ARTICLE

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The case for screening in early life for 'non-treatable' disorders: ethics, evidence and proportionality. A report from the Health Council of the Netherlands

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In the Netherlands, the call to add 'non-treatable' disorders to the newborn bloodspot screening programme has found a sympathetic ear with the Government. In 2019, the Health Council of the Netherlands was formally asked for advice on the conditions under which bloodspot screening for such disorders might be offered. Here we present the reasoning and the recommendations of the resulting report, and briefly discuss its reception. The report holds on to the classical view that screening must benefit the child, but argues for a wider account of child benefit than only in terms of substantial health gains. However, screening for 'non-treatable' disorders would still require evidence of a favourable benefits to harm ratio. The report presents a framework for such screening, but concludes that apart perhaps from Duchenne Muscular Dystrophy (DMD), no or only very few 'non-treatable' disorders would at present meet its criteria. Setting up a screening programme that might benefit only a small percentage of families struggling with uncertainty about their child's diagnosis would not seem proportional. Instead, the Government is advised to invest in a better infrastructure for early referral, testing and care. The reaction to the report from proponents of such screening shows that the dividing line in the debate is not about whether screening neonates for 'non-treatable' disorders is acceptable in itself. It is rather whether such screening should be regarded as catering to a parental 'right to know', or as a public health service that should be subject to standards of evidence and proportionality.

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INTRODUCTION

Ever since the introduction of tandem mass spectrometry allowed expanding the range of disorders tested for in newborn bloodspot screening (NBS), screening authorities in different countries have faced the challenge of how to delineate the scope of testing. As observed in an international review, each country has found its own way of meeting this challenge, with the result that 'no two countries' screening programmes are the same' [1]. Whereas almost all refer to the same classical WHO principles as originally formulated by Wilson and Junger, these serve as higher level criteria that are then differentially adapted in the form of more specific requirements, for instance with regard to the type of evidence of benefit that would be needed for including conditions in the programme.

A recurring issue in this connection is the preliminary question of the intended beneficiary. This is fundamental because the answer defines what the programme aims to achieve and for whom. Usually screening aims to achieve health gains for those tested, and this of course is also how the classical aim of NBS is understood: to significantly improve health and prevent severe disability or even death among participating children through the early identification and treatment of rare but serious disorders [2]. However, as several commentators (experts and patient organisations) have suggested, there are further stakeholders whose interests would deserve to be taken into account, stakeholders who might benefit from newborn screening for a much wider range of conditions than those traditionally considered 'treatable' [3, 4]. Notably, this pertains to parents and families: knowledge about the presence of an untreatable disorder in a child at an early stage could spare them the burden of a 'diagnostic odyssey', provide them with carrier information relevant to further reproductive planning, and help them prepare for the future in the light of information about their child's health prospect [2]. Society at large would be a further beneficiary, with future children profiting from scientific insights resulting from wider screening for rare disorders for which no treatment is currently available [5].

While this is a core debate in the literature that promises to be intensified with scenarios of introducing genomics-based testing in the near future [6, 7], it has had only limited impact on actual screening programmes thus far. As remarked by the authors of the review quoted earlier, the shift towards acknowledging a wider range of beneficiaries 'is less apparent' in the context of policy. They explain this in the light of the public health character of these programmes, where anything less than clear health benefits weakens their justification, would have significant implications for counselling services, and might threaten the success of these programmes in terms of their traditional child-health focused aim [1].

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As a consequence, many countries see a persistent tension between more conservative NBS-policies on the one hand and parents' advocacy groups on the other, with the latter criticising the former for failing to acknowledge how family and societal benefits would provide a justification for much wider screening panels in NBS.

In this paper, we report how the most recent chapter in this debate has played out in the Netherlands, where the call from patient organisations to also screen for 'non-treatable' disorders found a sympathetic ear with the Government. In 2019, the Health Council of the Netherlands was formally asked by the State Secretary of Health, Welfare and Sports for an advice on the conditions under which bloodspot screening for such disorders might be offered, either as integrated in the current programme for NBS, or as a separate screening early in life. This led to a report by the Health Council's Standing Committee on Preconception, Prenatal & Neonatal Screening that was presented to the State Secretary in 2020 [8]. Here we present the reasoning and the recommendations of the report, and briefly discuss its reception.

DEFINITION OF 'NON-TREATABLE'

With this assignment, the Committee first of all had to clarify how the notion of a 'non-treatable' disorder might be understood. Obviously, the distinction between conditions that are treatable and those that are not, is blurred. For instance, Duchenne Muscular Dystrophy (DMD) is often classified as a non-treatable condition, whereas treatment with steroids have been deemed effective in delaying damage [9, 10]. And indeed, as many healthcare professionals and patient organisations have argued, there is almost no condition that cannot be 'treated' in the form of supportive care that increases a patient's quality of life. The Committee decided it was not necessary to solve this issue. For the sake of its report, it sufficed that candidate disorders would be those that are presently regarded as ineligible for NBS on the basis of a lack of evidence that screening would lead to substantial health gains for the child. Using this as a working definition of 'non-treatable' would also best fit the motivation behind the Government's request for advice.

BENEFITS FOR THE CHILD BEYOND TREATMENT

A fundamental issue was the notion of benefit. According to the Committee there was no reason for supposing that 'non-treatable' in the sense of the proposed working definition meant that screening for the relevant disorders could not be beneficial for the child. Early identification of such disorders may enable (experimental) interventions that have the potential of reducing health damage and furthering quality of life [11, 12]. Even if this does not (yet) amount to evidence for substantial health gains (as that would make the disorder a candidate for present NBS), it may still benefit the child even if mainly in the sense of improved psychosocial wellbeing. Moreover, prevention of diagnostic delay may benefit the child in different ways, either directly, through avoiding iatrogenic and psychosocial harm, but also indirectly through avoiding harmful psychosocial effects on the parents and the family [2, 13]. What this also shows is that at least part of what is often referred to as 'family benefits', should be regarded as benefits for the child as well. One may also think here of the indirect benefit for the child itself of screening results that would enable the parents to avoid the birth of a sibling needing a similar degree of care and attention [2, 13, 14].

On the basis of this wider account of child benefit than proven substantial health gains, the Committee concludes that, in their view, there is no reason for regarding screening for 'non-treatable' disorders early in life as fundamentally at odds with the classical aim of NBS. However, this wider account of benefit would still require evidence, not only that those benefits are real, but also that they outweigh the possible harms that screening may also bring. As many 'non-treatable' disorders come with a large degree of phenotypic variation and are too rare for the course of disease to be fully understood, prognostic uncertainty is a potential cause for adverse effects, including unnecessary stress and anxiety for the parents and the family.

FRAMEWORK

For the per disorder assessment that would be necessary to decide about the screening panel, the Committee presents a framework in which evidence of benefit for the child, at least in terms of improved psychosocial wellbeing, is a core criterion. The report acknowledges that providing more than a weak underpinning for the claim that this criterion can be met, may well be elusive. While many studies have confirmed that (prospective) parents have a positive attitude towards neonatal screening for'non-treatable' disorders [15], this should not be mistaken (or misrepresented) as evidence for child-benefit. For many 'untreatable disorders' such evidence may presently consist of little more than data about psychosocial harm caused by diagnostic delay combined with indications that screening would help to avoid at least part of that harm. With regard to the concern that early knowledge would instead have a negative effect on family dynamics (the so-called 'loss of golden years' argument), the report remarks that the available research has not found evidence for such an effect, but studies are limited and not well comparable [16, 17]. Further elements of the framework are meant to support the requirement of a positive benefit to harms ratio for the full population of those being tested: there must be a reliable test, phenotypic variation must be limited, and there must be sufficient data about the natural course of the disease. If these conditions are not met, the drawbacks will certainly prevail. In order to avoid an infringement of the child's right to future autonomy, the clinical manifestation of the disorder must precede adolescence [18].

If screening for certain 'non-treatable' disorders might on balance be beneficial, further preconditions include voluntary participation on the basis of an informed parental decision, and the availability of (genetic) follow-up testing and care for those with an abnormal result, ideally in a centre with specialised expertise for the disorder in question. From a societal and public health point of view, a core issue is the possible impact on the present NBS-programme. A specific concern is that the requirement for parents to explicitly 'opt in' to also have their child tested for 'non-treatable' disorders may render participation in regular NBS less obvious. Here the Committee suggests that screening for 'non-treatable' disorders might be offered separately at a somewhat later occasion, for instance in combination with a standard youth healthcare contact in the first months of the child's life [2]. An alternative approach to mark the difference with standard NBS might be to use a separate blood-spot card for this additional screening [19].

Finally, screening for 'non-treatable' disorders must be of added value in comparison to other approaches to improve the wellbeing of children born with such conditions in order to justify societal burdens and costs [2]. Without such added value there is no ground for screening as a public health programme for which tax-payer funding might be considered.

CANDIDATE CONDITIONS

The Committee has tried to identify 'non-treatable' disorders for which in the light of the above criteria, screening would be justified. The most obvious candidates were DMD and Fragile X syndrome (FXS), not just in view of their relative frequency, but also because some experience with screening for these conditions is available [14, 20–23]. These (pilot) programmes have not revealed significant negative psychosocial effects on the families,

but neither do they answer the question whether screening would on balance be beneficial for the child. This would have to be assumed in the light of avoiding on average two years of diagnostic delay for boys with these X-linked conditions, as well as in that of enabling the parents to avoid the birth of a second boy with the same disorder. Moreover, for boys with DMD, early treatment with corticosteroids has potential health benefits that may eventually make this disorder a candidate for inclusion in regular NBS [9, 10, 24]. No such prospects exist for FXS. For both conditions, concerns about unsolicited findings are an important point of attention [13, 25]. A specific issue with FXS screening is that it leads to finding both full and premutation carriers. Although the latter will not have FXS, they are at risk of developing later onset FXS-associated disorders including FXS-associated tremor/ataxia syndrome and (for women also) FXS-associated primary ovarian insufficiency [13]. Moreover, for both DMD and FXS screening, a reliable and cost-effective testing method is still to be developed [21, 22]. Screening for FXS should ideally be only done in boys, which raises additional challenges for counselling and logistics.

The Committee concludes that in the light of the above criteria, the case for screening is strongest where concerning DMD. With regard to screening for FXS, the possible benefits for the child are less obvious, whereas the drawbacks, especially in view of the clinical implications for premutation carriers, are significant. In the light of this, a convincing case that FXS-screening would be justified, seems more difficult to make. Of course, there may be further 'non-treatable' disorders that would need to be considered, but as these tend to come with large phenotypic variation and are too rare to be well explored, the expectation is that (apart perhaps from DMD) no or only very few 'non-treatable' disorders would at present meet this report's criteria.

A MORE PROPORTIONAL APPROACH

In view of this meagre yield, the report suggests that screening for 'non-treatable' disorders may not be the best approach to supporting families who struggle with uncertainty about their child's diagnosis. In an hypothetical screening programme for DMD and FXS in the Netherlands, testing all 90.000 boys per year would lead to finding 18 with each disorder. At the same time 3500 children are born yearly who will present with some form of developmental delay. For the larger part, this group would not benefit from a screening programme targeting only one or two 'non-treatable' disorders. However these families could be helped with a better infrastructure for early referral, testing and care. Investing in an early-referral infrastructure would be more proportional than screening for a few specific 'non-treatable' disorders, as the benefits would accrue to a much larger group of children, while avoiding the potential negative effects of screening for 'non-treatable' disorders. The report accordingly concludes that at the moment there is no convincing case to be made for a screening programme for such disorders, and advises the Government rather to support and expand existing initiatives of University Medical Centres to build a nation-wide early referral infrastructure.

With regard to the reproductive benefits that parents would accrue from screening, the Committee maintains that reproductive (preconception or prenatal) carrier screening would seem the better approach for securing these. The Netherlands is one of the countries presently exploring the pros and cons of an expanded carrier screening offer to all couples of reproductive age [26]. However, it should be noted that de novo variants (a significant cause of genetic disease) will not be picked up by reproductive carrier screening. This is especially relevant for DMD, which in a third of cases emerges de novo.

PUBLIC HEALTH BENEFIT VERSUS A PARENTAL RIGHT TO KNOW

The importance of the report is that it may help overcoming the stalemate in the discussion by acknowledging that there may be benefits for the child beyond treatment that should count in the debate about the scope of genetic testing early in life. As a consequence, the case for considering screening for 'non-treatable' disorders does not depend on weighing in potential benefits for other beneficiaries (family, society) than the child itself. Ethically, this is an important point: advocating screening for 'non-treatable' disorders is not as such at odds with the principle that for screening to be acceptable there must at least be evidence of net benefit for the persons screened. By taking this position, the report upholds if not the letter than the spirit of the accepted normative framework for screening.

In this regard, the reaction to the report from one of the patient organisations with a longstanding history of advocating wider neonatal screening, is interesting. In a letter to the State Secretary of Health, Welfare & Sports, the Dutch Patient Alliance for Rare and Genetic Diseases (VSOP) argues that the report's "one-sided emphasis on scientific evidence" ignores the importance of freedom of choice and of a parental 'right to know' [27]. What this reveals is that the dividing line in the debate is not about whether screening neonates for 'non-treatable' disorders is acceptable in itself, but about how such screening should be accounted for. Is it an option the state should provide, solely because there are parents of affected children who would have wanted to know earlier? Or is it a public health service that we may want to consider for reasons of solidarity and justice [28]? On the former reading, what counts is primarily how parents define the personal utility of such screening for themselves and their families. On the latter, any population screening programme for 'non-treatable' disorders should still be subject to standards of evidence and proportionality.

REFERENCES

1. Jansen ME, Metternick-Jones SC, Lister KJ. International differences in the evaluation of conditions for newborn bloodspot screening: a review of scientific literature and policy documents. Eur J Hum Genet. 2016;25:10–6.
2. Ross LF. Screening for conditions that do not meet the Wilson and Jungner criteria: the case of Duchenne muscular dystrophy. Am J Med Genet A. 2006;140:914–22.
3. Bailey DB Jr., Beskow LM, Davis AM, Skinner D. Changing perspectives on the benefits of newborn screening. Ment Retard Dev Disabil Res Rev. 2006;12:270–9.
4. EURORDIS. The Voice of Rare Disease Patients in Europe. Key principles for newborn screening. Brussels: EURORDIS. https://eurordis.org/newbornscreening 2021.
5. Alexander D, van Dyck PC. A vision of the future of newborn screening. Pediatrics 2006;117:S350–4.
6. Berg JS, Agrawal PB, Bailey DB Jr, Beggs AH, Brenner SE, Brower AM, et al. Newborn sequencing in genomic medicine and public health. Pediatrics. 2017;139:e20162252.
7. Remec ZI, Trebusak Podkrajsek K, Repic Lampret B, Kovac J, Groselj U, Tesovnik T, et al. Next-generation sequencing in newborn screening: a review of current state. Front Genet. 2021;12:662254.
8. Health Council of the Netherlands. Screenen op niet-behandelbare aandoeningen vroeg in het leven [Screening for non-treatable disorders early in life]. The Hague: Health Council of the Netherlands https://www.gezondheidsraad.nl/documenten/adviezen/2020/09/30/screenen-op-niet-behandelbare-aandoeningen-vroeg-in-het-leven 2020.
9. Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. Cochrane Database Syst Rev. 2016;5:CD003725.
10. McDonald CM, Mercuri E. Evidence-based care in Duchenne muscular dystrophy. Lancet Neurol. 2018;17:389–91.
11. Ke Q, Zhao ZY, Mendell JR, Baker M, Wiley V, Kwon JM, et al. Progress in treatment and newborn screening for Duchenne muscular dystrophy and spinal muscular atrophy. World J Pediatr. 2019;15:219–25.
12. Tassone F. Newborn screening for fragile X syndrome. JAMA Neurol. 2014;71:355–9.

13. Bailey DB Jr, Skinner D, Davis AM, Whitmarsh I, Powell C. Ethical, legal, and social concerns about expanded newborn screening: fragile X syndrome as a prototype for emerging issues. Pediatrics. 2008;121:e693–704.
14. Parsons EP, Clarke AJ, Hood K, Lycett E, Bradley DM. Newborn screening for Duchenne muscular dystrophy: a psychosocial study. Arch Dis Child Fetal Neonatal Ed. 2002;86:F91–5.
15. Plass AM, van El CG, Pieters T, Cornel MC. Neonatal screening for treatable and untreatable disorders: prospective parents' opinions. Pediatrics. 2010;125:e99–106.
16. Wade CH, Wilfond BS, McBride CM. Effects of genetic risk information on children's psychosocial wellbeing: a systematic review of the literature. Genet Med. 2010;12:317–26.
17. Wakefield CE, Hanlon LV, Tucker KM, Patenaude AF, Signorelli C, McLoone JK, et al. The psychological impact of genetic information on children: a systematic review. Genet Med. 2016;18:755–62.
18. Ross LF, Clayton EW. Ethical issues in newborn sequencing research: the case study of BabySeq. Pediatrics. 2019;144:e20191031.
19. Parsons EP, Clarke AJ, Hood K, Bradley DM. Feasibility of a change in service delivery: the case of optional newborn screening for duchenne muscular dystrophy. Community Genet. 2000;3:17–23.
20. Chung J, Smith AL, Hughes SC, Niizawa G, Abdel-Hamid HZ, Naylor EW, et al. Twenty-year follow-up of newborn screening for patients with muscular dystrophy. Muscle Nerve. 2016;53:570–8.
21. Moat SJ, Bradley DM, Salmon R, Clarke A, Hartley L. Newborn bloodspot screening for Duchenne muscular dystrophy: 21 years experience in Wales (UK). Eur J Hum Genet. 2013;21:1049–53.
22. Wotton T, Wiley V, Bennetts B, Christie L, Wilcken B, Jenkins G, et al. Are we ready for fragile X newborn screening testing? Lessons learnt from a feasibility study. Int J Neonatal Screen. 2018;4:9.
23. Tassone F, Pan R, Amiri K, Taylor AK, Hagerman PJ. A rapid polymerase chain reaction-based screening method for identification of all expanded alleles of the fragile X (FMR1) gene in newborn and high-risk populations. J Mol Diagn. 2008;10:43–9.
24. Verhaart IEC, Aartsma-Rus A. Therapeutic developments for Duchenne muscular dystrophy. Nat Rev Neurol. 2019;15:373–86.
25. Gatheridge MA, Kwon JM, Mendell JM, Scheuerbrandt G, Moat SJ, Eyskens F, et al. Identifying non-Duchenne muscular dystrophy-positive and false negative results in prior Duchenne muscular dystrophy newborn screening programs: a review. JAMA Neurol. 2016;73:111–6.
26. Schuurmans J, Birnie E, van den Heuvel LM, Plantinga M, Lucassen A, van der Kolk DM, et al. Feasibility of couple-based expanded carrier screening offered by general practitioners. Eur J Hum Genet 2019;27:691–700.
27. VSOP Patient alliance for rare and genetic diseases. Letter to the State Secretary in response to the Health Council's report 'Screening for non-treatable disorders early in life'. Soest: VSOP. https://vsop.nl/actueel/de-vsop-pleit-voor-een-aangepast-besliskader-voor-de-hielprik/ 2020.
28. Newson AJ. The promise of public health ethics for precision medicine: the case of newborn preventive genomic sequencing. Hum Genet. 2021, https://doi.org/10.1007/s00439-021-02269-0. Online ahead of print.

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