# Universal screening for familial hypercholesterolaemia in newborns

## *Time for general practice to contribute*

**Tom Brett**

**FAMILIAL HYPERCHOLESTEROLAEMIA** (FH), an autosomal dominant genetic condition, affects one in 250 people in Australia. FH is characterised by markedly elevated low-density lipoprotein cholesterol levels from birth, resulting in the accelerated onset of atherosclerotic cardiovascular disease (ASCVD) that would occur in middle years if left untreated.[1] The risk of premature ASCVD in FH-positive adults aged 20–39 years is 100-fold greater than individuals without FH who are the same age.[2] Effective treatment for FH is available, but 90% of individuals remain undiagnosed and therefore untreated.[2] The biggest gaps exist among young people and in primary care.[1,3,4] It is time for this situation to be substantially mitigated, and we, as general practitioners (GPs), need to play our part.

The key to the better detection and management of FH is early diagnosis, followed by an appropriate ongoing heart-healthy diet and appropriate medications (usually statins) from 8–10 years of age.[3] Children with FH managed this way can expect to live a normal lifespan and avoid premature ASCVD.[3,4] The disease begins in childhood, not in adulthood.[1,3–5] Thus, widespread FH screening before the disease has time to significantly progress is essential.[3]

Parents from the Netherlands,[6] Australia[7] and the UK[8] are supportive of phenotypic and genetic testing of children for FH. In the US, various state health departments have implemented universal screening programs through cholesterol testing of children aged 9–11 years.[9,10] I am advocating for newborn screening to be considered as an alternative, but promising, option for improved detection of FH in Australia.

Australian newborn bloodspot (NBS) programs have successfully operated for over 50 years and currently screen for 25 rare genetic conditions in the 24–72 hours after birth.[11] Newborns screening positive are urgently recalled for confirmatory diagnostic testing, with parents receiving information about the condition and management/treatment options. There is growing international interest in the possible utilisation of genomics to increase the number of conditions screened for in newborns. In Australia, research programs exploring the application of genomics to newborn screening were recently funded by the Medical Research Future Fund.[12]

A significant advantage of using Australian NBS programs to screen for FH would be their near universal uptake; I therefore believe that adding FH to Australia's NBS programs should be evaluated using the decision-making criteria of the NBS National Policy Framework.[11] This deliberation would determine whether the benefits outweigh the risks, the latter including potential diagnostic stigma, psychological aspects and anxiety about the disorder.[13,14] Like other conditions already screened for by NBS programs and fitting the Framework's criteria, FH is a disease detectable at birth and has a well-known natural history.[1,3–5] In addition, it has a safe treatment[5] that is both clinically[4] and financially[15] cost-effective. There are viable tests for FH, and applying these to existing NBS programs appears technically feasible because dried blood spots are suitable sources of both markedly raised total and low-density lipoprotein cholesterol levels,[13] as well as suitable for next-generation sequencing analysis.[10,16]

However, FH differs from other conditions currently included in Australian NBS programs with its mode of inheritance being mostly dominant (a much rarer, more severe recessive form of FH (LDLRAP) also exists).[17] Basically, the common form of FH is passed from one generation to the next. Because FH can remain asymptomatic for many decades, multiple blood relatives of babies diagnosed with FH could

also unknowingly be affected and have significant risk of ASCVD themselves. Thus, in addition to the benefits to babies identified with FH via the NBS program, reverse cascade testing could deliver familial benefits through subsequent expedited diagnosis of parents, siblings and other blood relatives,[18–20] with exclusion from intensive further monitoring of those testing negative. This multiplying beneficial potential from screening newborns for FH would add a new aspect to be deliberated using the NBS National Policy Framework.

Increased GP engagement in cascade testing within families, together with subsequent facilitation of appropriate models of care for those diagnosed with FH, offers enormous untapped opportunities to reduce future ASCVD deaths.[3–5] The feasibility and efficacy of child–parent reverse cascade testing for FH in the UK have already been shown.[8] In May 2020, Australia introduced a Medicare rebate for specialist genetic testing of high-risk FH phenotypes.[21] GPs can subsequently arrange genetic testing among first- and second-degree relatives of patients with a confirmed FH pathogenic variant.

Another difference that would arise if FH were included as part of Australian NBS programs is that considerably more babies would screen positive than currently occurs, because FH is a relatively common condition. The anticipated detection rate of 1 in 250 babies[8] would necessitate an appropriate way to ensure that all babies who screen positive are recalled for review and subsequent scaling-up of the delivery of care model for FH to those with a confirmed diagnosis.

My position is that screening for FH should be evaluated for addition to NBS programs[11] in Australia. Because almost 90% of Australians visit a GP each year[22,23] and up to 100% of newborns are similarly seen, I propose that GPs would be best placed to have a lead role in delivering the FH model of care to diagnosed infants and their families. GPs are ideally placed and experienced in the delivery of care through the lifespan, including the coordination of multidisciplinary care for complex conditions. In the case of FH, this care could include the involvement of paediatricians, cardiologists, lipid specialists, counsellors and genomic medicine, where available.[1] New bottom-up infrastructure grounded in primary care is needed that can showcase FH as the exemplar for precision medicine and precision public health, as well as consolidate GPs as stewards and advocates for appropriately applying genetics and genomics. Universal genetic screening of newborns for FH should be provided in Australia.

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