Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Review of processes in use to inform the expansion of newborn bloodspot screening programmes

2 July 2021

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.
HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

Foreword

The National Screening Advisory Committee (NSAC) was established in 2019 as an independent advisory committee to play a strategic role in the development and consideration of population-based screening programmes in Ireland. The role of the NSAC is to provide advice to the Minister for Health and Department of Health on new screening proposals and proposed changes to existing screening programmes. The Health Technology Assessment (HTA) directorate within the Health Information and Quality Authority (HIQA) has been requested by the Department of Health to provide evidence synthesis support to the NSAC under an agreed work programme.

There are a number of population-based screening programmes in existence in Ireland. These include those delivered by the Health Service Executive (HSE) National Screening Service as well as other screening programmes delivered by the HSE. Within newborn screening, the National Newborn Bloodspot Screening Programme (NNBSP) delivers newborn bloodspot screening (NBS), or, the 'heel prick test', which is completed in the first 72 to 120 hours of life.

Currently in Ireland eight conditions are screened for within NBS, with a ninth condition undergoing implementation. Participation in the NBS programme in Ireland is high, with an estimated uptake of 99.9%, indicating a considerable degree of confidence in the programme, and the programme has been acknowledged as one of the most successful national public health initiatives. Each year, the NNBSP identifies approximately 110 babies in Ireland with one of the conditions screened for through the programme.

At the request of the NSAC, the purpose of this report is to describe work undertaken by the Evaluation Team at HIQA to summarise evidence for a number of elements relevant to decision-making on the expansion of NBS programmes. Elements of interest included: (i) the range of conditions screened for in international NBS programmes; (ii) the processes for condition proposal, prioritisation and selection for evidence review; (iii) the decision-making processes leading to the inclusion of a condition in international NBS programmes; (iv) the role of emerging technology in NBS programme expansion. A multidisciplinary Expert Advisory Group was convened to consider the evidence outlined and provide expert input to the report.

HIQA would like to thank the Evaluation Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.

Dr Máirín Ryan

Deputy CEO & Director of Health Technology Assessment

Health Information and Quality Authority

Acknowledgements

HIQA would like to thank all of the individuals and organisations who provided their time, advice, and information in support of this work. In particular, thanks are due to Professor Sian Taylor-Phillips, Warwick Medical School, University of Warwick, and to the members of the Expert Advisory Group (EAG).

HIQA further notes that the findings set out in the advice represent the interpretation by HIQA of the available evidence and do not necessarily reflect the opinion of all members of the Expert Advisory Group.

The membership of the EAG was as follows:

Dr Jennifer Brady	Consultant Clinical Biochemist, Children's Health Ireland (CHI) at Temple Street
Dr Abigail Collins	Consultant in Public Health Medicine, National Cancer Control Programme, National Newborn Bloodspot Screening Programme
Dr Ellen Crushell	Consultant Paediatrician with a special interest in Inherited Metabolic Disorders, CHI at Temple Street and Crumlin hospitals; Co-Clinical Lead, Paediatric/Neonatology National Clinical Programme HSE/RCPI
Dr Patricia Harrington	Deputy Director, Health Technology Assessment, HIQA
Mr Les Martin	Parent to, and advocate for, children with a rare condition detectable by newborn screening
Ms Vicky McGrath	Chief Executive Officer, Rare Diseases Ireland
Ms Loretta O'Grady	Chief Medical Scientist, Newborn Bloodspot Screening Laboratory, Children's Health Ireland (CHI) at Temple Street
Dr Máirín Ryan (Chair)	Director of Health Technology Assessment & Deputy Chief Executive Officer, HIQA
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Conflicts of Interest

None declared.

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List of abbreviations

ADA-SCID	adenosine deaminase deficiency - severe combined immunodeficiency
AHW	Alberta Health and Wellness
EU	European Union
EUCERD	EU Committee of Experts on Rare Diseases
EUnetHTA	European Network for Health Technology Assessment
EUNENBS	European Union Network of Experts on Newborn Screening
EURORDIS	European Organisation for Rare Diseases
ELSI	ethical legal and social implications
EVIDEM	Evidence and Value: Impact on DEcision Making tool
GA1	glutaric aciduria type 1
GR	Health Council of the Netherlands
HCU	homocystinuria
HIQA	Health Information and Quality Authority
HSE	Health Service Executive
HTA	health technology assessment
INESSS	Institut National d 'Excellence en Santé et en Services Sociaux (Quebec HTA agency)
INSPQ	Institut National de Santé Publique du Québec
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IRT	immunoreactive trypsinogen
ISNS	International Society for Neonatal Screening
IVA	isovaleric acidaemia
KPI	key performance indicators
LIMS	Laboratory Information Management System
MCDA	multi-criteria decision analysis
NBS	newborn bloodspot screening
NSC	National Screening Committee (UK)
NSO-AC	Newborn Screening Ontario – Advisory Council
NSU	National Screening Unit (New Zealand)
MCADD	medium chain acyl-CoA dehydrogenase deficiency
MS/MS	tandem mass spectrometry
MSSS	Ministry of Health and Social Services (Quebec)
MSUD	maple syrup urine disease
NBS	newborn bloodspot screening
NMR	nuclear magnetic resonance
NNBSL	National Newborn Bloodspot Screening Laboratory
NNBSP	National Newborn Bloodspot Screening Programme
NSAC	National Screening Advisory Committee

PCR	polymerase chain reaction
PKU	phenylketonuria
RCT	randomised controlled trial
RIVM-CvB	National Institute for Public Health and the Environment (Netherlands)
SCID	severe combined immunodeficiency
SMA	spinal muscular atrophy
TREC	T-cell receptor excision circle
UK	United Kingdom
US	United States

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Advice to the National Screening Advisory Committee

The purpose of this review is to describe evidence for a number of elements relevant to decision-making on the expansion of newborn bloodspot screening (NBS) programmes. Elements of interest include: (i) the range of conditions screened for in international NBS programmes; (ii) the processes for condition proposal, prioritisation and selection for evidence review; (iii) the decision-making processes leading to the inclusion of a condition in international NBS programmes; (iv) the role of emerging technology in NBS programme expansion. The Health Information and Quality Authority (HIQA) agreed to undertake this review following a formal request from the National Screening Advisory Committee (NSAC).

The key findings of this review, which informed HIQA's advice, are:

- NBS forms part of a public health screening programme of infants shortly after their birth and aims to detect conditions that are treatable but not clinically evident at the time of birth. The testing involved in NBS is largely performed by measuring metabolites, enzyme activity, or other biomarkers, in samples of blood collected on filter paper following pricking of the infant's heel. Currently, in Ireland, the National Newborn Bloodspot Screening Programme (NNBSP) involves the testing of an infant's blood for eight conditions, with a ninth condition (that is, ADA-SCID) currently undergoing implementation.

- Through a detailed account of current international processes from a selection of countries deemed relevant to the Irish context, supplemented by consideration of academic reviews of policy-making processes, this review identified information on processes relevant to decision-making on the expansion of NBS programmes. This work is intended to facilitate NSAC in their development of defined processes for policy-making.

- Specifically, the objectives of the review were to: identify the conditions screened, outline processes for proposal, prioritisation and selection of conditions for evidence review, outline decision-making processes for condition inclusion, and discuss the role of emerging technology in programme expansion.

- Information on practices in place for the countries of interest (which included Australia, Canada, Denmark, Germany, Italy, the Netherlands, New Zealand, the United Kingdom (UK), and the United States of America (US)) was derived from national screening or government authority websites and

supplemented with descriptive information extracted from academic literature.

- In terms of conditions currently screened for, a distinct heterogeneity was observed in the number, and types, of conditions screened for across countries, with an additional regional variation within a number of countries. Direct comparisons between countries were limited by the level of detail provided by individual screening authorities, differential reporting of updates to screening programmes, and differences in nomenclature and conventions for the grouping of conditions.
    - Of the countries included, the number of conditions screened for ranged from nine (UK) to 40 (Italy), with varying levels of expansion in recent years and a number noted to currently have conditions under review or in the process of piloting implementation.
- With regards to processes for the inclusion of conditions in NBS programmes:
    - Countries within this review varied in terms of who can propose a condition for assessment, with some restricting this to designated screening committees. Open calls for conditions have been implemented by a number of countries with subsequent consideration by an expert group for formal prioritisation and or selection.
    - Jurisdictions increasingly rely on the use of formal evidence review processes. There is a general consensus that scientific advice should be based on published, peer-reviewed evidence, which has been reviewed by experts and supplemented with expert opinions when required.
    - In terms of the type of evidence to be considered, variation was noted across the countries included; however, it was noted that RCT evidence alone is likely to be insufficient when considering NBS programme expansion and expert opinion may be required. Where possible, systematic approaches to evidence review should be used in order to minimise bias.
    - Structured frameworks to support decision-making were used in a number of countries.
- The following perspectives and concepts were noted following review of the academic literature in addition to consideration of policy documents:

- There is substantial international variation in the use of evidence to inform individual NBS recommendations. Particular variation is noted in the use of systematic review methodology to support decision-making, for example, in evaluation of the evidence for test accuracy, benefits of early detection, and potential harms of over-diagnosis.

- The level of evidence considered appears to influence decision-making, with a lower likelihood of a positive recommendation observed when systematic review methods are applied.

- The paucity of RCT evidence to support the effectiveness of screening for certain rare diseases is noted. In the absence of such evidence, it is suggested that reviews should particularly focus on the diagnostic accuracy of the test, the potential harm of over-diagnosis, and the benefits of early detection. In the absence of high-quality RCTs, several countries rank the level of evidence, such that higher levels of evidence are given more weight.

- The use of decision analytic modelling methods may provide flexibility to incorporate effectiveness evidence from all available sources, including interventional studies (for example, RCTs), observational studies, and expert opinion. Such models allow for the incorporation of the uncertainty associated with each parameter input into the model.

- The use of multi-criteria decision analysis (MCDA) for the ranking of conditions following gathering of scientific evidence may help to structure decision-making and to improve transparency and consistency. However, given various challenges associated with applying this method, such as establishing consensus regarding weights to be applied and subjective assessment of conditions against criteria, decision-making relying exclusively on an MCDA ranking approach may be inappropriate.

- Almost all countries included in the present review explicitly identify the child as the beneficiary of screening. A number of countries also identify the family as beneficiaries within the screening process, however these benefits are typically stated as being secondary to those of the child.

- Consideration of the ethical consequences of screening versus not screening is noted across the international literature and is consistent

with the apparent approach adopted by most countries. The process may involve highlighting any relevant ethical issues, evaluation of the ethical implications of alternative actions, weighing of these against each other, and establishment of justification for an action to be taken.

- A number of frameworks were identified, which may have potential use in NBS decision-making, particularly in identifying and addressing critical issues in the implementation of such decision-making processes. However, challenges may still remain regarding assessing a condition against a decision framework, for example, in the interpretation of whether a decision-making criterion within the framework is satisfied and, relatedly, the selection of cut-off values for rare conditions.

- Formal governance arrangements for population screening are noted to be relatively new in most jurisdictions. It has been consistently recommended that an overarching, independent, multidisciplinary group be in place to provide recommendations to government; this is considered important in order to balance competing influences and demands, particularly as the technological landscape of NBS evolves.

- Governance of NBS has historically relied on the input of clinicians, scientists and others centred around a 'genetics' interest, as opposed to consistent involvement of public health representation. Governance arrangements that address NBS alongside other population screening initiatives may allow for broader involvement of interests beyond a primarily genetics focus.

- The range of stakeholder perspectives considered has been noted to influence the evaluation criteria for NBS programmes. Those limited to a genetics interest may include an increased focus on evaluation criteria specific to rare disease, while those that also include a public health and or a specific maternal and child health focus may use more general evaluative criteria. Adoption of a broader perspective is also consistent with increased consideration of screening as a comprehensive pathway which requires concern for both short and long-term outcomes.

- Decision-making criteria applied in different countries for expansion of NBS programmes differ, though criteria are largely derived from the principles proposed by Wilson and Jungner (1968) for the early detection of disease.

However, unique challenges of NBS often prevent the straight-forward assessment of a screening programme against established criteria. Examples of criteria which are particularly challenging include: the need for an accepted treatment for patients with recognised disease, the existence of a suitable test or examination, a clearly defined target population, and planned programme evaluation.

- There are a number of ethical, social and legal implications that should be considered within any expansion of NBS programmes and a detailed examination of these implications at a condition-specific level is required. These include: the impact of true positive and false positive tests on the child and family, the potential for over-diagnosis, over-treatment or medicalisation of the child when considering conditions that may not be fully penetrant (for example, where a child is found to have a genetic mutation, but does not fully experience the expected signs and symptoms of the associated condition), the nature of the beneficiaries and the net benefit accrued, and issues around consent. However, the ethical implications associated with expansion should be carefully balanced against the ethical implications of adopting a 'do nothing' approach in expansion; careful weighting and balancing of the risks and benefits of both including a given condition and not including the same condition is required.

- For the majority of countries identified, the role of technology did not appear to be a clear deciding factor within decision-making for the expansion of NBS programmes. Tandem mass spectrometry (MS/MS) was a commonly highlighted technology implemented, which allows for the testing of a wide array of metabolites with a high degree of sensitivity and specificity, and enables new conditions to be added to an existing MS/MS metabolic panel, thus providing opportunities for expansion. However, technology such as MS/MS may constrain or encourage expansion towards consideration of certain conditions, for example, as dependent on equipment and implementation requirements. The advent of genetic or genomic-based testing methods has also been noted as a turning point in prompting the development of robust policy-making processes to meet the decision-making challenges posed by the potential of these screening methods.

- Considering the potential for the opportunities provided by MS/MS technology to drive the expansion of NBS programmes, there are important factors which must be considered, and processes which must be carried out, with respect to implementation.

- There are significant resource requirements for the establishment of additional laboratory processes, clinical pathways, and programme delivery components otherwise, which are associated with the implementation of a recommendation for expansion. These may include equipment costs and other capital costs (for example, laboratory space), staffing costs, and the time required for processes of laboratory verification, protocol development and care pathway development. The lengthy time to implementation noted in some programmes has been observed to be improved by recruitment of additional staff to deliver the appropriate services. While efficiencies in implementation may be gained through the addition of several conditions to a metabolic panel in parallel, this remains dependent on appropriate resourcing of implementation processes.

Arising from the findings above, HIQA's advice to the National Screening Advisory Committee is as follows:

- Ireland's NNBSP is comparable in range to the programme offered within the UK, screening for a lower number of conditions than many European countries. Italy, for example, among European countries, screens for a significantly larger number of conditions. It is important to note that the number of conditions screened reflects local differences with respect to policy-making processes and local inputs to such processes. Given the complexities of NBS, the number of conditions screened should not be interpreted as representing the relative merits of an individual programme.
- Expansion of NBS programmes presents opportunities to reduce morbidity and mortality associated with screen-detectable conditions and to lift the burden of the 'diagnostic odyssey' for families wherein the child presents symptomatically to healthcare services. However, the balance of benefits and harms associated with screening for many potential candidate conditions is uncertain and, in some cases, countries have retrospectively removed conditions from their programmes due to harms resulting from over-diagnosis and over-treatment of certain conditions. Ethical consequences of expansion of NBS programmes also include, for example, the considerable psychosocial consequences of false positive results. As such, it is recommended that for each candidate condition presented for decision-making, a thorough assessment be performed of the available evidence for the benefits, harms and ethical consequences of screening versus not screening.

- In order for decision-making on NBS expansion to be transparent and consistent, an explicit, structured approach to each aspect of policy-making on this topic should be prepared.
- Governance of each component of the NBS expansion policy cycle should be clearly outlined; institutions and authorities tasked with agenda setting, assessment of conditions for inclusion, and decision-making on inclusion, should be formalised, and stakeholder involvement processes should be described.
- Broad stakeholder involvement should be sought to ensure balanced involvement of the expertise and perspectives of different groups, for example, interest coalitions focused on technological innovation in rare disease diagnosis and treatment versus broader population health perspectives with respect to national screening programmes.
- Generally, certain aspects require consensus ahead of assessment of individual conditions or groups of conditions for potential inclusion in NBS programmes:
    - Condition proposal, prioritisation and selection processes: Proposal of conditions for potential inclusion in NBS programmes may be performed using, for example, an annual call for proposal of conditions (that is, a passive approach) or proposal may occur proactively, for example, via an expert group of clinical and scientific experts aligned with NBS governance. It is important to note that a call for proposals may result in large numbers of applications, thereby necessitating a robust prioritisation process by an oversight committee. Furthermore, traditionally underrepresented groups of citizens may not be in a position to participate equally in proposal processes.
    - The exact criteria against which a proposed condition is assessed should be agreed and formalised.
    - In terms of assessment processes, a HTA-based approach is in keeping with approaches outlined by NSAC thus far regarding the assessment of screening programmes. Decision-making is required regarding the exact domains that should be considered, and the approaches to their consideration, in the context of an NBS HTA. For example, the nature and strength of the evidence to be considered, the sources which may provide expert opinion, and the role of cost-

effectiveness or decision-analytic modelling approaches, require agreement.

  - Assessment of the benefits of screening requires a clear understanding of the scope of benefits to be considered, that is, whether benefits are accrued by the child only, or additionally by the family or broader society. The beneficiary should be clearly defined. If more than one beneficiary is identified, the relative weighting of benefits should be specified.

  - Approaches to support decision-making range from numerical-based ranking methods such as multiple-criteria decision analysis, to frameworks or checklists to structure discussions, to simple consensus-oriented meetings. There is a trade-off to be made between values such as transparency and timeliness of decision-making processes, and this balance requires consideration ahead of the adoption of a process.

- As per decision matrix and framework approaches used internationally, feasibility and readiness for implementation should be assessed alongside assessment of the potential benefits and harms associated with screening. Early consideration (for example, following proposal of a condition for assessment) of the likely resource implications of a positive screening recommendation should be performed to aid in planning, where appropriate. Such consideration may represent a possible criterion for the prioritisation and selection of conditions for assessment, particularly where consideration of a 'batch' of conditions may be more practical than serial recommendations for conditions.

- NBS expansion policy-making should adopt a life-cycle approach such that long-term patient follow-up and programme evaluation needs are taken into account in recommendations regarding NBS programmes.

- Regardless of the direction and extent of expansion of the national NBS programme, efforts should be focused on protecting the existing screening processes in place, and the public confidence therein; expansion must not jeopardise existing operations. International experience of large-scale expansion suggests that rapid implementation efforts and or under-resourcing of implementation can result in negative consequences such as high numbers of false positives (and the harmful effects caused by this) and insufficient follow-up of patients diagnosed with a screen-detected condition.

1 Introduction and methodology of review

1.1 Background to the request

The National Screening Advisory Committee (NSAC) was established in 2019 as an independent advisory committee to play a significant strategic role in the development and consideration of population-based screening programmes in Ireland. The Health Information and Quality Authority (HIQA)'s Health Technology Assessment (HTA) directorate has been requested by the Department of Health to provide evidence synthesis support to the NSAC under an agreed work programme. The present document outlines the findings of the first workstream review conducted by HIQA on behalf of NSAC.

This review has aimed to systematically identify information on processes relevant to decision-making on the expansion of newborn bloodspot screening programmes. In particular, the review aims to present an up-to-date account of current international processes from a selection of countries deemed relevant to the Irish context. The findings of this review will be provided to the NSAC to inform its deliberations with regard to strategic decision-making processes for expansion of the National Newborn Bloodspot Screening Programme (NNBSP).

In line with this aim, the following objectives for the review were listed as follows:

- Describe evidence, at an individual country-level, for the following elements relevant to decision-making on the expansion of newborn bloodspot screening programmes:
    - what are the conditions that are screened for in existing blood spot screening programmes?
    - what is the process for topic (condition) proposal, prioritisation procedures, and the selection of topics for evidence review?
    - what are the decision-making processes that lead to the inclusion of a condition in an individual country's (or region's) newborn bloodspot screening programme?
    - what is the role of emerging technology in programme expansion (e.g., the impact of adoption of tandem mass spectrometry on expansion, novel laboratory assays)?

1.2 Methodology used in review

The full methodology used for this review is outlined in a separate protocol document agreed with the Department of Health and the Chair of NSAC. Overall, this project largely involves an international review of practices in place, including decision-making processes, for the expansion of international newborn bloodspot screening (NBS) programmes, focusing on countries considered to be of particular relevance to the Irish public health decision-making context.

A starting list of countries for review was identified from a 2017 publication by Jansen et al., comprising a review of international differences in the evaluation of conditions for NBS.[1] This review identified the following countries as having long-standing NBS programmes with clear information on NBS decision-making processes: Australia, Canada, Denmark, Germany, the Netherlands, New Zealand, the United Kingdom (UK), and the United States of America (US). This review further systematically searched academic literature from 2011 to 2021 to identify whether decision-making processes are clearly described for any additional countries within the European Economic Area; as a result of this process, Italy was added to the list of countries for thorough consideration of decision-making processes. The search strategy and criteria used to identify academic literature are detailed within the protocol document accompanying this review, while the numbers of articles identified at each stage of the systematic literature search are documented in a PRISMA diagram included in Appendix 1.

Information on practices in place for the countries of interest was derived from national screening or government authority websites and supplemented with descriptive information extracted from academic literature. Such information primarily included the format of existing NBS programmes, the nature of recent expansion that has taken place, and processes relevant to decision-making on expansion. This information is summarised within data extraction tables presented within the Appendices of this report and is described narratively within the main text. Commentary from peer-reviewed academic literature on decision-making processes is also described, including recommendations or descriptions of particular approaches.

Information on technology used in NBS programmes, conditions which may be screened for, and ethical, legal and social implications of expansion of NBS, is included in order to contextualise the information on decision-making processes in NBS programmes outlined later in the document. This contextual information is largely drawn from sources identified within the academic literature search conducted for the review, but it is important to note that the literature used to inform these sections has not been systematically assessed and synthesised.

1.3 Approaches used in review

Types of screening

Newborn screening to identify heritable or congenital disorders may involve various forms of screening methods from laboratory-based tests to bedside tests. The latter may include tests of hearing, hip function, or cardiac function (pulse oximetry-based tests).

The purpose of the present review is to consider expansion specifically of the NBS programme. The scope of this review will therefore be limited to consideration of laboratory-based newborn screening tests using whole blood samples. Where information presented from particular jurisdictions includes involvement of other sample types (e.g., urine-based testing) or other forms of testing (e.g., bedside testing such as hearing tests) and it is not possible to separate this information, this will be noted. Furthermore, in line with the majority of current practice in NBS programmes, the focus of this review will be on the application of currently used biochemical testing methods (for example, use of metabolite biomarkers to detect metabolic disorders) to an expanded number of conditions for NBS, as opposed to exploring the potential use of whole exome or whole genome screening of bloodspot material for the potential detection of a far greater scope of conditions. However, as molecular genetic-based testing methods are in use in NBS programmes in some jurisdictions for either first-line or confirmatory screening for certain conditions (for example, genetic testing methods for detection of cystic fibrosis or ADA-SCID), such screening tests will be included alongside consideration of biochemical screening tests in current use.

Capture of NBS literature based on terminology used

While NBS is inherently concerned with the study of heritable disorders, the term 'genetic screening' was considered inadequate for the purposes of the present review as a descriptor for programmes of NBS. This is because this term has been used to describe screening using technologies that examine variation in multiple genes or across the whole genome as well as to describe screening aimed at identifying heritable diseases. Furthermore, with respect to screening of heritable diseases, the term 'genetic screening' has been used to describe preconception screening, prenatal screening, and screening of children and adults, in addition to screening of newborns. As such, this review has focused on identifying literature which specifically considers NBS as opposed to that which broadly focuses on processes for genetic screening programmes. Similarly, search approaches used in the present review to identify relevant literature primarily focused on 'newborn bloodspot screening' as opposed to 'newborn screening' generally, in order to increase the specificity of search findings. The potential for relevant literature to be

missed within this context is noted as a limitation within the Discussion section of this review.

Scope of processes considered

The topic of this review is to describe decision-making processes with respect to expansion of NBS programmes, including the processes by which additional conditions are identified and prioritised for consideration. Processes related to the implementation of expansion of conditions within a NBS programme (once expansion is agreed), or processes relating to monitoring, quality assurance, and evaluation of existing NBS programmes, are not considered within the scope of the present review, but may be referred to where information on the processes of interest cannot be clearly distinguished.

Systematic approach to literature review

In line with the objectives outlined in the protocol document associated with this review, systematic search methods were used to identify information on processes for the consideration of conditions and associated decision-making with respect to the expansion of NBS programmes. Individual NBS programme authorities within the countries reviewed were contacted to verify the information included within this report.* In the course of this report, additional information (for example, on ethical issues, organisational issues, description of technology and conditions of interest) has been provided for context and discussion purposes. However, in the interests of pragmatism within the time constraints associated with this review, systematic approaches have not been adopted to identify the relevant literature associated with these issues.

Scope of report with respect to overall findings

While this report aims to provide examples of processes in place for the consideration of conditions and associated decision-making with respect to expansion of NBS programmes, it is not within the remit of the present report for HIQA to assess the relative merits of individual processes or country-specific approaches. Where identified, commentary within the academic literature on the merits or potential disadvantages of certain approaches will be provided.

*Responses received after submission of this report to NSAC will be accepted and incorporated into the final report for publication

2 General introduction to NBS

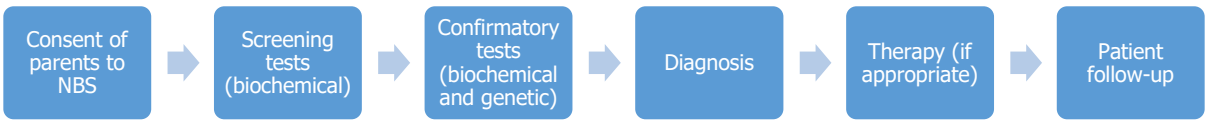
NBS forms part of a public health programme of screening of infants shortly after their birth and aims to detect conditions that are treatable but not clinically evident at the time of birth. In general, the rationale for performing NBS is to identify infants who are at risk of these conditions at an early stage, to confirm the diagnosis, and to intervene so as to prevent or reduce the clinical consequences of the condition. As such, the aim of NBS programmes is primarily to identify disorders which, if left undiagnosed and untreated, pose risks of developmental delay, severe disability, or premature death.

NBS programmes are often overseen and implemented by national health authorities and involve offering screening to all infants born in the jurisdiction, for a defined panel of treatable disorders. This panel is defined by the authorities involved, and can vary greatly internationally, and inter-regionally.

The testing involved in NBS is largely performed by measuring metabolites, enzyme activity, or other biochemicals, in samples of blood collected on filter paper following pricking of the infant's heel. In addition to NBS, some newborn screening programmes involve bedside tests to screen for conditions such as hearing loss (using automated auditory brainstem response) or congenital heart defects (using pulse oximetry).

Where the NBS panel test yields a positive result, the infant associated with the test typically undergoes further testing to determine whether this is a true positive and to what extent they may be clinically affected. Follow-up testing involves the expertise of clinical geneticists and paediatricians who specialise in the relevant condition(s). Figure 1 provides a simplistic schematic of the process involved in NBS.

Figure 1: Process of newborn bloodspot screening



In line with the testing processes underway, clinical pathways and support services must be in place in order to support parents or guardians following their notification of a positive test result in the screened child, and to provide follow-up monitoring and treatment of the child where a diagnosis is established. Overall, within NBS, it is essential that appropriate communication is in place with families so that they

understand the need for newborn screening in the first instance and know what actions to take in response to positive newborn screening results.

2.1 Ireland's National Newborn Bloodspot Screening Programme (NNBSP)

In Ireland, NBS, otherwise known as the 'heel-prick' test, is offered for every newborn baby, and is carried out, with the consent of the infant's parents, when the infant is between 72 hours and 120 hours of age.[2] Following the test, parents are contacted only if the test results are abnormal, usually when the infant is one to two weeks old.[2] Screening cards, which hold the dried bloodspots, are currently stored securely for ten years following the test and are destroyed thereafter.[3]
The NNBSP currently tests the baby's blood for the presence of the following eight conditions:[4]

- phenylketonuria (PKU)
- homocystinuria
- maple syrup urine disease (MSUD)
- classic galactosaemia
- congenital hypothyroidism
- cystic fibrosis
- medium chain acyl-CoA dehydrogenase deficiency (MCADD)
- glutaric aciduria type 1 (GA1).

Participation in the NBS programme in Ireland has been stated in recent years to be at 99.9%[2, 3, 5] and has previously been acknowledged as one of the most successful national public health initiatives,[3] indicating a considerable degree of confidence in the current programme overall. Each year, the NNBSP identifies about 110 babies in Ireland with one of the above conditions.[6]

Governance and organisation of Ireland's NNBSP
Notably, governance of Ireland's NNBSP does not fall under the Health Service Executive (HSE) National Screening Service, which comprises national population-based screening programmes aimed at detecting breast cancer, cervical cancer, bowel cancer, and diabetic retinopathy. In contrast, newborn screening in Ireland is integrated within the overall health service provided to newborn babies and involves the co-operation of many entities involved in screening and follow-up processes, such as:

- sample collection
- sample transport
- sample analysis

- recording of results
- referral and management of children diagnosed with a screen-detected condition.

Figure 2 illustrates how the NNBSP is currently situated within a governance structure responsible for various child health screening and surveillance programmes within the Health Service Executive (HSE). Figure 3 further illustrates the governance structure specific to the NNBSP, reflecting the complexity of interaction between the different parts of the health service responsible for providing NBS.

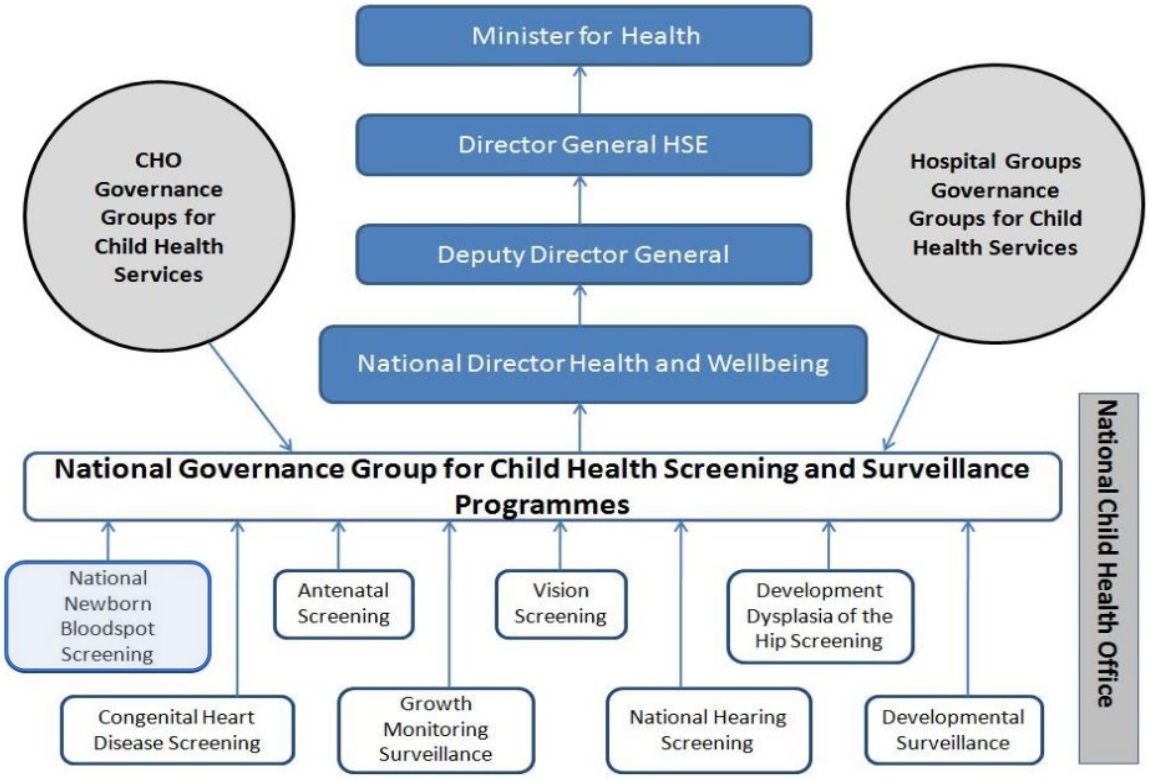


Figure 2: National Governance Structure for Child Health Screening and Surveillance Programmes[7]

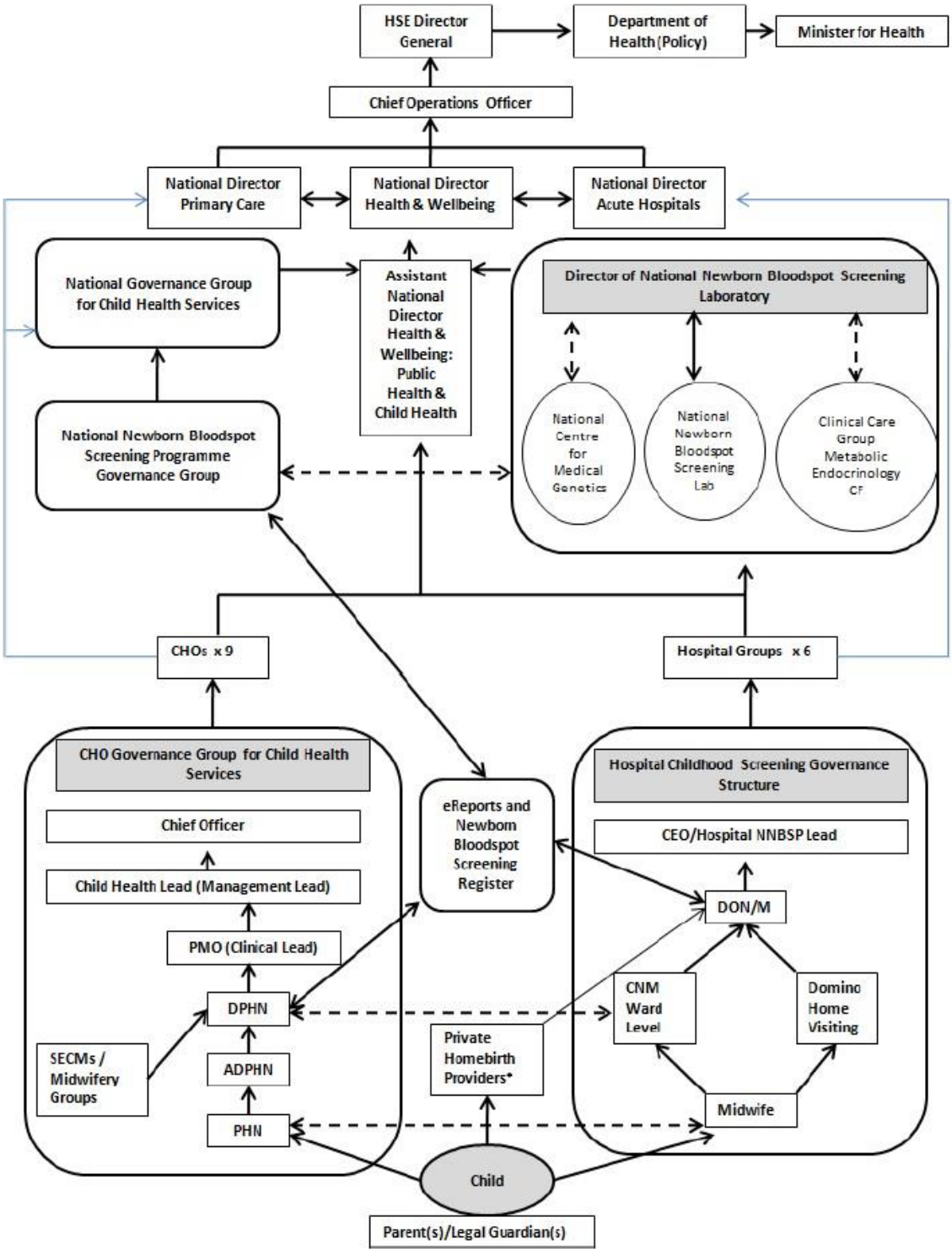


Figure 3: National Newborn Bloodspot Screening Governance Structure[7]

History of inclusion of conditions within the NNBSP

NBS was first performed as a screening programme in Ireland in 1966; this took the form of the Newborn Screening Programme for PKU, which was implemented approximately four years after the first newborns were screened for this condition in the US states of Massachusetts and New York.[7] Over the years further conditions were screened for, such as homocystinuria in 1971, maple syrup urine disease and classic galactosaemia in 1972, and congenital hypothyroidism in 1979.[8-10] Considering more recent years, cystic fibrosis was included in the list of conditions screened within the NNBSP from 1 July 2011.[11] As of the publication in 2014 of the 'National Rare Disease Plan for Ireland 2014-2018', the HSE established and implemented a governance structure for the NNBSP.[9] In part, the NNBSP Governance Group is responsible for providing multidisciplinary advice, to the Director of Childhood Screening, regarding strategic direction of the programme, and thereby considers proposals to expand the programme (see Figure 3).[7] Under this governance structure, screening for MCADD and GA1 commenced in December 2018.[7]
In 2018, the Scoping Inquiry into the CervicalCheck Screening Programme (the 'Scally Report') was published, which recommended the establishment of a National Screening Committee to advise the Department of Health and the Minister for Health on all new proposals for screening and on revisions to current programmes.[12] The NSAC was established following this report, as an independent advisory committee, and held its first meeting in November 2019. At its meeting on 17 July 2020, the National Screening Advisory Committee approved the application by the NNBSP Governance Group to add ADA-SCID (adenosine deaminase deficiency-severe combined immunodeficiency) to the list of conditions screened under the NNBSP.[13] Following the positive recommendation from the NSAC, the Minister for Health accepted the recommendation, and as of April 2021, the HSE is making arrangements for inclusion of this condition in the programme.[14, 15]

It is noteworthy that in recent years, there has been a growing interest in expanding the NNBSP in Ireland. For example, the National Screening Advisory Committee Bill, brought before Seanad Éireann in September 2020, formally proposes the consideration by the NSAC of the expansion of NBS, thereby establishing such consideration on a legal footing.[16]

Current decision-making processes for conditions included in the NNBSP

The 2018 edition of 'A Practical Guide to Newborn Bloodspot Screening in Ireland',[7] published by the National Newborn Bloodspot Screening Laboratory (NNBSL), states that conditions which form part of the NNBSP have been selected because they all have a relatively high incidence within the Irish population and because they fulfil, in

part or in full, the criteria which have been set out internationally for newborn screening.
These criteria are stated to include the following:[7]

- the conditions screened are treatable
- there is a test available which is easily applied to large population groups
- there are few false positive and false negative results, that is, the test is reliable
- the incidence of the conditions in the community is sufficiently high to warrant screening
- the cost of screening makes the process cost-effective.

Furthermore, for all of the currently included conditions, early diagnosis and treatment significantly improves the clinical outcome.[7]

More recently, the NSAC has outlined decision-making approaches with respect to screening generally, and NBS. During 2020, the NSAC progressed the development of a standardised application process and methodology for assessing new applications for population-based screening programmes in Ireland, though complete information on this process and methodology is yet to be published as of April 2021.[15] Thus far, the committee has approved a formal standardised application process and procedure for new population-based screening programmes, with a separate process in development for amendments to current programmes, through the use of an annual call.[17] Currently, it is intended that anyone can put forward an application. The NSAC has also outlined criteria for the viability, effectiveness and appropriateness of a screening programme, which were developed in line with the Wilson and Jungner criteria for appraising the validity of a screening programme.[18] As noted by Cornel et al.,[19] for example, the Wilson and Jungner principles for screening were originally published in 1968 as a guideline to evaluating whether screening would be beneficial for a variety of conditions; many countries have operationalised these principles as criteria in different ways, tailoring criteria to regional or national practice and to the specific setting of NBS.

Specifically with respect to NBS, the NSAC annual report, in commenting on decision-making for expansion, states that there are 'two clear approaches for policy-makers to consider with regard to the expansion of bloodspot screening, namely 'an epidemiological approach' and 'a technology-driven approach'.[15] The 'epidemiological approach' is described as an approach involving comprehensive investigation and assessment of the likely achievable benefits, harms, and costs of an entire screening programme pathway, as considered against internationally recommended screening criteria and informed by Irish epidemiology. This would be in keeping with a HTA approach. The NSAC notes that this strategy is reflected in

the Committee's approach to the evaluation of the evidence for a new programme.[15] The 'technology-driven approach' alternatively involves maximising the opportunities provided by advancements in screening technology (for example, the potential to include newer assays as part of expanded use of tandem mass spectrometry screening), with a lesser upfront emphasis on assessment of the overall benefits, harms, and costs of the programmes. The NSAC further notes that in considering the most suitable approach in Ireland, the Committee emphasised the need to be robust and consistent in evaluating the expansion of the programme in line with its adopted NSAC criteria for appraising the viability, effectiveness and appropriateness of a screening programme.[18]

3 Technology used in NBS programmes

The following section provides contextual information on the technology of NBS, including sampling and testing approaches. An introduction to ethical implications of this technology and its application is provided later in this report (see section 5).

3.1 Sample collection

NBS programmes most commonly use whole blood samples collected on filter paper. In some jurisdictions, umbilical cord blood samples have been used; Finland and Malta have previously been noted among European countries for their predominant use of cord blood samples, but have switched in recent years to dried bloodspot testing.[20] While urine samples were originally used to test for PKU prior to the development of the dried bloodspot test, urine samples have also been used to test for other conditions in recent years. In Quebec, a voluntary newborn urine screening programme complements the standard NBS programme; a sample is collected at 21 days after birth and is submitted to a provincial laboratory to test for an additional panel of conditions. This unique programme is used to detect disorders that may not be identifiable in bloodspots either because of the lack of appropriate biomarkers or the time of collection at two days of age, which might be too early to detect a biochemical abnormality.[21] This is the case, for example, for hyperornithinaemia–hyperammonaemia–homocitrullinuria (Triple H) syndrome, a urea cycle disorder that is more prevalent in French-Canadians.[21] Analysis of urine samples, using nuclear magnetic resonance (NMR) spectroscopy to detect metabolic disorders, has also been suggested by some researchers as a potential non-invasive approach to newborn screening for consideration within NBS programmes.[22]

3.2 Laboratory testing

As NBS programmes involve screening for a range of different conditions which require different methods of detection, a variety of laboratory-based testing approaches are used and are applied to varying extents across jurisdictions and within individual NBS programmes. These include, amongst other methods, tandem mass spectrometry (MS/MS) (primarily used for the detection of metabolites), immunoassays (for the detection of conditions such as congenital hypothyroidism and congenital adrenal hyperplasia), colorimetric or fluorometric assays, and molecular techniques (for the detection of conditions such as cystic fibrosis and severe combined immunodeficiency disorder, SCID).

MS/MS is used for the majority of tests that take place in Irish and international NBS programmes. This equipment allows for the testing of a wide array of metabolites and provides a high degree of sensitivity and specificity, and new screening targets

may be added to an existing MS/MS metabolic panel, dependent on the analytical kit which is used with the tandem mass spectrometer. For example, within Ireland's NNBSL, the 'NeoBase™ 2 Non-derivatized MSMS kit' is currently used.[†] This kit allows for the evaluation of concentrations of certain amino acids, succinylacetone, free carnitine and acylcarnitines, nucleosides and lysophospholipids. Notwithstanding the potential of this kit to screen for a large number of metabolic conditions, if a decision were made to screen for a condition which required the use of a different kit, this may have consequences for NNBSL equipment and processes. For example, such a decision may necessitate the purchase of an additional MS/MS analyser, the implementation of different laboratory processes, and the requirement for additional staffing, amongst other impacts on day-to-day operations.

As such, while it has been suggested that addition of conditions to an existing panel may be accomplished at a minimal incremental cost,[(23)] there are substantial factors (including additional costs) which must be considered, and processes which must be carried out, with respect to the implementation of an expanded metabolic panel; these processes are summarised in section 3.6 ('Expansion of an NBS programme in practice').

Second-tier and confirmatory testing; example of cystic fibrosis screening

Laboratory testing processes in NBS are multicomponent and include subsequent testing of samples following an initial positive screen result in order to confirm a diagnosis.[(24)] The interpretation of an abnormal MS/MS result involves comparison with established cut-off values (high, low, or both) chosen by one of various statistical analysis approaches (use of percentiles, multiple standard deviations added to the mean value, or a threshold of disease ranges).[(24)] Following this interpretation, a more in-depth evaluation of the significance of an abnormal result may be performed with reference to established protocols, leading ultimately to follow-up with the family. Given the potential for both false positives and false negatives, and the importance of avoiding additional contact with the child and family until a conclusive result is established, NBS also relies on further testing of the original sample obtained from the child, known as 'second-tier testing' or '2TT'.[(24)]

Second-tier and confirmatory testing may include analyte-specific assays to confirm any elevations detected, functional studies to determine enzyme activity, or genetic testing to identify disease-causing mutations. For example, the algorithm for newborn screening for cystic fibrosis in Ireland involves firstly testing the levels of immunoreactive trypsinogen (IRT) in the blood spot.[(7)] This analyte is a metabolic product which accumulates in patients with cystic fibrosis due to blockage of

[†] Personal communication with members of the EAG representing the NNBSL

excretion pathways by the thick mucus secretions associated with the condition. Following the detection of high levels of IRT, the blood spot sample is carried forward for DNA testing to identify mutations associated with cystic fibrosis. If positive results are identified through mutation analysis, the baby will be recalled without delay to undergo a sweat test (measurement of the chloride concentration in the baby's sweat) in the baby's local HSE designated paediatric cystic fibrosis centre (located in Dublin, Cork, Limerick and Galway). Dependent on the number of mutations identified through genetic analysis (two versus one), a positive sweat test result either confirms the diagnosis or leads to further DNA analysis to identify whether the baby is a genetic carrier of the condition or is diagnosed as having the condition. If the baby is considered to be a carrier as opposed to having the condition, the parents are referred for genetic counselling.[7]

Considering Ireland's NNBSP, the national laboratory (NNBSL) is fully integrated with Children's Health Ireland (CHI) at Temple Street Department of Paediatric and Laboratory Medicine, ensuring, for currently screened conditions, the rapid confirmatory testing of abnormal results and the biochemical monitoring of children with an established diagnosis.[7] In the case of some conditions screened, for example, Maple Syrup Urine Disease, suspected cases of a condition trigger urgent admission of the baby for hospital-based testing until conclusive results are known and it is considered that discharge to the baby's home is appropriate.[7]

3.3 Historical development of laboratory testing in NBS

Early newborn bloodspot screening approaches (1960s) involved testing for PKU with the use of a bacterial inhibition assay to measure the levels of phenylalanine in blood samples. Since the development of the original bacterial inhibition assays, technological advances in NBS have included, but are not limited to, the use of radioimmunoassay, colorimetric and fluorometric immunoassays, isoelectric focusing, high-performance liquid chromatography, MS/MS, and molecular genetic-based testing (for example, tests based on DNA fragments or whole exomes).[25] The development of MS/MS technology in the 1990s was a particularly important advance in NBS as it allowed for multiplex testing; simultaneous testing of an array of metabolic conditions could be performed using a single 3 millimeter-sized specimen punched from a dried blood spot.[25] Further, MS/MS served to increase screening capabilities through improved sensitivity and specificity of testing.[25] MS/MS was particularly well-suited to the analysis of amino acids and acylcarnitines, thereby permitting the detection of amino acid, organic acid, and fatty acid oxidation disorders.[25]

Over time, further assays and extraction kits have been developed to allow for extraction, from bloodspot samples, of additional types of metabolites and their

subsequent identification and quantification by MS/MS. Amongst metabolic disorders, this has technically enabled screening also for purine and peroxisomal metabolic disorders. Advances in the late 1980s and early 1990s enabled the extraction of DNA from dried blood spots. This technically enabled the dual use of blood spot specimens for both biochemical and molecular genetic (DNA-based) tests. DNA-based testing has, however, been applied in NBS programmes to a limited extent to date;[25] this is discussed further in the following section.

3.4 Genetic testing

Overall, genetic testing approaches are outside of the remit of the present review in the context of the primary focus being the examination of current decision-making processes for expansion of NBS programmes. However, several points are useful to note, for context, with respect to these emerging technological approaches in NBS programmes.

Genetic testing approaches may include molecular genetic testing methods which do not involve sequencing (for example, PCR of specific genetic targets), sequencing of individual genes, or sequencing of sets of genes, or whole genome sequencing.[23] With respect to severe combined immunodeficiency (SCID), a group of disorders characterised by dysfunction of T-lymphocytes, international NBS programmes typically perform screening using T-cell receptor excision circle (TREC) assays and quantitative PCR (that is, detection and quantification of DNA biomarkers).[26] This molecular genetic testing method, which does not involve sequencing approaches, has been noted as establishing the feasibility and utility of DNA-based, high-throughput screening.[27] Like tandem mass spectrometry, this approach may be adapted to additional conditions, for example, spinal muscular atrophy.[27]

DNA-based testing has also been used in some NBS programmes as a second-tier test for conditions such as cystic fibrosis, as noted above with respect to the screening algorithm for cystic fibrosis within Ireland's NNBSP.[7, 25] Second-tier molecular testing may be performed after a primary test, using the same specimen, in order to improve sensitivity and specificity, increase the speed of diagnosis and treatment, and reduce the number of false-positives.[25] DNA-based testing has also recently expanded to other uses in NBS programmes and as part of the diagnostic work-up following a positive newborn screen.[25]

In relation to DNA sequencing approaches, a recent publication reported on an evaluation of whole-exome sequencing as an alternative to MS/MS for the detection of metabolic disorders.[28] This study examined blood spot samples and data for almost all cases of metabolic disorders among 4.5 million infants born in California between 2005 and 2013. The study results concluded that whole-exome sequencing

was insufficiently sensitive or specific to serve as a primary screen for most metabolic disorders detected in NBS. However, whole-exome sequencing may add value in secondary or confirmatory testing.[28] Furthermore, it is noted that many potentially treatable conditions other than metabolic disorders may be readily detected using genomic technologies; these may include early-onset seizure disorders, cardiac arrhythmias, cardiomyopathies, disease of the blood or bone marrow, liver diseases and kidney disorders.[23]

The advent of whole-exome and whole genome sequencing poses further policy-making challenges beyond those currently considered in processes for the expansion of NBS.[29] While these sequencing approaches may be highly effective in the identification of certain disorders, genome-wide sequencing results in the identification of far more information about the individual than that generated by conventional testing.[23] This gives way to many ethical challenges, for example, where genomic screening identifies risk factors for disorders which are yet to be fully described, or for disease which may not manifest in the lifetime of the individual.[30] It has been argued that the emergence of genetic technologies is likely to be a significant turning point for NBS and that carefully considered policy-making approaches are needed which can successfully navigate the changing environment.[29]

3.5 Role of technology in NBS programme expansion

Technology may be considered to influence NBS programme expansion in at least two important ways. Firstly, developments in technology provide opportunities for NBS to expand. Conversely, technology may constrain expansion where implementation factors slow expansion or technology required for other downstream processes (for example, confirmatory testing, diagnostic work-up and follow-up, or treatment) are less available; such factors are discussed in greater detail in section 3.2 and section 3.6.

Opportunities for expansion

With the implementation of MS/MS for the screening of metabolic disorders in Ireland and internationally, the number of metabolic disorders which may be screened is not primarily limited by the technology, but rather by the decision-making that takes place by authorities responsible for the delivery of NBS programmes.[20] Expansion of NBS programmes by way of expanded MS/MS has been noted in many countries; Cornel et al. note that a 'technology push' was already observed in the 1980s with the use of MS/MS.[20] Nonetheless, among countries which use MS/MS, the number of conditions screened for within NBS programmes ranges from between nine and 50.[20, 29] As such, decision-making in

countries with lower numbers of included conditions is clearly impacted by factors other than the availability of a screening test.

As an example of technology-driven expansion, when expanded NBS using MS/MS was introduced in New Zealand in 2006, around 25 different fatty acid oxidation disorders and organic acidaemias were added to the screening panel.[31] The suggested rationale for inclusion of these conditions was that expert opinion at the time considered these suitable and MS/MS made this feasible; individual disorders were not considered in detail as little information was available at the time for many of the rare conditions.[31] Wilson et al. include this information in an article on the decision in 2017, following a review against New Zealand's NBS screening criteria, to remove carnitine uptake disorder from the panel of conditions screened; this decision had been taken in light of the risks and harms of screening for this condition outweighing the benefits, given a largely asymptomatic disease profile observed and a potentially harmful treatment being administered.[31]

Constraining expansion, or encourage expansion dependent on technological factors

A review of international differences in the evaluation of conditions, notes that technological developments have been included in some countries' criteria against which a condition is assessed with regard to its suitability for NBS.[1] For example, such criteria may include the stipulation that the analysis for consideration could be multiplexed with technologies already in use.[1] Relatedly, in the context of consideration of expansion of NBS with a number of conditions simultaneously, it is important to consider the degree to which such expansion may be readily implemented. As discussed in section 3.2, expansion may be constrained by the particular equipment and materials in place, for example, whether a currently used analytical kit permits the analysis of biomarkers for the condition of interest, or whether an additional kit, and consequently potentially an additional tandem mass spectrometer, is required. Also, following a positive recommendation for inclusion of a condition in a programme, lengthy processes of laboratory verification must take place in addition to clinical and public health processes (for example, planning for communication with stakeholders and establishment of appropriate clinical pathways). Such processes may benefit from efficiencies where multiple conditions may undergo simultaneous validation and verification. Furthermore, it has been suggested that modern technology drives the possibility, and sometimes the need, to evaluate groups of conditions at once.[29] The rate or efficiency with which specific conditions may be successfully integrated into NBS programmes, a factor which is dependent on validation processes, may therefore be considered as a potential factor in decision-making processes.

3.6 Expansion of an NBS programme in practice: Implementation of an addition to the screening panel with an example from the Irish setting

While it is technically possible in some cases to expand the number of conditions included in an NBS programme screening panel using existing equipment, the practical implementation of such expansion is a highly complex and resource-intensive process. A recent survey of US state NBS programmes identified that lengthy periods of time are required for implementation following the point of decision-making to expand; among states implementing screening for the metabolic conditions MPS 1 and Pompe disease, the median time required for implementation was found to be 66 months for MPS 1 (95% CI 33, 75) and 75 months for Pompe disease (95% CI 45, 99).[32] When considering the individual components of 'readiness', laboratory readiness was one of the lengthier processes identified, requiring about 39 months. Facilitators to readiness included collaboration with other NBS programmes and recruitment of staff, while lack of staff, or inability to hire laboratory and follow-up staff, were the most frequently noted barriers.[32]

A large extent of the processes involved in implementation of a screening programme involves verification of the new screening process ('new screen'). All screening programmes aim for 100% sensitivity (that is, no false negatives) and a minimal number of false positives, but in practice these outcomes not achievable. There are always some limitations of programmes, whether technical, clinical, financial, organisational, or otherwise, which mean that some cases will go undetected.

It is therefore important for all screening programmes to know what the projected rate of false negatives and false positives will be with the introduction of a new screen. To ensure this is achieved, extensive laboratory verification of any new screen is required.

The following section provides a short summary of the steps, including verification processes, that are required when adding a new condition ('new screen') to the existing panel of conditions screened within the Irish NNBSP. This summary uses the example of the implementation of ADA-SCID that is currently underway in Ireland and was requested by members of the Expert Advisory Group for inclusion within this report.

Summary of steps required when adding a new screen to the NNBSP

The newborn bloodspot screening process is a multi-tier process which involves many stakeholders and steps (see also Figure 3, section 2.1). If a commercial test kit is available for the new candidate screen, this will preferably be installed and optimised by the vendor technical support team on site in the NNBSL. If no commercial kit is available, an assay will need to be set up and validated by the NNBSL staff, requiring considerably longer time. Whether a commercial kit or an in-house non-kit method is being used, extensive verification studies will be performed to ensure reliability of results.

An example of the process being followed for ADA-SCID implementation is outlined below:

1. Define screening case definition for ADA-SCID
2. Verification of CE-marked diagnostic newborn bloodspot screening dried blood spot tandem mass spectrometry test kit. This process includes the following steps:
    a. Engage with kit supplier to schedule a technical specialist to come on site to the NNBSL and optimise kits on the existing laboratory tandem mass spectrometers
    b. NNBSL draft and approve a laboratory verification plan for ADA-SCID, to include re-verification of five existing mass spectrometry screens (PKU, MSUD, HCU, GA1 and MCADD)
    c. Verification experiments, which examine, at a minimum, precision, accuracy, analytical sensitivity, linearity, and instrument comparisons.
    d. Clinical studies, comparison with an existing method, and inter-laboratory comparisons, where possible.
3. Decide on dried blood spot sample criteria for laboratory verification process in order to establish population distribution statistics and associated 95% Confidence Intervals.
   Samples must be:

    - anonymized
    - of good quality
    - obtained from babies who are:
        - no more than two weeks old
        - greater than 36 weeks gestational age
        - not transfused
        - on normal feeds
    - taken at between 72 and 120 hours.

Data to be collected must include:

- mean
- median
- percentiles.

4. Establishment of cut-offs, based on percentile data, for all conditions screened on the tandem mass spectrometer (MS/MS). This involves acquisition of percentile data from a large number of newborn screening samples (>5,000) using criteria defined above.
5. Engagement between NNBSL and the Laboratory Information Management System (LIMS) provider. This involves defining software changes necessary to implement all required changes to various components of the LIMS for addition of the new condition. The testing algorithm is integrated into the existing LIMS, followed by extensive testing for all result permutations.
6. Development, testing and integration of follow-up protocols into the current LIMS. Reconfiguration of electronic and hard copy patient reports to accommodate the new analyte is also required.
7. Quality assurance: it must be ensured that all laboratory procedures are in compliance with ISO 15189 (the international standard for requirements for quality and competence within medical laboratories).
8. Scoping and agreement of the protocol for follow-up of a screen positive result on routine dried bloodspot samples. This protocol should be in line with existing NNBSL procedures for other screen positive conditions.
9. Decide on second tier follow-up protocol and agree algorithm for this.
10. Scope and agree the clinical pathway for screen positive babies:
    a. Identify the clinical centres or laboratories that will be responsible for follow-up diagnostic testing and for pathways for samples into and out of these centres.
    b. Identify the clinical centres responsible for follow-up care and treatment, and the pathway for patients into the clinical centre.
11. Select suitable key performance indicators (KPIs) for the programme, for example, laboratory turnaround time for samples and time until either clinical review and reassurance or diagnosis. Monitor these KPIs as part of the programme.
12. Establish processes for monitoring of usual parameters for screening programme quality assurance. Examples of such parameters include sensitivity, specificity, positive predictive value, and negative predictive value.
13. Consider programme review and check points for quality assurance.

Communication plan

A communication plan is required for all stakeholders. Such stakeholders include, at a minimum:

- Parents/guardians
- public health nurse representation (Director of Public Health Nursing)
- midwife and maternity unit representation (Director of Midwifery)
- clinical teams in maternity units and paediatric hospitals which receive referrals for screen positive patients.

In particular, clinical teams need to be aware of, and support and follow, agreed pathways for further investigation and follow-up.

The following also require revision when a new screen is added to the overall programme:

- NBS website
- parent information leaflets, including translations
- training modules such as those hosted on HSE's online learning and development portal 'HSELanD'
- 'A Practical Guide to Newborn Screening in Ireland'[7]
- sample takers' guide
- HSE Standard Operating Procedure.

4 Types of conditions targeted by NBS Programmes

Given the purpose of this review and the variation in the number of conditions screened within international NBS programmes, detailed descriptions of individual conditions are outside of scope. Groups of heritable conditions which may be detected by newborn bloodspot screening include disorders of metabolism, haemoglobinopathies (for example, sickle cell disease, thalassaemia syndromes), endocrine disorders (for example, congenital hypothyroidism and congenital adrenal hyperplasia), immunodeficiency disorders (severe combined immunodeficiency disorder), neuromuscular disorders (for example, Duchenne muscular dystrophy, spinal muscular atrophy), and other individual conditions such as cystic fibrosis.[33]

Conditions within these groupings may be further classified according to the biochemical process or process otherwise that is affected (see Appendix 2, Table App2.1). Furthermore, some conditions may fall under different groupings; for example, where a condition presents primarily as a neuromuscular syndrome but where the disorder is metabolic in pathology. As discussed in section 3, conditions may be screened for using different technologies; metabolic disorders are usually screenedusing MS/MS technology, but may also be screened using alternative methods. Conditions outside of the metabolic disorder class, for example, cystic fibrosis, may be less possible to screen for using MS/MS. Additional nuances relating to conditions screened for in NBS programmes include the fact that biomarkers may be common to several conditions. For example, screening for methylmalonic acidurias or propionic acidaemia results in detection of vitamin B_{12} deficiency in newborns due to the common biomarker propionylcarnitine (C3);[34] in the case of vitamin B_{12} deficiency, this is not a heritable metabolic disorder, but may result from maternal nutritional deficiency.[35] As such, if a certain condition is added to a NBS programme and the primary biomarker represents a biomarker for other conditions, it must be accepted that the conditions for which the biomarker is common are effectively screened for also.

5 Ethical, legal and social implications associated with expansion of NBS programmes

It is beyond the scope and capability of the present review to assess the consequences, in terms of benefits, harms, costs, and ethical, legal, and social implications (ELSI), of expanded NBS. Nonetheless, in examining processes to inform decision-making on NBS expansion, it is important to contextualise this examination with respect to consideration of the underlying issues which result in the need for decision-making processes. Therefore, the following highlights some examples of relevant considerations, as gathered from scoping searches of the NBS literature. This section represents a high-level overview of the ethical implications associated with the expansion of NBS programmes; it is expected that any formal consideration of a condition for expansion should be accompanied by a detailed assessment of the associated ELSI implications. It is further noted that additional work is underway to develop a draft ethics framework for the NSAC (though not specific to NBS), which may help to inform future assessments.[17]

Many authors have provided commentary on the ethical issues surrounding the expansion of NBS programmes.[23, 36-44] Friedman et al., for example, provide a discussion of ethical and public policy issues raised by current newborn screening practices.[23] The authors note that the types of conditions that have been added to some NBS programmes, as a result of the possibilities afforded by MS/MS, have challenged conventional ethical norms with respect to screening. Importantly, some of these conditions are not fully penetrant, that is, not all infants who display the pathogenic biomarker go on to develop the disease. Also, in some cases, among infants who develop the disease, they may do so at varying ages including up to adulthood, or may vary widely in disease severity or response to treatment. Consequently, some infants may undergo unnecessary diagnostic procedures and treatments, and they and their families may experience increased levels of stress and anxiety faced with future uncertainty. The authors note that concerns have similarly also been raised about the nature of the benefits to the child screened, as the concept of 'treatable' illnesses has been expanded from the intention of 'preventing' symptoms to including the intention of 'reducing symptoms to some degree, prolonging life, or avoiding long diagnostic quests once symptoms appear'.[23]

The concept of benefits being accrued specifically by the child being screened has also come into question; advocates for expanded screening in some cases suggest that interventions which have not been proven to be effective in reducing morbidity or mortality overall may benefit some children and their families, or families may wish to have the opportunity to participate in research.[23] Furthermore, providing

families with information about an infant's carrier status for a recessive genetic disorder, while of no immediate clinical benefit to the child, may provide information to the parents to help them in decision-making about future pregnancies. The authors note that while expanding the scope of benefits to be considered may not be unethical, such consideration does represent a shift in the goals of newborn screening away from the benefit to the infant screened, and thereby necessitates re-examination of its ethical justification.[23]

With respect to public health considerations and the potential over-diagnosis of some infants (that is, the detection of disease that would never have caused symptoms within the individual's lifetime), the authors also note the health economic consequences of providing diagnostic procedures and treatments where such intervention may have been unnecessary, particularly if the available treatment is expensive or associated with serious risks of adverse events.[23] Furthermore, the expansion of NBS programmes may have implications for issues of consent. In many jurisdictions, though not in Ireland, NBS has been established as compulsory under a public health mandate. With respect to such mandated programmes, following the expansion of programmes to include conditions with wider phenotypic variability, unclear risk associations, and more invasive or less effective treatments, there are concerns that the justification for mandatory screening or implicit consent has been compromised.[23] While these concerns do not apply to Ireland's NNBSP in its present form, which seeks consent from parents before proceeding with NBS, it is important to ensure public confidence in NBS to ensure continued high participation rates.

The impact of expanded NBS on the psychosocial experience of parents and families has been explored in numerous qualitative and quantitative studies, though differing perspectives have been observed with discrepant findings. Grob notes that research on public and parental opinions about screening consistently points to high levels of support for expanded panels.[38] However, interpretative qualitative analysis by Grob et al. has suggested that screening expansion within the US has had significant unintended consequences, and the author outlines four 'notable repeated findings' to this effect as follows:[38]

(i) newborn screening may in some cases induce long-term feelings of regret and grief in parents in relation to the time period following an abnormal screening result wherein parent-child bonding was interrupted
(ii) screening may result in medicalisation of early childhood, where parents struggle with diagnostic uncertainty
(iii) preventive health regimes following abnormal screening results can be intense, and families are not all equally well positioned to implement them
(iv) an "urgency narrative" associated with NBS, combined with parents' or

> guardians' commitment to safeguarding their children's health, discourages public critique.

The author further highlights that investigations of psychosocial impact frequently aim to assess whether there are lasting effects on parent-child bonding as a result of childhood screening, such as in the form of 'vulnerable child syndrome'. However, while results of qualitative research undertaken in this area suggest that the impact of screening in this respect is significant, it does not tend to cause lasting disruptions between the parent(s) and child; rather, in the long-term, a sentiment of regret over time lost and the emotional impact following an abnormal result is observed.

While the psychosocial and physical impacts of false positive results are frequently discussed within the literature, Goldenberg et al. further note the significance of false negative results.[43] The authors emphasise that while this form of result tends to be less common when considering NBS programmes, given the extensive quality control measures in place, they are not non-existent and are an outcome that should be considered in the context of harms associated with NBS programmes. Such false negatives may result in delayed diagnosis and treatment, drawing diagnostic evaluation away from the true condition due to false reassurance of clinicians and families.

Implications for policy-making

The potential harms associated with NBS expansion have been extensively documented. However, it has also been suggested that arguments regarding the potential harms associated with early identification of disease have been used as a reason not to add them to a screening programme, leading to a 'do nothing' approach; hence, the potential harms are perceived, but the consequences of not acting are not fully appreciated.[37]

While there are harms associated with expanding NBS programmes without full consideration of the complexities within the process, there are also harms associated with a 'do nothing' approach. In a similar vein, when evaluating the potential harms associated with false positives, this should be balanced against consideration of the 'diagnostic odyssey' (that is, the diagnostic steps the patient undergoes between the first onset of symptoms and the final diagnosis of their condition) experienced by the symptom-detected child and family, particularly in the case of rare diseases, and the impact that NBS may have on reducing this element. As such, the need has been stated to evaluate all relevant ethical issues when considering NBS expansion, followed by an evaluation of the ethical dimensions of alternative actions; after careful weighting of both evaluations, a justification of any action taken is then provided. A 2014 systematic review of ethical, legal and social issues in relation to

expansion of NBS examined studies published from January 2006 to October 2013, and summarised the broad range of opinions expressed on each topic.[42] The authors concluded that there are multiple stakeholders, perspectives and values to consider, and identified two critical points of disagreement between contributors:

- 'What is the aim of screening?'
- 'What evidence do we need prior to implementation that screening will deliver the anticipated net benefit?'[42]

Considering policy implications, the authors concluded that the simplest approach would be to screen only where there is randomised controlled trial (RCT) evidence demonstrating morbidity and mortality reductions for the infant screened, but that this would present an ethical dilemma due to the lack of feasibility to produce such evidence in the case of rare disease. This ethical dilemma was considered to be ameliorated by expanding the definition of benefit to include reducing the 'diagnostic odyssey', providing information to parents, and increasing research on these conditions. However, this approach would in turn result in further ethical dilemmas due to the:

- lack of consent by the child to the screening
- lack of adequately informed parental consent
- potential harm to children resulting from false positive or indeterminate results
- opportunity cost to society of resources expended on screening.

Furthermore, the authors noted the extent of advocacy and lobbying for the introduction of screening programmes, particularly by parents of children affected by disorders which may be screened by NBS; the authors stated that while such advocacy should be considered by policy-makers, they must also consider the interest of children and parents who will be negatively affected by the introduction of screening as a result, for example, of false positive results, indeterminate results, or overtreatment, particularly as such people cannot advocate against expanded screening as they are as yet unidentified.[42]

6 International NBS programmes: conditions screened

Section key points

- This chapter outlines the number, and types, of conditions screened in NBS programmes within the specified countries of interest to this review. Caution is required when interpreting results given challenges encountered in sourcing and extracting current information for a number of the included countries.
- A distinct heterogeneity was observed in the number, and types, of conditions screened for across countries, with an additional complexity in terms of regional variation within a number of countries. Direct comparisons between countries were limited by the level of detail provided by individual screening authorities, differential reporting of updates to screening programmes and differences in nomenclature and in the grouping of conditions.
- Of the countries selected for the present review:
    - the US recommends 35 core conditions for inclusion in NBS with variation noted by state
    - provinces and territories in Canada, as of 2015, were homogeneous for three conditions in NBS while the total number of conditions screened varied from five to 30. In recent years, Alberta and Quebec have individually added four conditions, while Ontario has removed four
    - approximately 25 conditions are screened for in Australia, with regional variation noted
    - New Zealand's newborn metabolic screening programme includes 23 conditions. A number of conditions have been removed in recent years following reassessment of clinical and or cost benefit
    - as of 2021, Denmark includes 18 conditions in NBS with the addition of three conditions since 2012
    - Germany includes 19 conditions, with recent expansion including SMA and sickle cell disease

- The Netherlands has detailed expansion to 24 conditions as of 2021, with expectations of expanding to eight further conditions in the coming years
- a mandated list of 40 conditions has been implemented in Italy; however, despite legislative acts at the national level ongoing regional variation is documented
- nine conditions are screened for in the UK, with expansion from five implemented in 2015.

- A number of countries were further noted to have conditions currently under review or pilot assessment.

6.1 Caveat regarding comparison and counting of conditions screened

The present review aims in part to provide a summary of the extent of conditions screened for in individual countries. However, caution is suggested in interpreting the presented summary text, below, and summary tables (Appendices) due to difficulty in comparing across countries. This difficulty arises partly due to differing levels of inclusion of conditions within different regions in some countries (for example, Canada, Australia), and sometimes discrepant detail in national screening authority sources, for example, due to differential reporting of recent updates to NBS programmes. Furthermore, and perhaps more importantly, comparison is challenged by differences in the nomenclature used to list and count conditions.

Several challenges in comparing disorders screened across programmes within the US have been identified.[45] Confusion arises where different jurisdictions may refer to either the name of the disorder, the analyte deficiency, or the analyte screened for, and do so in a non-systematic way. Counting the number of disorders screened creates further confusion as multiple variations of a single disorder may be counted in different ways or not counted at all. It is also noted that within the US setting, there has historically been competition among screening programmes (public and private) to offer the largest number of screening disorders due to a *"consumer perception that more is better"*; as such, there may be incentives to list or describe the number of conditions screened in a misleading manner.[45]

6.2 Comparison and counting of conditions within the present review

For the purposes of the present review, Appendix 2, Table App 2.1 illustrates the

range of individual conditions screened for within NBS programmes in countries overall, and regions within countries, selected for the present review: Australia, Canada, Denmark, Germany, Italy, the Netherlands, New Zealand, UK and US. Lists of conditions were derived from screening authority websites and/or academic literature such that the most updated and detailed source was selected. This table aims to visually depict the differences in the extent of conditions included across screening programmes, and to illustrate which conditions are screened for across the majority of programmes. Efforts have been made to group variants of disorders to allow for clearer comparison across countries, but it is important to note that absolute counts of the numbers of conditions screened may be subject to interpretation. Meanwhile, Appendix 3, Table App 3.1, details the number of conditions reported to be screened for, as stated within the sources identified. It is important to note that some countries may include, within this number, certain conditions which are not detected by bloodspot screening, for example, conditions detected using hearing tests or pulse oximetry; such conditions are not within the scope of the present review but may not always be clearly separated from the overall figure quoted. As such, in addition to the challenges of comparison noted in the preceding section, this may give rise to discrepancies between Appendix 2, Table App 2.1 and Appendix 3, Table App 3.1.

Additional information on conditions screened by countries outside those included in the present review, as well as those featured in the present tables, may be found in the academic literature. This includes reviews of the international situation with respect to NBS programmes, which considered countries under major worldwide regions,[46, 47] and a 2018 survey of conditions screened in 51 European countries, with some additional data collection in 2020.[20] This survey collected data from members of the International Society for Neonatal Screening (ISNS) and screening laboratories involved in national NBS programmes. Overall, summary observations regarding the extent of screening panels include the following:

- In the US, since selection of the initial 29 core conditions (of which 20 may be screened with MS/MS) and 25 recommended secondary targets for the Recommended Universal Screening Panel (RUSP), six additional core conditions have been recommended along with one secondary target; therefore, 35 core conditions are recommended for NBS as part of the RUSP.[47, 48]

- In Canada, where NBS decision-making is made at provincial and territorial level, only three conditions were included in all NBS programmes as of 2015 (PKU, congenital hypothyroidism, and MCADD) and the number of conditions routinely screened varies from five to over 30 across programmes.[46] In 2019, four disorders were added to the panel in Alberta,[49] while in Ontario,

C5OH-related targets (Methylcrotonyl-CoA Carboxylase Deficiency , Beta-Ketothialase Deficiency, Hydroxymethylglutaric CoA-Lyase Deficiency, and Multiple Carboxylase Deficiency) were removed from the panel.[50] The National Institute of Excellence in Health and Services (INESSS) of Quebec has considered a range of conditions for addition to the NBS panel in the region. Seven conditions were reviewed in 2019, two of which were recommended for addition (methylmalonic acidaemia and propionic acidaemia). Nine further conditions were considered in 2020, two of which were recommended for addition (homocystinuria and cellular carnitine uptake deficiency).[51]

- NBS operates in Australia across the six federated states and two territories. Screening is funded by state and territory governments, which operate independently of each other. Newborns are screened for around 25 genetic and metabolic conditions with some variation by state/region.[52] A NBS Framework at the national level was introduced in 2018.[53] Congenital adrenal hyperplasia was recommended for screening in 2019.[54]

- In the New Zealand newborn metabolic screening programme, 23 conditions are included.[55] In 2015, a number of conditions were removed from the screening programme as it was found that there was no clinical benefit to the child. Also, in 2017 a further two conditions were removed; these included carnitine transport defect (due to a high number of false positives) and tyrosinaemia (following analysis of the cost-effectiveness of an alternative test being investigated).[31, 56]

- Across European countries, as of 2018, the panel of screened conditions varied from none to over 30 conditions. Of 51 European countries for which survey data were provided, 24 were found to screen for more than 10 conditions.[20] The introduction of MS/MS technology in many laboratories across Europe was associated with a considerable increase of screening for amino acidaemias (for example, MSUD, Tyrosinaemia type 1, CIT type1), organic acidaemias (for example, GA1, IVA, PA, MMA) and fatty acid oxidation disorders (for example, MCAD, LCHAD, VLCAD). The International Society for Neonatal Screening (ISNS) survey report suggests that budget and financial factors are not the primary causes of the current heterogeneity across programmes, though these do play a role.[20] Countries with similar economic status may present different screening panels, and these differences can sometimes be so extensive that they cannot be explained by epidemiological assessment; these differences are therefore likely to reflect the approaches taken by each country's NBS panel of experts.[20] For the European countries examined in the present review, documents examined showed that the

number of conditions screened for ranged from nine (UK) to 40 (Italy). Further details, along with examples of expansion in recent years, are provided in the following section.

6.3 Examples of expansion in recent years

Denmark

In Denmark, the screening panel increased from 15 conditions in 2009 to 18 by 2021, with the inclusion of isovaleric acidaemia (IVA) in 2012, cystic fibrosis in 2016, and SCID in 2020. Currently, spinal muscular atrophy (SMA) is under review for addition to the panel.[57]

Germany

The German NBS programme screens for 19 conditions using enzymatic tests and immunochemistry as well as MS/MS. Molecular-based NBS has not been broadly implemented and plays a confirmatory, third-tier role in screening, specifically for cystic fibrosis. SMA and sickle cell disease were approved for inclusion in the panel in December 2020.[58]

Netherlands

The Health Council of the Netherlands (GR) advised the government health ministry, upon request, to make the following changes to expand the NBS programme:[59]

- 2005: advice to add 14 conditions
- 2011: advice to add one condition (cystic fibrosis)
- 2015: advice to add 14 conditions, thereby expanding from 17 to 31 conditions
- 2019: advice to add one condition (SMA).

With respect to the expansion in 2015, the National Institute for Public Health and the Environment (RIVM-CvB) suggested a phased implementation of these conditions over a five-year period. This phased implementation is noted to be in contrast with the expansion which took place following the advice issued in 2005, where it was recommended that all proposed additions be implemented by 2007;[59] this relatively quick expansion was considered to have led to 'suboptimal results', specifically involving high numbers of false positive cases. As of January 2021, the national NBS programme has been expanded to include 24 conditions.[59] It is expected that the programme will be expanded with an additional eight conditions in the coming years.[59]

Italy

The Italian screening programme started in 1992 with phenylketonuria, congenital hypothyroidism and cystic fibrosis. The development of analytical technology (in particular MS/MS) simplified the analyses of screening, increasing the number of diagnosable pathologies enabling extended screening. This led to the mandated extension in 2016 to 40 conditions (Law 167/2016 and Ministerial Decree 2016).[60] Decision-making is national with legislative acts; however, regional variation in implementation is noted in terms of the conditions screened and coverage attained.[61]

Spain

While Spain has not been included within this review for the purpose of consideration of decision-making processes, an academic review described recent expansion within the country.[47] Between 2000 and 2015, there were significant differences in the NBS programmes of the different autonomous regions, as many only included two or three conditions, while others included more than 20. In July 2013, the Consejo Interterritorial (Inter-territorial Council) of the National Health System of Spain approved NBS programmes to test for endocrine and metabolic disorders, which would thereon be included in the nationwide basic services portfolio of the National Health System. Thus screening programmes could be implemented in all regions of Spain in a uniform manner and based on rigorous quality criteria. It was recommended that seven diseases be included in the proposed NBS programme throughout Spain, four of which are metabolic disorders.[47] All the autonomous regions in Spain now adhere to including the minimum seven diseases in their respective NBS programmes except for Galicia, where screening for sickle cell disease is not included. However, while some standardisation has been achieved, there is still considerable variation in the maximum number of included conditions across the country, with some regions continuing to screen for many more conditions.

UK

Screening for nine conditions is carried out by the National Health Service NBS programme. The screening panel increased from five conditions to nine conditions in 2015.[62] An evaluation of screening for SCID is scheduled to begin in 2021, while screening for tyrosinaemia is under active consideration.[63]

7 Processes for inclusion of conditions in programmes

Section key points

- This chapter outlines the processes for the inclusion of conditions in NBS programmes, including processes relating to proposal, prioritisation and selections of conditions for review, processes and methodologies for assessment of conditions, and decision-making processes and criteria for condition inclusion.
- Expansion of NBS screening may be considered in terms of a policy cycle model, consisting of five phases: (1) agenda setting (condition proposal); (2) policy advice (condition assessment); (3) policy decision (decision on a condition); (4) implementation (addition of a condition); (5) evaluation (quality assurance and improvement). It is recommended that a structured approach be in place for each domain of this policy cycle model to ensure appropriate governance of the programme. Furthermore, criteria for decision-making may be adapted to ensure they consider aspects of implementation and evaluation of NBS programmes.
- Countries vary in terms of who can propose a condition for assessment, with some restricting this to designated screening committees. Open calls for conditions have been implemented by a number of countries with subsequent consideration by an expert group for formal prioritisation and or selection. As an example, the US allows for open submissions, but advises the use of a multidisciplinary team in the submission process.
- Jurisdictions increasingly rely on the use of formal evidence review processes. In some cases, for example the Netherlands, decision-making processes consider both independent scientific advice provided by a national assessment body, and feasibility assessment from bodies charged with overseeing the implementation of NBS programmes. There is a general consensus that scientific advice should be based on published, peer-reviewed evidence, which has been further reviewed by experts and supplemented with expert opinions when required.
- In terms of the type of evidence to be considered, variation was noted across the countries included; however, it was noted that RCT evidence is likely to be insufficient when considering NBS programme expansion and expert opinion may be required, though, where possible, systematic

approaches to evidence review should be used in order to minimise bias. Evidence on ethical, social and legal concerns should also be considered.

- A number of countries use structured frameworks to support decision-making. For example, a framework applied in the Netherlands outlines the requirements which must be in place before a final positive decision to expand screening is made. This assessment framework covers topics such as the test method and clinical follow-up, but also communication and education issues, costs related to testing, and legal requirements. This framework is intended to be used to avoid important aspects relating to a decision being overlooked prior to a final decision.

Activities relating to the expansion of NBS may be framed in terms of 'the public health policy cycle', that is, five phases which translate to specific activities relating to NBS policy.[59] These phases are presented, using the terminology of the present review, in Figure 4. The phases of primary interest to the present review include 'agenda setting', 'policy advice', and 'policy decision', though issues of implementation and evaluation are likely to inform the former phases also. Also, the remit of the present review involves consideration of 'policy advice' and 'policy decision' under a single overall heading of 'decision-making processes', with the understanding that assessment processes may not necessarily be in place in all jurisdictions, particularly where a policy-making approach less focused on the public health perspective is in place (see discussion of the concept of 'interest coalitions' in section 8 of this review).

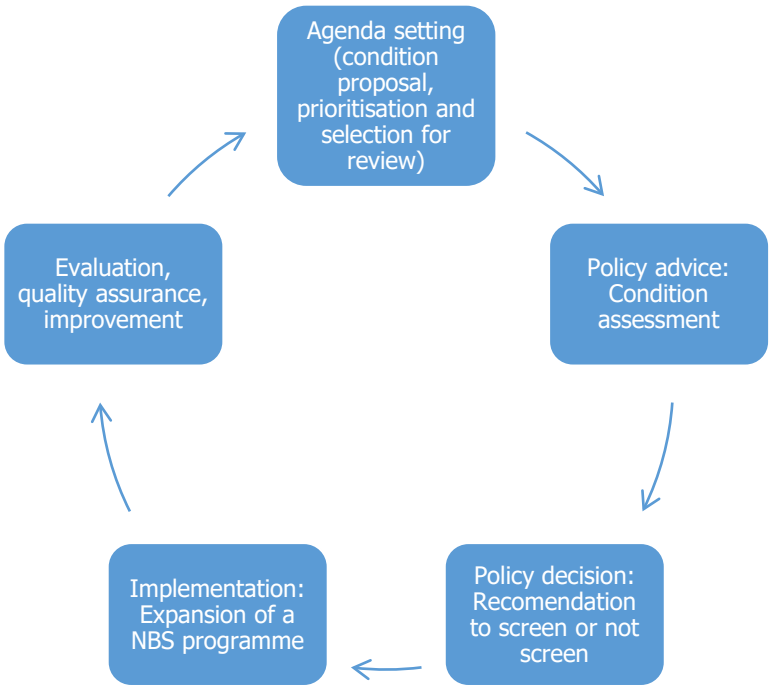


Figure 4: Public health policy cycle with respect to NBS expansion *(Adapted from Jansen et al.* [59])

The present review builds on the work of Jansen, Metternick-Jones, and Lister,[1] which explored international differences in the evaluation of conditions for NBS, and also the work of Seedat et al.,[64] which considered international differences in policy-making processes and criteria for general screening programmes and genetic screening programmes. This review involved examination of both scientific literature and policy documents to understand what factors influence NBS decision-making criteria and how conditions are assessed against them.

7.1 Overall country profiles for NBS processes

Information on decision-making processes for individual countries included in this review was extracted from policy documents, and from academic literature where more up to date or more detailed information was available. This information is detailed in tabular form in Appendix 3, under the following table headings:

- characteristics of NBS programmes in individual countries reviewed
- processes for proposal, prioritisation and selection of conditions (screening indications) for review
- processes and methodologies for review and synthesis of evidence on

screening effectiveness

- decision-making processes in place for screening recommendations
- criteria considered within decision-making (see also section 9).

The following narratively summarises this information at individual country level, while the subsequent sections summarise broadly across countries.

Australia

In Australia, anyone can propose a condition to be considered for inclusion on the panel, with the programme management committee recommending a prioritised list of proposed conditions to the standing committee on screening.(65) The selection of conditions for review depends on a number of factors including availability of resources, level of evidence, complexity and whether economic analysis will be included. The framework for decision-making in Australia involves assessment of the condition, the screening test, the treatment or management strategy available, and additional considerations by the standing committee on screening, who then advise the Australian Health Ministers Advisory Council. It should be noted that there is some regional variation as the State governments can decide what conditions to include in their programme.

Canada

The Alberta Health and Wellness (AHW) ministry in the province of Alberta, Canada determines what conditions are screened for and facilitates co-ordination with stakeholders.(66) The Australian 'Population Based Screening Framework'(67) guided the selection of conditions for review. The evidence assessment for inclusion of new conditions to the panel is conducted by a number of HTA based organisations.(68) This process involves the use of appropriate evidence and information for decision-making regarding the public provision of health technologies and services. It is unclear how this evidence assessment is then incorporated into the decision-making process for panel expansion.

The Newborn Screening Ontario – Advisory Council (NSO–AC) determines whether changes are needed to the current screening process including the addition/removal of a condition from the panel.(69) The NSO-AC developed a formal review process to evaluate potential new screening targets and existing targets in the province of Ontario. NSO-AC is responsible for providing advice and guidance to Newborn Screening Ontario, as well as the Ministry of Health and Long-Term Care and the Ministry of Children, Community and Social Services.(70) The advisory council meets a minimum of four times a year. For decision-making, a quorum is set at 50% + 1,

with a goal of decision by consensus. Jansen highlights that dichotomous recommendations are made (that is, the addition, or removal, of the condition under review, or a recommendation of no change).[71]

In 2013, the Quebec Ministry of Health and Social Services (MSSS) requested the National Institute for Excellence in health and Social Services (INESSS [Quebec HTA agency]) to draw up a list of diseases that would be most relevant to consider for inclusion in the programme.[72] After consultation with experts and with the agreement of the MSSS, it was concluded which diseases would be evaluated. In total, 21 conditions were assessed. Narrative reviews were carried out to determine the severity of the condition, the proposed treatment of the condition, and the ethical, psychosocial and organisational challenges posed by screening. Exhaustive searches were also performed to obtain information on screening test performance, efficacy, and efficiency of an expanded NBS programme. A multi-criteria decision analysis (MCDA) approach was chosen for the assessment due to the difficulty in deciding on the relative importance of screening for each of the 21 conditions.[73] The 14 criteria for assessing the relevance of screening, proposed by the UK's National Screening Committee and amended by the Institut National de Santé Publique du Québec (INSPQ), served as an analytical framework.[73] The Committee of Experts first determined the relative weighting of seven decision-making criteria. A score was attributed to each condition for each decision-making criterion. The results were evaluated using the Evidence and Value: Impact on DEcision Making tool (EVIDEM) in order to assign a rank importance to each condition.[73]

Subsequent assessments have been undertaken in 2019 and 2020;[74, 75] individual assessments were undertaken per condition with a total of 16 assessments completed and four positive recommendations to the MSSS. For each condition assessed, the INESSS Excellence Committee considered the extent of the health problem, the natural history of the disease, the nature of unmet need, the ability to detect disease in a timely manner, the effectiveness of early treatment and of newborn screening, the performance of the neonatal blood screening test, and the ethical, organisational and cost considerations associated with screening. These were assessed using a multi-criteria decision analysis grid to guide formulation of recommendations.

Denmark

It is not clear from the governmental websites [76, 77] how conditions are proposed for review for inclusion in the Danish newborn blood spot screening programme. A 2012 comparative review of 22 decision-making processes in Europe, [78] reported that a HTA report was provided in Denmark to support its decision-making process and that service providers were strongly involved in the decision-making.

Germany

The method evaluation subcommittee can decide to commission a review from the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG, German HTA agency) on the current state of medical knowledge for a condition that is proposed to be included on the panel for the German newborn screening programme.[58] Criteria used to decide if a condition should be reviewed include: potential early treatment benefit; feasibility and design of screening for the condition(s) and assessment of the medical necessity.[79] Joint Federal Committee has responsibility for screening processes. The Joint Federal Committee plans to review the screening programme, and to update it if necessary, taking into account mortality, morbidity, developmental disorder, unwanted events and the health-related quality of life of the child.[80]

Italy

The Rare Diseases Observatory (Osservatorio Malattie Rare)[81] provides an open document for consideration of conditions to be included in the national NBS programme. However, it is unclear if such documents are formally submitted to or considered by decision-makers. The Ministry of Health, in collaboration with national agencies and scientific societies, submits to periodic review at least every three years of the list of conditions, with particular regard to the evolution of scientific evidence in diagnostics and therapeutics.[82] While a HTA assessment may be performed it is not clear how the decision-making process operates, though the establishment of the Extended Neonatal Screening Working Group in 2020 may have a role in this.

Netherlands

The governance of NBS expansion in the Netherlands involves three main bodies.[59] Firstly, the Ministry of Health, Welfare and Sport is politically responsible for the programme, including governance of legality and funding issues. Secondly, the Centre for Population Screening of the National Institute for Public Health and the Environment (RIVM-CvB) is responsible for co-ordinating the NBS programme, directing it and managing implementation to ensure public values and clinical care are aligned. Thirdly, the Health Council of the Netherlands (the 'GR') is an independent national scientific advisory body, which provides advice to ministers and parliament on public health and research into health and healthcare. The processes in the Netherlands have been outlined as involving generation of scientific advice, study of feasibility, and decision-making.[59]

Considering condition proposal, the agenda for expansion of a programme is defined by the health ministry.[59] In order to develop advice to inform a decision on a condition, the 'GR' summarises scientific evidence in response to questions posed by the Ministry. The scientific advice issued by the 'GR' is based on published, peer-reviewed evidence, which is further reviewed by experts and supplemented with expert opinions when required. Topics considered within the scientific advice range from the appropriateness of the test to practical aspects, such as quality control after the test is introduced, and cost-effectiveness. Depending on the advice of the 'GR' and the initial decision of the Ministry, a report on feasibility will also be sought from the implementation body (RIVM-CvB). The feasibility study aims to explore the execution of the screening, and is informed by grey literature and expert opinion information, as well as prevalence estimates, characteristics of available tests, and consensus on clinical follow-up in Dutch hospitals. In recent decision-making processes for expansion of the Dutch NBS programme (2015 onwards), a stakeholder process was facilitated by RIVM-CvB to gain expert opinion regarding the practical feasibility of screening. Ad hoc expert groups were established for each condition, or group of conditions, with changes made to the composition of the group depending on the nature of the condition. An evaluation framework (see Appendix 4) was used to gather information and to structure the discussion.

Considering decision-making, the health ministry is charged with making a decision on expansion of the programme, considering both the scientific advice of the 'GR' and the feasibility report of the RIVM-CvB. Decision-making incorporates consideration of the speed of the implementation of the expansion, as well as consideration of the individual conditions.[59]

New Zealand

A condition can be proposed for consideration for addition or removal by the National Screening Unit (NSU). The NSU considers the completeness of the information and appropriateness of the request based on the proposal form.[56] The NSU Clinical Governance Group then decides on the basis of information provided by the Newborn Metabolic Screening Programme (NMSP) Technical group, and the Antenatal and Newborn Screening Clinical Oversight Group, which conditions should be added. Previous reviews have highlighted the use of a comprehensive decision-making framework and consensus-based approach in New Zealand.[71, 78] Possible recommendations to the NSU Clinical Governance Group include:

- recommend universal screening
- recommend targeted screening
- recommend pilot study
- recommend against screening.

United Kingdom

Any individual or organisation can submit suggestions for new screening programmes to the UK National Screening Committee (NSC) through an annual call. Prioritisation and selection of conditions to be reviewed are aided by evidence summaries developed by the evidence team supporting the UK NSC using rapid review methodologies.[83] The UK NSC meets three times per year and makes recommendations to ministers in the four UK nations on all aspects of population screening. The UK NSC receives all consultation responses at the meeting at which the review is discussed. Before the meeting, the committee receives: the evidence review showing the volume, direction and summary of the published literature; a paper bringing together all consultation responses in full; a cover sheet prepared by the evidence team which summarises the review project and makes a recommendation. The aim of the discussion at the UK NSC meeting is to make a consensus decision. Where a consensus is not achievable, a voting system is used. Where further evaluation is considered appropriate, the options may include primary research, systematic review, cost-effectiveness assessment, modelling or further rapid review. The UK approach appears to require higher levels of evidence, specifying RCT evidence, and incorporates focus on development of clinical guidelines; this approach may be considered to be highly aligned with public health principles.[1] In terms of the outcome of decision-making, the UK NBS programme has expanded to a lesser extent than other European countries.

United States

To propose a condition for consideration by the Committee for the Recommended Uniform Screening Panel, individuals or organisations are expected to form multi-disciplinary teams with clinicians and/or researchers, advocacy and/or professional organisations and interested consumers or individuals. To apply, a proposal package must be completed including a cover letter, letters of support, a conflict of interest disclosure form, a proposal form and supporting data and references.[84] There is a defined process for prioritisation of review of conditions to be considered for addition to the screening programme. The Committee decides if sufficient evidence is available, and votes to assign, or not assign, the proposed condition to the external Condition Review Workgroup.

The decision-making authority is the Federal Advisory Committee. The final decision is made by the Secretary of Health and Human Services. The Federal Advisory Committee discusses and deliberates on the evidence presented by the Condition Review Workgroup. The committee uses a decision matrix (Appendix 5) to guide their final decision and votes to recommend or not recommend addition of the proposed condition to the Recommended Uniform Screening Panel for the

consideration by the Secretary of Health and Human Services. The Advisory Committee's decision-making process includes assessment of the net benefit of screening for proposed conditions, informed by systematic evidence reviews generated by the independent Condition Review Workgroup.[43]

European level processes

In a recent review of NBS programmes in Europe including authors from the ISNS, it was noted that policy recommendations or direct oversight for NBS are not in place currently at the European or EU level.[20] The heterogeneity observed in the number of conditions screened across European countries is echoed by heterogeneity in the policies, processes, and procedures for the implementation of NBS at the individual country level and in the additional complexity when considering the regional variation within certain countries in Europe.[20, 85, 86]

The prospect of harmonising NBS practices at the European level has previously been explored. The Council of the EU, through the EU Committee of Experts on Rare Diseases (EUCERD), completed a synthesis exercise in 2011, which included a survey of EU countries' current practices, examination of the scientific evidence, and expert clinical opinion.[87] Clinical expertise was sought from the European Union Network of Experts on Newborn Screening (EUNENBS), a purposefully established group which outlined 70 opinions with respect to the elements of NBS processes, as well as a proposal for a decision matrix that could be used by member states to systematically expand (or contract) screening for certain conditions.[88, 89] This decision matrix is reproduced in Appendix 6. The EUNENBS recognised that the interests of the child should be paramount in the development of NBS policy and that diversity between populations and different funding scenarios should determine how each NBS service is structured. However, the benefits of a centralised expert and authoritative body were also recognised and it was recommended that such centralised bodies should provide guidelines for local health systems. Collectively, an opinion was reached by the EUCERD endorsing collaborative engagement between member states, while maintaining the principle of subsidiarity (that is, countries retain responsibility for healthcare).[20, 85, 86]

While respecting the principle of subsidiarity at the European level, advocacy groups such as EURORDIS have suggested that EU standardisation in practices such as sample collection, sample processing, follow-up and information shared to parents should be implemented.[86] Furthermore, the group advocates for consistency in approaches across Europe and the enactment of an EU-level Expert Working Group to facilitate collaborative tasks such as knowledge sharing, horizon scanning, joint HTA assessments, criteria for expansion and guideline development.[90]

The European Network for Health Technology Assessment (EUnetHTA) has developed a core model for the HTA evaluation of screening technologies in general.[90] While the model does not outline a methodology for the evaluation of NBS explicitly, it does emphasise the importance of ethical considerations when evaluating this form of screening.

7.2 Summary of proposal, prioritisation and selection procedures

Method for proposal of a condition

In terms of the proposal of a condition to be considered for assessment, Australia and the UK provide open processes in which anyone can propose a condition for consideration. New Zealand provides a proposal form, but it is unclear who can propose a condition for consideration. The US facilitates the open proposal of conditions, but advises that individuals or organisations wishing to propose a condition should form a multidisciplinary team comprising researchers and or clinicians with expertise in the area, professional organisations with insight to the condition, and interested individuals. The Canadian territories included in this report, Italy, and Germany cite the use of an oversight committee for consideration of conditions for assessment.

Prioritisation of review of conditions

While the process of condition proposal was relatively clear for a number of the included countries, processes regarding prioritisation of conditions for assessment were less defined. A number of countries reference the use of designated committees, which consider conditions for assessment, but do not formally detail prioritisation. The US, in particular, has a formal Nomination and Prioritisation Working Group while the UK employs the use of evidence summaries generated through rapid review methodologies to inform prioritisation processes.

Selection of conditions for review

The process of selecting conditions for review and formal assessment varied between the countries included in this report. A number of countries outlined consideration by a formal oversight committee with some providing explicit criteria on whether a condition should move to formal review; these most often included the sufficiency of the evidence base as a key criterion for enabling appropriate assessment. For example, the US emphasises the availability of sufficient evidence to review, the UK produces evidence summaries to inform the process, while Australia further assesses logistical considerations such as the availability of staff and resources to complete the review and whether an economic analysis is to be completed.

A systematic review of international policy-making processes and criteria was performed by Seedat et al. in 2014,[64] considering separately each of (i) general screening programmes; (ii) genetic screening programmes, the latter partly including

NBS programmes. Proposal and selection processes specific to NBS programmes were not explored. However, with respect to general screening approaches, the review found that considerations across countries for deciding topics included:

- urgency
- need
- current practice relating to the condition
- importance of the health problem
- known natural history
- detectable latent stage of disease
- timing of most recent review
- availability of new evidence
- potential impact of recommendations in clinical practice
- interest of the public or care providers
- variation in care and potential to decrease that variation
- sufficiency of evidence
- existence of new evidence (especially high-quality evidence in a stable field)
- potential for change to a prior recommendation.[64]

A further review, published in 2017, of academic literature discussing policy-making processes in NBS summarised methods for a proposal, prioritisation and selection of a condition as two main approaches;[29] these comprised a horizon scanning approach and a more *ad hoc* approach influenced by external drivers such as advocacy. The former approach was described as a structured process involving an independent body, which undertakes horizon scanning to identify relevant conditions to be considered within an evidence-based evaluation process. Using this approach, potential conditions are identified and recommended for further in-depth review through initial assessment against criteria. While this approach has been applied in several countries, the authors of the review found that the majority of the literature examined suggested an *ad hoc* approach occurring such that conditions become the focus of an assessment for inclusion in NBS programmes in response to new technologies, broader disease definition, insight into pathophysiology, and or advocacy. The authors note that past NBS expansion has been strongly influenced in an *ad hoc* manner by technological drivers, while advocacy (by clinicians, scientists, and citizens) is a current key driver for change in NBS.[29]

7.3 Summary of decision-making processes

Assessment and scoring

Considering practice as described in policy documents (see Appendix 3, Tables App 3.3 and App 3.4), it is noted that most countries have not followed a purely

quantitative approach, and instead summarise relevant studies combined with expert opinions.[1] Assessment against each criterion then occurs through a consensus process informed by discussions with several stakeholders.[1] In a review, which specifically considered assessment processes in place, the authors noted 'unanimous support' throughout the literature for a robust assessment process based on criteria[29], but highlighted debate regarding the exact criteria that should be used, and the subjective interpretation of criteria, as per consensus processes. While this approach permits the consideration of ethical, legal and social issues, it may contribute to lower transparency due to subjective assessment and ranking of evidence.[1, 29] This lack of transparency has also been observed in a review of 22 decisions on expansion of NBS in Europe, as well as findings that, historically, the effectiveness evidence appears to have been interpreted more positively than would be expected with application of the principles of evidence-based medicine.[78]

US and Danish approaches have emphasised explicitly scoring conditions against criteria,[1] with the aim of improving transparency. The US uses a decision matrix to rate the magnitude and certainty of the net benefit, to the population of newborns, of screening for a proposed condition. This decision matrix includes consideration of the capability of state newborn screening programs for population-wide implementation, and evaluation of the feasibility and readiness of states to adopt screening.[91] The intention of this decision matrix is to bring increased quality, transparency, and consistency to evaluation of conditions for inclusion in NBS.[91] It is noted that while the US and Denmark both applied a quantitative scoring system, the Danish assessment has been less 'technology-driven' than the US, with less emphasis on availability of multiplex screening and economic considerations, resulting in fewer additions to NBS programmes.[1]

Role of cost-effectiveness evidence

A comparative review of 22 decision processes in Europe examined funding decisions for newborn screening and considered specifically the role of assessment of costs, cost-effectiveness and budget impact considerations in decision-making.[78] The authors found that the assessment of costs or cost-effectiveness was based on a cost estimate rather than a full economic evaluation in 73% of the 22 decisions examined by the authors, and found that consideration of economic aspects had minor relevance in the decisions studied. The authors suggested that this may be as a result of low incremental direct costs of screening, or due to the high uncertainty in the effectiveness evidence, thereby limiting meaningful analysis of cost-effectiveness.

Formulation of recommendations

The majority of countries reviewed issue recommendations using a categorical approach (See Table App 2.4: Qualification of Recommendation). The recommendation approaches of the UK and the US have been contrasted and the focus within the US on implementing screening noted.[1] For example, the US recommendations specify that where screening is not recommended, approaches should be recommended that would enable future screening, for example, a pilot study.

Public consultation and appeals processes

Consideration of the outcomes of decision-making processes, for example, satisfaction with processes generally or with particular decisions made, is outside of the scope of the present review. However, it is noteworthy that some processes include public consultation activities or other opportunities for quality improvement of processes. For example, the UK National Screening Committee conducts reviews of their processes, including consideration of whether the Committee continues to operate to the most robust evidence base and criteria available internationally. This review has previously included public consultation on a range of questions relating to the processes in place for assessment of screening programmes.[92] The UK is also notable for including a process of public consultation within individual assessments of conditions for NBS; such public consultation responses are published along with the results of individual assessments.[93] However, as noted within their review of public consultation processes, at the time of publication of the report in 2015, there was no process in place for appealing against an NSC decision.[92] It is not clear whether appeals processes are in place for other countries considered within the present review.

8 Perspectives and concepts in current processes

Section key points

- There is substantial international variation in the use of evidence to inform individual NBS recommendations. Particular variation is noted in the use of systematic review to support decision-making, particularly in relation to evidence of test accuracy, benefits of early detection, and potential harms of over-diagnosis.
- The level of evidence considered influences decision-making, with a lower likelihood of a positive recommendation observed when more stringent criteria for evidence review are applied.
- The paucity of RCT evidence to support the effectiveness of screening for certain rare diseases is noted. In the absence of such evidence, it is suggested that reviews should particularly focus on the diagnostic accuracy of the test, the potential harm of over-diagnosis, and the benefits of early detection. In the absence of high-quality RCTs, several countries use categories to rank the level of evidence, such that higher levels of evidence are given more weight.
- The use of decision analytic modelling methods may provide flexibility to incorporate effectiveness evidence from all available sources, including interventional studies (for example, RCTs), observational studies, meta-analyses, and expert opinion. Such models allow for the incorporation of the uncertainty associated with each parameter input into the model.
- The use of multi-criteria decision analysis (MCDA) for the ranking of conditions following gathering of scientific evidence may help to structure decision-making and improve transparency and consistency. However, given various challenges associated with applying this method, decision-making relying exclusively on an MCDA ranking approach may be inappropriate.
- Almost all countries included in the review explicitly identify the child as the beneficiary of screening. A number of countries also identify the family as beneficiaries within the screening process, however these benefits are typically stated as being secondary to those of the child.
- Consideration of the ethical consequences of screening versus not screening is highlighted in the majority of the international literature and is consistent with the apparent approach adopted by most countries. The process typically

involves identification of any ethical issues, evaluation of the ethical dimensions of alternative actions, weighing of these against each other, and establishment of justification for an action to be taken.

- A number of frameworks were identified which may have potential use in NBS decision-making. While noted to be useful in identifying and addressing critical issues for implementation, challenges may still remain regarding cut-off values for the conditions included given their rarity.
- Formal governance arrangements for population screening are noted to be relatively new in most jurisdictions. Governance arrangements that address NBS alongside other population screening initiatives may allow for broader involvement of interests beyond a primarily genetics focus.
- The range of stakeholder perspectives considered has been noted to influence the evaluation criteria for NBS programmes. Those limited to a genetics interest include evaluation criteria specific to rare disease, while those that also include a public health and or a specific maternal and child health focus, use more general evaluative criteria. Adoption of the broader perspective is consistent also with increased consideration of screening as a comprehensive pathway which requires concern for both short and long-term outcomes.

8.1 Use of evidence synthesis methods and likelihood of recommending NBS expansion where such methods are used

A systematic review and meta-analysis published in 2018 examined the association between use of a systematic review approach within the decision-making process and national decisions on inclusion of conditions in NBS.[94] The authors examined 93 reports assessing a total of 104 conditions across 14 countries, considering 276 individual NBS recommendations. Only 22% of the recommendations were based on systematic review evidence. The evidence on test accuracy was not evaluated in 42% of recommendations and the evidence around benefits of early detection and potential harms of over-diagnosis were not evaluated in 30% and 76% of reviews, respectively. The authors found that the odds of making a decision to recommend screening were significantly lower when a systematic review was used than when no systematic review was used (odds ratio 0.17, 95% confidence interval 0.07 to 0.43, $p<0.001$). Also, there was an association between greater consideration of test accuracy in the review and a recommendation against screening. Considering policy

implications of the findings, the authors recommend that, whenever possible, a systematic review of the literature should be undertaken as part of policy decisions on whether to commence screening; this recommendation is supported by findings cited by the authors which suggest that expert opinion is more likely to underestimate harms and overestimate benefits.[95] The authors further suggest that systematic review work could be performed more efficiently by pooling evidence synthesis capacity across countries; reviews could be adapted to local populations and prevalence and help to reduce discrepancies in international screening policy.[94]

With regard to the forms of evidence available to inform systematic reviews, the authors of the 2018 systematic review acknowledge the particular challenges with respect to the evidence base available for NBS.[94] As NBS programmes largely consider rare diseases, and as such conditions are not conducive to the generation of RCT evidence, there may be an absence of suitable evidence. The authors suggest that under these circumstances, a review of whether to screen for a condition should consider the evidence for each pathway to result in benefit or harm; such review should particularly consider the diagnostic accuracy of the test, the potential harm of over-diagnosis, and the benefits of early detection.[94]

The challenges of the evidence base have also been identified in another review of international differences with respect to decision-making on NBS.[1] This review noted that many authors recommend the use of alternative evidence in the context of rare disease decision-making and the scarcity of RCT evidence; such alternative evidence may include expert opinion, or alternative approaches to considering the evidence, such as decision analytic models or HTA frameworks.[1] With regard to what is used in practice, the authors note that among the eight countries reviewed by the authors, only the UK was found to have a criterion that evidence from high-quality RCTs must be available. Meanwhile, several countries use categories to rank the level of evidence, such that higher levels of evidence are given more weight.[1]

8.2 Decision analytic modelling approaches

Considering the scientific approaches to consideration of the evidence, decision analytic modelling methods have been noted as providing the flexibility to incorporate effectiveness evidence from all available sources.[96] Such sources may include interventional studies (for example, RCTs), observational studies, meta-analyses, and expert opinion. Importantly, decision analytic models allow for the incorporation of the uncertainty associated with each parameter input into the model.

Quebec serves as a model for the use of multi-criteria decision analysis (MCDA) for the ranking of conditions following gathering of scientific evidence.[73] MCDA is a

decision analytic method which involves selection of criteria *a priori* and attribution of specific weights to each criterion. For example, using an MCDA approach, 'severity of the condition in untreated cases' might be weighted higher than 'timely availability of test results', depending on the agreed preferences of those performing the analysis. Once criteria and weights are decided, conditions are scored for each criterion, the score is weighted, and a composite score for each condition is generated across the criteria. This process thereby theoretically allows transparent ranking of conditions. As discussed in section 7.1, this approach was applied in Quebec in 2013 by the INESSS (Quebec HTA agency).[73] While Belgium falls outside the list of countries included within the present review with respect to consideration of policy-making processes, it is noteworthy that the Belgian HTA agency (Belgian Health Care Knowledge Centre, KCE) performed a pilot study in 2016, based on the Quebec experience with MCDA in 2013, in order to study the MCDA method for NBS condition prioritisation.[97] Key findings of the report included that selection of criteria was difficult, that assessors have divergent opinions requiring broad discussion, that scoring of conditions against the criteria was difficult with a limited scale (due to little discrimination between conditions) and that careful attention should be paid to ensure that assessors represent all relative viewpoints and that essential arguments are not overlooked. The report concluded that decision-making requires a more objective and transparent approach overall, and that MCDA may help to structure decision-making and improve transparency and consistency, but that decision-making relying exclusively on an MCDA ranking approach may be inappropriate.[97]

8.3 Consideration of the beneficiary of screening

The importance of specifying the beneficiary of screening was stressed in an academic review which considered policy-making processes [29]; to support assessment of the appropriateness of a condition, there needs to be a clear understanding of who will benefit, what is the perceived benefit, and how this benefit should be weighted in decisions.

The academic literature affirms the goal of newborn screening as primarily being to benefit the screened child through the facilitation of timely treatment and management of conditions.[1] With the exception of Italy, all countries included within the present report were noted to explicitly highlight the child as being the beneficiary of newborn screening processes. A number of countries or regions included also identify the family as being beneficiaries within the screening process; these include the US, UK, Netherlands, Quebec, Alberta and Australia (see Appendix 3, Table App 3.2). However, this statement, and the corresponding assessment of benefits, comes most often secondary to the child.[1] Australia notably takes account

of the well-being of the child and family both in support or discouragement of screening for certain conditions (that is, the diagnosis of a condition early may not necessarily improve the health and well-being of the family overall). It has been noted that a shift in the focus of the beneficiary beyond the newborn would likely lead to a vast increase in the number and type of conditions eligible for screening, particularly in the context of future genetic screening approaches; this is because many conditions may incur a benefit to the family by providing information on reproductive options compared to screening for a limited number of conditions to allow the newborn to incur a direct clinical benefit.[29]

8.4 Consideration of ethical consequences

As discussed in section 5 of this report, the majority of the literature on consideration of newborn screening refers to the importance of consideration of the ethical consequences of screening versus not screening. The use of a three-part framework[98] to make decisions has been suggested. The framework proposes an analysis of any ethical issues, followed by an evaluation of the ethical dimensions of alternative actions, and, following the weighing of these against each other, the establishment of justification for an action to be taken.[37] The authors note that this would be in contrast to a strict rule-based approach and would allow a wider range of factors to be considered. The authors further suggest that they have observed decision-making regarding NBS, in practice, to follow this approach.

8.5 Examples of frameworks or models in use in different countries

Policy frameworks have been suggested to be essential for policy-makers to ensure that NBS programmes can effectively respond to changing environments (for example, the emergence of new technologies).[29] A framework approach, considering all aspects of the policy cycle (see Figure 4, section 7 of this report) is suggested to enable a systematic, continuous policy process that may anticipate developments as opposed to being reactive and overly influenced by external drivers.[29] Considering the decision-making element of the policy-cycle, several frameworks have been suggested by authors or groups for potential use in NBS decision-making.[29] A description of a recently developed framework from the Netherlands and a proposed model for use across EU countries are provided here as examples.

'Go/no go' framework example from the Netherlands

A 'go / no go' framework to enable a final decision to permit expansion to proceed has been outlined for the Netherlands. This was developed in response to the

Netherlands embarking on a significant expansion of its national NBS programme.[59] This framework outlines the requirements that must be in place before screening commences and is based on international framework examples from Australia, Ontario, Denmark, New Zealand, the UK and the US, which emerged from a 2017 review of differences in the evaluation of conditions for NBS.[1] The 'go / no go' framework is reproduced in Appendix 4 of this report. The framework includes 13 domains for evaluation, ranging from typical consideration of the condition to be screened and the testing approach through to organisational and implementation factors. Thus far, this framework has been used for the evaluation of eight conditions in the Netherlands. The authors reporting on this framework comment that it was useful in identifying and addressing critical issues for implementation, but that it was challenging to decide cut-off values for the conditions included given their rarity.[1] Also, as the clinical follow-up plan is not always straightforward, this led to challenges in reaching consensus or would lead towards a "no go" recommendation.

Proposed decision-making matrix for use by EU member states' NBS programmes

In 2009, the European Commission sought guidance on how to further implement NBS screening in a responsible way. A panel of experts on NBS was established and proposed in 2011 a model for use by EU NBS programmes to systematically inform the expansion (or contraction) of screening mandates. This decision-making matrix is reproduced from Cornel et al.[88] in Appendix 6 and includes considerations such as desirability and feasibility of the proposed programmes, implementation issues and programme quality assurance. Further discussion of EU-wide approaches to NBS policy-making processes is provided in section 7 of this report.

8.6 Governance of NBS programmes

Formal governance arrangements for population screening are noted to be relatively new in most jurisdictions, and reflect the state's need to involve policy actors and expertise from outside government, notably medical practitioners and medical science, when developing population screening policy.[99] It is suggested that governance arrangements which address NBS alongside other population screening initiatives may allow for broader involvement of interests beyond a primarily 'genetics' focus, and may allow NBS to thereby benefit from wider expertise:

> *"Bringing NBS out of its silo and into a multi-disciplinary governance framework-placing it as one among many population screening programs, especially those relevant to maternal-child health, is of salutary importance"*[99]

With respect to governance of decision-making, a review of academic literature on this topic observed a consistent recommendation for an overarching, independent,

multidisciplinary group to provide recommendations to government in order to balance competing influences and demands.[29] Furthermore, it has been suggested that an advisory committee should provide advice throughout the policy cycle, for example, on implementation, development, review, modification, and cessation (for individual components) of NBS.[29]

8.7 Interest coalitions involved in processes

Three 'interest coalitions' involved in the governance of NBS, as observed to varying extents in different jurisdictions, have been described.[99] These interest coalitions include 'genetics', 'public health' and 'maternal and child health', as outlined in Table 1.[99] It has further been suggested that governments have historically relied predominantly on the 'genetics' interest coalition, which comprises scientists, clinicians, patient advocates, industry, and state actors sympathetic to these interests, and which has advanced a commitment to rare genetic disease.[99]

In contrast, the interest coalitions of 'public health' and 'maternal and child health' have been more variably drawn upon to inform policy. As an example, it has been noted that in the US, where the 'genetics' interest coalition has held a high level of involvement and authority in policy-making, in contrast with the 'maternal and child health' focus, there are evaluation criteria specific to NBS and explicit concessions are made in policy-making for rare disease, there is no process for reconsideration or deletion of conditions on the panel, and NBS in mandatory in most states.

In contrast, in the UK, where the three described interest coalitions have a similar level of involvement in decision-making, but where primary and maternal healthcare holds the most authority, different organisational features of NBS are observed: there are general evaluative criteria (as opposed to specific to NBS), both additions and deletions to the panel are considered, and NBS requires informed consent.[99] It has been noted, however, that over time, across the UK, Canada, New Zealand and US, there has been an overall increased reliance on formal evidence review processes, drawing on well-established public health principles, with consideration of both additions and deletions to screening panels. Additionally, increased consideration has been given to screening as a comprehensive pathway which requires concern for both short and long-term outcomes.

Table 1: Interest coalitions with roles in the governance of newborn screening

Interest coalition	Governance focus	Core values
Genetics	Testing proficiency	- permissive approach to technological expansion in advance of robust evidence - focus on rare disease - valuing information, including reproductive risk information.
Public health	Evidence	- balance of benefits and harms across population - attention to screening as 'pathway' with ultimate clinical benefits as goal - requirement of high quality evidence to justify intervention.
Primary maternal and child health (variable composition, e.g. US: medical UK: community-based)	System of care delivery (e.g. parent engagement, sample collection, follow-up)	- focus on children and families - attention to family wellness and patient engagement - primary care.

Adapted from Miller et al.[99]

8.8 Perspective of patient representative groups (EURORDIS)

The European Organisation for Rare Diseases (EURORDIS), a non-governmental patient-driven alliance, outlined 'key principles for newborn screening' in a position paper published in January 2021.[86] As discussed in section 7 of this report, this organisation seeks, in part, the harmonisation of NBS programmes across Europe. Among the 11 principles outlined in this position paper, the organisation makes the following points with respect to policy-making processes:

- All stakeholders should be involved in the different stages of the screening process.
- Transparent and robust governance is needed to expand screening programmes. Each country or region should have a clearly defined, transparent, independent, impartial and evidence-based process for deciding which conditions should be covered by the screening programme.
- The governance of screening programmes should be explicit, comprehensive, transparent and accountable to national authorities.
- The evaluation process on the inclusion or exclusion of diseases in screening programmes must be based on the best available evidence, which reflects the health economic evidence but which is not determined only by the health economy.

- Centres affiliated with the European Reference Networks should be integrated into the care pathways of different health systems and should be considered as preferred partners in providing recommendations on neonatal screening policies.

9 Criteria to be considered as part of decision-making processes

Section key points

- Criteria for decision-making in relation to the expansion of NBS programmes were collated based on policy documents identified for the nine countries including in this review as well as international evidence reviews.
- Decision-making criteria applied in different countries for expansion of NBS programmes differ, including with respect to their level of detail. However, criteria are largely built on the principles proposed by Wilson and Jungner (1968) for the early detection of disease.
- A distinction is drawn between screening 'principles' and screening 'criteria'. Principles address core values as to whether or not screening is worthwhile. Criteria define what it means to achieve and monitor the principle in practice. These adapted criteria are considered to increase the transparency of decision-making as the requirements to fulfil a criterion become more straightforward and well-defined.
- Unique challenges of NBS often prevent the straight-forward assessment of a screening programme against established criteria. Examples of criteria which are particularly challenged include: the need for an accepted treatment for patients with recognised disease, a suitable test or examination, a defined target population, and planned programme evaluation. Specific issues relate to the lack of robust RCT evidence, and the reduction in mortality and morbidity that would be required for a treatment to be considered acceptable.
- Recent screening frameworks place more emphasis on ensuring informed choice, equity and access, quality of care, and cost-effectiveness.
- Criteria used are typically high-level. However, a number of countries include more detailed checklists with others using an analytical framework which is adapted to each review. Inclusion of additional criteria focused on issues such as implementation readiness and quality assurance have also been noted.

This review collated criteria for decision-making used by different countries. This collation is based on information gathered from policy documents that were identified for the different countries included in this review. These criteria are displayed in Appendix 3, Table App 3.5.

The principles proposed by Wilson and Jungner (1968) for the early detection of disease are cited in the majority of the literature on decision-making with respect to expansion of NBS.[100] These principles are as follows:

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

A distinction has been made between screening 'principles' and screening 'criteria'.[19] Specifically, it is suggested that principles represent core concepts and values, while criteria define what it means to achieve and monitor the principle in practice. While the original principles described by Wilson and Jungner address the question of whether or not screening is worthwhile, it is noted that revised versions of the principles pay more attention to how screening programmes should be implemented.[19] Furthermore it has been identified that in recent screening frameworks, more attention has been placed on ensuring informed choice, equity and access, quality of care and cost-effectiveness.

A 2017 review of the scientific literature and policy documents examined international differences in the evaluation of conditions for NBS screening. [1] The concept of 'definition of criteria' with respect to NBS expansion processes was considered and defined as representing the questions or statements against which evidence is assessed in order to consider the appropriateness of screening for a condition. The scientific literature was noted to be rich with examples of the wide range of criteria used to assess conditions. These criteria vary in their level of detail, but are largely built on the Wilson and Jungner principles, having been translated into more detailed criteria to incorporate consideration of NBS-relevant technologies and/or to permit exploration of matter of ethics.[1] These adapted criteria are considered to increase the transparency of decision-making as the requirements to fulfil a criterion become more straightforward and well-defined.[1] Considering policy documents, the authors observed that criteria used are largely high-level, though

some countries include a more detailed checklist, for example, Ontario includes a list of 48 questions across five categories, and some countries include criteria focused on issues such as implementation readiness.[1]

With respect to the high-level nature of many criteria, it is important to note that the unique challenges of NBS often prevent the straight-forward assessment of a screening programme against criteria. Four criteria are noted to be particularly challenged in this respect[19]:

(i) there should be an accepted treatment for patients with recognised disease
(ii) there should be a suitable test or examination
(iii) there should be a defined target population
(iv) programme evaluation should be planned from the outset.

For example, with respect to the treatment criterion, it is not always clear what reduction of mortality and morbidity would be required for a treatment to be considered 'acceptable' and 'for patients with recognised disease'. The challenges of the evidence base associated with this criterion, that is, the lack of robust RCT evidence, further complicates assessment against this criterion. Additional criticisms regarding the lack of suitability of the original Wilson and Jungner principles relate to the idea that these principles were developed to evaluate individual conditions, while modern technology is conducive towards the possibility or even need to evaluate groups of conditions at once.[29]

It has been noted that in Denmark, Finland, France, Germany, Italy, the Netherlands, Sweden, the UK, Australia, and New Zealand, national and regional organisations have updated and amended the Wilson and Jungner principles to fit their local context and to use their own versions to make policy recommendations and decisions about screening.[94] In contrast, the US Preventative Services Task Force has developed an analytical framework which is adapted to each review. The analytical framework includes three components to determine the balance of benefits and harms from implementing screening:

- test accuracy to detect a condition of interest
- the benefit of early detection, and, consequently, treatment after screening as compared with later detection as a result of symptoms
- the extent of over-diagnosis.

A 2017 review of international decision-making processes for NBS [1] observed quantitative and qualitative differences in the criteria applied in different countries in their review of international decision-making processes for NBS. The number of criteria focusing on the condition, test and treatment was higher in New Zealand,

while the Netherlands and the UK included more criteria relating to implementation aspects of a screening programme, for example, the need for a quality assurance programme.

Several authors have suggested refining and widening the list of criteria to be considered for expansion of NBS. For example, Forman et al. note that the Wilson and Jungner criteria are frequently referred to as a 'gold standard' for screening, but suggests that the original authors' intention was for the criteria to be adapted and developed within differing situations.[37] Forman et al., suggest that these criteria should be expanded to reflect changes in perspectives over time and the unique situation presented by NBS wherein decision-making is made by, and directly impacts upon, the baby's parents. Expanded criteria suggested by Forman et al. include the following:[37]

- Screening in the absence of an accepted treatment may be appropriate when it will provide information of benefit to the child or the family.
- Benefit or harm to the family should be considered a benefit or harm to the child.
- Decisions about screening should include community values, rights and duties alongside any cost-effectiveness assessment.
- Action in the face of uncertainty may be justified in exceptional circumstances.

10 Discussion

Currently, nine genetic or congenital conditions are recommended for inclusion within Ireland's NBS programme, with screening in place for eight of these conditions and a further condition undergoing implementation.

Various screening technologies are currently used, including MS/MS technology, which technically would enable screening to be performed for a large array of metabolic conditions, in particular. Improvements in other assays and the advent of the use of genomic technology in international NBS programmes may enable further far greater expansion. Ireland, like the UK, screens for a relatively modest number of conditions within the national NBS programme, in contrast with some European countries, such as Italy, which screen for over 30 conditions. It is important to note that international comparisons of the range of conditions screened is likely to reflect complex decision-making processes and local inputs. These may include differing opinions with respect to assessment of conditions against criteria, differences in practice with respect to organisational structure and laboratory implementation, differing levels of tolerance for false positives and false negatives, and differing local epidemiology with respect to condition prevalence and the genetic composition of the local population.

Among countries which have adopted MS/MS technology and which use similar assessment approaches to evaluate conditions, (for example, Denmark and the US), different levels of expansion of NBS programmes have occurred, reflecting country-specific contexts, preferences and priorities, and subjective use and interpretation of criteria. For example, different countries prioritise different criteria overall and different levels of evidence for use in assessment against criteria.

Furthermore, there is divergent opinion among stakeholders and across countries on issues such as what the precise aim of screening should be and what level of evidence should be considered to attain that aim. While calls for expansion of NBS programmes are focused towards the aim of reducing, through early detection, significant morbidity and mortality associated with conditions proposed for inclusion within the programmes, there are significant ethical and practical considerations associated with expansion, highlighting the importance of robust and transparent processes.

Processes identified

Overall, this review identified increased use of formally outlined governance structures for NBS policy-making processes. With respect to proposal and prioritisation processes, several countries have defined procedures for the proposal

of conditions. It may be the case that, in other countries, proposal processes for screening programmes generally are in place, similar to the process under development by the NSAC, and that this may be used for NBS proposal.

Considering evaluation of a condition for inclusion in NBS, several *a priori* decisions need to be made ahead of assessment, in order to enable a transparent, consistent approach. For example, there must be agreement on perspectives regarding the screening beneficiary, that is, the degree to which benefits or harms to the family (or society) beyond the infant are considered. This may be specified within the list of criteria against which conditions may be assessed, which, in many cases internationally, include consideration of ethical issues and practical issues relating to the feasibility of screening and its implementation. The assessment itself should ideally be based on the highest standards of evidence available, though many jurisdictions permit the incorporation of expert opinion to mitigate gaps in the evidence base resulting from the rarity of the condition.

In order to ensure rigour of assessment, established evidence synthesis approaches such as systematic review and decision analytic modelling may be used. Given the time and capacity burden associated with such assessment approaches, leveraging of existing resources, including through HTA networks such as EUnetHTA, may help improve efficiency. Across the jurisdictions examined, it is apparent that a formal evidence review process is an integral part of most international NBS programmes. However, the approaches used in such evidence review, and the relative weighting of the importance of robust high-quality evidence by decision-makers, is not necessarily transparent across the board. Furthermore, research suggests that, in the context of evidence synthesis approaches, use of more robust approaches such as systematic review have been associated with a lower odds of expansion of NBS programmes.

While assessment may result in clarification of the scientific findings with respect to NBS, for example, test performance and effectiveness of screening, a formal decision-making approach must be agreed to translate the findings of assessments into decisions. Pre-specified criteria enable the targeting of evidence to be collected, but there should ideally also be clarity regarding the extent to which different criteria factor. Examples have been identified of the use of multi-criteria decision analysis approaches to inform NBS decision-making. These allow for a transparent and systematic approach to decision-making as they involve the *a priori* weighting of different criteria, and the scoring of conditions, resulting in a numerical assessment to allow for prioritisation of conditions. However, this approach is not without challenges, as the weighting of criteria requires up-front decision-making and subjective assessments of evidence are likely to occur. Less formal or complex decision-making processes may involve efforts to reach consensus using an ethical

framework of consideration of benefits and harms of screening, with an emphasis on expert opinion. Importantly, where expert opinion is relied upon, the perspective of the individuals or groups of experts should be carefully considered and, ideally, balanced; as noted within this review, different stakeholders or interest coalitions (for example, proponents of technological innovations in screening versus proponents of a population-level or public-health based approach) may represent divergent opinions and may focus decision-making towards a particular perspective.

It is therefore important that the composition of expert or advisory groups involved in decision-making appropriately reflects the healthcare ethos and values of the country, and that broad representation is in place to allow for consideration of various perspectives.

Frameworks, such as those used within the Netherlands for the evaluation of conditions by stakeholders, may serve to structure these discussions and function as a transparent, final checklist for confirming a recommendation should proceed. Notably, the Netherlands highlight the phased implementation of final NBS expansion decisions as an important lesson learned following early, more rapid, implementation of advice; previous rapid implementation resulted in negative consequences, for example, high numbers of false positive results. Similarly, it is noteworthy that a number of countries and regions (see section 6) have removed, or suspended, conditions from their NBS panels in recent years, including New Zealand and Ontario.[50, 55] Reasons given for such removal or suspension of conditions included the number of false positive tests observed following screening, a lack of clinical benefit to the child, the proportion of asymptomatic individuals identified, and lacking cost-effectiveness relative to other screening options.

Such changes to NBS programmes highlight the importance of the reassessment of conditions based on evolving scientific evidence and programme evaluation. The UK NSC conducts regular updates of previous assessments with a pathway also provided for individuals to highlight new evidence in the interim period between updates, which can initiate an early review of a condition.[83]

Selection of processes

It is not within the scope of the present review to conclude on the merits or disadvantages of individual approaches. Also, it is apparent from the literature that there is no one decision-making solution when it comes to NBS.[1] However, certain principles relating to decision-making processes may be drawn out from this review.

For example, it is important to bring quality, transparency, and consistency to the evaluation of conditions for NBS, and to include assessment of feasibility and

readiness to implement programmes.[91] Also, as noted within section 2 of this review, the NSAC has previously emphasised the need to be robust and consistent in evaluating the expansion of NBS in line with the NSAC Criteria for Appraising the Viability, Effectiveness and Appropriateness of a Screening Programme.[18] The NSAC annual report further refers to the concept of an approach based on health technology assessment principles as being reflected in the NSAC's established approach to the evaluation of the evidence for a new programme.

Certain observations may be made with respect to the implementation of different decision-making processes. For example, it is important to consider that if a robust and systematic decision-making process is adopted (for example, thorough comprehensive assessment of a screening opportunity in terms of its diagnostic accuracy, clinical effectiveness, cost-effectiveness and ELSI implications), this is likely to be costly in terms of resources and time required for such assessment to be carried out. The opportunity cost of such assessment is the more timely introduction of a new NBS screening programme. However, this timeliness must again be weighed against the costs, in terms of harms to the population and to the overall NBS programme, of a decision which is subsequently identified to have been inappropriate. As such, a balance must be struck between the need for rigorous assessment of a new screening programme and the need to minimise delays in introduction of screening programmes for those which do provide a net benefit to population health. Where possible, existing resources, for example, existing assessment frameworks and evidence synthesis outputs, should be leveraged to avoid duplication of effort.

Practicalities of assessment and implementation

Considering the practicalities of what is considered within assessment processes, as noted, the availability of RCT-level evidence of effectiveness may be limited when considering rare diseases. As such, assessments will likely remain reliant on the 'best available evidence', which may take a variety of forms beyond RCTs.

In this way, decision-making may encompass expert opinion; however, when considering this form of evidence it is important to consider the definition of 'expert' in light of the objectives of the assessment. For example, an expert may be considered to be a clinical expert with medical expertise relating to the condition being assessed, a patient with lived experience of the condition, or an advocacy representative with experience of the impact of the condition.

Furthermore, when considering rare diseases, the availability of local expertise may be limited, necessitating the identification of, and engagement with, international experts in the area. Additionally, when considering elements such as disease

prevalence, the use of international registry data may be practical where Irish data are limited. With respect to involvement of stakeholders, broad representation is key to incorporate various perspectives integral to the success of an NBS programme; such stakeholders include, amongst others, the family, laboratory personnel, public health expertise and clinical staff involved in various aspects of NBS clinical governance.

In terms of the feasibility of expanding NBS programmes, there are important factors to consider beyond the specific condition being proposed. These may include resource requirements, operational oversight, and implementation processes. From a laboratory perspective, it may make practical sense for a number of conditions to be recommended for expansion in tandem (that is, if deemed appropriate for expansion, a number of conditions could be implemented concurrently to avoid duplication of certain implementation steps). Similarly, from an assessment and decision-making perspective this may be more efficient. However, such an approach would need to be balanced in terms of the availability of resources, the complexity of the verification processes, and the clinical pathways required for each condition to be implemented. Nonetheless, while there will be diversity at the granular level of conditions being considered for expansion, there may be similarities in terms of high-level practicalities for implementation that could be evaluated early in the decision-making process; as such, efficiencies may be gained in early consideration of such conditions together.

Additional factors for consideration within assessment and decision-making processes include the potential interaction between the NBS question under consideration and existing national clinical and public health programmes For example, the recommendation for the addition of ADA-SCID to the NNBSP reflects the survival benefits of early identification and treatment of children with this condition. However, the recommendation of this condition is also influenced by childhood vaccination policy within Ireland; in the context of a childhood immunisation schedule involving live vaccines, which could pose important risks to those with unidentified severe immunodeficiency,[101] the beneficial effects of screening for this condition are greater, as they extend beyond mitigating the effects of the condition in isolation. Furthermore, decision-making processes for NBS may benefit from knowledge exchange and harmonisation of processes with the HSE National Rare Diseases Office, or the HSE Rare Diseases Medicinal Products / Technology Review Committee, for example.

Strengths and limitations of the present review

Considering the present review, this report benefits from adopting a systematic and structured approach, the examination of both academic and policy documents, and

its building on the work of existing reviews which have considered and compared international NBS policy-making processes.

However, there are several limitations that must be considered. Firstly, while evidence synthesis typically favours a systematic review approach, the present review did not meet the criteria for a fully systematic review. Several topics were requested to be explored, and as these topics require different approaches to information gathering, these could not all be addressed under a unified systematic review. A systematic search approach was, however, used in order to gather the literature evidence in as unbiased a manner as possible. Due to significant time constraints, the large volume of literature and policy documents considered, and the primarily descriptive nature of the review, quality assessment of sources was not conducted. However, with respect to documents concerning policy-making processes, these documents were subject to pre-specified inclusion criteria as per the review protocol.

Considering the details reported within the present review with respect to a given country's NBS programme composition and associated policy-making processes, it is possible that information may have been missed or misrepresented. This may arise due to a lack of publication of information on national authority websites, a lack of detail within the academic literature, or failure to capture certain documents as a result of the search terms used potentially not being sufficiently sensitive (see section 1.3). As discussed within section 6, issues surrounding differences in nomenclature used may further complicate the findings of the present report.

This review took a pragmatic approach to the selection of countries for inclusion. The initial minimum set of countries for review was identified from a 2017 academic review of international NBS programme policy-making processes, which noted robust decision-making processes in place for eight countries. All eight countries represent public health decision-making contexts considered of interest to the Irish setting and were therefore included. Furthermore, the results of the systematic search for academic literature were used to identify whether decision-making contexts for other countries, specifically within Europe, had been described. As such information was available with respect to Italian NBS, Italy was added to the list of countries for full grey literature review. Given the varying approaches identified in the nine countries examined, it is reasonable to expect that these countries represent a suitable sample for the illustration of differences in approaches to NBS policy-making. However, it is acknowledged that important alternative approaches may have been missed, particularly due to the search for additional countries to include within the review being limited to European countries.

Furthermore, it is important to note that, in the consideration of a review of policy-

making processes, the evaluation team for the present review represents a subset of the HIQA Health Technology Assessment Team. As such, in the interests of reflexivity, it is likely that the authors may subjectively consider examples of decision-making processes or literature in favour of a public health or HTA-based approach.

As a result of the above limitations, the present review may not necessarily represent a comprehensive and fully updated census of NBS practice and policy-making processes for the included countries, or may include a degree of subjectivity with respect to approaches outlined. Nonetheless, the review serves to highlight and consider differences in approaches taken internationally in order to provide for discussion of processes which may be developed for NBS policy-making in Ireland.

11 Conclusion

To facilitate NSAC in the development of defined processes for decision-making in the expansion of the NBS programme, this review sought to provide a detailed account of current international processes from a selection of countries deemed relevant to the Irish context, supplemented by consideration of academic reviews of policy-making processes. The findings of the review highlight differences in the number of conditions screened for by countries internationally and in policy-making processes to support expansion of NBS programmes.

The balance of benefit and harm associated with expansion requires careful consideration and will be dependent on factors specific to individual conditions.

Generally, there are important ethical, legal and social implications to be taken into account, which impact a range of stakeholders including, but not limited to, the child, family, and healthcare workers providing screening and follow-up services. In order for decision-making on NBS expansion to be transparent and consistent, an explicit, structured approach to each aspect of policy-making on this topic should be prepared. To ensure transparency at each stage of the policy-making life-cycle, individual components of policy-making require careful consideration, and consensus is needed on these aspects prior to the formal assessment of conditions amenable to expansion. Such components include: definition of beneficiary or beneficiaries, explicit processes for condition proposal, prioritisation and selection, agreement on specific criteria for assessment, the precise forms of assessment and methodologies to be used, clarity regarding stakeholder involvement, and robust and transparent processes for decision-making. Specifically regarding a life-cycle approach, evaluation of feasibility and implementation factors should be built into assessment processes, and importance should be placed on planning for long-term appraisal strategies.

Regardless of the direction and extent of expansion of the national NBS programme, efforts should be focused on protecting the existing screening processes in place, and the public confidence therein. To ensure expansion does not jeopardise existing operations, clearly defined and transparent processes within each component of the policy-making life-cycle for NBS programme expansion, and early consideration of the resource implications of expansion, are crucial.

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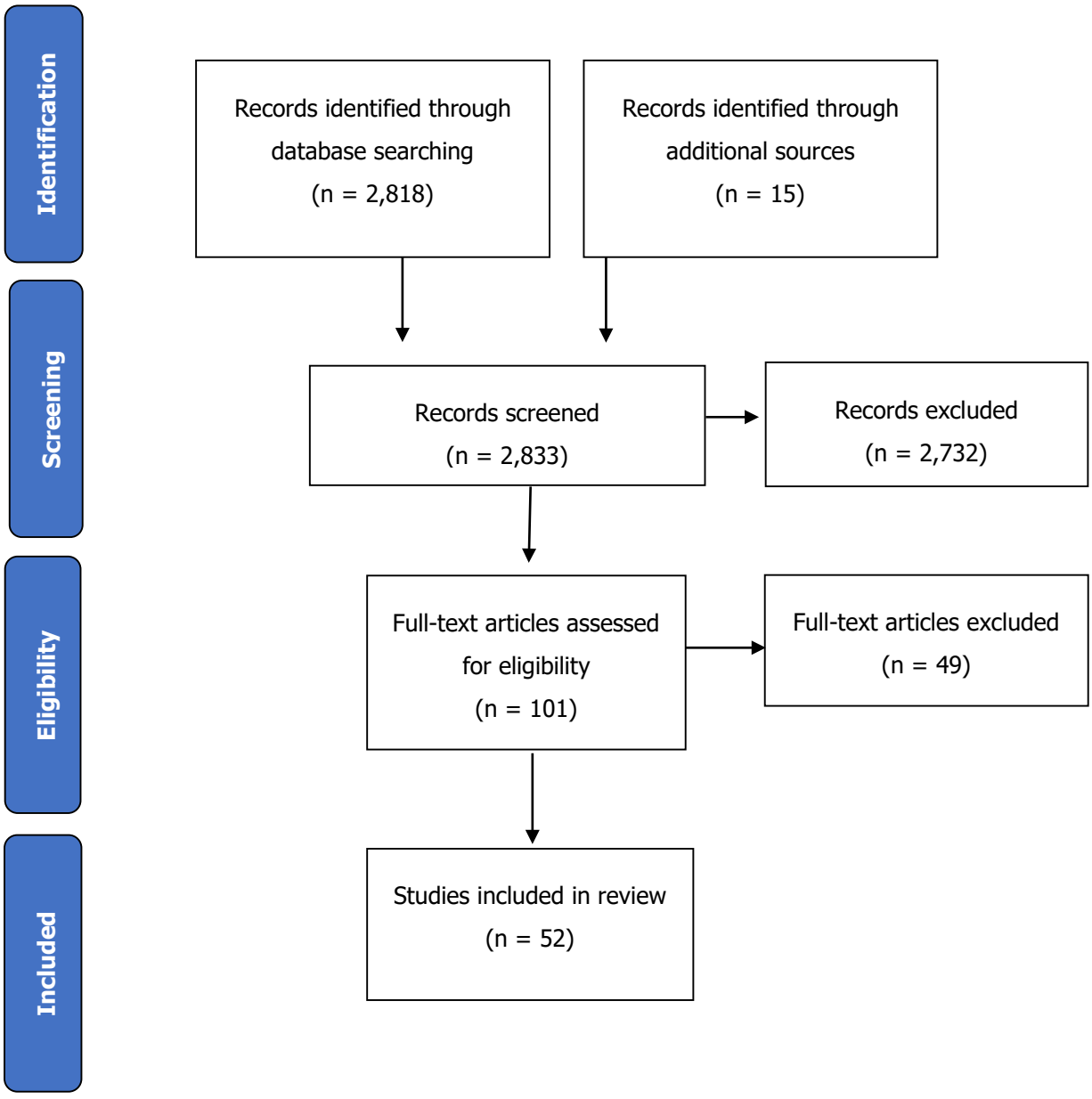
Appendices

Appendix 1: PRISMA diagram of academic article selection for review of processes

Figure App 1.1 PRISMA flow diagram of academic search results



Appendix 2: Data extraction table outlining conditions screened for within NBS programmes

Table App 2.1: Conditions recommended to be screened for within individual countries or regions included in this review

Notes:

- Please see text, section 6 of this report, for caveats relating to the comparison of countries or counting of conditions screened.
- List of conditions to be screened is advisory (as opposed to required) in some cases, for example, US.
- There may be regional variation in screening programmes within individual countries beyond that depicted in the below table.
- Ireland included as reference. Note: ADA-SCID screening recommended in 2020, though yet to be implemented.

Group	Condition	Acronym	Ireland	Victoria (AU)	Alberta (CA)	Ontario (CA)	Quebec (CA)	Denmark	Germany	Italy	Netherlands	New Zealand	UK	US
Metabolic disorders														
Amino acid disorders	Maple syrup urine disease	MSUD	X	X	X	X		X	X	X	X	X	X	X
	Homocystinuria	HCU	X	X		X				X		X	X	X
	Phenylketonuria	PKU	X	X	X	X	X	X	X	X	X	X	X	X
	Tyrosinaemia type I	TYR1			X	X	X	X	X	X	X			X
	Tyrosinaemia type II	TYR2		X						X				
	Tyrosinaemia type III	TYR3								X				
	Biopterin cofactor biosynthesis deficiency	BIOPT (BS)								X				
	Glycine N-methyltransferase deficiency	GNMT								X				
	Methionine adenosyl transferase I/III deficiency	MAT								X				
	S-adenosylhomocysteine hydrolase deficiency	SAHH								X				
	3-methyl glutaconic acids (3-methylglutaconyl-CoA hydratase deficiency)	3MGCA								X				
	2-methyl 3-hydroxybutyril-CoA dehydrogenase deficiency	2M3HBA								X				

	Isobutyril-CoA dehydrogenase deficiency	IBG								X				
Organic acidaemias	3-Hydroxy-3-methylglutaric aciduria	3HMG		X	X					X	X			X
	3-methylcrotonyl-CoA carboxylase deficiency	3MCC		X			X^			X	X			X
	Beta ketothiolase deficiency	BKT		X						X				X
	Cobalamin disorders			X	X	X				X				X
	Methylmalonic acidaemia	MMA		X	X	X	X^	X		X	X	X		X
	Glutaric acidaemia type 1	GA1	X	X	X	X	X	X	X	X	X	X	X	X
	Multiple carboxylase deficiency* *(subsets in grey)*	MCD		X	X	X		X	X	X	X	X		X
	Holocarboxylase synthetase deficiency	HCSD		X				X		X				X
	Biotinidase deficiency	BIOT			X	X		X	X	X	X	X		
	Isovaleric acidaemia	IVA		X	X	X		X	X	X	X	X	X	X
	Propionic acidaemia	PA		X	X	X	X^	X		X	X	X		X
Fatty acid oxidation disorders	Carnitine palmitoyl transferase 1 deficiency	CPT1		X					X	X	X	X		
	Carnitine palmitoyl transferase 2 deficiency	CPT2		X					X	X		X		
	Carnitine uptake defect	CUD		X	X	X		X		X				X
	2 Carnitine-acyl carnitine translocase deficiency	CACT		X					X	X		X		
	Glutaric acidaemia type II (Multiple acyl-CoA dehydrogenase deficiency)	MADD		X						X		X		
	Medium-chain acyl CoA dehydrogenase deficiency	MCADD	X	X	X	X	X	X	X	X	X	X	X	X
	Mitochodrial trifunctional protein deficiency	TFP		X	X	X	X			X		X		X
	Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency	LCHAD			X	X	X	X	X	X	X	X		X
	Very long chain acyl CoA dehydrogenase deficiency	VLCAD		X	X	X	X	X	X	X	X	X		X
	2-methylbutyryl-CoA dehydrogenase deficiency	SBCAD								X				

	Medium / short chain 3-hydroxy-acyl-CoA dehydrogenase deficiency	M / SCHAD								X				
	Short-chain acyl-CoA dehydrogenase deficiency	SCAD								X				
LSD	Hurler Syndrome	MPS1				X					X			X
CMD	Classical Galactosaemia	GALT	X		X	X		X	X	X	X	X		X
	Galactose kinase deficiency	GALK									X			
	Glycogen Storage Disease Type II (Pompe)	GSD II												X
Urea cycle disorder	Argininosuccinic aciduria	ASA		X		X	X	X		X		X		X
	Hyperargininaemia	ARG					X^			X				
	Citrullinaemia type I	CIT		X	X	X	X^			X		X		X
	Citrullinaemia type II	CIT2					X^			X				
	Triple H syndrome	HHH					X^							
PD	X-linked adrenoleukodystrophy													X
Endocrine disorders (ED), haemoglobinopathies (H), immunodeficiency (ID) and other disorders														
ED	Congenital adrenal hyperplasia	CAH			X	X		X	X		X	X		X
	Congenital hypothyroidism	CH	X	X	X	X	X	X	X	X	X	X	X	X
H	Sickle cell disease	SCD			X	X	X		X		X		X	X
	Alpha thalassaemia										X			
	Beta thalassaemia										X			X
ID	Severe combined immunodeficiencies	SCID			X	X		X	X		X	X		X
Other	Cystic fibrosis	CF	X	X	X	X	X	X	X	X	X	X	X	X
	Spinal muscular atrophy	SMA				X			X					X

Key: CMD - Carbohydrate metabolism disorders; HD - ED - Endocrine Disorder; Hemoglobinopathy; ID - Immunodeficiency; LSD - Lyososomal storage disorder; PD - Peroxisomal disorder.
*Due to variation in conventions for the grouping of conditions, the 'MCD' grouping may also indicate screening for biotinidase deficiency and or holocarboxylase synthetase deficiency
^Screened by urine in Quebec (Canada) with assessments on whether these conditions should be tested via bloodspot completed by INESSS in 2019.

Appendix 3: Data extraction tables outlining processes for NBS programmes in included countries

Table App 3.1: Characteristics of NBS programmes in individual countries or regions reviewed

Country *Body responsible for delivering NBS* **Data source(s), URL Date of publication or last update**	**Number of conditions currently included in programme** **Regional variation in th conditions included**	**Role of technology in decision-making or expansion of programme 2011-2021**	**Information on expansion/changes of programme 2011-2021**	**Programme participation rates**
Australia *Australian Health Ministers Advisory Council (AHMAC), advice supplied by the Standing Committee on Screening (SCoS)* Australian Government Department of Health. *Newborn bloodspot screening* **(54)**, https://www.health.gov.au/health-topics/pregnancy-birth-and-baby/newborn-bloodspot-screening#national-policy-framework Updated 24 November 2020 Australian Government Department of Health. *Newborn Bloodspot Screening National Policy Framework***(53)** https://www.health.gov.au/sites/default/files/documents/2020/10/newborn-bloodspot-screening-national-policy-framework.pdf Published May 2018	Approximately **25** conditions (territorial variation) (54) State and territory governments fund the NBS programmes. Each state and territory decides which conditions to screen for.(54) For example, galactosaemia is not screened for in Victoria.	Tandem mass spectrometry used from 1998 in two states and in all programmes by 2005.(53)	NBS National Policy Framework was introduced in 2018. This framework aims to provide a robust, transparent process for national decisions on the conditions screened.(53) Congenital adrenal hyperplasia was recommended for screening in 2019(54). See here for report.	**99%** (>300,000 babies every year).(54) Of babies screened, around 1 in every 1,000 has a condition that would otherwise have gone undetected.(54) About 1–2% of babies tested require repeat or subsequent diagnostic testing.

Australian Government Department of Health. *Nomination forms for requesting the assessment of a condition for addition to or removal from Newborn Bloodspot Screening*[102] https://www.health.gov.au/resources/publications/nomination-forms-for-requesting-the-assessment-of-a-condition-for-addition-to-or-removal-from-newborn-bloodspot-screening Published November 2019				
Canada (Alberta) Alberta Health Services *Alberta's NMS Program 2019 Panel Expansion Evaluation Summary*[49] https://www.albertahealthservices.ca/assets/info/hp/nms/if-hp-nms-2019-panel-expansion-eval-summary.pdf Published June 2020 Alberta Government. *Health Evidence Reviews*[103] https://www.alberta.ca/health-evidence-reviews.aspx Updated – unclear Institute of Health Economics. *Alberta STE report: Newborn Bloodspot screening for galactosaemia, tyrosinaemia type 1, homocystinuria, sickle cell anaemia, sickle cell/beta-thalassaemia, sickle cell/hemoglobin C disease, and severe combined immunodeficiency*[104]	Screens for **21** treatable disorders.[49] In Canada, Therrell et al. (2015) note the federal government has no formal role in newborn screening. Healthcare (and NBS) is the responsibility of the 10 provinces and 3 territories, with the notable exception of specific populations of aboriginals, inmates of federal prisons, military, and newly arrived immigrants and refugees.[46]	*(No information identified using search methodology applied in this review)*	In 2007, 14 disorders were added to the panel.[105] In 2019 four disorders were added to the panel: classic galactosaemia (GALT), tyrosinaemia type 1 (TYR1), severe combined immunodeficiency (SCID), and sickle cell disease (SCD).[49]	In 2018–2019. 99.4% of registered infants screened (52,005/52,313).[105] Screened infants who received abnormal results requiring clinical follow up: 0.36% (188/52,099).[105] Infants with an abnormal screen result who received abnormal diagnostic outcomes: 29.26% (55/188).[105]

http://www.ihe.ca/download/newborn_blood_spot_screening.pdf March 2016 De Souza et al. (2019) **(105)** Therrell et al. (2015)**(46)**				
Canada (Ontario) *Newborn Screening Ontario (NSO) is under the stewardship of the Government of Ontario. The Newborn Screening Ontario Advisory Council (NSO-AC) is responsible for providing advice and guidance to the NSO, as well as the Ministry of Health and Long-Term Care and the Ministry of Children, Community and Social Services.* Newborn Screening Ontario. *About NSO, Our team***(106)** https://www.newbornscreening.on.ca/en/about-nso/our-team Last updated – 2021 Canadian Agency for Drugs and Technologies in Health. *Newborn Screening for Disorders and Abnormalities in Canada***(107)** https://www.cadth.ca/media/pdf/Newborn_Screening_es-26_e.pdf Published August 2011 Newborn Screening Ontario. *Panel review* **(69)**	**25+** conditions screened for(108) Therrell et al. (2015) note federal government has no formal role, with responsibility devolved to provinces/ territories.(46)	*(No information identified using search methodology applied in this review)*	A review of cystic fibrosis screening recommended the addition of a third-tier test (sequencing of the CFTR gene) to the existing CF screening algorithm in an effort to improve the positive predictive value.(69) Review of C5OH-related targets in 2016 recommended removal of C5OH-related targets from the Newborn Screening Ontario panel.(69) Details of this decision can be found here. Quinn (2020) cites SCID currently being implemented or under pilot.(109)	Of approximately 140,000 babies born in Ontario each year, approximately 139,000 screen negative, approximately 1,300 screen positive (0.9%), and approximately 200 are true positives (0.14%).(108)

https://newbornscreening.on.ca/en/about-us/nso-governance/panel-review Last updated 2021 Newborn Screening Ontario. *Screening results*[108] https://www.newbornscreening.on.ca/en/screening-results/results-overview/numbers Updated – unclear Therrell et al. (2015) [46] Quinn et al. (2020) [109]				
Canada (Quebec) *The Ministry of Health and Social Services (MSSS) of Quebec has responsibility for the NBS program. The National Institute of Excellence in Health and social services (INESSS) provides the Ministry with assessments of the appropriateness on including additional disorders in the NBS programme* Quebec government. *Blood and Urine Screening in Newborns*[110] https://www.quebec.ca/en/health/advice-and-prevention/screening-and-carrier-testing-offer/blood-and-urine-screening-in-newborns/diseases-screened Updated July 2021	**11** diseases are screened for by blood and **7** diseases by urine.[110] Therrell et al. (2015) note federal government has no formal role, with responsibility devolved to provinces/ territories.[46]	In 2017, seven conditions that were screened for using urine analysis were assessed for screening using bloodspot sampling and MS/MS. Two were subsequently recommended. In 2013 the expansion of the newborn screening programme was related to the availability of MS/MS with screening for BIOT, GALT and HCS being initiated in parallel with the expansion of MS/MS screening. [111]	In 2013 the INESSS was asked to advise on 21 conditions that could be screened for. Nine of the 21 conditions were already part of the programme. They concluded that all of the conditions of interest should be screened for, but to varying degrees.[111] In 2019 and 2020, INESSS published detail evaluations of 16 conditions. There were 4 positive recommendations. See also 'Role of technology' column	*(No information identified using search methodology applied in this review)*

National Institute of Excellence in Health and Services (INESSS). *Advisability of expanding the Quebec Newborn Blood Screening Program*[111] https://www.inesss.qc.ca/en/publications/publications/publication/advisability-of-expanding-the-quebec-newborn-blood-screening-program.html Updated 24 September 2013 INESSS. *Screening for inborn errors of metabolism**: https://www.inesss.qc.ca/publications/repertoire-des-publications/publication/depistage-des-erreurs-innees-du-metabolisme.html Updated 16 September 2019 INESSS. *Neonatal screening for nine inborn errors of metabolism**[75] https://www.inesss.qc.ca/en/publications/publications/publication/evaluation-de-la-pertinence-du-depistage-neonatal-sanguin-de-neuf-erreurs-innees-du-metabolisme.html Updated 31 July 2020 INESSS. *Neonatal screening for inborn errors of metabolism: ethical issues, public perspective, and patient, parent and caregiver perspective*[112] https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Depistage/INESSS_Neonatal_Ethic_Summary.pdf Published July 2020			regarding change of sampling approach resulting in addition of two conditions specifically to the bloodspot screening programme.	

Denmark Statens Serum Institut. *The Danish State Serum Institute (SSI) investigates newborn babies for a variety of congenital diseases.*[113] Statens Serum Institut. *Screening af Nyfodte** www.ssi.dk/nyfoedte Last updated Sep 4, 2020	**18** serious congenital diseases screened with one further condition proposed.[20] No regional variation noted	*(No information identified using search methodology applied in this review)*	The screening panel increased from 15 (in 2009) to 18 by 2020: these increases included IVA (since December 2012), CF (since May 2016),and SCID (since February 2020).[113]	**99.85%** of Danish newborns are screened[113] Overall prevalence of the diseases included in the programme 1:3,900 (up to 2019).[113]
Germany *Directive of the Federal Joint Committee on the early detection of diseases children (G-BA).* Gemeinsamer Bundesaussschuss. *Richtlinie: des Gemeinsamen Bundesausschusses uber die Fruherkennung von Krankheiten bei Kindern**[114] https://www.g-ba.de/downloads/62-492-2432/Kinder-RL_2020-12-17_iK-2021-04-01.pdf Last updated December 2020 Hohenfellner et al. (2019)[115] Lüders et al. (2021)[116]	**19** conditions are screened. No regional variation noted.	Technology used: Photometric tests, fluorometric, MS/MS, PCR, HPLC, IRT, PAP-test, capillary electrophoresis Molecular-based NBS, has not been broadly implemented; in Germany, it plays a confirmatory, third-tier role in screening for cystic fibrosis.	December 17, 2020 – Addition of screening for spinal muscular atrophy and sickle cell disease.	Estimated to be approaching **100%** Data from 2006-2018 indicates an overall prevalence of 75 per 100,000 for target conditions in newborns in Germany (6917 from 9,218,538 births).[116]

Italy* *Coordination Center for Neonatal Screening within the Istituto Superiore di Sanità (Higher Institute of Health) and the Extended Neonatal Screening Working Group (established 2020)* Instituto Superiore Di Sanità. *Expanded Newborn Screening and Neonatal screening** **(82)** https://www.iss.it/screening-neonatali Updated - unclear Instituto Superiore Di Sanità*. Rare diseases* **(117)** https://www.iss.it/web/iss-en/newborn-screening Updated – unclear Ministry of Health. *Neonatal screening** **(118)** http://www.salute.gov.it/portale/temi/p26.jsp?lingua=italiano&id=1920&area=saluteBambino&menu=nascita Updated 14 April 2021 Legislation 2016 **(119)** https://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=55762&completo=true Published August 2016 Legislation 2019* **(120)** https://www.gazzettaufficiale.it/eli/gu/2018/12/31/302/so/62/sg/pdf	Approximately **40** inherited metabolic conditions which are screened are regulated by two legislative acts. (Law 167/2016 and Ministerial Decree 2016)(117) Initial in 1992: phenylketonuria, congenital hypothyroidism and cystic fibrosis (Law 104/1992). Mandated extension in 2016 to 40 conditions (Law 167/2016 and Ministerial Decree 2016).(121) Decision-making is national with legislative acts; however, regional variation in implementation is noted in terms of the conditions screened and coverage attained.	The development of analytical technology (in particular MS/MS) was described as simplifying the analyses involved in screening, increasing the number of diagnosable pathologies, and enabling extended screening. Law 167/2016 requires that the panel must be updated in line with technical and medical progress.	2016: Legislation to extend screening to 40 conditions. Le Marca (2021)(122) and Ministry of Health refer to a recent proposal under 2019 Budget Law (Article 1 c. 544) to extend screening to other metabolic defects, with screening for lysosomal diseases active in Tuscany and Triveneto. Quinn et al. (2020)(109) highlights screening for SCID in Tuscany.	Two implementation reports (2017 and 2018) describe implementation outcomes across regions. Coverage rates have been increasing over time however ongoing regional variation noted. In particular, variation was noted in laboratory access for MS/MS technology. Loeber et al. (2021)(20) cites **96.7%** of infants screened.

Published 31 December 2018 Ministerial Decree 2016*[121] https://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=56764&completo=true Published October 2016				
The Netherlands *The programme is coordinated by the Centre for Population Screening (CvB) of the National Institute for Public Health and the Environment (RIVM)* Jansen et al. (2021)[59] National Institute for Health and Environment. *Newborn Blood spot in the Netherlands Monitor 2017*[123] https://www.pns.nl/sites/default/files/2019-11/Monitor%20Newborn%20Blood%20Spot%20Screening%202017.pdf Published 2017 Health Council of the Netherlands. *Neonatal Screening: new recommendations*[124] https://www.healthcouncil.nl/binaries/healthcouncil/documents/advisory-reports/2015/04/08/neonatal-screening-new-recommendations/advisory-report-neonatal-screening-new-recommendations.pdf Published 2015	Screening offered for **24** conditions (February 2021) No regional variation noted	The Committee expects major developments, particularly in the field of screening at the DNA level. The consequences are expected to be far-reaching, not only for neonatal screening, but also for pre-conception and prenatal screening.[124]	Before 2019 NBS used an ad hoc committee when evaluation was needed. The Health Council of the Netherlands advised on the addition of 14 conditions in 2005, advised on the addition of cystic fibrosis in 2011, advised on adding 14 conditions in 2015, and advised on adding spinal muscular atrophy in 2019.[59] Jansen (2021) notes the NBS programme has been expanded from 17 to 24 conditions since January 2021 with extension to 32 conditions planned in the coming years.[59] Quinn (2020) and Jansen (2021) note that SCID currently under pilot and being gradually implemented.[59, 109]	NBS participation rate was **99.2%** in 2017 (n=169,883); 476 children were referred of which 181 had the diagnosis confirmed.[123] Loeber et al. (2021) reported uptake rate as **99.3%**.[20]

Loeber (2021)[20]				
New Zealand *The National Screening Unit (NSU) has responsibility for the Newborn Metabolic Screening Programme (NMSP). The NMSP Technical group and Antenatal and Newborn Screening Clinical Oversight Group provide expert advice for the programme* NSU. *Newborn Metabolic Screening Programme*[125] https://www.nsu.govt.nz/pregnancy-newborn-screening/newborn-metabolic-screening-programme-heel-prick-test/about-test Updated: December 2017 NSU. *Newborn Metabolic Screening Programmes Annual Report 2018*[126] https://www.nsu.govt.nz/system/files/page/newborn-metabolic-screening-programme-annual-report-2018-12nov2019_final.docx NSU. *Newborn Metabolic screening programme Policy Framework*[127] https://www.nsu.govt.nz/system/files/page/newborn_metabolic_screening_programme_policy_framework_june_2011.pdf Published June 2011	Currently screen for **23** conditions[125] National based programme[1]	*(No information identified using search methodology applied in this review)*	In 2015 the following conditions were removed from the screening programme as they were found to have no clinical benefit to the child: ▪ 3 methylcrotonyl-CoA carboxylase deficiency ▪ 3-hyroxy-3-methylglutaryl-CoA lyase deficiency ▪ multiple CoA carboxylase deficiency ▪ 3-methylglutaconyl-CoA-hydratase deficiency ▪ beta-ketothiolase deficiency ▪ 2-methyl-3-hydroxybutyryl CoA dehydrogenase deficiency. In 2017 due to the high number of false positive results and lack of true cases detected: ▪ carnitine transport defect screening was ceased	In 2018 (most recent annual report) 57,880 of 58,163 babies born were screened, representing a national coverage rate of **99.5%** (range at district health board level 97.3-100%). The programme identifies approximately 50 to 60 newborns with metabolic disorders each year.[126]

			▪ tyrsosinaemia screening was suspended. In 2017 also, SCID was added to the programme.	
United Kingdom *UK National Screening Committee (UK NSC)* Public Health England. *Newborn bloodpot screening: programme overview*[62] https://www.gov.uk/guidance/newborn-blood-spot-screening-programme-overview Updated on 8 November 2018 UK NSC. *Guidance: Criteria for appraising the viability, effectiveness and appropriateness of a screening programme*[128] https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme Updated 23 October 2015 O'Leary and Maxwell (2015)[89] UK NSC. *Guidance: Newborn Blood spot screening data collection and performance analysis report*[129] https://www.gov.uk/government/publications/newborn-blood-spot-screening-data-	Screens for **9** conditions[62] The UK NSC makes recommendations to ministers in the 4 UK countries.[62] Protocols and pathways are different for each of the countries. While the programme is designed to target nine specific disorders. significant findings from screening which may lead to the identification of additional conditions are reported and the patient referred to an appropriate clincial pathway (such as tyrosinaemia, galactosaemia, short branched chain acyl-CoA dehydrogenase deficiency, hydroxyprolinaemia, glutaric aciduria type 2, methionine	Technology has a permissive effect allowing the consideration of additional disorders, but is not the primary driver for change.[63]	The screening panel increased from 5 conditions to 9 conditions in 2015. An evaluation of screening for SCID is scheduled to begin in 2021, while screening for tyrosinaemia is under active consideration.[63] Northern Ireland added screening for Maple syrup Urine disease, isovaleric acidaemia, glutaric aciduria type 1 and homocystinuria in March 2020.	England and Northern Ireland reported coverage of more than **95.0%.** (England **97.8%,** Northern Ireland **98.2%**).[129] <u>Screen positive rates in UK for 2019:</u> - congenital hypothyroidism, 7.60 per 10,000 babies - sickle cell disease, 4.08 per 10,000 - cystic fibrosis, 4.17 per 10,000 - PKU, 1.24 per 10,000.[129]

collection-and-performance-analysis-report/newborn-blood-spot-screening-data-collection-and-performance-analysis-report-1-april-2018-to-31-march-2019#report-summary Updated 16 March 2021	adenosyltransferase deficiency, biopterin disorders).[63]			
United States *The Advisory Committee on Heritable Disorders in Newborns and Children advises the Secretary of the Department of Health and Human Services (HHS) on the most appropriate tests, technologies, polices, guidelines and standards, including which conditions should be on the recommended uniform screening panel (RUSP)* US Department of Health and Human Services. *Newborn Screening*[130] https://www.nichd.nih.gov/health/topics/newborn/conditioninfo/infants-screened Updated 1 September 2017 Dayno et al 2020 (Thesis)[131] https://scholarshare.temple.edu/handle/20.500.12613/2763 Published 2020 Health Resources and Services Administration (HRSA). *The advisory committee on heritable disorders in newborns and children.*[132] https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-	RUSP has **35 core conditions** and **26 secondary conditions** that are recommended for newborn screening.[131] A condition on the newborn screening panel is classified as a "secondary condition" if it is identified unintentionally when screening for one of the core conditions, or as a consequence of confirmatory testing for an out-of-range result of a core condition. Individual states decide which conditions to screen for in their NBS programme. Most states screen for the majority of disorders on the RUSP, but may also screen for additional disorders.[48]	In 2018, the Committee supported the development of a Newborn Screening Technology Compendium report.[132] Most states multiplex SMA screening with newborn screening for SCID. The adoption of screening for SMA has been facilitated by the ability to screen for SMA and SCID simultaneously in the same testing system and workflow.[133]	Peake and Bodamer (2017) note expansion including lysosomal storge disorders (LSDs) in New York State and Missouri in 2006 and 2013, respectively. Pilot programmes have also been performed in Washington State. Several other states have since passed legislation requiring mandatory screening for LSDs, including Illinois, New Mexico, and New Jersey.[134] De Barber (2014) lists five conditions assessed since 2011: 22q11.2 deletion syndrome, MPS 1 (a-L-iduronidase deficiency), Pompe disease, X-linked adrenoleukodystrophy, X-linked adrenoleukodystrophy.[135]	Approximately 4 million infants are born in the United States each year. Participation is reported as **99.9%** or higher in most states. 12,500 newborns each year are diagnosed with one of the core conditions detected through newborn screening. This means that almost 1 out of every 300 newborns screened is eventually diagnosed.[130]

recommendations/reports/2018-achdnc-report-congress.pdf Published 2018 Health Resources and Services Administration. *Recommended Uniform Screening Panel*[48] https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html Last reviewed February 2020	All states currently require newborn screening for at least 29 health conditions. Most states allow parents to opt out for religious or other reasons.[130]			

Abbreviations SCoS standing committee on screening (Australia), AHW Alberta Health and Wellness, NSO-AC Newborn Screening Ontario – Advisory Council, MSSS The Quebec Ministry of Health and Social Services, INESSS National Institute for Excellence in health and Social Services, INSPQ Institut National de Santé Publique du Québec, G-BA Gemeinsamer Bundeausschuss (Federal Joint Committee – decision-making body in the German healthcare system, IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for quality and efficiency in healthcare review – Germany), AGENAS Ministry of Health, Istituto Superiore di Sanità, NSU the National Screening Unit (New Zealand), NMSP Newborn Metabolic screening programme (New Zealand), NSC National Screening Committee (UK)

*Accuracy may be impeded as documents translated using Google Translate

Table App 3.2: Processes for proposal, prioritisation and selection of conditions (screening indications) for review

Country Source(s)	Perspective regarding screening beneficiary	Method of proposal of condition to be considered for addition	Prioritisation of review of conditions to be considered for addition	Selection of condition(s) for review
Australia Australian Government Department of Health. *Newborn Bloodspot Screening National Policy Framework* https://www.health.gov.au/health-topics/pregnancy-birth-and-baby/newborn-bloodspot-screening Updated 24 November 2020	Child Family/ community	Anyone in Australia can propose a condition to be added or removed from the NBS program. The standing committee on screening (ScoS) considers conditions for assessment once a year.(65)	The Program Management Committee makes an initial assessment of all applications and provides a recommendation to ScoS as to which of the proposed conditions merits more detailed assessment. The recommendation provided is based on the information in the proposal forms.	Progression of and timing of the detailed review are dependent on a number of considerations, including: ▪ availability of staff and resources to support the review ▪ the level of evidence available in Australia and internationally ▪ the complexity of the issues being considered ▪ whether an economic analysis is being considered.
Canada (Alberta) Alberta Government. *Newborn metabolic screening* https://www.alberta.ca/newborn-metabolic-screening.aspx Updated - unclear Alberta Government. *Alberta newborn metabolic screening program*	Patient and family-centred care	Alberta Health and Wellness (AHW) determines what conditions are screened for and facilitates co-ordination with stakeholders.(66)	For health reviews generally (including NBS), the selection process tries to answer the following questions:(103) ▪ Is the review topic considered high-priority for the Alberta government and healthcare system? ▪ Will the review have a wide-reaching and or significant impact on how care is delivered? ▪ Is there pressure for change?	Guided by Australian Population Health Development Principal Committee's Screening Subcommittee, in its document "Population Based Screening Framework".(67)

Abbreviations SCoS standing committee on screening (Australia), AHW Alberta Health and Wellness, NSO-AC Newborn Screening Ontario – Advisory Council,

https://open.alberta.ca/publications/9780778582892 Updated January 2011 Alberta Government. *Health Evidence Reviews*[103] https://www.alberta.ca/health-evidence-reviews.aspx Updated – unclear			▪ Is there willingness to change? ▪ Is there a health system decision-maker who will use review results to affect change? ▪ What is the likelihood that change will happen?	
Canada (Ontario) Newborn Screening Ontario. *Panel review* https://newbornscreening.on.ca/en/about-us/nso-governance/panel-review (Last update unclear)	Child[1]	The NSO-AC (Newborn Screening Ontario – Advisory Council) review of existing targets of the NSO panel is a quality improvement initiative. It involves determining whether changes are needed to the current screening process, including potential removal of a disease from the panel.[69] Ontario presents criteria as a set of specified questions. There are 48 questions divided into five categories: condition, test, treatment, stakeholder support, and experience from other jurisdictions.[1]	A formal process is used by NSO-AC to evaluate potential new screening targets and existing targets in the province of Ontario.	An example of criteria for review of conditions currently included in the screening panel is as follows: C5OH-related targets were selected for review (removal from panel) due to the: ▪ number of asymptomatic individuals that were being identified through screening. ▪ high number of false positives ▪ low positive predictive value.[69]
Canada (Quebec) INESSS. *Assessment of the appropriateness of newborn bloodspot screening by tandem mass spectrometry for seven inborn errors of*	Child Family[1]	In 2013 and 2017, the Quebec Ministry for Health and Social Service (MSSS) mandated the Institute National Excellence in Health and Social Services (INESSS) to assess the appropriateness of adding certain conditions to neonatal blood screening.	After consultation with experts and with the agreement of the MSSS, it is agreed which diseases would be evaluated.	The appropriateness of expanding the neonatal screening program was assessed in 2013 by the INESSS. In 2017 the INESSS was mandated to reassess the relevance of screening nine

metabolism *: https://www.inesss.qc.ca/publications/repertoire-des-publications/publication/depistage-des-erreurs-innees-du-metabolisme.html Updated 16 September 2019 INESSS. *Assessment of appropriateness of screening neonatal blood deficiency biotinidase (BIOT)** https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Depistage/BIOT_depistage_neonatal_FS.pdf Published 2020 INESSS. *Neonatal screening for nine inborn errors of metabolism** https://www.inesss.qc.ca/en/publications/publications/publication/evaluation-de-la-pertinence-du-depistage-neonatal-sanguin-de-neuf-erreurs-innees-du-metabolisme.html Updated 31 July 2020		The prioritisation and selection of conditions to be evaluated for screening is performed by the Ministry of Health and Social Services.		specific inborn errors of metabolism. Seven of these were assessed first for bloodspot screening using MS/MS which were currently detected using urinary analysis. These assessments were made separately and published in 2019 and 2020.

Denmark Danish Health Authority. *Biochemical screening for congenital disease in newborns* https://www.sst.dk/-/media/Udgivelser/2008/Publ2008/CFF/Screening/biokemisk_screening,-d-,pdf.ashx?la=da&hash=823169F2C7B1C3AF4ACA25ADA6786294B5F0A28F Last updated 2008 Statens Serum Institut. *Screening of newborns programme* https://nyfoedte.ssi.dk/ Updated - unclear	Child	In 2005, the Danish Health and Medicines Authority set up a working group to assess the need for adjustments to the screening assessment process based on the existing practical, organisational and administrative framework for the activity.[136] As there is limited knowledge about the natural history, spectrum of severity and effect of treatment in rare diseases, evidence about benefit may only be obtained during prospective screening and therefore gradual adjustments to an NBS programme are needed. The organisation noted that conditions may be assessed for removal due to high false positive rates, new evidence of a benign natural history, or presentation before screening.[136]	*(No information identified using search methodology applied in this review)*	*(No information identified using search methodology applied in this review)*
Germany Gemeinsamer Bundeausschuss. *Directive of the Federal Joint Committee on the early detection of diseases children**[114] https://www.g-ba.de/downloads/62-492-2432/Kinder-RL_2020-12-17_iK-2021-04-01.pdf	Child [1]	The evaluation subcommittee can decide to commission a review by IQWiG (HTA agency) on the current state of knowledge for a condition that is proposed to be included on the panel.[58]	*(No information identified using search methodology applied in this review)*	Criteria used to decide if a topic should be reviewed for inclusion: ▪ potential early treatment benefit ▪ feasibility and design of screening for the condition(s) ▪ assessment of the medical necessity[79] ▪ Wilson and Jungner criteria.

Last updated December 2020 Gemeinsamer Bundesausschuss. *Kinder-Richtlinie: Neugeborenen-Screening auf 5q-assoziierte spinale Muskelatrophie.*[79] https://www.g-ba.de/beschluesse/4617/ Published 2021				
Italy* Coordination Center for Neonatal Screening within the Istituto Superiore di Sanità (Higher Institute of Health) and the Extended Neonatal Screening Working Group (established 2020). *Neonatal Screening*[82] https://www.iss.it/screening-neonatali Updated - unclear Italian Ministry of Health. *Neonatal screening*	*(No information identified using search methodology applied in this review)*	Periodic review of conditions every two years by the Extended Neonatal Screening Working Group. The Rare Diseases Observatory (OsservatorioMalattie Rare) provides an open document for consideration of conditions to include; however, it is unclear if such documents are formally submitted to or considered by the decision-makers.	Periodic review, at least every three years, of the list of diseases to be searched for through neonatal screening, in relation to the evolution over time of scientific evidence in the diagnostic-therapeutic field for rare genetic diseases. Performed by the Extended Neonatal Screening Working Group (made up of experts in the field of newborn screening, representatives of institutions (Ministry of Health, Istituto Superiore di Sanità, AGENAS) and of rare disease patient associations).	Periodic review (at least every two years) of the list of diseases to be considered for neonatal screening, in relation to the evolution over time of scientific evidence in the diagnostic-therapeutic field for rare genetic diseases. Performed by the Extended Neonatal Screening Working Group (made up of experts in the field of newborn screening, representatives of institutions (Ministry of Health, Istituto Superiore di Sanità, AGENAS) and of rare disease patient associations).

http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=1920&area=saluteBambino&menu=nascita[137] Updated 14 April 2021 Legislation 2016 https://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=55762&completo=true Legislation 2019 https://www.gazzettaufficiale.it/eli/gu/2018/12/31/302/so/62/sg/pdf Ministerial Decree 2016 https://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=56764&completo=true				
The Netherlands Health Council of The Netherlands. *Advisory report neonatal screening – updated recommendations* https://www.healthcouncil.nl/documents/advisory-reports/2015/04/08/neonatal-screening-new-recommendations Published 2015	Child Family	Fischer[78] highlights trigger as "Explicit specification of criteria" rather than "ad hoc".	*(No information identified using search methodology applied in this review)*	For selecting conditions for inclusion, the committee have previously assessed: ▪ what conditions were screened for in other countries ▪ which conditions had improved test or treatment options that had become available in recent years

				▪ expert consultation on conditions that seem promising for inclusion.[124]
New Zealand NSU. *Newborn Metabolic screening programme (NMSP) policy framework*[127] https://www.nsu.govt.nz/system/files/page/newborn_metabolic_screening_programme_policy_framework_june_2011.pdf Published 2011	Child Family[1]	A proposal form is sent to the National Screening Unit (NSU) and is considered with input from a Metabolic Physician, the Programme leader and director and the Governance Team Chair.[56] Figure 7 of the 2011 policy framework document provides further details. The removal of a screened disorder can be requested using a separate form. NMSP Governance Team (the 'NMSP Technical Group' and the 'Antenatal and Newborn Screening Clinical Oversight Group') provide recommendations to the NSU Clinical Governance Group on changes to screened disorders or the introduction of new technology.	Detailed stepwise process by which proposed conditions are considered by NSU and assessed for whether further information is required. If information is sufficient, the proposed conditions are considered by NMSP governance team for appropriateness of assessment.	The NSU considers the completeness of the information and appropriateness of the request from the proposal form, followed by subsequent consideration by NMSP. Should a condition not be considered appropriate for assessment this is fed back to the nominee.
United Kingdom Public Health England. *Newborn Blood spot screening programme overview* https://www.gov.uk/guidance/newborn-blood-spot-screening-programme-overview Last updated November 2018 UK NSC. *Evidence review process*	Child	Any individual or organisation can submit a topic for consideration. Stakeholders can submit suggestions for new screening programmes through the annual call for topics. Provision is also made for stakeholders to propose modifications (big changes) to screening programmes and suggestions for early updates of screening recommendations.[62] The NBS programme is part of the national population screening programme. The UK National Screening Committee (NSC) reviews the evidence for screening	Topics are screened for relevance and then they undergo a triage process which includes an externally produced report. The committee decides if further evaluation is warranted.	Triaged by screening committee for appropriateness of formal assessment including assessment of evidence summaries. The scope of screening that is within the UK NSC's remit is considered on a case by case basis.[83] UK NSC evidence summaries are developed using rapid review methodologies.[83] Depending on the topic, systematic review, primary research, cost effectiveness assessments, modelling, or

https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process Updated 5 September 2017		in particular circumstances, e.g. when a proposal for a new topic which has not been previously reviewed by the committee is submitted.		further rapid reviews may be requested.
United States Health Resources and Services Administration. *Recommended Uniform Screening Panel* https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html**(48)** Last reviewed February 2020 Health Resources and Services Administration. *Nominate a condition.*(84) https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/nominate.html Reviewed January 2020 Dayno (2020, thesis) https://scholarshare.temple.edu/handle/20.500.12613/2763**(131)** Published 2020	Child Family	Individuals or organisations are expected to form multi-disciplinary teams with clinicians and/or researchers, advocacy and/or professional organisations and interested consumers or individuals. To apply, a proposal package must be completed including a cover letter, letters of support a conflict of interest disclosure form, a proposal form and supporting data and references.(84)	*(No information identified using search methodology applied in this review)*	The Committee's Nomination and Prioritisation workgroup reviews the completed Nomination Package and compiles a summary for Committee consideration. The Committee decides if sufficient evidence is available, and votes to assign, or not assign, the proposed condition to the external Condition Review Workgroup. Proposers whose conditions are not assigned to the Condition Review Workgroup are provided with feedback.

MSSS The Quebec Ministry of Health and Social Services, INESSS National Institute for Excellence in health and Social Services, INSPQ Institut National de Santé Publique du Québec, G-BA Gemeinsamer Bundeausschuss (Federal Joint Committee - decision-making body in the German health care system, IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for quality and efficiency in health care review - Germany), AGENAS Ministry of Health, Istituto Superiore di Sanità, NSU the National Screening Unit (New Zealand), NMSP Newborn Metabolic screening programme (New Zealand), NSC National Screening Committee (UK)

*Accuracy may be impeded as documents translated using Google Translate

Table App 3.3: Processes and methodologies for review and synthesis of evidence on screening effectiveness

Country (Source)	Type of review	Who completes review	Appraisal of evidence Quality assurance?
Australia Australian Government Department of Health. *Newborn Bloodspot Screening National Policy Framework*[53] https://www.health.gov.au/sites/default/files/documents/2020/10/newborn-bloodspot-screening-national-policy-framework.pdf Published May 2018 Australian Government Department of Health. *Nomination forms for requesting the assessment of a condition for addition to or removal from Newborn Bloodspot Screening*[102] https://www.health.gov.au/resources/publications/nomination-forms-for-requesting-the-assessment-of-a-condition-for-addition-to-or-removal-from-newborn-bloodspot-screening Published November 2019	A detailed review involving an assessment of all available evidence on screening for the condition in question, in line with the decision-making criteria in the provided framework. The policy framework states that, due to likely differing levels of evidence available to assess the criteria and sub-points, the best available evidence and information should be drawn upon. This should include, where available: high-quality studies, international experiences, programme and condition expertise, other relevant sources of information and evidence.[53]	Time-limited working group complete the detailed review[53]	*Appraisal of evidence:* Jansen (2017) highlights how evidence is rated (for example from high to low using a hierarchical study approach).[1] *Quality assurance:* *(No information identified using search methodology applied in this review)*

Canada (Alberta) Alberta Government. *Alberta newborn metabolic screening program*[66] https://open.alberta.ca/publications/9780778582892 Updated January 2011 Alberta Government. *Health Evidence Reviews*[103] https://www.alberta.ca/health-evidence-reviews.aspx Updated – unclear Institute of Health Economics. *Alberta STE report Newborn Bloodspot screening for galactosaemia, tyrosinaemia type 1, homocystinuria, sickle cell anaemia, sickle cell/beta-thalassaemia, sickle cell/hemoglobin C disease, and severe combined immunodeficiency*[104] http://www.ihe.ca/download/newborn_blood_spot_screening.pdf March 2016	Policy-driven HTA reports are used, which include an analysis of the social and system demographics, technological effectiveness, and economic implications of a health technology.[104] An example from 2016 is the 'Alberta STE report'. In the STE report it is stated that: This process involves the use of appropriate evidence and information for decision-making. The Alberta NMS Program uses a population-based screening approach to reduce the burden of disease in the community through early detection and treatment of select treatable conditions. The review uses accepted principles for decision-making for the introduction of population-based screening programmes as outlined by the Australian Population Health Development Principal Committee's Screening Subcommittee, in its document "Population Based Screening Framework" (Australian Framework).[104]	The Ministry of Health collaborates with various organisations to conduct reviews:[103] ▪ Institute of Health Economics ▪ University of Alberta, Health Technology and Policy Unit ▪ University of Calgary, Health Technology Assessment Unit ▪ Canadian Agency for Drugs and Technologies in Health	*Appraisal of evidence:* HTA method used with quality assessment based on study design. Unclear if scoring method employed.[104] *Quality assurance:* *(No information identified using search methodology applied in this review)*
Canada (Ontario) Newborn Screening Ontario. *Panel review* [69]	Jansen highlights the use of a HTA model taking different types of evidence into consideration.[1]	*(No information identified using search methodology*	*Appraisal of evidence:* While a HTA model is used, no scoring method is reported.[1]

https://newbornscreening.on.ca/en/about-us/nso-governance/panel-review Updated 2021		*applied in this review)*	*Quality assurance:* *(No information identified using search methodology applied in this review)*
Canada (Quebec) INESSS. Advice on expanding the Quebec newborn blood screening program[111] https://www.inesss.qc.ca/en/publications/publications/publication/advisability-of-expanding-the-quebec-newborn-blood-screening-program.html Updated 24/09/2013 INESSS. *Relevance of expanding the neonatal blood screening program in Quebec**[138] https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Genetique/INESSS_Depistage_neonatal_sanguin.pdf Published 2013 INESSS. *Assessment of the appropriateness of offering neonatal blood screening by MS/MS for seven inborn errors of metabolism already offered by urine screening**: https://www.inesss.qc.ca/publications/repertoire-des-	HTA-based process Narrative reviews carried out to identify the importance of the health problem and the treatment of each disease as well as the ethical, psychosocial and organisational challenges of newborn blood screening.[138] Extensive searches of the published literature carried out in order to identify the performance of screening tests in relation to individual diseases as well as the safety, effectiveness and efficiency of an expanded screening program.[138] A clinical excellence committee then deliberates to consider recommendations in light of the extent of the health problem, the natural history of the disease, the nature of unmet need, ability to detect disease in a timely manner, the effectiveness of early treatment and newborn screening, the performance of the neonatal blood screening test, and ethical, organisational and cost considerations associated with screening.	INESSS completes reviews Search for scientific literature conducted by a librarian and scientific professionals.[138] Staged process with consideration of scientific evidence initially by INESSS clinical excellence committee. This process aims to decide if organisational, establishment and economic analysis should be undertaken. Collective deliberation by committee to establish recommendations to Ministry.	*Appraisal of evidence:* Jansen (2017) highlight the use of a HTA model taking different types of evidence and quality appraisal into consideration, but no scoring method is reported.[1] *Quality assurance:* Deliberation by INESSS clinical excellence committee over all relevant scientific and contextual information prior to formulation of recommendations.

publications/publication/depistage-des-erreurs-innees-du-metabolisme.html Updated 16 September 2019 INESSS. *Neonatal screening for nine inborn errors of metabolism**[75] https://www.inesss.qc.ca/en/publications/publications/publication/evaluation-de-la-pertinence-du-depistage-neonatal-sanguin-de-neuf-erreurs-innees-du-metabolisme.html Updated 31 July 2020			
Denmark Statens Serum Institut. *Screening of newborns* https://nyfoedte.ssi.dk/ Update – unclear	Fischer (2014) highlights that for MCADD and CAH, effectiveness was assessed through expert opinion and systematic literature review.[78] Cost assessed through a formalised cost estimate. Lund (2012) highlights the use of a seven-year pilot programme ahead of inclusion of conditions in the routine screening programme from 2009 onwards.[139]	*(No information identified using search methodology applied in this review)*	*Appraisal of evidence:* Jansen (2017) highlight the use of a HTA model taking different types of evidence into consideration.[1] Lund (2020) highlights decision on the current panel was based on results from the pilot period and a review which included scoring of the screening potential for selected diseases.[136] *Quality assurance:* *(No information identified using search methodology applied in this review)*

Germany Gemeinsamer Bundeausschuss (G-BA) Federal joint committee. *Early detection of diseases in children*[140] https://www.g-ba.de/english/ https://www.g-ba.de/themen/methodenbewertung/ambulant/frueherkennung-krankheiten/kinder/ Updated 2021 IQWIG. *General Methods.*[141] https://www.iqwig.de/en/about-us/methods/methods-paper/ Updated November 2020 G-BA. *The Federal Joint Committee and its Subcommittees.{Gemeinsamer Bundeausschuss (Federal Joint Commmittee), 2021 #223}* https://www.g-ba.de/downloads/17-98-2899/2021-03-01_G-BA_Grafik_Plenum-Unterausschuesse_EN_bf.pdf Updated March 2021	A HTA style of assessment is applied by IQWIG. When assessing early detection methods, the same levels of evidence apply as for diagnostic methods with special consideration of the requirements for screening tests, reference tests and interventions that are relevant for screening. Review of other EU countries' decision-making in order to assess the basis on which these countries make the decision for inclusion.	IQWIG (HTA agency) complete the review and the plenary (of the Federal Joint Committee, G-BA) sets up sub-committees to consider the evidence and prepare its decisions.	*Appraisal of evidence:* RCT-level evidence is preferred; however, in the case of an expected dramatic effect, and in rare diseases, other study types are considered and qualified as appropriate.[141] *Quality assurance:* IQWIG assessments undergo internal and external quality assurance checks, alongside targeted and public consultations.[141]
Italy*	HTA assessment, performed by the National Agency for Regional Health Services, is noted in the 2016 legislation which refers to the types of newborn screening to perform.	National Agency for Regional Health Services (Note: 2016 act which	*Appraisal of evidence:* *(No information identified using search methodology applied in this review)*

Istituto Superiore di Sanità (Higher Institute of Health). *Neonatal screening**[82] https://www.iss.it/screening-neonatali Updated – unclear Italian Ministry of Health. *Neonatal screening**[82] http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=1920&area=saluteBambino&menu=nascita Legislation 2016*[119] https://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=55762&completo=true Legislation 2019*[120] https://www.gazzettaufficiale.it/eli/gu/2018/12/31/302/so/62/sg/pdf Ministerial Decree 2016 *[121] https://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=56764&completo=true		may no longer be relevant given the establishment of Extended Neonatal Screening Working Group in 2020).	*Quality assurance:* *(No information identified using search methodology applied in this review)*
The Netherlands Jansen et al. (2021)[59] National Institute for Health and Environment. *Newborn Blood spot in the*	Expert opinion, stakeholders, systematic literature review, HTA. Advice from GR (Health Council of the Netherlands) independent scientific report. *Implementation evaluation* Following advice by the GR, the Ministry of Health, Welfare and Sport (VWS) decides whether to expand the programme and	The GR is an independent advisory body who provides a scientific report. The RIVM-CvB (Centre for	*Appraisal of evidence:* Jansen (2017) highlight the use of a HTA model taking different types of evidence into consideration.(1) *Quality assurance:*

Netherlands Monitor 2017[123] https://www.pns.nl/sites/default/files/2019-11/Monitor%20Newborn%20Blood%20Spot%20Screening%202017.pdf Published 2017 Health Council of The Netherlands. *Advisory report neonatal screening – updated recommendations*[124] https://www.healthcouncil.nl/documents/advisory-reports/2015/04/08/neonatal-screening-new-recommendations Published 2015	assigns RIVM-CvB to study the feasibility of adding conditions. To initiate the feasibility study, the GR advice is complemented with additional information from grey literature and expert opinion.[59] An evaluation framework (with the focus on characteristics related to the execution of screening, such as availability of a test method in the Netherlands) is used and includes aspects such as Dutch prevalence numbers, test characteristics, and consensus in clinical follow-up in Dutch hospitals.[59]	Population Screening of the National Institute for Public Health and the Environment) provides a feasibility study.	*(No information identified using search methodology applied in this review)*
New Zealand NSU. *New Born Metabolic Screening Policy Framework*[127] https://www.nsu.govt.nz/system/files/page/newborn_metabolic_screening_programme_policy_framework_june_2011.pdf Published 2011	Information required by the Newborn Metabolic Screening Programme Governance Team may include:[127] ▪ cost benefit analysis ▪ evidence review ▪ stakeholder consultation including Maori ▪ literature review ▪ international review.	*(No information identified using search methodology applied in this review)*	*Appraisal of evidence:* Evidence is graded using the Harbour & Miller (2001)[142] criteria for grading evidence in evidence-based guidelines: Hierarchy of evidence from A to E. *Quality assurance:* *(No information identified using search methodology applied in this review)*
United Kingdom Metternick-Jones et al. (2015)[52]	Rapid review of the literature initially.[63] Evidence summary projects are undertaken in 3 stages; commissioning, document development, and sign off.[83]	The evidence team, part of the UK NSC Secretariat, is responsible for managing the	*Appraisal of evidence:* The UK NSC will generally consider submissions informed by higher levels of evidence to be stronger. Higher levels of evidence include

UK NSC. *Evidence review process*[83] https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process#when-a-proposal-is-made-to-modify-or-make-big-changes-to-a-current-screening-programme Published September 2017	Depending on the topic, following triage there may be a requirement for systematic review, cost effectiveness assessment, modelling, primary research, or further rapid reviews. A separate process is used when a condition is being considered for removal. This consists of a triage assessment, whereby an externally produced literature search is undertaken. This search aims to identify whether any papers have been published to: 1) address screening programme cessation, 2) report harms from screening and 3) report the balance of harms and benefits from screening.	evidence review process to ensure UK NSC recommendations remain up to date.[83] The team commissions evidence reviews on behalf of the UK NSC (contracted out). Experts in review methods and techniques are commissioned to undertake each review.[83]	systematic reviews, randomised controlled trials and test accuracy studies with consecutively enrolled or randomly selected samples from a relevant population.[83] Assessment of the quality of the literature refers to recognised checklists and methods. *Quality assurance:* If there is sufficient evidence, an external review is undertaken by an expert in the field. The review is then circulated among key stakeholders and the public for their input (3-month public consultation process) and then considered for endorsement by NSC.
United States Health Resources & Services Administration. *Recommended Uniform Screening Panel: Nominate a Condition*[84] https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/nominate.html Last Reviewed: January 2020 Health Resources and Services Administration.	Systematic evidence-based review and updates.[84] Key questions guiding the review are from four topic areas:[133] ▪ Natural History and Clinical Detection ▪ Screening and Short-Term Follow Up ▪ Treatment and Long-Term Follow Up ▪ Public Health Impact. For consideration of implementation, the Advisory Committee include a review (a Public Health Impact Assessment) of the capability of state newborn screening programmes to implement comprehensive screening; this includes consideration of feasibility and readiness. This assessment examines readiness by the NBS program:[91, 143]	The external Condition Review Workgroup conducts the review and presents the final report to the Committee.[84]	*Appraisal of evidence:* Quality assessment of included studies dependent on study design. Jansen (2017) highlights level of evidence is ranked, with higher levels preferred.[1] *Quality assurance:* *(No information identified using search methodology applied in this review)*

Review of Newborn Screening Implementation for Spinal Muscular Atrophy Final Report **(133)** https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/sma-nbs-implementation-report.pdf Kemper et al. (2014)**(91)** Jansen et al. (2017)(1) Kellar-Guenther et al (2020)(143)	▪ to obtain authority to screen ▪ to conduct laboratory testing ▪ to interpret and report results ▪ to track bloodspot specimens, and ▪ to have coordinated systems for diagnostic evaluation ▪ to evaluate outcomes. As of 2018, all evidence-based reviews include an estimate of the cost to the state of adding a proposed and reviewed condition to the state's newborn screening panel.		

Abbreviations: GR Health Council of the Netherlands, VWS Ministry of Health, Welfare and Sport, RIVM-CvB Centre for Population Screening of the National
Key: ACHDNC Advisory Committee on Heritable Disorders in Newborns and Children; SCoS standing committee on screening; AHMAC Australian Health Ministers' Advisory Council; GR Health Council of the Netherlands; IEM Inborn errors of metabolism, MSSS Ministère de la Santé et des Services sociaux; NSO-AC Newborn Screening Ontario Advisory Council; RIVM-CvB Centre for Population Screening of the National Institute for Public Health and the Environment; RUSP Recommended Uniform Screening Panel UK NSC UK National Screening Committee; NSO-AC Newborn Screening Ontario Advisory Council

*Accuracy may be impeded as documents translated using Google Translate

Table App 3.4: Decision-making processes in place for screening recommendations

Country Source(s)	Stakeholder involvement	Decision-making/recommendation-issuing authority	Decision-making process description	Qualification of recommendation
Australia Australian Government Department of Health. *Newborn Bloodspot Screening National Policy Framework* [54] https://www.health.gov.au/health-topics/pregnancy-birth-and-baby/newborn-bloodspot-screening#national-policy-framework Updated 24 November 2020 Standing Committee on Screening. *Congenital adrenal hyperplasia assessment summary*[144] https://www.health.gov.au/sites/default/files/documents/2020/02/newborn-bloodspot-screening-condition-assessment-summary-congenital-adrenal-hyperplasia_0.pdf Published 2020	The Standing committee on screening includes specified stakeholders including governmental representatives and a diversity of clinical expertise (includes different territorial representation).[53]	Based on the outcome of the detailed review, SCoS provides a recommendation for consideration to AHMAC. Where necessary the recommendation will be accompanied by preliminary cost implications. If the recommendation is supported by AHMAC, state and territory governments are then responsible for funding and establishing any other requirements around adding conditions, taking into account local contexts.[54] The example of congenital adrenal hyperplasia assessment summary can be found here *Stages of decision-making process*[54] 1. Proposal completed after seeking guidance from relevant experts. 2. Program Management Committee reviews proposal, makes recommendation	The detailed review provided to SCoS by the time-limited working group is conducted against agreed decision-making criteria (see table 3.5). At completion of the detailed review a recommendation is made to SCoS as to whether an economic analysis is needed and whether, based on the information assessed, the condition should be added to the program. SCoS arrives at a final recommendation.[54] Structured consideration of four elements: the condition, the screening test, the intervention, additional considerations. Jansen (2017) notes a consensus-based approach.[1]	Recommendations are categories for including a condition or dichotomous when removing a condition: 1. When considering including a condition in newborn bloodspot screening, possible recommendations include: ▪ screening is recommended ▪ a pilot is recommended and specific issues flagged for investigation ▪ based on the current evidence and understanding of a condition, screening is not recommended at this time. However, there may be merit in revisiting this condition in the future if further evidence emerges. ▪ Screening is not recommended.

Country Source(s)	Stakeholder involvement	Decision-making/recommendation-issuing authority	Decision-making process description	Qualification of recommendation
		3. Proposal and recommendation received by SCoS 4. Initial review conducted with input from clinical and programme experts 5. SCoS decision whether to review further 6. Detailed review by time-limited working group 7. Recommendation provided to SCoS. 8. In some cases an economic evaluation is required 9. SCoS arrives at a final recommendation 10. Recommendation provided to AHMAC via relevant Principal Committee. 11. If condition to be added, State and territory governments responsible		2. When considering removing a condition currently screened, possible recommendations include: • Continue screening. • Cease screening.
Canada (Alberta) Alberta Government. *Alberta Newborn Metabolic Screening Program - Policy document*[145] https://open.alberta.ca/dataset/77d4bdaa-3c1a-42ae-a1f3-4fcf221da53a/resource/4f4aaf	Stakeholders are involved, however it is unclear who specifically is included.[145]	Alberta Health Services determine the screening panel.	*(No information identified using search methodology applied in this review)*	*(No information identified using search methodology applied in this review)*

Country Source(s)	Stakeholder involvement	Decision-making/recommendation-issuing authority	Decision-making process description	Qualification of recommendation
db-f8ae-4806-aea8-686b8c3e7165/download/Newborn-Metabolic-Screening-Policy-2010.pdf March 2010				
Canada (Ontario) Newborn Screening Ontario. *NSO governance*[70] https://www.newbornscreening.on.ca/en/about-nso/nso-governance Updated - unclear Jansen et al. (2017)[1]	The membership of the Council consists of experts in the condition, screening, and health evaluative sciences from across the province. There are also ex-officio representatives from the CHEO Board, NSO, the Ministry of Health and Long-Term Care, and the Ministry of Children, Community and Social Services.[70]	NSO-AC is responsible for providing advice and guidance to NSO. The purpose of the NSO-AC includes providing provincial stakeholders a forum to directly influence the direction of current and future NSO programs, to guide and provide strategic advice to the NSO program in a changing rare disease and screening landscape, and to guide and advise the Ministry of Health and Long-Term Care and the Ministry of Children, Community and Social Services on matters related to the NSO program and newborn/childhood screening.[70]	The council meets a minimum of four times a year. For decision-making, quorum is set at 50% + 1, with a goal of decision by consensus.[70]	Jansen (2017) notes dichotomous recommendations (that is recommend screening or not recommend screening).[1]
Canada (Quebec) INESSS. *Advice on expanding the Quebec Newborn Blood Screening Program**[111] https://www.inesss.qc.ca/en/publications/publications/publication/advisability-of-	For the 2013 report, an expert committee was formed which was made up of 12 members including representatives from MSSS, patients, citizens and the	The MSSS ultimately decides which conditions should be screened for, taking into consideration the INESSS assessment. To establish the importance of screening for each disease,	In the 2013 report the Committee of Experts first determined the relative weighting (out of 100) of seven decision-making criteria:[138] The results were evaluated using the Evidence and Value: Impact on DEcision Making tool (EVIDEM)	In 2013, it was recommended that all 21 conditions should be screened for but that these should be brought in gradually in three waves (which take into account that some are detectable

Country Source(s)	Stakeholder involvement	Decision-making/recommendation-issuing authority	Decision-making process description	Qualification of recommendation
expanding-the-quebec-newborn-blood-screening-program.html Updated 24 September 2013 INESSS. *Assessment of the appropriateness of offering neonatal blood screening by MS/MS for seven inborn errors of metabolism already offered by urine screening** https://www.inesss.qc.ca/publications/repertoire-des-publications/publication/depistage-des-erreurs-innees-du-metabolisme.html Updated 16 September 2019 INESSS. *Neonatal Screening for Nine Inborn Errors of Metabolism**[75] https://www.inesss.qc.ca/en/publications/publications/publication/evaluation-de-la-pertinence-du-depistage-neonatal-sanguin-de-neuf-	different disciplines concerned by the screening of IEMs.[138] Re-assessments of conditions in 2019 and 2020 have been undertaken as individual assessments of conditions. These assessments were informed by contextual and experiential data obtained from: ▪ an advisory committee ▪ consultations with representatives of patient associations ▪ consultation with patients, parents and caregivers ▪ consultation of citizens	multi-criteria decision analysis was used to order conditions with regard to their appropriateness for screening.[138] For assessments completed in 2019 and 2020, recommendations were formulated for each individual condition assessed through deliberations by the INESSS excellence committee.	in order to assign a rank importance to each disease.[138] The 2019 and 2020 reports on individual conditions cite the use of a multi-criteria decision analysis grid to inform the formulation of recommendations.	by the same marker and therefore cannot be separated at this stage)[138] The 2019 and 2020 assessments collectively resulted in four positive recommendations and twelve negative recommendations for condition expansion. Jansen (2017) notes use of categorised recommendations.[1]

Country Source(s)	Stakeholder involvement	Decision-making/recommendation-issuing authority	Decision-making process description	Qualification of recommendation
erreurs-innees-du-metabolisme.html Updated 31 July 2020 INESSS. *Relevance of expanding the Newborn blood screening in Quebec**[138] https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Genetique/INESSS_Depistage_neonatal_sanguin.pdf Published 26 April 2013 Jansen et al. (2017)[1]	▪ a monitoring committee.			
Denmark Fischer et al. (2014)[78] Jansen et al. (2017)[1]	Fischer (2014) highlights stakeholder involvement in the assessment of MCADD and CAH :[78] ▪ Information provision: payer, patients, academia, HTA agency ▪ other type of participation: providers, government, HTA agency	*(No information identified using search methodology applied in this review)*	Jansen (2017) notes a qualitative scoring matrix approach.[1]	Jansen (2017) notes dichotomous recommendations (that is recommend screening or not recommend screening).[1]

Country Source(s)	Stakeholder involvement	Decision-making/recommendation-issuing authority	Decision-making process description	Qualification of recommendation
Germany Gemeinsamer Bundeausschuss (G-BA) Federal joint committee. *Early detection of diseases in children*[140] https://www.g-ba.de/english/ https://www.g-ba.de/themen/methodenbewertung/ambulant/frueherkennung-krankheiten/kinder/ Updated – unclear IQWIG. *General Methods.*[141] https://www.iqwig.de/en/about-us/methods/methods-paper/ Updated November 2020 G-BA. *The Federal Joint Committee and its Subcommittees.*[146] https://www.g-ba.de/downloads/17-98-2899/2021-03-01_G-BA_Grafik_Plenum-Unterausschuesse_EN_bf.pdf Updated March 2021	The Federal Joint Committee is a public legal entity comprising the four leading umbrella organizations of the self-governing German healthcare system: the National Associations of Statutory Health Insurance Physicians and Dentists, the German Hospital Federation, and the Central Federal Association of Health Insurance Funds. In addition to these four pillar organizations, patient representatives also participate in all sessions; they are entitled to put topics on the agenda, but not to vote.	The Joint Federal Committee has responsibility for screening processes. No later than two years after the guideline has come into force, the responsible subcommittee of the G-BA is expected to assess the success of Advanced Newborn Screening and recommend any changes to the regulations.	Jansen (2017) notes a consensus-based approach.[1] The plenary is made up of 3 impartial members, 2 members of the DKG (German Hospital Federation), 2 members of the KBV (National Association of Statutory Health Insurance Physicians), 1 member of the KZBV (National Association of Statutory Health Insurance Dentists) and 5 members of the GKV-SV (Federal Association of Statutory Insurance Funds). The subcommittee examines the consistency of the results and the transferability of the study results to the care context. In the case of screening examinations, these are additional requirements such as the determination of the test properties in a screening environment as well as recording the entire screening pathway.	Jansen (2017) notes dichotomous recommendations (that is, recommend screening or not recommend screening).[1] Every year the DGNS publishes a quality report on newborn screening with a two-year delay.[147]

Country Source(s)	Stakeholder involvement	Decision-making/recommendation-issuing authority	Decision-making process description	Qualification of recommendation
German Society for Neonatal Screening. *National Screening Report Germany 2018.*[147] https://www.screening-dgns.de/Pdf/Screeningreports/DGNS-Screeningreport-e_2018.pdf Jansen et al. (2017)[1]				
Italy* Istituto Superiore di Sanità (Higher Institute of Health). *Neonatal screening**[82] https://www.iss.it/screening-neonatali Updated – unclear Italian Ministry of Health. *Neonatal screening**[118] http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=1920&area=saluteBambino&menu=nascita Updated 3 March 2021	Yes - The Extended Neonatal Screening Working Group is made up of experts in the field of newborn screening, and representatives of institutions (Ministry of Health, Istituto Superiore di Sanità, AGENAS) and of rare disease patient associations.	*(No information identified using search methodology applied in this review)*	*(No information identified using search methodology applied in this review)*	*(No information identified using search methodology applied in this review)*
The Netherlands Jansen et al. (2021)[59] Health Council of the Netherlands. *Neonatal*	Stakeholders are included in process, both when programme is expanded with new disorders and in	Three governmental bodies are involved in the assessment and implementation of NBS: ▪ Ministry for Health, Welfare and Sport, which has political responsibility for	Jansen (2017) notes a consensus-based approach.[1] ▪ The GR has a pre-natal and neonatal screening committee	The committee distinguishes the following categories of conditions: Category 1: conditions that qualify for inclusion.

Country Source(s)	Stakeholder involvement	Decision-making/recommendation-issuing authority	Decision-making process description	Qualification of recommendation
screening recommendations[124] https://www.healthcouncil.nl/documents/advisory-reports/2015/04/08/neonatal-screening-new-recommendations Published 8 April 2015	evaluating the existing programme.	NBS and defines the NBS-policy, including the legal and policy framework. It is also responsible for the programme's funding and facilitation of the co-ordination of the programme, which is delegated to RIVM-CvB ▪ the GR, which is an independent national scientific advisory body, advises ministers and parliament on issues relating to public health ▪ RIVM-CvB, which coordinates the national NBS programme, directs NBS, and manages the implementation to ensure that the legal and policy frameworks, the public values, and clinical care are aligned.	which provides independent scientific advice. ▪ The Ministry decides whether or not the programme should be changed. ▪ The RIVM-CvB performs a feasibility study and advises on timelines for implementation of the conditions . ▪ For each condition, a final decision to start screening is made by the Ministry, based upon final advice by the RIVM-CvB. *Implementation framework* Go/no go framework developed in 2016. A condition-specific implementation plan is produced, based upon the framework.	Category 2A: conditions that require further study. Category 2B: conditions that may be considered for inclusion after weighing the advantages and disadvantages, including cost-effectiveness. Category 3: conditions that do not qualify for inclusion.
New Zealand NSU. *Newborn Metabolic Screening Programme Policy Framework*[127]	Yes, professional stakeholders engaged including colleges, consumers, organisations and	NSU Clinical Governance Group (the 'NMSP Technical Group' and the 'Antenatal and Newborn Screening Clinical Oversight Group') decide on the basis of information provided by the	Metternick-Jones et al. (2015) highlight the use of a comprehensive decision-making framework.[52]	Recommendations to the NSU Clinical Governance Group:[127] ▪ Recommend universal screening

Country Source(s)	Stakeholder involvement	Decision-making/recommendation-issuing authority	Decision-making process description	Qualification of recommendation
https://www.nsu.govt.nz/system/files/page/newborn_metabolic_screening_programme_policy_framework_june_2011.pdf Published June 2011 Jansen et al. (2017)[1] Metternick-Jones et al. (2015)[52]	groups on programme documentation and changes to the programme.[127]	NMSP Governance Team which conditions should be added.[127]	Jansen et al. (2017) note the use of a consensus-based approach.[1]	▪ Recommend targeted screening ▪ Recommend pilot study ▪ Recommend against screening. If endorsed, additional steps may include:[127] ▪ pilot studies ▪ development of treatment protocols ▪ documentation of laboratory requirements ▪ documentation of treatment options and funding ▪ consultation with treatment providers ▪ consultation with other providers ▪ development of referral pathways.
United Kingdom Public Health England. *Newborn blood spot screening: programme* [62] https://www.gov.uk/guidance/newborn-blood-spot-screening-programme-	Stakeholders are listed for each condition considered by the steering committee. Specific criteria are outlined for selection of organisations and	The UK NSC meets three times per year and makes recommendations on all aspects of population screening to ministers in the 4 UK countries.	Members are asked to move to a recommendation. The aim of the discussion at the UK NSC meeting is to make a consensus decision. Where a consensus is not achievable a voting system is used.[83]	The committee is asked to decide whether the:[83] ▪ current recommendation should be retained or whether further work is necessary before making a recommendation

Country Source(s)	Stakeholder involvement	Decision-making/recommendation-issuing authority	Decision-making process description	Qualification of recommendation
overview#conditions-screened-for Updated 8 November 2018 UK NSC. *Evidence review process*[83] https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process Updated 5 September 2017 UK NSC. *Criteria for appraising the viability, effectiveness and appropriateness of a screening programme*[128] https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme Updated 23 October 2015 UK NSC. *Appendix C: Stakeholder Information*[148]	individuals to be involved in the process. Groups include:[148] ▪ national groups representing patients and carers ▪ organisations representing healthcare professionals ▪ standard setting and guideline development bodies ▪ clinical expertise. A stakeholder review is undertaken during the commissioning stage to identify any potential new stakeholders in the review in question.[148]		The UK NSC receives all consultation responses at the meeting at which the review is discussed. Before the meeting the committee receives:[83] ▪ the evidence review showing the volume, direction and summary of the published literature ▪ a paper bringing together all consultation responses in full ▪ a cover sheet prepared by the evidence team which summarises the review project and includes a recommendation.	▪ topic should be archived or revisited as part of the regular review cycle. Where further evaluation is considered appropriate, the options may include primary research, systematic review, cost effectiveness assessment, modelling, or further rapid review.[83]

Country Source(s)	Stakeholder involvement	Decision-making/recommendation-issuing authority	Decision-making process description	Qualification of recommendation
https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/appendix-c-stakeholder-information Updated 5 September 2017 UK NSC. *Template for request to screen*[149] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/470130/UK_NSC_cover_sheet_template.pdf UK NSC. *Evidence Review Process*[83] https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process#when-a-proposal-is-made-to-modify-or-make-big-changes-to-a-current-screening-programme				
United States Health Resources and Services Administration. *Federal Advisory Committees – Nominate a condition*[150]	ACHDNC may invite up to 15 organisations to serve as Organisational Representatives.	Federal Advisory Committee. The final decision is made by the Secretary of Health and Human Services.[150]	The Committee discusses and deliberates on the evidence presented by the Condition Review Workgroup. The committee uses a decision matrix to guide their final decision.[150]	The recommendation by the Committee is expressed as a rating using the following classifications: A1-4, B1-4, C1-4, D 1-4 and L1-4. The

Country Source(s)	Stakeholder involvement	Decision-making/recommendation-issuing authority	Decision-making process description	Qualification of recommendation
https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/nominate.html Last reviewed 2020 Health Resources and Services Administration. *Heritable Disorders – About the Committee* **(151)** https://www.hrsa.gov/advisory-committees/heritable-disorders/about/index.html Last reviewed December 2020 Health Resources and Services Administration. *Evidence based reviews of Newborn Screening for Spinal Muscular Atrophy (SMA)***(152)** https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/sma-final-report.pdf Published 13 March 2018 Kemper et al. (2014)**(91)**	These representatives participate in ACHDNC meetings to provide relevant expertise and perspectives to committee members during their deliberations and discussions. Organisational Representatives do not vote and are not considered official members.(151)		The Committee votes to recommend or not recommend addition of the proposed condition to the RUSP for consideration by the Secretary of Health and Human Services.(150) Goldberg (2016) highlights the Advisory Committee's decision-making process includes assessing the net benefit of screening for proposed conditions, informed by systematic evidence reviews generated by the independent Condition Review Workgroup.	letter rating describes the net benefit to the population of newborns screened, while the number relates to the state's capability to offer comprehensive newborn screening.(91)

Key: ACHDNC Advisory Committee on Heritable Disorders in Newborns and Children; SCoS standing committee on screening; AHMAC Australian Health Ministers' Advisory Council; GR Health Council of the Netherlands; IEM Inborn errors of metabolism, MSSS Ministère de la Santé et des Services sociaux;

NSO-AC Newborn Screening Ontario Advisory Council; RIVM-CvB Centre for Population Screening of the National Institute for Public Health and the Environment; RUSP Recommended Uniform Screening Panel UK NSC UK National Screening Committee; NSO-AC Newborn Screening Ontario Advisory Council

*Accuracy may be impeded as documents translated using Google Translate

Table App 3.5: Criteria considered within decision-making

Country (Source)	Criteria used for decision-making
Australia Australian Government Department of Health. *Newborn Bloodspot Screening National Policy Framework* https://www.health.gov.au/health-topics/pregnancy-birth-and-baby/newborn-bloodspot-screening Last updated 24 November 2020	**The condition:** 1. The condition should be a serious health problem that leads to significant morbidity or mortality. 2. There should be a benefit to conducting screening in the newborn period. 3. The natural history of the condition, including development from latent to declared disease, should be adequately understood. **The screening test:** 4. There should be a suitable test protocol to identify the presence of the condition. 5. The test protocol should, on balance, be socially and ethically acceptable to health professionals and the public. **The intervention:** 6. Healthcare services for diagnosis and management should be available so that these services can be offered if there is an abnormal screening result. 7. There should be an accepted intervention for those diagnosed with the condition. **Additional considerations:** 8. The benefit of screening a condition must be weighed against its impact on the programme as a whole.
Canada (Alberta) Institute of Health Economics. *Alberta STE report Newborn Bloodspot screening for galactosaemia, tyrosinaemia type 1, homocystinuria, sickle cell anaemia, sickle cell/beta-thalassaemia, sickle*	Based on the Australian framework: ▪ The condition must be an important health problem and have a recognizable latent or early symptomatic stage. ▪ The test for each condition must be highly sensitive and specific, be validated and safe, have a relatively high positive and negative predictive value, and be acceptable to the target population, including important subgroups. ▪ The treatment for each condition must be effective, available, easily accessible, and acceptable to all patients with the recognized disease or condition. ▪ There should be clear evidence that screening and treatment leads to better outcomes than finding and treating the disease at a later stage. ▪ Systems should be in place for evidence-based follow-up assessment of all people with a positive screen, regardless of rurality, ethnicity, socioeconomic status, or disadvantage status.

Country (Source)	Criteria used for decision-making
cell/haemoglobin C disease, and severe combined immunodeficiency[104] http://www.ihe.ca/download/newborn_blood_spot_screening.pdf March 2016	▪ Ongoing management referral protocols must be established for individuals who have the condition detected through the screening program. ▪ The overall benefits of screening outweigh the harm.
Canada (Ontario)	*(Information on criteria not readily identifiable from the sources examined)*
Canada (Quebec) INESSS. *Relevance of expanding the newborn blood screening program in Quebec** https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Genetique/INESSS_Depistage_neonatal_sanguin.pdf September 2013 INESSS. *Assessment of the appropriateness of screening neonatal blood for biotinidase*	***Health Problem*** 1.1 The disease to be detected must constitute a significant health problem. 1.2 The epidemiology and natural evolution of the health problem, including the development of the latent state at the declared stage, are understood adequately [satisfactorily] and there is a risk factor, a marker of disease, latent condition or symptomatic stage early which make it detectable. 1.3 All feasible and effective primary preventive interventions were set up. ***Treatment*** 2.1 There is an effective treatment or intervention for patients detected by screening and evidence that early treatment provides better results than late treatment. 2.2 Evidence-based guidelines allow for determine which patients to treat and which treatments are appropriate for them. 2.3 The clinical management of the health problem and the results of the patient management must be optimal before participating in the Program (to ensure that screening and follow-up are carried out under the best clinical and administrative conditions). ***Screening test*** 3.1 The screening test must be simple, safe, precise and valid (sensitive and specific to the desired anomaly, applicable to large numbers). 3.2 The frequencies of appearance of the different values of the test for the target population must be known and a threshold used to determine a positive result must be defined and accepted. 3.3 The test is acceptable to the population.

Country (Source)	Criteria used for decision-making
deficiency (BIOT) https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Depistage/INESSS_DepistageNeonatal_Biotinidase.pdf Published 2020	3.4 There is an agreed guide to the additional clinical investigation concerning people with a positive screening result and options available to these people. ***Programme*** 4.1 The effectiveness of the Program in reducing mortality and / or morbidity has been proven by high quality studies. 4.2 It has been proven that the entire Program (testing, procedures clinical, treatment and intervention) is clinically, socially and ethically acceptable to healthcare professionals and the public. 4.3 The benefits of the Program are considered greater than the damages physical and psychological caused by tests, clinical procedures and treatments. 4.4 The opportunity cost of the entire Program must be judged reasonable compared to overall healthcare spending required. 4.5 There needs to be a programme management and monitoring plan integrating recognized quality assurance criteria. 4.6 The personnel and the installations necessary for the test, the interventions diagnosis, treatment and management of the Program should be available from the start of the Program. 4.7 Consideration should be given to all other options for managing illness (improving treatment, offering other services, for example) to ensure that there is no new, more effective intervention or that could not be done better with current resources. 4.8 Evidence-based information explaining the consequences of the test, diagnostic investigation and treatment should be made available to potential participants in order to help make an informed decision. 4.9 It is necessary to anticipate possible public pressures aimed at expanding screening eligibility criteria, reduce screening intervals and to increase the sensitivity of the test, and to be able to justify scientifically the decisions relating to these parameters. ***Additional considerations*** Efficacy, expert opinion, innocuity, and ethical considerations
Denmark	*(Information on criteria not readily identifiable from the sources examined)*
Germany Federal Committee. *Screening of newborns for early detection of type I*	The Joint Federal Committee reviews the screening program, and to update it if necessary with consideration of: ▪ mortality (overall survival, disease-specific survival) ▪ morbidity ▪ developmental disorder ▪ unwanted events

Country (Source)	Criteria used for decision-making
tyrosinemia using tandem mass spectrometry https://www.g-ba.de/downloads/40-268-4609/2017-10-19_Kinder-RL_Tyrosinaemie-Screening_TrG.pdf	▪ health-related quality of life of the child.
Italy	*(Information on criteria not readily identifiable from the sources examined)*
The Netherlands Health Council of The Netherlands. *Neonatal screening* https://www.healthcouncil.nl/binaries/healthcouncil/documents/advisory-reports/2005/08/22/neonatal-screening/advisory-report-neonatal-screening.pdf 2005 (Criteria from Genetic Screening report in 1994)	1. A genetic screening programme must relate to a health problem or to a condition which can lead to such a problem in those being tested or in their descendants. 2. The target group of the screening programme must be clearly defined. 3. The purpose of the programme must be to enable the participants to determine the presence or the risk of a disorder or carrier status, and to take a decision on the basis of that information. 4. Practical courses of action must be open to the participants. 5. Participation in a genetic screening programme should be completely voluntary and should be conditional on consent based on good information. 6. The target group should be supplied with good quality, comprehensible information. 7. A test method should be available which is suited to the objective of the screening. 8. There should be sufficient facilities for follow-up testing, to carry out the selected courses of action and to inform and support the participants. 9. The procedures used for the storage of medical information and cellular material must incorporate adequate measures to protect both the personal privacy of the participants and their rights regarding their personal data and cellular material. 10. If scientific research is carried out within the framework of screening, the participants should be properly informed about this in advance. 11. Provision should be made for continual quality assurance of the effectiveness, efficiency and safety of the test procedure, any follow-up work, as well as information and support given to the participants.

Country (Source)	Criteria used for decision-making
	12. When weighing up the benefits and drawbacks for the participants in the programme, the final balance should be clearly biased towards to benefits. To assist with this evaluation, those proposing a screening programme must provide information about: a. the prevalence of the disease or disorder in the target group; b. the natural course of the disorder, and the variation in degrees of severity; c. those target groups which are eligible for testing and the considerations which led to selection of the proposed target group and the proposed time of life for testing; d. the specificity, sensitivity and predictive value of the test method to be used and the burden which such testing imposes on participants; e. the available courses of action if a health problem or carrier status is revealed; f. the time allowed by the procedure for consideration and possible implementation of the choices made; g. the potential psychological, social and other repercussions (both positive and negative) of an offer and of participation or non-participation in the screening, for the person to be tested and for members of their family or for groups within the community; h. the likelihood of erroneous results, the possible consequences of this for participants and the measures taken to limit any harm which such an error might cause; i. what guarantees there are to prevent participants experiencing unjustified impediments (as a result of their participation or non-participation in the screening programme or follow-up testing) to obtaining employment or private insurance cover; j. The costs which are linked to the screening and to the attainment of the requisite infrastructure.
New Zealand NSU. *Newborn Metabolic Screening: Policy framework.* https://www.nsu.govt.nz/system/files/page/newborn_metabolic_screening_programme_policy_framework_june_2011.pdf	*The condition* ▪ Should be an important health problem potentially leading to significant morbidity or mortality, and for which early identification appears likely to be of benefit to the infant. In some disorders, a benefit for the family may be important, where the condition is untreatable and may lead to early mortality, but where a definitive diagnosis might be aided by the performance of the screening test. *The proposed test* ▪ Should be simple, safe, reliable, validated *The treatment* ▪ There should be established treatment or intervention which as the potential to prevent or ameliorate the clinical consequences of the disease. *What else will be found?* ▪ ethics: Harms/benefits, false positives

Country (Source)	Criteria used for decision-making
Published June 2011	▪ screening criteria ▪ test availability ▪ impact on the programme ▪ national considerations ▪ international considerations ▪ literature reviews ▪ opportunity cost. Template for Governance Team discussion can be found here.
United Kingdom UK NSC. *Criteria for appraising the viability, effectiveness and appropriateness of a screening programme* https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme Updated 23 October 2015	**The condition** ▪ The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood. ▪ All the cost-effective primary prevention interventions should have been implemented as far as practicable. ▪ If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications. **The test** ▪ There should be a simple, safe, precise and validated screening test. ▪ The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed. ▪ The test, from sample collection to delivery of results, should be acceptable to the target population. ▪ There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals. ▪ If the test is for a particular mutation or set of genetic variants the method for their selection and the means through which these will be kept under review in the programme should be clearly set out. **The intervention** ▪ There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered. ▪ There should be agreed evidence based policies covering which individuals should be offered interventions and

Country (Source)	Criteria used for decision-making
	the appropriate intervention to be offered. **The screening programme** ▪ There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened. ▪ There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public. ▪ The benefit gained by individuals from the screening programme should outweigh any harms, for example from over-diagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications. ▪ The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource. **Implementation criteria** ▪ Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme. ▪ All other options for managing the condition should have been considered (such as improving treatment or providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available. ▪ There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards. ▪ Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme. ▪ Evidence-based information, explaining the purpose and potential consequences of screening, investigation and preventative intervention or treatment, should be made available to potential participants to assist them in making an informed choice. ▪ Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

Country (Source)	Criteria used for decision-making
United States Kemper et al. *Evidence-based Review of Newborn Screening for Spinal Muscular Atrophy (SMA): Final Report* https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/sma-final-report.pdf Published 13 March 2018 Kemper et al.[133] *Review of SMA NBS Implementation* https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/sma-nbs-implementation-report.pdf	***Perrin et al. (2010) criteria*** ***(1) Information about the condition itself*** Is the condition well defined, what is its prevalence and incidence (including key clinical variations), and what is its natural history (including the spectrum of severity and variations by key phenotypic or genotypic characteristics). ***(2) Evidence regarding screening and screening tests*** What methods are available to screen newborns for the condition; what are their accuracy; their ability to distinguish early versus late onset cases; their sensitivity, specificity, and predictive values; analytic and clinical validity; and the feasibility of implementing these methods for universal screening? What are the potential harms or risks of screening? What is known about costs and cost-effectiveness of screening? What pilot testing has taken place in population studies or clinical groups? ***(3) Evidence regarding diagnostic methods*** What are the methods and costs of diagnostic testing (similar to those about the screening test) and availability and capability of diagnostic centres? ***(4) Evidence regarding treatment*** For treatment, does presymptomatic or early symptomatic treatment improve health outcomes and, if so, more than treatment after symptoms develop? What is known about the efficacy and effectiveness of treatment? What is the relationship between treatment timing and treatment outcomes? What are the potential harms or risks of treatment? Is treatment standardized, and where appropriate, is it Food and Drug Administration approved? ***(5) Economic evaluation*** The costs and cost-effectiveness of screening. What incremental costs are associated with the use of the screening test in (state) newborn screening programs? What are the costs of diagnosis and the failure to diagnose in the presymptomatic period? What is the availability of treatment and the costs associated with treatment? Kemper et al key questions from SMA report. Key topic and questions developed from general analytical framework ***Kemper et al. key questions (adding SMA to the RUSP panel)*** ***Natural History*** Key Question 1: What is the natural history and epidemiology with and without newborn screening? ***Screening- short-Term Follow-Up, and Diagnostic Confirmation*** Key Question 2: What is the evidence that newborn screening for the disease leads to improved health outcomes compared to usual clinical care? Key Question 3: Screening and short-term follow-up/diagnostic confirmation methods? (What is the analytic validity or clinical validity of the newborn screening approaches used to detect different forms of the condition using high-throughput methods in generalizable populations? What diagnostic testing methods are available to confirm or identify

Country (Source)	Criteria used for decision-making
Publication date not reported. Perrin et al. (2010) https://www.nature.com/articles/gim201024	these phenotypes? What screening or diagnostic methods, if any, are available to predict or inform age of onset or disease severity during newborn screening?) Key Question 4: What are the harms associated with newborn screening for the condition to the individual or the family? ***Treatment and Long-term Follow-Up*** Key Question 5: What are the standard treatments for the condition and evidence for their effectiveness? Do follow-up protocols exist for the management of the condition that do not require immediate initiation of treatment? What is known about the effectiveness of follow-up protocols in modifying intermediate health outcomes? Does early initiation of treatment improve primary health outcomes (overall survival, other important health outcomes) when the condition is caught early or through newborn screening compared with usual clinical care? How does this vary by phenotype Key Question 6: Does initiation of treatment modify the intermediate health outcomes when the condition is detected through newborn screening or other methods of presymptomatic detection and diagnosis in childhood compared with usual clinical care? How does this vary by phenotype? How strong is the association between changes in intermediate outcomes of (e.g., biomarkers) of the condition and changes in health outcomes? Key Question 7: What are the effects of treatment on secondary health outcomes? Key Question 8: What are the harms associated with treatments for the condition in early childhood, for symptomatic and presymptomatic patients? How does this vary by phenotype? Key Question 9: What is the impact of newborn screening on the Public Health of the population on projected numbers affected? Key Question 10: What is the impact of implementing newborn screening of the condition on the U.S. Public Health System? What is the status of U.S. state newborn screening programs in expanding screening panels to include the condition?

*Accuracy may be impeded as documents translated using Google Translate

Appendix 4: 'Go/no go' evaluation framework used in the Netherlands

Reproduced from: Jansen ME, Klein AW, Buitenhuis EC, Rodenburg W, Cornel MC. Expanded Neonatal Bloodspot Screening Programmes: An Evaluation Framework to Discuss New Conditions With Stakeholders. *Front Pediatr*. 2021 Feb 22 [cited 2021 Mar 31];9. [59] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7938310/

Supplementary table 1. ***Go / no go*** **framework**. To visualize the checklist a traffic light method was introduced. If the answer to a question does not hamper implementation, the right column contains a green square ☐. If the answer is not an acute obstruction to proceed with the implementation, but is not according to the initial expectations of the experts and/or further exploration is needed, the right column contains an orange triangle ▲. If the answer makes the expansion of the neonatal heel prick screening test with this condition impossible (for now), the right column contains a red circle ●.

- Condition (clearly defined, prevalence, incidental findings, mild variants, genetic carriers).
- Method of testing (number of tiers, test possible on dried bloodspots, amount of blood needed, analytes, cut-off points, post-analytical tool needed?, laboratory equipment and test kits, quality standards, interference of test with test on other conditions?, demands on logistics and personnel of laboratory).
- Predictive value (true positive, false positive, false negative) acceptable?
- Time of heel prick screening
- Transfer to cure (referral policy, policy for further diagnostics set?, known centre of expertise?, enough capacity in hospitals?)
- Consequences for the primary process of the heel prick screening?
- Organization of the screening in order?
- Changes in quality policy required?
- Adaptation of materials for communication and information needed?
- Information- and communication technology in order?
- Monitoring and evaluation possible?
- Ready for implementation?
- Effect on costs?

Conditions

a. Is the target disease for the screening defined without ambiguity? What are the envisaged findings?	
b. Is information available (within reasonable margins) on the prevalence of the condition in the Netherlands or internationally?	
c. Are there secondary findings that might be detected after following the various test steps? What secondary findings might be detected? Is information available for all possible incidental findings regarding prevalence, clinical relevance and the extent to which they are treatable? Is information available on how detection of these secondary findings may affect the benefit-risk ratio of screening? Is this effect acceptable? Can the secondary findings be shielded? If not, should the secondary findings be reported? If so, is information available on how that will take place?	
d. Will the screening detect mild variants of the condition? Is information available for these mild variants regarding prevalence, clinical relevance and the extent to which they are treatable? Is information available on how detection of these mild variants may affect the benefit-risk ratio of screening? Is this effect acceptable?	
e. Will the screening also identify genetic carriers of the condition? Is information available on what that carrier status means for those involved, in a physical and psychological sense? Is information available on how identification of these carriers may affect the benefit-risk ratio of screening? Is this effect acceptable? Do the genetic carriers have to be reported? If so, is information available on how that will take place?	

Testing method

a. Is information available on the different test steps?	
b. Can the different test steps be performed on the available dried blood spot samples?	
c. Is information available on how much blood/sample material is needed for the different test steps? Is this amount of blood/sample material available?	
d. Do the different test steps place any exceptional requirements on storage of the blood/sample material? Can these requirements be met?	

e. Have the analytes for testing and the corresponding cut-off points (including those of any ratios or algorithms to be used) for the various test steps been determined, including for exceptional groups?	
f. Are post-analytical tools needed to achieve acceptable (clinical) sensitivity and specificity? If so, is the use of these post-analytical tools possible (from the start of screening)?	
g. Is information available on which equipment and test kits are needed to carry out the various test steps? If so, are these devices and test kits available?	
h. Are commercial tests of sufficient quality available for the various test steps, and do they offer sufficient guarantees for continuity of supply? If not, are other suitable tests available?	
i. Are the characteristics of the tests (analytical precision, accuracy, sensitivity and specificity) compliant with current quality standards?	
j. Do one or more test steps interfere with testing for other conditions? If so, is this acceptable or can it be changed in good time?	
k. Is information available on the requirements imposed on the laboratory set-up for implementation of the different test steps? Can these requirements be met at the start of screening?	
l. Is information available on what implementation of the different test steps will require in terms of laboratory logistics and personnel? Can the laboratories meet these requirements at the start of screening?	

Predictive value

a. What numbers of TP, FP and FN results are produced by the successive test steps? Are the numbers of FP and FN results after following the various test steps considered acceptable? *Provisional estimate (per year):*	

TP – True positive	
FP – False positive	
FN – False negative	

Timing of blood sampling

a. Do the different test steps place any exceptional requirements on the timing of the neonatal blood spot screening? Can these specific requirements be met? If not, are the consequences for the benefit-risk ratio of screening considered acceptable?	

Healthcare and transfer to cure

a. Has the referral policy including referral terms been established, also for the Dutch Caribbean? Are those involved aware of this policy?	
b. Has the policy for further diagnostics and treatment been established, also for the Dutch Caribbean? Are those involved aware of this policy?	
c. Is it clear which centre of expertise is involved in diagnostics and treatment? What is the role of this centre of expertise? Are those involved aware of this?	
d. Is it clear how the screening will impact healthcare capacity (in terms of scope, expertise and funding)? Is this capacity available at the time that screening will start, or can it be made available?	

Primary process

a. Does the expansion of the neonatal heel prick screening to include this condition affect the primary process of the heel prick screening programme?	
b. Is an in-house test being used? If so, can all additional measures be taken in time for the condition to be added?	
c. Is sex selection applied during screening? If so, can all additional measures be taken in time for the condition to be added?	

Organisation, tasks and responsibilities

a. Is the organisation of the programme and of the various parties involved in the programme (particularly the Centre for Population Screening, the Department for Vaccine Supply and Prevention Programmes, screening laboratories, the reference laboratory, diagnostics and healthcare) sufficiently well-structured that the condition can be added to the neonatal heel prick screening programme?	

Quality policy

a. Does the scenario need to be adjusted?	

b. Is it necessary to adjust the national quality requirements (in the roadmap), and is it possible to do so in good time?	
c. Is it necessary to adjust the guidance for healthcare providers (or arrange for it to be adjusted) and is it possible to do so in good time?	
d. Does the expansion of the neonatal heel prick screening to include this condition have consequences for quality assurance? If so, can these consequences be mitigated? If so, by whom and how?	
e. Is it possible (e.g. by organising national or regional meetings, adapting e-learning modules and providing instruction sessions for screeners) to promote expertise for the expansion of the neonatal heel prick screening to include this condition for the various groups of professionals within the given time frame?	

Information and communication

a. Is it necessary and possible to arrange additional informed parental consent for the expansion of the neonatal heel prick screening to include this condition?	
b. Is it necessary and possible to adjust the general information materials for the expansion of the neonatal heel prick screening to include this condition?	
c. Is it necessary and possible to develop new results letters for the expansion of the neonatal heel prick screening to include this condition?	
d. Is it necessary and possible to adjust the Good Result Message for the expansion of the neonatal heel prick screening to include this condition?	
e. Is additional information needed for the RIVM Information Point and, if so, can this be achieved in time?	
f. Is additional information needed for the RIVM website (such as one or more FAQs) and, if so, can this be achieved in time?	

Data management

a. Will the new information system NHS (nwPraeventis) and the new LIMS be available in time to add this condition? If not, is it possible to adapt Praeventis and NEONAT in good time to support the newly added condition (or arrange for that to happen)? If not, are alternatives available with regard to data management?	

b. Is the ICT functionality flexible enough to handle the necessary process steps with regard to the heel prick card, add new letters to the system, set up short-cycle monitoring and log new indicators?	
c. Do the NEORAH and/or DDRMD database (registration database for metabolic diseases) need to be adapted? If so, can this been achieved in good time (including testing) before the start of the national screening?	

Monitoring and evaluation

a. Is it possible to subject the number of referrals and the number of repeated first heel pricks to short-cycle monitoring?	
b. Is it possible to closely monitor the results of diagnostics and the timely nature of diagnostics for this condition?	
c. Is it possible to develop new indicators for this condition to monitor the primary process properly?	
d. Is it possible to develop new target and signal values for this condition?	
e. Is it necessary and possible to set up Long Term Follow Up for this condition? If so, what is the time frame and what would be needed for that?	

Caribbean Netherlands

a. Does the NHS-CN roadmap need to be adapted in terms of tasks and responsibilities for the new condition? If so, is it possible to achieve that adjustment?	
b. Is it necessary and possible to set up a pilot shipment to test whether the high temperatures and air humidity in the Caribbean Netherlands negatively affect the reliability of the analyses carried out in the screening laboratory in relation to the condition to be added? Will the results of that pilot be known in time for the condition to be added to the programme?	
c. Is it possible to arrange: a follow-up protocol for diagnostics and treatment of this condition, and approval in writing and confirmation by the BES Healthcare Office and by the Ministry of Health, Welfare and Sport arising from this follow-up protocol as a prescribed care path?	

Implementation

a. Does a tendering procedure still need to take place before the new condition can be added to the neonatal heel prick screening programme? If so, is this tendering procedure expected to be completed on time?	
b. Does anything need to be adapted in the legal regulations for the European or Caribbean Netherlands? If so, can this be achieved in time?	

Costs

a. Is it clear what the effect will be on the structural costs of adding the new condition, and is this effect included in the price of neonatal heel prick screening?	

Appendix 5: US decision matrix

US Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) decision matrix for the recommendation of a nominated (proposed) condition.[150]

NET BENEFIT/ CERTAINTY			READINESS			FEASIBILITY	
			Ready	Developmental	Unprepared		
SIGNIFICANT Benefit	Certainty	HIGH	**A1** Screening for the condition has a high certainty of significant net benefits, screening has high or moderate feasibility. Most public health departments are ready to screen.	**A2** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments have only developmental readiness.	**A3** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments are unprepared for screening.	Feasibility	HIGH or MODERATE
			A4 There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.				LOW
		MOD	**B 1-4** There is moderate certainty that screening would have a significant benefit.				----
Small to ZERO Benefit	Certainty	MOD/HIGH	**C 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a small to zero net benefit.				----
NEG Benefit			**D 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a negative net benefit.				----
---		LOW	**L 1-4** There is low certainty regarding the potential net benefit from screening.				----

Appendix 6: Decision-making matrix for use by EU member states' programmes

The following model was proposed in 2011 by the European Union Network of Experts on Newborn Screening as a model for use by EU NBS programmes to systematically inform the expansion (or contraction) of screening mandates. Reproduced from Cornel et al.[88]

1. Does your country or health-care jurisdiction have a neonatal screening program?
    a. If no: start neonatal screening for congenital hypothyroidism (the reason for the choice of congenital hypothyroidism is twofold: (1) congenital hypothyroidism is (one of) the most prevalent congenital disorders, the prevalence being largely independent of ethnicity; (2) the screening and confirmatory methodology is relatively simple. All European countries that contributed to the current Practices Document (http://www.iss.it/cnmr/prog/cont.php?id=1621&lang=1&tipo=64) screen for congenital hypothyroidism.).
2. If YES, consider disorders for which a neonatal screening program exists elsewhere, or for which research shows promising results. For each disorder:
    a. Can, according to international experience, considerable, irreparable damage be prevented by neonatal screening or other benefits for the patient and the family be achieved? Assessment includes:
        I. The condition sought should be an important health problem (W&J1).
        II. There should be an accepted benefit for patients with recognized disease (W&J2).
        III. There should be a recognizable latent or early symptomatic stage (W&J4).
        IV. The natural history of the condition, including development from latent to declared disease, should be adequately understood (W&J7).
    b. Is, according to international experience, a good test available? (Sensitivity, specificity, positive predictive value and acceptability) Assessment includes:
        I. There should be a suitable test or examination (W&J5).
        II. The test should be acceptable to the population (W&J6).
        III. There should be an agreed policy on whom to treat as patients (W&J8).
3. If both questions YES, consider desirability in your country/region:
    a. Is the disorder an important health problem *in your country*?
    b. Is the test acceptable for the population from cultural/ethical perspective (unintentional findings; carrier status; mild and late-onset forms).
4. If the previous questions are answered YES, consider the feasibility:
    a. Compare the burden of the disorders for the health system with the cost of screening, with a view to ensuring equity of access to healthcare and considering other feasible options.

I. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole (W&J9).

II. What is the birth prevalence of the disorder(s)?

b. Can facilities be made available for adequate surveillance, prevention, treatment, education, counseling and social support? Assessment includes:

I. Facilities for diagnosis and treatment should be available (W&J3).

II. Case finding should be a continuing process and not a 'once and for all' project (W&J10).

III. Is a good test available in your country?

IV. Are sufficient diagnostic specialists available?

V. Is treatment available in your country?

VI. Are sufficient treatment specialists available?

VII. Are there patients' associations which may provide support to the patient and/or the family?

5. If NBS is considered desirable and feasible, take care of adequate quality of the program, including:

a. Training of relevant health-care providers.

b. Information to prospective parents.

c. Informed consent, both general and specific, on communication of carrier status information and sample storage for research use.

d. Procedures for blood spot sampling, laboratory handling and storage of cards.

e. Protocols for communication of health-care providers in case of positive results.

Published by the Health Information and Quality Authority (HIQA).
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