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Screening for Life: Perspectives From Adult Metabolic Specialists on Newborn Screening for Inherited Metabolic Diseases

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ABSTRACT

The number of inherited metabolic diseases (IMDs) in newborn screening (NBS) programs has increased significantly in the past decades. For some of the IMDs included in NBS (e.g., tyrosinemia type I), there are clear and substantial health benefits of NBS, while for others (e.g., very long chain acyl CoA dehydrogenase deficiency and 3-methylcrotonyl CoA carboxylase 1 deficiency), this is less clear as NBS identifies individuals who are asymptomatic or have milder forms of the disease. Therefore, knowledge of the full disease spectrum (including later onset forms) is needed when setting diagnostic metabolite cut-offs for NBS. Insights into the clinical, genetic and biochemical characteristics of different patient subsets can be used to redefine NBS protocols to identify patients with more severe forms of the disease who are most likely to benefit from identification in the newborn period. These insights require life-long monitoring of individuals identified based on symptoms versus those identified by NBS to determine long-term health outcomes and quantify the benefits of NBS. Adult metabolic specialists should be included in the development of NBS programs to provide data from this long-term monitoring and to contribute specific knowledge about later onset phenotypes of the IMDs included in NBS programs. The goal should be to develop NBS programs that identify newborns that benefit from early disease detection and treatment, without increasing psychological, social and management burden for individuals who may develop disease in adulthood with milder phenotype or potentially even not at all.

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1 | Introduction

The object of screening for a disease is to discover those among the apparently well who are in fact suffering from disease. A public health paper on the principles and practice of disease screening was commissioned and published by the World Health Organization, establishing the guiding principles for screening programs [1]. For inherited metabolic diseases (IMDs) the screening process has been focused on newborn screening (NBS), allowing conditions to be identified at birth, before symptom onset and the occurrence of lasting damage. This started with the screening for phenylketonuria (OMIM 261600) in the 1960s, in dried blood spots (DBS) from the neonates [2]. In the following decades, more conditions e.g., galactose-1-phosphate uridylyltransferase deficiency, (OMIM 230400) and biotinidase deficiency (OMIM 253260) were added to the screen [3]. These initial enzymatic assays were labour intensive and expansion of the program was limited by the availability of substrates for different conditions. Technological developments, particularly the development of mass spectrometry-based methods in the 1990s, led to further expansion of IMDs that could be added to the NBS programs. This allowed to through put large number of samples for more conditions and produced reliable results in a timely manner [3, 4]. In the last 10 years, genetic testing has become technically feasible for NBS and is being explored as a possible way to screen for even more conditions at birth.

The inclusion of disorders in NBS programs varies significantly worldwide, influenced by regional healthcare priorities, available resources and cultural considerations [5]. Health Resources and Service Administration (HRSA) has published a list of Recommended Uniform Screening Panel (RUSP) for the states in the USA. In the USA and Australia, most states screen for over 30 disorders, including a wide range of IMDs, while European countries such as Germany, France and Switzerland typically screen for fewer than 20 conditions, often prioritizing those with more robust evidence of health benefit of NBS. Conversely, nations like Saudi Arabia and Japan have expanded their NBS panels to include rare regional disorders, reflecting a tailored approach to population needs.

2 | Expanding Cohort of Adult Patients With IMD and Impact on NBS

Currently the number of adults with IMDs exceeds the number of children and approximately half of them are diagnosed in adulthood [6]. This cohort is likely to expand even further in the future. The increase in adult IMD patient numbers is partially the result of improved survival in paediatric patients due to advances in diagnosis, therapies and care. An even larger contribution is the increasing recognition and diagnosis of IMDs clinically presenting in adulthood, demonstrating the broad phenotypic spectrum of many of the IMD included in NBS programs. This is achieved by improved diagnostic techniques, particularly wider availability of genetic testing, and continuous efforts in education and training on IMDs in adult metabolic medicine [7, 8].

For most disorders added to the NBS programs, cases with severe early childhood onset symptoms were well documented and pre-symptomatic treatment was known or expected to prevent symptoms, irreversible organ damage and early demise. However, the impacts of expanded NBS on late-onset forms, with symptom onset ranging from late childhood to late adulthood, or incomplete penetrance were not always considered. Some of the conditions detected by NBS may be more appropriately categorised as 'risk factors' for metabolic decompensation under stress and not as disease, since there are no symptoms under normal circumstances in daily life. For most disorders, the distinction between early and late-onset forms cannot be made at the time of screening and all screen positive individuals are treated as at risk for the severe early-onset symptoms. If these patients then remain free of symptoms throughout childhood, it may be unclear whether this is a result of early treatment or related to a late onset expression of the disease. For some disorders, such as primary carnitine deficiency (OCTN2 deficiency, OMIM 212140) and glutaric aciduria type I (GA1, OMIM 231670), positive NBS results in a healthy child can be caused by abnormal values in the mother who, until the NBS of her child, was not aware that she had an IMD and may have had minor symptoms or none at all. It is often unclear whether these mothers should be treated. In a recent systematic review by Schanbel-Besson et al., the major hurdle identified in applicability of the Wilson and Junger criteria to current NBS programs was the incomplete understanding of natural history and phenotypic diversity or heterogeneity of rare diseases prior to NBS implementation [9].

Since input for screening programs comes mostly from paediatricians with, so far, no or very little input from adult IMD clinicians, the wide range of clinical presentations in adult patients may have been overlooked when developing NBS programs. Ongoing technical advancements, such as whole genome sequencing (WGS), are very likely to complicate the NBS landscape in the coming years. Input from physicians who treat patients with all forms of the screened disorders is needed to guarantee maximal health benefit for affected neonates, whilst minimizing negative effects for individuals who do not benefit from identification in the newborn period, such as those with milder, adult-onset forms and healthy individuals with genetic and biochemical variations that lack clinical consequences. Lifelong follow-up will also provide insight into residual disease burden and emerging complications despite early treatment, which may not become apparent for decades after treatment commencement. In this article, we will highlight some examples of disorders eligible for NBS or already included in NBS programs, where knowledge of the disease course in adulthood is essential to optimise NBS.

3 | Successes and Pitfalls of Current IMD NBS Screening Programs

NBS for phenylketonuria is an example of a highly successful screening program. Early identification and treatment changed the phenotype from severe cognitive and motor impairment necessitating lifelong care to normal development, with patients leading a fully independent life comparable to that of non-affected persons [10]. NBS for tyrosinemia type I (OMIM 276700) has similarly dramatic effects with prevention of hepatic, renal, ophthalmic, haematological and cognitive adverse

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events [11]. For other conditions that are included in many NBS programs, the benefit of NBS is less clear because of the identification of many individuals who might not have developed symptoms without treatment. Examples are very long chain acyl CoA dehydrogenase deficiency (VLCADD, OMIM 201475), carnitine palmitoyltransferase II (CPTII) deficiency and 3-methylcrotonyl CoA carboxylase 1 deficiency (3-MCCD, OMIM 210200).

VLCADD can cause life-threatening metabolic decompensation, especially in the first years of life, characterized by hepatopathy, hypoglycemia and/or cardiomyopathy [12]. NBS and subsequent early treatment (limiting fasting time, dietary measures and supportive treatment) can prevent hypoglycemic events and the associated neurological damage in patients with some residual VLCAD enzyme activity [13]. However, the majority of patients identified through NBS have higher residual VLCAD enzyme activity, and thus higher fatty acid oxidation capacity, and may not be at risk for early-onset symptoms [13, 14]. Pre-NBS, these patients were diagnosed in late childhood/early adulthood, after suffering from repeated rhabdomyolysis and/or significant exercise intolerance or never developed symptoms at all. Current dietary and supportive treatment does not fully prevent the occurrence of adolescent- or adult-onset skeletal muscle symptoms [15]. However, as all NBS patients are treated from birth, the actual benefit of early treatment (if any) on the risk of metabolic decompensation in these milder patients is not easy to determine. More data are needed to determine if patients with the later onset form of the disease, characterized by higher residual long chain fatty acid oxidative capacity and primarily skeletal muscle involvement, benefit from NBS.

The same problems are encountered in NBS for CPTII deficiency, another fatty acid oxidation disorder. There are three forms of the disease: 1) a neonatal form (OMIM 608836), which is almost always lethal and neonates become symptomatic before NBS results can be reported, 2) an early childhood hepato-cardiomuscular form (OMIM 600649) where NBS and subsequent early treatment may provide significant health benefit and 3) a late childhood/adulthood skeletal muscle only form (OMIM 255110) [16]. The latter group is by far the largest in populations of European descent and these patients present with myalgia, exercise intolerance and/or rhabdomyolysis in later childhood or far into adulthood. Dietary support and preventive measures may lower the number of rhabdomyolysis episodes but does not fully prevent them [15]. Thus, patients suffering from the myopathic form of the disorder may not benefit from early detection by NBS. They are likely to receive unnecessary intensive treatments (dietary and preventive measures) and develop muscle symptoms and rhabdomyolysis regardless of early treatments. Potential negative effects of presymptomatic diagnosis and treatment are the risk of weight gain or obesity related to nutritional recommendations, anxiety about health and increased health care consumption. Longitudinal data on the disease course, in combination with detailed genetic, biochemical and functional data, ideally gathered in a multicentre, international database by paediatric and adult metabolic experts, are needed to identify the specific CPTII deficiency patient subset who will benefit from NBS. These studies should actively involve adult metabolic specialists to ensure appropriate long-term follow-up and interpretation of adult-onset manifestations. The goal would be to identify biomarkers predicting disease course (severe early childhood multisystem disorders versus later onset predominantly skeletal muscle involvement with limited response to therapy) and to understand the relative benefit of NBS for patients at both ends of the spectrum. Ultimately, this may lead to narrowing the NBS diagnostic protocols to target only severe VLCAD and childhood onset CPTII deficiency. This will prevent cost and negative impact on health perception associated with overdiagnosis of milder disease forms.

3-MCCD is an anomaly in leucine catabolism that may be better classified as a risk factor for metabolic decompensation than an actual disease since most individuals with this biochemical trait remain asymptomatic [17]. The strongest evidence to support the benign nature of this biochemical trait is the identification of asymptomatic mothers by NBS of their child [17]. On the other hand, life-threatening metabolic decompensations with hypoglycaemia, ketonemia and severe metabolic acidosis can occur in a minority of young children and even in individual adult cases [18–20]. This has led to debate on whether or not to screen for this disorder, and several countries have discontinued screening for 3-MCCD [21]. On top of the screening dilemma, there is also the question of the appropriate duration and intensity of monitoring and treatment of screen-positive individuals. In general, neonates and young children are most susceptible to metabolic decompensations, potentially because of the high metabolic rate normalized for body weight relative to older children and adults. This means that the stringency of the preventive measures should be loosened as patients get older. Potentially, adults with 3-MCCD only need instructions to avoid extreme energy demands and metabolic stressors, in addition to an emergency protocol to be followed in case of a metabolic decompensation. Many adult patients do not follow the recommendations on avoidance of fasting or extremely strenuous exercise, and this provides insight into the actual metabolic capacity of these individuals. To determine the appropriate level of care, long-term follow-up data on 3-MCCD patients identified clinically and through NBS should be collected.

4 | Identification of Mothers With IMDs Through NBS of Their Children

Screening newborns for the presence of IMDs using metabolites can lead to the identification of genetic metabolic traits in their biological mothers. Examples of transporter or enzyme deficiencies that can be identified this way are VLCADD, 3-MCCD, primary carnitine deficiency (PCD) and glutaric aciduria type I (GA1) [22, 23]. Typically, these mothers are asymptomatic at the time of the diagnosis, and it is unclear whether their reduced enzyme or transporter activity puts them at risk for developing symptoms and whether they should be monitored and/or treated.

For instance, asymptomatic mothers of newborns who test positive for GA1 on NBS can be biochemically indistinguishable from those presenting early in life with a severe encephalopathic crisis. They can have alterations on their brain MRI, suggesting potential long-term toxicity of the elevated glutaric and 3-hydroxyglutaric acid levels [24]. However, most mothers with this biochemical phenotype, with bi-allelic variants in the glutaryl-CoA dehydrogenase gene, are completely asymptomatic

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[25] and it is not known if these imaging abnormalities are predictive of future neurological symptoms. Whether or not those individuals benefit from lifelong clinical and radiological follow-up and carnitine treatment is questionable. It raises the question about whether the mothers should be informed that NBS of their child could lead to identifying a disorder in them. Such an informed consent process about incidental findings, while routine in other clinical situations such as trio exome sequencing, would be logistically challenging within the current structure of most NBS programs.

NBS for PCD identifies more mothers with a reduced carnitine transporter activity than newborns with PCD. Investigations into the biochemical, clinical and genetic characteristics of these adults have provided insights that can be used to improve NBS for PCD. The mothers with reduced carnitine transporter activity are generally asymptomatic or have non-specific symptoms such as fatigue and myalgia with an uncertain relation to the biochemical trait. DBS and plasma carnitine levels in these mothers do not differ significantly from patients with severe PCD presenting with early-onset symptoms [26]. However, the mothers identified with reduced carnitine transporter activity through screening of their children often carry variants in the *SLC22A5* gene that have not been found in clinically identified patients, and their residual carnitine transport activity is significantly higher [26]. In addition, only very few mothers (< 5%) identified through NBS of their child have shown any cardiac complications that could be attributed to PCD (ventricular arrythmias, dilated cardiomyopathy) and can be prevented by treatment [27]. Based on studies describing clinically identified and screening identified newborn and maternal individuals with PCD, two groups of individuals can be distinguished: 1) those with severe *SLC22A5* variants resulting in very low carnitine transporter activity are at risk for metabolic decompensation early in life and cardiac complications throughout life, and 2) asymptomatic individuals, carrying *SLC22A5* variants only found in screening populations, who are at low risk for the development of overt clinical PCD manifestations. The latter should not be considered a disease but rather a benign genetic trait or, at most, a factor contributing to the overall lifetime risk of developing arrythmia or cardiomyopathy. Mothers identified through NBS for PCD often fall into the latter group, and omitting investigating them might be justified. NBS for PCD could be focused on identifying newborns with severe PCD only. To improve NBS for PCD, further research is needed into biomarkers, other than measuring carnitine activity in fibroblasts, to distinguish between the two groups. An international open access PCD database including information on *SLC22A5* variants, residual transporter activity, clinical and biochemical characteristics would be of great value to aid rapid determination of severity once a newborn is referred because of low carnitine through NBS.

For all relevant IMDs identified by NBS, consensus should be reached on what, if any, diagnostics in mothers are advised if the condition is not present in the child. Such decisions should not be left to individual doctors for individual cases. If diagnostics in mothers are recommended (e.g., measuring the B12 status in case of an unexplained elevated methylmalonic acid level in the child), this should be mentioned in the information on NBS provided to the parents at the time of screening.

5 | Insights in the Full Disease Spectrum Is Needed to Guide Appropriate IMD NBS Programs

These examples illustrate that current NBS screening methods based on biochemical markers will identify all phenotypes of IMDs. However, treatment may only benefit the severe, early-onset form of the disorder. The more invasive the treatment (e.g., hematopoietic stem cell transplantation (HSCT) or gene therapy), the more important it becomes to have a full understanding of all types of disease presentations to guide treatment decisions. Here we give the examples of metachromatic leukodystrophy (MLD, OMIM 250100) and adrenoleukodystrophy (ALD, OMIM 300100) to illustrate the importance of data collection of patients with late-onset disease forms, as well as long-term follow-up of childhood diagnosed patients. These considerations can be extended to NBS for several other conditions including lysosomal storage disorders such as Pompe disease, Fabry disease and Niemann-Pick type B.

In MLD, pathogenic variants in *ARSA* (OMIM 607574) lead to impaired arylsulfatase activity, causing sulfatide accumulation and subsequent peripheral and central nervous system damage [28]. The disorder can be categorized into early-onset (late-infantile and early-juvenile) and late-onset (late-juvenile and adult) diseases. Early-onset MLD progresses rapidly, leading to severe disability and death within years, whereas late-onset MLD progresses more slowly over decades often with predominant cognitive symptoms [29, 30]. Treatment in early disease stages (HSCT for late-juvenile and adult-onset MLD and HSCT-assisted gene therapy for early-onset MLD) can halt or decelerate disease progression, greatly improving disease outcome [31–33]. The emergence of gene therapy (atidarsagene autotemcel, Libmeldy) has accelerated the inclusion of MLD in some NBS programs as most patients are currently diagnosed too late to be eligible for treatment [34].

NBS pilots for MLD are in progress in several places globally, with Norway becoming the first country to start screening in January 2025. A three-tier screening method based on sulfatide quantification, arylsulfatase activity measurement and genetic testing shows promising results [35, 36]. Both early-and late-onset MLD patients are potentially identified using this strategy. Phenotypic prediction is necessary to determine the appropriate treatment strategy as early-onset MLD should be treated before the age of 12 months, whilst recommendations for later-onset forms are to monitor and treat only when signs of subclinical disease develop [37]. In clinically diagnosed cohorts, early-onset MLD is the most prevalent form in most populations, while adult MLD is the least observed subtype [38]. It remains unclear whether this disparity is partly due to underdiagnosis or other factors and if the proportion of individuals with later-onset forms will increase with the introduction of NBS. Research suggests that residual enzyme activity can help distinguish early from late-onset MLD, though current enzymatic assays remain complex, with challenges such as enzyme thermic instability [39, 40]. Integrating enzyme activity data with known genotype–phenotype correlations shows promise, but further research is necessary to rely on this strategy in daily practice [41].

With the introduction of NBS, the landscape of MLD care is expected to change over time. The current focus on severely

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affected children managed primarily by paediatric neurologists and metabolic paediatricians will shift to a broader and older population that includes treated early-onset patients and individuals with late-onset MLD, requiring long-term care and monitoring. These aspects should be anticipated when introducing NBS for MLD.

ALD (OMIM 300100) is an X-linked peroxisomal disorder that illustrates many of the challenges of expanded NBS. ALD presents differently in males and females. About one third of boys and likely more than half of adult men will develop a fatal rapidly progressive leukodystrophy called cerebral ALD (cALD) [42, 43]. Other presenting symptoms in males are adrenal insufficiency (80% with onset in adolescence or adulthood) and adrenomyeloneuropathy (AMN) (with full penetrance in men). Females may develop some symptoms of AMN later in life, but less than 1% develop adrenal insufficiency or cALD [44]. There is no approved disease-modifying treatment for females or for males with AMN. Males identified in the earliest stages of cALD can be treated with HSCT or, in childhood cases, gene therapy (available in a few countries) [42]. Adrenal insufficiency can be treated by glucocorticoid and mineralocorticoid replacement. As HSCT and gene therapy are not effective in males with later stages of cALD, ALD has been identified as a target for NBS.

The American College of Medical Genetics (ACMG) first recommended NBS for both males and females for ALD in 2017 [45]. This recommendation assumed that the prevalence of the childhood onset form of cALD would develop, if left untreated, in 31%–57% of the identified males. Males can be identified through NBS or through cascade screening triggered by NBS. Most studies reporting NBS results for ALD are short-term, so they cannot provide information on the phenotype of the patients identified through NBS. Minnesota identified 32 newborn males with ALD in the first 5 years of their screening program, and 2 of those (6.2%) have developed cALD [46] in follow-up reports, although the NBS cohort is still too young to get a firm estimate of the risk of the cerebral phenotype. Phenotype data for patients identified with cascade screening are available from the first year of screening in Minnesota [47]: 67836 newborns were screened, identifying 9 males and 5 females with a pathogenic *ABCD1* variant (2 of whom had a positive family history of ALD so would have been picked up with cascade screening of the index case). Cascade screening of these 14 cases revealed 17 males and 24 females carrying a pathogenic *ABCD1* variant. Only one of those 17 males (5.9%) had the treatable form of cALD in this study.

Phenotype prediction is difficult in ALD. Biomarkers such as neurofilament light chain can be used to detect children at risk of cALD but these perform less well in adults [48]. Interpretation of molecular testing to confirm the diagnosis can also be challenging as it has been estimated that 62% of missense variants identified through NBS are of uncertain pathogenicity [49]. Long-term (> 20 years) follow-up of the ALD NBS cohort will be required to determine if this is an example of the 'phenotypic drift' (NBS identifying more patients with milder phenotypes than would have been ascertained clinically) that has also been seen with the implementation of NBS for other disorders such as 3MCCD and PCD as discussed above.

There are no therapeutic benefits to early identification of female ALD patients. One way to limit the harms of NBS of ALD is to only report results of NBS for ALD in males. This approach has been taken by some NBS programs, including in the Netherlands [50], but most programs report positive results in females, using the rationale that this would lead to cascade testing of family members and genetic counseling for the parents (in terms of the risk of having an affected male in subsequent pregnancies) and other family members [51]. Such justification is problematic for several reasons. First, genetic counseling is not widely accepted by the public as an indication for NBS [52] as publicly funded NBS is a process that does not involve informed consent. Identifying infant girls with a specific genetic trait for the purpose of cascade testing of their relatives is a grey ethical area. Key principles for NBS [53] place the health of the infant as the highest priority but also discuss benefits in terms of informed reproductive choices for the parents and other family members. However, NBS is not performed for other late-onset diseases where these same arguments could be made, such as genetic forms of amyotrophic lateral sclerosis or Huntington disease. Second, in most programs, the metabolite thresholds of NBS for ALD do not identify all females (i.e., the ratio of females to males is not 2:1) which means that there is a lack of equity in terms of access to genetic counseling and cascade testing. Also, as not all females with ALD are identified through NBS, this could lead to delays in diagnosis for symptomatic females later in life, as clinicians may think that ALD has been excluded by NBS. Third, there is a lack of consensus on appropriate follow-up protocols for females, leading to a high degree of variability in the follow-up of female infants identified with NBS, with some patients receiving no follow-up at all [54], which is contrary to the principles of NBS and can increase anxiety for families. This is consistent with previous reports showing that NBS health care infrastructure is not tailored to manage adult-onset conditions [55]. Last, but not least, uncertainties exist regarding the psychological and social harms of NBS identification of late-onset conditions, as discussed below.

6 | Inclusion of Genetics in NBS Programs Requires Broad Input for Variant Classification

Genetic tests have entered the realm of NBS and their application is picking up speed. Screening workflows for multiple IMDs now integrate genetic testing, functioning either as a stand-alone diagnostic tool or as part of a tiered screening strategy. In addition, a significant number of studies explore the possibility of whole exome/whole genome sequencing to detect a broader range of genetic disorders through NBS (e.g., the Generation study in the UK, https://www.isrctn.com/ISRCTN10894729). Whilst the attraction of genetic screening is clear given its ability to detect the majority of conditions eligible for NBS using a single test, there are significant downsides to this approach. One of the main problems is variant classification and reporting. Reporting only class IV (likely pathogenic) and class V (pathogenic) variants ensures high specificity but low sensitivity, as class III variants of unknown significance (VUS) are excluded. Including VUS increases sensitivity but reduces specificity, as many may not be disease-causing. Several techniques that can separate 'hot' from 'cold' VUS [56] cannot be used or are unattractive in the context of NBS. For example, segregation analysis to determine

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the pathogenicity of a variant detected by NBS means subjecting likely asymptomatic individuals to diagnostic tests, potentially further increasing uncertainty regarding genetic findings. This is very different from testing family members in the context of an index patient with a clinical phenotype, in which a specific genotype–phenotype correlation is looked for in other family members.

Adding genetic tests as combined first tier or second tier test to metabolic testing might be a valuable option as exploratory studies indicate that it may significantly lower the false positive rate and reduce the time to diagnosis for several IMD. However, added diagnostic yield and cost effectiveness need to be evaluated for each disorder separately before genetic testing is added to the screening algorithm [57, 58].

Another problem with genetic NBS for IMD is that even if a class IV or V variant or a combination of variants is detected, this does not mean that these will cause childhood-onset disease. The more we learn about the spectrum of IMDs, the clearer it becomes that reduced activity of an enzyme or transporter does not always mean early onset, severe disease as illustrated above. Intermediate enzyme or transporter activity may result in very slowly progressive disease, becoming symptomatic late or very late in adult life.

To improve disease course prediction, independent, multicentre, open access, well curated phenotype–genotype databases are needed. They require independent funding and involvement of adult metabolic specialists. Examples of such databases are the MLD initiative disease registry (https://www.mldinitiative.comeu/) and the ABCD1 Variant Registry (https://adrenoleukodystrophy.info/mutations-and-variants-in-abcd1).

7 | Risks and Burden of Expanded NBS Programs for Adult Patients Are Not Being Considered

One of the primary tenets of NBS is to screen for disorders where identification early in life will change the outcome. This statement does not imply that all diseases where early diagnosis improves outcomes should be included. For example, early diagnosis of classical Fabry disease, an X-linked lysosomal storage disorder, likely leads to better outcomes of disease specific therapy with enzyme replacement [59, 60], but female patients and male patients with non-classical Fabry disease may not require treatment until the third decade of life or, in some cases, not at all [61, 62]. These patients form the majority of individuals identified by the current NBS programs that include Fabry disease [63]. In addition, the incidence of Fabry disease identified by these NBS programs was much higher compared to clinically identified Fabry disease [63], another example of 'phenotypic drift'.

There are several risks to using NBS as a vehicle to enhance diagnosis of rare diseases. It may lead to the use of healthcare resources for follow-up of individuals who may remain healthy for decades, limiting resources available for more pressing health care matters. Diagnosis by NBS for late-onset diseases can also lead to psychological harms for both patient and family members [64]. For example, parents of newborns diagnosed with type I Gaucher disease through newborn screening show increased psychological distress even though Gaucher disease is a condition that is not life-threatening and for which there is very effective treatment [65]. Qualitative research has shown that a majority of patients with adult-onset chronic diseases would have preferred not to know about their condition at a time when they were asymptomatic [66], describing this as a 'time bomb'. There can also be significant harms related to the ability of the patient to get a job, health, or mortgage insurance [64] and these harms are not prevented by current genetic non-discrimination laws in many countries [67]. The wide phenotype of any given disorder identified through NBS means that, for some diseases, individuals carrying a genetic and biochemical trait are identified who may never need any therapy. This phenomenon could cause patients and families to lose confidence in the process of NBS and opt out, with potentially severe consequences for those disorders like PKU and tyrosinemia type I where the benefits of NBS are truly life-altering [68]. To keep NBS accessible for all newborns, it should be acceptable for (virtually) all parents. In some cases, such as ALD and Fabry disease, proponents of NBS have advocated that the possibility of genetic counselling is the reason for screening female newborns, so birth of an affected male sibling or transmission to the next generation (male offspring of the screened baby girl) can be prevented. However, not all individuals contemplating pregnancy will accept preconception or prenatal diagnosis. In this example, we need to consider both the parents of the affected female infant and the infant herself when she gets older. Using NBS to provide genetic counselling to the parents impacts the autonomy of the female infant by removing her ability to consent to diagnostic choices in the future. Since the diagnosis does not primarily improve her childhood health, it does not fall within the scope of NBS as laid down in the Wilson and Junger criteria. Literature has shown that public acceptance of the risks of NBS when used as a tool to provide reproductive risk information is very low [52]. A child is more than a future parent and decisions regarding carrier screening should take place in the preconception period with informed consent.

The adult perspective on the risks of NBS has thus far only been engaged from the viewpoint of the adults as parents. Parents will risk almost anything in terms of their own health to reduce the diagnostic odyssey for their children [69]. However, when you ask those same adults, they may not be willing to accept risks such as those described above to get an earlier diagnosis of a late-onset condition for themselves [69]. This is the difference between engagement with adults as *patients* rather than *parents* and the adult voice as a potential patient has been lacking in stakeholder consultations on NBS to date.

As NBS programs have a predominantly pediatric focus, there may be a lack of awareness amongst stakeholders of the challenges outlined here such as (i) the harms that may occur when asymptomatic or minimally symptomatic patients are identified due to the burden of long-term monitoring and excess of preventive measures and (ii) lack of data on the impacts (if any) of treatment on later onset forms of the disease. For these reasons, we strongly advocate that all NBS panels should include both adult healthcare providers and adult patient representatives to make sure this adult perspective is included in a multiple stakeholder view on NBS programs [70]. In addition, every effort should be made to avoid NBS

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decisions being influenced by pharmacological industries. Future research on expanded NBS needs to ensure that these long-term risks to adults are adequately captured. Realistically, full separation of those that will and will not benefit from NBS for IMDs will never be possible, and it will be important to weigh the benefits for the individuals spared severe morbidity or even mortality against the harm done to those undergoing unnecessary treatment.

8 | Conclusion

Advances in diagnostic technologies have expanded the ability of NBS to detect a wider range of biochemical and genetic abnormalities at lower cost. This benefits infants with severe, early-onset, treatable IMDs, but also raises challenges. Many IMDs span a spectrum from severe disease to benign biochemical variants with no clinical impact. Patients with later-onset forms may present differently and respond variably to treatment. Diagnosing mild or asymptomatic conditions in infancy can lead to psychological, social and medical burdens, including unnecessary lifelong treatment and anxiety. Long-term outcomes – educational, reproductive and access to care – must be assessed over decades. Adult metabolic specialists, who manage IMDs into adulthood, offer essential insights into disease progression and treatment value. As NBS often identifies all forms of a disorder, their input is crucial in refining strategies to target those who truly benefit from early detection, while minimizing harm to those who will not benefit from diagnosis in the first years of life.

Author Contributions

This work was initiated and designed by Mirjam Langeveld and Fanny Mochel. Written by Mirjam Langeveld and Sandra Sirrs. All co-authors have carefully reviewed the manuscript and given their input in several rounds of revisions.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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