2 Newborn Screening for Inborn Errors of Metabolism

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2.1 Introduction

Newborn screening was first applied to the detection of phenylketonuria (PKU) by a bacterial inhibition assay pioneered in 1961 by Guthrie, who was also responsible for the introduction of the use of a dried blood sample [1]. This was followed by further bacterial inhibition assays to detect other aminoacidopathies (maple syrup urine disease, homocystinuria, urea cycle disorders and so on) but only screening for PKU was widely adopted. In 1975 Dussault described screening for congenital hypothyroidism (CH) [2], and since then other disorders covered in some screening programmes have included congenital adrenal hyperplasia, the galactosaemias, cystic fibrosis, biotinidase deficiency, glucose-6-phosphate dehydrogenase deficiency and many others. The application of tandem mass spectrometry to newborn screening was first described in 1990 [3]. This new technology has greatly changed both newborn screening and the diagnosis of many inborn errors of metabolism.

2.2 General Aspects of Newborn Screening

2.2.1 Aims and Criteria

The initial aim of newborn screening was to identify infants with serious but treatable disorders, so as to facilitate interventions to prevent or ameliorate the clinical consequences of the disease. In recent years, with the advent of tandem mass-spectrometry which can detect many disorders at one time, and hence the ability for early detection of currently untreatable disorders (► below), there has been discussion about how the aims of screening might be widened to encompass a benefit to families, rather than individual babies.

The classic criteria for screening are those of Wilson and Jungner [4]. More recently the World Health Organisation has published guidelines [5] as has the United States [6], and the United Kingdom National Screening Committee has extended the Wilson and Jungner criteria [7]. In reality the criteria can be simplified and reduced to two main considerations which would justify screening for any specific disorder: there should be a benefit from neonatal detection, and the overall benefit should be reasonably balanced by the costs of all kinds: the financial costs (opportunity costs) and the cost of the harm, if any, to individuals by early detection of the disorder, or false assignment of a positive or negative result. It is important to remember that newborn screening covers the whole process from sampling to the appropriate referral of an affected baby for the start of treatment, and assessment of overall outcome.

2.2.2 Sensitivity, Specificity, and Positive Predictive Value

In assessing screening tests and understanding the screening process, some definitions are important:

Sensitivity: The proportion of subjects with the disorder in question detected by the test.
Specificity: The proportion of subjects without the disorder that have a negative test result.
False negative rate: The percentage of affected subjects not detected by the test.
False positive rate: The percentage of healthy subjects with a positive test result.
Positive predictive value: The chance that a positive result actually indicates an affected individual. Similarly, a negative predictive value is the chance that a negative result excludes the disorder. These values depend not only on the specificity or sensitivity of the test, but also on the frequency of the disorder.

The sensitivity of a test depends to a large extent on chosen cut-off values, and is a balancing act: the higher the sensitivity the lower the specificity. The sensitivity and specificity of course will vary according to decisions about cut-off points and what range of false positive and negative results can be tolerated in a particular programme.

2.2.3 Technical Aspects of Newborn Screening Tests

Blood-collection-paper Samples

Newborn screening tests are mainly carried out on blood spots dried on specially manufactured filter paper, usually obtained by heel-stick. Although various forms of venous blood sampling may also be used, filter paper blood samples will be considered here.

Methods

A wide variety of technologies can be applied to filter paper samples, including bacterial inhibition assays, chromatographic techniques, enzyme-linked immunosorbent assays (ELISA), fluorescent immunoassays (FIA), radioimmunoassays (RIA), and most recently electrospray ionisation tandem mass spectrometry (MSMS). Methods for newborn screening prior to MSMS screening are well-described by Therrell [8]. DNA analysis is also performed as a part of some screening tests. The methodology to some extent varies with the analyte of interest (for example, hormone analyses are usually immunoassays), and cost, sensitivity and specificity vary according to the method used. While quantitative results are obtained, the precision of tests using a paper sample is less than for a plasma or serum sample because of the matrix, collection process, haematocrit variations and so forth.