Newborn screening: new developments, new dilemmas

N J Kerruish, S P Robertson

Scientific and technological advances are lending pressure to expand the scope of newborn screening. Whereas this has great potential for improving child health, it also challenges our current perception of such programmes. Standard newborn screening programmes are clearly justified by the fact that early detection and treatment of affected individuals avoids significant morbidity and mortality. However, proposals to expand the scope and complexity of such testing are not all supported by a similar level of evidence for unequivocal benefit. We argue that screening for genetic susceptibility to complex disorders is inherently different from standard screening and, while of potential value, must be considered separately from conventional testing.

Recent scientific and technological advances are lending pressure to expand the scope of newborn screening programmes. The ability to examine DNA in the Guthrie specimen has opened up opportunities to screen for many disorders that previously were difficult to identify in the newborn, among them susceptibility to type 1 diabetes, severe combined immunodeficiency, fragile X syndrome, hereditary haemochromatosis, and lymphoblastic leukaemia. Inherently, there is great potential to improve child health, but these proposals also challenge our current perception of newborn screening programmes. There are major differences among many of the disorders currently being considered for inclusion in newborn screening programmes. Here we will focus on one illustrative example—whether newborns should be screened for genetic susceptibility to type 1 diabetes. We begin by examining conventional newborn screening using a standard ethical framework to judge how current practice reflects recommended, established screening criteria. Using the same framework, we then consider the ethical issues involved in expanding newborn screening to include genetic susceptibility testing.

A BRIEF DESCRIPTION OF STANDARD NEWBORN SCREENING

Newborn screening is one of, if not the, most efficient and effective of all screening programmes. It originated with the development of the “Guthrie test” for detecting the metabolic disorder, phenylketonuria (PKU). Subsequently, other disorders have been added to screening programmes. Although the exact list differs among, and sometimes within, countries, testing for PKU and hypothyroidism is universal in the developed world.

Blood samples are collected between 2 and 5 days of age, analysed at central laboratories and results released within a few days. For positive results, confirmatory tests are necessary, but treatment is usually instituted within 10–14 days of birth. For PKU this usually means the baby avoids any of the sequelae of the untreated condition, such as seizures and severe developmental delay. Most countries report coverage rates of 95–100% of the population for this type of screening.

HOW ARE NEWBORN SCREENING PROGRAMMES APPRAISED?

The basic premise underlying newborn screening is that it should do significantly more good than harm. To ensure that this is the case, standard criteria are used for determining which disorders are appropriate to screen for. The criteria developed for the World Health Organization (WHO) (box 1) have been the gold standard for many years. These criteria cover aspects of the disease, its treatment, the scientific validity of the tests, and the organisational infrastructure associated with the screening programme. Although ethical issues related to screening programmes are peripheral to these guidelines, their explicit purpose is to ensure that benefits of screening outweigh harms, and consequently they cannot be ignored in any ethical analysis. Ethical, scientific, and practical issues in newborn screening are closely intertwined and it is not possible to discuss each set of issues in complete isolation. The following analysis therefore draws on some of the screening criteria as well as employing four standard moral principles to highlight other ethical issues.

ETHICS OF STANDARD NEWBORN SCREENING

The aim of this section is not to analyse standard newborn screening exhaustively but to highlight some of the most important ethical issues and demonstrate that standard newborn screening is at least ethically acceptable, if not ethically mandatory. The discussion will concentrate on screening for PKU as this has been described as the “gold standard” against which screening for other disorders should be reviewed.

Benefits and harms of standard newborn screening

Knowledge of PKU

Although application of some of the WHO criteria is subjective, PKU is undeniably an important health problem. Despite its relative rarity (approximately 1 in 10–15 000), it causes
Box 1: WHO Wilson–Jungner criteria for appraising the validity of a screening programme

Knowledge of the disease
- The condition must be an important health problem
- There should be a recognisable latent or early symptomatic stage
- The natural history of the condition, including development from latent to declared disease, should be adequately understood

Knowledge of the test
- There should be a suitable test or examination
- The test should be acceptable to the population
- Case finding should be a continuing process and not a "once and for all" project

Treatment for the disease
- There should be an accepted treatment for patients with recognised disease
- Facilities for diagnosis and treatment should be available
- There should be an agreed policy concerning whom to treat as patients

Cost considerations
- Costs 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

significant morbidity. Additionally, the natural history of the disease is well described and a clear latent period exists during which diagnosis and initiation of treatment allow near complete avoidance of symptoms.

Testing for PKU
The harms associated with screening are addressed less directly in the WHO criteria but largely relate to the testing process. Newborn blood collection does incur minimal, short lived pain for the baby but long term complications are very uncommon. Laboratory testing for PKU is cheap, simple, and reliable. The incidence of false negative results (a missed diagnosis of PKU) through screening is negligible, but a small (<1%) risk of false positive diagnosis on the first sample does exist. Most parents are reassured by the subsequent negative test result but there is some evidence that parental anxiety can persist and result in longstanding disturbance of parent–child interaction. Clearly minimising the number and impact of false positive results must be a key component of a good newborn screening programme.

Treatment for PKU
Without screening it is difficult to diagnose PKU early and untreated children have progressive and severe neurological damage. Early diagnosis, facilitated by screening and prompt institution of appropriate treatment, results in growth and development within the normal range.

Autonomy and standard newborn screening
Consent for newborn screening
Issues relating to consent are not specifically addressed in the WHO criteria but are clearly central to any ethical analysis of screening programmes. The issue of informed consent for newborn screening has been controversial, as is reflected in the considerable variation at both policy level and in the practical delivery of programmes. For instance, the WHO guidelines consider newborn screening to be sufficiently important to override parental refusal, stating that "newborn screening should be mandatory and free of charge if early diagnosis and treatment will benefit the newborn". This sentiment is reflected broadly in state guidelines in the USA, with screening being mandatory in some instances, but not in other countries, including the UK, Ireland, Australia, and New Zealand.

Consent practices are poorly described and probably vary markedly within and among different jurisdictions. Most newborn screening programmes provide information sheets for parents and it is likely that many consent processes operate on an opt-out basis, whereby parental consent is assumed if no objections are voiced.

Despite this lack of consensus and practice variation it is probable that in most cases screening occurs without serious breach of parental autonomy and the best interests of the baby are protected. Many newborn screening programmes have developed strategies to deal with the few cases where these values do appear to conflict.

Distributive justice and standard newborn screening
The WHO screening criteria clearly state that the cost of case finding (including diagnosis and treatment of patients diagnosed as having PKU) should be economically balanced in relation to possible expenditure on medical care as a whole. A recent economic analysis of standard newborn screening in the UK has demonstrated that the practice is clearly cost effective.

Ethics of standard newborn screening: summary
The WHO criteria continue to be useful in considering the harms and benefits of screening for PKU. Although adverse effects of screening exist, they are not severe and accrue in a limited number of people. When these, and other ethical concerns relating to consent practices, are balanced against the significant benefits of preventing serious and permanent neurological impairment newborn screening programmes are clearly justified. The overall ethical acceptability of newborn screening is beyond doubt, and its provision, in the light of the above evidence, should be mandatory.

NEW DEVELOPMENTS, NEW DILEMMAS
Advances in molecular genetic diagnostics now mean that it is feasible to test whole populations of newborns for genetic susceptibility to common disorders, such as diabetes and asthma. Some claim comprehensive genetic screens of this nature soon after birth will fundamentally change the way health care is delivered. Others question the veracity of this statement, and the ethical consequences of integrating genetic susceptibility testing into clinical practices such as newborn screening need evaluating.

Our illustrative example (box 2), although hypothetical, is presently implemented within research programmes in Finland, Norway, and the USA. We will apply the same ethical appraisal previously applied to standard newborn screening, and highlight differences between these new programmes and current practice, drawing firm conclusions about the ethical acceptability of new proposals.

Benefits and harms of screening newborns for genetic susceptibility to diabetes
Knowledge of diabetes
Returning again to the WHO screening criteria, type 1 diabetes is one of the commonest chronic childhood diseases, with a rising incidence (3–4% per year in most developed
Box 2: Newborn screening for genetic susceptibility to diabetes

In the maternity ward, Jackie and Richard are offered a new test that can determine whether their newborn daughter Chloe has a genetic predisposition to type 1 diabetes. The test detects genetic variants (polymorphisms) that confer either a high risk (8%) or moderate risk (1.7–2.6%) of developing Type 1 diabetes (compared with a national average risk of approximately 0.7%). Jackie and Richard think the test is a good idea but are a little surprised when they are told some weeks later that Chloe does have the high risk genes. As a result Chloe needs to be monitored throughout childhood for the appearance of antibodies in her blood—the earliest sign of diabetes, often occurring years before any symptoms.

The next year, although Chloe remains well and her antibody tests have all been negative, Jackie and Richard do frequently think about the possibility of her developing diabetes. While searching the internet they find information indicating that standard cows’ milk can trigger diabetes in children whereas a new type of milk, containing a different protein, does not.21 Although their family doctor informs them that this effect is scientifically unproved Jackie and Richard are keen to try to help their daughter and therefore change Chloe’s milk, despite the additional expense and lack of evidence.

countries), particularly in the 0–4 year age group. A long prodromal phase precedes the onset of clinical disease providing an opportunity to institute preventive measures. At present a diagnosis of type 1 diabetes means lifelong treatment with injected insulin, a regimen that is challenging, particularly for very young children. Undoubtedly, diabetes is a significant health problem and preventing or delaying its onset is highly desirable.21 Although type 1 diabetes seems an attractive option for a newborn screening programme there are important features of the genetic susceptibility test itself that present the potential for significant harm.

What is genetic susceptibility testing?

Development of common multifactorial diseases such as diabetes and asthma is determined jointly by genes and environment.22 Testing for common genetic variations (polymorphisms) that confer predisposition to disease is termed genetic susceptibility testing, and is increasingly feasible on a large scale as laboratory techniques improve. This type of testing is different from that traditionally used in newborn screening programmes as the information provided contains a much greater component of uncertainty. Whereas a positive newborn screening test for PKU means that the biochemical disorder is already present and the disease will develop rapidly without treatment, a positive susceptibility test gives an individual information about their personal risk of developing a disease sometime in the future. This type of information is derived from population genetic studies and is usually presented in terms of a probability estimate or odds ratio. For individuals, considerable uncertainty remains as to whether they will develop the condition and, if so, when. In this respect, genetic susceptibility tests do not necessarily adequately fulfil the WHO screening criteria for a suitable and acceptable test and may present significant potential for harm.

Preventive treatment for diabetes?

Newborn screening for PKU facilitates early diagnosis and treatment of affected children, resulting in avoidance of debilitating symptoms. Similarly, the principal justification for screening to detect those at risk of type 1 diabetes is that they will be able to modify this risk and prevent the onset of clinical disease. Although prevention trials are under way, this is not possible at present.23 Some benefits for children like Chloe may exist, in that childhood type 1 diabetes diagnosed through a screening and follow up programme has a less severe onset and a milder clinical course in the first year after diagnosis.24 Nevertheless, lifelong insulin therapy is still required for these children, a fact not changed by susceptibility testing. Perhaps most telling, the majority of children identified as genetically susceptible will not develop diabetes and will consequently not benefit at all from screening or surveillance.

Potential preventive measures

Identification of preventive measures for diabetes would clearly shift the balance of benefits and harms in a favourable direction and fulfil the WHO screening criterion that treatment should be available. However, serious questions remain concerning the likely compliance of at risk individuals, or in this case parents, with recommended lifestyle modifications or medications. Experience with adults and children in other contexts has shown very variable success rates,25–28 with some studies originating in the newborn period even reporting increases in “risky” behaviour.29

Who is the patient?

Although the availability of a preventive measure is desirable and fulfils one WHO criterion, it presents difficulties with another. Having a clear policy on who to treat as a patient may be difficult in the context of genetic susceptibility testing. Up to 15% of the whole population of newborn babies possess diabetes susceptibility genes30 and could potentially be targets for education programmes aimed at modifying lifestyle risk factors.31 Alternatively, if an agent that prevents onset of clinical diabetes is developed it is unlikely to be administered to all genetically susceptible children, necessitating immunological surveillance (blood tests measuring levels of autoantibodies that predict the onset of clinical diabetes) throughout childhood to determine who to treat. This is scientifically and practically complex, expensive and potentially distressing for the children involved.

Both of these hypothetical prevention strategies rely upon clearly identifying a large group of genetically susceptible children and continuing to do so throughout childhood. Although not obviously patients, they could perhaps be viewed as a new class of “pre-patients” — although not patients in the way we usually think of them. Having a clear policy on who to treat as a patient and fulfils one WHO criterion, it presents difficulties with another. Having a clear policy on who to treat as a patient may be difficult in the context of genetic susceptibility testing. Up to 15% of the whole population of newborn babies possess diabetes susceptibility genes and could potentially be targets for education programmes aimed at modifying lifestyle risk factors. Alternatively, if an agent that prevents onset of clinical diabetes is developed it is unlikely to be administered to all genetically susceptible children, necessitating immunological surveillance (blood tests measuring levels of autoantibodies that predict the onset of clinical diabetes) throughout childhood to determine who to treat. This is scientifically and practically complex, expensive and potentially distressing for the children involved.

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Forewarned is forearmed?

How important are these psychosocial effects when testing is performed in the newborn period? Some studies indicate that it may be psychologically beneficial to know one’s child’s medical diagnosis when the disorder is presymptomatic. Parents may prefer early diagnosis through screening, even for untreated diseases such as Duchenne muscular dystrophy, and there is little evidence that early diagnosis produces greater distress than diagnosis by conventional methods.32 The declared advantage of this is that parents can prepare themselves emotionally and practically.33 Other
commentators argue that early knowledge of a serious disorder, such as cystic fibrosis, is likely to cause more harm than good if there is no effective remedy. This argument is plausible if, for example, the interaction between parents and child was somehow affected by the news that the baby had an ultimately fatal disease.

How does this discussion relate to testing newborns for genetic susceptibility to diabetes? It is true that Chloe's parents are now primed to pre-empt her potential illness in many ways. However, there are critical differences between susceptibility tests and tests for fully penetrant monogenic diseases, such as cystic fibrosis and Duchenne muscular dystrophy. Measures of disease susceptibility do not provide the “benefit of certainty” that is associated with tests for monogenic disease. Rather they highlight a specific level of uncertainty. Any physical, emotional, or practical preparation that Chloe’s parents make will have been pointless if Chloe never develops diabetes, as most children with increased risk genotypes will not. It would be bad enough if Chloe’s parents’ preparation for her developing diabetes had been unnecessary. It would be worse if it were actually harmful.

Vulnerable children?
The psychosocial effects of this period of parental preparation or surveillance are difficult to predict and study but one recent report has suggested that some subgroups of women remain significantly anxious at least a year after their baby's diabetes genetic susceptibility test. Anxiety and “over-reaction” is distressing for parents, but may also have far reaching consequences for children themselves. If parents view their “at risk” child as actually being ill or “uniquely vulnerable” they may over-attribute symptoms to the perceived risk status. For instance, additional fluid intake may be misconstrued as symptomatic of incipient diabetes rather than indicative of the typical fluctuations in fluid intake during childhood, resulting in unnecessary worry and medical intervention. It is also well recognised that parents can interact differently with a child if they misinterpret their risk of illness, potentially contributing to childhood behavioural problems and even disordered illness behaviour later in life. This is particularly pertinent in the newborn period when the bond between parents and child is developing and when external influences can have a profound and permanent effect on child development.

Later in childhood, children identified as being at genetic risk of disease may feel stigmatised or different from their peers, which may also significantly affect their social development. This has been clearly described in relation to healthy carriers of monogenic conditions: we simply do not know if it will occur with genetic susceptibility to multifactorial conditions.

Testing in the absence of preventive treatment
In the absence of definitive therapy there may be increased potential for harm. As in Chloe’s case the natural parental urge to protect one’s child may drive a search for preventive or therapeutic strategies. Chloe’s parents’ choice to alter her milk intake is unlikely to be harmful, but other similar interventions may not be so innocuous. Studies on screening for hypercholesterolaemia have reported that some parents restrict their child’s diet to the extent that they become malnourished. Similarly, identification of a genetic predisposition to haemachromatosis in a child could lead to unnecessary restriction of iron intake with adverse neurodevelopmental effects. In the case of susceptibility testing these negative effects may accrue in large numbers of children who were never destined to develop the condition to which they are “susceptible”. One might argue that these reactions could be remediated by educative measures but this would require considerable resource allocation, and may still be only partially effective. Even with optimal counselling services concepts of risk are difficult to convey, and reactions depend upon a complex interplay of individual characteristics.

Finally, it is not only the children who test positive for the increased risk genotype who may be harmed. Having a low risk genotype for a multifactorial disease does not eliminate the possibility of the condition developing. For the currently used susceptibility tests for diabetes it simply means that the risk is low (less than 1 in 1500). It is imperative that parents of these children are not falsely reassured, and they still recognise the symptoms of developing illness were these to develop.

Overall, the frequency and severity of adverse psychosocial reactions to newborn screening for genetic susceptibilities is currently difficult to predict, and there is an urgent need for further research in this area.

Autonomy and genetic susceptibility testing
Informed consent
The uncertainty inherent in susceptibility testing and the lack of evidence for an unequivocal benefit to harm ratio also impacts upon consent issues. Although it may be acceptable to use an “opt-out” parental consent scheme for standard newborn screening with its clear and major benefits, this would not be reasonable for susceptibility tests. Guidelines concerning best practice in genetic testing advise for the provision of clear and simple information and time for consideration before embarking on testing. Offering newborn susceptibility tests at an emotional time and when the blood sample had already been obtained for standard newborn screening is not optimal and may lead to unusually high uptake rates. Similarly the communication of positive test results to a potentially large number of individuals and the provision of ongoing support would require a significant departure from established newborn screening practice if some of the potential harms discussed above are to be avoided. Even so, individual differences in attitude to risk, family functioning, and social support mean that reaction to testing is likely to vary markedly. Introducing new counselling measures to address these issues would seriously challenge traditional practices surrounding newborn screening and stretch the limited resources currently applied to it.

Childhood and autonomy
Results from genetic susceptibility tests are not only probabilistic but they are also predictive. They do not demonstrate a disorder (such as PKU) is present but that it may occur some time later in childhood. Most official policies concerning predictive genetic testing strongly advise against testing children for a disease in which surveillance, preemptive, or definitive medical treatment is not available in childhood. This approach protects the child’s future autonomy to self determine whether or not to be tested and does not violate the future adult’s right not to know.

Alternative arguments that children’s best interests should not be considered in narrow, medical terms but according to a broader definition including biological, social, and psychosocial elements, have challenged the prohibition on predictive genetic testing in childhood. Self knowledge (including genetic test results), it is argued, can promote more autonomous decision making and allow better psychosocial adjustment. Knowledge of one’s risk of developing diabetes throughout childhood could be viewed as enhancing a child’s developing autonomy. Although convincing when considering fully penetrant, monogenic disorders this argument does not necessarily follow for susceptibility tests. It would be
difficult, and potentially harmful, for Chloe or her parents to try to plan their family life on the basis of such a poorly predictive test.

Finally, predictive genetic testing could possibly lead to discrimination in later life by insurance companies or potential employers. How the type of information generated from genetic susceptibility testing for common multifactorial diseases fits into this picture is currently unclear and difficult to predict.

**Distributive justice and susceptibility testing**

It is currently not feasible to perform an accurate economic analysis of screening programmes for conditions like type 1 diabetes. Even if a preventive measure were developed a large number of genetically susceptible children would require monitoring throughout childhood for there to be a significant reduction in the incidence or severity of type 1 diabetes. Effects such as altered illness behaviour in people who were “perceived as vulnerable or sickly” during childhood are difficult to study and quantify but could represent a significant burden to the health system. Any evaluation of the cost effectiveness of genetic susceptibility screening programmes will need to carefully consider these complex issues.

**SUMMARY**

Comparative ethical analysis of standard newborn screening and potential expanded screening for genetic susceptibility to diabetes highlights some major differences between the two. This fact alone does not imply that such screening is automatically ethically unacceptable but does suggest that these differences should be examined in detail. The uncertainty associated with this type of genetic information and difficulty in precisely defining who is a patient mean that several WHO criteria are not adequately fulfilled. There is significant potential for psychosocial harm, particularly when testing is performed in the newborn period and in the absence of definitive therapy. It is not currently possible to comprehend fully the significance of these potential harms as they are difficult to quantify and poorly researched but some of the negative effects may be considerable, both at the level of individual families and on a population basis.

**CONCLUSION**

Like conventional newborn screening, the proposal to add genetic susceptibility testing to these programmes has the laudable ultimate aim of reducing childhood disease. However, this type of screening presents a very different set of potential harms, centred around the probabilistic nature of the information, potentially maladaptive parental reactions to this level of uncertainty, and perceived breaches of the autonomy of the child being tested.

Current newborn screening programmes are highly efficient, reduce morbidity, and save lives. This may be a double edged sword when considering expansion of such programmes. On the one hand, the infrastructure associated with current programmes provides an unparalleled opportunity to distribute the benefits of expanded testing across the whole population. Of course this also means widespread distribution of any associated harms. Tempting as it may be to use existing service infrastructure, programmes designed to deliver genetic susceptibility testing would need to operate outside the current paradigm, since safeguards against potential harms and consent procedures must be inherently different.

Presently, we consider screening the general population of newborns for genetic susceptibility to diseases such as diabetes ethically unacceptable. However, this may change as knowledge of disease pathogenesis, as well as harms and benefits of testing grows, new strategies for prevention are developed, and costs change. Decision making that integrates all of these factors is an ethical imperative. If sufficient attention is not paid to these issues then two outcomes are likely. Firstly, iatrogenic harms may reach a level whereby the net benefit of expanded screening becomes questionable. Secondly, and perhaps less obviously, public confidence in the whole newborn screening process may waver and uptake rates of even standard newborn screening may decline. The resultant rise in mortality and morbidity would represent the ultimate harm; the technological imperative to expand and diversify newborn screening, if ill-considered, could subvert and defeat what is at present an undeniable public health good.

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