
Neonatal Screening

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To the State Secretary of Health, Welfare and Sport

Re: Presentation of advisory report on Neonatal Screening
Your ref: IBE/E 2399824
Our ref: U-887/PB/sl/752-D
Appendices: 1
Date: 22 August 2005

Dear State Secretary,

In response to your request for advice dated 12 August 2003, I hereby present an advisory report on the screening of newborns. It has been prepared by a Health Council Committee that I established and was reviewed by the Standing Committee on Genetics and the Standing Committee on Medical Ethics and Health Law.

The Committee considers the screening criteria that have already been formulated by the Health Council in the past to be adequate. The screening should be in the interests of the newborn child, the information should be clear, and the treatment must be accessible to patients. The Committee does not recommend screening for untreatable diseases.

The Committee recommends that newborns should be screened for 18 disorders for which diagnosis and treatment shortly after birth produce a substantial health gain for the majority of patients. In the case of 1 of these 18 conditions, the Committee recommends that research first be conducted with a view to developing a suitable test method. A rough cost estimate has been included as an appendix in the advisory report.

The Committee also recommends that information should be given to parents during the pregnancy, rather than after the child is born.

I endorse the Committee's recommendations.

Yours sincerely,
(signed)
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Neonatal Screening

to:

the Minister of Health, Welfare and Sport

No. 2005/11E, The Hague, The Netherlands 22 August 2005

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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-

ipation 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.

Introduction

Virtually every child in the Netherlands is screened shortly after birth for three disorders that require rapid detection in order to prevent or limit problems of physical and mental development. A blood specimen is taken by means of a heel prick for these investigations.

New developments are taking place in this area. Improvements in analytical technology (notably mass spectrometry) make it possible to rapidly and reliably detect many more disorders (Rin04). The Health Council has organised a workshop at which the technical, clinical, ethical and legal aspects of these developments were discussed (GR03a, GR03b).

It is not only the development of mass spectrometry that has expanded the possibilities for neonatal screening. Research into hereditary disorders has afforded greater insight into biochemical abnormalities. In addition, more data have emerged on the birth prevalences of disorders that could be eligible for neonatal screening.

A further important development is the change in the demographic composition of the population. For example, sickle cell disease traditionally occurs mainly in Africa, but migration has meant that this condition is now also regularly found in the Netherlands.

This introduction begins with a brief description of the present screening programme and then discusses what questions have arisen with regard to that pro-

gramme, how the Health Council Committee has arrived at this advisory report, and finally how the report is arranged.

1.1 The current screening programme

Within the current neonatal screening programme, research is being conducted on phenylketonuria (PKU), congenital hypothyroidism (CHT) and adrenogenital syndrome (AGS). Providing they are detected early, these disorders can be effectively treated: PKU with a diet, and CHT and AGS with medications.

1.1.1 *Phenylketonuria*

Newborns with PKU exhibit no outward clinical symptoms. Brain damage resulting in mental retardation takes place over time in untreated patients. If treatment is only instituted later in life, then the brain damage is impossible to repair.

PKU is an autosomal recessive disorder, meaning that both parents carry a mutation but are not themselves sick. The likelihood of a child of these parents developing PKU (i.e. inheriting the abnormal gene from both parents) is thus 1 in 4. This disorder occurs in 1 in 18,000 children in the Netherlands.

PKU is a metabolic disorder in which phenylalanine, an amino acid, is not converted into tyrosine owing to a deficiency of the enzyme phenylalanine hydroxylase. Deficiencies occur in varying degrees. Milder forms are sometimes designated as hyperphenylalaninemia (or non-PKU hyperphenylalaninemia). This should also be distinguished from an enzyme deficiency that is caused by a deficiency in the cofactor tetrahydrobiopterin (BH4).

Brain damage is, to a large extent, prevented by severely restricting the amount of phenylalanine in the diet. How strict the diet is and how long it needs to be followed depends on the degree of deficiency. Pregnant patients should adhere to a strict diet, since high concentrations of phenylalanine are also harmful for the future child (which will not, as a rule, itself have PKU). If hyperphenylalaninemia is caused by a BH4 deficiency, then this substance is administered.

PKU can be identified from an enzymatic colour reaction to the presence of phenylalanine or by tandem mass spectrometry. A total of 206,000 blood specimens (collected by heel prick) were screened in 2002 by means of the colour reaction. A marked increase in phenylalanine was identified in 16 cases and the newborn child was referred to the pediatrician for further investigation (TNO04). A questionable result was obtained on 21 occasions, whereupon a second heel

prick was requested and, in 10 cases, the child subsequently underwent further investigation. Fifteen of the 26 children who were referred to the pediatrician were found to have PKU and 10 had hyperphenylalaninemia (TNO04).

1.1.2 *Congenital hypothyroidism*

Like PKU, CHT cannot be identified from symptoms in newborn patients. However, this disorder also gives rise over time to irreversible brain damage. Furthermore, physical growth is retarded and various organ dysfunctions occur. CHT has a birth prevalence of 1 in 3,200 and is not usually hereditary.

The cause of CHT is generally an absent or underdeveloped thyroid gland. The regulation of the thyroid gland may also have been disrupted at the level of the pituitary gland or the hypothalamus.

Treatment of CHT consists of administering tablets containing thyroid hormone (in the form of T₄). This results in normalisation of the relevant thyroid hormone blood levels (T₃ and free T₄) within a few days.

CHT can be diagnosed by determining the concentration of thyroid hormone in the blood specimen and, if values are low, measuring the concentrations of thyroid stimulating hormone and thyroid hormone binding protein for verification purposes. In 2002, 336 children in the Netherlands were referred to a pediatrician for further investigation on account of excessively low thyroid hormone levels (95 of them after a second heel prick). This further investigation showed that 65 children had CHT (TNO04). Investigation of a 6-year cohort revealed that 2,604 children were referred to a pediatrician, 18 per cent of them were found to have CHT, and that six of these patients were missed (sensitivity was 98.5 per cent and specificity 99.9 per cent; see Section 2.2.2). There were 5,310 second heel pricks (Lan05).

1.1.3 *Adrenogenital syndrome*

The disruption associated with AGS (adrenogenital syndrome, congenital adrenal hyperplasia) can lead to severe salt loss, dehydration and death during the first few weeks of life. Brain damage may also occur in the first few years. AGS is sometimes manifested at birth in girls by masculinisation of the sex organs, while there are no outward signs of the disease in boys.

AGS is an autosomal recessive inherited disorder with a birth prevalence of 1 in 12,000. It is caused by a deficiency of the hormone cortisol, generally in combination with aldosterone deficiency. This disruption also leads to an excess of certain other hormones. In the majority of cases, the deficiencies arise from a

deficit in the enzyme, 21-hydroxylase (CYP21), but they can also be caused by deficiencies of other enzymes, such as 11 β -hydroxylase (CYP11B1).

Treatment consists of administering hydrocortisone (in the form of an oral solution or tablet) in order to normalise the levels of cortisol and fludrocortisone (on account of the aldosterone deficiency). A feedback process also normalises other hormones. Surgical correction of the sex organs is performed in girls. Treated patients develop almost normally, though height is somewhat retarded and fertility is reduced in women (Sti03).

AGS is diagnosed by using a fluoro-immunochemical technique to measure the concentration of 17 α -hydroxyprogesterone in the blood. An elevation is subsequently followed by a check to ascertain whether AGS is the cause. The degree of increase that is required before further investigation is indicated depends upon the duration of the pregnancy. In 2002, 43 children were referred to a pediatrician for further investigation (7 of them after a second heel prick), with 13 children being found to have AGS (TNO04).

Neonatal screening for AGS was introduced in the Netherlands in 1997. In international terms, neonatal screening for AGS is less common than for PKU and CHT, partly because female patients are sometimes already identified at birth and partly on account of uncertainty over the applicable cut-off values of 17 α -hydroxyprogesterone. If the results are positive, then the literature recommends closer analysis of the blood specimens – either using tandem mass spectrometry or by performing a mutation analysis – in order to reduce the number of false-positive results (Lac04, Kos05).

1.1.4 *Performing the heel prick*

The screening procedure is described in the National Neonatal Screening Plan for AGS, CHT and PKU (Ins01).

The heel prick should be performed on day 4, 5, 6 or 7 – preferably on day 4 (with the day of birth as day 0). Around 50 per cent of heel pricks are carried out on day 4 (with 1 per cent being performed before the stated time and 2 per cent thereafter). The screening laboratory will have received 79 per cent of the blood spot cards by three days after sample, while a further 15 per cent arrive on the fourth day after sampling (Elv03).

Four circles that are filled with blood by bringing the filter paper into contact with the blood spot on the heel are marked on the blood spot card. The newborn's data are also recorded on the card. The data on around one-tenth of the cards are incomplete, and the quality or quantity of blood is insufficient in 0.8 per cent

(Elv03). The participation rate is high, with only a few dozen of the 200,000 babies born annually in the Netherlands having no blood spot card.

1.2 The questions to be answered

In the light of the tandem mass spectrometry technique and our understanding of mechanisms and prevalence, questions are being raised as to which disorders can be screened for using a heel prick test. These questions stem from various quarters. Some are raised by medical researchers, some from clinicians, and still others from representatives of parents' and patients' organisations.

Some of the questions concern the criteria that have been formulated for genetic screening. Are these still adequate and sufficiently concrete to be applied to the neonatal screening programme? In the light of the recent developments, do more disorders satisfy the criteria for neonatal screening than was previously the case? When can a given screening result be described as 'substantial'? Important criteria as far as the screening of newborns is concerned are whether individuals who are identified as having an abnormality can be expected to derive substantial benefit from the prevention or treatment of an illness, and that the disadvantages of screening should be reasonably proportional to this benefit (GR89, GR94). A further factor to be considered here is the advantage of detecting untreatable disorders at an early stage (including the avoidance of unnecessary investigations and delay in diagnosis). There is also some discussion over the concept of 'treatability' *per se*. A separate request for advice with regard to this concept was submitted to the Health Council on 22 March 2004.

The State Secretary of Health, Welfare and Sport requested advice from the Health Council on 12 August 2003 concerning the current level of knowledge about neonatal screening (see Annex A). Three key questions are answered in this advisory report:

- 1 Are the standard screening criteria adequate for the screening of newborns?
- 2 In the light of the new developments, which disorders must be included in the neonatal screening programme?
- 3 What requirements need to be applied with regard to information and informed consent, especially if the number of disorders to be screened for is increased?

1.3 The Committee and its working methods

The Committee that has produced this advisory report – henceforth referred to simply as 'the Committee' – has discussed the current situation with regard to

neonatal screening and the questions to be answered by the report. The membership of the Committee is listed in Annex B.

The Committee has consulted a number of experts: Dr M Peters (Emma Children's Hospital/Academic Medical Centre, Department of Paediatrics); Dr PC Giordano (Leiden University Medical Centre, Hemoglobinopathy Laboratory); Dr S Kölker (University of Heidelberg, Department of Paediatrics); and Ms H Meutgeert (Director of the Dutch Association for Adults and Children with Metabolic Diseases). In addition, the Secretary of the Committee has had discussions with Dr JE Dankert-Roelse (VU Medical Centre, Department of Paediatrics), Prof. JM Aerts (Academic Medical Centre, Department of Biochemistry, Amsterdam) and Dr G Pals (VU Medical Centre, Department of Molecular Diagnostics). Scientific literature concerning neonatal screening has been consulted via PubMed and OMIM (<http://www.ncbi.nlm.nih.gov>). Use has also been made of the following standard textbooks: *The Metabolic and Molecular Bases of Inherited Disease*, Eds. CR Scriver *et al.* (Scr01) and *Screening-Handbuch. Fachschrift zum Neugeborenen-Screening auf angeborene Stoffwechselstörungen und Endokrinopathien* [Screening Handbook. Article on the Screening of Newborns for Inborn Errors of Metabolism and Endocrinopathies], B Liebl *et al.* (Lie02), and Health Technology Assessment reports (Sey97, Dav00, Gre04 and Pan04).

1.4 Structure of the advisory report

The advisory report is organised as follows. The Committee considers the criteria for the screening of newborns in Chapter 2. It differentiates between criteria that relate to the general purpose of the screening, criteria that are geared towards the assessment of specific disorders, and criteria that apply to the performance of the screening. The following aspects have received particular attention: the treatability of disorders; the benefits of screening in terms of shortening the diagnostic process or improving the possibilities for care; adverse implications of screening for the newborn child; information concerning the fact that individuals may be carriers of genetic mutations (without themselves being directly affected); and the ways in which a screening programme affects individuals other than the newborn. Chapter 3 includes discussion of several disorders that might possibly be eligible for inclusion in the neonatal screening programme. The issues considered here are clinical symptoms, heredity, prevalence, molecular basis, treatability and the possibilities for testing. An overview of these disorders is presented in Annex E, together with the Committee's ratings. Chapter 4 deals with the task of informing the parents and the giving of consent. Then, the Committee addresses

issues arising in connection with the introduction of the screening programme in Chapter 5. This is followed by its conclusions and recommendations in Chapter 6.

Criteria for neonatal screening

The Health Council has already published (in the 1989 advisory report entitled *Heredity: Science and Society*; GR89) its views on the criteria that need to be satisfied by screening programmes. That report was predicated on the criteria formulated by Wilson and Junger (Wil68). In its 1994 advisory report on Genetic Screening, the Council scrutinised the requirements that a genetic screening programme needs to fulfil (GR94). The criteria from these publications, as well as the respective guidelines of the International Society for Neonatal Screening (www.isns-neoscreening.org) and the Maternal and Child Health Bureau in the United States (MCH05), are included in Annex C.

The Committee bases its assessment on the screening criteria formulated by Wilson and Junger (Wil68), and more specifically on the Health Council's own criteria for genetic screening (GR94). These criteria relate to various aspects of screening programmes. Some of the criteria are more important than others, with the availability of an effective treatment and a good test method being regarded as the most important factors (GR94, Cra03).

The Sections that follow successively discuss criteria relating to the purpose of the screening (2.1), the disorder(s) for which screening is performed (2.2) and the operational prerequisites (2.3). Section 2.4 focuses on the concept of treatability.

Test results can sometimes lead to the conclusion that a child, and therefore one or both parents, is a carrier for a particular disorder (without an affected child

having been born). In most cases, both parents of an affected child are carriers. It must be clear what information is being provided in this regard (2.5).

Section 2.6 includes a discussion of the fact that the implementation of a neonatal screening programme also has implications for individuals other than those who are directly affected.

2.1 The purpose of neonatal screening

The purpose of neonatal screening is to detect disorders for which interventions shortly after birth have obvious benefits over interventions that either cannot take place without screening or can only take place at a later stage. Interventions do not only include treatments (such as the administration of a medicine or a diet), but also preventive measures (such as the avoidance of fasting in connection with certain fatty acid metabolism disorders).

2.1.1 Health gain

The Committee has discussed the nature of the benefits that are of relevance to the evaluation of a neonatal screening programme. The key point is that these are, for the most part, benefits for the newborn child. The interests of family members, healthcare workers, and society as a whole are of secondary importance. The benefits sought by the Committee are primarily health related (to be henceforth referred to as direct benefits), but they may, on the other hand, also be related to the diseases for which screening is being performed (henceforth referred to as indirect benefits). The potential health gain must be substantial and clear, and not merely statistically significant or else lacking in factual support.

According to the Wilson and Junger criteria, the condition sought should be an important health problem. Severe congenital and hereditary abnormalities may be deemed eligible for screening on account of their far-reaching consequences (Wil68, God03). Classic examples of clear benefits of neonatal screening are the results of early interventions in patients with PKU and CHT. Without neonatal screening, the diagnosis of these disorders will usually be made at a stage of the disease in which irreversible damage has already occurred (especially as far as brain development is concerned). The screening of newborns for the presence of AGS also yields a substantial health gain. An important element here is the fact that these disorders are associated with serious effects that cannot be repaired after a late diagnosis. The existing treatments can then only prevent further deterioration. A second important element is the fact that without screening the diagnosis would, in many cases, be made considerably later. For example,

newborns with PKU or CHT do not yet display any visible outward signs or characteristic symptoms.

2.1.2 Better diagnostics and care

In addition to health gain (a direct benefit), screening can also have indirect benefits for the newborn child, such as an improvement in diagnostics or care. It is thus sometimes possible to avoid a difficult diagnostic process. If a shortening of the process also leads to a health gain, then there are both direct and indirect benefits.

The identification of patients with a hereditary disorder also brings to light parent carriers (NB: this should not be confused with the screening of parents for carrier status). This discovery allows future family planning choices to be made in families with what are usually serious hereditary disorders. It goes without saying that it would be preferable if this option had been available at an earlier stage (e.g. as part of preconception care). The opportunity to make choices is a benefit for the family, and sometimes also for the newborn child. If, for example, caring for a patient is so time-consuming or physically demanding that the birth of a second patient will mean that this care can no longer be properly provided, then there may be a benefit for the person who actually undergoes the screening. The indirect benefits for the patient and the benefits for the family may result in screening being contemplated where there is little if any direct benefit to be had. Patients' organisations have taken the view that screening should not automatically be ruled out even if no treatment is available (Poo99b). The Committee shares this opinion. This type of screening will, for the time being, require a licence pursuant to the WBO. It will, of course, be necessary to undertake a critical appraisal of potential candidate disorders in order to determine whether the newborns who undergo the screening suffer any health damage, whether there is a good test method, and whether the stated benefits are of a sufficient magnitude.

2.2 Prerequisites concerning the disorders

Sufficient knowledge needs to be available about the disorders for which screening is to be performed (e.g. concerning their natural course). A further essential prerequisite is the availability of a good test method.

2.2.1 *Knowledge about the disorder*

According to the criteria that have been outlined above, the disorders for which screening is to be performed need to be clearly defined. The Health Council's advisory report on Heredity: Science and Society stated that the natural course of these disorders should be well known (GR89). The report on Genetic Screening also included information about prevalence and variation in severity among the criteria (GR94).

Clinical, biochemical and biomolecular research have brought about a sharp increase in the number of disorders that satisfy these requirements. Thus, a greater insight has been gained into prevalence (partly through large-scale research using mass spectrometry; Mil90, Ras97, Zyt01). More light has also been shed upon the complexity of various enzyme systems, and thus upon the nature of various deficiencies (Scr01). Molecular research has thus revealed many genes and mutations in those genes (see, for example, Online Mendelian Inheritance in Man, www.ncbi.nlm.nih.gov/Omim).

Even though the condition has been clearly defined, there may be differences in the way it manifests itself or there may be borderline cases. The clinical symptoms can vary, since there are different mutations that do not have the same consequences. But substantial variations are also known to occur within the same mutation in many different hereditary disorders (Wol97). These variations are, in part, attributable to the impact that other genes have on the clinical picture. A detailed example is provided by the widely researched thalassemias (see Section 3.14), where secondary and even tertiary genetic factors (so-called 'modifiers') can be identified (Wea01a).

Environmental influences also have a major impact on the way in which a disorder manifests itself. An example is the effect of feeding in patients with medium-chain acyl-CoA dehydrogenase deficiency (MCAD deficiency), a metabolic disorder (see Section 3.12). Serious crises can occur after fasting, with some patients falling into a coma. If patients receive regular nourishment, then the deficiency seldom gives rise to clinical symptoms.

2.2.2 *Test method*

The availability of a good test method is a prerequisite for newborn screening. The development of tandem mass spectrometry, in particular, has meant that this precondition has been satisfied for a series of errors of metabolism.

Data on sensitivity and specificity are of major importance when evaluating a test method. High sensitivity means that virtually all patients can be identified using the test. High specificity signifies that few people are erroneously classified as patients.

In order to determine the sensitivity of a test method in a neonatal screening programme, one must know the number of patients for which a positive test result has not been obtained. This is, however, sometimes difficult to discover. In order to ascertain the actual number of patients, pediatricians are often asked to indicate those patients who have not been detected by screening. This is only possible if these patients have been correctly diagnosed. Retrospective testing of heel prick blood can also be a useful way of determining the sensitivity of a particular method. In order to assess the sensitivity of a screening programme, it is necessary to undertake critical evaluations of epidemiological data relating to the disorders for which screening is performed and to unexplained neonatal deaths (Loe99).

Specificity is less difficult to determine, since the number of false-positive results (positive results in the absence of clinical disease) usually emerges in the course of follow-up investigations. Annex G presents data concerning the specificity of the neonatal screening of a number of disorders investigated with tandem mass spectrometry. High specificity is extremely important in connection with a mass screening programme in order to restrict the need for follow-up investigations. In the Netherlands, for example, a neonatal screening test with a specificity of 99.92 per cent – as would be expected with tandem mass spectrometry screening for methylmalonic acidemia (Sch03b) – would produce approximately 160 false-positive results per year, which would require follow-up investigation. The relationship between true-positive and false-positive results (the positive predictive value) is strongly influenced by prevalence. Predictive value usually increases in direct proportion to the prevalence of the disease. In Germany, for example, the specificity of tests for MCAD deficiency and glutaric aciduria type I was found to be identical (99.98 per cent), and yet the likelihood of a positive result being a true positive is 26 and 4.8 per cent, respectively. This occurs because MCAD deficiency is more than four times as common (Sch03b).

It is also important to note in this connection that sensitivity and specificity are usually dependent on what cut-off values are chosen for the laboratory results. If the value chosen is such that sensitivity is extremely high, then this can, in some cases, be at the expense of specificity. Conversely, specificity can also often be increased by selecting a different cut-off value. The number of false-positive results will then decrease, but this in turn often leads to patients

being missed (i.e. lower sensitivity). This problem does not arise if the results for patients and healthy subjects are markedly different. In other cases, it may be necessary to assess more than one laboratory result (as with the homocystinuria test, where it is necessary to look not only at the increase in the methionine concentration but also at the ratio between the concentrations of methionine, on the one hand, and phenylalanine and leucine, on the other). If an abnormal level of one or more metabolites in heel prick blood does not allow an unequivocal diagnosis, then further investigation is required. Depending on the outcome, either the heel prick is repeated or the child is admitted for investigation. Because follow-up investigation causes anxiety among the parents and is a burden for the child, it is important that a test method should require little follow-up investigation.

Follow-up investigation is fairly often required in premature infants. False-positive results are more common among these children because their metabolism functions less efficiently than that of children who were born around term. Another type of complication is the fact that certain tests reveal evidence of more than one disorder. This situation arises in connection with PKU and hyperphenylalaninemia, and also in multiple acyl-CoA dehydrogenase deficiency, which overlaps with other fatty acid metabolism disorders.

In practice, it is sometimes possible for sensitivity *and* specificity to increase (e.g. as a result of the introduction of new techniques and analytical methods). The Committee therefore believes that research into test methods is important and that there should be ongoing evaluation of the methods used and the results obtained.

2.3 Operational prerequisites for screening

Notwithstanding the nature of the disorders for which screening is performed, the screening must satisfy certain general prerequisites. It is essential that screening should be accepted by parents and by the professional groups concerned, such as obstetricians, general practitioners and pediatricians.

First and foremost, this means that there must be adequate provision of information. The information given to parents must give a clear picture of what the screening entails and it must be comprehensible to them. This definitely also applies when the screening programme is extended, in which case particular attention needs to be paid to the information regarding disorders with a less favourable prognosis than those for which screening is currently performed. If screening has taken place and a parent is identified as a carrier but the newborn child does not have a disorder, then proper information must be supplied, if

requested (see Section 4.4.5). Annex I includes the current written information about the heel prick. Annex J contains the written information that is provided in Germany with regard to screening for 13 disorders.

Second, participation in screening programmes must be voluntary. Neonatal screening constitutes a special situation in this respect, since it is not the voluntariness of the individuals that are to be screened that is at issue, but that of the parents. Since parents are considered to act in the interests of the child, the nature of the voluntariness is different from that associated with adult screening programmes. There are, in fact, countries where participation is not voluntary but compulsory (that is, participation in neonatal screening is regarded as part of the duty of care that parents have towards their children, though cost considerations also play a role). Chapter 4 includes further discussion of voluntariness.

Other prerequisites are the safeguarding of privacy, quality control and the accessibility of treatment and counselling. Various measures have been incorporated in the present system for this. Personal data are not accessible to third parties, and medical research takes place in an anonymised manner and only with parental consent. Clear agreements have been reached with regard to the storage and use of data. The safeguarding of privacy has a major bearing on the acceptance of the screening.

The quality of the screening programme is partly monitored by testing control specimens and by tracking average results over a period of time. Periodic evaluation of the results is important to prevent inaccuracies from creeping in.

Follow-up diagnostics, information and treatment of disorders for which screening has been performed should be available and accessible to all patients and to the concerned families..

2.4 Treatability

The request for advice that was issued by the State Secretary of Health, Welfare and Sport called for attention to be paid to the concept of treatability. Utmost caution is required when screening for untreatable disorders. Screening for serious diseases that are impossible to treat or prevent requires a licence pursuant to the Population Screening Act (WBO).

The fact that a condition is treatable means that a treatment exists that is known to be effective. As was explained in an earlier Health Council advisory report, 'effectiveness' means that significant improvements can be achieved with the treatment in a clinical setting (GR91). 'Treatability' does not imply that the treatment leads to a cure. In the case of some disorders, the patients can, in fact, be cured (for example, bacterial infections can be cured by using antibiotics).

With many disorders, however, the treatment results only in partial recovery, or a slowing of the disease process. A cure is not possible using the current treatments in the case of hereditary disorders, because the alteration of the relevant gene cannot be reversed. In some cases, the treatment may well lead to a symptom-free state – as is the case, for example, with the administration of thyroid hormone to a patient with congenital hypothyroidism. It is also possible that the treatment may only be effective in certain patients. Thus, some patients with homocystinuria (see Section 3.8) experience a rapid improvement following administration of pyridoxine (vitamin B6), whereas other patients with this condition show no response.

Treatability alone is insufficient, however. The purpose of the neonatal screening programme is to detect disorders for which early intervention brings considerable benefits for the newborn child. The treatment must therefore result in a substantial health gain (as opposed to one that is merely statistically significant), which can, in part, be achieved through early detection. If a condition can be effectively treated without prior screening, as is often the case in disorders with reversible symptoms, then screening is not appropriate for that condition. The same applies in the case of disorders that clearly manifest themselves in the first few days of life. The Health Council will take a closer look at the concept of ‘treatability’ and the associated problems in a separate advisory report.

2.5 Information about carrier status

If neonatal screening reveals a newborn child to be affected, then it often emerges that the parents are carriers of the disorder in question. CHT is an exception, since this disorder is not, in the majority of cases, hereditary (see Section 1.1.2). In most other cases, inheritance is autosomal recessive, meaning that both parents are carriers (that is, they are not themselves sick, but carry the mutation on one of the two genes.) There is then a 25 per cent likelihood that any subsequent child will also be affected. In the case of X chromosome-linked inheritance, the mother is the carrier (i.e. she has the mutation on one of the two X chromosomes). Female carriers of X chromosome-linked disorders often display clinical symptoms, but to a much lesser extent than affected boys. The likelihood of a subsequent male infant being affected is 50 per cent, as is the likelihood of a subsequent girl being a carrier. The affected parents need to be informed about these risks.

Screening for hereditary disorders can also provide information about the carrier status of the child. This is the case if the laboratory test with which an abnormal protein or metabolite is detected in patients also produces an anomalous

lous result in carriers. The same applies in the case of tests that are used to investigate the presence of DNA mutations. Examples are the abnormal hemoglobin that is found in carriers of a sickle cell mutation, or a mutation in the DNA in carriers of cystic fibrosis. If the newborn child is a carrier, then it follows that one, or both, parents (and possibly other children) are carriers. The parents should be alerted to these possible outcomes prior to screening. Information of this kind can, in practice, give rise to misunderstandings with regard to the health of the carriers (Par03). Questions that need to be answered include exactly how the parents can be informed, to what extent (and how) other immediate and extended family members should be notified, and what follow-up investigations might be offered. One problem lies in the fact that it is not always possible to determine for certain whether only one parent is a carrier (as is the case with, for example, cystic fibrosis, where not all mutations are known). Informed consent is required from the parents before information about carrier status can be provided (see Section 4.4.5).

2.6 Implications for others

The implications of neonatal screening are not confined to the parents and any other immediate and extended family members. Screening also has ramifications for individuals and organisations that are involved in a professional capacity.

The scope of the programme and the range of diseases included are important for the professional groups that provide information about screening and its results. This is because of the required investment of time and in continuing education. Expansion of the programme will be accompanied by an increased workload. This is particularly likely if disorders are added that are associated with large numbers of carriers. In the interests of completeness, it should also be noted that equipment manufacturers and the pharmaceutical industry also stand to benefit from the introduction of screening programmes.

2.7 Conclusion

The criteria formulated by the Health Council in previous advisory reports (GR89, GR94) are adequate for the screening of newborns. These criteria indicate the requirements that are to be met by the screening objectives and what additional constraints apply. If the number of disorders included in the screening programme is increased, then particular attention needs to be paid to the information that is provided, which then becomes more complicated, as is discussed in Chapter 4.

Disorders assessed for neonatal screening

PKU and CHT always feature among the disorders for which newborns are screened in various countries. AGS is also included in the screening package in the Netherlands and certain other countries. Elsewhere, infants are also often tested for galactosemia and biotinidase deficiency, while sickle cell anemia and cystic fibrosis also regularly feature in the screening programmes. The character and number of other disorders for which screening is performed vary markedly. Mention is made in the international literature of more than 40 disorders for which newborns are screened (see Annex D). The Human Genetics Commission in the UK recently addressed the question of whether it is not possible to screen the entire genome (as opposed to merely those regions that differ from one individual to another) in newborns. The Commission rejected this proposition owing to ethical, legal and social objections (HGC05). The Health Council's Committee on Neonatal Screening also rejected this type of neonatal testing, which reveals untreatable disorders and conditions that only would occur later in life.

This Chapter discusses (in alphabetical order) disorders for which screening is not currently performed in the Netherlands. The majority of them are listed in Annex E. A number of disorders have also been included that, though they do not feature in the present screening programme, have been identified in the literature as potentially appropriate candidates for neonatal screening. A few extremely rare, untreatable diseases for which screening is performed in certain countries remain undiscussed. The same applies to predispositions such as for diabetes

mellitus Type I (Ker05). Screening for predispositions does not conform to the criteria as they were formulated in Chapter 2. For the diseases that are discussed, we look successively at their main clinical characteristics, heredity, birth prevalence, molecular basis, treatment, and the laboratory test that is used for screening purposes. These disorders can be divided into three categories, based on the likely effect of timely treatment:

- 1 Disorders for which detection and treatment immediately after birth have been shown to prevent serious and irreversible damage to health. PKU, CHT and AGS fall into this Category.
- 2 Disorders for which it is still unclear whether diagnostics and treatment of newborns serve to prevent serious, irreversible damage, or where this applies to a lesser extent. Examples are α 1-antitrypsin deficiency (Section 3.1) and urea cycle disorders (Section 3.16).
- 3 Disorders for which early diagnosis seldom (if ever) prevents damage to health. An example is Duchenne dystrophy (Section 3.4). Some of these disorders are included in screening programmes abroad because there is considerable room for improvement in terms of diagnostics or care (see Section 2.1.2) and because genetic counselling may provide the parents with more family planning options.

As far as the disorders in Category 1 are concerned, the Committee has considered whether there are contraindications that make screening problematic (e.g. a lack of proper test methods). In the case of categories 2 and 3, it has looked into whether there are, in fact, compelling grounds for the introduction of screening (providing that a good test method is available).

3.1 α 1-antitrypsin deficiency

The clinical symptoms of α 1-antitrypsin deficiency consist of lung disease and liver problems (Lar78, Cox01). Patients usually develop chronic obstructive pulmonary disease (COPD) between the ages of 30 and 50. These problems emerge earlier in smokers (Reg98). Severe liver disease, in many cases accompanied by jaundice, occurs during childhood in 20 per cent of patients, (Sve76). Around half of the adult patients suffer from liver disease (Ber72).

α 1-antitrypsin deficiency is an autosomal recessive disorder that occurs in varying degrees of severity. The severe ZZ-form (see below) is estimated to occur in 1 in 42,000 newborns in the Netherlands (Dijk80, Cox01).

The disorder is caused by mutations in the α 1-antitrypsin protein, which usually give rise to a deficiency in this protein, rendering the lungs more vulnerable.

Inclusion bodies of α 1-antitrypsin are formed in the liver, which can also result in damage to this organ. The best known mutation results in the so-called Z-form of α 1-antitrypsin (due to an amino acid substitution of valine by alanine; Cox01).

The main priority when treating α 1-antitrypsin deficiency is to avoid smoking, even passively. Smoking has a highly negative impact on life expectancy (Lar78). There is no treatment for the liver disorders, but the same support measures are adopted as for other forms of liver disease (e.g. avoidance of fatty foods). Transplantation may be considered in patients with liver cirrhosis. Research is being conducted into the possibility of administering α 1-antitrypsin (Juv04, San04). Lung damage can be reduced through the avoidance of passive (and, in later stages, active) smoking. This disorder consequently falls into Category 2.

Neonatal screening for α 1-antitrypsin deficiency can be performed by first determining the concentration of bilirubin in the blood and, if this is elevated, measuring the level of α 1-antitrypsin. Because increased bilirubin levels also occur in connection with other liver problems, various follow-up investigations will be required. However, direct measurement of α 1-antitrypsin in the ZZ-form is also possible (the level of α 1-antitrypsin in patients is generally 15 to 20 per cent of the average). Neonatal screening for α 1-antitrypsin deficiency was performed in Sweden in the 1970s, but this was subsequently discontinued owing to the minimal benefit and the attendant psychological stress for the parents (Lau75, Sve76, The85). It is unclear whether the addition of testing for α 1-antitrypsin to the neonatal screening programme would, indeed, confer a health gain. Furthermore, this liver disorder is recognisable (by the presence of neonatal jaundice). Consequently, the Committee does not recommend the introduction of neonatal screening for α 1-antitrypsin deficiency.

3.2 Biotinidase deficiency

Biotinidase deficiency is a rare condition which is commonly accompanied by neurological abnormalities and skin complaints (Wol01, Gru04). Symptoms are sometimes visible as early as one week after birth, but they sometimes only manifest themselves several years later; the median is three months. The neurological abnormalities are usually epileptic seizures and developmental disturbances of the brain. Nearly half of the patients have balance disorders (ataxia) and loss of hearing and/or vision. Skin disorders and a specific form of baldness frequently occur. The metabolic disturbance can lead to coma (in 10 to 20 per cent of patients) and death.

The inheritance of biotinidase deficiency is autosomal recessive (both parents are carriers of a mutation, but are not themselves sick). In the US, severe deficiency occurs in 1 in 112,000 newborns and partial deficiency in 1 in 129,000 (activity below 10 per cent and between 10 and 30 per cent of the average normal value, respectively). A prevalence of 1 in 87,500 was found in Germany, where many newborns have been screened for biotinidase deficiency (Zab02).

Biotinidase is an enzyme that releases biotin (a vitamin) from the bound form. Deficiency of this enzyme leads to a deficiency of biotin. Biotin is a necessary prerequisite for the activity of several other enzymes (carboxylases). The symptoms of biotinidase deficiency are therefore similar to those of biotin deficiency. Hence, it is not surprising that patients with a biotinidase deficiency can be effectively treated by administering biotin. Although the majority of clinical symptoms disappear at a dose of 5 to 20 mg (free) biotin per day, the neurological damage can only be partially repaired (Bak94, Wol01). Research indicates that early treatment can prevent this damage (Web04).

Administration of biotin can also be used to treat holocarboxylase synthase, as well as biotinidase, deficiency (see Section 3.9, Isovaleric acidemia and related disorders).

Neonatal screening for biotinidase deficiency is practised in several countries. There is a simple test for detecting the activity of this enzyme, and it can be performed with a small amount of material (biotinyl p-aminobenzoate; Hea84, Pet89, Wei89). Because this disorder is associated with the circulation of abnormal metabolites in the blood, it is possible to detect biotinidase and holocarboxylase synthase deficiencies by tandem mass spectrometry (Bon00). However, this may also detect other disorders (depending on what method is used; see Annex F).

Deficiencies of biotinidase and holocarboxylase synthase can both be readily detected and treated. Treatment shortly after birth serves to prevent serious damage. These disorders fall into Category 1. The Committee recommends that newborns be screened for these deficiencies.

3.3 Cystic fibrosis

The key features of cystic fibrosis (CF) are chronic obstructive pulmonary disease, pancreatic fibrosis and hepatic fibrosis (Rat03).

The lung infections experienced by CF patients are mainly attributable to *Pseudomonas aeruginosa* and *Staphylococcus aureus*. They frequently occur in the first few months of life. The large majority of patients experience nutritional problems. Enzymes from the pancreas are excreted too slowly, resulting in poor

absorption of nutrients and damage to the pancreas. Pancreatic damage can lead to diabetes. Almost all men with CF are infertile due to a condition known as secondary azoospermia (meaning that there is no passage of sperm). Fertility is normal in female patients.

CF is autosomal recessive and, compared with other hereditary disorders, it is common among the white population. The birth prevalence in the Netherlands is around 1 in 3,600 (meaning that 1 in every 30 inhabitants is a carrier of a mutation) (Sch01).

CF is caused by mutations in the gene that encodes the so-called cystic fibrosis transmembrane regulator (Rio89, Row05). More than a thousand different mutations have been described (CFM05). No obvious connection has been discovered between the type of mutation and the severity of the disease (although a broad distinction can be drawn between 'severe' and 'mild' mutations; Lai04). Thus, patients who are homozygous for the most common mutation (F508del) present substantially different clinical pictures, which indicate that other factors play an important role in the disease process.

CF is a treatable condition. The life expectancy of CF patients has risen sharply in recent decades, from 8.4 years in 1969 to 32 years in 2000 (data from the US, Rat03). There is a consensus in Europe that intensive antibiotic therapy is advisable in order to combat lung damage from *P. aeruginosa* (Dor00). Furthermore, contact between patients is to be discouraged in order to prevent the spread of infection. Lung transplantation may be considered in endstage of the disease. Administration of enzymes can greatly improve nutritional status, though this will not return to a normal level. There is likewise a European consensus with regard to optimal nutritional strategy (Sin02). Despite the secondary azoospermia, fertilisation may be achieved through surgical retrieval of spermatozoa and application of a technique known as ICSI (intra-cytoplasmic sperm injection). It is inadvisable for women with poor lung and liver function to become pregnant.

Neonatal screening for CF is currently based on a two-stage procedure. First, immunoreactive trypsinogen (IRT) is measured in blood collected by heel prick. An elevated IRT level indicates that the newborn could have CF. The second stage consists of DNA testing. The diagnosis is confirmed if two mutations causing CF are detected. The lack of a suitable screening method for all mutations is problematic, as is the fact that not all mutations are known. Screening is therefore not 100 per cent sensitive. Using a DNA panel consisting of 36 mutations that are commonly found in the Netherlands, it is estimated that two mutations are detected in 86 per cent of patients. Sensitivity is lower in the Turkish popula-

tion group, where it is estimated that no mutation would be detected with an elevated immunoreactive trypsinogen using this panel in a third of the newborn CF patients and only one mutation would be detected in around half of the patients. The prevalence of carriers in this population group is approximately 1 in 50, and the birth prevalence of CF is therefore around 1 in 10,000. CF is far less common in other non-indigenous population groups.

The sensitivity and specificity of the test can be increased by referring newborns with an elevated IRT and one mutation for a sweat test. This approach is employed in certain US states (Com04) and in France (Mun05). In France, a second (adapted) IRT test is performed if the IRT is elevated in the absence of mutations. If this test produces an anomalous result, then the newborn is also referred for a sweat test. Newborns are also referred for a sweat test in the US protocol without having been identified as carrying a mutation, but only with the top 0.2 per cent of IRT values.

The sweat test involves collecting a certain amount of sweat under controlled conditions and then determining the chloride level. Chloride levels are abnormal in virtually all CF patients. However, the sweat test is time consuming and it is sometimes difficult to perform in the first few weeks of life. The test is therefore increasingly being replaced in clinical practice (including in the Netherlands) with mutation analysis.

The provisional results of neonatal screening in France have been published (Mun05, Bro05, Rou05). The results of the two-stage procedure in the US are also known (Com04). Based on these findings, it can be estimated that the addition of CF to the neonatal screening programme in the Netherlands would result in more than 600 newborns without CF being referred for a sweat test, or, a second IRT test would be performed 1,200 times and a sweat test more than 200 times (see calculations in Annex H). Although the screening is complicated, early detection appears to cost less than the current clinical diagnostics (Bro05). However, the large number of follow-up investigations means that a more specific technique would be very welcome. Research into potentially automated laboratory techniques* designed to identify large numbers of mutations could give rise to methods that would minimise the number of false-positives.

By virtue of the two-stage technique, carriers are also being detected among the newborns (i.e. those who have an elevated IRT *and* have inherited a mutation

* Multiplex ligation-dependent probe amplification, denaturing gradient gel electrophoresis, temperature gradient gel electrophoresis, single-strand conformation polymorphism, conformation-sensitive gel electrophoresis, heteroduplex analysis and denaturing high-performance liquid chromatography.

that is included in the DNA panel from one parent). This could apply to well over 400 newborns per year in the Netherlands.

Whether early diagnosis leads to a better outcome is under discussion. A meta-analysis of studies into the cost-effectiveness of neonatal CF screening (published in 2001) allowed the conclusion that there was little controlled research and little evidence that there is any benefit to be derived (Mer01). Research conducted in Wisconsin, US (Far01) showed that screening (diagnosis at an average of 13 weeks) led to significantly better growth parameters than were recorded in the unscreened patients (diagnosis at an average of 100 weeks; evaluation over a 13-year period with a full analysis of the results at four years of age). However, the lung disorders were not significantly reduced (Far01). It can also be concluded from a small-scale study conducted in France that growth was better among screened patients, but that the lung problems had not been diminished (Sir03). No significant difference was found between cognitive function in screened and unscreened patients (Kos04). Various assessments have been made in the course of discussions over the introduction of neonatal CF screening about the possible advantages and disadvantages (Wil02b, Bon03, Far03a, Lyo03, Gro04, Rou05). The fact that treatment confers a substantial health gain is beyond dispute. The question is, however, how big a contribution do diagnostics immediately after birth make to this health gain? One important consideration is the fact that, in the most severely affected patients, the diagnosis is made shortly after birth on the basis of the clinical picture (in the Netherlands, this takes place at an average of 11 months of age). The delay in the diagnosis is therefore usually longest in the milder forms of CF, which makes it more difficult to assess what health gain is to be obtained from screening. Some experts consider that the health gain – and in particular the improved feeding status and the beneficial effects that this has on further treatment – is such that screening is to be recommended (see, for example, MCH05). Others see insufficient evidence that early initiation of treatment produces better results (Bun04). The Committee places CF in Category 2, but notes that it is a borderline case.

Early diagnosis of CF may spare the newborns what is usually a prolonged and difficult diagnostic process. This process includes periods of sickness that can be avoided. The number of hospital admissions is also reduced if the child is diagnosed and treated early (Gro04). Information about the hereditary nature of the condition allows parents to make informed family planning choices, which may be in the family's interests. In view of the above-mentioned potential benefits of neonatal screening for cystic fibrosis, the Committee recommends that CF should be included in the screening package as soon as methods are available

that make the primary screening test more specific, thereby giving rise to a reduction in the required numbers of follow-up investigations with sweat tests. The Committee therefore recommends that research should be conducted in the near future into better methods of screening for CF.

3.4 Duchenne muscular dystrophy

Boys with Duchenne muscular dystrophy have been found to be incapable of running in early childhood (Eme93). The disease is progressive: patients require a wheelchair from around 9 years of age and respiratory support from early adulthood. The myocardium is usually also affected in addition to the skeletal muscles. Mental retardation occurs in some patients (And02). Patients generally die in the second or third decade of life.

Duchenne muscular dystrophy is an X chromosome-linked hereditary disorder. Women who carry a mutation on one of the two X chromosomes are carriers and their (heart) muscles are either unaffected or else only mildly to moderately affected (Hoo99). The disease occurs in 1 in 4,000 boys. The birth prevalence falls in countries where genetic counselling and prenatal diagnostics are available for families in which the dystrophy occurs.

The cause of the dystrophy is a mutation in the gene (Bon88), which encodes a protein in the muscle membrane. Without that protein, muscle breakdown will occur (Dun02). Some mutations lead to a partially functioning dystrophin or a reduction in that protein. In this case, the muscular dystrophy is less severe and is then termed Becker muscular dystrophy, which occurs in around 1 in 20,000 boys. There are also mutations that only affect the myocardium (Mun03). An overview of the mutations encountered in patients with Duchenne and Becker muscular dystrophy, and other muscular dystrophies, can be found at <http://www.dmd.nl/>.

A great deal of research has been conducted into possible treatments for muscular dystrophy patients, but no effective therapy is yet available (Deu03, Khu03, Man04). The disease therefore belongs in Category 3.

It is possible to screen newborns for Duchenne dystrophy by determining the activity of a muscle enzyme in blood. These enzymes occur in greatly increased amounts as a result of the muscle breakdown. The enzyme creatine kinase is the most widely used. Increases are not only detected in patients with Duchenne dystrophy, but also in several other muscle diseases (such as the limb-girdle dystrophies and Becker dystrophy) and in muscle damage caused by other aetiologies. Follow-up investigation (DNA diagnostics, for example) may clarify the situation. In a minority of patients, however, no definitive explanation will be found.

Screening for Duchenne dystrophy is not associated with any direct benefit for the newborn child. The Health Council noted in 1994 that the benefit for the newborn child in this situation lies in the possibility of counselling, while for the parents it lies in the choices that are created in the event of a subsequent pregnancy (GR94). It has been suggested that an early diagnosis could adversely affect quality of life in the preclinical period before the symptoms emerge. However, research into possible psychosocial disadvantages of neonatal screening has not revealed any increase in anxiety or any adverse effect on the parent-child relationship (Par02, Gre04). Because screening does not yield any direct benefit and only a marginal indirect benefit, and because the screening will also unintentionally identify milder muscular dystrophies, the Committee does not consider it advisable to include Duchenne dystrophy in the screening programme.

3.5 Galactosemia

The clinical characteristics of the classic form of this disorder are liver and kidney failure, which are fatal if left untreated (Hol01, Bos04c). Weight loss and lethargy usually occur in the first few weeks of life. Less severe forms of galactosemia also occur in addition to the classic form.

Galactosemia is an autosomal recessive inherited disorder. The classic form has been identified in around 1 in 80,000 newborns in Germany (Mat86, Lie02) and 1 in 23,000 in Ireland (Hon93). Birth prevalence in the Netherlands is 1 in 33,000 (Bos04b).

High concentrations of galactose occur in the blood and tissues of patients. This substance is derived from lactose, and hence milk and dairy products are the source of galactose. This substance is normally converted into glucose by a number of enzymes. Galactosemia occurs in individuals who are deficient in these enzymes. Besides the classic form of galactosemia (galactose-1-phosphate uridylyltransferase deficiency) there are also less severe forms (deficiencies of galactokinase and uridine diphosphate galactose 4'-epimerase).

Rapid recovery is promoted by a diet with the minimum possible level of galactose. Retrospective research in Germany revealed that 19 out of 49 patients from the period prior to neonatal screening died of galactosemia, whereas this only occurred in 1 of the 99 patients after the introduction of screening (Sch03c). Galactosemia is therefore placed in Category 1. However, cognitive impairments and speech disorders are usually found to occur over time in spite of treatment, as is failure of the ovaries in female patients (probably because galactose is also formed in the body in the absence of milk or dairy product consumption; Bad96,

Bos02, Arn03). Delayed cognitive development has also been identified in treated patients in the Netherlands (Bos04a).

Newborns can be screened for galactosemia using either a microbiological, fluorimetric or mass spectrometric technique. The first two methods are based on determination of the enzyme activity (the Beutler method) and produce few false-negative results. If the blood specimens have been stored at too high a temperature, then false-positives may occur. Screening is based on quantitative analysis of hexose monophosphates using tandem mass spectrometry (Jen01). The results may be influenced by the absorption of nutrients. The number of false-positives can be greatly reduced by means of mutation analysis (Dob03). Neonates are screened for galactosemia in the US. In Europe, this occurs in, among other countries, Germany, Ireland, Austria and Switzerland (Zab01). On the other hand, screening programmes have been abandoned in Poland and Norway (Sch03c).

The health gain to be achieved through neonatal screening is partly dependent on the age at which the diagnosis is made without screening. In the Netherlands, this would usually occur within two weeks, and virtually always within one month (Bos03). The health of patients who were immediately put on a low-galactose postnatal diet was no better than that of the other patients (Bos04a). Little is known about mortality in the Netherlands, though this is unlikely to be much different from the situation in Germany (Scho3c) and other countries (Hol01). In the opinion of the Committee, neonatal screening would almost completely eliminate this mortality. The Committee therefore recommends that galactosemia be included in the screening programme.

3.6 Glucose 6-phosphate dehydrogenase deficiency

Glucose 6-phosphate dehydrogenase deficiency (G6PD deficiency) often manifests itself in the first week of life as jaundice. Breakdown of red blood cells also occurs in children and adults under the influence of medicines, certain foods or infections (Luz01). Among the medicines that cause this breakdown are the anti-malarial drug primaquine, certain sulphonamides, acetylsalicylic acid and nitrofurantoin. Other known causes of anemia in G6PD patients are the eating of broad beans – whose botanical name, *Vicia faba*, led to the coining of the term favism (Beu93) – and use of vitamin K. It can also be caused by various infections (e.g. hepatitis A, pneumonia and typhus).

More than 400 million people around the world are estimated to have G6PD deficiency. The majority of the affected individuals are not troubled in any way by the deficiency (Beu93, Luz01). The gene is located on the X chromosome and

clinical symptoms are consequently far more common in men than in women. Prevalence is high in regions where malaria occurs or used to occur – e.g. Central and West Africa, South-East Asia and the Mediterranean region (notably Sardinia and Egypt). In the Netherlands, the deficiency is especially prevalent among people of Surinamese descent, but also in those originating from Greece, Turkey, Morocco and Indonesia.

The condition is caused by more than 400 different mutations which result in a deficiency of the G6PD enzyme. The red blood cells are particularly sensitive to deficiencies in this enzyme, since the metabolite of G6PD (NADP) is not produced by other enzymes (Beu93, Jol01, Luz01).

Treatment is mainly symptomatic. Neonatal jaundice due to G6PD deficiency is treated in the same way as other forms of jaundice. The problems caused by medication can usually be resolved by switching to other drugs. Because these measures can usually be taken without difficulty in neonatal jaundice (providing that adequate diagnostics have been performed), the health gain from screening is relatively small. G6PD deficiency falls into Category 2.

Neonatal screening is performed in some South-East Asian countries, such as Singapore, where the deficiency is very common (Jos03). A semi-quantitative fluorimetric test can be used for screening purposes. However, the majority of girls with this X chromosome deficiency are not detected using this technique (Ain03). The Committee does not recommend screening for this disorder in the Netherlands, since it is clinically recognisable and offers limited health gain.

3.7 Glutaric aciduria type I (glutaryl CoA-dehydrogenase deficiency)

Glutaric aciduria type I (GA-I) – sometimes also known as glutaric acidemia type I – is a metabolic disorder accompanied by severe brain damage (Goo01). The older designation, glutaric aciduria type II, has been superseded by multiple acyl-CoA dehydrogenase deficiency (see Section 3.12.2).

GA-I usually manifests during the first year of life after a crisis provoked by a period of fasting (e.g. in connection with an infectious disease). The damage is most pronounced in the striatum, a part of the brain that controls posture and movement. The disease therefore results in severely impaired posture and involuntary movements (Bri95, Str03).

GA-I is an autosomal recessive disorder. The birth prevalence in Germany is 1 in 100,000 (Lie02), in Sweden it is 1 in 30,000 (Kyl80) and in Australia (New South Wales and Capital Territory) it is 1 in 90,000 (Wil03).

The disorder is caused by a deficiency in the enzyme, glutaryl CoA-dehydrogenase. This enzyme is required for the breakdown of glutaryl CoA, which is

formed by the amino acids lysine and tryptophan. In GA-I patients, disruption of this breakdown process leads to an accumulation of certain organic acids (glutaric acid, 3-hydroxy glutaric acid and glutaconic acid).

Treatment consists of administering L-carnitine and limiting protein intake, together with an infusion of insulin and glucose in the event of a crisis (Sec86, Goo01). The carnitine serves to remove organic acids. The brain damage is, however, irreversible. High doses of riboflavin have a beneficial effect in some patients. It has been estimated that 70 per cent of the patients would remain free of clinical symptoms if the treatment is initiated shortly after birth (Hof96, Goo01; survey by Dr S Kölker, Heidelberg). Although the treatment is ineffective in some patients, the health gain obtainable from screening is sufficiently great that it justifies assigning the disorder to Category 1.

Newborns can be screened for glutaric aciduria type I by tandem mass spectrometry based on an elevation of glutaryl carnitine. The question of optimal cut-off points is still being debated (Sup03). There is also overlap with multiple acyl-CoA dehydrogenase deficiency, which is not treatable but can be distinguished from glutaric aciduria type I by means of additional tests.

In view of the health gain achievable by a significant proportion of the patients, the Committee recommends that glutaric aciduria type I be included in the screening programme.

3.8 Homocystinuria

Homocystinuria is a metabolic disorder that leads to dislocation of the ocular lens and thrombosis due to deterioration of the blood vessels. Early symptoms are myopia (as a result of subluxation of the lens) and skeletal abnormalities (Mud01, Lie02). This is also followed later in life by arterial and venous thrombosis (at 25 years of age in 50 per cent of the patients; Wil97), accompanied by severe psychomotor retardation and other neurological phenomena (Lie02). In addition to classic homocystinuria, the disorder also occurs in less severe forms that are characterised by anemia (megaloblastic anemia) and milder forms of mental retardation (Lie02).

Homocystinuria is an autosomal recessive disorder. The prevalence of the classic form is estimated at 1 in 150,000 newborns in Germany (Lie02), 1 in 65,000 in Ireland (Yap03), and 1 in 180,000 in Australia (Wil03). The milder forms appear to be less prevalent than the classic form (Mud01).

This disorder is related to deficiencies of various enzymes and transport systems (Mud01, Ros01). Methionine released during the physiological conversion of proteins undergoes further conversion via the intermediary product, homocys-

teine. This intermediary product accumulates if the enzyme required for conversion (cystathionine β -synthase, CBS) is missing and, to a lesser degree, if the remethylation of homocysteine into methionine is impaired by serious deficiencies in folic acid or vitamin B12. As a result of this accumulation, homocystine is excreted in the urine. Classic homocystinuria is caused by CBS deficiencies, which can be classified as either pyridoxine (vitamin B6)-dependent or pyridoxine responsive (according to whether or not administration of pyridoxine has an effect on enzyme activity). The milder forms are caused by defects in the conversion of homocysteine into methionine (remethylation), which requires cobalamin (vitamin B12) and various transport proteins and enzymes (including methylene tetrahydrofolate and methionine synthase; Ros01, Lie03, Sib03).

Depending on the type of enzyme deficiency, some patients remain symptom-free following administration of pyridoxine, whereas others show little or no response (Wil97, Klu99, Yap01). The former group is estimated to account for 40 per cent of the patients with a CBS deficiency (Mud01). The others can be treated with a low-methionine diet and administration of betaine (a substance that promotes the conversion of homocysteine). These treatments can greatly reduce the number of thrombosis incidents and prevent mental retardation (Mud01, Yap03). Treatment of milder forms entails administering such compounds as hydroxycobalamin or betaine (depending on the type of disorder) and has a good prognosis in many cases (Ros01). Based on these findings, homocystinuria belongs in Category 1.

Neonatal screening by tandem mass spectrometry is based on the increase in the concentration of methionine in the blood. False-negative results could result from low protein intake or early blood collection, and false-positives from, among other things, high protein intake (Nau89, Lie02). Apart from CBS deficiency, increased concentrations of methionine can also be attributed to tyrosinemia, severe liver disease and several very rare deficiencies (methionine adenosyltransferases, S-adenosylhomocysteine hydrolase or glycine N-methyltransferase; Cha96, Mud01, Aug03). Screening can also be based on the homocysteine concentration. Although this requires an additional step in the tandem mass spectrometry procedure, sensitivity to remethylation defects is higher and the number of false-positives will probably be lower (Ref04, Feb04).

Neonatal screening is aimed at patients who are homozygous (meaning that they have inherited a deficient gene from both parents). The magnitude of the health risk facing the heterozygotes (individuals with one defective gene, who include the parents of identified patients) is not yet known. Heterozygotes usually have moderately increased blood levels of homocysteine that are associated

with an increased likelihood of pregnancy complications (Kuj04, Ste04). Epidemiological research also suggests a greater likelihood of cardiovascular incidents (Eik99), but this was not confirmed in a large prospective study in the Netherlands (Bre03). The implications of identifying heterozygotes (patients' parents and any siblings) via neonatal screening are unclear. Interventions aimed at lowering homocysteine concentrations do not appear to have any effect (in patients who have suffered a stroke; Too04). It is also significant from a practical standpoint that the above-mentioned heterozygotes represent only a small minority of the individuals with increased homocysteine blood levels. Other explanations for this include low concentrations of vitamins B12, B6 and folic acid. Kidney disorders also lead to increased homocysteine levels (Lie02).

Although there is (as was pointed out above) some overlap with other disorders, the Committee believes that screening for homozygous homocystinuria can be recommended in view of the anticipated health gain.

3.9 Isovaleric acidemia and related disorders

The conversion of the amino acid leucine can be disrupted by various enzyme deficiencies (Swe01). The best known of these is isovaleric acidemia, whereby the amount of isovaleric acid in the blood is increased due to a deficiency in the enzyme isovaleryl-CoA dehydrogenase. Deficiencies in the enzymes 3-methylcrotonyl-CoA-carboxylase, HMG-CoA lyase and holocarboxylase synthase also disrupt the conversion of leucine, thereby giving rise to harmful increases in isovaleric-acid derivatives (among other substances).

3.9.1 *Isovaleric acidemia*

The acute form of this disorder is associated with the following clinical symptoms in the first two weeks of life: listlessness, refusal of food and, sometimes, hypothermia and seizures. There is usually also an unpleasant body odour. Around half of the patients have this acute form. Similar symptoms are observed in the other patients, but they are intermittent. Patients are then said to have the chronic form.

Isovaleric acidemia and related conditions are autosomal recessive hereditary disorders. The birth prevalence of isovaleric acidemia in Germany is 1 in 62,000 (Sch03b).

This disorder is caused by a deficiency in the enzyme isovaleryl CoA dehydrogenase, resulting in an accumulation of isovaleric acid (and the glycine and carnitine derivatives of this acid).

Treatment consists of restricting protein intake (aimed at reducing the amount of leucine) and supplementation of other amino acids. Glycine and carnitine can be administered in order to lower the concentration of harmful isovaleryl compounds (Coh78, Roe84). A glucose infusion is administered in the event of metabolic crisis. Without treatment, the acute form of the disease leads to coma and death. Mental retardation may occur in patients with the chronic form. Patients usually develop normally if the treatment is initiated before neurological damage has occurred. Isovaleric acidemia therefore falls into Category 1. It should be noted that severe metabolic crises can occur in a substantial proportion of patients from the first week of life. Neonatal screening is possible using tandem mass spectrometry. The increased concentration of isovaleric acid is easy to demonstrate, but the increase may be small in patients with the chronic form when they are not in the midst of a sickness episode. Detection of isovaleric acid implies that patients with the extremely rare deficiencies of multiple acyl-CoA dehydrogenase and 2-methylbutyryl-CoA dehydrogenase are also identified.

Despite the fact that the disorder manifests in many patients even before results of the screening can be known, the clinical benefit is sufficiently great to warrant screening.

3.9.2 *Related disorders*

Three enzyme deficiencies cause disorders that are related to isovaleric acidemia, namely deficiency of 3-methylcrotonyl-CoA carboxylase, HMG-CoA lyase and holocarboxylase synthase (Scr01).

Deficiency of 3-methylcrotonyl-CoA carboxylase gives rise to metabolic crises in early life that can cause permanent neurological damage (Swe01). The severity of the disorder varies greatly. While some patients have died young, others remain symptom-free in spite of the deficiency (Lie02). Insufficient data are available on birth prevalence (Koe03).

Treatment consists of restricting leucine intake by means of a diet and administration of carnitine, which can prevent metabolic derangements.

Deficiency of HMG-CoA lyase leads to severe metabolic crises in the first year of life (hypoglycaemia, hyperammonaemia). As a result, patients may die or suffer neurological damage such as epilepsy and mental retardation. The disorder is rare and the birth prevalence is not known (Swe01).

Patients are to be treated with a reduced-protein and reduced-fat diet, which can in many cases prevent metabolic crises (Wys86, Bak93). Administration of carnitine may promote the elimination of harmful substances.

Deficiency of holocarboxylase synthase gives rise to metabolic crises (ketoacidosis, hyperammonaemia), accompanied by respiratory problems (Wol01). Many patients have skin rash. The birth prevalence of this rare condition is not known. Patients can be treated with biotin (10 mg per day), as a result of which almost all of them remain episode-free (Gom71, Wol01). Without treatment, patients can soon die.

These disorders fall into Category 1 (as has already been noted in Section 3.2 with regard to holocarboxylase synthase deficiency). As in the case of isovaleric acidemia, metabolic crises often start in the first few weeks of life.

The three enzyme deficiencies mentioned above are associated with an increase in the concentration of 3-hydroxyisovaleric acid. These disorders can therefore be detected by tandem mass spectrometry. Neonatal screening takes place in Germany and parts of the US and Australia (Sch03b, Koe03, Wil03). Screening is also recommended for in the Netherlands.

3.10 Lysosomal storage diseases

This section briefly outlines what lysosomal storage diseases are and why neonatal screening for these disorders is under discussion (see Section 3.10.1). The possibilities are then explained through reference to a number of examples (Section 3.10.2).

3.10.1 Introduction

Lysosomal storage diseases occur as a result of the accumulation of substances that are normally converted within lysosomes (subcellular units that contain a series of metabolic enzymes). If a lysosomal enzyme is missing, then certain substances cannot be broken down. Storage of these substances interferes with the functioning of various organs. More than 40 lysosomal storage diseases have been described (see, for example, Scr01, pp. 3371-3894). They are divided into four groups (mucopolysaccharidoses, lipidoses, glycogenoses and oligosaccharidoses), according to the type of substance that is stored. The clinical symptoms vary markedly, even within a given disorder. Brain damage occurs in many cases, but some storage diseases are mainly associated with problems in the muscles or liver. The heredity of the majority of these diseases is autosomal recessive. A few have an X chromosome-linked heredity pattern.

The introduction of new forms of therapy has raised the question as to what level of health gain is achievable from neonatal screening for lysosomal storage diseases. Foremost among the new treatments are enzyme therapy and stem cell

transplantation. The missing lysosomal enzyme can be prepared using recombinant DNA (Pet03, Des04). Best known are the lysosomal enzymes that are used in patients with Gaucher's disease and Fabry's disease (Anderson-Fabry). The concentrations of harmful substances in blood and certain organs can decrease markedly as a result. Brain damage has, however, proved difficult to limit with this form of therapy because the enzyme does not pass the blood-brain barrier. In some cases, there is still insufficient data available on the efficacy of the enzyme therapies that have been developed. There is also uncertainty over the availability of certain enzymes for reasons of cost.

Another form of therapy is stem cell transplantation. This involves transplanting stem cells from blood (following stimulation of bone marrow cells), bone marrow or umbilical cord blood so that these cells can provide the missing enzyme (Hoo98, Esc05). However, stem cell transplantation requires a suitable donor and such a person is by no means always available. In addition to these forms of therapy, there is sometimes an alternative means of removing the accumulated products (e.g. administration of cysteamine to patients with cystinosis).

The rapid developments in the therapeutic arena have led to calls for neonatal screening for certain lysosomal disorders (Mei04). Early treatment is particularly important with a view to preventing damage to the brain and the skeleton. It should also be borne in mind that stem cell transplants are most likely to succeed at a very early age. An initial step in the detection process could be to measure membrane proteins of lysosomes in blood. Accumulation of storage products in these regions of the cell accelerates breakdown and the membrane proteins that are released can therefore be used as markers (Mei04). A further possibility is to determine the presence of storage products in blood (from the heel prick) by tandem mass spectrometry (Li04, Wan05).

Effective treatments are available for a number of lysosomal disorders (see Section 3.10.2). If stem cell transplantation is the only technique that offers the prospect of substantial health gain, then it is important to note that a donor is not always available and that complications can occur. If enzyme therapy is available and the condition is not characterised by brain damage, then it is important to quantify the extra benefit that can be obtained through neonatal screening. In the case of Fabry's disease and Gaucher's disease (type I), for example, the damage that is caused by storage products appears to be reversible using enzyme therapy (Wil04b).

In the following Section we discuss four somewhat arbitrary examples of lysosomal disorders: cystinosis, Fabry's disease, Gaucher's disease and Pompe's disease.

3.10.2 Examples of lysosomal diseases (cystinosis, Fabry's, Gaucher's, Pompe's)

Cystinosis

There are three different forms of cystinosis: infantile, adolescent and nephropathic. The symptoms of infantile cystinosis (the most severe form) are delayed growth, excessive thirst and frequent urination, accompanied by a risk of dehydration. It presents in the first three to nine months and is caused by kidney problems (Fanconi's syndrome). The cornea becomes clouded in the first year of life by crystalline inclusion bodies (Gah02, Lev04). There is also a form of cystinosis with later onset that occurs around the tenth year of life and has a slower course, and a form in which the kidneys are not damaged.

This disorder is inherited as an autosomal recessive trait. Prevalence in the Netherlands is estimated at 1 in 100,000 to 200,000. A prevalence of 1 in 179,000 has been identified in Germany (Man85).

The disease is caused by mutations in the CTNS gene, which encodes the protein cystinosin (Tow98). If that protein is not functioning properly, then the transport of cystine from the lysosomes is disrupted (Kal01). Storage of cystine in the lysosomes leads to crystallisation that damages the kidneys and the eyes (and sometimes also the brain and muscles).

Cystinosis can be treated by administration of cysteamine, either orally or in the form of eye drops (Tho96, Gah02). This considerably delays damage to the kidneys or eyes. However, some patients (14 per cent) do not tolerate cysteamine (Gah02). If renal function declines too markedly, then dialysis and/or a kidney transplant is indicated.

Because early initiation of treatment prevents a great deal of damage, the condition belongs in Category 1. There have therefore been calls for newborns to be screened by DNA testing (mutation analysis of the cystinosis gene; Gah03). However, one problem is that not all mutations that result in cystinosis have been mapped. Furthermore, the isolation of DNA for neonatal screening with a view to investigating a series of mutations in CTNS would entail a considerable expansion of the neonatal screening programme, whereas the number of patients involved is small. If disorders can be diagnosed by tandem mass spectrometry, then expansion of the screening programme will only result in a relatively minor increase in the screening workload. At this point in time, however, it is not possible to screen for cystinosis using tandem mass spectrometry. Even though cystinosis falls into Category 1, neonatal screening for this disorder is not advisable until such time as proper test methods are available.

Fabry's disease

The clinical symptoms of Fabry's disease are pain (and other sensory disturbances) and abnormalities of the heart, eyes, kidneys and skin (Lin00).

The inheritance of this disorder is X chromosome-linked. The prevalence is estimated at 1 in 40,000 males. Female carriers can be asymptomatic, but they may also present a severe clinical picture.

The cause of the disease is a deficiency of the lysosomal enzyme alpha-galactosidase, which results in accumulation of specific glycolipids in endothelial cells, neurons, skin and cornea.

As was noted in 3.10.1, enzyme therapies have been (or are being) developed for the treatment of several lysosomal storage diseases. Recombinant alpha-galactosidase A (agalsidase) has been found to produce normal blood levels of the storage product (globotriaosylceramide) in patients with Fabry's disease (Wil04b). Pain and fatigue are also reduced (Guf04). A proper assessment of the benefits of neonatal screening will require more data regarding the outcome of therapy. There is evidence to suggest that the damage to the vascular wall is reversible. For the time being, the condition appears to belong in Category 2.

In a report published in 2001, the Health Care Insurance Board (CVZ) indicated that the clinical data were still insufficiently clear and pointed out that the costs of enzyme therapy were high (€120,000 per year). It recommended that enzyme therapy should be made available in a research context, based on standard treatment procedures (CVZ01).

Neonatal screening based on enzyme activity (tested via heel prick blood) is unreliable because the enzyme is heat labile. Blood specimens would therefore need to be frozen. Researchers have reported that an immunochemical method, combined with determination of saponin C, would also be feasible (Ful04).

In view of the uncertainties surrounding possible treatments and the screening method, screening cannot be recommended at this point in time.

Gaucher's disease

The most common symptoms of Gaucher's disease are enlargement of the spleen and liver, brittle and painful bones, and bleeding (Beu01, Fos03). Patients are categorised according to the damage that takes place in the nervous system. The overwhelming majority of patients belong in type I, in which this damage does not occur. This is in contrast to types II and III (the so-called acute or subacute neuronopathic form of the disease). Eye problems are often the first manifesta-

tion of neurological damage. Children with the acute form often die in the first few years of life. The diagnosis is made during childhood in two-thirds of type I patients. Some individuals have the enzyme deficiency, but remain free of symptoms.

Gaucher's disease is inherited as an autosomal recessive trait. The prevalence in the Netherlands is at least 1 in 86,000 (Poo99a). The disease is caused by storage of glucocerebroside due to a deficiency in the enzyme glucocerebrosidase (lysosomal β -glucosidase).

Patients with type I can be treated with a recombinant enzyme (Hol96, Bal04). This usually repairs the organ damage. If the spleen is greatly enlarged, then (total or partial) removal may be considered. The bone problems can be alleviated through the use of bisphosphonates. Another fairly widely known and long used treatment option for patients with Gaucher's disease is stem cell transplantation (Rin95). Owing to the risks associated with this procedure, enzyme therapy is preferable in patients with type I Gaucher's disease. Efforts are also being made to use enzyme inhibitors to combat the accumulation of storage products (e.g. miglustat; Cox03a). Because many of the clinical symptoms displayed by patients with type I Gaucher's disease are reversible, neonatal screening would probably confer little health gain and the disorder therefore belongs in Category 2.

As no treatment is available for the neurological damage that occurs in patients with type II and III Gaucher's disease, these fall into Category III.

The diagnosis can either be made using enzyme analysis or by DNA testing (Beu01). Enzyme analysis would be unsuitable for neonatal screening because the concerned enzyme is labile. (Blood specimens need to be frozen and material from a blood spot card cannot be used.) It should, in fact, be possible to detect the majority of patients by DNA testing using a blood spot card. A substantial number of carriers (who have only inherited a mutation from one parent and are therefore not sick) would then also be identified. Furthermore, individuals who would not develop any clinical symptoms would be classified as patients. Moreover, the test would reveal type II and III patients who are difficult (if not impossible) to treat. The Committee does not recommend screening on account of the possibility of test results of this kind occurring and the fact that patients may recover if treatment is initiated after symptoms emerge.

Pompe's disease (glycogen storage disease type II)

The clinical symptoms of glycogen storage disease type II vary considerably (Hir01). In the most severe form, the cardiac and skeletal muscles, the brain and the liver are seriously affected. The patients with this so-called infantile form usually die in the first few years of life. At the other end of the spectrum is a slowly increasing muscle weakness that begins in adulthood (also known as acid maltase deficiency). The prevalence is 1 in 40,000.

Glycogen storage disease type II is caused by a deficiency in the lysosomal enzyme α -glucosidase. As a result, glycogen is inadequately broken down and causes damage in many different tissues. Treatment is possible with the recombinant enzyme α -glucosidase (Plo91). Research into the effect produced by the enzyme in four patients with the infantile form showed improvements. The children reached four years of age; one patient does not require respiratory equipment; and all patients displayed improved muscular strength (Hou04). Even in patients with acid maltase deficiency, the enzyme therapy was found to produce marked improvements in the skeletal muscles (Win04). Although a considerable improvement was recorded, the Committee puts Pompe's disease in Category 2 because these studies concern only a small number of treatments and little is still known about the long-term results. In particular, it is not known to what extent brain damage is prevented. Nor do we know yet whether treatment needs to be initiated shortly after birth in order to obtain an optimal outcome in patients with the infantile form. There is uncertainty over the availability of the enzyme and the accessibility of the treatment (Hou04). Until recently, fibroblasts or fresh blood were required for the screening (and the diagnostics). Methods have recently been developed for determining the activity of the enzyme α -glucosidase in blood from the blood spot card (Li04).

In view of the uncertainties regarding the results and the availability of treatments, the Committee does not recommend the screening of newborns for Pompe's disease. It is clear, however, that the developments in this area may warrant a re-evaluation of this advice.

3.11 Maple syrup urine disease

The metabolic disorder maple syrup urine disease (MSUD) is named after the smell of the patients' urine, which is caused by the breakdown products of isoleucine. Symptoms in the first or second week of life are lethargy, variable muscle tone and seizures. The patients develop brain oedema (accumulation of fluid in the brain), which is mainly caused by the high concentrations of leucine and 2-

ketoisocaproic acid. Without treatment, the majority of patients die in the first few months of life (Lie02).

In addition to the classic form, there are also several milder forms (intermediate and intermittent). Delayed psychomotor development (usually in the second year of life) has been identified in patients with intermediate MSUD. The intermittent form is characterised by balance disorders and crises, which can lead to coma after infections or a high protein load.

MSUD is an autosomal recessive inherited disorder that has a worldwide occurrence of 1 in 185,000 newborns. The condition is far more common in Pennsylvania (US), and has been identified (using tandem mass spectrometry) in 1 in 250,000 screened newborns in Germany ((Sch03b).

The disease develops because certain amino acids (leucine, isoleucine and valine) are inadequately broken down. These amino acids and the related keto acids accumulate and cause damage in the brain. The defective conversion is due to mutations in components of the protein complex that is biochemically known as branched-chain 2-keto acid dehydrogenase (Chu01, Nel03).

The treatment consists of a special diet and rapid intervention (glucose and insulin infusions) in patients who experience metabolic crises. The diet is synthetic and contains the minimum required levels of the problematic amino acids. Blood levels of such amino acids as leucine are monitored. Many patients who receive treatment develop normally or almost normally (Chu01, Mor02, Hel05). Careful counselling is required, since severe metabolic crises can still occur in early childhood (Chu01, Mor02). Administration of a high dose of thiamine has a beneficial effect in a number of patients. MSUD falls into Category 1.

The classic form of MSUD is detected by tandem mass spectrometry through the increase in the concentration of leucine, isoleucine and allo-isoleucine. Because the protein complex that is deficient in MSUD patients is still developing in the newborn child (and especially in premature infants), the available leucine can still only be converted slowly, which gives rise to a false-positive result. In the intermittent and intermediate forms, on the other hand, the protein complex may still be so active that no abnormal result is obtained, and the diagnosis can only be made during a disease phase. However, the number of false-positives is not so high (approximately 1 in 10,000 screened newborns; Sch03) that screening is inappropriate. In view of its severe course and the possibilities for treatment, the Committee recommends the inclusion of MSUD in the programme.

3.12 Medium-chain acyl-CoA dehydrogenase deficiency and related disorders

Defects in the metabolism of fatty acids (fatty acid oxidation) lead to energy deficits that can cause severe clinical symptoms. The conversion of fatty acids may be insufficient owing to deficiencies of various enzymes, the best known of which is the medium-chain acyl-CoA-dehydrogenase (MCAD).

3.12.1 *Medium-chain acyl-CoA-dehydrogenase deficiency*

MCAD deficiency is an autosomal recessive inherited disorder that manifests itself after fasting (e.g. as a result of an infection). Patients begin to vomit and become lethargic. Without treatment, the patient may fall into a coma and die. Cases of cot death (sudden infant death syndrome) have also been described (Iaf94; see also Section 3.12.2). The clinical symptoms generally present in the first few years of life. However, cases have been documented of children and adults with an MCAD deficiency that have no symptoms (Der04). Retrospective research on heel prick blood from more than 100,000 British newborns has identified a deficiency in eight children. One patient had died, four had experienced one or more crises, and two children had no symptoms (in one case, the findings were unclear; Pou01). Retarded brain development has been identified in later life in an estimated one-third of the patients who had come through a crisis (Iaf94).

MCAD deficiency occurs in more than 1 in 12,000 newborns in the Netherlands and it is, in many cases, caused by the same mutation (G985A; Vri96, GR03a). Clinical symptoms are identified in the first week after birth in approximately 1 in 8 of the patients. There has been some discussion in the literature over the prevalence of mild forms (Roe01, And01, Zsc01). It is likely that a considerable number of patients are missed, both in the Netherlands (Der05) and elsewhere.

The enzyme MCAD converts medium-chain fatty acids. This conversion is important for the supply of energy to the cells of the body. Other enzymes are required for the conversion of (very) long-chain and short-chain fatty acids (see Section 3.12.2).

Treatment is largely based on avoidance of fasting. Advice on the need for regular feeding is important (Nen05). However, if a metabolic crisis takes place, then intravenous administration of glucose is required. Carnitine is also used

(Roe01). The treatment is effective and can prevent irreversible damage. MCAD deficiency therefore falls into Category 1.

Tandem mass spectrometry analysis can be used for neonatal screening. The test method is both highly specific and highly sensitive (Pou01, Zyt01, Sch03b). Although there is an overlap with multiple acyl-CoA dehydrogenase deficiency (see Section 3.12.2), the prevalence of this disorder is very low. It has been suggested as an alternative to screening that all prospective parents should be given detailed informed about feeding. There is, however, some doubt over the effectiveness of this approach (Hol03).

Given the potential health gain, the Committee recommends that neonatal screening should be performed for MCAD deficiency.

3.12.2 *Related fatty acid-oxidation disorders*

Besides MCAD deficiency, there are more than 20 other enzyme or transport protein deficiencies that give rise to disorders of fatty acid oxidation. The most widely cited disorders have been included in the following table (Wan99a, Roe01, Sim02, Tei03).

Table 1 Selection of fatty acid-oxidation disorders

Short-chain acyl-CoA dehydrogenase deficiency	Category 3
Medium-chain acyl-CoA dehydrogenase deficiency	Category 1
Very-long-chain acyl-CoA dehydrogenase deficiency	Category 1
Multiple acyl-CoA dehydrogenase deficiency (formerly known as glutaric aciduria type II)	Category 3
Long-chain hydroxyacyl-CoA dehydrogenase deficiency	Category 1
Trifunctional protein deficiency	Category 2
Carnitine palmitoyl transferase deficiency type I / type II	Category 1/2
Carnitine/acylcarnitine translocase deficiency	Category 2

The severity of these abnormalities, which are almost always autosomal recessive, varies markedly. Whereas individuals with a deficiency may be symptom-free, there are also forms that prove fatal shortly after birth. Research into the cause of sudden infant death in the US and Canada has revealed a metabolic disorder in 66 out of more than 7,000 children who died, with 50 of these cases involving fatty acid oxidation (Cha01). Previously deceased siblings present no exception in families where this disorder was identified, but deficiencies have also been identified in some asymptomatic family members (Bok03, Koe03, Spi03, Tyn99). It is unclear to what extent these family members are at risk for developing a severe metabolic crisis, which appears to occur even in adulthood

(Iaf94, Sme98). Serious complications of pregnancy – notably HELLP (haemolysis, elevated liver enzymes, low platelet number) syndrome – have been described in patients with long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency (Roe01).

There are few data regarding the birth prevalence of fatty acid-oxidation disorders (other than MCAD deficiency). Research into the results of neonatal screening in Germany, the US and Australia has shown this deficiency to be responsible for more than half of these disorders (Sch03b, Hof04, Wai03, Wil03).

As with MCAD deficiency, treatment of patients is based primarily on the avoidance of fasting. If a metabolic crisis should occur, then intravenous glucose is administered. Patients are sometimes given carnitine and riboflavin. If the conversion of (very) long-chain fatty acids is inadequate, then a low-fat, high-carbohydrate diet may be prescribed (Roe01, Zab02). There is, however, still a lack of standardised and substantiated dietary advice (Sol02).

Based on treatment outcomes, the Committee assigns both very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency and MCAD deficiency to Category 1. Patients diagnosed with long-chain acyl-CoA dehydrogenase deficiency are also deficient in VLCAD and likewise belong in this Category. Patients with short-chain (hydroxy) acyl-CoA dehydrogenase and multiple acyl-CoA dehydrogenase deficiencies, on the other hand, are difficult to treat and these disorders fall into Category 3.

Trifunctional protein deficiency is characterised by a disturbance in certain enzyme activities, namely LCHAD, long-chain ketoacyl-CoA thiolase and long-chain enoyl-CoA hydratase (Wan99a, Spi04). Some patients experience serious cardiac and skeletal muscle problems (rhabdomyolysis) and peripheral neuropathy, for which no effective treatment is available. Patients who are only deficient in LCHAD activity may benefit from early treatment (San05). Trifunctional protein deficiency belongs in Category 2 and LCHAD deficiency in Category 1.

Carnitine deficiency can be attributable to an abnormality in the transport of carnitine or carnitine derivatives (such as palmitoylcarnitine) across extracellular or intracellular membranes. Causes include deficiencies of carnitine palmitoyl transferase type I and the organic cation/carnitine transporter (OCTN2; Tei03, Rub04). Patients can be effectively treated by administering carnitine. These two disorders fall into Category 1.

In the majority of patients, deficiency of carnitine palmitoyl transferase type II is only identified later in life as a result of skeletal muscle problems. There is also an early-onset form that usually has a fatal outcome (Roe01, Sig03, Bon04).

Type II transferase deficiency falls into Category 2, as does carnitine/acylcarnitine translocase deficiency.

These disorders usually lead to abnormal blood levels of certain substances (acylcarnitine derivatives), which can be detected by tandem mass spectrometry (Koe03, Sch03a). Abnormal results are not always specific to a particular disorder (see Annex F). They may, for example, be indicative of a MCAD deficiency, multiple acyl-CoA dehydrogenase deficiency (Roe01) or various carnitine deficiencies (Shi03).

The Committee recommends the inclusion of testing for VLCAD and LCHAD deficiency in the neonatal screening programme. Although certain forms of carnitine deficiency also fall into Category 1, insufficient knowledge is available regarding their course and the overlap with partially or completely untreatable disorders is too great to justify the recommendation that screening should be performed for this deficiency.

3.13 Methylmalonic and propionic acidemia

The breakdown of certain amino acids, fatty acids and cholesterol leads to the formation of propionate, which is converted, via methylmalonate, into succinate. Disruption of these conversions can lead to the accumulation of propionic acid or methylmalonic acid in blood and tissues (Fen01). These substances disrupt the metabolism (often in the first week of life).

3.13.1 Methylmalonic acidemia

Methylmalonic acidemia is characterised by lethargy, growth and developmental disorders, vomiting and coma (Fen01). Symptoms are already visible in the first few weeks in some patients, but later-onset forms have also been described. There are also individuals with methylmalonic acidemia who are free of symptoms (Mat83, Led84).

Methylmalonic acidemia is an autosomal recessive disorder. The prevalence is low. Rates of 1 in 125,000 (in Germany; Sch03b) and 1 in 140,000 have been identified among newborns (in Australia; Wil03).

Under normal conditions, methylmalonate is converted into succinate. This conversion may be disrupted by a deficiency of the enzyme methylmalonyl-CoA mutase or the co-factor that is required for this enzyme, a vitamin B12 derivative (adenosyl cobalamin). Co-factor deficiencies can take various forms and are termed cobalamin defects (cblA, cblB, cblC, cblD and cblF; Fen01, Suo04).

Accumulation of methylmalonate can lead to metabolic disturbance, which is characterised by high concentrations in patients' blood and urine (Fen01).

Treatment consists of a set diet (with protein levels adjusted in order to minimise the formation of methylmalonate precursors), cobalamin (vitamin B12), carnitine and direct intervention in the event of a metabolic crisis. Administration of cobalamin is effective in those patients whose residual enzyme activity can be increased. Movement disorders and renal problems will, however, occur over time (Hor04). The forms of the disorder where cobalamin is effective fall into Category 2, since early treatment may possibly confer a health gain, while the others belong in Category 3.

Methylmalonic acidemia can be detected by tandem mass spectrometry through the presence of propionylcarnitine in the blood. Deficiencies of propionyl-CoA carboxylase, holocarboxylase synthase and biotinidase are then also detected. The two last-named deficiencies can, in fact, also be identified by testing for another substance (hydroxyvalerate). The amount of methylmalonate is determined in order to distinguish between methylmalonic acidemia and propionyl-CoA carboxylase deficiency.

Given the uncertainty that surrounds both the definition of the disorder and the treatment outcomes, the Committee does not consider that screening is advisable at this point in time.

3.13.2 *Propionic acidemia*

Accumulation of propionic acid is usually manifested as lethargy, accompanied by vomiting and dehydration, and followed by coma as a result of ketoacidosis in 40 per cent of the patients, some patients exhibit blood cell and platelet deficiencies. These symptoms often occur in the first week of life.

Propionic acidemia is an autosomal recessive disorder with a very low birth prevalence. Screening of newborns in Germany and Australia by tandem mass spectrometry has revealed 1 patient in 250,000 and 360,000 screened individuals, respectively (Sch03b, Wil03).

The condition is caused by a deficiency in the enzyme that converts propionate into methylmalonate, propionyl-CoA carboxylase (Hom68, Fen03).

Treatment consists of a restricted-protein diet, regular feeding, carnitine and metronidazole (to combat production of propionate by micro-organisms in the gut; Mee96, Fen01). Because the effect is limited, propionic acidemia falls into Category 2.

Propionyl-CoA carboxylase deficiency can be detected by tandem mass spectrometry. This also serves to identify any patients with methylmalonic aciduria, holocarboxylase synthase deficiency and biotinidase deficiency.

The Committee does not recommend the inclusion of this disorder in the screening programme because of the limited therapeutic outcome and the early manifestation of the disease.

3.14 Hemoglobinopathies

Sickle cell disease and thalassemia are disorders that are caused by abnormal or deficient hemoglobin, the key protein in the red blood cells. These so-called hemoglobinopathies are common in regions where malaria is endemic because these abnormalities confer some protection against this disease.

3.14.1 Sickle cell disease

Sickle cell disease is characterised by severe vascular occlusions that are caused by hemoglobin abnormalities and gives rise to a red blood cell deficiency (Dav00, Gio00, Fix02, Bee05). As a result many different organs and tissues are damaged, notably the spleen that renders patients particularly sensitive to infections. This may be accompanied by an acute (and sometimes fatal) lung condition. Brain infarcts occur at an early age in more than 10 per cent of patients. Accelerated breakdown of red blood cells gives rise to chronic anemia ('sickle cell anemia'). Bone necrosis occurs in many patients.

Sickle cell disease is caused by structural defects in hemoglobin (the protein responsible for the transport of oxygen), as a result of which the red blood cells have an abnormal, sickle-like shape (hence the name 'sickle cells') and may coagulate.

Other autosomal recessive disorders involving hemoglobin include the thalassemias, in which there is little or no synthesis of this particular protein. Combinations are also possible in which the child has inherited a sickle cell gene from one parent and a thalassemia gene from the other.

The birth prevalence of sickle cell disease and thalassemia has risen substantially in the Netherlands as a result of immigration from regions where malaria is (or was) endemic (Sch04). Carriers of one mutated hemoglobin gene have the advantage of being less susceptible to this disorder, since infected red blood cells are broken down faster. More than ten per cent of the population originates from such regions (first to third generation; Gio00). For people of West African descent, the risk of carrying a sickle cell gene can be as high as 25 per cent

(Hei01, Wea01b). In the Netherlands, the risk of being a carrier affects around 130,000 people from the Antilles and Aruba, nearly half of the country's 329,000 Surinamese immigrants, 18,000 from Ghana and 16,000 from Cape Verde (CBS04, CBS05). Although the risk of carrying a thalassemia gene is smaller, a larger group of people are affected (the Mediterranean region, the Middle East and South-East Asia; the Netherlands has 401,000 inhabitants who originate from Indonesia). The total birth prevalence of children with sickle cell disease or thalassemia in families with parents from these regions in the Netherlands is estimated to be at least 1 in 1,000 (Gio00). Based on a total of 40,000 births per year (CBS04), at least 40 patients would be born every year. Researchers have recently produced an estimate of 60 patients per year (Gio04), around 80 per cent of whom will suffer from sickle cell disease and 20 per cent from thalassemias (Gio00, Gio04). Neonatal screening is an important tool in caring for families with an increased risk of sickle cell disease, but so are preconception counselling and prenatal screening of the parents (Wie97, Sch98, Rhe98, Gio00).

Treatment of patients with sickle cell disease consists of blood transfusions and preventive measures against infections (antibiotics and extra vaccinations; Fix02, Cla03). Mortality and morbidity are declining considerably thanks to early preventive treatment (Gas86). Sickle cell disease therefore falls into Category 1.

The only treatment that can lead to a cure is stem cell transplantation. However, this requires a suitable donor and there are also other objections (Wal96, Gaz05). A great deal of research is being conducted into other therapeutic possibilities (Vic02).

Individuals can be screened for sickle cell disease by using high pressure liquid chromatography or isoelectric focussing, and possibly also by tandem mass spectrometry (Wil04c), to test for abnormal hemoglobins (Dav00). This screening also reveals certain forms of thalassemia. The Dutch Society of Obstetrics and Gynaecology's Guideline on Basic Prenatal Care (NVOG Guideline 46, dated June 2002) recommends identification of groups at high genetic risk of anemia and, if indicated, performance of hemoglobin electrophoresis.

Screening also identifies newborns who have inherited a sickle cell gene from one of their genetic parents (Lai96, Lee00). Based on the prevalence rate that was mentioned earlier, this would amount to 2,000 cases of sickle cell disease a year, with the other parent also being a carrier in around 125 cases. As was noted in Section 2.5, this raises the question as to what information should be provided to the parents. The interests of any other children in the family also need to be taken into consideration. Research indicates that non-Western immi-

grants are frequently unaware of the risks that hereditary disorders posed for their children (Tal04). The information provided with regard to the implications of being a carrier should be accordingly modified.

As far as sickle cell disease is concerned, there is also the question of whether neonatal screening ought to be introduced at the regional or at the national level. Given that the prevalence in some regions is considerably higher than the average, regional screening would be more efficient. However, a number of newborn patients would then be missed. Furthermore, the demarcation of regions would introduce an arbitrary element. Another possible way of increasing the *a priori* likelihood of identifying hemoglobinopathy is to base screening on the ethnicity of the biological parents. Researchers have pointed out that this raises certain practical problems. For example, the parents are sometimes not sufficiently well informed about their origins. Furthermore, they may dislike being questioned about their origins and having such information recorded. Finally, those who carry out the screening have to cope with extra administration and responsibilities (Dav00, Asp03).

In its recently published annual report on Perinatal Care in the Netherlands 2001, the Dutch Perinatal Registration Foundation (SPRN) emphasised the fact that care providers have no precise definition of the various ethnic categories and that the breakdown by ethnicity in the national obstetric data registration system is flawed. Furthermore, around 1.5 per cent of the women who gave birth to singletons during that year were recorded as being of 'unknown ethnicity' and around 2.5 per cent as 'mixed/other ethnic group'. Even in moderately urban and rural areas, 1 per cent of the mothers of singletons are still of mixed European and non-European heritage. Moreover, the 'mixed ethnic origin' group can be expected to grow in the future. Identification of high-risk couples will therefore become progressively less reliable in the years to come.

In view of the health gain to be achieved and the complications of regionally or ethnically based screening, the Committee recommends that screening for sickle cell disease be introduced nationwide.

3.14.2 *Thalassemia*

This disorder occurs in various forms. The severity varies considerably and depends partly on the type of mutation (Wea01a). Treatment initially consists of performing blood transfusions in order to combat the anemia (Lo02). As this usually requires many transfusions, iron overload occurs, for which the chelating drug deferoxamine (or deferiprone) is administered. Several other measures besides transfusions are required in connection with organ damage (Lo02). Stem

cell transplantation is the only means of affecting a cure (Gaz05). A number of transplants have also been performed in the Netherlands (Bal03).

Thalassemias fall into Category 2, since neonatal screening provides little health gain in patients with these disorders. The diagnosis of thalassemia is usually made in a timely manner based on the anemia (NHG03). The best-known screening programme for thalassemia is the study that was conducted in Cyprus on carrier status prior to marriage, which led to a considerable reduction in the number of affected newborns (Gio00). As has been noted, sickle cell disease screening by testing for abnormal hemoglobins also reveals certain forms of thalassemia. Although the benefits for the concerned individuals are limited, the Committee does not regard this as a conclusive argument against screening for sickle cell disease.

3.15 Tyrosinemia

Tyrosinemia type I (hepatorenal tyrosinemia; Mit01) may present as a bleeding tendency or some other sequela of liver failure. There are also patients with pain and paralysis. In the long term, many patients develop kidney disorders and carcinoma of the liver (Rus01, Sau02). This disorder is inherited as an autosomal recessive trait. The birth prevalence is low. Tandem mass spectrometry screening identified one patient among 250,000 newborns tested in Germany and two patients among 360,000 in Australia (Sch03B, Wil03). Tyrosinemia type I is caused by a deficiency in the enzyme fumarylacetoacetase, which is involved in the breakdown of the amino acid tyrosine (Ber98). Patients are treated partly with a diet containing a limited amount of tyrosine and phenylalanine, and partly by prescribing an enzyme inhibitor – NTBC (2(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione; Hol00) – in the tyrosine degradation pathway. Around 10 per cent of the patients ultimately require a liver transplant. The risk of a patient developing liver adenomas and renal impairment is greatly reduced if treatment can be instituted soon after neonatal screening. Tyrosinemia type I falls into Category 1.

Type II (oculocutaneous hypertyrosinemia; Mit01) is characterised by eczema and ocular and neurological abnormalities (Rus01). This is also an autosomal recessive inherited disorder. One patient was identified among 360,000 newborns in Australia (Wil03). The cause is a deficiency in the enzyme tyrosine aminotransferase, which catalyses the first step in the breakdown of tyrosine. Treatment consists of lowering the concentration of tyrosine by means of a diet. This disorder falls into Category 2 because the outcome of this treatment is not as yet sufficiently clear.

Patients with tyrosinemia type III have neurological abnormalities and/or develop mental retardation. Inheritance is autosomal recessive. The birth prevalence is very low. The disorder is caused by a deficiency in the enzyme 4-hydroxyphenyl pyruvate dioxygenase, which is involved in the breakdown of tyrosine. Mutations in this enzyme have also been detected in people with hawkinsinuria (Tom00), a form of tyrosinemia characterised by a metabolic disturbance which can be treated with a diet. As the therapeutic outcome is very limited, this disorder falls into Category 3.

Tyrosinemia can be detected with the aid of tandem mass spectrometry (Zyt01). One problem here is the fact that elevated concentrations of tyrosine occur fairly often in newborns, probably because the activity of the enzyme 4-hydroxyphenylpyruvate dioxygenase is still low. Premature birth, and food that is high in protein and low in vitamin C, can cause transient tyrosinemia. It is possible to make the test specific for tyrosinemia type I and greatly reduce the number of false-positives by also measuring the amount of succinyl acetone in the blood specimen (All04). The Committee recommends that screening should be performed for tyrosinemia type I, even though the number of patients is very low.

3.16 Disorders of the urea cycle

Patients with a disorder of the urea cycle often experience serious feeding problems in the first week of life, with vomiting, refusal of food and neurological symptoms such as convulsions and coma. There is a high risk of death (Bru01, End04). The symptoms emerge later in some patients, and they are then less severe. Periods of lethargy, vomiting, refusal of food and growth retardation are sometimes accompanied by neurological symptoms.

Inheritance of urea cycle disorders is either autosomal recessive or X chromosome-linked. Estimates concerning total birth prevalence range from 1 in 8,200 newborns (Bru01) to 1 in 40,000 to 50,000 (App00, Wil04a).

The disorders are caused by deficiencies in the enzymes ornithine transcarbamylase, carbamylphosphate synthase, argininosuccinate synthase (citrullinemia type I), argininosuccinate lyase and arginase. These deficiencies lead to metabolic disturbances caused by elevated concentrations of ammonia in the blood, since there is ineffective removal of excess nitrogen as urea. The first-mentioned deficiency is X chromosome-linked. Women with a mutation on one of the two X chromosomes are also often affected. Arginase deficiency typically leads to mental retardation and muscle paralysis rather than to metabolic disturbances (Bru01).

Treatment consists of limiting protein intake, giving nutritional supplements and administration of benzoate or phenylbutyrate in order to remove ammonia (Wil04a). A number of patients have undergone a liver transplant. Although the results of the treatment are better than in the past, the prognosis is poor in many cases (Bac03, Wil04a, End04). The disorders therefore fall into Category 2.

Urea cycle defects can be detected using tandem mass spectrometry. Deficiencies in ornithine transcarbamylase and carbamylphosphate synthase are identified by reduced citrulline, deficiencies in argininosuccinate synthase and argininosuccinate lyase by increased citrulline, and deficiencies in arginase by increased arginine (Zyt01, Cha03). Deficiency in argininosuccinate lyase can also be detected via increased argininosuccinate (Sch03b). Testing based on reductions in citrulline produces many false-positive and false-negative results (especially in female patients with an ornithine transcarbamylase deficiency). In many cases, severe clinical symptoms will already be apparent before the results of neonatal screening are known. For this reason, and because therapeutic outcomes are limited, the Committee does not recommend screening for urea cycle defects.

Information and consent

4.1 Introduction

The provision of information to parents has various functions. Proper information can boost the willingness of parents to participate in a screening programme. It is also important to prevent disquiet or anxiety over the outcome of the screening. Dissatisfaction and anxiety are more often encountered among parents who feel that they have not received adequate information (Wai03, Gre04). Quite apart from these considerations, the provision of information has a crucial role to play in connection with the task of securing informed consent for screening.

The application of the informed consent requirement in connection with neonatal screening raises several questions. To some extent, these questions become increasingly pressing as more and more disorders are added to the screening package. In Section 4.2 we look at the various elements of the informed consent requirement and, on this basis, we also assess the problems that surround current and future screening practice. Then, in Sections 4.3 and 4.4, we discuss the provision of information and consider whether it might be justifiable to impose less strict requirements with regard to information provision about the heel prick than for information relating to other medical procedures. This question is answered in the negative. The Committee then considers what implications this has for the provision of information about neonatal screening. Finally, we look in Section

4.5 at the giving of consent, which is inextricably linked with the parents' duty of care towards their children.

4.2 Ethical and legal requirements concerning informed consent

The principle of informed consent means that the care provider may only conduct research or administer a treatment if the patient or client (or his/her representative) has given his/her consent based on prior information. This principle is rooted in highly complex ethical and legal considerations and has been enshrined in the so-called 'Medical Treatment Agreement Act' (WGBO; Section 7: 448 ff Netherlands Civil Code [BW]). It can be broken down into various component parts: the actual provision of information; the comprehension of the information; the voluntariness of the choice; and the consent itself. These aspects are discussed below, with particular attention to the informed consent procedure for the heel prick (Ros04).

4.2.1 Provision of information

Parents should be put in a position where they can make a judicious choice. To do so, they require relevant information about the screening procedure. The WGBO stipulates that clear (and, if required, written) information should be provided with regard to the nature and the purpose of the screening, its consequences and risks, the alternatives, and the broader implications. In theory, it must be assumed that a broader duty to inform applies in connection with screening. Essentially, screening is a test procedure which has neither been requested by parents nor prompted by a symptom. Furthermore, it is possible that serious disorders may come to light (even though there is, in fact, little chance of this happening). Moreover, specific circumstances pertaining to the parents (e.g. unfamiliarity with screening or family problems) may necessitate the provision of more detailed information. Finally, the parents' questions will need to be answered (as far as possible). As far as the heel prick is concerned, the information to be provided will need to include answers to the following questions:

- What is the infant being screened for?
 - What does the screening entail?
 - What are the anticipated benefits and disadvantages?
 - How important is it that parents should have their child screened?
 - Is it possible that results have implications for us and for family members or previous children?
 - Are the data produced by heel prick testing confidential?
-

- What happens to the blood spot cards once the testing has been completed?
- What happens in the event of non-participation in the screening?
- Who can we turn to with any additional questions?

More specifically, this information could encompass the following issues: information about the nature, prevalence and severity of the disorders for which screening is to be carried out; the importance of early diagnosis; the possibilities for treatment and/or other benefits for the person concerned; the fact that some test results require confirmation or give rise to false alarm (Indeed, it should be pointed out that it is frequently impossible to set parents' minds at rest after an initial abnormal result that later turns out, after all, to be normal.); the fact that cases can be missed and that not all diseases are detectable (thus neonatal screening does not allow a child to be given a clean bill of health); and further information about use of residual material from the heel prick for medical research and about protection of privacy. It is also relevant for the parents to know whether a test method may provide information about the implications of being a carrier. Last, but by no means least, it is important that parents should understand, based on the information provided, that they do, in fact, have a choice.

The information provided under current screening practice only partly satisfies these requirements. The information about the disorders is brief. It does not go into different manifestations of the disorders (milder or more severe) or the possibility of false-positives and false-negatives. It is also noticeable that the possibility of forgoing screening is not explicitly mentioned, which is particularly relevant in the light of the 'invasive' nature of the heel prick procedure.

4.2.2 *Comprehension*

Parents are not obliged to digest and comprehend all of the information. They may choose to be spared further information or explanations (and therefore comprehension). But the person who provides the information in that case needs to make certain that the parents have chosen to do this, and that they have not simply overlooked the information.

The requirement that the information provider must have sufficient reason to believe that parents have understood the information about the heel prick poses a number of problems. First, we are dealing with a highly complicated issue and disorders that are rare. This problem becomes greater still when the number of disorders that are screened for is increased and when further complex aspects also come into play (such as the identification of carrier status in newborns). Second, the first few days after the birth are unlikely to be a good time for parents to

digest information about screening. This problem can, however, be overcome to a certain extent (see Section 4.4).

4.2.3 *Voluntariness*

The fact that participation must be voluntary to some extent defines the way in which the screening is offered. It is, in several respects, true to say that current screening practice is characterised by a certain degree of pressure or directive-ness: the possibility of forgoing screening is not explicitly articulated. The heel prick specimen is collected by a nurse whose visit to the home may well be by arrangement, but is unlikely to have been specifically requested. Finally, the fixed screening package can also be regarded as a form of pressure. Although the fact that this is a voluntary choice implies that there are certain limits on that pressure, it should be noted that parents are acting on their child's behalf. The effort that is required by the screening process is small – as too is the risk of damage occurring as a result of the knowledge that is imparted. And yet the benefit to be gained in such cases is great. It is therefore necessary to put the parents' right to decide into perspective: Parents have a duty of care and should act in the interests of the child.

4.2.4 *Consent*

Parents should consent to the performance of screening in their child. This means explicit consent. According to Article 7:466 of the Dutch Civil Code, presumed consent can only be deemed to apply if the screening is of a 'radical' nature. Although the blood sampling is, essentially, a minor intervention, the results of the testing may have far-reaching consequences, and consequently this must be assumed to be a 'radical' procedure. In principle, verbal consent should suffice; however, parents can demand to have the consent put down in writing (Art. 7:451 BW).

The question of consent is dealt with in a somewhat implicit fashion in the current fact sheet (Annex I). The intention here is clearly to minimise the number of non-participants, since parental refusal to participate can cause irreparable damage to the child. A more obvious course of action as far as parents who refuse consent are concerned is to speak to them about their motives in order to ensure that they do not forgo the heel prick on erroneous grounds (such as irrational anxiety). The parents may also be reminded of the aforementioned duty of care that they have towards their children.

4.3 Current information about the heel prick

Provision of information about the heel prick currently consists of handing out a fact sheet when a birth is registered at the local government offices (see Annex I). This fact sheet contains information about the importance of early detection and treatment of AGS, CHT and PKU, about the timing and the method of blood sampling, and about the communication of abnormal results or results that need to be confirmed. This is followed by passages regarding the protection of personal data and retention of residual material for the purposes of quality control and medical research, with the possibility of lodging an objection to the latter. The fact sheet also states – albeit somewhat implicitly (‘We hope that you give your consent...’) – that it is possible to refuse the heel prick. The fact sheet is available in Dutch (in accordance with Ministry of Health, Welfare and Sport policy). The same information is available on the internet, with the possibility of following links to the disorders in question (www.czmedicinfol.nl). Although this is not stated in the fact sheet there are translations into Arabic, German, English, French, Spanish and Turkish on the website www.entadministraties.nl (see > heel prick screening > information pack > heel prick fact sheet). The Committee recommends that the information about neonatal screening also be made directly available in these languages. A large group of people are affected by this state of affairs. According to Statistics Netherlands, 314,699 people from Morocco were resident in the Netherlands as at 1 January 2005 (167,375 of whom are first-generation immigrants), and 357,911 people from Turkey (of whom 194,865 are first generation) (CBS05).

4.4 Information provision within an expanded screening package

In Sections 4.2 and 4.3, we considered the requirements surrounding informed consent and the current provision of information with regard to the heel prick test. A number of problems were pointed out at the same time. We will look below at how the above-mentioned requirements can be satisfied in connection with an expansion of the screening programme, while at the same time considering how to improve the existing procedure.

4.4.1 Information content within an expanded screening package

Since test results can have far-reaching consequences, the information that is provided about the nature and occurrence of the diseases for which infants are

screened must also be clear and complete if the screening programme is expanded. This is not altered by the fact that the disadvantages and the burden associated with this screening are minimal and that the potential benefits are great. If the screening programme is expanded, then there is a risk that parents could be inundated with so much information that they are no longer able to comprehend it. This means that the information must be geared towards the key decisions that the parents have to make, with the possibility of directing parents towards more detailed sources of information should they require it. Nor does the parents' duty of care detract from the fact that they are entitled to receive proper information and the wherewithal to make their own decisions.

All things considered, there is thus no reason why expansion of the screening programme should result in information provision being subject to requirements that are any less strict than those that were set out in Sections 4.2 and 4.3. On the contrary, it is precisely because the screening package is being expanded that even stricter demands need to be imposed on the way in which the task of providing information is concretised.

To conclude, it is vitally important to evaluate the information that is provided and the influence that is exerted in persuading parents to accept the screening (and, if necessary, to modify this information).

4.4.2 *How information is provided and in what form*

It is not so much the expansion of the package itself that aggravates problems surrounding information and comprehension, as it is the need for this package to include disorders which, from the perspective of the parents, differ markedly in significant respects. If the screening package is extended with disorders that are reasonably similar in terms of severity and treatability, then relatively little 'extra' information and explanation actually needs to be added. The more 'uniform' the disorders are (at least from a lay perspective), the easier it is to explain whether and why it makes sense to participate. This means that the requirements and possibilities surrounding informed consent could also have an impact on the question as to which other disorders might be incorporated into the screening programme in the future.

Even closer attention than is already the case must therefore be given to the form of the information. It is important to note that there are currently a wide range of information options from which to choose (including not only written material, but also video, CD-ROM and the internet) – though, according to surveys, the fact sheet is the key information source (Gre04). Furthermore, the possibility of staggering the provision of information could be more fully exploited.

See Annex J for an example of a concise information sheet for parents (Germany: *Elterninformation* [Information for Parents]). Good examples of recently developed information packs can also be found on the website of the 'UK Newborn Screening Programme Centre', a national steering committee for neonatal screening that was created in the UK in 2002 in order to ensure the quality of antenatal and neonatal screening (<http://www.newbornscreening-bloodspot.org.uk>).

4.4.3 *Timing of information provision*

The first few days after the birth are unlikely to be a suitable time for the parents to digest information about neonatal screening. Interviews with 115 parents in 13 focus groups in Chicago revealed that only a tiny minority could remember post-natal information that was provided about neonatal screening and that in around one-third of the focus groups not a single parent could remember anything about neonatal screening (Cam04). It makes more sense to discuss neonatal screening during antenatal check-ups (e.g. in the third trimester, when childbirth and the puerperium are also discussed). There is then still time to answer questions and, if necessary, to supply more information.

4.4.4 *Improving training and organisation of obstetric care*

Observers have commented on the differences that exist in the time devoted to information provision in obstetric practice and the ways in which this is managed. The discipline of the information provider also varies. All of these factors are likely to influence the quality of the information that is ultimately provided. The increase in screening programmes has brought a commensurate increase in the needs and expectations of the patients, developments which have not been adequately reflected in the training and organisation of obstetric care. If the screening programme is to be expanded, then it will be necessary to invest in the development of instruments for evaluating and testing this programme. In addition, the relevant healthcare workers will need to receive further training with regard to both the content of the information and its provision. The UK Newborn Screening Programme Centre has also published a number of documents, including a handbook for health professionals that contains the key information about the diseases for which screening is performed. In addition, guidelines are available with advice on carrying out screening. Finally, a presentation (including illustrative slides) is available for the benefit of local teams (<http://www.newbornscreening-bloodspot.org.uk/>).

4.4.5 *Information about carrier status*

The results of neonatal screening for a given disease can be expressed in one of three ways: not affected, affected or carrier. The present screening programme does not reveal carrier status among newborns since the tests are of a quantitative nature (although there is, in certain cases, some overlap between mild forms of the disorder and carrier status). Qualitative analysis may identify an abnormal protein or an abnormal DNA sequence that indicates carrier status. This means that one or both parents are also carriers and therefore has implications with regard to information provision and further investigation involving the parents and their relatives. It will therefore place greater demands on healthcare workers' time. It may also cause the parents unnecessary anxiety and concern. Furthermore, it is questionable how much of the information that is provided will sink in and still be available at the point in time when it is ultimately of value to the child itself, and at what point in its life the child ought to be given this information. The Committee views the parents as the most appropriate individuals to inform children, when the time is right, that neonatal screening has identified them as carriers.

Substantial numbers of carriers are identified during screening for sickle cell disease and carrier status is also relevant when screening for CF (see Section 3.14). It is questionable whether all parents wish to know whether they are carriers (in London it was found that around half of the carriers wanted further information; Dav00). Parents ought therefore to be given the option of forgoing information about carrier status at the point in time when the information is provided (during pregnancy, as advocated in Section 4.4.3). If, however, they should ask for carrier screening after receiving the information, then this request can be satisfied if this is medically indicated (owing to a family history of the disorder in question or, in the case of hemoglobinopathy, the geographical origin of the affected individuals). Carrier screening for CF would also require the development of a suitable screening method (see Section 3.3). Easily accessible consultation should be available (e.g. at the clinical genetics centres) for those individuals who are identified as carriers in the course of neonatal screening.

4.5 **Managing consent within an expanded screening package**

It was concluded in the previous section that the standards imposed on the provision of information with regard to the heel prick test must be no less strict if the screening programme is expanded (quite the contrary, in fact). The question

arises as to how the other component of the informed consent requirement is to be assessed in this regard. In particular, we must ask ourselves whether there are grounds for exerting any pressure on the parents, and thereby imposing limits on the voluntariness of consent. Furthermore, it is open to question whether parents should also have choices within the range of screening services that they are offered.

4.5.1 *Voluntariness of participation*

As we have seen, the basic premise of neonatal screening is that the parents are free to grant or withhold their consent to participate. In the case of a hospital birth, the heel prick is, for obvious reasons, collected at the bedside, whereas for home births a house call is made. Does this not overly compromise parents' freedom to decide? The Committee does not feel that this is the case. For example, the home visit takes place simply because after a home birth it is more convenient to carry out the heel prick in the home than elsewhere. Furthermore, the home visit means that parents do not overlook the offer of screening. Thus, the home visit is not intended to make it difficult for the parents to refuse screening. On the contrary, it is perceived as an opportunity to meet the parents and to prevent the appointment being forgotten.

Moreover, the Committee notes that 'freedom' is not the same thing as 'freedom from obligation'. This is particularly important if screening may provide substantial (health) benefits. Indeed, one argument advanced for formalising parental decision-making is the fact that the heel prick is in the child's interests and that parents are considered to make decisions with this in mind. On the other hand, the disorders in question (although they are serious) have an extremely low birth prevalence, and there are also disadvantages associated with the screening. Another argument sometimes cited in this connection is the need to create equal opportunities to health care. The underlying idea here is that a more informal programme is primarily used by people who already enjoy better health on account of their education and socio-economic background. The question is, however, whether it would not be more appropriate to tailor information to the needs of disadvantaged groups.

In the Committee's opinion, it is permissible to appeal to parents' sense of responsibility towards their children. More specifically, this means that in the event of a refusal (which, in fact, only rarely occurs; TNO04), the care provider must seek to discuss the situation with the parents in order to ascertain their motives. It may be that insufficient information has been provided or the information has not been properly communicated to the parents, or there may even be

a question of anxiety or insufficient confidence in the doctor. One can then consider to what extent the objections can be overcome. After an intensive dialogue of this type, however, the Committee feels that the decision ultimately reached by the parents will have to be respected, even if this entails a refusal to participate. The Committee rejects imposing a child protection measure in such a case, as has sometimes been advocated in the literature (Ros04). From a legal standpoint, participation would then, of course, be mandatory.

4.5.2 *Choices*

The introduction of choices for the parents would be more in keeping with the informed consent requirement, but this approach carries the risk that the level of participation might fall and the number of errors could rise. There is also a possibility that the efficiency of the programme could be impaired. On the other hand, if the neonatal screening programme were to be extended in future with disorders that are less obvious candidates for screening, then participation also becomes a less obvious course of action. There is also a danger that the screening programme itself could be called into question. This means, first and foremost, that great care must be exercised when selecting the disorders for which screening is to be performed. It is conceivable that screening may be broken down in the future into two packages: a basic package for readily treatable disorders, and a screening package comprising diseases whose inclusion is unlikely to meet with universal approval. No such division is under discussion at this point in time, since the health gain that stands to be achieved from neonatal screening has been the central criterion during the drafting of this advisory report.

Implementation

The prospect of a substantial number of disorders being added to the present neonatal screening programme also raises questions with regard to implementation. The Committee has focused its attention in the first instance on the current state of knowledge with regard to screening, but it also proposes to raise a number of points that are of interest as far as the question of introduction is concerned. These relate to the timing of information-giving and the requesting of consent, the timing of the heel prick, the amount of blood that is collected, the organisation of the National Steering Committees and the procedure for any further programme expansions that might be undertaken in the future.

5.1 Timing of information-giving and consent

As was explained in Chapter 4, the Committee does not consider the first few days after the birth as a very suitable time to inform parents about the heel prick. It would be preferable to do so at some time during the pregnancy when the parents are also provided with other relevant information. This gives them more opportunity to consider the information and to then make a well-founded decision shortly after the birth.

In practice, this means incorporating the provision of information into the programme of antenatal support. The people providing this support, who are usually obstetricians and general practitioners, should therefore be provided with the

requisite facilities. Although they do not require detailed knowledge of the disorders for which screening is performed, they do need to be able to refer people with questions (e.g. about the course of rare disorders or the possibilities for pre-natal diagnostics) to other information sources.

When information is provided, consideration must be given to all relevant aspects of the heel prick. The current informed consent procedure can be followed when the heel prick is actually collected. Having received the timely information that the Committee recommends, parents will be better prepared to make their informed choice known at that time.

5.2 Timing of the heel prick

As things currently stand, the heel prick should preferably take place on postnatal day 4, possibly on day 5, 6 or (at the latest) on day 7. The day of birth is regarded as day 0 (*Draaiboek Neonatale Screening* [National Neonatal Screening Plan]; Ins01). It is irrelevant what time of day the child is born or the heel prick is performed. The disadvantage of counting the time in days is that other systems are also used (in the hospital setting, for example) in which the day of birth is regarded as the first postnatal day.

Using the current sensitive measurement techniques, the analyses can be performed in blood specimens that have been collected from 48 hours postpartum. It is inadvisable to take blood specimens any earlier since the metabolic processes (and in particular the thyroid gland) have yet to sufficiently stabilise.

Indicating the timing of the heel prick in hours has the advantage that it avoids the above-mentioned disparities in day-based counting methods. The Committee proposes that the following wording should be included in the National Plan: ‘The heel prick should preferably be collected between 48 and 96 hours after the birth. If necessary, blood sampling can also take place even later, but this must be no more than 168 hours (7 times 24 hours) after the birth. Sampling any earlier than 48 hours postpartum is highly inadvisable.’

5.3 Required amount of blood

The blood spot card is marked with circles that are to be filled with blood. There are four of these circles in the current screening programme. In practice, one in ten of the cards has circles that are found not to have been completely filled on. Although the increase in the number of screened disorders that has been recommended by the Committee is theoretically workable with four correctly filled circles, it will therefore be necessary to ask for six circles in practice.

5.4 National Steering Committee

A National Steering Committee on Neonatal Screening (LBNS) has been operating since 2003 under the auspices of the Health Insurance Council (CVZ), on which the professionals and bodies involved in the screening programme (the vaccination authorities, RIVM, TNO/KvL (Organisation for Applied Scientific Research/Quality of Life), the Health Care Inspectorate (IGZ), the Ministry of Health, Welfare and Sport and the Dutch Association of Health and Social Care Insurance Companies) are represented. Advisory committees set up by the Dutch Society for Paediatrics (NVK) for each of the three disorders that are currently included in the screening programme report to the LBNS. The chairmen of the advisory committees have a seat on the LBNS.

The LBNS mainly monitors the overall logistics of the programme (blood specimens, timeliness, reporting, reports), whereas the advisory committees are concerned with recommendations for clinical follow-up, diagnostics and the treatment of each disease. Since it is impractical to form a new advisory committee for each disorder that is added to the programme, the Committee is considering amalgamating the advisory committees for a cluster of disorders (for example, endocrinological disorders, metabolic disorders, CF and hemoglobinopathies).

5.5 Future expansion

In our discussion of various disorders, we have stated that a great deal of research is being conducted that will open up new possibilities for the screening of newborns and the treatment of neonatal disorders. An example is the lysosomal storage diseases (Section 3.10), for which both screening techniques and treatments are being developed. It goes without saying that consideration needs to be given to these developments, and, where appropriate, there should also be scope for pilot research.

The Committee has deliberated over what procedure ought to be followed when further disorders are considered for inclusion in the neonatal screening programme. In Chapter 2 we discussed the framework within which this assessment can take place. This advisory report has been produced for the new disorders that are currently coming under consideration (partly due to the possibilities afforded by tandem mass spectrometry screening). It is possible that the National Steering Committee and the advisory committees (see Section 5.4), including any newly created Committees, could be given a role in this procedure in the future. These

Committees can formulate proposals for any expansions of the programme, whereupon the Minister may, if necessary, request advice from the Health Council.

Conclusions and recommendations

In the Committee's opinion, the classic criteria for screening are a good starting point for the assessment of neonatal screening programmes. The objectives and parameters specified in the Health Council's 1994 advisory report on *Genetic Screening* are adequate for this assessment.

According to these criteria, the key concern is the health gain that stands to be achieved for the newborn child as a result of screening. Programmes should be geared towards well-defined disorders, and proper test methods and treatments should be available. The Committee concludes that the present neonatal screening package satisfies these requirements. According to these criteria, however, there are further disorders that qualify for neonatal screening. Substantial improvements have been made in the possibilities for both diagnosis and treatment.

The Committee has evaluated the possibilities and limitations of neonatal screening for a series of disorders for which infants are screened abroad and in the Netherlands, and also for some that are not currently included. Annex E gives an overview of the disorders that have been assessed, the results of this assessment and the recommendation for neonatal screening. In addition to PKU, CHT and AGS, it is recommended that screening should be performed for the following 15 disorders (in alphabetical order):

- 1 biotinidase deficiency,
 - 2 cystic fibrosis (conditional recommendation),
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- 3 galactosemia,
- 4 glutaric aciduria type I,
- 5 HMG-CoA lyase deficiency,
- 6 holocarboxylase synthase deficiency,
- 7 homocystinuria,
- 8 isovaleric acidemia,
- 9 long-chain hydroxyacyl CoA dehydrogenase deficiency
- 10 maple syrup urine disease,
- 11 MCAD deficiency,
- 12 3-methylcrotonyl-CoA carboxylase deficiency,
- 13 sickle cell disease,
- 14 tyrosinemia I,
- 15 very-long-chain acyl-CoA dehydrogenase deficiency.

In the case of the disorders numbered 1 and 3-15, it is possible that early diagnosis may prevent a great deal of irreversible damage to health. Neonatal screening for CF (number 2) can greatly improve the patients' feeding status and considerably reduce morbidity. As was explained in 3.3, a better screening method for CF is needed in order to avoid much follow-up investigation in non-patients. The Committee recommends that research into test methods for CF screening should be commissioned in the near future.

Treatment of the disorders consists of administering vitamins (numbers 1, 6, 7 and 12) or carnitine (numbers 4, 5, 8 and 12, and possibly 11), possibly in conjunction with a diet (numbers 3, 5, 7-12, 14 and 15), antibiotics and enzymes (number 2), or else transfusions and infection prophylaxis (number 13). In the case of certain disorders (numbers 1-3, 5, 6, 8 and 12), the disease will manifest itself in some patients in week 1 postpartum, while this is unusual in others.

CF, MCAD deficiency and sickle cell disease are fairly common (more than ten newborns per year in the Netherlands), whereas the other disorders are rare. The total number of children identified by screening as having a disorder now averages 88 per year (82 - 94). The recommended expansion is expected to lead to an average of 177 detections per year (159 - 195; not including CF). If CF is included, the average is 232 per year (214 - 250). As was mentioned in Chapter 3, the screening will unintentionally result in a few patients with disorders that are difficult or impossible to treat being diagnosed shortly after birth. Expansion will also lead to an increase in the number of false-positives. For the disorders screened by tandem mass spectrometry, more than 200 newborns per year are likely to fall into this Category (Sch03), whereas a relatively small number of

follow-up investigations are required for the other disorders. Estimates of the number of follow-up investigations associated with sickle cell disease carrier status vary markedly.

The Committee has compared its conclusions and recommendations with recent announcements concerning neonatal screening abroad.

An advisory report on newborn screening was recently published in the United States at the request of the Maternal and Child Health Bureau (MCH05). The fundamental tenets of this report (included in Annex C) have been worked up into a score for various disorders. According to the advisory report, 29 disorders are candidates for screening, with MCAD deficiency recording the highest score and CF the lowest. The present advisory report recommends screening for fewer disorders. The difference lies primarily in the evaluation of the health gain that stands to be derived: the US list of 29 diseases contains several that can only be expected to provide a minor benefit. Furthermore, that list features several disorders for which screening produces a substantial overlap with non-treatable disorders.

In the UK, the Human Genetics Commission has recently addressed the question of whether it is possible either to screen the entire genome in newborns or merely those regions of the genome that differ from individual to individual. The UK committee rejects this proposition on account of ethical, legal and social objections (HGC05). The Committee that has produced the present advisory report is also unwilling to allow this type of neonatal testing, which would reveal both untreatable disorders and disorders that only occur later in life.

A decision was recently taken in Germany to extend neonatal screening to include 14 disorders (Bun04). The key differences between the German situation and the list recommended in this advisory report lie in the omission of sickle cell disease, which is due to the different composition of the population, and CF, for which the evidence of health gain as a result of early treatment is still regarded as insufficiently certain. There is also some difference in the assessment of the health gain that might be achieved in the case of a few rare disorders.

Expansion of the screening programme imposes further demands with regard to the provision of information. In view of the fact that those being tested are not mentally competent, the parents make a decision for, and in the interests of, their newborn child. That decision should be based on proper information. Given the complexity and the differing information needs, it is possible to offer the information in a stratified manner, i.e. as a general part with appendices and possibly references to websites, video clips, etc. The Committee recommends that this information should also be provided in several other languages in addition to

Dutch. Mention should also be made of the programme's limitations (e.g. the fact that follow-up investigation may be necessary and that not all disorders are detected). Screening for sickle cell disease and cystic fibrosis requires the provision of additional information concerning carrier status. The information should be formulated in such a way that parents are able to give truly informed consent.

The Committee does not consider the timing of the current information provision to be ideal. It recommends that information provision and the discussion of informed consent should take place during the pregnancy (e.g. during the third trimester in conjunction with an antenatal check-up, so that there is time to answer questions and provide more detailed information. The Committee also considers it important that the information should be evaluated at the appropriate time.

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- A The request for advice
 - B The committee
 - C Genetic screening criteria
 - D Disorders mentioned in the literature for which neonatal screening is performed
 - E Overview of disorders and ratings
 - F Overlap among disorders screened by mass spectrometry
 - G Specificity of neonatal screening by tandem mass spectrometry
 - H Sensitivity and specificity of current cystic fibrosis screening methods
 - I Written information on the heel prick
 - J Information for parents
 - K Costs of neonatal screening
 - L Abbreviations

Annexes

The request for advice

On 12 August the State Secretary of Health, Welfare and Sport addressed the following request for advice to the President of the Health Council (letter reference: IBE/E 2399824):

In the “Monitoring Report on Ethics and Health 2003”, which was published by the Centre for Ethics and Health (CEG) on 16 May, the Health Council considered the ‘alerting’ advisory report entitled “Screening of Newborns for Congenital Metabolic Diseases”. The findings of a Health Council-organised workshop on technical, ethical and legal aspects provided a useful platform for this advisory report. It is clear from this report that various new developments are taking place in the field of neonatal screening. Improvements in analytical technology are making it possible to rapidly and reliably detect a wide range of disorders, especially using mass spectrometry. This should pave the way for a considerable scaling up of the heel prick screening programme, which will also make it feasible to screen for non-treatable disorders.

These developments are giving rise to questions from various quarters regarding neonatal screening. Some of these questions come from medical researchers, some from clinicians and others from representatives of patient organisations. The questions relate to screening by mass spectrometry, the changing prevalence of certain diseases, and the extent of the health gain justified by neonatal screening. In many cases, observers are asking whether certain disorders ought not to be included in the screening programme.

In the light of these developments and in response to the above-mentioned 'alerting' advisory report, I would ask you to advise me on the current state of knowledge with regard to neonatal screening.

At the same time, I would like you to consider whether the screening criteria formulated by the Health Council some time ago, as outlined in the advisory reports entitled "Heredity: Science and Society" and "Genetic Screening", are still adequate and whether these criteria are sufficiently specific to be applied to the neonatal screening programme.

An important point to consider in connection with these criteria is the concept of 'treatability'. Following consultation between ourselves, it has been decided that the Health Council will publish a separate advisory report on this topic. You will receive a formal request to this effect in due course. I anticipate that some of the results of that advisory report will prove useful for the advisory report on neonatal screening and that this will be predicated on the basic principle that utmost caution is required when screening for untreatable or unpreventable disorders.

I then ask you to indicate, partly on the basis of your answer to the first question, which disorders should be considered for inclusion in the neonatal screening programme.

Finally, would you kindly explore the ethical, legal and social aspects of this issue? What moral questions will be raised by the expansion of neonatal screening? Will it still be possible to satisfy the requirement of express consent? I look forward to receiving your advisory report in late 2004.

Yours sincerely,
The State Secretary of Health, Welfare and Sport,
Clémence Ross-van Dorp

The Committee

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gynaecologist, University Medical Centre, Utrecht
 - Prof. MF Niermeijer, *Vice-Chairman*
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Professor of Community Genetics; VU University Medical Centre,
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 - Prof. JCJ Dute
Professor of Health Law; Erasmus Medical Centre, Rotterdam
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- Dr PA Bolhuis, *Secretary*
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The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Genetic screening criteria

Criteria from the Health Council's 1989 advisory report 'Heredity: Science and Society'

- 1 The natural course of the disorder in question should be well known. The group of people to be tested should also be fully informed of this.
- 2 Prevention or treatment of the disorder should be possible. Accordingly, the screening of newborns or of young adults can only be justified where prevention or treatment (in those individuals detected as having an abnormality) can be expected to produce substantial results.
- 3 The test used should be reliable and should have a satisfactory predictive value. Those being tested should be aware that the screening test is sometimes not diagnostically specific, so that supplementary diagnostic investigation may sometimes be required. The test should clearly distinguish between sufferers, potential sufferers and carriers (i.e. those who have no heightened personal genetic risk of getting a disease but who do run such a risk of having a handicapped child).

The benefits of screening for those who (correctly) receive a positive result from the screening should be proportionate to the drawbacks for those who (incorrectly) have a positive (false positive) or negative (false negative) result. These drawbacks are: tests which (in fact) prove to be unnecessary in the case of a false positive sometimes including surgery. In the case of a false negative, no further action is taken.

- 4 Informed consent is vitally important. Those participating in the study must do so entirely voluntarily, which implies that neither direct nor indirect compulsion should be applied. Another condition is that participants should be well informed concerning the nature and significance of the study as well as about the risks attached to it. The emotional reactions of those involved when
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confronted with a correct or incorrect test result or the suspicion that an abnormality is present are often underestimated. Accordingly, when setting up a screening programme it is necessary to inform potential participants about this.

- 5 During the programme, the privacy of those involved must be respected. Screening involves a very real and distinct risk that certain individuals will be stigmatised, thereby damaging their social position. Strenuous efforts should be taken to avoid such a risk, including exercising professional secrecy.
- 6 It is necessary to maintain contact with general practitioners and others who will have access to the results of screening and who must provide support and guidance to individuals being tested.

It is essential that the benefits of screening are reasonably proportional to the possible drawbacks (GR89).

The Wilson and Junger criteria

- 1 The condition sought should be an important health problem
- 2 There should be an accepted treatment for patients with recognised disease
- 3 Facilities for diagnosis and treatment should be available
- 4 There should be a recognisable latent or early symptomatic stage
- 5 There should be a suitable test or examination
- 6 The test should be acceptable to the population
- 7 The natural history of the condition, including development from latent to declared disease, should be adequately understood
- 8 There should be an agreed policy on whom to treat as patients
- 9 The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
- 10 Case-finding should be a continuing process and not a 'once and for all' project.

Criteria from the Health Council's 1994 advisory report 'Genetic Screening'

- 1 A genetic screening programme must relate to a health problem or to a condition which can lead to such a problem in those being tested or in their descendants.
 - 2 The target group of the screening programme must be clearly defined.
 - 3 The purpose of the programme must be to enable the participants to determine the presence or the risk of a disorder or carrier status, and to take a decision on the basis of that information.
 - 4 Practical courses of action must be open to the participants.
 - 5 Participation in a genetic screening programme should be completely voluntary and should be conditional on consent based on good information.
 - 6 The target group should be supplied with good quality, comprehensible information.
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- 7 A test method should be available which is suited to the objective of the screening.
 - 8 There should be sufficient facilities for follow-up testing, to carry out the selected courses of action and to inform and support the participants.
 - 9 The procedures used for the storage of medical information and cellular material must incorporate adequate measures to protect both the personal privacy of the participants and their rights regarding their personal data and cellular material.
 - 10 If scientific research is carried out within the framework of screening, the participants should be properly informed about this in advance.
 - 11 Provision should be made for continual quality assurance of the effectiveness, efficiency and safety of the test procedure, any follow-up work, as well as information and support given to the participants.
 - 12 When weighing up the benefits and drawbacks for the participants in the programme, the final balance should be clearly biased towards to benefits. To assist with this evaluation, those proposing a screening programme must provide information about:
 - a the prevalence of the disease or disorder in the target group;
 - b the natural course of the disorder, and the variation in degrees of severity;
 - c those target groups which are eligible for testing and the considerations which led to selection of the proposed target group and the proposed time of life for testing;
 - d the specificity, sensitivity and predictive value of the test method to be used and the burden which such testing imposes on participants;
 - e the available courses of action if a health problem or carrier status is revealed;
 - f the time allowed by the procedure for consideration and possible implementation of the choices made;
 - g the potential psychological, social and other repercussions (both positive and negative) of an offer and of participation or non-participation in the screening, for the person to be tested and for members of their family or for groups within the community;
 - h the likelihood of erroneous results, the possible consequences of this for participants and the measures taken to limit any harm which such an error might cause;
 - i what guarantees there are to prevent participants experiencing unjustified impediments (as a result of their participation or non-participation in the screening programme or follow-up testing) to obtaining employment or private insurance cover;
 - j The costs which are linked to the screening and to the attainment of the requisite infrastructure.
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- 1 Neonatal screening, an accepted medical intervention
 - 1.1 Newborn screening to detect treatable metabolic and other disorders is now an accepted part of routine neonatal health care in almost all countries with well-developed medical services, and is becoming established in many countries in less well-developed regions.
 - 1.2 Detailed recommendations for screening policy will vary from country to country and region to region, depending on local economic, political and medical factors and public health organisation.
 - 1.3 Guidelines have been published for neonatal screening in general for many parts of the world as well as for specific disorders.
 - 1.4 Some guidelines for neonatal screening have stipulated the need for evidence derived from high-quality randomised controlled trials showing benefit from presymptomatic diagnosis. Such evidence may not always be obtainable. Either there is already so strong a perception of benefit that trials will not be ethical (for example with phenylketonuria or hypothyroidism), or else the very large numbers required in each arm of the trial for relatively rare diseases and the prolonged follow-up required make formal trial virtually impossible.
 - 1.5 There are several general principles about genetic screening and testing that are widely accepted. These have been included in a World Health Organisation document "Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Service". The International Society for Neonatal Screening endorses in the main these principles and offers the following general guidance for the conduct of neonatal screening programs.

 - 2 General Recommendations

For a range of disorders neonatal screening is recommended provided that:

 - i There is considered to be a direct benefit to the neonate from early diagnosis;
 - ii The benefit is reasonably balanced against financial and other costs;
 - iii There is a reliable test suitable for neonatal screening;
 - iv There is a satisfactory system in operation to deal with diagnostic testing, counselling, treatment and follow-up of patients identified by the test.

 - 3 Organisation of Programmes
 - 3.1 The screening programme comprises the sum of the operations necessary to ensure that as far as possible all neonates in the target population are tested, all necessary follow-up is done and all cases found are adequately treated with a minimum of delay and equitably.
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- 3.2 Screening programmes should be organised and controlled by a body in which health professionals participate. It is recommended that the body take advice about the general operation of the screening programme from multidisciplinary expert sources.
 - 3.3 Screening tests should where possible be carried out in large centralised laboratories, so that costs can be kept low and expertise gained and kept.
 - 3.4 Laboratories should have appropriate expertise, preferably combined with some form of accreditation. Where a system exists, external assessors should review programmes to ensure that suitable tests, quality assurance, cut-off points, follow-up procedures, and screening audit processes are in operation.
 - 3.5 Regular assessments of screening programme performance should be undertaken and must include test sensitivity, specificity, positive predictive value, timeliness of reporting, and outcome of diagnosed patients. Outcome assessment should include short and long-term evaluation.
 - 3.6 Health care authorities have a responsibility to ensure that tests are available to all neonates born in their region.
- 4 Legal and Ethical Considerations
- 4.1 The public should be kept well informed about screening programmes. As far as possible, written information should be provided to parents before testing.
 - 4.2 Legal considerations will vary widely according to local laws.
 - 4.3 Where neonatal screening is mandated, there should be provision for parents to refuse the test on behalf of their neonate, where there is some religious or other ground for objecting to participation. Parents refusing the test should be made aware of the possible consequences.
 - 4.4 The privacy of the patient and the family should be carefully protected, and results not disclosed other than to appropriate health professionals without the consent of the parents. Specific attention must be paid to the possible future detrimental effects of such information.
 - 4.5 Each programme should develop a policy for the storage and possible later use of neonatal specimen cards, including provisions for the protection of the privacy of the individual and family.
- 5 Research
- 5.1 Continuing research into the natural history of disorders actually or potentially detectable by screening and into biochemical characteristics of particular disorders which might prove to be the basis for useful screening tests in the future is a valid part of any screening programme. Research into the effectiveness of early treatment is also vital, and such research should be facilitated by the screening programme.
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- 6 Recommendations for screening for specific disorders
 - 6.1 Screening should be recommended unequivocally for conditions where there is a demonstrated benefit from early diagnosis, the benefit is balanced against financial and other costs, there are suitable tests, and follow-up services are available for management. (As demonstration of benefit for most disorders relevant to neonatal screening has seldom been achieved by randomised control trials, see section 1.4, lower orders of evidence should be taken into consideration).
 - 6.2 Screening can be recommended, if resources permit, for conditions for which there is a demonstrated benefit from early diagnosis, suitable tests and follow-up services are available, but the benefit may or may not be balanced against financial and other costs depending on the available technology, the frequency of the disorder in the region and other local circumstances.
 - 6.3 A pilot screening programme should be recommended for disorders where benefit to the neonate from early diagnosis appears probable, it is likely the benefit will be balanced against financial and other costs if suitable technology is available, there are tests available which are very likely to be suitable, and there are follow-up services available.
 - 6.4 Screening tests should not be recommended if indications of advantage from early diagnosis are lacking or uncertain, or the test is unsuitable, or does not detect those cases in which there might be an advantage.
 - 6.5 There are several disorders which may be detected as an incidental finding when screening for a recommended disorder. Properly constituted research programmes into the utility of screening for these conditions should be encouraged.
-

Maternal and Child Health Bureau. Newborn Screening: toward a uniform screening panel. Report for public comment. Executive summary (MCH05).

Establishing Principles

The following basic principles were developed as a framework for defining the criteria by which to evaluate conditions and make recommendations.

- 1 Universal newborn screening is an essential public health responsibility that is critical to improve the health outcome of affected children.
 - 2 Newborn screening policy development should be primarily driven by what is in the best interest of the affected newborn, with secondary consideration given to the interests of unaffected newborns, families, health professionals, and the public.
 - 3 Newborn screening is more than testing. It is a coordinated and comprehensive system consisting of education, screening, follow-up, diagnosis, treatment and management, and program evaluation.
-

- 4 The medical, home and the public and private components of the screening programs should be in close communication to ensure confirmation of test results and the appropriate follow-up and care of identified newborns.
 - 5 Recommendations about the appropriateness of conditions for newborn screening should be based on the evaluation of scientific evidence and expert opinion.
 - 6 To be included as a primary target condition in a newborn screening program, a condition should meet the following minimum criteria:
 - It can be identified at a phase (24 to 48 hours after birth) at which it would not ordinarily be clinically detected;
 - A test with appropriate sensitivity and specificity is available for it;
 - There are demonstrated benefits of early detection, timely intervention and efficacious treatment of the condition being tested.
 - 7 The primary targets of newborn screening should be conditions that meet the criteria listed in #6 above. The newborn screening program also should report any other result of potential clinical significance.
 - 8 Centralized health information data collection is needed for longitudinal assessment of disease-specific screening programs.
 - 9 Total quality management should be applied to newborn screening programs.
 - 10 Newborn screening specimens are valuable health resources. Every program should have policies in place to ensure confidential storage and appropriate use of specimens.
 - 11 Public awareness coupled with professional training and family education is a significant program responsibility that must be part of the complete newborn screening system.
-

D

Disorders mentioned in the literature for which neonatal screening is performed

Literature : International Society for Neonatal Screening: Neonatal Screening in Europe (<http://www.isns-neoscreening.org/facts.htm>), Newborn screening U.S.A. (<http://genes-r-us.uthscsa.edu/nbsdisorders.pdf>)

Adrenogenital syndrome
Argininaemia (arginase deficiency)
Argininosuccinase (argininosuccinate lyase) deficiency
Biotinidase deficiency
Carbamoyl phosphate-synthase deficiency
Carnitine palmitoyl transferase deficiency type I
Carnitine palmitoyl transferase deficiency type II
Carnitine/Acylcarnitine translocase deficiency
Carnitine transporter deficiency
Citrullinaemia
Congenital hypothyroidism
Cystic fibrosis
2,4 dienoyl-CoA reductase deficiency
Deafness
Duchenne muscular dystrophy
Galactosemia
Glucose-6-phosphate dehydrogenase deficiency
Glutaric aciduria type I

Holocarboxylase synthase deficiency
Homocystinuria
Hyperammonaemia, Hyperornithinaemia, Homocitrullinaemia (HHH) syndrome
HMG-CoA lyase (3-hydroxy-3-methylglutaric acid-CoA-lyase) deficiency
Isobutyryl-CoA dehydrogenase deficiency
Isovaleric acidemia
Long-chain hydroxyacyl-CoA dehydrogenase deficiency
Malonic aciduria
Maple Syrup Urine disease
Medium-chain Acyl-CoA dehydrogenase deficiency
Medium-chain 3-ketoacyl-CoA thiolase deficiency
3-Methylcrotonyl-CoA carboxylase deficiency
Methylmalonic acidemia
2-Methylbutyryl-CoA dehydrogenase deficiency
3-Methylglutaconyl-CoA hydratase deficiency
Mitochondrial acetoacetyl-CoA thiolase (3-ketothiolase) deficiency
Multiple acyl-CoA dehydrogenase deficiency
Nonketotic hyperglycinaemia
5-Oxoprolinuria
Phenylketonuria
Propionic acidemia
Sickle cell disease
Short-chain acyl-CoA dehydrogenase deficiency
Short-chain hydroxyacyl-CoA dehydrogenase deficiency
Thalassemia
Tyrosinemia
Trifunctional protein deficiency
Very long-chain acyl-CoA dehydrogenase deficiency

E**Overview of disorders and ratings**

Disorder (deficiency)	Description#	Analytical method#	Treatment#	Health gain# Category	Section	Committee's recommenda- tion #
α -antitrypsin	+	+	+/-	2	3.1	-
Adrenogenital syndrome	+	+	+	1	1.1.3	n.a.
Biotinidase	+	+	+	1	3.2	+
CF	+	+	+	2	3.3	+
CHT	+	+	+	1	1.1.2	n.a.
Carnitine disorders	+/-	+/-	+/-	1,2	3.12.2	-
Cystinosis	+	-	+	1	3.10.2	-
Duchenne	+	+	-	3	3.4	-
Fabry's	+	-	+/-	2	3.10.2	-
Galactosemia	+	+	+	1	3.5	+
Gaucher's	+	-	+	2	3.10.2	-
G6PD	+	+	+	2	3.6	-
Glutaric acidemia type I	+	+/-	+	1	3.7	+
HMG-CoA lyase	+	+	+	1	3.9.2	+
Holocarboxylase	+	+	+	1	3.2, 3.9.2	+
Homocystinuria	+/-	+	+/-	1	3.8	+
Isovaleric acidemia	+	+	+	1	3.9.1	+
LCHAD	+	+	+	1	3.12.2	+
MCAD	+	+	+	1	3.12.1	+
3MCC#	+	+	+	1	3.9.2	+
Methylmalonic acidemia	+/-	+	-	2,3	3.13.1	-
MSUD	+	+	+	1	3.11	+

PKU	+	+	+	1	1.1.1	n.a.
Pompe's	+	+	+/-	2	3.10.2	-
Propionic acidemia	+	+	-	2	3.13.2	-
SCAD#	+	+	-	3	3.12.2	-
Sickle cell disease	+	+	+	1	3.14	+
TFP#	+	+	-	2	3.12.2	-
Thalassemia	+	+	+/-	2	3.14	-
Tyrosinemia I	+	+	+	1	3.15	+
Urea cycle disorders	+	+/-	-	2	3.16	-
VLCAD	+	+	+	1	3.12.2	+

Description: clinical course and definition of the disorder.

Analytical method: good sensitivity and specificity.

Treatment: treatment or prescription that results in considerable improvement.

Health gain: health gain obtainable from screening.

Recommendation: + and - , recommended/not recommended for screening.

Abbreviations not used elsewhere:

n.a. : not applicable (is included in the current screening programme),

3MCC: 3-methylcrotonyl coxylase deficiency,

SCAD: short-chain acyl CoA dehydrogenase deficiency,

TFP: trifunctional protein.

F

Overlap among disorders screened by mass spectrometry

If disorders are detected by tandem mass spectrometry, some overlap may occur owing to the presence of abnormal amounts of a metabolite in patients with more than one disorder. In the following overview, this overlap is indicated for disorders that fall into category 1. If it is possible to base detection on various derivatives, we indicate which one is meant.

Biotinidase deficiency

Identification is based on 3-hydroxyisovalerylcarnitine. Overlap with holocarboxylase synthase deficiency (1), HMG-CoA lyase deficiency (1), ketothiolase deficiency (3) and 3-methylcrotonyl-CoA carboxylase deficiency (1). Based on propionylcarnitine, there is overlap with holocarboxylase synthase deficiency (1), propionic acidemia (2) and methylmalonic acidemia (2).

Carnitine/acylcarnitine translocase deficiency

Identification is based on a low concentration of free carnitine and high concentrations of many long-chain acyl- and hydroxyacylcarnitines. Overlap with carnitine palmitoyl transferase deficiency type II (2), long-chain hydroxyacyl-CoA dehydrogenase deficiency (1), multiple acyl-CoA dehydrogenase deficiency (3) and very long-chain acyl-CoA dehydrogenase deficiency (1).

Carnitine palmitoyl transferase deficiency type I

Identification is based on a high concentration of free carnitine and low concentrations of palmitoyl and oleoylcarnitine. Overlap with carnitine palmitoyl transferase deficiency type II (2), carnitine/acylcarnitine translocase deficiency (2), long-chain hydroxyacyl-CoA dehydrogenase deficiency (1),

multiple Acyl-CoA dehydrogenase deficiency (3) and very long-chain Acyl-CoA dehydrogenase deficiency (1).

Glutaric aciduria type I

Identification is based on glutarylcarnitine. Overlap with multiple acyl-CoA dehydrogenase deficiency (3), but distinguishable from this condition by increased concentrations of other acylcarnitines.

Holocarboxylase synthase deficiency

For overlap see biotinidase deficiency.

Homocystinuria caused by deficiencies of cystathionine beta synthase, methionine adenosyltransferases, S-adenosylhomocysteine hydrolase, glycine N-methyltransferase. Overlap with other hypermethioninaemia is the same as for severe liver disease (1-3) and tyrosinemia (1-3). Although a separate, specific tandem mass spectrometry analysis is available, this requires additional analysis.

HMG-CoA lyase deficiency

No overlap based on 3-methyl-3-hydroxyglutarylcarnitine, but there is overlap with 3-hydroxyisovaleryl, 2-methyl-3-hydroxybutyrylcarnitine (see biotinidase deficiency).

Isovaleric acidemia

Overlap with pivaloyl-containing antibiotics, 2-methylbutyryl-CoA dehydrogenase deficiency (3) and multiple acyl-CoA dehydrogenase deficiency (3).

Long-chain hydroxyacyl-CoA dehydrogenase deficiency

Overlap with trifunctional protein deficiency (2).

Medium-chain acyl-CoA dehydrogenase deficiency

Overlap with multiple acyl-CoA dehydrogenase deficiency (3).

3-Methylcrotonyl-CoA carboxylase deficiency

Overlap based on tiglyl- and 3-methylcrotonylcarnitine with propionyl-CoA carboxylase deficiency (1), biotinidase deficiency (1), holocarboxylase synthase deficiency (1) and ketothiolase deficiency (3).

Tyrosinemia type I

Overlap with tyrosinemia type II (2) and type III (3).

Specificity of neonatal screening by tandem mass spectrometry

The specificity of a screening method depends on what cut-off points are chosen for the laboratory results. If broader parameters are applied, there is less risk of a false-negative result (in other words the sensitivity increases). Narrower parameters result in higher specificity (fewer false-positive results) and therefore fewer follow-up investigations.

The specificity of neonatal screening by tandem mass spectrometry has been investigated in the United States, Australia and Germany (Zyt01, Wil03). The following tandem mass spectrometry data have been published with regard to the disorders which the Committee recommends for inclusion in the neonatal screening programme (Zyt01, Sch03). A specificity of 98.85 per cent of the total programme has been published for the screening performed in Australia (Wil03). By way of comparison, the specificity for AGS in the current Dutch screening programme is 99.98 per cent, and for CHT and PKU it is 99.9 per cent (TNO04).

The researchers consider it likely that virtually all of the patients with the disorders for which tandem mass spectrometry screening is performed will be detected; the sensitivity would therefore be almost 100 per cent (Wil03, Sch03).

Table 2 Specificity of tandem mass spectrometry screening by disorder (in percent).

Disorder	Specificity	
	Zyt01	Sch03
Glutaric aciduria type I	99.98	99.98
HMG-CoA lyase deficiency	99.98	-
Holocarboxylase synthase deficiency	-	99.99
Homocystinuria	99.96	-
Isovaleric acidemia	99.98	99.99
Long-chain hydroxyacyl CoA dehydrogenase deficiency	>99.99	>99.99
Maple syrup urine disease	99.99	99.99
MCAD deficiency	99.98	99.98
3-methylcrotonyl-CoA carboxylase deficiency	99.98	-
Tyrosinemia I	99.98	99.98
Very-long-chain acylCoA dehydrogenase deficiency	>99.99	99.98
Phenylketonuria	99.96	99.95

H

Sensitivity and specificity of current cystic-fibrosis screening methods

The sensitivity and specificity of CF screening is dictated by the chosen cut-off value of increases in immunoreactive trypsinogen (IRT), the quality of the so-called sweat test, and the number of mutations tested in newborns with an elevated IRT.

Research in the US (Com04) among more than 323,000 newborns produced the following results. The aim was to increase the specificity of the screening by following up an elevated IRT value with DNA testing and only then conducting a sweat test. A panel of 27 mutations was used. The diagnosis of CF was ultimately made 112 times in the investigated group. In two of these infants, no increased IRT-value was detected and the screening was therefore false-negative. In the top 0.2 per cent of IRT values a sweat test was performed even if no mutation was detected. Three patients were identified via this route. Mutation analysis was performed in the top 5 per cent of IRT values (approximately 16,000 newborns). Two mutations were detected 82 times, and one mutation 957 times. In the latter group, a sweat test was conducted which ultimately proved negative in 6 of the 25 patients in this group. In these 6 patients, the diagnosis was made on clinical grounds. This means that the screening protocol failed in 8 of the 112 patients.

Prevalence in Massachusetts is around 1:3000 and in the Netherlands it is 1:3600. Allowing for the fact that 200,000 babies are born per year in the Netherlands, this would mean:

- 55 patients, 1 of whom would be missed (on average) because of a low IRT;
- 40 patients with two detected mutations;
- approximately 450 newborns with 1 mutation; where if a sweat test were to be performed on 12 patients, 10 of them would have a positive sweat test;
- and a sweat test is performed on around 200 newborns with IRT >99.8 per cent and no mutation, revealing 2 patients.

The adoption of this protocol in the Netherlands would therefore reveal 52 patients per year, miss 3 patients and require a sweat test in newborns without CF on around 640 occasions.

The results of France's national neonatal CF screening programme have been published (Mun05, Bro05). The method used was a two-stage screening programme: IRT testing followed by a mutation panel initially consisting of 20 CF mutations and subsequently (from 2004 onwards) 30 mutations. Whenever one or two mutations were detected, the child was invited to undergo a sweat test at a cystic fibrosis centre. Patients found to have a high IRT without any known mutation or a high IRT and refusal of DNA testing were offered a repeat IRT test on day 21, with a sweat test being offered to patients whose trypsin remained persistently elevated.

A total of 1,143,248 newborns were screened in 2002 and 2003. The group with elevated IRT (the highest being 0.68 per cent) consisted of 7,782 newborns, 7,604 of whom underwent a DNA test. Either one or two CF mutations were detected in 820 children, with 169 having two mutations – and, in all probability, CF. In 65 of the remaining 651 infants (10 per cent), the diagnosis of CF was confirmed by means of a sweat test. It is still not known whether 44 of these 651 children did, in fact, have CF (17 have been lost to follow up, 18 await further investigation and 9 have died). In 740 of the nearly 7,000 children with a high IRT but no known DNA abnormality, an increase was also detected on a second occasion and a sweat test was performed, whereupon the diagnosis of CF was made in 12 cases. In the case of the children with high IRTs for whom DNA testing was refused, CF was diagnosed in 3 cases.

A total of 1,578 newborns have been seen at a CF centre, 249 (15.8 per cent) of whom turned out to have CF. In 169 cases, the diagnosis was based on two known mutations, in 65 it was based on one known mutation and a high sweat test result, in 12 on a repeatedly high IRT without any known mutation but with a high sweat test score, and in 3 on a repeatedly high IRT, refusal of DNA testing and a high sweat test score. Furthermore, in 33 of the 249 infants the CF diagnosis was already known before the screening result (5 prenatal diagnostics; 28

meconium ileus). CF was detected during neonatal screening in 1 in 4,590 newborns; with at least 7 patients being missed (Bro05).

A total of 586 children in France have been identified as healthy carriers of CF in the course of the screening programme. The carrier frequency among the newborns with a high IRT was 1/13. This study reports on years in which the panel of 20 mutations was used. If the 30-mutation panel had been used, 86 per cent of the mutations would have been detected (instead of 82 per cent).

If it were extrapolated to Dutch conditions, this form of screening would, at a rough estimate, produce the following annual findings (subject to some uncertainty, since the precise number of patients in France is not yet known):

- 1,360 newborns with an elevated IRT, including
- 30 patients with two mutations (using a panel of 20 mutations),
- 84 newborns with one mutation, with 8-9 being identified as patients after a sweat test and continuing uncertainty with regard to around 5 children,
- more than 1,200 newborns without a detected mutation, with 140 of them being found to have an elevated IRT at the second test on day 21; a further 2 to 3 patients are identified in the sweat test, and 5 to 8 cases are still uncertain,
- at least 2 patients would be missed.

Adoption of the French protocol in the Netherlands would identify approximately 41 patients per year, miss at least 2 patients, and produce an unclear outcome in 10 to 13 cases. 1,200 repetitions of the IRT test would be required and around 210 sweat tests would be performed in newborns without CF.

Thus the methods employed in the United States and France have relatively poor sensitivity (i.e. a number of patients are missed) and specificity (i.e. a great deal of clinical investigation is still required in unaffected newborns after IRT and mutation analysis).

Written information on the heel prick

Heel-prick testing in newborns

Dear parent(s),

Every child in the Netherlands is screened for a number of congenital disorders shortly after birth:

- AGS (adrenogenital syndrome). This is a disease of the adrenal gland which disrupts hormone production. AGS occurs in 1 in 12,000 children.
- CHT (congenital hypothyroidism). This disorder is caused by an underactive thyroid gland. CHT occurs in more than 1 in 3,000 children.
- PKU (phenylketonuria). This is an inherited metabolic disorder. PKU occurs in 1 out of 18,000 children.

Rapid detection is extremely important in order to prevent or limit damage to physical and mental development. If detected at an early stage, these disorders are readily treatable (PKU with a diet, CHT and AGS with medicines).

The screening and the result

Within one week of the birth an obstetrician, district nurse, general practitioner or maternity home-care assistant visits you at home and collects a few drops of blood from your child using a heel prick. If your child is still in hospital, the heel prick is performed there. The blood is screened in a laboratory. If the amount of blood collected proves to be insufficient for the tests, the heel prick is repeated.

You will *not* receive any notification if the result of the laboratory test is *good*.

Sometimes it is not possible to determine the result for certain straight away, in which case a second heel prick is collected (generally no more than two weeks after the first heel prick). You will always be notified of the results of this second test.

Privacy

The personal and medical data from the blood tests are included in a register which is governed by the provisions of the Personal Data Protection Act (WBP). The data are used exclusively for the purpose for which they were provided.

Medical research

The laboratory stores the remainder of the blood that has been collected for 1 year after the heel-prick test so that it can, in exceptional circumstances, check the previous test. The remaining blood is then available for a period of 4 years for medical research into other congenital abnormalities in order to investigate whether it is possible to develop prevention programmes for these conditions. This research is conducted anonymously. Your consent will be requested separately if the researcher should nevertheless wish to make use of your child's personal data.

Should you have objections to the remaining blood being made available for anonymous medical research, you can have this noted on the blood-spot card. The remaining blood is then destroyed 1 year after sampling.

We hope that you will give your consent to the screening of your child for the congenital diseases AGS, CHT and PKU. You will not incur any costs in connection with the screening procedure.

The vaccination authorities

If your child has still not undergone a heel-prick test 8 days after the birth, you should telephone the vaccination authorities in your region:

Groningen	050-3686350
Friesland	050-3686350
Drenthe	050-3686350
Overijssel	0529-455717
Flevoland	0529-455717
Gelderland	026-4429242
Utrecht	0346-550040
North Holland (except for Amsterdam)	0346-550040
Amsterdam	020-5555460
South Holland (except for Rotterdam)	079-3418238
Rotterdam	010-4339517
Zeeland	0113-224080
Noord-Brabant	013-5400688
Limburg	046-4529910

In Nederland wordt elk kind kort na de geboorte onderzocht op enkele aangeboren ziektes. Snelle opsporing en behandeling zijn van groot belang om schade aan de lichamelijke en geestelijke ontwikkeling te voorkomen. Deze folder beschrijft om welke ziektes het gaat en hoe het onderzoek bij uw kind zal plaatsvinden.

All children born in The Netherlands are tested soon after birth for certain congenital disorders and diseases. Early identification and treatment are of the utmost importance if baby's physical and psychological development is to progress normally. This leaflet explains which disorders and diseases the tests look for, and how the tests are carried out.

Aux Pays-Bas, tous les enfants sont examinés peu après leur naissance pour détecter la présence éventuelle de plusieurs maladies congénitales. La rapidité du dépistage et du traitement sont d'une importance capitale pour la prévention des troubles du développement physique et mental. Ce dépliant indique de quelles maladies il s'agit et comment s'effectuera l'examen de votre enfant.

In den Niederlanden wird jedes Kind kurz nach der Geburt auf einige vererbte Fehler untersucht. Die schnelle Entdeckung und die Behandlung sind von großer Bedeutung für die Vorbeugung gegen einen Schaden bei der körperlichen und geistigen Entwicklung. Diese Broschüre informiert Sie über die Krankheiten, um die es geht, und über die Weise, wie Ihr Kind untersucht wird.

En Holanda todos los niños recién nacidos son examinados para detectar posibles enfermedades congénitas. Un rápido descubrimiento y tratamiento son de gran importancia para poder evitar daños en el desarrollo físico y mental. Este folleto describe las enfermedades de las que se trata y de qué forma va a realizarse el examen de su niño.

Hollanda'da her çocuđun, dođduktan kýsa bir süre sonra dođduđtan olabilecek bazı hastalýklarýn olup olmadýđý arařtırýlýr. Erken teđhis ve tedavi, bedensel ve zihinsel geliřmedeki olası zararý önlemek açýsýndan büyük önem tađýr. Bu brořür, sözü edilen hastalýklarýn hangileri olduđu ve çocuđunuzda arařtırmanýn nasýl yapýlacađý hakkýnda bilgileri içerir.

Information for parents

Information for parents about neonatal screening in Germany (Bun04).

<http://infomed.mds-ev.the/sindbad.nsf/0/2e1593d2df9c087dc1256fd5002624eb?OpenDocument>

Liebe Eltern,

die Geburt Ihres Kindes liegt gerade hinter Ihnen. Die meisten Kinder kommen gesund zur Welt und bleiben es auch. Es gibt jedoch seltene angeborene Erkrankungen, die bei Neugeborenen noch nicht durch äußere Zeichen erkennbar sind. Diese Erkrankungen können bei ca. einem von 1000 Neugeborenen auftreten. Unbehandelt können diese Erkrankungen zu Organschäden, körperlicher oder geistiger Behinderung führen. Um diese Erkrankungen zu erkennen, wird eine Früherkennungsuntersuchung für alle Neugeborenen angeboten (erweitertes Neugeborenencreening).

Warum werden Früherkennungsuntersuchungen durchgeführt?

Seltene angeborene Störungen des Stoffwechsels und der Organfunktion sollen rechtzeitig erkannt werden. Durch eine frühzeitige Behandlung möglichst bald nach der Geburt können die Folgen einer angeborenen Erkrankung dieser Kinder meist vermieden werden. Deshalb finden seit über 30 Jahren bei allen Neugeborenen Blutuntersuchungen statt. Diese Stoffwechseluntersuchung wurde nun wesentlich verbessert, weitere behandelbare Erkrankungen sind in die Untersuchung eingeschlossen worden.

Wann und wie wird untersucht?

Im Laufe des zweiten bis dritten Lebensstages (36. bis 72. Stunde nach der Geburt), ggf. zusammen mit der zweiten Vorsorgeuntersuchung Ihres Kindes, der U2, werden wenige Blutstropfen (aus der Vene oder Ferse) entnommen, auf die dafür vorgesehene Filterpapierkarte getropft und nach dem Trocknen sofort zu einem Screeninglabor geschickt. Dort werden die Proben unverzüglich mit speziellen, sehr empfindlichen Untersuchungsmethoden untersucht.

Auf welche Krankheiten wird untersucht?

Hypothyreose, Adrenogenitales Syndrom (AGS), Biotinidasemangel, Galaktosämie, Phenylketonurie (PKU) und Hyperphenylalaninämie (HPA), Ahornsirupkrankheit (MSUD), Fettsäurestoffwechseldefekte (MCAD-Mangel, LCHAD-Mangel, VLCAD-Mangel), Carnitinzyklusdefekte, Glutaracidurie Typ I, Isovalerianacidämie (Krankheiten nachfolgend beschrieben).

In der Summe findet man bei ungefähr einem von 1000 Neugeborenen eine angeborene Erkrankung. In den meisten der betroffenen Familien gab es vorher noch nie derartige Erkrankungen. Da die betroffenen Kinder bei der Geburt noch völlig gesund erscheinen können, ist das Neugeborenencreening wichtig, um die Kinder rechtzeitig vor schweren Erkrankungen und deren Folgen, wie z. B. Störungen der geistigen und körperlichen Entwicklung, zu bewahren.

Aus dieser Untersuchung allein lassen sich keine Aussagen über familiäre Risiken ableiten.

Wer erfährt das Testergebnis?

In jedem Falle erhält der Einsender der Blutprobe (Arzt in der Geburtsklinik, Hebamme) innerhalb weniger Tage einen schriftlichen Befund vom Screeninglabor. In dringenden Fällen wird zusätzlich direkt mit den Eltern Kontakt aufgenommen. Geben Sie deshalb für die Testkarte Ihre Telefonnummer und Ihre Anschrift an, unter der Sie in den ersten Tagen nach der Geburt erreichbar sein werden. Früherkennung und Frühbehandlung für betroffene Neugeborene sind nur möglich, wenn alle Beteiligten — Eltern, Klinik bzw. Kinderarzt und Screeninglabor — ohne Zeitverlust zusammenarbeiten, damit die Untersuchungsergebnisse rechtzeitig erhoben und kontrolliert werden.

Was bedeutet das Testergebnis?

Das Ergebnis eines Screening-Testes ist noch keine ärztliche Diagnose. Mit dem Testergebnis können entweder die betreffenden untersuchten Störungen weitgehend ausgeschlossen werden, oder eine weitere diagnostische Untersuchung bei Verdacht auf eine Erkrankung erforderlich machen, z. B. durch eine Wiederholung des Testes. Eine Wiederholung eines Testes kann aber auch notwendig sein, wenn zum Beispiel der Zeitpunkt der Blutabnahme nicht optimal war.

Können diese Krankheiten geheilt werden?

Alle genannten Stoffwechseldefekte und endokrinen Störungen sind angeboren und können deshalb nicht geheilt werden. Jedoch können die Auswirkungen dieser angeborenen Störungen mit einer entsprechend frühzeitigen Behandlung vermieden oder zumindest vermindert werden. Die Behand-

lung besteht in einer Spezialdiät und/oder in der Einnahme von bestimmten Medikamenten. Stoffwechselfachspezialisten stehen für die Beratung und Betreuung im Verdachts- oder Krankheitsfall zur Verfügung.

Die Teilnahme am Neugeborenen-Screening ist freiwillig. Die Kosten der Untersuchung werden von den gesetzlichen Krankenkassen übernommen.

Das Ergebnis der Untersuchung unterliegt der ärztlichen Schweigepflicht. Die Testkarten werden nach einem Zeitraum von drei Monaten vernichtet.

Ihr Einverständnis umfasst nur die oben genannten Zielerkrankungen.

Wir sind mit der Untersuchung einverstanden.

Datum, Unterschrift mind. eines/r Personensorgeberechtigten

Erweitertes Neugeborenen-Screening

Elterninformation

zur Früherkennung von angeborenen Stoffwechselerkrankungen
und endokrinen Störungen bei Neugeborenen

Costs of neonatal screening

Various researchers have produced estimates of the costs of newborn screening programmes. Some analyses have also included the costs per life-year gained. The results of these estimates vary, especially on account of differences in the assessment of the costs of follow-up investigations. The following is a summary of the most significant results. The Committee has not discussed these estimates in detail because in many cases the basic data are not available. This applies especially to the findings on quality adjusted life years (QALYs). The publications are, however, sufficiently well substantiated to allow conclusions to be drawn with regard to the order of magnitude of the costs, which are low compared with other screening programmes. It is also apparent that there are cost savings to be made by combining a number of methods, and from the fact that patients for whom a diagnosis is made in the course of screening will require less investigation at a later date. Furthermore, there is less treatment based on inaccurate diagnosis. For the purposes of calculating costs, the following groups of diseases have been identified in connection with the techniques used: diseases for which testing is performed by tandem mass spectrometry, biotinidase deficiency and galactosemia, sickle-cell disease and CF.

In a detailed cost-benefit analysis, the costs of tandem mass spectrometry for newborn screening (including the costs of specimen transportation and interpretation of results) are estimated to be \$15 per test (Sch02). Screening is therefore performed for a series of other metabolic diseases besides MCAD deficiency. In the Netherlands, the laboratory costs of tandem mass spectrometry screening are

estimated to be €7 to €7.5 per test, with reagents and equipment costing €5.6 per test and with each of 5 laboratories employing 0.8 full-time equivalents at HLO (advanced research technician) level (€45,700) and 0.2 full-time equivalents at academic level (€18,300). For 200,000 newborns per year, this makes a total of €1.45 million.

If there are positive results, follow-up tests must take place (both for true and false-positive results). A US study has estimated the cost of follow-up investigations for MCAD deficiency at \$200, and for other disorders at an average of \$1,000 per follow-up investigation (depending on the need for hospital admission, etc). The costs per newborn child then come to \$6, with the range of costs being broad (\$1.2 to \$12) (Sch02). Not all of the disorders included in this study are recommended for inclusion in the Dutch screening programme and the costs of follow-up investigations are probably lower here than abroad. An estimate has been made, based on the number of positive results detected in Germany by tandem mass spectrometry for the disorders recommended for screening in this advisory report (more than 300 positive results per 250,000 newborns, not including PKU; Sch03). The costs of follow-up investigation consist of the costs of the obstetrician or general practitioner, and where applicable the costs of first aid and hospital admission, amounting to an estimated €200 to 800 per follow-up investigation. Taking €500 as the average, this gives a total of €120,000 for the 200,000 infants born in the Netherlands every year.

Researchers have also calculated how much would be saved if the current PKU screening were to be replaced with tandem mass spectrometry analysis for PKU and MCAD deficiency (Pan04). The changeover would produce a saving of £23,000 in laboratory costs per 100,000 newborns per year in the UK. In the Netherlands this would save an estimated €1.5 per test (approximately €300,000 per year).

The costs of neonatal screening for galactosemia and biotinidase deficiency are comparable with the costs of the current PKU and AGS screening programme. A typical cost breakdown for biotinidase testing would be €0.8 per test for reagents and equipment and €0.6 in wages (in 5 laboratories: 0.4 full-time equivalents at MLO (intermediate) level and 0.05 full-time equivalents at HLO/academic level, €14,400 plus €3,400 x 5). For 200,000 births, this would give a total of €250,000 per year. The laboratory costs may fall over time if tandem mass spectrometry methods are employed (providing the number of false-positive results can be curbed).

In a systematic review of sickle-cell disease screening, the costs of the test have been estimated at £3-4 per newborn child (if 50,000 or more tests are performed in a laboratory every year; Dav00). This would make the estimated cost

in the Netherlands €1.5 per test for reagents and equipment and, for wages, €90,000 plus €34,000 (5 x 0.5 full-time equivalents at MLO level and 0.1 full-time equivalents at HLO/academic level). For 200,000 births, this adds up to a total of €430,000 per year.

According to British researchers, the costs of information provision to parents and subsequent follow-up investigation in the event of carrier status being detected would amount to £334 (Dav00). More than half of the couples in London and around a third in New York and Baltimore wanted to receive information about carrier status. Assuming that information is to be provided to 40 to 80 per cent of the couples, these costs would amount to €0.5 to €1.0 million in the Netherlands (1,000 to 2,000 carriers per year at €500 per carrier). The total cost of sickle-cell disease screening is estimated to be between €1.0 and €1.5 million per year.

The costs of CF screening in the United States have been calculated per diagnosed CF patient (the IRT test is combined with DNA testing of a series of mutations, see Appendix H; Lee03). The researchers compare the result (\$4.6 per newborn child) with the cost per diagnosis without screening, which amounts to \$5.0. The cost reduction is attributed to a decrease in the number of sweat tests (Lee03). Neonatal screening for CF is also reported to have reduced costs in France (Bro05).

The total cost of expanding the screening programme (not including CF, see table below) is €2.7 to €3.4 million based on an annual birth rate of 200,000 (€13 to €17 per child).

Screening produces diagnostics savings in the true-negative results group: repeat screening will not usually be performed in children with symptoms which without screening would provide grounds for performing these diagnostics. There is also a saving with regard to the true-positive results, since diagnostic testing is avoided (and sometimes also extra hospital admissions). The biggest savings are attributable to the fact that irreversible damage to health is prevented in this group.

Table 3 Estimate of the costs of expanding neonatal screening in millions of euros.

	Tandem mass spectrometry	Biotinidase	Galactosemia	Hemoglobino-pathy	Total
Laboratory costs	1.45	0.25	0.25	0.43	2.38
Costs of follow-up investigation	0.05 to 0.2	0.05	0.05	0.5 to 1.0	0.65 to 1.3
Saving for PKU	0.3				0.3
Total	1.28	0.3	0.3	0.93 to 1.43	2.73 to 3.38

Estimates have been given in the literature of the number of life years that can be gained and the costs that would be incurred per QALY. It is estimated that the replacement of current PKU screening with tandem mass spectrometry analysis for PKU and MCAD deficiency would result in 59 life-years gained per 100,000 newborns (Pan04). Some researchers point out that there is insufficient 'robust clinical evidence' to properly substantiate the calculations for other disorders (Pan04). Other researchers arrive at the following figures: \$5,600 per QALY for a series of disorders screened by tandem mass spectrometry, albeit with a large confidence interval (from \$0 to \$17,100 per QALY; Ven03); \$6,000 per QALY for MCAD deficiency only; and no less than \$15,200 for a series of disorders (Ins02). The previously mentioned cost-benefit analysis adds up to \$5,800 per QALY with an interval of \$700 to \$11,000; Sch02).

These costs can be compared with those of other programmes. An RIVM report on the cost-effectiveness of vaccinations gives €38,000 per QALY for the pneumococcal vaccine and €11,000 per QALY for the meningococcal vaccine (RIVM00). The CBO consensus on cholesterol-lowering drugs gives a figure of €18,000 (Fl 40,000) per life year gained (CBO98). An analysis conducted by the Institute for Medical Technology Assessment (iMTA) indicates sums of €35,000 to €55,000 per QALY for disorders that are accompanied by substantial to severe limitations (iMTA01). The costs per QALY of neonatal screening are therefore low compared with those of other interventions. According to the Wilson and Junger criteria, the costs of screening including follow-up diagnostics and treatment should be in proportion to total healthcare costs (Wil68). From the analyses that have been cited here it would appear that the proposed expansion of neonatal screening satisfies this requirement.

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Abbreviations

<i>AGS</i>	adrenogenital syndrome
<i>BIO</i>	biotinidase
<i>BH4</i>	tetrahydrobiopterin
<i>CBS</i>	cystathionine beta-synthase
<i>CHT</i>	congenital hypothyroidism
<i>CF</i>	cystic fibrosis (mucoviscidosis)
<i>GA-I</i>	glutaric aciduria type I
<i>GALT</i>	galactosemia
<i>G6PD</i>	glucose 6-phosphate dehydrogenase
<i>IRT</i>	immunoreactive trypsinogen
<i>LCHAD</i>	long-chain hydroxyacyl-CoA dehydrogenase
<i>MCAD</i>	medium-chain acyl-CoA dehydrogenase
<i>MSUD</i>	maple syrup urine disease
<i>PKU</i>	phenylketonuria
<i>VLCAD</i>	very-long-chain CoA dehydrogenase
<i>WBO</i>	the Dutch Population Screening Act
<i>WGBO</i>	the Dutch Medical Treatment Agreement Act
