# Newborn screening for inborn errors of metabolism

Hugh Lemonde
Maureen Cleary
Anupam Chakrapani

## Abstract

Newborn screening is a process that is designed to detect and alter the natural history of conditions that would otherwise cause significant morbidity or mortality within a population. As technology has advanced and enabled an ever greater number of conditions to be screened for, decisions as to which conditions should be included in newborn screening programmes has become increasing difficult with widely varying practises across the globe. In the UK newborn screening hopes to identify five conditions, two of which are inborn errors of metabolism. Commencing in 2015, a further four inborn errors of metabolism will be included in the national screening programme after completion of a 2 year pilot study. The UK screening programme is regulated by the Department of Health through the National Screening Committee (UK NSC) and clear recommendations exist regarding management and follow-up of positive screen results. The future of newborn screening is becoming increasingly interesting and controversial, in particular with the introduction of pilot schemes in the US that are evaluating the use of whole exome/genome sequencing from newborn blood spots.

**Keywords** glutaric aciduria type I; homocystinuria; isovaleric aciduria; maple syrup urine disease; medium chain acyl-CoA dehydrogenase deficiency; newborn screening; phenylketonuria; tandem mass spectrometry

## Early history of newborn screening

Screening an unselected population in the newborn period was pioneered in the early 1960s by Robert Guthrie, an American microbiologist who recognised the potential benefit in the early detection of phenylketonuria (PKU). The underlying pathology of PKU had been elucidated in the 1930s. Two decades later, treatment by dietary restriction of phenylalanine was shown to be effective in preventing the neurological progression of the disorder in an infant sibling of an older child with symptomatic PKU. However, the neurological impairment caused by PKU is not reversible and Guthrie recognised that pre-symptomatic detection of PKU would be critical in altering the natural history of this disorder. He developed a simple test based on a bacterial inhibition assay that could detect raised phenylalanine from a dried blood spot collected on filter paper from a neonate (this method of sample collection is still employed to this day in newborn screening programmes worldwide). Other tests for PKU existed, such as the ferric chloride diaper test that identified phenylalanine in urine, but Guthrie's test was simple, reproducible and relatively inexpensive. These were crucial features that allowed the test to be implemented on a statewide then nationwide scale on all newborns in the US. Universal PKU screening was subsequently introduced across the UK in 1969. Congenital hypothyroidism was added to the UK national newborn screening programme in 1981, cystic fibrosis in 1991, and medium chain acyl-CoA dehydrogenase (MCAD) Deficiency and sickle cell disease in 2004.

## Principles of newborn screening

The introduction of universal testing for PKU led to a difficult question — what other conditions *can* we screen for and what conditions *should* we screen for? This is still fiercely debated to this day and has resulted in different approaches to newborn screening across the globe. This problem was first formally addressed by the World Health Organisation (WHO) in 1968 when it published criteria for newborn screening programmes as written by Wilson and Jungner (Table 1a). PKU fitted nicely into these criteria and a case to screen for PKU is easily made. As technology has advanced we now have the ability to rapidly and inexpensively screen for many conditions (more than 50) from a single blood spot. Thus the emphasis has shifted from what *we can* test toward what *we should* test for. Many different screening criteria have been proposed over the years and a recent synthesis of these criteria was published by the WHO in 2008 and the criteria used by the UK National Screening Committee are summarised in Table 1b

By way of example, a notable success in newborn screening is medium chain acyl-CoA dehydrogenase (MCAD) deficiency. MCAD deficiency is one of the most prevalent inborn errors of metabolism and its natural history is well understood; it is a condition causing episodic illness most commonly precipitated for the first time by intercurrent illness between the ages of 6 months and 2 years. Prior to screening an estimated one in three children would die or have severe neurological sequalae as a result of their first decompensation. Treatment of the condition is relatively straightforward — supply of adequate carbohydrate during intercurrent illness prevents decompensation. One comprehensive study has suggested a reduction by 74% of severe decompensation and/or death after the introduction of newborn screening. In contrast, a notable screening failure was that of histidinaemia. Approximately 3.5 million children in the states of Massachusetts and New York were screened over a 20 year period with many children being started on low histidine diets. Although it was well established that the diet would reduce histidine levels, it became apparent that histidinaemia is a normal variant and did not cause a clinical phenotype. Paucity of understanding the natural history of this condition caused many children to undergo dietary modifications and multiple blood tests unnecessarily, the burden on families and cost to the state being substantial. This screening programme no longer exists.

***Hugh Lemonde*** *ARCS MRCPCH PhD is a Registrar in Paediatric Metabolic Medicine in the Department of Metabolic Medicine, Great Ormond Street Hospital, London, UK. Conflict of interest: none acknowledged.*

***Maureen Cleary*** *FRCPCH is a Consultant in Paediatric Metabolic Medicine in the Department of Metabolic Medicine, Great Ormond Street Hospital, London, UK. Conflict of interest: none acknowledged.*

***Anupam Chakrapani*** *MD DCH FRCPCH is a Consultant in Paediatric Metabolic Medicine in the Department of Metabolic Medicine, Great Ormond Street Hospital, London, UK. Conflict of interest: none acknowledged.*

## Screening criteria (published by WHO) and changes over the decades

**a) Wilson and Jungner criteria of 1968**

- The condition sought should be an important health problem.
- There should be an accepted treatment for patients with recognised disease.
- Facilities for diagnosis and treatment should be available.
- There should be a recognisable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be an agreed policy on whom to treat as patients.
- 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.
- Case finding should be a continuing process and not a 'once and for all' project.

**b) Abridged version of UK Screening criteria from the NSC (http://www.screening.nhs.uk/criteria)**

The condition
- The condition should be an important health problem.
- The epidemiology and natural history of the condition should be adequately understood.
- Cost-effective primary prevention interventions should have been implemented.
- If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood.

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 should be acceptable to the population.
- There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result.
- If testing for mutations, clear guidance as to which mutations are screened for should be defined.

The treatment
- There should be an effective evidence based intervention for patients identified.
- There should be evidence based policies covering which individuals should be offered treatment and the appropriate treatment.
- Management of the condition should be optimised in all healthcare providers prior to participation in a screening programme.

The screening programme
- There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.
- There should be evidence that the complete screening programme is clinically, socially and ethically acceptable to health professionals and the public.
- The benefit from the screening programme should outweigh the physical and psychological harm.
- The cost of the screening programme should be economically balanced in relation to expenditure on medical care as a whole
- All other options for managing the condition should have been considered to ensure that no more cost-effective intervention could be introduced.
- There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
- Adequate facilities should be available prior to the commencement of the screening programme.
- Evidence-based information 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.
- If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.

**Table 1**

It is interesting to consider the way in which different countries approach newborn screening and apply screening criteria. Comparing the UK and the US highlights the different approaches to newborn screening practise. The UK can be considered to be relatively conservative — currently five conditions (soon to be nine — see below) are included. Each one has a well defined natural history, established treatment, evidence to support the efficacy of the screening test whilst the benefit to the screened individuals versus the burden on the population as a whole has been considered. The US has a more liberal approach, with the federal government (Health Resources and Services Administration — HRSA) mandating states to screen for 31 core conditions and recommends a further 26. However individual states have autonomy and can include conditions not on the federal list. A number of these conditions include those with uncertain clinical significance (e.g. methylcrontyl CoA carboxylase deficiency and