Universal screening for familial hypercholesterolaemia: how can we maximise benefits and minimise potential harm for children and their families

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Purpose of review

Universal Screening programmes to identify subjects with familial hypercholesterolaemia (FH) have been the subject of much recent interest. However, any screening programme can cause harm as well as having potential benefits. Here we review recent papers using different ages and strategies to identify subjects with FH, and examine to what extent the publications provide quantitative or qualitative evidence of benefit or harm to children and adults.

Recent findings

Three studies have been published over the last 2 years where Universal Screening for FH has been carried out in infancy, at the time of routine vaccinations, or at preschool age. Next-generation sequencing of all known FH-causing genes has been used to determine the proportion of screened individuals, who have total or low-density lipoprotein cholesterol (LDL-C) concentrations above a predetermined threshold (such as >95th percentile), with genetically confirmed FH.

Summary

While we fully support the concept of Universal Screening for FH, which appears feasible and of potential clinical utility at all of the different ages examined, there is little data to document potential benefit or how to mitigate potential harms. Future study protocols should include collection of such data to strengthen the case of roll out of Universal Screening programmes.

Keywords

maximising-benefit, minimising-harm, proportion variant-positive

INTRODUCTION

FH is a monogenic autosomal dominant disorder resulting in elevated total and low-density lipoprotein cholesterol (LDL-C) from birth and premature cardiovascular disease (CVD) [1]. An individual who carries a pathogenic variant (also known as a mutation) in any one of four different genes (*LDLR/APOB/PCSK9/APOE*) has heterozygous FH (HeFH), whereas individuals who carry two copies have homozygous FH (HoFH). Rarely, carriers of two variants in a combination of genes can also have the lipid profile of HoFH [2]. Guidelines on the management of FH recommend that an adult individual with FH should be offered intensive lipid-lowering therapy (LLT) to reduce their LDL-C concentration to at least 50% of their baseline value, with European guidelines proposing that LDL-C should be lowered to 1.8 mmol/l, or 1.4 mmol/l in the presence of CVD [3]. Children with a diagnosis of HeFH are offered dietary and lifestyle advice, with LLT usually offered by the age of 8–10 years [4]. The world-wide and UK prevalence of individuals carrying an FH-causing variant is around 1/280 [5▪], suggesting there are over 500 000 children and 2 million adults with FH in Europe, of whom probably <10% are currently identified [1].

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KEY POINTS

- Universal Screening in children for familial hypercholesterolaemia (FH) is feasible and cost effective.

- Universal Screening at the time of routine immunisation (12 months) or at preschool age in countries where a routine health check is mandatory have both been piloted successfully.

- Universal Screening by measuring lipids in blood spots taken at birth is technically feasible and trials to determine specificity and sensitivity are underway.

- While the potential benefits to the identified child and their relatives of an early diagnosis of FH are clear, the potential harms and ways to mitigate them are less well studied.

In most countries, identification of individuals with FH is predominantly achieved by opportunistic case finding of hypercholesterolaemia in primary and secondary care, supplemented by cascade testing of potentially affected family members, of whom, for first degree relatives, on average 50% will also have FH. Cascade testing has been shown to be feasible, acceptable, and cost effective [6] and is widely used in many countries. However, case finding numbers would improve greatly if this were supplemented by a Universal Screening strategy. FH fulfils all the Wilson and Jungner principles for screening, and has the benefit of reaching people across the whole socio-economic spectrum, and should help to reduce health inequalities, as CVD is the largest cause of premature mortality in deprived areas [7]. Policy documents stress the potential benefits of Universal Screening [8■] and are supported by patient groups in many countries. However, although not widely acknowledged, as was noted by Gray and Austoker in 1998 'All screening programmes do harm; some do good as well, and, of these, some do more good than harm at reasonable cost' [9]. In order to ensure that roll out of Universal Screening for FH does more good than harm at reasonable cost, we first review recent papers on FH Universal Screening, then discuss the different sources of harm and benefit from contrasting screening protocols, and present various approaches where potential harm could be mitigated and benefits maximised.

CURRENT FAMILIAL HYPERCHOLESTEROLAEMIA UNIVERSAL SCREENING PROTOCOLS

We carried out a search of published literature over the last 3 years using the terms FH and Universal Screening, including only those where genetic analysis had been performed. As shown in Table 1, comparison with two historical studies from the UK [10] and Slovenia [11■■] was made with three primary data publications in the past 2 years [12■■–14■■]. Two groups reported methods to obtain lipid measures from dried blood spots taken at birth [15,16■] but neither have reported genetic findings.

All identified studies measure plasma total cholesterol (TC) or LDL-C and/or ApoB and set a threshold above which an individual was designated as 'likely to have FH' and a sample sent for genetic testing. Next-generation sequencing (NGS) of at least *LDLR, APOB* and *PCSK9* genes was used and any child carrying a designated FH-causing variant was given the diagnosis of definite FH. This genetic information was then used to test the parents, and sometimes other first-degree relatives, to identify further variant-positive individuals.

In the UK primary care study [10], TC and blood for FH genetic analysis was obtained through a heel prick blood sample taken at ~12 months of age during routine immunisation (for Measles/Mumps/Rubella (MMR)). Of the 10 094 babies tested, 93 were above the 99th percentile, 20 of those were identified as carrying an FH-causing variant. Since all screened babies had a limited FH test, 17 more with TC below the threshold were also found to carry an FH-causing variant. Reverse-cascade testing of parents identified the expected number of variant carriers, who were subsequently offered LLT. In Slovenia, an unspecified number of preschool children had TC measured and those above two thresholds (Table 1) were referred for genetic testing. This led to the identification of 76 variant-positive children, followed by testing of their relatives

In the three recent studies, the number of screened children ranged from 448 to >160 000, with variant detection rates in those sent for genetic analysis ranging from 9.4% to 61.2%, depending on the stringency of triage of the above threshold children. The overall prevalence of genetically confirmed FH was 1/150 in the Australian study but considerably lower than the predicted 1/280 in the other studies (1/380 to 1/700), as expected if a significant proportion of variant carriers actually have LDL-C below the threshold used.

MINIMISING HARM AND MAXIMISING BENEFIT

As shown in Fig. 1 there are a number of clear potential benefits to a Universal Screening programme, whether it is carried out at birth, in infants or at preschool age. Children are not routinely offered LLT until the age of 8–10 years, therefore

Table 1. Showing two historical US studies in Slovenia and UK (Yellow rows) plus 3 studies published in last 2 years (blue rows)

Study country	Age at screening	Number screened	Threshold for genetic test	Number found M+ (prevalence)	Comment (percentage carrying a mutation)	Reference
UK	12 months (routine MMR vaccination)	10 095	99th %ile TC> 6.0mmol/l	20 (1/500)	Samples from 92 children > threshold sent for genetic test (21.7%). All children had limited FH genetic test[a] with 17 < threshold carrying a mutation. Overall prevalence 1/273	[10]
Slovenia	Preschool	Unclear	TC >6.0 mmol/l + no family history CVD TC>5.0 mmol/l + family history CVD	76	280 children referred, 170 genotyped (44.7%)[b]	[11▪▪]
Australia	12 months (routine MMR vaccination)	488	95th %ile TC>5.3 mmol/l	3 (1/150)	32 had TC >5.3 mol/l and were sent for genetic testing, with 3 carrying a mutation (9.4%)	[12▪▪]
Slovenia and Germany	2–6 years	154.658/ 12 133	LDL-C >3.5 mmol/l	219 (1/706)[c] 26 (1/466)[c]	813 sent for genetic testing (26.9%)[c] 132 sent for genetic testing ((29.7%)[c]	[13▪▪]
Japan	9–10 years	15 665	96.3%ile 3.6 mmol/l	41 (1/380)	580 had LDL-C> threshold of whom (after exclusion of secondary causes) 67 sent for genetic testing (61.2%)	[14▪▪]

[a]All children tested for 50 common FH-causing variants in *LDLR/APOB/PCSK9* with those >99 percentile also having NGS.
[b]Likely to be an overestimate since some of the variants reported as pathogenic and likely to be VUS or benign.
[c]Data presented here excluding those with VUS.

the primary benefit to the child is the adoption of a healthy lifestyle, extending to other members of the child's family so parents and siblings may also benefit. Cascade testing of first-degree relatives allows the identification of not only the FH parent and siblings but extended family members, though this is highly dependent on the availability and access to genetic testing services locally.

The primary benefit to the child is that their genetic diagnosis is used to identify their affected parent allowing for timely initiation of LLT, thereby reducing their future risk of cardiovascular disease morbidity and mortality.

This benefit is directly underpinned by evidence that children in a family where one parent has suffered a premature death have poorer mental health and educational achievement [17,18]. Where an FH child has been identified at a young age, LLT can be considered by the age of 10 years, meaning their accumulating LDL-C Burden can be prevented [19] protecting their future cardiovascular health. A further potential benefit of Universal Screening at the age of 5–6 years is that there will be less delay before LLT is considered with less chance of the child being lost to follow-up, and therefore denied the potential benefit of the screening programme.

Concerns regarding potential harm or to less than optimum benefit are more complex. Testing the parents of a child identified with an FH-causing variant, and finding that neither parent carries the variant, would raise the possibility of nonpaternity or more remote possibilities such as baby mix-up at birth, both of which are likely to cause upset within the family. Reported nonpaternity rates are surprisingly high, with a review of published data reporting rates from 0.8% to 30% (median 3.7%) [20]. Neither parent carrying the variant found in the child could be explained as a *de novo* variant. We are aware of only one such report of *de novo* variant in an FH family with biological parentage confirmed using genetic markers [21]. Regardless, every Universal Screening programme should have a standard operation procedure to deal with this issue should it arise.

Guidelines for the management of children with FH emphasise the utility of adapting healthy behaviours, but it is possible that some parents may incorrectly perceive this to mean that both fat and calorie intake should be restricted, leading to reduced growth and development. If the child is seen as 'sick', and prevented from for example social situations where high-fat food is offered (such as at a friend's birthday party) this may lead to mental health issues and isolation. One report from Norway documents a roughly twofold higher prevalence of eating disorders in individuals with FH than the general population [22▪] reinforcing the importance of appropriate dietary counselling for FH given by an experienced healthcare professional.

While modelling has shown that Universal Screening at any age is likely to be highly cost-effective [23,24], this is based on a number of assumptions about a high rate of the uptake and adherence to LLT. It is expected that every parent with a Universal Screening-identified child with
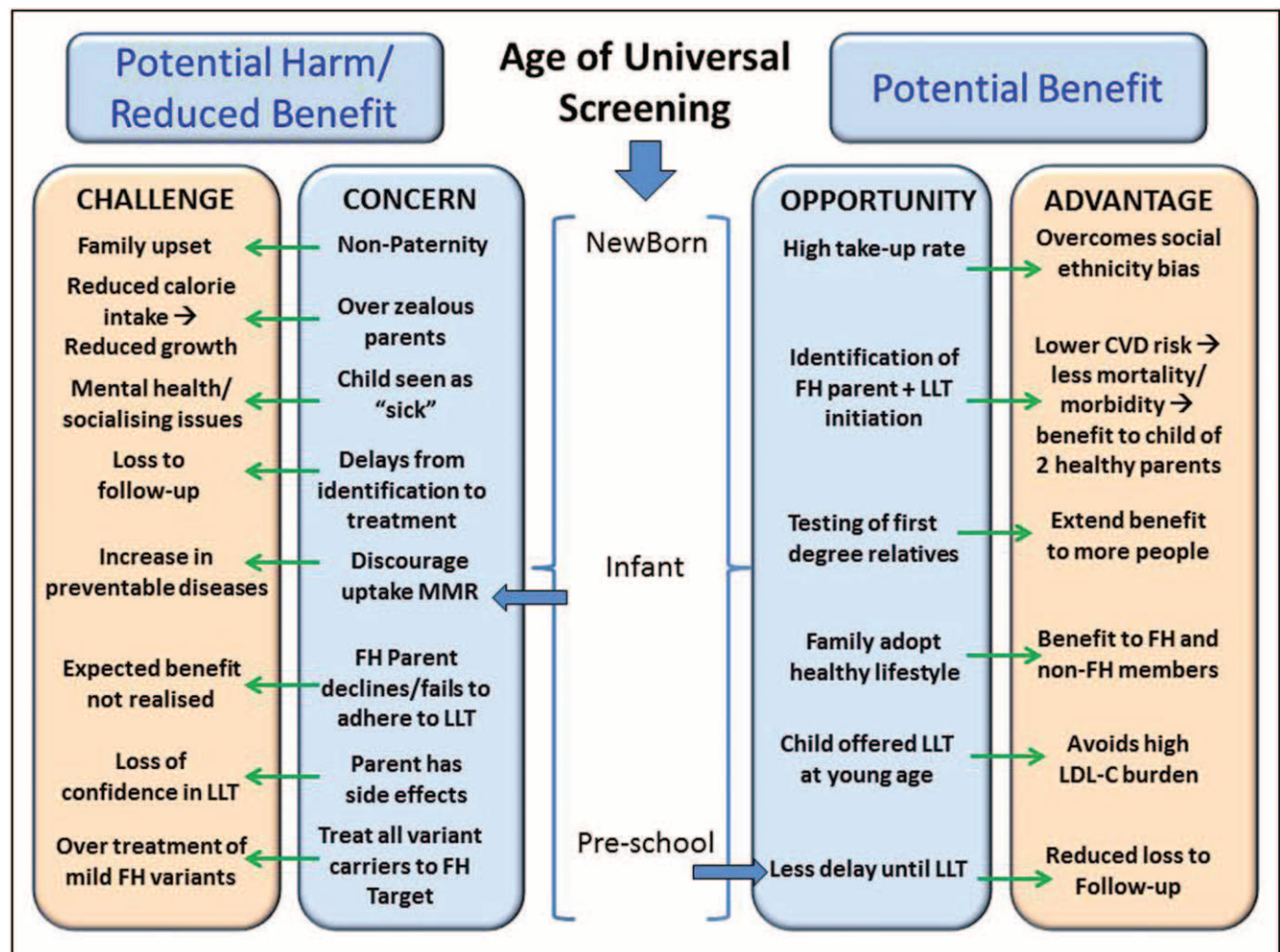
FIGURE 1. Showing potential benefits and potential harms or reduced benefit associated with Universal Screening for familial hypercholesterolaemia at different times in infancy and childhood.

HeFH will agree to having a genetic test, and if positive will initiate and adhere to lifelong LLT. However, it is certain that a proportion of such individuals may develop adverse effects and stop LLT because of this or other reasons, such as inability to pay for medication. In such cases, the long term benefit predicted from Universal Screening, and used in cost-effectiveness modelling, will be less than expected. Often when a child is identified by Universal Screening as carrying an FH-causing variant, there may be no strong family history of hyperlipidaemia or of premature CVD and uptake of genetic testing may be low [25]. By contrast, when cascade testing is carried out from an index case having a clinical diagnosis of FH, including significantly elevated LDL-C plus a personal and/or family history of premature CVD, the tested relatives know they are from a family with high CVD risk. As such they may be more willing to be tested, and more interested in taking LLT if found to be variant positive. If adverse effects to LLT occur, there may be a

loss of confidence in the use of such medication, leading to the parent being less enthusiastic about their child taking LLT. Ensuring FH is managed by an experienced FH HCP will minimise this risk through appropriate management and education. Finally, when a child has been identified to be FH positive as a baby or infant, there must be a robust mechanism in place for ensuring follow-up for at least 7–8 years, when a repeat lipid measurement would be mandatory in deciding on initiation of LLT. We are unaware of any report of extended cascade testing of family members or follow-up of the children identified in the Slovenia or UK by Universal Screening programmes [10,11""], and for both of these, the children would now be over 10 years of age so should have been considered for LLT.

One other potential area of harm is that for all the screening programmes examined, informed consent for lipid and DNA testing of the baby, infant or child was of course obtained from the parent, who had been provided with information about FH and

time to consider to consent or not. The child therefore has not had any say as to whether or not they would choose to be screened. An unknown proportion may, when reaching maturity, regret having been tested, and further work on this needs to be carried out. There are different considerations in the setting of newborn screening, when usually only genetic diseases of immediate impact on the health of the baby are examined, but with little information or time given to consider consent. It is currently unclear how best to provide parents with the information they would need to make an informed decision to consent for the additional testing of a newborn baby for an adult onset disease like FH.

LIMITATIONS OF UNIVERSAL SCREENING PROGRAMMES

For FH Universal Screening programmes based on having a genetic test in those with a high initial lipid measurement, a significant proportion of FH-variant-carrying individuals will be missed. Children with monogenic FH do not all have TC above the threshold for further investigations, and for example in the UK pilot study [10], 46% of children with monogenic FH had TC below the 99th centile. While monogenic FH children who have TC below the 95th centile would be expected to have a lower future risk of CVD than those above the cut-off, their risk is still high. It has been reported that CVD risk is at least twofold higher in monogenic FH than variant negative individuals irrespective of their absolute concentration of LDL-C [26]. Additionally, the LDL-C concentration in some of the variant negative children may increase as they get older. These families will not have follow-up and, even if they are told that FH has not been fully excluded, they may interpret the result this way.

A second issue is the carriers of the *APOB* p. (R2527Q) variant that will be identified by any screening programme. In the UK, in adults with clinical FH where an FH-causing variant can be detected, around 5% carry this *APOB* variant [27] while in the UK pilot study, 40% of the monogenic FH group were identified with this variant [10]. This high prevalence is not unexpected, and from publicly available databases [1], it can be estimated that the frequency of this *APOB* variant in the UK is approximately 1/800 However, patients with this variant typically present with a milder phenotype than those with *LDLR* variants, both in terms of blood concentrations of LDL-C [27] and of future risk of CVD [28]. Therefore, it is likely that any screening programme based on an initial lipid measurement will identify some individuals with a relatively low future risk of CVD who may then be inappropriately treated with intensive LLT to achieve guideline target LDL-C concentrations designed for those with *LDLR*-FH [3]. Currently there is insufficient data in this cohort of children of the benefit of LLT or of future CVD risk, and for children carrying this *APOB* variant, a family history of early onset CVD, including in female relatives, should be taken into account when LLT is considered.

A third limitation is the identification of children carrying a Variant of Uncertain Significance (VUS). All genetic testing can identify a VUS, and rigorous and FH-specific criteria have been developed to guide laboratories about this [29]. In the UK diagnostic laboratories over the last few years, from 19 124 index cases tested, 3–5% had a VUS [30]. The laboratory issues a report stating that a VUS has been identified, and the diagnosis of FH cannot be confirmed without additional data. If such data becomes available, the laboratory re-issues the report stating that the variant is now reclassified as likely to be FH-causing, or that it is likely to be benign. Having a clear protocol of how children identified with a VUS will be managed would be helpful to reduce the potential harm of misleading information being given to parents and families.

A fourth concern is that with every FH programme which refers all children with a lipid measure over a threshold for genetic testing, only a small proportion will be found to carry an FH-causing variant. In the studies shown in Table 1 this ranged from 10% to 61%. The UK study proposed to use the 95th percentile as the threshold for genetic testing in future Universal Screening. For 1000 children screened, this translates into 50 children referred for genetic testing of whom a maximum of 3–4 would be likely to carry an FH-causing variant for a detection rate of 8%. While the care-pathway for the genetically confirmed FH children is usually well mapped out, there is much less clarity about the remaining children who have LDL-C above the screening threshold. We believe that the potential high CVD risk of these children should not be discounted simply because they do not carry a monogenic cause of FH. While some of these children may have elevated TC concentration due to environmental factors (e.g. diet), most are likely to have inherited a greater-than-average number of common LDL-C raising single nucleotide polymorphisms (SNPs). This polygenic aetiology was demonstrated by Talmud *et al.* [31] and subsequently validated [32]. Data from several longitudinal studies have shown that high cholesterol concentrations in childhood persist into adulthood, increasing the risk of premature CVD. For example, a recent paper [33] examined whether childhood risk factors

among 38 589 participants, were associated with CVD in adulthood. 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%. We propose that children identified with TC >95th centile, undergo clinical assessment from a paediatric healthcare professional to exclude secondary causes of hyperlipidaemia and to provide healthy lifestyle advice. A single recall at the age of 8 years is recommended to re-assess the lipid profile and reinforce lifestyle and dietary advice. For those children with persistently high LDL-C, LLT should be considered after evaluating additional CVD risk factors.

CONCLUSION AND FUTURE RESEARCH

Whilst we fully support the aims of Universal Screening for FH, we believe that there should be agreement about measures to be put in place to run alongside the programmes to enhance potential benefits and mitigate potential harms. In particular, identifying 5% of the tested children as having 'high' cholesterol but then subsequently not offering any systematic follow-up to around 90% of these children is a potential source of harm. This could be mitigated by follow-up to reduce future CVD risk by offering dietary and lifestyle advice as well as LLT as appropriate. While patient groups are reported to be in favour of FH Universal Screening in newborns [34,35], as pointed out [9], following identification through a screening programme 'we have to be cautious and distinguish between patient gratitude on the one hand and objective evidence of reduced mortality on the other'. Research should be carried out to follow up identified children at least until they have reached teenage years, to document what proportion will be offered LLT by the age of 10 years and adhere to the prescribed medication and what proportion of children are lost to follow-up, fail to attend clinic visits, or decline treatment. Since there will be additional costs from seeing all variant negative children with TC >95th centile for one baseline clinical assessment and one follow-up visit a full economic analysis would be beneficial. Follow-up of the variant negative children with LDL-C >95th centile should be undertaken, monitoring unwanted effects on anxiety, false reassurance, or control of lipid concentration, which a previous study suggests are likely to be modest [36]. Whilst our proposal requires commissioning of additional resources, we believe tailored monitoring throughout childhood should be mandatory once a modifiable coronary risk factor has been identified which could predispose any child to an enhanced risk of premature CVD in adulthood.

Conflicts of interest

S.E.H. is the Medical Director of a UCL Spin-off company that offers genetic testing for cardiovascular risk including for FH. U.R. and L.P.B. have no conflicts of interest to declare.

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■■ of outstanding interest

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New guidelines include updated criteria for the clinical diagnosis of HoFH and the recommendation to prioritize phenotypic features over genotype. Having LDL-C >0 mmol/l (>400 mg/dl) is suggestive of HoFH and warrants further evaluation. Provides state-of-the art discussion and guidance to clinicians for interpreting the results of genetic testing and for family planning and pregnancy.
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The study included 140 439 European, 4067 South Asian, and 3906 African participants in the UK BioBank. No statistical difference in the prevalence of an FH-causing variant was observed (1/288 in European, 1/260 in African, and 1/226 in South Asian. Carriers of an FH-causing variant had significantly higher LDL-C concentration than noncarriers in every ancestry group. There was no difference in mean (statin-use adjusted) LDL-C concentration in FH-variant carriers depending on their ancestry background.

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Universal Screening for FH has been recognized by the European Commission Public Health Best Practice Portal as an effective strategy. Recommendations presented here emphasize that every country should have an FH screening programme adapted from existing strategies to best fit the individual country's healthcare system. Governments should provide financial support for these programmes and related care, and further research to optimize care and implementations should be conducted.

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Slovenia's program of universal FH screening in preschool children consists of a two step approach: (1) universal hypercholesterolemia screening in preschool children at the primary care level; (2) genetic FH screening in children referred to the tertiary care level according to clinical guidelines (with additional cascade screening of family members). Between 2012–2016, 280 children were referred for having TC > 6 mmol/l (231.7 mg/dl) or >5 mmol/l (193.1 mg/dL), with a positive family history of premature CVD. 170 were genotyped, 44.7% had an FH disease-causing variant.

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With an 8.9% opt-out rate, in Slovenia of 154,658 screened children, 813 with TC >3.5 mmol/l (135.3 mg/dl), were sent for genetic testing. Of these 219 (27% were mutation +ve and 42 (5%) carried a VUS. in Germany, of 12,133 screened children, 132 had TC >3.5 mmol/l of whom 26 (19.7% were mutation +ve and 18 (13.6%) carried a VUS. In Slovenia, 99 parents from 83 families approached (38% of the mutation positive children identified) were tested and in 9.6% of the families the parent with the higher TC levels was negative for the tested variant.

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15 665 children aged 9 or 10 years underwent the universal lipid screening as part of the annual health checkups for the prevention of lifestyle-related diseases. The LDL-C levels of 140 mg/dl corresponded to the 96.3 percentile values. 580 had LDL-C over this threshold of whom (after exclusion of secondary causes) 67 were sent for genetic testing in the whom 41 had FH causative mutations.

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Among 38 589 participants (3–29 years at recruitment), over a follow up of ~35 years there were 319 fatal or nonfatal CVD events. Smoking history as an adolescent, high blood pressure or body mass index were all strongly 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%.

34. Bowman FL, Molster CM, Lister KJ, *et al.* Identifying perceptions and preferences of the general public concerning universal screening of children for familial hypercholesterolaemia. Public Health Genomics 2019; 22:25–35.

Thirty randomly selected individuals were invited to attend a forum and 17 attended. They were presented with information from a variety of perspectives and asked to discuss the information provided to identify points of consensus and disagreement. 16/17 deemed universal screening of children for FH to be acceptable with 15/16 believing this was best performed at the time of an immunisation.

35. Tobik K, Orland KM, Zhang X, *et al.* Parental attitudes and ideas regarding newborn screening for familial hypercholesterolemia. Matern Child Health J 2023; 27:978–983.

Parental perspectives for inclusion of FH on routine newborn screening were examined using telephone interviews. All interviewees indicated that they would be interested in having their child be screened for FH : reasons supporting screening included knowing their child's diagnosis, the ability to screen family members for FH, incorporation of lifestyle changes, and access to preventive care. Negatives included increased stress or anxiety, knowledge, stigma, and the delay from diagnosis to initiation of pharmacotherapy for FH. Authors concluded further education of parents and clinicians is needed to ensure proper implementation.

36. Marteau T, Senior V, Humphries SE, *et al.* Psychological impact of genetic testing for familial hypercholesterolemia within a previously aware population: a randomized controlled trial. Am J Med Genet A 2004; 128A:285–293.