In the first section of this article, we briefly review the rationale for identifying and treating FH in childhood. In the second section, we extensively review the knowns and unknowns relevant to subject.

FH and childhood atherosclerosis
Atherosclerosis begins from conception, with evidence that in utero exposure to maternal high cholesterol impacts on arterial biology in the fetus (11, 12). Autopsy and imaging studies demonstrate that the atherosclerotic process begins in childhood and progresses in direct proportion to plasma LDL cholesterol levels (13, 14). Early signs of atherosclerosis in children with FH include elevated markers of vascular inflammation (15, 16), endothelial dysfunction (17, 18), increased pulse wave velocity (19), and increased carotid intima media thickness (CIMT) (20, 21). Early treatment with statins can reduce the progression of CIMT (22–24). This strengthens the case for early treatment of children with FH to reduce the impact on the cumulative life-burden of LDL cholesterol (Fig. 1) (25). This notion is supported by Mendelian randomization (MR) data indicating that exposure to a 1 mmol/l change in LDL cholesterol is associated with a 50% change in coronary heart disease (CHD) risk (26). However, while individuals with FH who are treated from a young age can have a normal life expectancy, FH remains largely under-diagnosed, especially in the young (25, 27).

Clinical care of FH
Several guidelines and models of care have been published for clinical services (25, 27–33). Components include
screening and detection, diagnosis, risk stratification, treatment, integration of clinical care, patient/family support, registries, and research and audit. However, there are several gaps in knowledge that need to be addressed.

DETECTION OF CHILDREN WITH FH

Current knowledge and practice. FH fulfills classical criteria justifying screening for a condition (34). Screening may be divided into universal or selective, and as opportunistic and systematic within each subcategory. Cascade testing is the method most commonly employed to screen the population for FH in countries around the world; but used alone, it fails to identify sufficient index cases (35). Recent studies propose a combination of universal and reverse cascade testing approaches, identifying the index case in childhood and proceeding to screen the child’s parents and close relatives (5, 36).

Suggestions for future inquiries. The optimal processes and pathways for the organization of childhood screening for FH.

Universal screening by phenotypic and genotypic approaches

Phenotypic strategy. Current knowledge and practice. Total or LDL cholesterol level measured between 1 and 9 years of age best discriminates between individuals with and without FH in the general population (37). A pilot study confirmed the feasibility and acceptability of screening for FH with a total cholesterol level at immunization in children aged 1–2 years (38).

In the US, universal screening of children aged 9–11 years for hypercholesterolemia has been proposed. This was part of an integrated guideline to improve cardiovascular (CV) health in young people and not directed at identifying children with FH. Uptake of this recommendation has been limited (39, 40). However, by focusing the screening on diagnosing FH and setting a higher cholesterol threshold (e.g., LDL cholesterol ≥ 4 mmol/l or ≥ 160 mg/dl), one can markedly reduce the number of false positives and only recall individuals with probable FH, who are likely to require pharmacological intervention to lower LDL cholesterol. Once an index case has been identified by a universal screening approach and the diagnosis confirmed, reverse cascade testing can identify other family members (5, 37).

Suggestions for future inquiries. i) The acceptability of universal screening by children/adolescents and parents and community perceptions. ii) The efficacy and cost-effectiveness of a phenotypic approach to universal screening of children for FH. iii) The feasibility and acceptability of alternative approaches to universal screening (e.g., university entry).

Genotypic strategy. Current knowledge and practice. The feasibility and efficacy of child-parent screening for FH has been demonstrated in a prospective study of children aged 1–2 years, who had a total cholesterol level measured at the time of an immunization, with subsequent testing for mutations. Using a cholesterol cut-off of the 95th percentile plus a FH mutation or a cut-off of the 99th percentile without a FH mutation for every 1,000 children screened, eight individuals (four children and four parents) were identified as having FH, of whom 80% had a FH mutation detected (5).
Futema et al. (36) evaluated this child-parent screening strategy in the Avon Longitudinal Study of Parents and Children. Using a two-stage model that included biochemical screening (total cholesterol) followed by next generation sequencing (NGS) of FH genes for all screen-positive samples, a total cholesterol cut-off of the 99th percentile resulted in a similar FH detection rate of 83% and a false-positive rate of 0.8%. The authors propose that including a NGS step for all screen-positive samples would eliminate false positive cases and improve the screening strategy for children with FH.

Slovenia is the only country that has successfully implemented a universal screening program for FH to date (41). Children are screened at 5 years of age and those with fasting total cholesterol $\geq 6$ mmol/l without a family history of premature CV complications or total cholesterol $\geq 5$ mmol/l with a positive family history have a repeat lipid profile and targeted NGS. A pathogenic FH mutation can be detected in 57% of participants with a positive biochemical screen.

Elevated cholesterol may be due not only to monogenic gene variants but also to polygenic gene variants, which may explain why mutations are often not detected in patients with phenotypic FH (42). Conversely, some patients with a pathogenic FH gene variant do not have hypercholesterolemia (5), but may still be at increased risk of CAD (6).

A recent Australian study demonstrated that universal screening of children for FH is likely to be acceptable to the general public and general practitioners (GPs) (43).

**SUGGESTIONS FOR FUTURE INQUIRIES.**

1. The cost-effectiveness of an integrated universal screening approach to FH in children coupled with reverse cascade screening of close relatives.
2. The contribution that polygenic gene variants make to the apparent phenotypic diagnosis of FH.
3. The role of protective modifier genes in masking the effect of pathogenic variants.
4. The natural history of children with pathogenic FH gene variants without elevated LDL cholesterol.
5. The natural history of children with high LDL cholesterol levels without FH.

**Selective screening**

_Cascade testing (systematic). Current knowledge and practice._

The codominant inheritance of FH supports cascade testing, where individuals considered at increased risk of FH owing to a family member having the condition are invited for testing; each first-degree relative of an index case has a 50% chance of having FH. Cascade testing can be performed by either genetic testing, if a family mutation has been established, or by LDL cholesterol levels (44). An average of two and up to eight new cases with FH may be identified for each newly diagnosed index case (44–46). Cascade testing is efficacious and cost-effective (45, 47, 48), particularly in adults (49, 50). Children with FH are most diagnosed by forward cascade testing following a diagnosis of a parent. In reverse cascade testing, parents are screened following diagnosis of a child.

The cascade screening program in The Netherlands has been the most successful worldwide, with up to 70% of all individuals with FH identified by 2014 (27, 46). This may be difficult to replicate in other countries. In Australia, a centralized cascade-screening program was established in 2007 (Fig. 2), but after almost 10 years, only 13% of adults and 4% of children <16 years of age were detected (J. Pang, personal communication). While many economic analyses report it to be cost-effective (45, 47, 48), in practice and with the exception of the Netherlands, cascade screening has been relatively ineffective in identifying the majority of individuals with FH in the community (51). This is predominantly owing to the failure to detect an adequate number of index cases in the community (35).

**SUGGESTIONS FOR FUTURE INQUIRIES.**

1. The effectiveness of cascade testing in the community via primary care.
2. The integration of centralized and primary care screening strategies.

_Opportunistic. Current knowledge and practice._

Selective screening of children for hypercholesterolemia was first recommended in 1992, based on a family history of premature atherosclerotic CV disease or hypercholesterolemia (52). Unfortunately, family history failed to identify the majority of children with FH (39, 53, 54), which led to the recommendation of a universal lipid screening program for children aged 9–11 years and young people aged 17–21 years (55).

Laboratory reporting systems have been developed to highlight individuals with cholesterol results suggestive of FH. The addition of interpretive comments and a phone call to the referring GP can increase the likelihood of a diagnosis of FH (56, 57). Electronic medical records and utilization of a computerized algorithm may be useful in detecting and diagnosing FH in primary care (58, 59).

**SUGGESTIONS FOR FUTURE INQUIRIES.**

1. The role of allied health groups in identifying patients with FH, e.g., pharmacists, school nurses, and coronary rehabilitation nurses.
2. The effectiveness of screening strategies for children in primary care settings.

**DIAGNOSIS**

_Current knowledge and practice._

The Dutch Lipid Clinic Network criteria are not valid in children, but Simon Broome criteria have specific LDL cholesterol cut-offs for this age group. Any child with a LDL cholesterol level $\geq 5$ mmol/l on two successive occasions has a high probability of FH (25). An LDL cholesterol level $\geq 4$ mmol/l in a child with a family history of premature CHD in a close relative and/or baseline high cholesterol in one parent indicates a high probability of FH (8, 25). If the parent has a genetic diagnosis of FH, an LDL cholesterol $\geq 3.5$ mmol/l in the child suggests FH (60, 61).

The diagnosis of FH in children usually follows cascade testing. Children over 5 years of age should be offered testing when a parent (or close relative in absence of parent) is identified with FH (25, 50). As a first screening test, a nonfasting lipid profile is sufficient (62), but LDL cholesterol levels should be measured at least twice over 3 months in a fasting state to confirm the diagnosis and secondary
causes of hypercholesterolemia must be excluded (31, 63). Detection of a pathogenic mutation in a child is the gold standard for the diagnosis of FH (Fig. 3) (25). Sitosterolemia, a very rare disorder, may mimic FH in childhood.

The diagnosis of homozygous FH (hoFH) can be made genetically, by identifying two pathogenic FH mutations, or phenotypically, in those with an untreated LDL cholesterol of >13 mmol/l together with the presence of cutaneous or tendon xanthomas before age 10 or elevated LDL cholesterol levels in both parents consistent with a diagnosis of heterozygous FH (64). There can, however, be a significant variation in LDL cholesterol levels in patients with hoFH, and recent reports have highlighted the variability in the expression of the clinical phenotype related to the presence of other modifier genes, gene-gene and gene-environment interactions, and epigenetic influences (4, 64, 65).

Fig. 2. Protocol for genetic cascade screening in Western Australia. Adapted from Bell and Watts (123).

Fig. 3. Potential strategy for diagnosis of FH in children and adolescents. Premature CHD is defined as a coronary event before age 55 years in men and age 60 years in women. Definite FH is defined as genetic confirmation of at least one FH-causing genetic mutation. Close relative is defined as first or second degree. Highly probable FH is based on clinical presentation (i.e., phenotypic FH), either an elevated LDL cholesterol (LDL-C) level ≥5 mmol/l in a child after dietary intervention or an LDL cholesterol level ≥4 mmol/l in a child with a family history of premature CHD in close relatives and/or baseline high cholesterol in one parent. Cascade screening from an index case with a FH-causing mutation may identify a child with elevated LDL cholesterol levels ≥3.5 mmol/l. Reproduced from Wiegman et al. (25).
SUGGESTIONS FOR FUTURE INQUIRIES. The definition of the diagnostic criteria for FH in children in diverse populations, including country-, gender-, and age-specific cholesterol thresholds.

RISK STRATIFICATION

CURRENT KNOWLEDGE AND PRACTICE. The risk of early CAD in individuals with FH is associated with the lifelong exposure to elevated LDL cholesterol levels. In addition, the presence of a FH mutation triples this risk at any LDL cholesterol level (6, 66). However, while individuals with FH who are untreated have a 20-fold increased risk of premature CHD, such an outcome is not inevitable (29). A variety of predictor variables have been proposed, including a combination of clinical and biochemical markers (67), genetic risk scoring systems (68), markers of inflammation (15), and different forms of imaging, such as endothelial function (69), CIMT (70), and coronary artery calcium scores (71). To date, none of these predictor variables has proven to be sufficiently robust to allow widespread use in clinical practice. Intuitively, traditional CV risk factors and a history of premature CHD in a parent increase the risk in the child and, thus, form part of the routine risk assessment for children with FH.

SUGGESTIONS FOR FUTURE INQUIRIES. i) The optimal form of CV imaging for children with FH. A simple to use, accurate, and noninvasive form of coronary artery imaging that indicates early atherosclerosis is needed. ii) The development of a life-time risk prediction model in children. iii) The biomarkers of CV risk.

MANAGEMENT

CURRENT KNOWLEDGE AND PRACTICE. Early treatment of FH with statins from childhood reduces the lifetime burden of LDL cholesterol and the rate of development of atherosclerosis (17, 22, 23, 25).

However, as a long-term prospective randomized controlled study comparing treatment of children with LDL cholesterol-lowering therapy or placebo is unlikely to ever be conducted, MR studies or “natures randomized controlled trials” can help fill evidence gaps (26). MR studies have demonstrated that several single nucleotide polymorphisms associated with lower LDL cholesterol levels are associated with a lower risk of CHD (72–74). However, while meta-analyses of statin trials have shown a 23% reduction in the risk of CHD for every millimole per liter lowering of LDL cholesterol (75, 76), meta-analyses of MR studies reveal a corresponding 50% reduction in the risk of CHD (72). This 2-fold difference in relative risk can be explained by the fact that the LDL cholesterol-lowering effect in MR studies commences from the time of conception, rather than when a statin is prescribed in later adult life. MR studies also suggest that the benefit of lowering LDL cholesterol levels is independent of the mechanism of action, with a similar magnitude of effect in genes coding for targets of statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs) (26). MR studies offer a rapid and powerful approach to answering clinically relevant questions, especially in children and young people, but are limited by the fact that they fail to recognize adverse events related to medications.

SUGGESTIONS FOR FUTURE INQUIRIES. i) The individual variation in the natural history of atherosclerosis to inform the timing and intensity of interventions to lower LDL cholesterol. ii) The risk/benefit of lifelong FH care for children, including assessment of age-appropriate treatment goals and long-term physical and psychological side effects of treatment.

Diet and lifestyle measures. CURRENT KNOWLEDGE AND PRACTICE. Adult FH registry data demonstrate that many FH patients are overweight or obese, smoke, and have type 2 diabetes, all preventable causes of CAD. Thus, because it is easier to learn good habits than to break bad habits, all children with FH should receive advice on lifestyle modifications, incorporating a healthy diet low in saturated and trans-fat (77), regular exercise, and avoidance of cigarette smoking, including environmental tobacco smoke exposure (25, 78). While lifestyle interventions alone are rarely sufficient to lower LDL cholesterol levels to recommended targets, establishing these in childhood reduces the likelihood of developing additional CV risk factors, meaning they should be promoted for all children with FH (31, 55).

SUGGESTIONS FOR FUTURE INQUIRIES. i) The effective methods of primordial prevention of non-cholesterol CV risk factors. ii) The effectiveness of different heart-healthy and culturally specific diets in childhood FH, including the role of specific nutrients and nutraceuticals.

Nutraceutical supplements. CURRENT KNOWLEDGE AND PRACTICE. Plant sterols and stanols are naturally occurring compounds that compete with and inhibit the absorption of cholesterol in the small intestine. A daily dose of 1.5–3 g in children with FH is safe, palatable, and reduces LDL cholesterol levels by 9–19% (79, 80), but does not restore endothelial function (81). Trials in adults have failed to demonstrate improvements in CV events, making it difficult to routinely recommend these supplements in children.

Many other supplements have been trialed in children with FH, including psyllium husk (82), fish oil (83), rape-seed oil (84), soy protein (85), policosanols (86), and red yeast rice extract (86), but none can be recommended at this time (87). Berberine (88) and Armolipid Plus (89) have been trialed in adults only.

SUGGESTIONS FOR FUTURE INQUIRIES. The efficacy, acceptability, and safety of nutraceuticals in children with FH, used alone or in combination with a low-dose low-frequency statin.

Pharmacotherapy. CURRENT KNOWLEDGE AND PRACTICE. Pharmacotherapy is almost always required and statins are the most commonly used as a first line agent (25). Statins lower
LDL cholesterol levels by up to 50% in children with FH, with most of the effect occurring at lower doses. Each subsequent doubling of dose achieves a further 6–7% reduction in LDL cholesterol levels (90).

Most guidelines recommend commencing treatment in boys and girls with FH from 8 years of age, although the decision to treat must be made in partnership with the child and family and be guided by the family history of CV events and the level of LDL cholesterol (25, 31). Treatment should be initiated at the lowest dose using the least potent statin and titrated up every 6–8 weeks, depending on the LDL cholesterol response. Guidelines suggest a target LDL cholesterol level of 3.5 mmol/l or a 50% reduction in LDL cholesterol from pretreatment levels (7, 25, 31). Following commencement of a statin or an increase in dose, a lipid profile and liver function tests should be repeated after 6–8 weeks, which equates to the maximal LDL cholesterol-lowering effect. Once LDL cholesterol targets have been achieved, a lipid profile and liver function tests should be repeated every 6–12 months throughout childhood, to confirm adherence and monitor for side effects of medication (31).

While there remains an ongoing debate regarding the magnitude of statin side effects in adults, particularly muscle-related complaints (91), side effects are rare in children and, if they do occur, are usually in the early stages of treatment and resolve spontaneously. There are limited long-term data for children treated with statins, but a recent study has provided reassuring results (23). In a 10 year follow-up trial of statins started in childhood, compliance was high and only 1.5% stopped statin therapy. There were no serious adverse events, such as hepatitis or rhabdomyolysis (23, 92). While further long-term studies are required, children and families should be reassured that current evidence suggests that statins have an excellent safety profile in children (25).

For children who fail to achieve LDL cholesterol targets, the addition of ezetimibe or a bile acid sequestrant may be considered (25, 31). Ezetimibe is a selective cholesterol absorption inhibitor that reduces LDL cholesterol levels by up to 20% when used as monotherapy or in combination with a statin (93, 94). Ezetimibe is approved for use from the age of 10 years in the USA and Europe and appears to be safe and well-tolerated. Bile acid sequestrants reduce LDL cholesterol levels by up to 10%, but their use is frequently limited by gastrointestinal side effects. The best-tolerated agent is colesevelam, which is approved from the age of 10 years in the USA, but not in Europe (95).

mAbs to PCSK9 (alirocumab and evolocumab) lower LDL cholesterol and are being used increasingly in adults with and without FH to achieve very low LDL cholesterol targets. It has been proposed that treatment of children with FH could potentially be delayed until adulthood, at which time a more aggressive cholesterol lowering approach could be initiated with PCSK9 mAbs (96, 97). Formal prospective studies of PCSK9 mAbs in children with FH are currently underway (ClinicalTrials.gov: NCT02392559, NCT02890992, and NCT02624869).

Before a statin is commenced in any female of childbearing age, specific advice must be given regarding contraceptive choices and this should be discussed at each outpatient review (31). All women planning pregnancy should be advised to discontinue statins 3 months before conception. However, while a range of congenital abnormalities have been reported in infants following in utero exposure (98), for women who do fall pregnant while taking a statin, they can be reassured that the likelihood of complications is small (99, 100). For pregnant women who need to continue cholesterol-lowering therapy, bile acid sequestrants are the only safe oral agent. In women with severe CAD or hoFH, LDL-apheresis (LDL-A) can be safely continued during pregnancy (98).

SUGGESTIONS FOR FUTURE INQUIRIES. i) The thresholds for commencing treatment in children with FH and a mutation, compared with those who have no mutation identified. ii) The long-term safety of statins and other cholesterol-lowering drug therapies in children. iii) Data on statin intolerance in children. iv) The role of new pharmacological agents (e.g., bempedoic acid, PCSK9 mAbs) in managing childhood FH. v) The impact of withholding statins and ezetimibe during pregnancy and lactation on CV outcomes of children born with FH. vi) Pregnancy outcomes, both CHD in mothers and CAD risk in offspring.

hoFH. CURRENT KNOWLEDGE AND PRACTICE. All children with hoFH should be cared for in a specialist pediatric center (64). Following diagnosis, treatment should be commenced with a statin and ezetimibe without delay. This combination therapy usually results in a 30–40% reduction in LDL cholesterol levels. Additional treatment with LDL-A should be commenced as soon as possible, ideally by age 5 years (64). Maintaining good quality of life is important during apheresis and can be improved by reducing the frequency of the procedure with the use of new biologics (101). Injectable mipomersen, an antisense RNA therapy, is approved in the USA from 12 years of age and oral lomitapide, a microsomal triglyceride transfer protein inhibitor, from 18 years. Both agents target the hepatic production of apo-B-containing lipoproteins (102). Both agents have been reported to cause fatty liver disease in adults. (25) PCSK9 mAbs can lower the frequency of apheresis in adults (103, 104).

Liver transplantation, alone or in combination with heart transplantation, is an option that cures the patient of their molecular defect, but replaces one serious disease with the need to take life-long immunosuppressant medication and the associated risks.

SUGGESTIONS FOR FUTURE INQUIRIES. i) The role of PCSK9 mAbs in decreasing the requirement for or frequency of LDL-A in children. ii) Trialling improved methods for administering LDL-A in children. iii) International registry data on outcomes of liver transplantation in hoFH. iv) The outcome of trials of gene therapy (AAV-8 LDL-R gene transfer therapy) for hoFH. v) The treatment of hoFH in remote regions and low-income countries (105).
vi) Psychological studies and support for families of children with hoFH.

Patient perspectives. Current knowledge and practice. Every individual has a self-perception on risk and preferences on care for FH. The family history of a coronary event impacts greatly on patients’ perceptions and awareness (106). Providing crisp and comprehensible information to children and families about FH and the risk of CV events is essential (107). Adolescence is a particularly challenging period when parents are making important decisions on their offspring’s behalf. However, adolescents must be given the opportunity to see their treating physician alone, without their parent, for at least a portion of each clinic visit, allowing the doctor an opportunity to learn about the priorities of the young person and to address sensitive issues such as sexual health/contraception and smoking (108). Patients with FH need to engage in a life-long treatment and unless they genuinely understand and believe in the benefits, medium- to long-term adherence is unlikely (109). FH support groups led by other FH-affected individuals, including those of the same generation should be encouraged and are a powerful way to encourage patient engagement by providing meaningful education and support for individuals and families. SuggestionS for future inquirieS. i) Approaches for involving children and adolescents in their care and shared decision making. ii) The most effective tools for education and support: social media (Instagram, Facebook, Twitter). iii) Quality of life studies to provide a better understanding of the child’s or adolescent’s perception of living with FH.

INTEGRATION OF CARE AND SERVICES

Current knowledge and practice. Optimal care of children and adolescents with FH requires a multidisciplinary framework integrated across primary care, pediatric specialist, and adult services (31). All children should be seen in a pediatric clinic at least yearly. Alternatively, a pediatrician should join the adult service to jointly review children (31). Family clinics may also be effective and convenient for patients. Access to a pediatric dietician, nurse specialist, genetics counselor, social worker, and clinical psychologist is essential. Shared care with the family GP is also recommended. Pathways for transition of adolescents from pediatric to adult services are essential (110). SuggestionS for future inquirieS. i) The effectiveness of family clinics compared with traditional clinics. This will improve services for children and families. ii) The specific role of allied health personnel in the care of pediatric FH. This may improve awareness and adherence with care and self-management later in adolescence. iii) The optimal strategies for integrating primary and specialist services. This may allow greater continuity of care of patients with FH. iv) The optimal pathways for transitional care. This is important to ensure continuity of care for adolescents with FH.

PATIENT SUPPORT GROUPS AND NETWORKS

Current knowledge and practice. Patient support groups and networks have a critical role in improving the care of children with FH. Empowering patients raises the awareness of FH in the community and improves collaboration between patient groups and the medical/scientific world (111). Patients and families are central for developing research programs (8). Patient advocacy groups can effectively lobby for improved care, including better access to and reimbursement for essential medications. SuggestionS for future inquirieS. i) The optimal strategies for recruiting and running family support groups and networks, including the role of social media. ii) Exploring strategies for promoting effective advocacy.

REGISTRIES AND CODIFICATION

Current knowledge and practice. Registries facilitate research and education and lead to better health outcomes for patients (112). Several FH registries have been established or are in development (111, 113–120). The longest existing pediatric registry started in the Netherlands in 1989 and has provided much of the information on which current knowledge is based (60, 121). A pediatric FH registry was also established in the United Kingdom in 2012 (122). As with registries, codification of FH is essential for health service research and funding. An ICD-10 code for FH was granted in the US in 2016. SuggestionS for future inquirieS. i) The definition and harmonization of data elements for international registries. ii) The use of pediatric registries in defining the long-term natural history of FH. iii) The development of a global network of inter-operable registries of children with FH. iv) The value of linking pregnancy registries with pediatric registries. v) Obtaining standardized codification of FH worldwide.

RESEARCH AND AUDIT

In this work, we have identified many unknowns in pediatric FH. These are summarized in Table 1, a research agenda for the future.

CONCLUSIONS

Children treated for FH can avoid premature atherosclerosis and should have a normal life expectancy. However, despite progress in care, several evidence gaps need to be filled. This can improve existing models of care for children with FH, which need to be pragmatic and context specific.
Aiming for optimal models of care will ultimately change the natural history of this common and life-threatening condition.

REFERENCES

1. Pang, J., A. C. Martin, T. A. Mori, L. J. Beilin, and G. F. Watts. 2016. Prevalence of familial hypercholesterolaemia in adolescents: potential value of universal screening? J. Pediatr. 170: 315–316.
2. Benn, M., G. F. Watts, A. Tybjærg-Hansen, and B. G. Nordvestgaard. 2012. Familial hypercholesterolaemia in the Danish general population: prevalence, coronary artery disease, and cholesterollowering medication. J. Clin. Endocrinol. Metab. 97: 3956–3964.
3. Watts, G. F., J. E. Shaw, J. Pang, D. J. Maglano, G. L. Jennings, and M. J. Carrington. 2015. Prevalence and treatment of familial hypercholesterolaemia in Australian communities. Int. J. Cardiol. 185: 69–71.
4. Sjouke, B., D. M. Kusters, I. Kindt, J. Besseling, J. C. Defesche, E. J. Sijbrands, J. E. Roeters van Lennep, A. F. Stalenhof, A. Wiegman, J. de Graaf, et al. 2015. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. Eur. Heart J. 36: 560–565.
5. Wald, D. S. J. P. Bestwick, J. K. Morris, K. Whylie, L. Jenkins, and N. J. Wald. 2016. Child-parent familial hypercholesterolaemia screening in primary care. N. Engl. J. Med. 375: 1628–1637.
6. Khera, A. V., H. H. Won, G. M. Peloso, K. S. Lawson, T. M. Bartz, X. Deng, E. M. van Leeuwen, P. Natarajan, C. A. Emdin, A. G. Bick, et al. 2016. Diagnostic yield and clinical utility of sequencing familial hypercholesterolaemia genes in patients with severe hypercholesterolaemia. J. Am. Coll. Cardiol. 67: 2578–2589.
7. Watts, G. F., S. Gidding, A. S. Wierzbicki, P. P. Toth, R. Alonso, W. V. Brown, E. Bruckert, J. Defesche, K. K. Lin, M. Livingston, et al. 2015. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. Eur. J. Prev. Cardiol. 22: 849–854.
8. Gidding, S. S., M. A. Champagne, S. D. de Ferranti, J. Defesche, M. K. Ito, J. W. Knowles, B. McCrindle, F. Raal, D. Rader, R. D. Santos, et al. 2015. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. Circulation. 132: 2167–2192.
9. Slack, J. 1969. Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. Lancet. 2: 1380–1382.
10. Stone, N. J., R. I. Levy, D. S. Fredrickson, and J. Vetter. 1974. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. Circulation. 49: 476–488.
11. Alkemade, F. E., A. C. Gittenberger-de Groot, A. E. Schiel, J. C. VanMunsteren, B. Rogers, L. S. van Vliet, R. E. Poelman, L. M. Havekes, K. Willems van Dijk, and M. C. DeRuiter. 2007. Intrauterine exposure to maternal atherosclerotic risk factors increases the susceptibility to atherosclerosis in adult life. Arterioscler. Thromb. Vasc. Biol. 27: 2228–2235.
12. Napoli, C., C. K. Glass, L. J. Witzum, R. Deutsch, F. P. D’Arimiento, and W. Palinski. 1999. Influence of maternal hypercholesterolemia during pregnancy on progression of early atherosclerotic lesions in childhood: fate of early lesions in children (FELIC) study. Lancet. 354: 1213–1214.
13. Mc Gill, H. C., Jr., and C. A. McMahan. 1998. Determinants of atherosclerosis in the young. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) research group. Am. J. Cardiol. 82: 307–337.
14. Newman III, W. P., D. S. Freedman, A. W. Voors, P. D. Gard, S. R. Srinivasan, J. L. Cresanta, G. D. Williamson, L. S. Webber, and G. S. Berenson. 1986. Relation of serum lipoprotein levels and systolic...
22. Wiegman, A., B. A. Hutten, E. de Groot, J. Rodenburg, H. D. Kusters, D. M., A. Wiegman, J. J. Kastelein, and B. A. Hutten. 2014. Increased inflammatory markers in children with familial hypercholesterolemia: a literature review. *Atherosclerosis.* 235:290–309.

21. Kusters, D. M., A. Wiegman, J. J. Kastelein, and B. A. Hutten. 2009. Family history of cardiovascular events and endothelial dysfunction in children with familial hypercholesterolemia. *Atherosclerosis.* 163:193–197.

20. Vlahos, A. P., K. K. Naka, A. Bechlioulis, P. Theoharis, K. Vakalis, E. Moutzouri, G. Miltiadous, L. K. Michalis, A. Siamopoulou-Mavridou, M. Elisa, et al. 2014. Endothelial dysfunction, but not structural atherosclerosis, is evident early in children with heterozygous familial hypercholesterolemia. *Pediatr. Cardiol.* 35:63–70.

19. Riggio, S., G. Mandruffino, M. A. Sardo, R. Indicida, N. Camarda, E. Imbalzano, A. Alibrandi, C. Saitta, S. Carej, T. Arrigo, et al. 2010. Pulse wave velocity and augmentation index, but not intima-media thickness, are early indicators of vascular damage in hypercholesterolemic children. *Eur. J. Clin. Invest.* 40:250–257.

18. de Jongh, S., M. R. Lilien, H. D. Bakker, B. A. Hutten, J. J. Kastelein, and E. S. Stroes. 2002. Family history of cardiovascular events and endothelial dysfunction in children with heterozygous familial hypercholesterolemia. *Circulation.* 106:367–370.

17. Vlahos, A. P., K. K. Naka, A. Bechlioulis, P. Theoharis, K. Vakalis, E. Moutzouri, G. Miltiadous, L. K. Michalis, A. Siamopoulou-Mavridou, M. Elisa, et al. 2014. Endothelial dysfunction, but not structural atherosclerosis, is evident early in children with heterozygous familial hypercholesterolemia. *Pediatr. Cardiol.* 35:63–70.

15. Narverud, I., K. Retterstøl, P. O. Iversen, B. Halvorsen, T. Ueland, S. M. Ulven, L. Ose, P. Aukrust, M. B. Veierod, and K. B. Holven. 2014. Markers of atherosclerotic development in children with familial hypercholesterolemia: a literature review. *Atherosclerosis.* 235:290–309.

14. Ueland, T., M. N. Vissers, A. Wiegman, J. Rodenburg, B. Hutten, L. Gullestad, L. Ose, N. Rifa, P. M. Rieder, J. J. Kastelein, et al. 2006. Increased inflammatory markers in children with familial hypercholesterolemia. *Eur. J. Clin. Invest.* 36:147–152.

13. de Jongh, S., M. R. Lilien, H. D. Bakker, B. A. Hutten, J. J. Kastelein, and E. S. Stroes. 2002. Family history of cardiovascular events and endothelial dysfunction in children with familial hypercholesterolemia. *Atherosclerosis.* 163:193–197.

12. Miller, H. D. Bakker, E. J. Sijbrands, and J. J. Kastelein. 2004. Arterial intima-media thickness in children heterozygous for familial hypercholesterolemia. *Lancet.* 363:599–600.

11. Kusters, D. M., A. Wiegman, J. J. Kastelein, and B. A. Hutten. 2014. Carotid intima-media thickness in children with familial hypercholesterolemia. *Circ. Res.* 114:307–310.

10. Wiegman, A., B. A. Hutten, E. de Groot, J. Rodenburg, H. D. Bakker, H. D. Buller, E. J. Sijbrands, and J. J. Kastelein. 2004. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA.* 292:331–337.

9. Kusters, D. M., H. J. Avis, E. de Groot, F. A. Wijburg, J. J. Kastelein, A. Wiegman, and B. A. Hutten. 2014. Ten-year follow-up after initiation of statin therapy in children with familial hypercholesterolemia. *JAMA.* 312:1055–1057.

8. Braamskamp, M. J. A. M., G. Langslet, B. W. McCrindle, D. M. Cassiman, G. A. Francis, C. Gagne, D. Gaudet, K. M. Morrison, A. Wiegman, T. Turner, et al. Effect of rosuvastatin on carotid intima-media thickness in children with heterozygous familial hypercholesterolemia: the CHARON study. *Circulation.* Epub ahead of print, June 7, 2012; doi:10.1161/CIRCULATIONAHA.112.251588.

7. Wiegman, A., S. S. Gidding, G. F. Watts, M. J. Chapman, H. N. Ginsberg, M. Cuchel, L. Ose, M. Averna, C. Boileau, J. J. Kastelein, et al. 2015. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur. Heart J.* 36:2425–2437.

6. Ference, B. A. 2015. Mendelian randomization studies: using naturally randomized genetic data to fill evidence gaps. *Curr. Opin. Lipidol.* 26:566–571.

5. Nordestgaard, B. G., M. Chapman, S. E. Humphries, H. N. Ginsberg, L. Masana, O. S. Descamps, O. Wiklund, R. A. Hegele, F. J. Raal, J. C. Defesche, et al. 2013. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur. Heart J.* 34:3478–3490.

4. Watts, G. F., S. S. Gidding, A. S. Wierzbicki, P. P. Toth, R. Alonso, W. V. Brown, E. Bruckert, J. Defesche, K. K. Lin, M. Livington, et al. 2014. Integrated guidance on the care of familial hypercholesterolemia from the International FH Foundation. *J. Clin. Lipidol.* 8:148–172.

3. Goldberg, A. C., P. N. Hopkins, P. P. Toth, C. M. Ballantyne, D. J. Rader, J. G. Robinson, S. R. Daniels, S. S. Gidding, S. D. Ferranti, M. K. Ito, et al. 2011. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J. Clin. Lipidol.* 5:133–140.

2. Watts, G. F., D. R. Sullivan, N. Poplawski, F. van Bockxmeer, I. Hamilton-Craig, P. M. Clifton, R. O’Brien, W. Bishop, P. George, P. J. Barter, et al. 2011. Familial hypercholesterolemia: a model of care for Australasia. *Atheroscler. Suppl.* 12:221–263.

1. Martin, A. C., J. A. Spitrakos, J. P. O’Leary, and M. A. Sardo. 2013. Familial hypercholesterolaemia in children and adolescents: a new paediatric model of care. *J. Paediatr. Child Health.* 49:E263–E272.

0. National Institute for Health and Clinical Excellence and the National Collaborating Centre for Primary Care. NICE clinical guideline 71. Identifying and managing familial hypercholesterolaemia. Accessed June 25 2017, at www.nice.org.uk/nicemedia/pdf/CG071NICEGuideline.pdf.

- Knowns and unknowns in pediatric FH 1773
118. Bellgard, M. I., C. E. Walker, K. R. Napier, L. Lamont, A. A. Hunter, L. Render, M. Radochonski, J. Pang, A. Pedrotti, D. R. Sullivan, et al. Design of the Familial Hypercholesterolaemia Australasia Network Registry: creating opportunities for greater international collaboration. *J. Atheroscler. Thromb.* Epub ahead of print. March 24, 2017; doi:10.5551/jat.37507.

119. Genest, J., R. A. Hegele, J. Bergeron, J. Brophy, A. Carpentier, P. Couture, J. Davignon, R. Dufour, J. Frohlich, D. Gaudet, et al. 2014. Canadian Cardiovascular Society position statement on familial hypercholesterolemia. *Can. J. Cardiol.* 30: 1471–1481.

120. Bamimore, M. A., A. Zaid, Y. Banerjee, A. Al-Sarraf, M. Abifadel, N. G. Seidah, K. Al-Waili, K. Al-Rasadi, and Z. Awan. 2015. Familial hypercholesterolemia mutations in the Middle Eastern and North African region: a need for a national registry. *J. Clin. Lipidol.* 9: 187–194.

121. van der Graaf, A., H. J. Avis, D. M. Kusters, M. N. Vissers, B. A. Hutten, J. C. Defesche, R. Huijgen, S. W. Fouchier, F. A. Wijburg, J. J. Kastelein, et al. 2011. Molecular basis of autosomal dominant hypercholesterolemia: assessment in a large cohort of hypercholesterolemic children. *Circulation.* 123: 1167–1173.

122. Ramaswami, U., J. Cooper, and S. E. Humphries. 2017. The UK Paediatric Familial Hypercholesterolaemia Register: preliminary data. *Arch. Dis. Child.* 102: 255–260.

123. Bell, D. A., and G. F. Watts. 2016. Progress in the care of familial hypercholesterolaemia: 2016. *Med. J. Aust.* 205: 232–236.