
Summary

Request for advice

A heel prick is used to take a sample of blood from practically all newborns in the Netherlands to screen them for three disorders: phenylketonuria (PKU), congenital hypothyroidism (CHT) and adrenogenital syndrome (AGS). Early diagnosis is necessary with metabolic diseases of this kind so that timely treatment can be given to prevent irreversible damage to health. Parents can also be informed about the likelihood of a repetition with any subsequent child.

Various developments mean it is now relevant to consider increasing the number of disorders for which newborns are screened. Firstly, medical research has resulted in further improvements in diagnostics and the therapies for severe diseases that affect newborns. Diagnostically, the development of tandem mass spectrometry is extremely important. This technique enables a large number of substances in the blood to be investigated, thereby revealing metabolic abnormalities. More medicines have also become available. Consequently, disorders can now be treated for which no therapy was available until recently. Screening newborns can therefore lead to patients receiving timely treatment. Diagnostic and therapeutic possibilities are expected to increase further in the near future. Moreover, demographic developments are also taking place that are important for screening programmes, such as the sharp increase in sickle cell disease owing to migration. Early detection of this disease can result in considerable health benefits. These developments have led to an expansion of the screening programme

for newborns in various countries. In the Netherlands, the State Secretary for Health, Welfare and Sport has asked the Health Council to examine whether the criteria for screening newborns are still adequate and whether it would be advisable to expand the screening package.

In this advisory report, the Health Council's Committee on Neonatal Screening discusses the criteria for screening newborns. The key concern is the health benefit that can be gained. On the basis of the criteria, more than thirty disorders have been assessed for which international reference literature suggests screening is beneficial. The report also discusses the fact that neonatal screening detects carriers (those who have inherited a mutation but are not themselves sick). These may be parents of patients but, in some cases, also newborns. The report also discusses the consequences that expanding screening would have for informing parents and requesting parental consent.

Criteria for screening newborns

Neonatal screening is intended to detect disorders in newborns for which interventions shortly after birth have obvious benefits. The benefits may be direct as well as indirect.

Screening has direct benefits if health gains can be achieved through timely treatment. If treatment also leads to recovery after later diagnosis, neonatal screening offers few if any benefits. Because there may also be objections to an extensive screening programme, due to worry from those concerned, for example, or objections to the costs of the programme, an important precondition is that the health gain for the child must be substantial. Indirect benefits occur if screening leads to improvement in the diagnostics or the care. In certain cases, the newborn can be spared a difficult diagnostics process and early diagnosis can sometimes enable timely support measures to be taken.

Neonatal screening can also offer benefits to other family members. Early diagnosis makes it possible to inform parents at an early stage about the heredity of the disorder. This offers family planning options (in terms of whether to have more children later). Although this possibility is a major benefit, the Committee believes it is not sufficient reason in itself for recommending neonatal screening for a particular disorder.

International reference literature contains many discussions about the criteria that screening should meet. The Health Council's Genetic Screening report included a summary of the purposes and conditions that ought to be met. The disorders should be clearly described, there should be a suitable detection method and the treatments should actually be available and accessible. Moreover, partic-

icipation in screening is voluntary and participants should be properly informed. The parents' informed consent is requested. They act on behalf of and in the interests of the newborns.

The Committee approached testing by firstly delineating the direct benefits to newborns. In particular, an assessment was made as to whether screening could prevent any considerable, irreparable damage to health. There is no doubt about this in some cases, such as PKU, CHT, AGS and some of the other disorders discussed below. Nonetheless, it is clear that screening cannot help prevent damage from some disorders, such as Duchenne muscular dystrophy and fragile X syndrome. There is also an intermediate category which is less clear or for which the health gain is not as great. The Committee therefore distinguishes between three categories, namely disorders for which considerable irreparable damage can be prevented (category 1), disorders for which this applies to a lesser degree or for which the evidence is inconclusive (category 2), and disorders for which neonatal screening does not prevent damage to health (category 3). The Committee then assessed the indirect benefits and quality of the available screening methods. For category 1, the Committee ascertained whether there are reasons for advising against screening, such as the lack of a proper test method. On the other hand, for categories 2 and 3, the Committee ascertained whether there are sufficient reasons for nevertheless considering screening (providing a proper test is available). The results of this test for the more than thirty disorders that were assessed are discussed below per category.

Considerable, irreparable damage can be prevented (category 1)

This category primarily covers disorders for which a proper test method based on tandem mass spectrometry exists, which is based on nonconformities in amino acid levels. These are homocystinuria, maple syrup urine disease, tyrosinemia type I and PKU. A complication of research into homocystinuria is that it also reveals other diseases, such as severe liver afflictions but the Committee does not believe this constitutes grounds for a principal objection to screening for homocystinuria.

A second group of disorders that are readily demonstrated using tandem mass spectrometry, but then based on nonconformities in acylcarnitine levels, are MCAD (medium-chain acyl-CoA dehydrogenase) deficiency, glutaric aciduria type I, HMG-CoA lyase (3-hydroxy-3-methylglutaric acid-CoA lyase) deficiency, long-chain hydroxyacyl-CoA dehydrogenase deficiency, very-long-chain acyl-CoA dehydrogenase deficiency, 3-methylcrotonyl-CoA carboxylase deficiency and isovaleric acidemia. Although patients with the last two diseases

mentioned sometimes display symptoms within the first week of life, screening is recommended for this group. A proper test method is available and many patients can derive a substantial health benefit from screening.

Disorders for which other proper test methods are available include biotinidase deficiency, holocarboxylase synthase deficiency, galactosemia, sickle cell disease, CHT and AGS. The first two extremely rare deficiencies could also be detected by tandem mass spectrometry but a few patients with a non-category 1 disorder would also be detected. In many countries, galactosemia is covered by the neonatal screening programme because early diagnosis enables prevention of problems with feeding (lactose). The Committee recommends screening for this group of disorders.

The following disorders come under category 1 but no suitable test is available or the test method does not provide sufficient differentiation from other disorders: cystinosis, carnitine palmitoyl transferase deficiency type I and carnitine transporter deficiency.

The Committee recommends inclusion of the following category 1 disorders in the neonatal screening programme (in alphabetical order): biotinidase deficiency, galactosemia, glutaric aciduria type I, HMG-CoA lyase deficiency, holocarboxylase synthase deficiency, homocystinuria, isovaleric acidemia, long-chain hydroxyacyl-CoA dehydrogenase deficiency, maple syrup urine disease, MCAD deficiency, 3-methylcrotonyl-CoA carboxylase deficiency, sickle cell disease, tyrosinemia type I and very-long-chain acyl-CoA dehydrogenase deficiency. The prevalence of MCAD deficiency and sickle cell disease are of the same order of magnitude as PKU and AGS. The others are rare. In many cases, the recommended screening would offer the indirect advantage of reducing the diagnostics process. A disadvantage would be that to verify screening findings, more follow-up research would be required than is required in the current screening programme. A few patients would also be detected with an untreatable form of a disorder.

Less substantial or insufficient evidence of prevention of damage to health (category 2)

The Committee has considered whether the direct and indirect benefits for newborns and the benefits for third parties, particularly other family members, are sufficiently large for recommending neonatal screening for certain disorders in this category. The disadvantages of screening weigh relatively more in this category and the Committee therefore believes caution is appropriate.

Category 2 includes cystic fibrosis (CF) and some lysosomal storage diseases. Treating CF leads to a substantial health benefit; however, there is some discussion about the degree to which neonatal screening contributes to this. What is clear is that neonatal screening results in a better feeding status and various experts therefore recommend screening. Early diagnosis of CF also provides indirect benefits; it spares the newborns an often protracted and aggravating diagnostics process, and helps avoid periods of sickness and hospital admissions (with additional risk of infections). Information on the hereditary character of the disorder enables the parents to make informed family planning choices. There are also disadvantages to screening for CF; a considerable amount of follow-up research is needed, also among unaffected newborns, and not all patients are detected. The specificity of screening could possibly be improved through more extensive mutation analysis.

The Committee believes that the sum of direct and indirect benefits is sufficiently large for CF to be included in the screening programme and recommends that research should be conducted soon into screening methods that deal with the aforementioned disadvantages. On condition that a method with a higher specificity is found, the Committee recommends including CF in the screening package.

Enzyme therapies have been developed for several lysosomal storage diseases. Other treatments are also available, such as stem cell transplants and remedies based on substrate inhibition. It is still unclear whether neonatal screening results in an improvement, especially if the storage leads to brain damage. However, the high tempo in which new treatments are being developed in the field of lysosomal storage diseases underscores the importance of timely evaluations of screening possibilities.

Symptoms appear for some category 2 disorders in the first days of life and lead to a diagnosis before the results of neonatal screening are known. There are also disorders in which the test method produces considerable overlap with untreatable disorders. On the grounds of the aforementioned arguments, the Committee recommends that, of the category 2 disorders, only CF (subject to the condition stated above) should be included in the screening programme.

No prevention of damage to health (category 3)

The Committee has considered whether there might be any diseases that qualify for screening for which no possibilities to prevent health damage exist but for which other sufficient and sufficiently large health benefits for the newborns and/or other family members could, nevertheless, arise from neonatal screening. As

for the other categories, the Committee also assessed whether neonatal screening could harm the persons screened. In accordance with criteria defined elsewhere for neonatal screening, the Committee's primary criterion was the interests of the screened person, in this case the newborn. From this point of view, the Committee does not recommend including category 3 diseases in the neonatal screening programme. Perhaps unnecessarily, the Committee points out that, pursuant to the Population Screening Act, screening for these diseases would require a licence.

Information and consent

Providing information on neonatal screening is not an easy matter because it involves relatively unknown and diverse disorders. The purpose of neonatal screening, which is to avoid irreparable health damage, has to be the primary concern. Information must also discuss the limits of the test methods, as well as a brief description of the disorders concerned and the fact that a carrier of the disease may be revealed.

The expansion that the Committee recommends would mean that the severity and treatment of the diseases would vary more than in the present screening programme. This complexity necessitates providing more information while ensuring that it is still possible for parents to understand it. This involves providing information they reasonably require to take their decisions on screening. Additional details should also be provided to parents who would like more information, also in other languages that are commonly spoken in the Netherlands.

Special attention needs to be paid to providing information about the possibility of screening revealing that a newborn is a carrier. This practically always means that one or both parents are also carriers. As with parents of an affected child, if required, adequate information must also be available on what being a carrier entails and on the disorder concerned.

The current screening programme pays relatively little attention to the question of requesting parental consent. The argument put forward for this is that parents are deemed to act in the interests of their child. However, the obviousness of that interest does not detract from the fact that informed consent is required for screening, also on account of the far-reaching consequences that may be connected with screening for severe disorders.

The Committee believes that the first few days after the child's birth are not the most suitable for providing information on the heel prick. To give parents the opportunity to make an informed choice, the Committee recommends providing the information during antenatal checkups.

The expansion of the screening programme, the more detailed information and the informed consent will demand more of the time of the professional groups that are directly involved (obstetricians, general practitioners, paediatricians), which will also have budgetary consequences.

Conclusion

The Committee recommends the addition of fifteen disorders to the neonatal screening programme. The programme's expansion is estimated to result in the detection of a total of 177 (159 to 195) patients per year, which is an average of 89 more than the present programme. The increase primarily concerns sickle cell disease (at least 40 patients) and MCAD deficiency (14 to 18 patients). The other twelve disorders will involve smaller numbers. Adding screening for cystic fibrosis would result in the early diagnosis of another 50 to 60 patients per year.