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# A landscape assessment of newborn screening (NBS) in Europe

## Executive summary

Newborn screening (NBS) has become an integral part of many public health programmes.[1] NBS programmes have minimised patient suffering which results from extended diagnostic pathways, as well as the irreversible damage to health due to late diagnosis. Furthermore, they have played a role in diminishing the longer-term disease burden on healthcare systems. NBS offers the prospect of diagnosis and treatment of serious conditions at an early stage, often prior to the onset of symptoms. Patients stand to gain the greatest benefit from treatment where it can be initiated in time to halt any irreversible disease progression and subsequent damage. Whilst the benefits of NBS are well established, there are important disparities across Europe in the number of diseases included in the panel of tests conducted on newborns – ranging from over 25 diseases in some countries, to as few as two in others. In recent years, we have seen encouraging increases in the number of rare diseases for which effective treatments are available.[2] If this trend continues, it promises substantial positive impact for both patients and healthcare systems, when combined with early diagnosis and the timely initiation of treatment. Many NBS programmes across Europe have recognised the need to utilise advances in clinical science and consequently have expanded the number of diseases for which they screen. As the treatment landscape for rare diseases and gene therapies evolves, the role of NBS as a critical driver of value and efficiency for European healthcare systems increases. NBS also encompasses equity and human rights dimensions. It helps reduce population health inequities, which could arise from unequal access to high quality diagnostic and treatment services.

This paper provides insights from a policy landscape assessment conducted between October 2020 to October 2021, outlining the differences in the composition and functioning of NBS programmes across 30 European countries. In addition, the paper looks to explain the observed differences through comparative analysis of specific policies governing periodic updates to NBS panels and explores the interplay of stakeholders involved in this process. Finally, this paper articulates the implications for policy change needed to make NBS programmes more patient-focused and better fit for purpose, as well as the role that decision-making stakeholders should play in driving the change towards optimising the positive impact of NBS programmes on patients and healthcare systems in the future.

## Background

Screening is the process of identifying members of a population who may have, or may be at risk of developing, a specific disease or condition. This generally involves the use of tests across a population in order to identify individuals who have certain risk factors (e.g. genetic) or are in the early stages of disease but are asymptomatic. An underlying concept of screening is that early detection benefits a patient's clinical outcomes and the healthcare system's public health outcomes.[3] A powerful example of this is newborn screening, which forms an integral part of public health programmes and has demonstrated a positive impact on patients and healthcare systems alike.[4]

Newborn screening using a dried blood spot is currently undertaken in all European countries. It involves the extraction of a few drops of blood from a baby's heel and is used to detect a variety of disorders which may hinder the baby's development, significantly impacting their future health and, in some cases, causing a premature death. Ideally, screening occurs within the first few days of a newborn's life. Detection, diagnosis and intervention resulting from NBS can support the mitigation of severe health problems at the earliest opportunity. Importantly, this not only provides physicians with a broader set of treatment and care options but also maximises the clinical benefit of treatment and disease management for patients.[5] For healthcare systems, a well-developed NBS programme can reduce waste by maximising direct clinical outcomes.[6]

In recent years, many NBS programmes across Europe have experienced some expansion, increasing the total number of diseases for which they screen.[7] This has partially been driven by increasing uptake of the technological capabilities that enable NBS, a key example being the application of tandem mass spectrometry.[8] Tests using tandem mass spectrometry for NBS are relatively inexpensive and can quickly process large numbers of samples.[9] Such technological developments have made a significant impact on both the number and types of diseases that can be screened.

An additional key factor driving the expansion of NBS programmes is the notable increase in the number of treatments, including gene therapies, that are now available to treat previously intractable rare diseases with few, if any, adequate treatment options. For some diseases, there is a markedly greater benefit to be derived from early and pre-symptomatic diagnosis and prompt treatment. Thus, there is an increased importance of NBS as a healthcare system, value-maximising, public policy tool in Europe. At the national level, NBS has become a regular feature of rare disease plans, with numerous countries developing policies to improve their NBS programmes.[10] At the European level, the EU Joint Action for Rare Diseases has supported this by calling for Member States to broaden the number of diseases included on their national screening panels. These efforts have been further championed by key stakeholders, such as EURORDIS, ISNS and IPOPI, who have worked individually and collaboratively to highlight the need to further develop and expand NBS programmes across Europe.[11,12]

Given the growing importance of NBS, this paper will: (a) provide insights on the differences in the current composition and functioning of NBS programmes across European countries; (b) explain the observed differences through comparative analysis of specific policies governing the periodic updates to NBS panels and (c) explore the interplay of stakeholders involved in this process. Finally, this paper will articulate the implications for policy change needed to make NBS programmes more patient-focused and suited for purpose, as well as the role that various stakeholders should play in driving the change towards optimising the positive impact of NBS programmes on patients and healthcare systems in the future.

## Methodology

To determine the current landscape for NBS programmes across Europe, we first conducted high-level research into national or regional/provincial NBS programmes across 30 countries and developed a comparative mapping, capturing the differences in NBS programmes across European countries.[13] Collation of information regarding the current number and type of diseases included in each country's NBS programme was used to develop a comparative "NBS matrix". This matrix was summarised in an infographic highlighting the differences in the diseases included in NBS programmes across Europe (see Figure 1 below). Further analysis involved a review of the current NBS literature using a predetermined information framework, drawing on academic papers, government reports and other grey literature. Following validation of this with in-country experts, we identified the fundamental aspects of each country's NBS programme and compared their similarities and differences across areas such as funding, management and the implementation time of recently approved panel expansions.

The second phase of our research involved an analytical deep-dive into NBS programmes that were deemed collectively representative of pan-European diversity. This analysis focused on the key national policies and regulations that govern NBS, as well as the stakeholders and institutions involved in the decision-making process. We investigated three key components of these national NBS programmes: the process of panel expansion, the role of national and cross-country policies and the involvement of key (non-)decision-making stakeholders.

To obtain a representative understanding of the broader NBS landscape across Europe, we selected 12 countries which are listed below in Table 1. The selection aimed to represent different geographical regions of Europe, as well as variation in levels of GDP/capita and types of healthcare systems. Following selection, each country was analysed to identify strengths and weaknesses in their NBS programmes. These findings were used to inform the identification of common themes across countries and the subsequent development of recommendations around the future evolution of NBS programmes across Europe.

**Table 1: Country selection criteria for the "deep-dive" analysis**

| Country | GDP/capita (US$)[14] | Healthcare system classification | Region |
|---|---|---|---|
| Sweden | 50,339 | National Health Services | Northern |
| Norway | 67,989 | National Health Services | Northern |
| United Kingdom | 39,229 | National Health Services | Western |
| France | 39,257 | Social Health Insurance | Western |
| Germany | 45,466 | Social Health Insurance | Western |
| Switzerland | 81,867 | Social Health Insurance | Western |
| Spain | 26,832 | National Health Services | Southern |
| Italy | 30,657 | National Health Insurance | Southern |
| Portugal | 21,608 | National Health Services | Southern |
| Poland | 15,304 | Social Health Insurance | Central and Eastern |
| Russia | 9,972 | Social based mixed system | Central and Eastern |
| Hungary | 15,373 | Social Health Insurance | Central and Eastern |

## Key findings

### Current European NBS landscape

As illustrated in the "NBS matrix" (Figure 1), we found that there are large disparities between countries in the number and types of diseases that are included in national NBS programmes. For example, some countries such as Italy, Portugal and Austria, screen for over 25 diseases as part of their national panel[15], with Italy leading the way in Europe by screening for more than 45 diseases. By contrast, many countries were found to screen for significantly fewer diseases, with the UK and France both testing for less than 10 diseases in their national panels, whilst Romania and Cyprus are only testing for two.

Figure 1 also highlighted trends in the frequency that each disease is included across NBS programmes, with phenylketonuria (PKU) and congenital hypothyroidism (CHT) being universally screened for across all 30 countries in-scope. It is noted that they have a relatively high incidence compared to other screened diseases (both have incidences of greater than 1 in 10,000, whilst other diseases included in programmes can have incidence rates as low as 1 in 250,000).[16] However, there are other diseases which have similarly high incidence rates, such as spinal muscular atrophy and sickle cell disease, that are nationally screened for in less than 30% of countries.

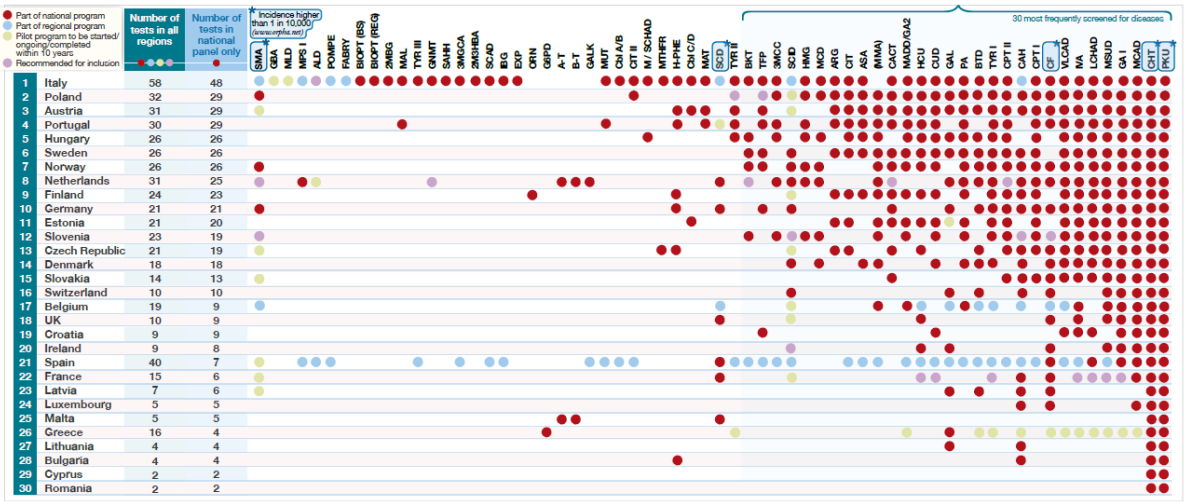
Comparisons of the key characteristics of NBS programmes across countries also provide some insights to explain differences in access to NBS. This includes elements such as:

- **Programme governance** – NBS programmes are run by governing bodies, which tend to operate at the national level, but can also be found regionally. In some cases, such as Spain, there are regional differences in NBS disease coverage, with some autonomous regions, such as Catalonia, testing for over 20 different diseases, whilst the national programme tests for less than 10.

- **Review process** – There are notable differences in the process by which countries update their NBS programmes. Some, such as the UK, do this on a recurring basis (e.g. annually), whilst others, such as Germany, do this on an ad-hoc basis.

- **Time to implementation** – There are challenges related to NBS programme expansion following approval of inclusion of new diseases, resulting in large variations in the implementation time across countries. Where some countries have taken less than one year to implement the most recent approval into their NBS programme (Denmark, Belgium and UK), implementation of decisions in other countries took three or more years (Greece, Romania and Portugal).

**Figure 1: Mapping of disease inclusion in NBS panels across 30 European countries**




Largescale version of Figure 1 provided on page 10

Source: CRA analysis; see end of document for disease abbreviations.

### Deep-dive assessment: Key barriers to panel expansion and implementation

Many countries have set themselves a goal to improve NBS. Government objectives are typically published in rare disease plans or national policies, mandating NBS programme improvements. This has been evident in numerous countries, such as France.[17] National policies act as a driver to include more diseases in NBS panels in some countries (e.g. Poland's current plan for screening programme expansion from 2019-2022). However, other countries, including the UK and Spain, which have both seen policymakers signal their intent for programme and national policy improvements, but have seen limited or no national panel expansions in recent years.

As such, while government mandates to improve NBS programmes are important, there are other key factors which drive NBS panel expansion. We have grouped these factors based on when they arise in the process:

#### 1. Factors affecting proposals for disease inclusion in the NBS panel

The first core process entails ensuring that proposals for disease inclusion in the NBS panel are on the agenda for the relevant decision-making bodies (e.g. HTA bodies or screening committees). Factors which impact this include: the involvement of non-decision-making stakeholders (e.g. patient advocacy groups) in increasing awareness and knowledge of the disease; the transparency, regularity and ease of the proposal submission process; and relevant resources and funding to support consideration of screening for an additional disease.

#### 2. Factors affecting review and approval

The review and approval of additions (and withdrawal) of diseases from the screening panel centres around the evaluation of proposals for disease inclusion (and exclusion). This entails ensuring that the evaluation criteria for inclusion are appropriate, clear and transparent (e.g. use of the Wilson and Junger criteria[18]); that timelines for review are carried out in a timely manner; and that external stakeholders are involved in the evaluation process, so that they can provide specialist expertise and/or patient perspectives.

### 3. Factors affecting implementation

The implementation process and the adherence to any timelines will be driven by key factors including having the necessary infrastructure and clinical expertise needed to carry out testing, as well as being able to allocate the level of funding that is needed to support the expansion of the NBS panel. Importantly, political willingness to support implementation timelines is also critical, as highlighted by policy in the UK which mandates implementation in England and Wales within 12 months of approval. In addition, where countries have a centralised national laboratory, other factors, such as government procurement policies, can also slow implementation times. This is seen in the Netherlands, where there is a lengthy tender process.

Upon developing the core processes, further analysis of the key factors that drive or inhibit NBS panel expansion led to the identification of 'key barriers', which could limit access to newborn screening. In addition to this, 'best practices' which contribute to addressing some of the identified challenges were also mapped across countries. See Table 2 below.

**Table 2: Barriers and best practices to improving NBS**

| Barriers | Best practices |
|---|---|
| • Complicated or undefined process for proposing panel expansion<br>• Infrastructure requirements (e.g. laboratory or staff) limit the rate of implementation of NBS expansions<br>• Lack of obligation to act on comments from non-decision-making stakeholders<br>• Variation in enforcement of implementation post-approval<br>• Lack of funding to support screening expansions<br>• Inconsistencies in evaluation processes among countries<br>• Criteria to demonstrate the value of screening | • Clear government mandates to improve NBS programmes<br>• Presence of a governance system to oversee NBS programme coverage<br>• Open and transparent application process for proposing programme amendments<br>• Horizon scanning and outward-looking policy evaluations<br>• Receptivity to non-decision-making stakeholder involvement in shaping the NBS agenda and evaluation process<br>• Adoption of clear criteria (e.g. Wilson and Jungner) to substantiate diseases inclusion<br>• Appropriate follow-up and referral pathways<br>• Political willingness to facilitate timely implementation (e.g. within 12 months) |

## Policy recommendations

Based on the identification of barriers and best practices, we have developed a set of policy recommendations for policymakers and other key stakeholders (including PAGs and KOLs) with influence on the NBS policy environment, to address these challenges and support future evidence-based expansion. These have been categorised in line with our three identified core processes:

**1. Factors affecting proposals for disease inclusion**

- NBS decision-making bodies should ensure regular consideration of proposed additional tests, as is done by countries such as UK and Norway.
- A periodic review process should be implemented for diseases already included in NBS programmes to mitigate against declines in their risk-benefit profile and highlight if a disease should no longer be included in a country's NBS panel.
- Engagement of patient professional representatives (e.g. patient advocacy groups and clinical experts) can drive political support for the establishment of national screening committees and enabling NBS expansion.
- Payers should ensure sufficient funding is in place for programme expansion, within scope.
- International collaboration between health decision-makers is needed to support wider considerations of evidence-based expansion proposals by aligning on consistent criteria for including new diseases into NBS programmes.

**2. Factors affecting review and approval**

- Decision-making bodies should be transparent in stating their processes, evaluation criteria and evidence requirements to facilitate the submission of panel expansion proposals.
- NBS decision-making bodies across (and within) countries should ensure their criteria are aligned to promote efficient evaluation processes, e.g. align on any criteria used to extend requirements from those of Wilson and Jungner.
- Authorities should consult patient and physician representatives at each stage of the expansion process to evaluate the inclusion of any additional diseases in the screening panel.
- To increase the transparency of decision-making on the inclusion of a new test, there should be a commitment to providing an explanation of how stakeholder input was evaluated and considered in the decision-making process.
- Assessments should consider the availability and clinical benefit of relevant treatments when assessing the potential value of a screening test for a specific disease.

**3. Factors affecting implementation**

- Countries should conduct mapping exercises of current laboratory locations and capabilities, to ensure that future updates to NBS programmes are implemented in a timely manner. Current barriers include the introduction of the test to the laboratories, as well as the design and introduction of the activities required following a positive test (e.g. diagnostic reconfirmation and patient and parental follow-up).
- Timely implementation of NBS needs to be incentivised through policy directives e.g. by the setting of targets around implementation timelines

## Conclusion

While there have been developments in NBS programmes across Europe in recent years, the increasing availability of genetic testing and advanced screening techniques, coupled with new, highly effective treatments should prompt countries to progress their NBS programmes further. More efficient and accelerated processes for NBS panel expansion will align the advancement of these programmes with the speed of medical innovation, maximising the benefit delivered to patients and healthcare systems. To do so, national and regional authorities should look to ensure that:

1. The expansion process is transparent and well equipped to facilitate efficient and timely evaluation of NBS expansion proposals.
2. The evaluation process for disease inclusion is transparent and includes input from external stakeholders, such as clinical experts and patient advocacy groups.
3. Appropriate funding and resources are dedicated to both testing infrastructure and clinical expertise to ensure efficient implementation of additional NBS tests after approval.

## Authors and transparency notice

**Tim Wilsdon** is a vice president, **Rowan Saada** is an associate and **Milan Ferguson** is an associate in the Life Sciences Practice at Charles River Associates (CRA).

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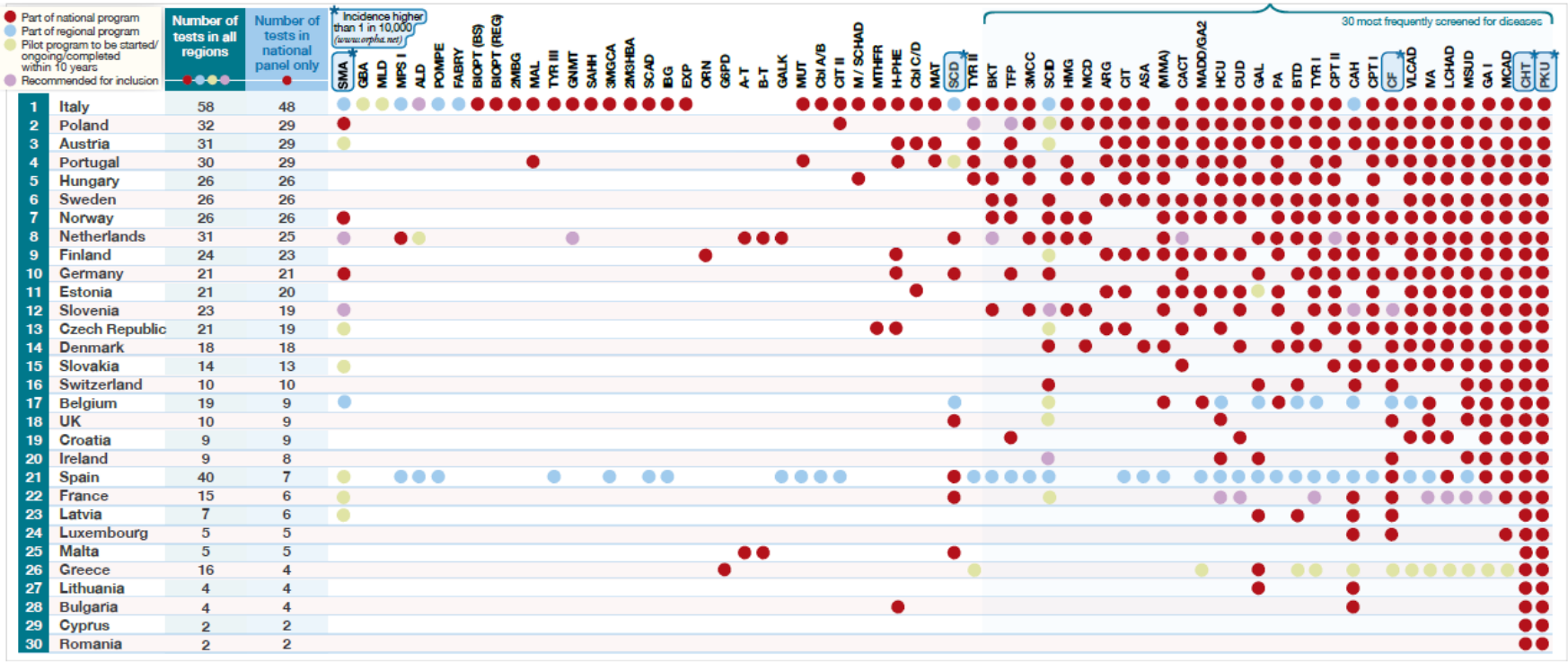
## Contacts

**Tim Wilsdon**
Vice President
+44-20-7664-3707
**twilsdon@crai.com**

**Rowan Saada**
Associate
+44-122-378-3925
**rsaada@crai.com**

**Milan Ferguson**
Associate
+44-207-664-3606
**mferguson@crai.com**

**Figure 1: Mapping of disease inclusion in NBS panels across 30 European countries**




Source: CRA analysis; see end of document for disease abbreviations.

## Abbreviations

- 2M3HBA = 2-Methyl-3-hydroxy butyric aciduria
- 2MBG = 2-Methylbutyryl-CoA dehydrogenase deficiency
- 3MCC = Deficit of 3-methylcrotonyl-CoA carboxylase deficiency
- 3MGCA = 3-methylglutaconic aciduria
- ARG = Arginase deficiency
- ASA = Argininosuccinic aciduria
- A-T = Alpha thalassemia
- BIOPT (BS) = Biopterin cofactor biosynthesis deficiency
- BIOPT (REG) = Biopterin cofactor regeneration deficiency
- BKT = Deficit of Beta-ketothiolase
- B-T = Beta thalassemia
- BTD = Defect of biotinidase
- CACT = Carnitine/acyl-carnitine translocase deficiency
- CAH = Congenital adrenal hyperplasia
- Cbl A = Methylmalonic acidemia
- Cbl B = Methylmalonic acidemia
- Cbl C = Methylmalonic Acidemia with Homocystinuria
- Cbl D = Methylmalonic acidemia with homocystinuria
- CF = Cystic fibrosis
- CHT = Congenital hypothyroidism
- CIT = Citrullinemia type I
- CIT II = Citrullinemia type II (Citrine deficiency)
- CPT I = Carnitine palmitoyl-transferase (L) deficiency
- CPT II = Carnitine palmitoyl-transferase II deficiency
- CUD = Lack of carnitine transport
- EURORDIS = European Rare Diseases Organisation
- EXP = Short-chain acyl CoA dehydrogenase deficiency
- FABRY = Fabry disease
- G6PD = Glucose-6-phosphate dehydrogenase
- GA I = Glutaric acidemia type I
- GA2 = Glutaric acidemia type II
- GAL = Galactosemia
- GALK = Galactokinase deficiency
- GBA = Gaucher disease
- HCU = Homocystinuria (CBS deficiency)
- HMG = 3-Hydroxy-3-methyl glutaric aciduria
- H-PHE = Benign hyperphenylalaninemia
- IBG = Isobutyrril-CoA dehydrogenase deficiency
- IPOPI = International Patient Organisation for Primary Immunodeficiencies
- ISNS = International Society for Neonatal Screening
- KOL = Key opinion leader
- IVA = Isovaleric acidemia
- LCHAD = Long-chain hydroxyacyl CoA dehydrogenase deficiency
- M / SCHAD = Short / medium chain 3-OH acyl-CoA dehydrogenase deficiency
- MADD = Multiplex acyl-CoA dehydrogenase deficiency
- MAL = Malonic aciduria
- MAT = Methionine adenosyltransferase deficiency
- MCAD = Medium-chain acyl CoA dehydrogenase deficiency
- MCD = Multiple carboxylase deficiency
- MMA = Vitamin B12 deficiency
- MPS I = Type I mucopolysaccharidosis
- MSUD = Maple syrup urine disease
- MTHFR = Homocystinuria due to MTHFR deficiency
- MUT = Methylmalonic acidemia
- OTC = Ornithine transcarbamylase deficiency
- PA = Propionic acidemia
- PAG = Patient advocacy group
- PKU = Phenylketonuria
- POMPE = Pompe disease
- SAHH = Deficit of S-adenosylhomocysteine hydrolase
- SCD = Sickle cell disease
- SCID = Severe combined immunodeficiency
- SMA = Spinal muscular atrophy
- TFP = Deficit of the trifunctional protein
- TYR I = Type I tyrosinemia
- TYR II = Tyrosinemia type II
- TYR III = Tyrosinemia type III
- VLCAD = Very long chain acyl CoA dehydrogenase deficiency

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- GNMT = Glycine N-methyltransferase deficiency


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[13] The list of the 30 countries in scope is provide within the NBS infographic (Figure 1)

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