Health Council of the Netherlands

Neonatal screening: new recommendations

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : presentation of advisory report *Neonatal screening: new recommendations*
Your reference : PG/OGZ/3120487
Our reference : I-1279/EA/msj/011-E
Enclosure(s) : 1
Date : April 8, 2015

Dear Minister

Shortly after birth, almost every baby in our country undergoes a heel prick test for a number of genetic diseases for which good treatment options are available. The current neonatal screening programme is based on two previous Health Council advisory reports: *Neonatal screening* (publication No. 2005/11) and *Neonatal screening for cystic fibrosis* (publication No. 2010/01). By your letter dated 28 June 2012 (ref PG/OGZ/3120487), you asked me to map out the current state of knowledge in this field and formulate recommendations on changes needed in the screening programme. In reply to your request, and having heard the Standing Committee on Health Ethics and Health Law and the Standing Committee on Genetics, I am pleased to hereby submit *Neonatal screening: new recommendations.*

Your request focuses specifically on the criteria for inclusion in neonatal screening, conditions currently eligible for inclusion in screening, and the question how incidental findings should be dealt with in the programme. The Committee formulating the advisory reports endorses the criteria from earlier advisory reports. The object of screening should remain advantage for the newborn, operationalised as health gain or the prevention of health loss. The Committee also considered whether screening for untreatable conditions should be included in the programme, but does not consider this indicated at this time.

The Committee recommends the addition of fourteen conditions to the neonatal screening programme. Three of these conditions are now reported as incidental findings of neonatal screening. It is vital that the inclusion of the newly added conditions be preceded by thorough pilot research. Additionally, the Committee recommends the removal of diagnostics for one condition from the current programme, as the test quality is insufficient.

If incidental findings are unavoidable in neonatal screening, the child's interest should take highest priority according to the Committee. Incidental findings should therefore be reported if this would benefit the child. If it will not benefit or perhaps even harm the child,

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it should not be reported. Reporting of carrier status in those cases benefits the parents only; furthermore, such reports may impair the clarity of the programme. The current practice of reporting carrier status in sickle cell disease should therefore be stopped, according to the Committee. Attention should continue to be given to reaching the population at risk. The Committee deems research necessary in this respect.

The Committee anticipates major developments in technology, enabling direct screening on genetic material. This foreseeably will give rise to further questions, and the Committee recommends monitoring developments.

I endorse the Committee's conclusions.

Yours sincerely,
(signed)
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to:

the Minister of Health, Welfare and Sport

No. 2015/08E, The Hague, April 8, 2015

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This report can be downloaded from www.healthcouncil.nl.

Preferred citation:
Health Council of the Netherlands. Neonatal screening: new recommendations. The Hague: Health Council of the Netherlands, 2015; publication no. 2015/08E.

ISBN: 978-94-6281-068-6

Contents

Executive summary

Shortly after birth, almost every baby in our country undergoes a heel prick test. At the moment, the blood thus acquired is tested for 17 diseases, for which early detection is important in order to prevent or limit health damage. The neonatal screening field is dynamic. Treatment options for some diseases have improved significantly in recent years, and there are also diseases that can be detected better than before. In addition, several social and ethical questions have arisen about the neonatal screening programme. Two issues are particularly salient: the exact goal of neonatal screening, and dealing with incidental findings, such as carrier status for diseases. Considering these scientific and social developments, the Minister of Health, Welfare and Sport decided to request advice from the Health Council of the Netherlands. Specifically, she also asked which diseases should be added to the neonatal screening programme. A specially appointed Committee drafted the requested advisory report.

Criteria for inclusion in the screening programme

There is broad international consensus on the criteria for inclusion of diseases in the neonatal screening programme. First, screening must be advantageous to the newborn. There must be substantial health gains, achieved through early intervention in severe diseases with a known natural course. The most important interventions are medication and diet adjustments. Additionally, the screening test must be of good quality. The clinical sensitivity (percentage of true positive

results) and specificity (percentage of true negative results) must be high. Broad acceptance of the screening programme is also required, via clear information provided to parents, voluntary participation, safeguarding privacy and good access to treatment and support in the event of a positive test result. The Committee strives to ensure the neonatal screening programme remains transparent, clearly advantageous to the child being screened.

Screening for untreatable conditions: an ongoing debate

A growing number of voices in the scientific community and in patient organisations are calling for the inclusion of certain untreatable conditions in the neonatal screening programme. Other advantages, beyond clear health benefits, ought to be considered. Some of these may benefit the child, particularly shortening of the diagnostic process and adjustment of family life to deal with the consequences of the disease. Parents may also benefit from screening for a condition for which there is no effective treatment. If a child has such a condition, this knowledge may provide parents with information for making future reproductive choices. There are also disadvantages. The child's right to an open future is harmed. Furthermore, such knowledge may cast a shadow over the newborn’s early life. As it is not self-evident that screening for untreatable conditions is in the best interest of the child, more extensive counselling would be necessary. This would place severe burdens on the current informed consent procedure.

All things considered, the Committee believes the potential advantages for the child are sufficient to warrant considering the inclusion of certain untreatable conditions in the screening programme. In the Committee's opinion, there must be solid scientific evidence that neonatal screening can prevent significant health damage due to slow, erroneous or invasive diagnostic testing. While this is not the case, a majority of the Committee believes such an extension to the screening programme to be undesirable. It may harm the transparency of the programme as a whole.

An example of this type of dilemma is screening for Duchenne muscular dystrophy. According to the Committee, there is currently insufficient scientific evidence for the severity of the disadvantages of late diagnosis for the child and for the advantages of early diagnosis via neonatal screening. In the Committee's opinion, neonatal screening for these diseases is not indicated.

Categories of conditions

All of the conditions under consideration must be evaluated in order to determine whether individual assessment criteria have been met, and the criteria must also be considered in relation to each other. The Committee distinguishes the following categories of conditions:

Category 1: conditions that qualify for inclusion
- Neonatal screening prevents significant, irreversible damage and/or yields substantial health gains for the child
- A test of proven quality is available

Category 2A: conditions that require further study
- Neonatal screening prevents significant, irreversible damage and/or yields substantial health gains for the child
- A test of proven quality is not (yet) available

Category 2B: conditions that may be considered for inclusion after weighing the advantages and disadvantages, including cost-effectiveness
- Neonatal screening yields health gains
- A test of proven quality is available

Category 3: conditions that do not qualify for inclusion
- Neonatal screening yields no health gains
- There may be other advantages for quality of life, such as shortening the diagnostic process (without prevention or limitation of damage to health).

New in neonatal screening: recommendations

Based on the assessment framework described above, the Committee recommends the following fourteen conditions be added to the neonatal screening programme:
- Beta thalassemia major (TM) and HbH disease
- Carnitine-acylcarnitine translocase deficiency (CACT)
- Carnitine palmitoyltransferase deficiency type 1 (CPT1)

- Carnitine palmitoyltransferase deficiency type 2 (CPT2)
- Galactokinase deficiency (GALK)
- Guanidinoacetate methyltransferase deficiency (GAMT)
- Methyl-acetoacetyl-CoA thiolase deficiency; ketothiolase deficiency (MAT)
- Methylmalonic acidemia (MA)
- Mucopolysaccharidosis type 1 (MPS I)
- Organic cation transporter 2 (OCTN 2)
- Propionic acidemia (PA)
- Severe combined immune deficiency (SCID)
- X-linked adrenoleukodystrophy (X-ALD).

The Committee would like to draw attention to the fact that responsible introduction requires solid pilot research, and outlines the requirements thereof. For one disease that is currently part of the neonatal screening programme, the test is of insufficient quality, and the Committee recommends removal of this disease, homocystinuria, from the programme.

Incidental findings and carrier status

Incidental findings do occur during neonatal screening: these are unintended findings that do raise questions. Some incidental findings may be foreseen. Incidental findings may be clinically meaningful, of unclear meaning or not clinically meaningful. The Committee focused primarily on the first category, and distinguished between two situations: actionable conditions – there are treatment or prevention options – and non-actionable conditions – there are no such options. Here too, the Committee places the child's interests first. It believes actionable conditions must always be reported to the parents, and that the parents' right to not know may not be called upon, even if the incidental finding in question may affect the parents or their other or future children.

Incidental findings that indicate a condition that cannot or can barely be influenced should not, in the opinion of the Committee, be reported. Reporting such information would harm the child's right to an open future. One exception is possible: should the disease manifest very early and the child may be spared a diagnostic odyssey. The principle of not reporting also applies to conditions that only manifest in adulthood.

An exceptional clinically meaningful incidental finding is carrier status. A majority of the Committee recommends not reporting carrier status of the child to the parents. In the Committee's opinion, the child's right to later decide for himself/herself about knowing or not knowing about carrier status is more

important than the interests of the parents in terms of making reproductive choices. Furthermore, it is undesirable for the informed consent procedure to focus extensively on what is not the purpose of the screening programme.

Carrier status for sickle cell disease should no longer be reported to parents as part of the neonatal screening programme, although this is current practice. The Committee recommends instead a study to identify the best method for informing the at-risk population for sickle cell disease about carrier status and related choices; this population is currently not being reached effectively. Where screening focused on reproductive choices is concerned, the Committee underlines the importance of carrier screening preconceptionally or prenatally.

Chapter 1

Introduction

Shortly after birth, almost every baby in the Netherlands is screened for 17 conditions where early detection is important to ensure timely treatment. The goal is to prevent or limit severe complications in physical and mental development. Such neonatal screening involves testing the blood taken by a heel prick.

The current neonatal screening programme is based in part on advisory reports of the Health Council of the Netherlands.[6,7] Scientific and technological developments are very dynamic. Treatment options for certain conditions have improved, and there are advances in the detection of other diseases. Additionally, social and ethical questions have risen about the programme, dealing mainly with the programme's goal and how to deal with incidental findings.

1.1 Request for advice and Committee

The above-described scientific and social developments prompted the Minister of Public Health, Welfare and Sport to request advice from the Health Council of the Netherlands (see Annex A for the full text). The primary questions are as follows:

1 Are the criteria for neonatal screening, as formulated in the previous neonatal screening advisory report, still adequate?
2 In view of recent scientific developments, which conditions should be included in the neonatal screening programme?
3 How should issues in the practical implementation of neonatal screening be dealt with: e.g. test methods for CF (cystic fibrosis) and HCY (homocystinuria) and the timing of the heel prick?
4 What is the right response to incidental findings and carrier status? What is the correct procedure for information and consent?
5 How can the neonatal screening programme be modified effectively and fast enough in the future on the basis of new scientific insights?

A special Committee was formed to answer these questions (see Annex B). As the Committee was preparing its advisory report, an additional question was asked about the quality of the cystic fibrosis and homocystinuria tests (question 3).

1.2 Committee methods and advisory report structure

In addition to the usual review of the scientific literature in this field, the Committee took additional actions. The committee organised a hearing about the option to screen for untreatable conditions. We also consulted experts on a number of specific conditions, either in a meeting or in writing (see Annex C).

The advisory report is structured as follows: Chapter 2 addresses the neonatal screening criteria. Particular attention is given to the goal of neonatal screening and the option to include untreatable conditions. Chapter 3 deals with metabolic diseases eligible for inclusion in the neonatal screening programme. Chapter 4 describes a number of immune and infectious diseases. In Chapter 5, the Committee indicates how the neonatal screening programme has functioned up to this point, with a specific focus on CF and HCY. Chapter 6 addresses how incidental findings and carrier status should be dealt with. Chapter 7 focuses on incidental findings in the screening for hemoglobinopathies. The practical implications for neonatal screening are discussed in Chapter 8, followed by a short look ahead (Chapter 9), and the primary conclusions and recommendations (Chapter 10).

Chapter 2

Neonatal screening criteria

The 2005 Health Council advisory report on neonatal screening contains a detailed description of criteria to be used. Using this as its point of departure, the Committee assessed the need for fine-tuning or reconsideration. Attention is given in this respect to the option to include severe, untreatable conditions in the programme.

2.1 Neonatal screening context

Neonatal screening is one of the preventive tests provided to the population as part of public health. An important characteristic of public health is that it is a proactive programme not based on requests for assistance and where individuals undergoing screening are healthy in principle. Screening always has disadvantages, such as the burden of sampling and testing, the possibility of false-positive and false-negative results, and the risks and disadvantages of additional diagnostics and treatment that may be required. That is why such screening always requires specific justification. It is essential that the advantages clearly outweigh the disadvantages.

Neonatal screening comes under the Population Screening Act (Wet op het bevolkingsonderzoek – WBO). This act aims to protect the population against screening that may jeopardise the physical and/or mental health of individuals undergoing such screening. The WBO stipulates that screening requires a license

when people are screened using ionising irradiation, for cancer, or for untreatable conditions. The concept of 'treatability' is relevant in the neonatal screening setting in particular. The WBO committee uses the following definition in this context:

A condition is considered untreatable when the scientific literature does not allow reliable conclusions about an anticipated favourable effect of medical intervention of a relevant size on clinical outcome measures, meaning mortality, morbidity or quality of life.[11]

2.2 The 2005 criteria

The 2005 advisory report described the goal of neonatal screening as follows:

The goal of neonatal screening is to detect conditions where interventions shortly after birth provide obvious advantages over interventions that cannot be performed without screening or only at a later stage. Interventions includes treatments such as the administration of medicines or diet, but also preventive measures such as the avoidance of fasting in certain lipid metabolism diseases.[7]

The criteria of the advisory report were largely based on the internationally accepted Wilson and Jungner criteria.[12]

Screening should benefit the newborn: direct health gain or improved diagnostics or care. Screening is performed for:

a severe conditions
b with a known natural history.

Tests of good quality are available

For the programme to be implemented, broad acceptance is required by:

a good information for parents
b voluntary participation
c privacy is ensured
d quality and accessibility of treatment, and support after a positive result are ensured.[7]

The criteria are discussed in detail and re-evaluated below. Other considerations are then presented that could impact the consideration for inclusion in the neonatal screening programme.

2.3 The criteria revisited

The 2005 Health Council advisory report distinguishes between direct and indirect advantages. Direct advantages are health gains for the newborn as a result of early intervention. Indirect advantages are the reduction of a diagnostic odyssey and the related period of uncertainty, improved care for the child after a more rapid diagnosis, parents being prepared for the manifestation of a severe condition in their child, and parents' ability to make reproductive choices.[7]

The Committee distances itself from the subdivision into direct and indirect advantages, mainly because the 'indirect advantages' are very diverse. Some 'indirect advantages' may directly benefit the child, such as a shorter diagnostic process and the adjustments to cope with the child's illness. There are also advantages to other parties than the child: the family and third parties. The Committee emphasises that family and child advantages are interrelated.

In the light of the above, the Committee opts for a new classification of the advantages of neonatal screening. The crucial question is: when are advantages to the child sufficient to include a condition in the national neonatal screening programme?

Advantages of neonatal screening:

1 the prevention of irreversible damage in the child and/or the achievement of substantial health gains for the child a reduction of the diagnostic process (timely) adjustments to life to cope with the disease
2 reproductive choices for parents
3 lower disease burden on society
4 expanded scientific knowledge.[15,16]

2.3.1 First and foremost, screening should benefit the newborn

The Committee endorses the previous advisory report, emphasising that neonatal screening should provide substantial health gains to the newborn. This is ensured in the current programme by screening for severe, treatable conditions. Advantages to the child are such that it can be concluded that not participating in the screening would be irresponsible. The heel prick is largely accepted[17], which may be related to the nature of the screening. The Committee aims to preserve the clarity of the neonatal screening programme, with evident advantages for the screened child.

Severe conditions

The current neonatal screening package focuses particularly on the detection of treatable, severe diseases. The question arises whether screening for diseases with a negative impact on quality of life but which are not severe, are also eligible for neonatal screening. If these diseases are prevalent enough, this may significantly reduce the disease burden on society. For such less serious diseases, health gain to the screened individual is more limited. Parents may then have good reasons to opt out of participation, whereas the programme emphatically aims for a high level of participation.

Natural history

An important question is what should be known about the natural history of the disease. This knowledge is usually very limited in the case of very rare conditions. For example, some metabolic diseases targeted for neonatal screening cannot be studied in depth because of limited patient populations. Sometimes it may be decided to include these conditions in screening on the basis of expert opinion.

Also, it can be difficult to describe the course of a condition, for instance due to phenotypical variation. When this is the case, some patients are affected severely and others to a much lesser degree. A large number of diseases are characterised by phenotypical variation. Phenotypical variation may result from mutations in different genes: genetic heterogeneity. Additionally, several mutations in the same gene may lead to differences in phenotypical expression: allelic variation. Finally, one and the same mutation as a result of (epi)genetic modification(s) and/or environmental factors may cause a variable phenotype.

Many diseases are characterised by a high level of phenotypical variation. One example is cystic fibrosis (CF), where different mutations cause a different disease burden; a group of mutations causes non-classical CF, another group causes classical CF, and other mutations again are new and their effects are unknown.

The crucial question is whether a test can distinguish between the various manifestations of a condition. If so, it may be decided to only screen for severe or treatable forms of the condition or forms that manifest early. If not, it is not always clear how variation in the condition in the group identified by screening should be dealt with; this could be a reason for non-inclusion in the neonatal screening programme.

2.3.2 *A test of good quality is available*

Clinical sensitivity and specificity of a test should be scientifically confirmed and of a high level. Good positive predictive value, where positive result means a high risk of disease, is necessary to limit burdens on parents and screening authorities where possible. Also, test quality may be unexpectedly low (see e.g. homocystinuria in Chapter 5). Importantly, timely evaluation of all tests is important to enable modifications where needed. If a test does not meet expectations in practice, this may be a reason to drop a condition from the screening programme.

Other considerations are also involved here. It is essential to regard test characteristics in relation to both the severity and prevalence of the condition, anticipated health gains, burden on parents and child from follow-up tests, and the effectiveness of the programme. Furthermore, the risk of incidental findings when using various test methods should be taken into account. For instance, some conditions can only be tested at the DNA level. Unavoidably, this leads to incidental findings of carrier status of the child. The Committee will address these issues in Chapters 6, 7 and 9.

2.3.3 *Broad acceptance of the programme*

Information for parents

Good information is essential to enable parents to make informed decisions. The information process has been amended since the expansion of the heel prick in 2007. A 2008 evaluation shows that this modification was generally successful. However, there remains room for improvement. Effective information for certain parent groups, particularly people with low educational levels or foreign backgrounds, appears problematic. Additionally, information for heel pricks performed in hospitals is less effective than for those performed elsewhere. Many parents are unaware they have a choice with respect to carrier status information and storage of heel prick cards for research purposes. Additionally, many parents would like to receive more information.[18] There have been proposals on an international level for more extensive parental information prior to screening.[11] Particularly where new conditions are added to the screening programme, the information process warrants attention.

As long as neonatal screening preserves its nature, a proactive offer of screening aiming for maximum participation is justified, and imperfect informed

consent is acceptable. The parents have the option to refuse, but this situation is avoided where possible as it is not in the child's interest. If the nature of the screening would change dramatically as a result of additions, extensive information is needed, while the basic information should be clear and simple in view of the goal of high participation.

Voluntary participation

Other than in some other countries, participation in the neonatal screening programme is voluntary in the Netherlands. But here again, parents are not always aware that neonatal screening is voluntary, and they frequently automatically agree to screening. Where the child's interests fully justify the programme, such automatic participation is acceptable.

Privacy safeguards

This criterion is undebated in the literature. It is an important matter when it comes to implementation, also because this may be an area of tension. For example, heel prick cards can be used for research purposes or to identify persons in the event of calamities.

Access to treatment and support after positive results

Costs of follow-up treatment are relevant in assessing the inclusion of a condition in the neonatal screening programme. Treatment often requires expensive (orphan) drugs. The long-term perspective should also be considered in such situations. It matters whether treatment is once-only (as in stem cell transplantation) or must be given for life (as in many forms of enzyme therapy). The availability of treatment must be reasonably guaranteed in order for a condition to be included in the neonatal screening programme. Furthermore, the availability of adequate treatment capacity should be ascertained in specific cases. It is also necessary to monitor and evaluate treatments.

2.4 Other considerations

Alternative or complementary measures and effectiveness

The question whether alternative or complementary measures will achieve the same goal as neonatal screening, should be considered. Is neonatal screening the

best or only method to limit experienced health problems? The United Kingdom uses the criterion that options for primary prevention for a certain disease must have been explicitly considered. One example could be primary preventive measures during pregnancy, as for infectious diseases.[19,20]

In this context the Committee explicitly points out the (increasing) options for preconceptional screening of carrier status for certain severe autosomal recessive or sex-linked conditions. The Committee endorses the conclusions from the 2007 Health Council advisory report *Preconceptiezorg; voor een goed begin* (Preconception Care; for a Good Start).[19]

Efficiency is problematic in conditions eligible for inclusion in neonatal screening, one of the reasons being the low prevalence of conditions and the resulting limited availability of data. In some cases the Committee deems the health gain such that inclusion of these diseases will virtually always be (cost) effective (category 1). When health gain is more limited, (cost) effectiveness should be explicitly considered (category 2B). The Committee implicitly considered effectiveness in formulating its recommendation.

2.5 Neonatal screening for untreatable conditions

Patient associations, including the Association of Collaborating Parents and Patients Organisations (VSOP), are in favour of optional inclusion of untreatable conditions in the neonatal screening programme. The scientific literature also discusses expansion of the neonatal screening with e.g. Duchenne muscular dystrophy,[21] and spinal muscular atrophy.[22-25] In addition, there have been projects that included neonatal screening for Duchenne muscular dystrophy.[8]

This prompted the Committee to discuss the option to include untreatable conditions in the neonatal screening programme extensively. The Committee first outlined the potential advantages of screening for untreatable conditions. This was then considered in the light of the goal of neonatal screening. Finally, the Committee considered the desirability of inclusion of untreatable conditions in the neonatal screening programme.

The Committee explored the potential advantages that are to be expected of neonatal screening for untreatable conditions which will primarily benefit the child and which may result in health gain. Relevant in this context are type 2 (accelerated diagnostic process) and type 3 (life adjustments to cope with condition).[16,26] The type 2 advantage may limit damage to health: the accelerated diagnostic process may prevent (excessively) invasive diagnostics or wrong treatments. Additionally, a protracted diagnostic process may affect the psychosocial well-being of the child and its family. The type 3 advantage

describes the ability to adjust family life after a condition is diagnosed. If a family is well prepared for the condition and its consequences, this will likely improve the child's well-being.

Another advantage (type 4) is the ability to make reproductive choices.[15] This primarily benefits parents, but is considered as a significant additional advantage.[27]

There is as yet little scientific evidence that the described advantages materialise and how sizeable these are. For instance, the Duchenne muscular dystrophy parent and patient association analysed the amount of damage that occurs as a result of delays, misdiagnosis and invasive diagnostics. However, these data have not been published yet and can therefore not be assessed scientifically.

Neonatal screening for untreatable conditions also has disadvantages. The first disadvantage is that screening for untreatable conditions in children can be considered an infringement on their right to an open future. A second disadvantage is that earlier knowledge of a condition may overshadow the first period with the newborn; the literature describes this as loss of the 'golden years'.[16]

Empirical data on the disadvantages of early knowledge of untreatable conditions are limited. A long-term psychosocial follow-up study in 20 families where Duchenne muscular dystrophy was diagnosed in a son through an opt-in neonatal screening programme, showed little psychosocial damage in these families as a result of early diagnosis.[28]

The Committee considers the potential advantages to the child sufficient to seriously consider inclusion of untreatable conditions. Prior to inclusion, sufficient scientific evidence must be available that the anticipated advantages exist and are sufficiently substantial. To clarify whether the Committee would recommend screening for untreatable conditions under special circumstances, we considered Duchenne muscular dystrophy in more detail, see Box 1.

A crucial question for the Committee is: does screening for untreatable conditions fit in the current neonatal screening programme as proactive government provision? Neonatal screening for untreatable conditions differs significantly from screening for treatable conditions. There are no advantages of screening in the sense of medication or dietary changes. In view of the more complex advantages and the fact that screening for untreatable conditions requires a license, a more extensive information and consent procedure would be needed.

Box 1 Duchenne muscular dystrophy

Boys with Duchenne muscular dystrophy generally develop gross motor control problems in their second year.[1] Duchenne muscular dystrophy is progressive, affecting all muscles including the heart. With supportive treatment and artificial respiration, boys nowadays reach an age of around 40 years.[2] Duchenne muscular dystrophy is an X-chromosomal recessive disease caused by mutations in the dystrophin gene. A dysfunctional dystrophin gene causes progressive muscular degeneration. The dystrophin gene is large and susceptible to mutations. Boys with Duchenne cannot reproduce. As a result of this and other factors, there is a large number of sporadic cases. Since prenatal diagnostics for Duchenne was introduced in the Netherlands, the incidence of Duchenne muscular dystrophy was shown to remain at the same level.[3]

There is no demonstrated, sufficiently effective treatment and therefore Duchenne muscular dystrophy is as yet considered untreatable. Some research does show positive effects of early steroid treatment.[4,5] The Duchenne screening test was validated in Wales, with acceptable specificity (99.7%) and positive predictive value (38%), however sensitivity (81.6%) is only moderate.[8,9] The time between first symptoms and final diagnosis of Duchenne muscular dystrophy is often long: 2.5 years on average.[1] Reasons for this include a lack of awareness among physicians and the fact that Duchenne muscular dystrophy may also present as a general developmental delay. Such a 'diagnostic odyssey' may impose a high burden on both parents and the child. Wrong diagnosis likely harms boys with Duchenne. Additionally, early diagnosis may have other advantages for children and parents, such as timely support at school and adequate psychological support. 54% of the children initially receive wrong treatments as a result of misdiagnosis, including surgery in 5% of the cases (Duchenne Parent Project). Scientific publications on these untoward consequences of delayed diagnosis are unavailable. The level of preventable health damage by early diagnosis can therefore not be evaluated. In conclusion, reproductive advantages after screening are particularly important in Duchenne muscular dystrophy. This condition is associated with relatively frequent new mutations and therefore many sporadic cases. A proportion of these sporadic cases is based on a new mutation in the patient himself. In this case there is no risk of recurrence. A portion of the sporadic Duchenne muscular

dystrophy cases is based on a new mutation in the mother. A mutation in the mother can be identified by preconception carrier screening. The risk for Duchenne female carriers to have an affected son is 25%. Some mutations occur in the mother's germline (so-called germline mosaicism), which cannot be identified in preconception carrier screening.[13,14] The recurrence risk in germline mosaicism is 7%.

There is insufficient evidence that screening for Duchenne as untreatable condition is sufficiently in the child's interest at this time; additional scientific evidence may prompt reconsideration. When there is good evidence that early treatment initiation may achieve significant health gains, Duchenne muscular dystrophy may be eligible for inclusion in the neonatal screening programme as treatable condition.

The Committee considers the potential inclusion of untreatable conditions as a matter of principle. A Committee majority feels that the addition of untreatable conditions is not (conclusively) in the screened child's interest. Additionally, inclusion of untreatable conditions changes the nature of neonatal screening: the addition of untreatable conditions diminishes the clarity of the programme as a whole and thereby undermines its sound justification. The Committee therefore recommends not to include untreatable conditions in the neonatal screening programme.

The Committee does have two additional recommendations. For specific, as yet untreatable conditions, research (requiringa license) can be designed (in parallel with neonatal screening) to answer the question whether early intervention or diagnosis will achieve significant health gains. Additionally, the Committee feels strongly about improving diagnostics and care for children with vague symptoms or delayed development.

2.6 Using the criteria

The assessment whether diseases and conditions are eligible for inclusion in the neonatal screening programme is not easily made. The Committee opts for a sharp definition of the screening goal, but qualitative weighing of criteria remains a necessity. The extent to which individual criteria are met and whether

inclusion in the programme remains advisable when all criteria are considered together, must be evaluated for all conditions. The classification described in table 1 largely parallels that from the 2005 advisory report, only category 2 is now subdivided.

Category 1: conditions that qualify for inclusion

- Neonatal screening prevents significant, irreversible damage and/or yields substantial health gains for the child
- A test of proven quality is available

Category 2A: conditions that require further study

- Neonatal screening prevents significant, irreversible damage and/or yields substantial health gains for the child
- A test of proven quality is not (yet) available

Category 2B: conditions that may be considered for inclusion after weighing the advantages and disadvantages, including cost-effectiveness

- Neonatal screening yields health gains
- A test of proven quality is available

Category 3: conditions that do not qualify for inclusion

- Neonatal screening yields no health gains
- There may be other advantages for quality of life, such as shortening the diagnostic process (without prevention or limitation of damage to health).

Chapter 3

Metabolic diseases

The 17 conditions currently eligible for neonatal screening include 13 metabolic diseases. Rapid progress in the research of these conditions necessitates periodic review which metabolic diseases merit inclusion in the screening programme. This Chapter will address this issue. The background document contains extensive information on all metabolic diseases reviewed below.[126]

3.1 Selecting diseases for inclusion

3.1.1 Identification

The Committee used a diversity of approaches to identify metabolic diseases for inclusion in the neonatal screening programme. Firstly, we ascertained which conditions are screened in other countries (see Annex D). Secondly, we investigated for which conditions improved heel prick tests or treatment options became available in recent years. And thirdly, the field was consulted on conditions that seem promising for inclusion.

3.1.2 Classification

In the previous Chapter the Committee outlined the criteria used for inclusion of conditions in the neonatal screening programme. These criteria can be used to include evaluated conditions in one of the categories 1, 2A, 2B or 3.

There are many metabolic diseases, each of them (very) rare. As a result, it is often impossible in practice to determine the quality of a treatment method using randomised controlled trials, the golden standard in efficacy studies. Furthermore, there is often phenotypical variation, which further complicates research. Consequently, the Committee mostly used case studies and case series as a basis for their evaluation. With the given scarcity of data, it may also be impossible to classify a condition. Such conditions were not considered in this advisory report.

3.2 Conditions in category 1

The neonatal screening programme may prevent significant, irreparable damage for conditions in this category. This often takes the form of preventing metabolic crises and associated morbidity or severe neurological damage. For more detailed information, we refer to the background document (reference to background document).

Category 1 Conditions where neonatal screening may prevent significant, irreparable damage and for which good test methods are available that have been tested within a neonatal screening setting.

Condition	Recommendation: Include in neonatal screening yes / no	Are there incidental findings	Is there broad phenotypical variation; if so, what is the focus of screening?	Which technical modifications are required for inclusion in screening?
Methylmalonic acidemia (MMA)	YES	Yes	Yes, primarily for the late-onset form	Relatively few: modification of the current screening technology. Pilot study
Propionic acidemia (PA)	YES	Yes	Yes, primarily for the late-onset form	Relatively few: modification of the current screening technology. Pilot study
Carnitine-acylcarnitine translocase deficiency (CACT)	YES	No	Yes, screening for all forms	Relatively few: modification of the current screening technology. Pilot study
Carnitine palmitoyltransferase deficiency type 1 (CPT1)	YES	No	No	Relatively few: modification of the current screening technology. Pilot study
Carnitine palmitoyltransferase deficiency type 2 (CPT2)	YES	No	Yes, screening for all forms	Relatively few: modification of the current screening technology. Pilot study
Methyl-acetoacetyl-CoA thiolase deficiency; ketothiolase deficiency (MAT)	YES	Yes	Yes, screening for all forms	Relatively few: modification of the current screening technology. Pilot study
Organic cation transporter 2; primary carnitine deficiency (OCTN2)	YES	No	Yes, screening for all forms	None. OCTN2 is already identified as incidental finding in the current screening programme

Mucopolysaccharidosis type 1, Hurler syndrome (MPS1)	YES	No	Yes, primarily for the severe Hurler phenotype	Introduction of new enzyme assay in the screening package. Pilot study needed
X-linked adrenoleukodystrophy[a] (X-ALD)	YES	Yes	Yes, primarily for the cerebral X-ALD form	Modification and expansion of the current screening technology. Pilot study needed
guanidinoacetate methyltransferase deficiency (GAMT)	YES	Yes	No	Modification of the current screening technology. Pilot study needed

[a] In male newborns only.

3.2.1 *Methylmalonic acidemia (MMA) and Propionic acidemia (PA)*

MMA and PA are members of the organic acid syndrome class. Both conditions are characterised by a high level of phenotypical variation. Patients may present both in the neonatal period and at higher ages. In the long term, these conditions cause severe neurological damage, and possibly coma and death. For a proportion of MMA patients, treatment consists in the administration of high-dose vitamin B12, usually in combination with dietary treatment. Other MMA patients did not respond to vitamin B12; dietary treatment is their only therapeutic option.

The same dietary treatment is indicated for PA. Especially late-onset patients benefit from early treatment initiation.[29] The screening test for MMA and PA consists of tandem mass spectrometric analysis of heel prick blood (C3 carnitine test).[30] The Committee recommends inclusion in the neonatal screening programme of MMA and PA based on health gains for the late-onset form.

3.2.2 *Carnitine-acylcarnitine translocase deficiency (CACT)*

CACT deficiency is a member of the fatty acid oxidation diseases class.[31] There is a broad phenotypical variation, where early-onset patients have more severe symptoms, including neurological symptoms and severe cardiovascular disease after a period of fasting. The phenotype of late-onset patients is milder.[32,33] The untreated condition causes severe brain damage, heart failure and eventually death. Treatment of CACT consists of diet and possibly medication.[32,34] Despite treatment, a proportion of patients dies of heart failure.[32] Preventing a first crisis by early initiation of dietary treatment is the primary advantage of neonatal screening for CACT.

The CACT test consists of tandem mass spectrometry of acylcarnitines in heel prick blood. The Committee recommends inclusion of CACT in the neonatal screening programme based on health gains for all forms.

3.2.3 *Carnitine palmitoyltransferase deficiency (CPT 1 and CPT 2)*

CPT 1 deficiency is a member of the lipid acid oxidation diseases class.[31] Clinical manifestations usually develop shortly after birth.[35] The untreated condition causes severe brain damage and eventually death. If metabolic crises are prevented, the prognosis is good. Treatment consists of the prevention of prolonged fasting. The CPT 1 test consists of tandem mass spectrometry of a acylcarnitine ratio.[35-38]

The Committee recommends the inclusion of CPT1 in the neonatal screening programme.

CPT2 deficiency is also a member of the lipid acid oxidation diseases class.[31] There are three clinical forms. Patients with the very severe neonatal form die within a month after birth. In many cases, the brains and kidneys have structural abnormalities. In the infantile (hepato-cardio-muscular) form, symptoms develop in the first years of life. Fasting or intercurrent disease may cause severe symptoms. The most prevalent form of CPT2 deficiency is the classical/adult (myopathic) form. Treatment of CPT2 deficiency consists of the avoidance of fasting and possibly medication (fibrates). Presymptomatic treatment will achieve health gains for patients with the infantile and adult forms. The test for CPT2 consists of tandem mass spectrometry of acylcarnitines.[39] The Committee recommends inclusion in the neonatal screening programme of the classical and infantile form of CPT2 based on health gains.

3.2.4 *Methyl-acetoacetyl-CoA thiolase deficiency; ketothiolase deficiency (MAT)*

MAT deficiency is characterised clinically by recurrent ketoacidosis episodes. Most patients present within the first two years of life (6-24 months). Recovery after the acute period is usually complete, but there may be residual neurological phenomena. Some patients remain asymptomatic up to adulthood.[40,41] Treatment consists of the avoidance of fasting and a mild low-protein diet, which gives a favourable prognosis.[41] When the diagnosis is known, severe complications such as irreversible neurological damage or death may be prevented. MAT screening consists of tandem mass spectrometry of an acylcarnitines ratio.[42-44] This test method has a considerable risk of false-negative results, but health gains for diagnosed patients are significant. The Committee recommends inclusion of MAT in the neonatal screening programme.

3.2.5 *Organic cation transporter 2 (OCTN2)*

OCTN2 deficiency (primary carnitine deficiency) causes fatty acid oxidation diseases.[31] There is broad phenotypical variation. Patients may present at young age with life-threatening hypoglycemia and liver disease or with cardiomyopathy, but also at adult age with fatigue and arrhythmias. OCTN2 deficiency can also be entirely asymptomatic.

OCTN2 deficiency can be effectively treated. Treatment consists of daily use of carnitine as medication. Screening for OCTN2 deficiency is done by measuring the total free carnitine level in the blood of the newborn using tandem mass spectrometry. OCTN2 deficiency is now diagnosed as an incidental finding in the current screening programme. The Committee recommends inclusion of OCTN2 in the neonatal screening programme.

3.2.6 *Mucopolysaccharidosis type 1 (MPS I)*

MPS I is a lysosomal storage disease and is characterised by broad phenotypical variation. The most prevalent phenotype (> 80 percent of MPS I patients) is the most severe: the Hurler phenotype.[45] Patients with this phenotype (MPS I-H) have progressive physical complaints in the first life year and progressive brain disease from around the second year. Untreated children with MPS I-H die in their second decade. The median age at which MPS I-H is diagnosed in the Netherlands is 10 months.[46] However, distribution is substantial. In patients with the much rarer, relatively milder phenotypes of MPS I (the Hurler/Scheie and Scheie phenotypes; MPS I-H/S and MPS I-S), most progressive physical complaints develop well before age 10. These milder phenotypes do not cause brain disease.

Treatment of MPS I-H consists of hematopoietic stem cell transplantation (HSCT). Early HSCT may prevent or limit cognitive deterioration in MPS I-H patients and prevents the progression of a number of physical symptoms.[47,48] The recent introduction of the technique using umbilical cord stem cells for HSCT significantly increased chances of finding suitable donors quickly and thereby improved the prognosis. For patients with the relatively milder phenotypes of MPS I (MPS I-H/S and MPS I-S), treatment consists of intravenous enzyme therapy (ERT, Aldurazyme).[48] This treatment can stop or reduce the progression of a number of physical complaints.

The screening method for MPS I is enzyme measurement. The introduction of umbilical cord blood as stem cell source significantly improved chances of

rapid and successful HSCT in MPS I-H. Early detection may achieve significant health gain. On this basis the Committee recommends the inclusion of MPS I in the neonatal screening programme.

3.2.7 X-ALD

X-ALD is a peroxisomal metabolic disease arising from mutations in the ABCD1 gene on the X-chromosome.[49,50] X-ALD causes three different clinical presentations in men: adrenal insufficiency (Addison-only phenotype) before the age of 18 years; progressive cerebral demyelinisation (cerebral ALD) before the age of 18 years; and myelopathy (adrenomyeloneuropathy phenotype) or combinations of these symptoms.[51] It cannot be predicted which symptoms will develop in men with X-ALD, even within the same family. In women, a form of adrenomyeloneuropathy usually develops at higher ages.[52]

Some forms of X-ALD in boys and men can be effectively treated.[51] Treatment of adrenal insufficiency consists of timely initiation of hormonal suppletion. Cerebral ALD is treated curatively by hematopoietic stem cell transplantation (HSCT), where stem cells can be used that have been isolated from umbilical cord blood enabling rapid transplantation.[53,54] Untreated cerebral ALD is virtually always rapidly progressive and lethal. Without screening, diagnosis is almost always too late for successful HSCT treatment. Adrenomyeloneuropathy is untreatable.

There is a reliable X-ALD test consisting of the measurement of metabolites in heel prick blood. Follow-up screening is needed using periodic MRI scans to detect the development of cerebral X-ALD before complaints or neurological abnormalities are found in the neurological examination, in order for curative stem cell transplantation to take place.

Screening for X-ALD is useful only in male newborns, as symptoms in women usually develop later and are untreatable. The Committee recommends inclusion of X-ALD in the neonatal screening programme for male newborns only. The possibility to screen only male newborns without loss of efficiency should be studied.

3.2.8 Guanidinoacetate methyltransferase (GAMT) deficiency

GAMT deficiency is a metabolic disease of the creatine metabolism. Patients present with delayed neurological development, epilepsy or a motor disease. Treatment consists of creatine supplements, possibly combined with other measures. Untreated GAMT deficiency causes progressive brain damage; early

treatment may prevent this damage.[55] A screening test for GAMT deficiency was developed very recently, with screening for guanidinoacetate and increased guanidinoacetate/creatine ratio. Results are positive, with only 0.08 percent false-positives and no false-positives after the second test. No false-negatives where found in two pilot studies.[56,57] The Committee recommends the inclusion of GAMT deficiency in the neonatal screening programme.

3.3 Conditions in category 2A

3.3.1 Pompe disease

Pompe disease (glycogen storage disease type II) is a lysosomal storage disease presenting with progressive muscular condition. The condition causes respiratory problems, motor problems and shortened life expectancy. The condition may manifest at any age. There is a spectrum where classical (infantile) and non-classical (non-infantile) presentations can be distinguished.[58]

The classical form of Pompe disease manifests shortly after birth and is characterised by progressive cardiomyopathy and muscular weakness. Virtually all untreated children die within the first year. Patients with the non-classical form have a more gradual history; the first symptoms do not manifest until (young) adulthood. Progressive muscular disease may render these patients dependent on a wheel chair and respiratory support, even in their youth.[58]

Intravenous enzyme therapy was registered as treatment for Pompe disease in 2006. This treatment has a positive impact on survival, hypertrophic cardiomyopathy and the attainment of development milestones in patients with the classical infantile form.[59] In patients with the non-classical form, a significant effect was demonstrated on walking distance, lung function, muscle strength, fatigue and survival.[60] The costs of enzyme therapy are very high and patients need medication for life. Against this background, a discussion took place in the Netherlands in 2012-2013 on the efficiency of reimbursement of this medicine in the non-infantile form of this condition.

The Committee feels that neonatal screening for Pompe disease should focus on the infantile form, seeing patients with the non-classical forms often can live many years, sometimes until far into their adult life, without symptoms. Furthermore, the treatment effect is relatively lower in these patients.

Screening by enzyme measurements will detect patients with the classical infantile form of the condition and the non-classical form. By mutation analysis, this latter patient group could be distinguished from patients with the classical, infantile form.

The Committee deems it inadvisable to not report these individuals with a non-classical, non-infantile form of Pompe disease. A way to screen directly and exclusively for the infantile form of Pompe disease is mutation analysis of the gene that codes for the deficient enzyme in this condition. The current state of technology however is insufficient to use mutation analysis as first-line test within the neonatal screening programme. However, the Committee expects this will become possible in the near future (see Chapter 9). The Committee does not recommend neonatal screening for Pompe disease.

3.3.2 Cerebrotendinous xanthomatosis (CTX)

CTX is caused by a defect in the bile acid synthesis. It is a condition with slowly progressive, eventually severe neurological symptoms.[61,62] CTX can be effectively treated with pharmaceuticals (bile acid supplements, possibly combined with statins). Earlier treatment initiation improves efficacy.[62,63] There is a promising test for the diagnosis of CTX in blood spots. However, the test is insufficiently validated in neonatal blood spots.[64] The Committee recommends this validation be performed as soon as possible using a research study. If this method meets the specificity and sensitivity criteria, the Committee recommends inclusion of CTX in the screening programme. The Committee currently does not recommend inclusion of CTX in the neonatal screening programme.

Category 2A Conditions where neonatal screening may prevent significant, irreparable damage but for which no good test methods are available that have been tested within the neonatal screening setting.

Conditions	Recommendation: Include in neonatal screening yes / no	Is there broad phenotypical variation, and if so, what is the focus of screening?	Committee considerations
Alpha-glucosidase deficiency; Pompe disease[a]	NO	Yes, only for the 'infantile' form	If a screening method is developed that only identifies patients with the infantile form, the infantile form of Pompe may be included in the screening programme, provided there are reasonable guarantees that treatment is/will remain available for identified patients
Cerebrotendinous xanthomatosis (CTX)	NO	No	The Committee recommends encouragement of a pilot study of the sensitivity and specificity of a previously developed screening method. If this method is developed and meets the specificity and sensitivity criteria, the Committee recommends inclusion of CTX in the screening programme
Phosphogluco-mutase 1 deficiency (PGM1)	NO	Yes, for all forms	The Committee recommends encouragement of a pilot study of the sensitivity and specificity of a previously developed screening method. If this method is developed and meets the specificity and sensitivity criteria, the Committee recommends inclusion of PGM1 in the screening programme
Cystinosisa[a]	NO	No	Reliable cystinosis screening currently appears possible only using mutation/gene analysis
Methylene tetrahy-drofolate reductase deficiency[a] (MTHFR)	NO	No	Reliable MTHFR screening currently appears possible only using mutation/gene analysis

[a] These conditions can be screened at the DNA level only, see Chapter 9.

3.3.3 *Phosphoglucomutase 1 deficiency (PGM1)*

Phosphoglucomutase 1 deficiency may cause low blood sugar levels and other symptoms, including heart failure. PGM1 deficiency may cause early death.[65,66] There is phenotypical variation.

Low blood sugar levels can be successfully treated by the administration of complex carbohydrates (such as corn starch) in the diet. Additionally, a few patients were successfully treated with dietary galactose supplements.[67]

A recent publication describes a test method for PGM1 deficiency in blood spots. This method has not yet been validated for the neonatal population.[67] The Committee recommends this validation be performed by a research study. If this method meets the specificity and sensitivity criteria, the Committee recommends inclusion of PGM1 in the screening programme. The Committee now does not recommend inclusion of PGM1 in the neonatal screening programme.

3.3.4 *Cystinosis and Methylene tetrahydrofolate reductase deficiency (MTHFR)*

Category 2B Conditions where neonatal screening may achieve more limited health gain and good test methods exist.

Conditions	Recommendation: Include in neonatal screening programme yes / no	Is there markedly broad phenotypical variation, and if so, what is the focus of screening?	Committee considerations
Galactokinase deficiency (GALK)	YES	No	Neonatal screening may prevent the development of (double-sided) cataract in patients with GALK deficiency. Double-sided cataract in newborns may cause irreparable loss of vision if not treated in time GALK deficiency screening does not lead to incidental findings
Argininosuccinate lyase deficiency (ASL)	NO	Yes	There is insufficient evidence that early treatment initiation significantly improves the disease history

A reliable detection technique is unavailable for these two conditions, which can be effectively treated. Not until mutation analysis in the first line of screening is possible, can inclusion be considered. See Chapter 9 for this test method.

3.4 Conditions in category 2B

3.4.1 Galactokinase (GALK) deficiency

Patients with GALK deficiency develop bilateral cataract in the first weeks of life.[68-70] The exact pathophysiology of cataract formation is unknown. Cataract that is not treated or too late, causes severe or even complete loss of vision, which may cause far-reaching damage in the child's development.[68,69]

Treatment of galactokinase deficiency consists of a low-galactose diet. Timely initiation of the diet (before the age of 2 months) prevents cataract formation and thereby visual impairment.[69-71] A reliable screening method is available for galactokinase deficiency.

GALK deficiency is classified under category 2B, as the preventable health damage is relatively less substantial than in some other metabolic diseases. Nevertheless, the Committee deems the health gain sufficient for inclusion in the screening programme and therefore recommends the inclusion of GALK deficiency in neonatal screening. However, an additional enzyme test is needed, which is why the Committee recommends having a pilot study performed first.

3.4.2 Argininosuccinate lyase deficiency (ASL)

ASL deficiency is a defect in the urea cycle. ASL patients may present with severe neurological symptoms as a result of hyperammonemia in the neonatal period. There is also a late-onset form, which manifests in youth and is largely characterised by cognitive limitations. Even though ASL can be treated with a low-protein diet, prognosis is poor.[72] If hyperammonemia develops, the risk of very severe brain damage is high. It is also unclear to what extent early treatment initiation in patients with the late-onset form can prevent brain damage and thereby cognitive limitations.[73] A good test is available, but it is associated with various incidental findings. The Committee expects that health gains from ASL screening are too limited and therefore does not recommend inclusion of this condition in the neonatal screening programme.

3.5 Conditions in category 3

Screening for metabolic diseases does not achieve health gain in newborns, and the Committee therefore recommends against inclusion of these diseases in the

neonatal screening programme. We refer to the background document for detailed information on these conditions.

Category 3 Conditions where no significant health gain is achieved with neonatal screening.

Conditions	Recommendation: Include in neonatal screening yes / no	Committee considerations
Multiple Acyl-CoA dehydrogenase deficiency (MADD)	NO	In the Committee's opinion, there is no evidence for sufficient health gain from detection by neonatal screening
Citrulinemia type 1	NO	In the Committee's opinion, there is no evidence for sufficient health gain from detection by neonatal screening

Chapter 4

Immune and infectious diseases

The scientific literature and foreign authorities identify three immune and infectious diseases as candidates for inclusion in the neonatal screening programme. In this Chapter, the Committee will assess to what extent these conditions satisfy criteria for inclusion.

4.1 SCID

Severe combined immune deficiency (SCID) is a severe primary immunodeficiency, which is virtually always fatal without treatment. SCID is a collective name for at least 21 gene defects that all cause absence of or defects in T-lymphocytes*, sometimes combined with problems in other cell types of the immune system. Virtually all diseases are caused by a defect of the normal T-cell development in the thymus gland. Severe recurrent infections start to develop beginning at age four to six months. Characteristic of SCID, these children have stunted growth and delayed development.

Treatment of SCID consists of hematopoietic stem cell transplantation (HSCT) with stem cells from the bone marrow or umbilical cord blood. If transplantation is performed before the age of 3.5 months and before the first severe infection, chances of success are highest. The time gained by neonatal

* These are IL2Rg, JAK3, IL7Ra, CD3G, CD3D, CD3E, CD3Z, ZAP70, lck, CD45, ADA, PNP, AK2, RAG1, RAG2, Artemis, LIG4, XLF, DNA-PKcs, XRCC4 and CORO1a.

screening is vital to SCID patients. Gene therapy or enzyme therapy is needed and better than HSCT in some forms of SCID.[74]

The SCID test method uses so-called TRECs (T-cell receptor excision circles), which are missing in SCID patients. Virtually all gene defects underlying SCID may be identified using TREC analysis, with the exception of the extremely rare ZAP70-SCID. There is now experience with neonatal screening using TRECs and the results are promising. Also new forms of SCID are found, and also other T-cell defects such as the DiGeorge syndrome as incidental findings. Some incidental findings are conditions that are untreatable.[75,76]

In the Committee's opinion, this disadvantage of unavoidable incidental findings does not outweigh the above-described advantage of improved treatment by early diagnosis. The screening test is indeed more complicated and expensive than other neonatal test methods, but would seem to stay within acceptable limits of efficiency. The Committee does consider an exact cost-benefit analysis indicated as part of the implementation test. The Committee classifies SCID in category 1 and therefore recommends inclusion in the neonatal screening programme.

4.2 XLA

A-gamma-globulinemia refers to a group of primary immunodeficiencies where the production of antibodies by B-lymphocytes is abnormal or B-cells are missing entirely. The most common form (85%) of this disease is XLA (X-linked a-gammaglobulinemia), caused by mutations in Bruton's tyrosine kinase (BTK) gene. Severe recurrent infections develop in affected boys starting in the second half of their first year. Untreated XLA results in chronic pulmonary disease and mortality at a young age (median 17 years). Most patients present with infections. In more than half of the cases these are severe infections, such as lower respiratory infections, sepsis, meningitis.[77] In a cohort study of 62 patients, 17 patients had male family members on the mother's side, with a history of early death following recurrent infections without a diagnosis. A large proportion of these children likely had XLA, in view of the hereditary pattern of XLA.[78]

Treatment consists of immunoglobulin preparations, combined as needed with prophylactic antibiotics. Infections are much less common in patients treated with these antibiotics. Nevertheless treatment is only partially effective and also very expensive; therapy must be given for life. Neonatal screening for XLA would enable earlier initiation of immunoglobulin therapy, which almost certainly would result in health gain. A proportion of the XLA patients presents

with lung damage, particularly patients diagnosed in a later stage. According to the Committee, this suggests that early diagnosis and treatment may prevent lung damage.

XLA can be identified in heel prick blood using the KREC test.[78-81] Additionally, a combined TREC/KREC test kit is being developed (Perkin-Elmer). In principle, the KREC test confirms all primary immunodeficiencies where B-lymphocytes are missing. The KREC test has already been used successfully in heel prick blood in Japan, New York and Sweden.[80] The Committee considers detailed identification of the exact characteristics of the KREC test in routine neonatal screening a requirement. It consequently includes XLA under category 2A and recommends initiation of a research study of the test characteristics. Inclusion in the neonatal screening programme can then be reconsidered.

4.3 Congenital cytomegalovirus

Cytomegalovirus (CMV) is a DNA virus and member of the herpes viral family. CMV infection usually causes few symptoms in healthy adults. Prenatal infection, perinatal infection in premature birth and infection secondary to an impaired or inhibited immune system can cause symptoms.[82]

Congenital CMV infections may cause severe neurological damage and sensorineural hearing loss. There is significant phenotypical variation: some children are born severely affected, whereas others are asymptomatic. Children with the poorest prognosis have severe neurological symptoms at birth. Of the other infected children born without symptoms, 13.5 percent will become symptomatic: hearing impairments in particular.[83]

Treatment with antivirals appeared effective for severely symptomatic children in a small RCT.[84] No uncontroversial intervention options exist for asymptomatic, congenitally infected children.[85] These children may be followed up intensively for hearing loss, but efficacy is unknown. Earlier detection of hearing loss, whether or not as a result of congenital CMV, results in improved speech development.[86]

A congenital CMV infection can be identified with considerable sensitivity (60-100%) and specificity (99.9%) in heel prick blood.[87] However, the test currently does not distinguish between groups that will and will not become symptomatic. This strongly limits the predictive value for hearing loss and other symptoms.

Neonatal screening for congenital CMV should focus on children who are asymptomatic at birth, where hearing loss or associated developmental problems

may be prevented. However, intervention will not prevent hearing loss; intensive follow-up screening for hearing loss is an option, but effects for this group have not been adequately studied yet. Furthermore, the group that will become symptomatic cannot (yet) be recognised in neonatal screening.

In view of the lack of health gain for detected asymptomatic children, the Committee includes CMV in category 3: it is now not eligible for inclusion in the neonatal screening programme.

The Committee does recommend the following primary preventive measures. Effective hand hygiene and preventing contact with saliva and urine of possibly infected children may reduce the number of infections.[20] The Committee therefore recommends inclusion of this information in the Zwanger (Pregnant) brochure (www.rivm.nl) and in a first visit to the obstetrician, and that this information be provided prior to conception. Congenital CMV should also be suspected in unexplained hearing loss. CMV can be diagnosed in a later stage by analysing blood from the heel prick card. The Committee also recommends additional studies of strategies to adequately recognise children who will become symptomatic in a later stage. Furthermore, research is needed into effective treatments for this group of children.

Chapter 5

Practical experience and modifications

Neonatal screening is evaluated once every year in the Netherlands. Sometimes things turn out different than expected. This is true for two conditions in particular: cystic fibrosis (CF) and homocystinuria (HCY). The Committee will ascertain which modifications are feasible or advisable.

5.1 A programme in development

Screening frequently identifies more sick children than expected. Evaluations by the Netherlands Organisation for Applied Scientific Research TNO and the central register of diagnosed metabolic diseases indicate that in the period 2007-2011 biotinidase deficiency was diagnosed much more frequently than expected based on historic data. The reason for this was that screening identified relatively many mild variations that initially were also regarded as patients. Pediatricians recently found that children with enzyme activity >20% do not require treatment. These children are now no longer diagnosed as patients. A significant proportion of patients detected at the time have such a mild picture that in retrospect, treatment was not necessary. Tightening the diagnostic criteria reduced the number of patients since 2012 substantially versus previous years.[88]

Cut-off points were changed for a number of conditions. The decision tree for congenital hypothyroidism was amended based on changed insights and statistical evaluation by TNO (Loeber, press com). The cut-off points or tests may be unsuitable for the Dutch population, something that may not always be

known prior to implementation of the test. Also, a new test kit of lesser quality may be introduced. This was initially the case in the introduction of galactosemia in the screening programme. Based on these experiences, the Committee recommends pilot studies for all candidate conditions for inclusion; also when initially few technical problems are anticipated.

5.2 Cystic fibrosis

5.2.1 Discussion items

Cystic fibrosis (CF) is a serious condition that has been included in neonatal screening since 2011. Two issues were debated prior to the implementation of CF screening.

Not until after the 2005 advisory report did it become clear that despite the lack of treatments for the underlying disease of CF, treatments are available to reduce and relieve symptoms. This improves growth and early diagnosed patients require lesser treatment than patients diagnosed at a later stage.[89] Screened CF patients have better nutritional status and lung function up to higher ages. Their life expectancy is also higher.[90] Additionally, there are therapeutic developments, such as ivacaftor, a medicine targeting the genetic defect by certain mutations, which is promising for a subset of CF patients.[91] In the Committee's opinion, health gain for screened patients is compelling, and neonatal CF screening should therefore certainly be continued.

At the time of the 2005 Health Council advisory report, there were concerns about the quality of the test procedure; a study for the best CF test in the Netherlands was therefore initiated. When the results of the so-called CHOPIN study were reported, the Health Council used this as a basis to recommend CF screening using a protocol where screening was started for two metabolites, followed by DNA analysis.[6]

5.2.2 False-negatives and change of policy

Two patients with classical CF were recently identified who had not been detected in the neonatal screening programme and therefore were false-negative. These children both had a deletion that could not be detected by the extensive second DNA step. The question arose whether perhaps more classical CF patients with such a deletion had been overlooked. All CF carriers from the CHOPIN study and neonatal screening were therefore called up for a sweat test. One other child in this group was found to have classical CF. The policy has now

been changed. All children who would previously have been designated as carrier, undergo a sweat test.

When CF screening indicators are calculated after (retroactive) implementation of the policy change, sensitivity goes down to 91 percent, which is lower than expected. As a result of the policy change, 22 (actual) carrier children will undergo a needless sweat test in order to diagnose an additional 3 sick children.

5.2.3 *Potential screening protocols*

The Dutch screening protocol combines various protocols. It is a combination of biochemical screening for immunoreactive trypsinogen (IRT) and pancreatitis associated protein (PAP), followed by initially limited mutation analysis (DNA step) and possibly extended mutation analysis (by sequencing of the exons and exon-intron transitions in the CFTR gene: EGA step), and a procedure to identify possibly overlooked patients (failsafe procedure). Predicted sensitivity and specificity of the strategy are 94.6% and 99.99%. The true sensitivity cannot be determined until after implementation and detection of a substantial number of children.[92] The screening protocol aims at minimising the number of healthy children referred for a sweat test and limiting the number of identified carriers and non-classical CF patients.

Alternative protocols include IRT, followed by PAP screening and IRT followed by mutation analysis. The first protocol has a higher number of false-positives and therefore lower validity. The second protocol, based on the usual IRT cut-offs, detects more carriers and non-classical CF patients versus the current procedure in the Netherlands, resulting in lower specificity. Furthermore, IRT followed by mutation analysis is less suitable for groups of non-North European descent, as relatively more rare mutations in the CF gene are found in this population. There are opportunities to improve screening.

The EGA step is unable to detect deletions. The MLPA technique (Multiplex Ligation-dependent Probe Amplification) may serve as an alternative: it is a fast, simple and cheap method to detect larger deletions with a very high resolution. The Committee recommends a pilot study in which MLPA examination is added to the EGA step. A minimal amount of DNA is needed for a reliable MLPA test. In practice this means an extra blood spot would be required. Additional MLPA analysis is performed in all patients in whom EGA demonstrates only one CFTR mutation. In this way, patients with a point mutation on the one allele and a larger deletion or duplication on the other allele may be detected. The advantage is that no carriers need to be called up for a sweat test, avoiding unnecessary burden and worries. The disadvantage of no longer performing sweat tests in patients with

only one demonstrated mutation after EGA is that patients with extremely rare mutations (not detected by MLPA either) will be overlooked.

A second modification is the content of the mutation panel used in the first DNA step. The R117H 7T-9T mutation in particular is the focus of discussion within the professional field, as this is a pathogenic mutation with the penetrativeness of only 0.03%.[93] Consequently, 16 babies were identified where the diagnosis of CF cannot be excluded with 100% certainty, but nor can it be demonstrated. This finding causes much unrest among the parents of these children. In order to optimise the screening, it could be considered to no longer regard R117H as positive. France screens for R117H 7T-9T, but the current consensus there is that this mutation should be removed from the package.

The Committee supports the strategy for unexpected false-negatives in CF screening and considers the policy change as an example of advancing science. It recommends a study of the technical feasibility of addition of the MLPA test to the EGA step in the screening protocol, in view of the more limited number of false-positives. The Committee assumes that the National Advisory Committee for Neonatal Screening - Cystic Fibrosis (ANS-CF) can give the Dutch National Institute for Public Health and Environmental Protection (RIVM) a weighed recommendation on improvements in the CF screening protocol.

5.3 Homocystinuria

5.3.1 False-positives and change of policy

Homocystinuria (HCY) is a metabolic disease that may cause short-sightedness and skeletal abnormalities. Arterial and venous thrombosis also develop. Severe psychomotor retardations and other neurological phenomena occur at a later stage. In addition to the classical form, less severe forms of HCY occur characterised by anemia (megaloblastic anemia) and mild mental retardation.[7] HCY screening in the Netherlands was postponed on 1 October 2010 in view of the large number of false-negatives.

5.3.2 Finding a better screening protocol

The initial protocol screened for elevated methionine (>80 uM). This would detect HCY on the basis of cystathionine beta synthase (CBS) deficiency. HCY can also be caused by methylene tetrahydrofolate reductase (MTHFR) deficiency or cobalamin (Cbl) defects (particularly CblC). These latter forms of HCY would not be detected using the original method, where MTHFR deficiency can be

effectively treated but not CblC. When developing new screening strategies for HCY, all treatable forms of HCY should be detected. The Committee sees two potential methods, which both need to be developed or validated.

The first method is measuring total homocysteine in the blood spots. Technically this is quite feasible, but it is currently unknown how many HCY patients this would detect. It is also unknown whether and which other diseases are characterised by total homocysteine. Thorough research is therefore needed before this screening method can be recommended.

A second method is direct screening for underlying mutations causing HCY. Genetic tests as a first step in heel prick screening are technically still beyond our reach. However, developments in this field are rapid. The MIPS test is a promising method according to the Committee (see also Chapter 9). Naturally, a genetic test first requires thorough validation.

The Committee concludes that HCY screening was rightly postponed. HCY is currently in category 2A, and the Committee therefore recommends removal of HCY from the neonatal screening programme. As soon as new test methods have proven their value, inclusion of HCY in the programme can be reconsidered.

Chapter 6

Incidental findings, including carrier status

One of the Minister's questions involves potential 'bycatch' or 'incidental findings' in neonatal screening: findings that were not intended. How should we deal with them? The Committee ascertains which types of incidental findings may occur and which interests they involve. We will then formulate basic principles for dealing with incidental findings.

6.1 A palette of incidental findings

Incidental findings may occur unexpectedly, but can sometimes be foreseen in neonatal screening: the occurrence of incidental findings may already be obvious from the choice of the test. This Chapter will not focus so much on the truly unexpected incidental findings. An ad hoc policy is already in place for this. Emphasis here is on foreseen incidental findings for which policy may be formulated. Incidental findings can be subdivided into categories on the basis of a number of distinguishing characteristics.

In line with a previous Health Council advisory report on incidental findings in diagnostics (2014)[94], they can be subdivided into three classes: clinically relevant findings; clinical findings (as yet) unclear; and findings that are not clinically relevant.[95]

Within the category of clinically relevant findings, further distinction can be made between actionable findings where treatment or prevention is possible, and non-actionable findings that may be relevant prognostically, but for which no

treatment or prevention is available. An actionable incidental finding may be impacted favourably using treatment options.[95] Examples of actionable incidental findings diagnosed in the current programme include beta thalassemia major and OCTN-2. Early detection of these conditions achieves substantial health gain for the child, provided they are treated. In conclusion, it is relevant whether incidental findings are important to the screened child itself or third parties, particularly the parents.

In this Chapter, the Committee will address the clinically relevant findings category in particular, as they impact the health and well-being of the child and/or its family.

6.2 Interests, basic principles and Committee opinion

In Chapter 2, the Committee outlined the criteria for deciding which diseases should be included in the neonatal screening programme. These criteria cannot be applied automatically to the question of incidental findings, but do provide guidance. The primary basic principle in the context of reporting incidental findings is that the child's interest should take highest priority.

6.2.1 Clinically relevant and actionable

Reporting incidental findings within this category is obviously in the child's interest. In the Committee's opinion, this means that parents should be informed of actionable, clinically relevant incidental findings. Parents do not have a right to not know in view of their child's interests, even if the incidental finding may impact themselves and their other or future children.[96] The Committee feels that clinically relevant and actionable conditions should be reported in the interest of the child.

6.2.2 Clinically relevant and non-actionable

If screening detects clinically relevant incidental findings that are not treatable or otherwise actionable, it is not in the child's direct health interest to report them. Reporting such findings to the parents may even harm the child's interests. It may cause worry and anxiety in the parents and their (growing) child about its future health, and may cause problems in terms of insurance and work. This situation is referred to as a child's right to an open future.[97] Anticipated damage dat de and problems to the child may also be limited, and offset by another advantage.

This is the case when a detected, but otherwise difficult to diagnose condition manifests early in life. If such an incidental finding were to be reported, a so-called prolonged 'diagnostic odyssey'could be avoided. If the condition manifests later in life, the advantages of reporting may also outweigh the disadvantages, but this becomes less likely.

The Committee takes the view that incidental findings suggesting non-actionable conditions should in principle not be reported to parents. An exception can be made for conditions manifesting very rapidly, but where diagnosis is difficult and possibly prolonged.

6.2.3 Carrier status

Carrier status is a clinically relevant incidental finding that may not become relevant for the child until he or she reaches the reproductive age. Carrier status is important to parents at an earlier stage.

In the current screening programme, carrier status for sickle cell disease in a newborn is reported to the parents, unless they indicated they do not wish to know. On the basis of carrier status information about the child, parents may obtain information about their own potential carrier status. Carrier status in a child always provides genetic information about the parents: one of the parents or both parents are also carrier of the condition. To use this information, parents must have themselves tested for carrier status. Once they know whether they are both carriers, they can make informed reproductive choices.

The child's knowing his or her carrier status can sometimes be in his or her interest. If carrier status reporting for the child is followed by carrier status tests in the parents, both parents turn out to be carriers, and this prompts reproductive choices preventing the birth of a seriously ill brother or sister, negative consequences of living with a chronically sick child are prevented not only for the parents, but also for the rest of the family (including the carrier in question).[98] This advantage is very indirect and fully dependent on the parents' next steps and choices.

Carrier status reports on the basis of neonatal screening may cause confusion for the parents: a child has just been born, the parents are often not (yet) thinking of subsequent pregnancies. Sometimes parents think (or this causes them to think) that carrier status has serious health consequences for their child.[99] Many parents indicate they wish to receive carrier status information about their child.[100] Extensive counselling is required to adequately explain carrier status information and potential reproductive choices.

Carrier status is much more frequently found than the recessive conditions for which the neonatal screening programme has been set up. If more conditions are included in neonatal screening with carrier status as unavoidable incidental finding, the number of carrier status findings will increase proportionally. A future development of screening at the DNA level will compound this problem.

The Committee foresees that if carrier status reporting to parents is continued, the screening programme will be disproportionally burdened by the necessity of extensive counselling for parents. This would quickly drown out the consent procedure of the neonatal screening itself.[101]

Importantly, reporting the child's carrier status to parents interferes with the child's privacy and right to not know.[102] Carrier status of children is reported in many countries, but little is known about the consequences.[103]

This practice is also being debated in the literature. Clinicians often feel an obligation to report, but the question is if this applies within the context of public healthcare.[102,104]

Weighing all factors, a Committee majority feels that reporting carrier status to parents to enable reproductive choices is inappropriate within the context of neonatal screening. Neonatal screening should not become carrier status screening in disguise, but remain a clear screening programme aiming for health gain in the screened child. Additionally, the Committee considers neonatal screening an unsuitable moment for carrier status reporting. The Committee regards the preconceptual phase as the appropriate moment for carrier status screening.

6.3 Conclusion

The Committee is of the opinion that incidental findings in a programme aimed at neonatal screening should be avoided where possible. In line with the Health Council advisory report on incidental findings in diagnostics[94], the Committee recommends to consistently opt for a test method with the lowest chance of incidental findings, provided multiple tests are available. If nevertheless an incidental finding occurs, the child's interest should take priority in the question whether it should be reported. In this connection, the Committee recommends that in principle only clinically relevant, actionable incidental findings should be reported. If such incidental findings are anticipated on a structural basis, the Committee recommends consideration as to whether these incidental findings in and of themselves are eligible for inclusion in the neonatal screening programme. Examples include OCTN2 and severe forms of thalassemia.

Incidental findings suggesting a condition that will not manifest until adulthood or a condition that is not actionable or hardly so, are in principle not eligible for reporting. A potential exception is the reporting of a non-actionable condition manifesting early in life. If the child does not have a long life expectancy, it cannot be harmed in its right to have an open future, but the child can be spared a diagnostic odyssey.

A Committee majority recommends not reporting the child's carrier status to parents within the context of neonatal screening. It realises that this position deviates from the conclusion of the previous Committee advising on heel prick screening.[7] The Committee raises a practical and fundamental argument for this.

Reporting imposes a high burden on the screening programme and may frustrate the programme. The Committee feels strongly about an unambiguous programme. Importantly, the information and consent procedure for screening should not be drowned out by counselling on how to deal with incidental findings. Additionally, the Committee feels strongly about protecting the child's interests as directly as possible. His interest to be able to decide himself, at a chosen moment, between knowing and not knowing, principally outweighs the parents' interests to make good reproductive choices, according to the Committee. We realise that good information is very valuable to parents in their reproductive choices. However, the Committee considers neonatal screening an unsuitable moment for carrier status reporting. The Committee finds carrier status screening in (prospective) parents in the preconceptual or prenatal period (followed by prenatal diagnostics in the child as needed) more suitable.

The Committee's position impacts the practice of dealing with incidental findings, and the reporting of sickle cell disease carrier status in particular. This is addressed in Chapter 7.

Chapter 7

Hemoglobinopathies and incidental findings

The previous Chapter addressed incidental findings and carrier status in a general sense. This issue is relevant in particular in sickle cell disease (SCD).

7.1 Sickle cell disease and other hemoglobinopathies

Sickle cell disease (SCD), beta thalassemia major (TM) and HbH disease are genetic hemoglobin diseases. SCD is caused by a structural abnormality in the betaglobin chain of the hemoglobin protein. This causes chronic hemolytic anemia, vascular occlusion in vital organs, painful bone crises, and increased susceptibility to infections with encapsulated bacteria. Sickle cell disease occurs mainly in the population originating in West and Central Africa. The majority of Dutch patients come from Surinam and various West African countries.[105]

TM is caused by reduced or non-production of the betaglobin chains of hemoglobin, resulting in chronic severe hemolytic anemia.[106] TM is found in the Mediterranean and (South East) Asian populations. Dutch patients mostly include people from Turkey, Morocco, China, Hong Kong and Iraq.[105]

HbH disease is caused by a markedly reduced production of the alpha-globulin chains of hemoglobin, which also causes moderately severe, hemolytic anemia.[107,108] HbH disease is prevalent in the (South East) Asian population. Dutch patients mostly include people from Hong Kong and China.[105]

7.2 Practical experience

7.2.1 SCD: 2005 advisory report

An advisory report was issued in 2005 to include sickle cell disease in the neonatal screening programme; the advisory report also addressed incidental findings of SCD screening. The then Committee did not consider the bycatch of severe forms of thalassemia a 'major impediment' to the inclusion of SCD in screening (p 75-76).[7] It recommended the reporting of these incidental findings, as SCD carrier status, unless parents had expressed prior objection.[7] Parents can express their wish not to receive information about SCD carrier status on the heel prick card. This is a so-called opt-out procedure. Some 4% of the parents have opted not to receive information in recent years.[18]

The desire to better inform the population at risk was the motivation to report SCD carrier status. Only 15 percent of the population at risk had knowledge of their carrier status. The Netherlands did not formulate policy on providing information to the population at risk in the first line. SCD carrier status reporting as part of the neonatal screening programme was considered an opportunity to improve this situation. Despite the reporting of carrier status on the basis of neonatal screening, the knowledge on hemoglobinopathy in the population at risk has virtually not expanded in recent years.[109]

7.2.2 Current screening scrutinised

SCD was included in the neonatal screening programme in 2007.[110] The SCD test used is high performance liquid chromatography (HPLC). Various hemoglobin forms are separated in this procedure. The normal forms are the foetal form (HbF) and the adult form (HbA). Abnormal forms are separated qualitatively and quantitatively in so-called peaks.

Certain peak patterns suggest the presence of severe hemoglobinopathy, in this case SCD, TM and HbH. Screening also identifies carrier status for SCD and some other SCD-related mutations (such as HbC, HbE, HbD). HPLC does not detect TM carrier status. Some alpha thalassemia carriers are identified.

A total of about 50 children with sickle cell disease are identified each year, and some 800 SCD carriers. The parents of the latter children group are informed of their child's carrier status. Carrier status of SCD-related mutations (such as HbC, HbE, HbD) are also detected, but not reported to parents.

The practice of reporting SCD carrier status is not without problems. Some GPs consider themselves ill equipped for conversations with parents on SCD carrier status. Furthermore, some GPs think that SCD carrier status may cause a slight health risk (anemia) in the child. They wrongly refer the child to a pediatrician.[109]

Only a small percentage of the parents is tested by the GP on the basis of carrier status reports, and only very few risk couples are referred to clinical genetic centres.[111,112] The number of referrals following introduction of carrier status reporting in 2007 has not increased.

A part of the group with an increased risk of SCD and thalassemias has inadequate health skills and includes a relatively high proportion of people with limited education. This may explain the limited number of parents applying for genetic counselling.[109,113] An additional problem is the obligatory deductible excess; consulting clinical genetic centres costs the parents (much) money, which may be perceived as a financial obstacle.

7.2.3 Criticism and Committee position

Incidental findings of SCD screening are now being debated. The opt-out procedure referred to under 7.2.1 for carrier status reporting is being criticised. Olsthoorn-Heim et al argue there is no obligation to report carrier status. The interest that is served is the parents' ability to make reproductive choices. However, strictly speaking, parents are not entitled to this information, as the screening is child-centred. But the information can be reported, provided there are no important objections.[114] The opt-out procedure is not the appropriate instrument for this. An opt-out system implies considerable pressure to be informed. Opt-in would be more logical if information is irrelevant to the child. In view of the child's primary interest, it may even be better not to report carrier status, according to these authors. They also point out that carrier status tests on behalf of parents would need to take place in the preconceptual period.[114] The Committee endorses this position.

The fact that SCD carrier status is reported but other related mutations are not, is a second point of criticism. These are mutations which in combination with BS may also cause SCD.

What does this mean in the light of considerations in Chapter 6?

In principle, a test that has no (or fewer) incidental findings is preferred, if the test has sufficient quality, is permanently available, and at a reasonable price.

There is a promising development in the hemoglobinopathy screening test. Tests are being performed in Belgium for SCD and TM using tandem mass spectrometry on trypsin-treated blood.[115,116] As in HPLC, this test method has incidental findings of carrier status. However, according to a recent publication, those who are sick can be specifically identified and the majority of carriers can remain undetected using an additional analytical step.[117] The Committee recommends a pilot study of the feasibility and validity of this test in the Dutch situation. In practice this will involve a change, because of the trypsin treatment and because it requires a separate mass spectrometric run.

Until this new technology can be implemented, we will need to consider how to deal with the incidental findings of the existing test in the near future. Incidental findings of other hemoglobinopathies are clinically relevant for the screened newborn and some can also be treated. The Committee examines in paragraph 7.3 whether the severe forms of TM and HbH disease are eligible for independent inclusion in the neonatal screening programme.

In principle, the Committee considers carrier status reporting inadvisable. A Committee majority consequently recommends not reporting SCD carrier status.

The Committee considers this a dilemma in view of the existing practise of carrier status reports for SCD and the limited resulting damage to the child. The Committee feels strongly about reaching the population at risk and therefore recommends a study in risk groups in high prevalence areas. The core question of the study is how the population at risk is best informed about (carrier status for) hemoglobinopathies. Carrier status reports on the basis of neonatal screening can be continued for the time being as part of such research. The Committee advises that this research focuses particularly on carrier status screening in the (prospective) parents in the preconceptional or prenatal period. Importantly, low socioeconomic status of a large proportion of the SCD risk group should be taken into account. Information and counselling require additional attention and it would seem wise to prevent financial barriers. Screening for SCD (carrier status) in the United Kingdom could perhaps provide inspiration for opportunities in the Netherlands.

7.3 Severe thalassemia and screening?

7.3.1 Beta thalassemia major (TM)

TM patients are asymptomatic at birth. Starting in about the third month of life, TM causes progressive severe anemia, which without screening is not detected clinically until a very late stage. Complications are life-threatening anemia with the risk of cardiac and respiratory failure and early death.[106]

TM patients are treated with chronic blood transfusions and daily folic acid and deironisation. Curative treatment is possible only by stem cell transplantation (HSCT).[118] The outcomes of HSCT improve with younger age of patients and fewer blood transfusions.[119] On the basis of these considerations, the Committee includes TM in category 1 and recommends independent inclusion of this condition in the neonatal screening programme.

7.3.2 HbH disease

HbH disease is caused by mutations in three of the four alpha-globin alleles. The alpha globin genes are needed to form hemoglobin (both BF and BA). Immediately after birth, the children have moderate to severe anemia.[107,108] The blood picture is very similar to iron deficiency, but iron supplements are ineffective and prolonged administration may cause severe iron accumulation. Treatment of HbH disease consists of the administration of folic acid, blood transfusions and strict monitoring for cardiac and respiratory failure. On the basis of these considerations, the Committee includes HbH disease in category 1 and recommends inclusion of this condition in the neonatal screening programme.

7.4 Conclusion

Neonatal screening for SCD is the primary example of a test with incidental findings in the current neonatal screening package. The Committee feels very strongly about avoiding incidental findings. The Committee therefore recommends a pilot study of a new screening method for SCD and severe forms of thalassemia without the occurrence of incidental findings. Until this technique is sufficiently validated, a way will need to be found to deal with the current incidental findings.

The Committee takes the view that early detection achieves sufficient health gains for beta thalassemia major and HbH disease to have them included independently in the neonatal screening programme.

With respect to carrier status, a Committee majority recommends discontinuation of SCD carrier status reporting. The Committee emphasises that the population at risk should be informed on Hb-pathy carrier status. The Committee proposes to initiate a study to answer the question how and when the high risk groups are best informed. Providing carrier status screening for prospective parents in the preconceptual or prenatal period should be considered in all cases. Carrier status reporting on the basis of neonatal screening may be continued in certain areas for the time being within the study setting.

Chapter 8

Practical implications

Up to this point, this document has addressed the content of the neonatal screening programme. For a high-quality programme, practical issues and opportunities of implementation must also be addressed. The Committee will consider the primary issues in this Chapter.

8.1 Timing and tempo of screening

The timing of the heel prick is impacted by a number of organisational issues and various characteristics of newborns. In general, the earlier heel pricks can be performed, the better detected children can be treated. In our country, heel prick screening is often combined with neonatal hearing screening. Hearing screening should not be performed until 96 hours after birth. Earlier hearing screening would significantly increase the number of false-positive results. Earlier heel pricks could therefore separate neonatal heel prick and hearing screening. A new hearing screening method is being studied, where screening could take place at an earlier time without an increase in the number of false-positive results.

Taking blood within 48 hours after birth is problematic, because some metabolites are strongly associated with the child's age. A number of values will deviate significantly, with a resulting increase in false-positives and false-negatives. Moving the time forward to 48-72 hours after birth will achieve a degree of health gain. It is estimated that in this way, over a period of years, one

additional child may achieve some health gain. The question is whether this is proportional in view of the required modifications.

The Committee suspects that optimising the current process may be beneficial. This requires a thorough analysis of each step in the implementation chain. The registration of a child for screening is now combined with registration of the child's birth at the register office, but increasingly, digital notifications of birth by the obstetrician to the RIVM Vaccinations and Prevention Programmes are being used. The delivery of heel prick cards to the regional screening laboratories continues to be an issue, as is the time needed for analysis and reporting of results and timely follow-up in healthcare.

8.2 Technical requirements

If the diseases recommended by the Committee are included in the neonatal screening programme, the screening laboratories must have the correct analysis methods and reagents available. Optimal implementation furthermore requires thorough pilot studies, as discussed in Chapter 5. The following issues are particularly important in this respect.

8.2.1 Analysis method

Analysis methods for newly screened diseases are regularly described. Usually these methods have not been adequately validated yet. In most cases, locally developed methods are used on a limited number of blood samples. Not rarely however, detailed validation for neonatal blood spots with an evaluation of numbers of false-positives and false-negatives is lacking. In order to satisfy the current quality requirements of a screening programme, a reliable (commercial) vendor who will want and be able to keep the method on the market for longer periods of time (multiple years) should be opted for. Preferably, interest in the disease in question should be such that various methods are available from which a responsible choice can be made.

8.2.2 Control materials

A screening laboratory should have materials with known concentrations of the measurement parameter(s) characteristic for the disease in question, the so-called internal controls. Suppliers of such control samples will not include the parameter in their package until there is sufficient interest for it in the field. Other than reagents, screening laboratories can sometimes create their own internal

controls, depending on the chemical complexity of the parameter. The selected method should allow for validation prior to routine application using sample material of persons who were diagnosed with the disease in question. Such validation should be repeated from time to time. Depending on prevalence, more or fewer diagnosed patients and more or less sample materials are available. Also the clinical diagnostic laboratories are very sparing with these materials. Seeing all screening programmes are faced with this issue, it is not easy to obtain patient materials from abroad.

8.2.3 *Required blood volume*

In the 2007 expansion, the number of collectors to be filled on the heel prick card was increased from 4 to 6, but the collectors have been made somewhat smaller. The total blood sample volume has increased by some 25 percent and is now about 500µl. This is usually sufficient to carry out the current programme. Further expansions (or refinements of the current programme, e.g. the MLPA method to demonstrate CF deletions) again raise the question of the required blood volume. For conditions detected in the same analysis run as the current, this is not a problem. However, if an entirely new analysis must be added, an increase in the required blood volume must be considered. An implementation test must demonstrate how much exactly. Also, there should be adequate consultations with those administering the heel prick in order to clarify the importance of sufficient blood volume to them. Furthermore, the parents' view should be taken into account. If they feel too much blood is required, this may reduce their willingness to participate.

8.2.4 *Programme complexity*

In view of the complexity of the neonatal screening programme, adequate consultation between the screening laboratory and other partners in the programme is needed, as indicated previously. Think of the optimal timing of blood sampling and the order of tested parameters if blood volume is insufficient. The Committee sees a role here for the Neonatal Heel Prick Screening Programme Committee and the various Neonatal Heel Prick Screening Advisory Committees of the Dutch Pediatric Association NVK.

For a number of conditions, only a limited but thorough pilot is needed within the current programme. These are Methylmalonic acidemia; Propionic acidemia; Carnitine-acylcarnitine translocase deficiency; Carnitine palmitoyltransferase deficiency; Methyl-acetoacetyl-CoA thiolase deficiency;

Organic cation transporter 2. Screening for GAMT deficiency requires a modification of the test method described in the American literature so as to make it suitable for the Dutch situation. This requires a more extensive pilot.

For MPS I-H and X-bound adrenoleukodystrophy, experience with screening is only very limited. There are limited pilot results and it will likely take some time for commercial methods and control materials to become available. It is important not to overburden screening laboratory capacity, which could compromise the quality of the programme.

A commercial method and control materials are available for Severe Combined Immunodeficiency. The first pilots with this method indicate that validation and optimisation within the context of Dutch neonatal screening does indeed require attention. The prevalence is not very high, but there will likely be sufficient patient material. Screening for Galactokinase deficiency may be regarded as an addition to galactosemia screening. There is sufficient knowledge available worldwide, but to our knowledge no commercial method is available yet.

The Committee recommends that sufficient time should be taken for modifications and pilot studies before including the diseases in the regular programme. In addition to technical modifications, effective inclusion of new diseases also requires modification of the information and registration systems, and training of the professionals involved. An implementation test will have to clarify how much time will be needed in total. Additionally, the Committee argues in favour of gradual implementation of the tests for the newly included diseases in the neonatal screening, so as to not compromise the quality of the current programme.

Chapter 9

Future developments

In the introduction, the Committee indicated that neonatal screening is very dynamic. These dynamics are felt particularly in direct screening on DNA of the newborn. A brief outline.

9.1 Targeted screening at DNA level

For some actionable conditions, no diagnosis is possible on the basis of the concentration of a specific metabolic product in the heel prick card. In such cases, diagnosis can usually be made at the DNA level. In other cases, diagnostics based on enzyme measurements cannot distinguish between patients with an infantile form of the condition (for which neonatal screening seems indicated) and a late-onset form (for which the Committee does not consider neonatal screening advisable at this time). This is the case in Pompe disease. It is likely that with research of the gene that codes for the enzyme, infantile patients can be identified, seeing usually only a limited number of mutations are involved.[120]

It would appear feasible to detect conditions that are primarily diagnosed at the DNA level in the relatively near future. A promising technique is targeted enrichment of DNA using the Molecular Inversion Probe (MIP) strategy, prior to DNA sequencing.[121,122] The technique is not yet sufficiently validated for use in diagnostics.[123] Research is needed to test the feasibility of its use within the neonatal screening programmes. This new technique may complement

techniques currently used in the neonatal screening programme. Additionally, the advantages and disadvantages of whole exome sequencing are now being investigated in the US as an alternative method to neonatal screening.[124]

The Committee is considering the use of DNA analysis for treatable metabolic diseases, possibly on the basis of MIP technology, in the neonatal screening programme.* This list is not exhaustive: there are still genetic conditions outside the metabolic disease arena that would qualify for DNA analysis in view of their treatability.

Interpretation of the results may be difficult because of the occurrence of changes in a gene that do not affect the function of the gene product (polymorphisms). If a change in the gene is found that is not known as a polymorphism nor as a pathogenic mutation, the term "Variants of unclassified significance (VUS)" is used. As this situation will occur regularly in neonatal screening, algorithms will have to be developed to ensure consistent interpretation. Additionally, it is important to identify those responsible for recontacting the screened child, if a VUS turns out to be a treatable, pathogenic mutation. Important issues were discussed in the recent description of Next generation sequencing.[125]

The Committee anticipates that neonatal screening at the DNA level will add value. It recommends a technical and financial feasibility study of the opportunities this new technology offers.

9.2 Recommendation on potential expansion

In conclusion, the Committee reviewed the possibility of expanding the neonatal screening programme over the upcoming years. The Committee recommends considering both the scientific and the social aspects of the matter. The Committee specifically recommends asking the Health Council to advise periodically on neonatal screening. In view of the tempo of developments described above, advice would seem to be needed within a few years. This will generally involve more complex issues. Simple modifications to the programme can be left directly to RIVM/Screening Centre CvB. Think of technological improvements or modifications of tests that have shown to be less effective in practice than expected.

* For example: tyrosine hydroxylase deficiency (TH); GTP cyclohydrolase deficiency (GTPCH; 1 allele mutated); Glucose transporter 1 (Glut1; dominant inheritance); Pyridoxine-dependent epilepsy (ALDH7A1); Thiamine transporter (SLC19A3); Infantile form of Pompe disease (GAA); Cystinosis (CTNS); Homocystinuria (CBS; MTHFR); Brown-Vialetto-van Laere syndrome type 2 (SLC52A2)

Chapter 10

Conclusions and recommendations

In this concluding Chapter, the Committee summarises its primary conclusions and recommendations. It will do so on the basis of the questions posed by the Minister.

10.1 Are the criteria still adequate?

Yes. This Committee also regards health gain for the newborn as the goal of screening. This justifies a proactive provision to screened persons who are as yet unable to decide for themselves. However, a treatment must exist that is not only effective but also available. Recent debate on the insured package shows that the availability of expensive treatments can in no way be taken for granted. The Committee considers a reasonable guarantee of permanent availability of treatment an essential precondition for inclusion of a disease in the neonatal screening programme.

This will preserve the current nature of neonatal screening as a programme that undoubtedly benefits the health of the screened newborn. The Committee considered whether neonatal screening for untreatable conditions is compatible with this nature. A Committee majority feels this is (currently) not the case.

The Committee adds the following two recommendations. In certain, as yet untreatable conditions, a study (requiring a license) can be designed to examine the possibility of significant health gain by early intervention or diagnosis (parallel to neonatal screening). Additionally, there should be a focus on

improvement of diagnostics and care for children with vague symptoms or delayed development.

In order to maintain effectiveness of the neonatal screening programme, alternative measures, e.g. primary prevention of infectious diseases, should be considered systematically for each candidate disease for inclusion in the neonatal screening programme. This will allow selection of the most efficient measure to achieve the intended health gain.

10.2 Which conditions may be added?

The Committee evaluated a large number of conditions to see to what extent criteria for inclusion in the neonatal screening programme were met. The following conditions are eligible in the Committee's opinion:

- Methylmalonic acidemia (MMA)
- Propionic acidemia (PA)
- Carnitine-acylcarnitine translocase deficiency (CACT)
- Carnitine palmitoyltransferase deficiency type 1 (CPT1)
- Carnitine palmitoyltransferase deficiency type 2 (CPT2)
- Methyl-acetoacetyl-CoA thiolase deficiency; ketothiolase deficiency (MAT)
- Organic cation transporter 2 (OCTN2)
- Beta thalassemia major (TM)
- HbH disease
- Mucopolysaccharidosis type 1 (MPS I)
- X-linked adrenoleukodystrophy (X-ALD)
- Galactokinase deficiency (GALK)
- Severe combined immune deficiency (SCID)
- Guanidinoacetate methyltransferase deficiency (GAMT).

Thorough pilot research is required to ensure appropriate implementation. In terms of screening method, the first eight conditions are very similar to the current package. In principle, minor parameter changes will suffice. However, a thorough implementation test and pilot remain necessary. OCTN2 and the hemoglobinopathies are currently detected as incidental findings. The Committee recommends a more extensive pilot study by the RIVM, the university hospitals or TNO for the other conditions. The tests for conditions 10 through 12 require the use of an enzyme assay. The screening technique for SCID is new in the Netherlands: it is the first technique to target DNA directly (but not for mutations) in the blood spots. Screening for GAMT deficiency requires a modification of a test method

described in the American literature so as to make it suitable for the Dutch situation. Here again, a more extensive pilot is required.

10.3 How do we deal with bottlenecks in practical implementation?

The Committee points out that in this and subsequent expansions, a thorough study of other practical bottlenecks will be required. Continued focus and thorough evaluation will be required in order to preserve programme quality. The Screening Centre CvB plays a central role in this respect.

Simple modifications to the programme, such as technological improvements and test modifications, may be left to the programme committee of the CvB/ RIVM.

With respect to CF, the Committee feels that continued optimisation of the test should be left to the CvB in collaboration with the neonatal screening programme committee and the CF advisory committee of the Dutch Pediatric Association (NVK). If specific tests actually (and continually) perform suboptimally, as is the case in HCY, then the diseases should be dropped from the programme until a better test becomes available.

10.4 How do we deal with incidental findings and carrier status?

Clinically relevant incidental findings suggesting actionable conditions should be reported to the parents, in the Committee's opinion. The Committee furthermore recommends consideration as to whether these conditions qualify independently for inclusion in the neonatal screening programme.

Clinically relevant, non-actionable incidental findings, such as untreatable conditions, are not reported in principle. An exception are the untreatable conditions that manifest very rapidly, which does not compromise the child's right to not know and to have an open future, while preventing a long diagnostic process. Carrier status is not yet clinically relevant or actionable for the child and should not be reported according to the Committee.

A Committee majority feels that carrier status reports may compromise and thereby undermine the clarity of the neonatal screening programme. Furthermore, it lets the newborn's interest, for whom carrier status reporting has no value yet, prevail over the parents' interest, for whom this can be important information. It recommends providing preconceptional or prenatal carrier status screening for (prospective) parents from populations at risk.

In the current programme, screening for sickle cell disease unavoidably leads to incidental findings. The clinically relevant, actionable conditions beta

thalassemia major and HbH disease should not only be reported, but also included independently in the neonatal screening programme, according to the Committee. The same is true for OCTN2, which is now reported as incidental finding. Carrier status findings should not be reported as part of the neonatal screening, as pointed out above.

The Committee therefore recommends that carrier status reporting for sickle cell disease be stopped. However, because carriers of hemoglobinopathies constitute a particular group with a lack of knowledge on genetics, the Committee does recommend setting up a study in the high prevalence areas, evaluating how this group can obtain knowledge on carrier status and potential consequences. As part of this study, carrier status reporting as a result of neonatal screening can be continued, in addition to the provision of preconceptional and prenatal carrier status screening.

10.5 How do we anticipate the future?

The Committee expects major developments, particularly in the field of screening at the DNA level. The consequences will be far-reaching, not only for neonatal screening, but also for preconceptional and prenatal screening. The Minister can ask the Health Council for additional advice in this connection. The Committee foresees a necessity for this in the relatively near future.

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A	Request for advice
B	The Committee
C	Consulted experts
D	Neonatal screening panels abroad (Europe, USA, Australia, Japan)

Annexes

Annex **A**

Request for advice

Letter of 28 June 2012 (reference PG/OGZ/3120487) of the Minister of Public Health, Welfare and Sport to the acting chairman of the Health Council of the Netherlands.

On the basis of the Health Council advisory report on ‘Neonatal Screening’ (August 2005), thirteen metabolic diseases and screening for sickle cell disease were added to neonatal heel prick screening in 2007, bringing the total to 17 conditions. Following the advisory report on 'Neonatal Screening for Cystic Fibrosis' (March 2010), I also added this condition to the package.

In their letter in 2010 (see appendix), the CvB informed me that experience over the past years with this programme, plus the (international) developments in this field have given rise to questions within the neonatal heel prick screening programme committee of Screening Centre CvB about the current screening programme. Consequently, I feel the time has come to ask the Health Council for a new advisory report.

The questions I wish to pose explicitly to the Health Council involve, firstly, the conditions for which screening takes place. International developments indicate that more and more treatable conditions may be eligible for inclusion in heel prick screening, such as Severe Combined Immune Deficiency syndrome (SCID), the Cytomegalovirus (CMV) and a number of metabolic diseases (including Pompe disease).

Secondly, how should we deal with incidental findings for other conditions or carrier status in the child? In the case of carrier status in the child, I would point out in particular: severe forms of anemia, such as beta thalassemia, HbH disease and sickle cell disease. Parents are currently informed automatically about one form of carrier status for sickle cell disease and not about other forms, but there would seem to be ethical and legal objections to this.

In this respect I would ask, thirdly, the fundamental question whether parents should be informed automatically about carrier status and in which manner. How does the Health Council advise on modification of the informed consent procedure for carrier status from opting out, as is the case now, to opting in? How could this be implemented in practice?

Fourthly, there is a question with respect to the implementation period of heel prick screening: is an earlier time of heel prick screening advisable? A number of countries perform heel prick screening at an earlier time. Does this achieve demonstrable health gain?

I ask the Health Council to advise on the state of science with respect to neonatal screening. Focus should be in particular on advice about needed changes with respect to the package of diseases used since 2007 (including the addition of cystic fibrosis in 2011). Importantly, when determining the value of proposed changes, the criteria formulated earlier for screening of newborns should be used (the Wilson & Jungner screening criteria and more specifically the Health Council criteria for genetic screening).

In conclusion, I ask the Committee to advise on the possibility to construct a framework for the evaluation of new developments and/or modifications in the package. Ideally, such a framework would simplify package modifications including the Health Council advisory reports. Is the framework described in the 2005 Health Council advisory report 'Neonatal Screening' still adequate? Can it be used by the CvB in recommendations on neonatal heel prick screening?

I look forward to receiving your advisory report at the end of 2013.

I am sending a copy of this letter to the CvB for their information.

signed
the Minister for Health, Welfare and Sport
Ms. E.I. Schippers

Annex **B**

The Committee

- Prof. D.D.M. Braat, *chairman*
  Professor of Reproductive Medicine, Radboudumc, Nijmegen
- Dr. B. van Beers (*up to 1 December 2013*)
  Philosopher of Law, Amsterdam Free University
- Prof. Foulon
  Professor of Gynecology and Obstetrics, University Hospital, Brussels Free University, Belgium
- Prof. V.V.A.M. Knoers
  Professor of Clinical Genetics, Utrecht University Medical Centre
- Dr. J.G. Loeber
  Biochemist, Formerly Dutch National Institute for Public Health and Environmental Protection, Bilthoven
- Dr. M.C. Ploem (*as of 1 December 2013*)
  Health Attorney, Amsterdam University Medical Centre
- Prof. F.J.T. Staal
  Professor of Molecular Stem Cell Biology, Leiden University Medical Centre
- Prof. M.F. Verweij
  Professor of Philosophy, Wageningen University and Research Centre
- E. van Vliet-Lachotzki, MD
  Genetics Policy Officer, Association of Collaborating Parent and Patient Associations, Soest

- Prof. R.A. Wevers
  Professor of Clinical Chemistry of Genetic Metabolic Diseases, Radboudumc, Nijmegen
- Prof. F.A. Wijburg
  Professor of Metabolic Diseases, Amsterdam University Medical Centre
- Dr. G.C.M.L Page-Christiaens, *advisor*
  Gynecologist, Utrecht University Medical Centre
- Dr. M. Peters, *advisor*
  Pediatric Hematologist, Amsterdam University Medical Centre
- Dr. Verkerk, *advisor*
  MD, Community Health, Epidemiologist, Youth Department, TNO, Leiden
- E. dekkers, *observer*
  Programme Coordinator, Neonatal Heel Prick Screening, Dutch National Institute for Public Health and Environmental Protection, Bilthoven
- M. Prins, *observer*
  Ministry of Public Health, Welfare and Sport, The Hague
- Dr. E.C.A. Asscher, *scientific secretary*
  Health Council of the Netherlands, The Hague

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 chairperson 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 inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex C

Consulted experts

Experts consulted during meetings:

- Prof. A. Clarke, Professor of Clinical Genetics, Cardiff University, Cardiff, Wales, UK
- Dr. E. Vroom, Chairman, Duchenne Parent Project
- Dr. A. Helderman-van den Enden, Clinical Geneticist, Maastricht University Medical Centre
- Dr. A.C.T.M. Vossen, Medical Microbiologist, Leiden University Medical Centre
- Dr. J.J.C. de Vries, MD, Microbiologist, Leiden University Medical Centre
- Dr. J. Dankert-Roelse, Independent Pulmonologist, Owl's Advice, Klimmen
- Dr. M. Nelen, Radboudumc, Clinical Molecular Geneticist, Nijmegen
- Dr. J.K. Ploos van Amstel, Clinical Molecular Geneticist, Utrecht University Medical Centre

The Committee received written input from a number of experts, in particular on metabolic diseases:

- Prof. F.J. van Spronsen, Pediatrician, Metabolic Diseases, Groningen University Medical Centre
- Dr. M.F. Mulder, Pediatrician, Metabolic Diseases, Amsterdam Free University Medical Centre
- Dr. A.M. Bosch, Pediatrician, Metabolic Diseases, Amsterdam Academic Medical Centre

- Dr. G. Visser, pediatrician, Metabolic Diseases, Utrecht University Medical Centre
- Dr. L. Kluijtmans, Clinical Biochemical Geneticist, Radboudumc, Nijmegen
- Dr. M.G. de Sain-van der Velden, Clinical Biochemical Geneticist, Utrecht University Medical Centre
- Prof. G.S. Salomons, Professor Clinical Biochemical Geneticist, Amsterdam Free University Medical Centre
- Dr. M. Williams, Pediatrician Metabolic Diseases, Erasmus MC, Rotterdam
- Dr. M.E. Rubio-Gozalbo, Pediatrician Metabolic Diseases, Maastricht University Medical Centre
- Dr. M.M.C. de Vries, Pediatrician Metabolic Diseases, Radboudumc, Nijmegen
- Dr. P.C.J.I. Schielen, Medical Biologist, Dutch National Institute for Public Health and Environmental Protection, Bilthoven
- Dr. E.A. Kemper-Proper, Clinical Chemist, IJsselland hospital, Capelle aan de IJssel
- A. van Wegberg, Dietician, Radboudumc, Nijmegen
- T. van den Hurk, dietician, Utrecht University Medical Centre
- Prof. B.T. Poll The, Professor of Pediatric Neurology, Amsterdam Academic Medical Centre
- Dr. M. Engelen, Pediatric Neurologist, Amsterdam Academic Medical Centre
- Dr. S. Kemp, Medical Biochemist, Amsterdam Academic Medical Centre
- Dr. J.J. Boelens, Pediatric Oncologist, Utrecht University Medical Centre
- Dr. M. Huigen, Clinical Biochemical Geneticist, Radboudumc, Nijmegen
- Dr. A. Verrips, Neurologist, Canisius Hospital, Nijmegen
- Prof. H. Blom, Professor of Clinical Biochemical Genetics, Freiburg Germany
- Dr. D. Lefeber, Clinical Biochemical Geneticist, Radboudumc, Nijmegen

The Committee had oral consultations with the following experts:

- Dr. E.B. van Veen, Attorney, Dutch National Institute for Public Health and Environmental Protection, Bilthoven
- Prof. J.J.M. van Dongen, Professor of Molecular Immunology, Erasmus MC, Rotterdam
- Dr. M. van der Burg, Immunologic Chemist, Erasmus MC, Rotterdam
- Dr. G.J. Driessen, Pediatrician-Infectiologist/Immunologist, Erasmus MC, Rotterdam

- Dr. R.G.M. Bredius, Pediatrician, Immunologist, Leiden University Medical Centre
- Dr. A.C. Lankester, Pediatrician, Immunologist, Leiden University Medical Centre
- Dr. A. Boelen, Endocrinologist, Amsterdam Academic Medical Centre
- Dr. L. Henneman, Health Scientist, Amsterdam Free University Medical Centre
- Dr. P.A. Bolhuis, Biochemist, Kampen

Annex **D**

Neonatal screening panels abroad (Europe, USA, Australia, Japan)

Diseases screened for elsewhere in Europe (but not yet in The Netherlands)

- argininosuccinic aciduria (asa)
- argininemia (arg)
- citrullinemia type I (citI)
- citrullinemia type II (citII)
- hypermethioninemia type I and II (htpI_III)
- tyrosinemia type II and III (tyrII_III)
- methylmalon acidemia + Clb A,B,C,D defects mmacbl
- propion acidemia (pa)
- MAD deficiency
- beta-ketothiolase deficiency (bkt)
- malon acidemia (mma/MAL)
- carnitine palmitoyltransferase deficiency type I and II (cptI+cptII)
- carnitine uptake defect (cud)
- Short-chain acyl-CoA dehydrogenase deficiency (scadd)
- Medium-short-chain acyl-CoA dehydrogenase deficiency (schadd)
- 2,4-Dienoyl-CoA transferase defitiency (decr/De-Red)
- UDP-galactose-4-epimerase defitiency (upd/GALE)

Diseases screened for in the US, but not in Europe (only core conditions)

- Severe combined immuno deficiency (SCID)
- Trifunctional protein deficiency (TFP)
- 3-hydroxy 3-methylglutaar aciduria/ 3-hydroxy 3-methylgluteratyl-CoAlyase deficiency (HMG)
- Holocarboxylase synthetase deficiency

Diseases screened for in Japan:

Newborn Screening Panel in Japan (Apr. 2013)

1 Endocrine Diseases
   - Congenital hypothyroidism
   - Congenital adrenalhyperplasia

2 Carbohydrate metabolism
   - Galactosemia

3 Tandem-MS/MS
   a Primary target diseases
      - phenylketonuria
      - maple syrup urine disease
      - homocystinuria
      - citrullinemia type 1
      - argininosuccinic aciduria
      - methylmalonic acidemia
      - propionic acidemia
      - isovaleric acidemia
      - 3-methylcrotonyl-CoA carboxylase deficiency
      - 3-hydroxy-3-methylglutaryl-CoA lyase deficiency
      - multiple carboxylase deficiency
      - glutaric aciduria type 1
      - MCAD deficiency
      - VLCAD deficiency
      - trifunctional protein deficiency
      - CPT-1 deficiency
   b Secondary target diseases
      - citrin deficiency(citrullinemia type 2)
      - 3-ketothyolase deficiency
      - CPT-2 deficiency

- carnitine acylcarnitine translocase deficiency
- primary carnitine deficiency (carnitine transporter defect)
- glutaric aciduria type 2.

Disease screened for in Australia

- Category 1 screening is strongly recommened (a proven advantage of early diagnosis, also after considerations of cost-effectiveness and follow-up is well organised).
- Primary congenital hypothyroidism (CH)
- Cystic fibrosis (CF)
- Disorders of amino acid, organic acid and fatty acid metabolism covered by
- analysis of aminoacids and acylcarnitines by tandem mass spectrometry.

- Amino Acid Disorders:
  - Argininemia (arginase deficiency)
  - Argininosuccinic aciduria (ASA lyase deficiency)
  - Citrullinemia (argininosuccinate synthase deficiency, citrin deficiency
  - Fumaryl acetoacetase deficiency (tyrosinemia Type 1)
  - Homocystinuria (cystathionine beta-synthase deficiency)
  - Maple Syrup Urine Disease (classical and variant)
  - Phenylketonuria (classical and intermediate)
  - Pterin defects
  - Tyrosine aminotransferase deficiency (tyrosinemia Type 2)

- Fatty Acid Oxidation Disorders:
  - Carnitine/acylcarnitine translocase deficiency
  - Carnitine transporter defect
  - CPT-1 deficiency (carnitine palmitoyl transferase deficiency 1)
  - CPT-2 deficiency (carnitine palmitoyl transferase deficiency 2)
  - LCHADD (3-hydroxy long chain acyl-CoA-dehydrogenase deficiency)
  - MCADD (medium chain acyl-CoA-dehydrogenase deficiency)
  - MADD (multiple acyl-CoA-dehydrogenase deficiency)
  - TFP (trifunctional protein deficiency)
  - VLCADD (very long chain acyl-CoA-dehydrogenase deficiency)

- Organic acid disorders:
  - Beta-ketothiolase deficiency (mitochondrial acetoacetyl-CoA thiolase deficiency)

- Cobalamin C defect (homocystinuria with methylmalonic aciduria)
- Glutaryl-CoA dehydrogenase deficiency (glutaria acidemia Type 1)
- Holocarboxylase synthase deficiency
- 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCoA lyase deficiency)
- Isovaleric acidemia
- Methylmalonic acidurias (mutase deficiency, CblA and CblB defects)
- Propionic acidemia
- 3-methylcrotonyl-CoA carboxylase deficiency
- 2-methylbutyryl-CoA dehydrogenase deficiency
- 3-methylglutaconyl-CoA hydratase deficiency

- Category 2 Screening is recommended in certain circumstances (a proven or expected advantage of early diagnosis, a good test and treatment, follow-up organized, the advantages sometimes outweigh the disadvantages)
  - Biotinidase deficiency
  - Galactosemias.