplinary care pathways, transitional services for adolescents and dedicated services for family planning and women during pregnancy
- Develop personalized treatment plans using shared decision-making, with culturally appropriate clear information
- Identify patients not receiving guideline-directed therapy and facilitate treatment using multifaceted strategies; use advocacy and peer support
- Use multiple and evidence-informed interventions to improve adherence to medication

key performance indicators, including patient-reported outcomes. Regular multidisciplinary case discussions can serve to establish local treatment standards and the development of a network of FH clinical centres for collaboration, education, and research. The incorporation of real-world clinical quality registry data can assess the safety and effectiveness of conventional and new drug therapies, provide a resource for clinical trials, as well as to advocate for policy change. Seeking government funding for developing specialized centres and access to new therapies, is particularly important for patients with HoFH.

The third set of recommendations addresses specific aspects of FH treatment, including liver transplantation for severe HoFH, care during pregnancy, and the management of children and adolescents. Prioritizing multidisciplinary care, shared decision-making, and ongoing auditing of outcomes are recommended for patients considering liver transplantation. Specialized care coordination should be provided for pregnant women with FH, which requires clear information during counselling sessions and the consideration of any sociocultural barriers to best practice care. Because FH is a genetic condition, a family-focused approach is necessary when managing children and adolescents, ensuring regular reviews, engaging in shared decision-making, behavioural counselling approach, and a smooth transition to adult services.

3.4. Core implementation strategies on lipoprotein apheresis

Lipoprotein apheresis demands a nuanced approach and a comprehensive framework for implementation (Table 4) [31]. Initially, patients under consideration for lipoprotein apheresis should undergo a thorough assessment, evaluating both physical and psychological suitability by specialists well-versed in lipidology and apheresis, with collaboration from other relevant experts as needed. Acknowledging potential limitations, therapeutic plasma exchange can act as an alternative, particularly in cases where lipoprotein apheresis is not available or feasible (e.g. children with HoFH with a small blood volume). Existing clinical infrastructure can be adapted to provide lipoprotein apheresis to enhance the accessibility, which may involve collaboration with haemodialysis units, transfusion medicine, and vascular surgery. A multidisciplinary team of specialties, encompassing lipidology, cardiology, vascular surgery, paediatrics, mental health care, nephrology, transfusion medicine, pharmacy, and nursing should be established to ensure a high standard of care. This team should conduct regular multidisciplinary case meetings, strategize for service improvement, and develop local guidance based on evidence-based standards. Continuous review of key performance indicators, including efficacy, tolerability, safety, and impact on patient-reported outcomes are recommended every 12 months. Apheresis units are encouraged to participate in national or international networks to foster collaboration, share experiences, and contribute to the establishment of a comprehensive clinical quality registry for patients undergoing lipoprotein apheresis.

4. Discussion

The IAS guidance core implementation strategies can be tailored into local solutions for health systems, policy makers, and clinicians to translate the guidance into routine care. Sarkies and Jones et al. outline three stages for embedding implementation science into the guideline development and translation process: 1) assess local barriers and enablers to implementation; 2) tailor implementation strategies; and 3) monitor, evaluate and sustain improvements in care [16]. Careful consideration of local contextual circumstances is required to understand the barriers and facilitators to change. Implementation science frameworks such as the Consolidated Framework for Implementation Research (CFIR) can be used to structure and categorise key factors, such as the available infrastructure, health care provider knowledge, levels of patient engagement, and availability of resources, to better understand what solutions might be needed [32]. Once these contextual factors are identified, tailored implementation strategies can be developed to address specific local needs. The Expert Recommendations for Implementing Change (ERIC) taxonomy of implementation strategies provides a taxonomy of implementation strategies that can be selected to address previously identified barriers and facilitators to change [29]. After adapting implementation strategies to local needs, efforts to integrate guideline recommendations into policy and practice must be monitored and evaluated to assess their impact. Evaluation frameworks such as the RE-AIM can be used to assess the reach, effectiveness, adoption, implementation and maintenance of local policies and programs to implement guidance recommendations into routine care [14].

4.1. Next steps in the implementation of guidelines into policy and practice

The key steps for implementing guidelines into policy and practice according to the Sarkies and Jones et al. [16] model adopted by the IAS guidance include: 1) assessing barriers and enablers to implementation; 2) tailoring implementation strategies; and 3) monitoring, evaluating and sustaining improvements in care [12]. Local implementation begins with an assessment of barriers and enablers to change to understand the nature of care gaps before operationalising potential solutions. Implementation tools such as the Theoretical Domains Framework (TDF) can assist with the assessment and categorisation of these barriers and enablers when consulting stakeholders who are responsible for adopting change in policy and practice [33]. Previous interview [34] and focus group [13] studies have identified barriers to FH detection at the patient (e.g. non-disclosure of family history), clinician (e.g. busy clinics), and system (e.g. lack of care pathway) levels in the US and Australia.

Once local contextual factors are well understood, implementation strategies can be tailored and operationalised to address identified barriers and enablers to change [35]. The Capability, Opportunity, Motivation, and Behaviour (COM-B) model is commonly used tool that can aid the development of evidence-based implementation strategies [36]. The COM-B model begins with a behavioural analysis of the barriers and enablers to clinical practice change and maps strategies according to whether they target different aspects of capability, opportunity, or motivation. Practically operationalising these strategies to meet local requirements involves specifying the actor (who), action (what), action-target (who is impacted), temporality (how often), and dose (how much) [35]. An exemplar cascade testing model was implemented in The Netherlands to identify people with FH [37]. The model mobilised trained nurses to identify first-degree relatives (actor/who) who visited the homes of all first-degree relatives of a confirmed FH index case (action/what). These nurses consented and obtained blood samples and health information from the first-degree relatives (action-target/who is impacted) shortly after an index case was

Table 4
Core implementation strategies on treatment of FH by lipoprotein apheresis (source: modified from Watts et al. [10] Use of this content is supported by Springer Nature Rights and Permissions).

- Establish a centralized apheresis unit staffed by accredited personnel; use advocacy and peer-support groups
- Assess suitability for treatment by a specialist; offer plasma exchange if lipoprotein apheresis is not available
- Adapt existing infrastructure to widen the clinical availability of apheresis; meet local and regional needs of care
- Establish regular multidisciplinary meetings involving a coalition of specialties that contribute to service delivery
- Use apheresis-specific key performance indicators and patient outcome and experience measures to iteratively improve services
- Participate in networks to share educational, clinical and research experiences; establish a comprehensive clinical quality registry of patients

identified (temporality/how often).

The monitoring, evaluation and sustainment of implementation forms part of routine quality assurance for new clinical processes and practices. Giesinger Health in the US provides an exemplar evaluation of the MyCode Community Health Initiative, whereby index cases could chose to share their FH diagnosis with blood relatives using one or a combination of three different implementation strategies [38]. The use of at least one strategy increased cascade testing rates, particularly if permission was granted for a genetic counsellor to contact relatives directly for risk notification [39]. However, the sustainability of FH screening programs such as the MyCode Community Health Initiative remains under-researched. Given the life-long impact of FH, it is crucial to sustain newly implemented FH screening programs over time. This will help identify individuals early and effectively reduce the risk of premature ASCVD.

5. Conclusions

Updating clinical practice guidelines and providing recommendations for implementation addresses the international calls to action on FH [6,25,26]. This synopsis of the IAS guidance core implementation strategies aims to assist health care policy makers, health care professionals, and patients to operationalise clinical recommendations in their local setting and develop specific strategies to improve care processes and outcomes. The core implementation strategies address both general issues (e.g. adapting interventions to local contextual circumstances) and specific issues (e.g. central coordination of family cascade testing). These implementation statements emerged as strong recommendations by consensus. Rapid growth in knowledge of diagnosis and therapeutics for FH necessitates a commensurate increase in the capacity to change practice and discourage unwarranted services. Future efforts could focus on developing localised implementation strategies, based on the IAS guidance recommendations and calls to action [40], to translate new knowledge into appropriate health policies and programs to support high quality care for people with FH and their families worldwide. This would include specific health policies and sustainable funding sources. Further applications of implementation science frameworks are required to plan, implement and evaluate practice in different contexts worldwide.

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Mitchell N. Sarkies: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gerald F. Watts:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Samuel S. Gidding:** Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Raul D. Santos:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Robert A. Hegele:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Frederick J. Raal:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Amy C. Sturm:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Khalid Al-Rasadi:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Dirk J. Blom:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Magdalena Daccord:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Sarah D. de Ferranti:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Emanuela Folco:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Peter Libby:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Pedro Mata:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Hapizah M. Nawawi:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Uma Ramaswami:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Kausik K. Ray:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Shizuya Yamashita:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Jing Pang:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Gilbert R. Thompson:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Data curation, Conceptualization. **Laney K. Jones:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

G.F.W. has received honoraria related to consulting, research and/or speaker activities from Amgen, Arrowhead, AstraZeneca, CRISPR Therapeutics, Esperion, Novartis and Sanofi. S.S.G. is a consultant for Esperion and is on a scientific advisory panel for Silence Therapeutics. R.A.H. has received honoraria related to consulting, research and/or speaker activities from Acasti, Akcea-Ionis, Amgen, Arrowhead, HLS Therapeutics, Pfizer, Novartis and Sanofi/Regeneron. F.J.R. has received personal fees from Amgen, LIB Therapeutics, Novartis, Regeneron and Sanofi-Aventis. A.C.S. is an employee and stockholder of 23andMe and an advisor to Nest Genomics. L.K.J. is a consultant for Novartis. M.N.S. has received personal fees from Amgen. K.A.-R. has received grants and personal fees from Sanofi and personal fees from Abbott and Novartis. D.J.B. has received grants for clinical trials and/or personal fees from Abbott, Akcea, Amgen, Amryt, AstraZeneca, Ionis, LIB Therapeutics, Novartis, Sanofi and Silence Therapeutics. S.D.d.F. has received personal fees from UpToDate. P.L. is an unpaid consultant to, or involved in clinical trials for Amgen, AstraZeneca, Baim Institute, Beren Therapeutics, Esperion Therapeutics, Genentech, Kancera, Kowa Pharmaceuticals, Medimmune, Merck, Moderna, Novo Nordisk, Novartis, Pfizer, and Sanofi-Regeneron; is a member of the scientific advisory board for Amgen, Caristo Diagnostics, Cartesian Therapeutics, CSL Behring, DalCor Pharmaceuticals, Dewpoint Therapeutics, Eulicid Bioimaging, Kancera, Kowa Pharmaceuticals, Olatec Therapeutics,

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