Current Atherosclerosis Reports (2023) 25:1083–1091
https://doi.org/10.1007/s11883-023-01177-0

REVIEW

# Should Familial Hypercholesterolaemia Be Included in the UK Newborn Whole Genome Sequencing Programme?

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Accepted: 19 November 2023 / Published online: 7 December 2023


## Abstract

**Purpose of Review** The UK National Health Service (NHS) has recently announced a Newborn Genomes Programme (NGP) to identify infants with treatable inherited disorders using whole genome sequencing (WGS). Here, we address, for familial hypercholesterolaemia (FH), the four principles that must be met for the inclusion of a disorder in the NGP.

**Recent Findings** Principle A: There is strong evidence that the genetic variants causing FH can be reliably detected. Principle B: A high proportion of individuals who carry an FH-causing variant are likely to develop early heart disease if left undiagnosed and not offered appropriate treatment. Principle C: Early intervention has been shown to lead to substantially improved outcomes in children with FH. Principle D: The recommended interventions are equitably accessible for all.

**Summary** FH meets all the Wilson and Jungner criteria for inclusion in a screening programme, and it also meets all four principles and therefore should be included in the Newborn Genomes Programme.

**Keywords** Familial hypercholesterolaemia · Whole genome sequencing · Newborn Genomes Programme · Healthy lifestyle · LDL-cholesterol burden · Homozygous FH

## Introduction

Familial hypercholesterolaemia (FH) is an autosomal dominant monogenic condition [1] that results in elevated low-density lipoprotein cholesterol (LDL-C) from birth, with the long-term consequences of premature cardiovascular disease (CVD). It is now known that the prevalence of heterozygous FH (HeFH) worldwide is around 1 in 250 [2], and recent data from the UK BioBank study has indicated that the prevalence in the UK is ~1 in 290 (95% confidence intervals of 1 in 264–316), with a similar frequency found in individuals from the Indian sub-continent and of African origin [3••]. This suggests that ~193,000 people in England have HeFH, of whom current estimates are that only 7% have been diagnosed [4]. In 2019, the NHS published a Long Term Plan (LTP) [4] which included the ambition to increase genetically diagnosed HeFH from 7% of the expected cases to 25% within five years. Increased genetic testing will enable the identification and treatment of those at the highest genetic risk of premature CVD and sudden cardiac death.

Individuals likely to have HeFH can be identified by searching general practice (GP) electronic notes to flag those with elevated LDL-C, an approach which has been shown to be feasible and cost-effective in the UK health system [5]. Recently, the concept of 'child-parent screening' (CPS) has been suggested [6] as an additional approach to address the challenges of FH identification by using children as the entry point for screening. Modelling of national data has shown that universal screening of infants alongside adult GP case finding as a unified approach would allow the NHS to reach its target of 25% in approximately seven years and provide a systematic long-term identification and prevention strategy [7].

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The feasibility of CPS was assessed in a large study in primary care [8]. Data was gathered from lipid profile results and FH genetic analysis obtained through a heel-prick blood sample. Covering a two-year period spanning 92 GP surgeries, the parents of 13,097 children were invited, of which 11,010 (84%) participated. The study identified 37 children carrying an FH-causing variant, suggesting a 1/273 prevalence of FH in the UK [8]. A further eight children with total cholesterol (TC) over the 99th centile on repeat measures but with no mutation were also designated as having FH. The study demonstrated the feasibility and acceptability of universal screening for FH in infants. For all FH-positive children, both parents were offered referral to an FH service for pedigree analysis and cascade testing of first-degree relatives with initiation of medical management where appropriate. From this group of children, the parents of 40 were tested and 40 new adults with FH were identified. Adults with FH were offered lipid-lowering therapy (LLT) as recommended [9], while children with FH would be given dietary and lifestyle advice and LLT considered by the age of 10 years in line with national guidance [9, 10].

As shown in Table 1, we have calculated the likely frequency of HoFH in the UK, using the data from the UK study of 12-month-old infants [8], which should give an estimate unbiased by premature mortality compared to estimates if data from adult studies were used. The study of 10,000 infants (20,000 alleles) identified 15 carriers of the *APOB* p.(Arg3527Gln) variant (allele frequency 0.00075), while 22 children carried an FH-causing *LDLR* variant (allele frequency 0.0011) [8]. Based on these data and using the Hardy-Weinberg equation, it can be estimated that per million people, there will be 1.20 *LDLR* true homozygotes or compound heterozygotes, 0.56 *APOB* homozygotes and 1.65 *LDLR+APOB* compound heterozygotes. Overall, the prevalence of HoFH is predicted to be 3.4 per million, and for the whole of the UK (~60 million), this results in an estimate of ~200 HoFH individuals.

An alternative approach to identify children with FH would be as part of a programme to perform whole genome sequencing (WGS) as part of the proposed Newborn Genomes Programme (NGP). This has been proposed following the success of the 100,000 genomes project, which conducted a pilot study involving 4660 participants from 2183 families, who included 161 disorders covering a broad spectrum of rare diseases. Overall, a genetic diagnosis was obtained in 25% of the probands, with diagnostic yields for intellectual disability, hearing disorders and vision disorders ranging from 40 to 55% [11•]. Currently, the UK Newborn Screening (NBS) programme uses biochemical methods and heel-prick blood spots to screen for eight inborn errors of metabolism (sickle cell disease [SCD], cystic fibrosis [CF], congenital hypothyroidism [CHT], phenylketonuria, medium-chain acyl-CoA dehydrogenase deficiency [MCADD], maple syrup urine disease [MSUD], glutaric aciduria type 1 [GAI] and homocystinuria [HCU]). PKU, MCADD, MSUD, GAI and HCU are inherited metabolic disorders, while some phenotypes present later (such as homocystinuria which presents in adolescence or adulthood) requiring ongoing monitoring, the infantile-onset phenotypes (such as congenital hypothyroidism which presents in early childhood) need early intervention to prevent increased morbidity and mortality.

The NGP intends to carry out WGS in 100,000 newborn infants over 2 years, which should result in the identification of up to 1000 babies with these and additional inborn errors of metabolism that may require treatment in childhood. To inform the NGP steering group of which disorders should be included, four principles have been proposed, and in order to be considered for inclusion, a disorder must meet all four principles. Here, we set out the data to demonstrate that FH fulfils these principles.

**Table 1** Predicted number of homozygous *LDLR, APOB* and compound heterozygous individuals in the UK (based on allele frequency in [8])

| FH-causing gene | Wald data[1] [95% CI] | Allele frequency [95% CI] | Number homozygotes/ million [95% CI][2] | Number expected in the UK (~60 million) [95% CI] |
|---|---|---|---|---|
| LDLR (any) | 22/20,000 [14–33] | 0.0011 [0.0007–0.00165] | 1.20[2] [0.49–2.7] | 72[2] [29.4–162] |
| APOB p.(Arg3527Gln) | 15/20,000 [8–25] | 0.00075 [0.0004–0.00125] | 0.56 [0.16–1.56] | 33.6 [9.6–93.6] |
| LDLR + APOB compound Homozygotes | NA | NA | 1.65 [0.56–4.13 | 99 [33.6–248] |
| Total | 37/20,000 [25–49] | 0.00185 [0.00125–0.00245] | 3.4 [1.28–8.4] | 204 [76.8–504] |

[1]10,000 children = 20,000 alleles

[2]Includes both true homozygotes and compound heterozygotes

The frequency of homozygous *LDLR* and *APOB* FH individuals and for those compound heterozygous for both an *LDLR* and *APOB* was estimated using an expansion of the Hardy-Weinberg equation, $p^2 + 2pq + q^2 + 2pr + 2rq + r^2 = 1$, where $p$ is the frequency of the common allele at the locus (wild type), $q$ is the frequency of the *LDLR* FH-causing rare allele, and $r$ is the frequency of the *APOB* FH-causing rare allele (p.(Arg3527Gln). 95% confidence intervals were estimated using standard binomial "exact" calculations

## Principle A: There is Strong Evidence that the Genetic Variant(s) Causes the Condition and Can Be Reliably Detected

HeFH is caused by carrying a pathogenic variant in one of four different genes. In the UK, around 93% of FH patients have a pathogenic variant in the gene for the LDL receptor (*LDLR*), ~5% have a mutation in the gene for apolipoprotein B (*APOB*) and ~2% in the gene for proprotein convertase subtilisin/kexin type 9 (*PCSK9*) [12]. Additionally, a three-base pair deletion in the gene for *APOE*, which deletes an amino acid (p.(Leu167del), has also been reported to mimic the FH phenotype [13]. In rare cases, a recessive inheritance pattern of elevated cholesterol is seen where the disorder may be caused by the child being homozygous for a pathogenic variant in the genes *LDLRAP1* [14] or *LIPA* [15]. Homozygous FH (HoFH) is caused by inheriting two FH-causing variants, one from each HeFH parent. The next-generation sequencing (NGS) panels for FH currently used in the UK diagnostic Genomic Laboratory Hubs (GLHs) include all four genes. The ClinGen database currently includes *LDLR, APOB* and *PCSK9* as being FH causing. The ClinGen activities include developing disease-specific criteria, and that for *LDLR* has already been completed [16], with similar recommendations for *APOB* and *PCSK9* being in the pipeline.

In the UK diagnostic laboratories over the last few years, from 23,855 index cases tested, 5126 were reported to have an FH-causing variant (a detection rate of 21.6%). In addition, 12,333 relatives have been tested, of whom 6168 (50%) were mutation carriers (K. Haralambos personal communication). In FH testing, the proportion of tests where a variant of uncertain significance (VUS) is identified is low, and rigorous criteria have been developed to guide laboratories about variant calling [16], which are universally used in the UK GLHs. Of the tested index cases, 2.8% were found to carry a VUS [17], which would not be reported as part of the newborn WGS programme.

While a DNA test for carrying an FH-causing variant is equally accurate at any age, identification of a carrier should be followed by confirmation from a blood lipid profile, and it is known that children likely to have FH already have significantly elevated cholesterol concentrations in cord blood [18, 19]. Although there is an overlap in cord blood TC concentrations between infants with and without FH, measurement of the lipid profile in infants shortly after the WGS result has been obtained will be a valid biochemical measure and will discriminate well. The discrimination is better at 1 year [6, 19], so a repeat (heel-prick) measure could be performed (e.g. at the time of 13-month immunisation) if requested by the parent or clinician or anytime within the first five years, during booster pre-school immunisation for example.

## Principle B: a High Proportion of Individuals Who Have the Genetic Variant(s) Would Be Expected to Have Symptoms that Would Have a Debilitating Impact on Quality of Life If Left Undiagnosed

### Heterozygous FH (HeFH)

FH causes high LDL-C in the blood from birth which leads to an increased risk of early CVD. If untreated, more than 50% of men with heterozygous FH (HeFH) will develop coronary heart disease (CHD) by the age of 50 and more than 30% of women by the age of 60 [20]. From both a multitude of randomised controlled intervention trials and Mendelian randomisation studies, it is now fully accepted that there is a causal relationship between elevated LDL-C and risk of CVD, and that a high LDL-C concentration in childhood is associated with an increased risk of CVD in adulthood. Data from many longitudinal studies have documented that elevated childhood concentrations of LDL-C track through life. A recent paper from the USA [21•] examined whether childhood risk factors are associated with CVD in adulthood. Among 38,589 (non-FH) participants (aged 3–29 years at recruitment), over a follow-up of around 35 years, there were 319 fatal or non-fatal CVD events. As expected, factors such as smoking history as an adolescent, high blood pressure or body mass index were all strongly associated with future CVD risk, but having an elevated cholesterol concentration in childhood was associated with future CVD risk. The risk of CVD for those with a cholesterol concentration in the top 13% was more than twice as high as for those with a cholesterol level in the bottom 20%.

It is currently unclear what proportion of newborns found to carry an FH-causing variant will have LDL-C >3.5 mmol/l by the age of 10 years and so will qualify for initiation of statin therapy according to UK and European guidelines. One study of 1512 healthy 9-year-olds (ALSPAC) found 6 children carrying an FH-causing variant, and 5/6 (83%) had LDL-C >3.5 mmol/l [22]. In the published CPS pilot study of 1-year-olds, 28/37 (76%) had LDL-C >3.5 mmol/l [8]. However, studies have shown that carrying an FH-causing variant is associated with an elevated risk of CVD, even in those with relatively low LDL-C concentrations. In a large study from the USA [23] using NGS for the known FH genes among 20,485 CHD-free individuals, 24 (1.7%) carried an FH-causing variant. As expected, in both non-FH and FH individuals, there was a clear and continuous gradient of increasing CVD risk with increasing quintiles of LDL-C concentration, but in each quintile, those carrying an FH-causing variant had markedly (2–3-fold) higher CVD risk than non-carriers. A similar relationship has been reported in healthy middle-aged men and women from the

UK Biobank [24]. This study compared CVD risk in 277 individuals carrying an FH-causing variant, with 2739 subjects matched for LDL-C who did not have a monogenic (or polygenic) cause for their phenotype. Compared to those with non-genetic high LDL-C, the mutation-positive group had 93% higher CVD, a difference which was not changed after adjustment for LDL-C concentration (as expected since mean LDL-C concentrations in both groups were similar). This higher risk is likely explained by the substantially higher accumulated 'LDL-C burden' in monogenic HeFH subjects since these individuals will have had genetically determined lifelong high LDL-C.

### Homozygous FH (HoFH)

In children, carrying two FH-causing variants or having an untreated LDL-C >13 mmol/l is considered diagnostic of HoFH. Both UK [25] and European [26••] guidelines recommend a diagnosis of HoFH as soon as possible and immediate initiation of LLT. In HoFH, very premature life-threatening asymptomatic coronary arterial disease develops within the first decade of life [25–27]. There is also evidence that the build-up of cholesterol deposits in HoFH occurs *in utero* [28]. An autopsy study of a 20-week-old HoFH foetus found multifocal lipid deposition, particularly involving the stromal cells of the thymus, spleen and skin and both the stromal and parenchymal cells of the kidney. One small focus of intimal lipid accumulation was found in the aorta and coronary arteries, and the esterified cholesterol content of most tissues was 1.5 times that of a control foetus [28].

### Parallels with Currently Included Disorders

Two of the disorders currently included for newborn screening from blood spots have parallels with the need for monitoring and later initiation of treatment which is recommended for FH. A child with MCADD usually requires no special treatment when well, apart from avoiding prolonged fasts. These children appear clinically normal, but intercurrent illnesses or prolonged fasting can lead to severe hypoglycaemia, coma and death. MCADD is a well-recognised cause of sudden infant death (SIDS) and even coma and death. The treatment includes simple management of avoidance of fasting and additional glucose polymer drinks during illnesses to prevent hypoglycaemia. Rarely, children may remain well until later childhood or even adulthood. The mortality rate in early infantile onset MCADD could be up to 25%, and in adults, undiagnosed, this could even be up to 50% [29]. Based on the risk in childhood, MCADD was first suggested for inclusion in the mid-1990s and was finally included in the Newborn Screening (NBS) Programme in 2003. The situation with PKU also has parallels with FH. Treatment consists of restriction of phenlyalanine from the early neonatal period. Without early identification in the newborn and early intervention, babies with PKU will develop catastrophic cognitive impairment. However, in some cases, babies are identified by NBS with hyperphenylalaninaemia, and these infants may not require strict dietary intervention daily but may need it during intercurrent illness. These examples highlight that not all children identified by the current NBS have an acute, urgent, life-threatening clinical presentation.

The need for early detection of FH is supported by many patient charities in the UK (the British Heart Foundation (BHF) and HEART UK) and Europe and the USA [30, 31https://www.heartuk.org.uk/) contains many videos and testimonials about the impact on a family of the sudden death of a relative due to CHD and their positive view of systematic testing of relatives and children to identify at-risk individuals before they develop coronary symptoms.

## Principle C: Early or Pre-symptomatic Intervention for the Condition Has Been Shown to Lead to Substantially Improved Outcomes in Children, Compared to Intervention After the Onset of Symptoms

### Heterozygous FH

The UK 2008/2017 NICE Guideline [9] on the management of FH contains 16 recommendations specifically targeted to the management of paediatric HeFH. These formed the basis of the HEART UK Statement of Care (SoC) [10], and there is good uniformity among UK paediatricians treating FH. The SoC recommends that children diagnosed with mutation-positive HeFH are seen by a paediatric FH specialist, advice given on healthy lifestyle throughout childhood and an individual care plan established. Dietary and lifestyle advice should include the whole family and age-appropriate national guidance followed for healthy eating and calorie intake for children.

Annual follow-up from the age of 8 years is recommended to reassess the lipid profile and consider statin initiation by the age of 10 years if LDL-C >3.5 mmol/L. In the UK Paediatric FH Register, more than 95% of children with HeFH had LDL-C above this threshold [32]. NICE guidance and clinical practice also take into account the age of onset of CHD in the family and the presence of other cardiovascular risk factors in the child. These UK guidelines are similar to those proposed by the European Atherosclerosis Society [33].

There are three different ways that early identification of a child with HeFH will lead to improved outcomes for the child.

## Short-term Benefits from Adopting a Healthy Lifestyle

All UK and European guidelines recommend a healthy diet and lifestyle for the management of children with HeFH. Dietary intervention with a low saturated fat diet has been shown in a randomised trial to result in a healthier diet and lower LDL-C levels in both adults and children with HeFH [34•]. Early dietary intervention benefits the whole family, particularly children whose dietary and lifestyle choices are developing and can be established for life [35]. The UK Paediatric Register has reported that significantly fewer children with HeFH are overweight or obese than age-matched UK general population children [36].

## Intermediate-term Benefit from the Identification of Their HeFH Parent

The method of screening at birth and identifying children with FH will allow timely cascade testing of parents and relatives. One parent of any child with an HeFH diagnosis will also be affected and, once identified, stands to benefit from immediate statin treatment, reducing their future risk of early CHD and death from myocardial infarction. Several studies have reported that parentally bereaved children are at increased risk for mental health problems as they grow up, including depression, anxiety and behavioural problems [37, 38]. Children in single-parent families may also show poorer educational achievement [39, 40]. In a study from three Nordic countries [41], parental death before the child was 18 years old was associated with a 50% increased all-cause mortality over around 30 years of follow-up, an effect that was independent of age at bereavement.

## Long-term Benefits from Reduction in their Risk of Early CVD

HeFH causes high cholesterol in the blood from birth, and this leads to an increased risk of early heart disease and stroke. Data from the UK Biobank has shown that carriers of an FH-causing variant have a considerably earlier onset of CHD, even when adjusting for their elevated LDL-C [24]. The UK (Simon Broome) FH Register has shown that if untreated, more than 50% of men with HeFH will develop CHD by the age of 50 and more than 30% of women by the age of 60 [20]. However, the register data also shows that life expectancy for HeFH patients is restored to near normal with early preventive treatment, particularly using high-intensity statins [42] and ezetimibe. The new generation of LLTs available that block PCSK9 activity [43] can help achieve even lower LDL-C concentrations, and the risk of CVD reductions is likely to be even larger.

As shown in Fig. 1, because of their rapidly increasing LDL-C burden [44], atherosclerosis develops early in children with HeFH. Studies using ultrasound of the carotid artery as a surrogate measure of the development of atherosclerosis have shown that by the age of 10 years, the mean carotid intima-media thickness (CIMT) of children with FH is significantly greater than that of their non-FH siblings [45], and if treated with statin LLT, this thickness declines over two years [46]. These data were the evidence on which NICE and HEART UK guidelines recommend consideration of statin initiation by the age of 10 years [9, 10]. Taking into account the concept of LDL-C burden, early identification improves the cost-effectiveness of the screening [47•].

The long-term safety of statin therapy started in childhood is an important issue. The accumulating data in children with FH supports the view that statin treatment from the age of 10 years has no short- or long-term adverse effects on growth or transition through puberty, and only rarely has any side effects, such as liver dysfunction and muscle pains, which are usually minimal [48]. These safety data are supported by findings from the UK FH Children's Register [19]. One recent study found no long-term safety issues after 20 years of follow-up and clear benefit in reduction of CHD events [49••].

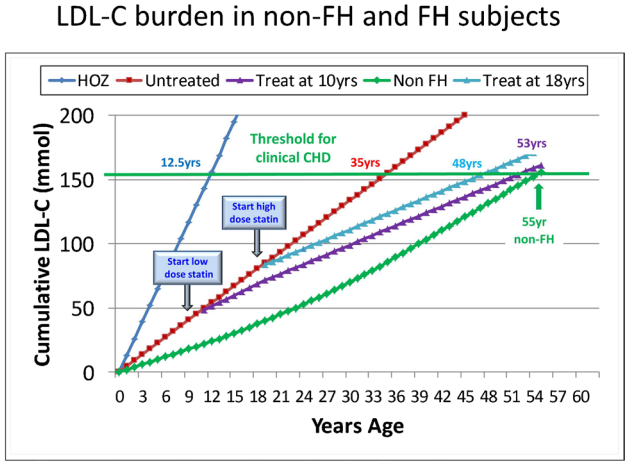


**Fig. 1** LDL-cholesterol (LDL-C) burden in non-FH and FH subjects depending on different ages of starting statin therapy. The LDL-C burden is calculated as the sum of the current LDL-C concentration × age in years. The cumulative LDL-C burden of a 55-year-old non-FH patient is 160 mmol, and it has been reached by an individual with HoFH by the age of 12.5 years, by an untreated-FH patient by the age of 35 years, by an FH patient treated since age 18 years by the age of 48 years and by an FH patient treated since the age of 10 years by the age of 53 years (from Vuorio A et al. Atherosclerosis. 2013 Feb;226(2):315–20, with permission from Elsevier) [44]

### Homozygous FH (HoFH)

As shown in Fig. 1, because of their rapidly increasing LDL-C burden, atherosclerosis develops early in children with HoFH, and by the age of 12–13 years, their LDL-C burden is equivalent to that of a 55-year-old non-FH individual. Survival analysis in patients with HoFH before and after the introduction of statins showed a considerable reduction in CVD events and deaths [50]. Prescription of drugs beyond licence is recommended in the context of a multidisciplinary team meeting. Initiation of LDL-apheresis is recommended from the age of 5 years if the LDL-C target of >3.5 mmol/l is not achieved [25, 26, 51], a long-term open-label study of the treatment of HoFH patients with evolocumab, has studied 106 patients, including 14 adolescents. LDL-C lowering was influenced by genotype; for example, mean reductions were −24% for LDLR defective, but only 6% for LDLR negative/negative patients. New agents such as inhibitors of ANGPTL3 have been shown to be effective in HoFH [52–54].

## Principle D: Conditions Screened for are Only Those for Which the Interventions are Equitably Accessible for All

### Heterozygous FH

Triage, diagnosis and management of FH is largely managed through specialist lipid clinics. Services in England and the devolved countries are well placed to manage children and family members diagnosed with FH through a newborn WGS screening programme. HEART UK has published a statement of care for children with HeFH [10] based on NICE [9] and European Guidelines [26••] which outlines the ideal care pathway for children with FH. These guidelines recommend that children with FH should be referred to and managed by a clinician with expertise in managing children with FH, i.e. a paediatrician. In recent years, there has been considerable investment to develop FH patient care pathways in the UK, with the HEART UK website (https://www.heartuk.org.uk/) identifying a network of over 100 clinics managing adults with FH and over 60 offering paediatric care. These have adequate capacity to manage the additional children and parents with FH identified through this programme. Currently, we do not have data to indicate whether it would be necessary to use different cut-offs for statin initiation in different ethnicities, and >3.5 mmol/l is recommended for all ethnic groups.

As well as national coverage of FH nurses who are already treating patients, training is also being delivered to general practice staff, GPs, nurses and pharmacists on how to deliver news of diagnosis and how to counsel parents [55, 56]. Treatment of children with FH will not be done by GPs, and pathways for children that are diagnosed through the NGP will follow the NICE-established pathway as outlined [9, 10].

### Homozygous FH (HoFH)

With an annual rate of ~700,000 live births, over the 2-year period of the NGP, there are likely to be 1.7 *LDLR* true homozygotes or compound heterozygotes, 0.8 *APOB* homozygotes and 2.3 *LDLR+APOB* compound heterozygotes born in the UK. Since there is high consanguinity in some ethnic groups, this overall figure of ~5 HoFH newborns over 2 years may be higher. However, since the NGP pilot will initially examine 100,000 infants, there is likely to be less than one HoFH child identified in the programme. There are currently 7 centres in the UK that offer apheresis [57], which will be able to offer this treatment to any identified child when appropriate.

## Conclusion

FH meets all the Wilson and Jungner criteria for screening [58] as well as all four of the principles that are required for a disorder to be included in the newborn WGS pilot. While lipid-lowering therapies are considered by the age of 10 years in children with HeH, early education on a healthy diet and lifestyle choices, including avoidance of smoking, are very important in the overall management. Early identification of homozygous FH by newborn WGS would result in early identification and treatment. For each HeFH child, the HeFH parent could be identified before a major CVD event and started on lipid-lowering therapies. If newborn whole genome sequencing does include FH, the child-parent screening programme based on cholesterol measurement at the 12-month time of immunisation would no longer be required. Identification of infants with FH by WGS is superior to the CPS protocol since all carriers of an FH-causing variant will be identified, but in the published pilot study [8], only 54% of the children carrying an FH-causing variant had a TC >95th centile, meaning 46% of mutation carriers would potentially be missed.

Based on the estimated ~1/290 prevalence of FH in the UK [3••], we would predict less than one child with HoFH and around 350 children with HeFH-causing variants will be identified, which would lead to the identification of an additional ~350 parents with HeFH and through cascade testing more than 700 HeFH siblings, and second-degree relatives. Lifestyle modification and LLT offered when age appropriate would significantly reduce the future CVD risk of these individuals, and the current NHS adult and paediatric lipid clinic infrastructure will be able to cope with

this number of patients. Detailed economic modelling has not been performed, but published data (on screening at 1 year) suggests that this programme would be highly cost-effective [59] and that any anxiety caused by receiving an FH DNA test is minimal [60]. This potential future universal genomics-based screening approach would circumvent the myriad problems of trying to identify FH using biochemical and clinical tests, allow early interventions as appropriate for the child and parent(s) and also remove the burden on the child, family and NHS of using a child-parent screening approach at 12 months.

**Acknowledgments** SEH is an Emeritus BHF Professor and acknowledges funding from the British Heart Foundation (BHF) (RG08/008) and the National Institute for Health Research and University College London Hospitals Biomedical Research Centre. The Paediatric FH Register has been previously supported by funds from the BHF, HEART UK, Cardiac Network Co-ordinating Group Wales, The Royal College of Physicians and a grant from the International Society of Atherosclerosis (Pfizer number 24052829). SEH and UR acknowledge funding from the National Institute for Health and Care Research Health Technology Assessment (NIHR HTA) (Award ID NIHR134993). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. Project information available at https://fundingawards.nihr.ac.uk/award/NIHR134993.

## Declarations

**Competing interests** SEH is the medical director of a UCL Spin-off company (StoreGene) that offers genetic testing for cardiovascular risk including for FH. SEH also reports payment for expert testimony from Verve Therapeutics (to self) and support from the European Atherosclerosis Society to attend EAS 2022 in Milan and 2023 in Mannheim. UR has received advisory board fees from Esperion and has no conflicts of interest related to this manuscript. NH has no conflicts of interest to declare.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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