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NEWBORN SCREENING

Expanded newborn screening: social and ethical issues

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Abstract Newborn screening and genetic testing have expanded rapidly in the last decade with the advent of multiplex (e.g., tandem mass spectrometry) and/or DNA technologies. However, screening panels include a large number of disorders, which may not meet all of the traditional screening criteria, established in late 1960s, and used for years to justify screening programs. After a period of expansion driven by technological advances, many reports have reconsidered the justification of expanded programs. Many factors have contributed to test-panel discrepancies between countries. The test-panel review methodology, the way health benefits are weighed against harms, and the socioeconomic–political environment all play a role. Expansion of screening also requires reconsideration of the infrastructure (ideally, in the context of national plans for rare diseases) to support testing, counselling, education, treatment, and follow-up. Consequently, economic aspects cannot be ignored and can be a limitation for expansion. New ethical questions have emerged: risks of discrimination or stigmatization, respect of the autonomy of persons to make decisions, parental anxiety resulting from a false positive test (especially when reporting to parents screening results for untreatable conditions identified as by-products of screening), etc. For disorders where there is not yet confirmation of benefit, it may be prudent to recommend pilot screening and to have a mechanism that can be used to adapt or even to stop a program.

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Abbreviations

CAH	congenital adrenal hyperplasia
CF	cystic fibrosis
CH	congenital hypothyroidism
DMD	Duchenne muscular dystrophy
MCADD	medium-chain acyl-CoA dehydrogenase deficiency
MS/MS	tandem mass spectrometry
NBS	newborn screening
PKU	phenylketonuria
SCD	sickle cell disease

Introduction

Newborn screening (NBS) tests have been designed to identify infants with severe disorders that are relatively prevalent and treatable (or controllable). Until the late 1990s, screening tests were relatively simple and inexpensive. Based on the success of the screening for phenylketonuria (PKU), programs have been extended with the same benefit to other conditions (congenital hypothyroidism, congenital adrenal hyperplasia, etc.) during the later decades of the twentieth century. More recently, newborn screening and genetic testing have expanded rapidly with the advent of multiplex and/or DNA technologies. In many countries, such expansion of NBS programs has been driven by technological advances, public pressure (lobbying of advocacy groups), the entry of large private laboratories providing NBS services, and international recommendation (in Europe in the context of harmonization of national plans for rare diseases). The traditional screening criteria (Wilson and Jungner 1968) have been

used for years to justify the inclusion of individual disorders in screening programs; however, screening panels now include a large number of disorders that may not meet all of these criteria. The question of whether or not expanded programs should be offered at the population level is more complex and is a challenge to health care providers, the medical screening community, and policy makers. The aim of this review was to collect and present various opinions concerning social and ethical aspects of expanded NBS programs.

Definitions

Rare diseases

A rare (orphan) disease occurs infrequently in the general population, defined in Europe as <1: 2,000 citizens (Programme of Community Action 1999–2003). Eighty percent of these diseases have identified genetic origins (genes or chromosomal abnormalities) and occur in 3–4% of births; others are caused by infections, degenerative, proliferative, or teratogenic agents; some can be caused by a combination of genetic and environmental factors.

Different categories of diseases need to be distinguished:

1. Disorders for which considerable, irreparable damage can be prevented e.g., PKU, congenital hypothyroidism (CH), medium-chain acyl coenzyme A (CoA) dehydrogenase deficiency (MCADD), at least for their typical forms.
2. Diseases for which screening and early care prevent acute morbidity but do not change the long-term complications, e.g., galactosemia (Schweitzer-Krantz 2003), sickle cell disease (SCD).
3. Disorders for which there is less substantial or insufficient evidence of damage prevention; for many organic acid, amino acid, or fatty acid metabolic diseases, it is not clear whether the outcome is better for patients identified in screening programs (Leonard et al. 2003).
4. Disorders for which damage to health cannot be prevented, e.g., Duchenne muscular dystrophy (DMD), although there are now trials of mutation-specific treatments for this disease (Mitrpant et al. 2009).

Definition of expanded screening program

In this report, expanded/extended/supplemental NBS programs do not only concern NBS by tandem mass spectrometry (MS/MS) but encompass the entire population of a screening program that until recently was restricted to a subpopulation (SCD in at-risk population; deafness in neonatal intensive care units) or screening for diseases that in the past were not considered to benefit from systematic screening because of their rarity or lack of proved efficient treatment.

History of NBS expansion

Historically, most NBS programs were established without evidence-based evaluation. For example, screening for PKU was based on a prediction that a dietary treatment would prevent mental retardation (Bickel et al. 1953). Since the late 1960s, criteria established by Wilson and Jungner (1968) have served to justify NBS programs. PKU screening successfully fulfilled these criteria. Programs were then extended, with success, to other conditions, such as CH (Dhondt and Farriaux 2000). However, an increasing number of conditions that can be detected by multiplex technologies do not fulfill all the Wilson and Jungner criteria. Since 2000, the progressive inclusion of tests for several diseases has been essentially driven by the technical possibilities of MS/MS technology. In 2005, the US ACMG (American College of Medical Genetics 2006) recommended 29 core disorders for which evidence of benefit was regarded as compelling. The list was endorsed by an assortment of organizations, including advocacy groups, professional associations, and national committees. Interestingly, many authors (Botkin et al. 2006; Tarini et al. 2006; Avard et al. 2007; Vallance et al. 2008; Moyer et al. 2008; Little and Lewis 2008) expressed serious reservations about the expansion of NBS programs that is taking place without full consideration of all the issues. In fact, a NBS program is not just a panel of screening tests. Ideally, it also integrates education, screening, follow-up, diagnosis, management, and evaluation (Therrell 2001). Consequently, a number of issues must be considered when implementing or expanding a NBS program (Table 1).

Criteria for choosing conditions to be included in expanding NBS programs

Concerning diseases that can be added to a program, many factors have contributed to test panel discrepancies between countries. “The test panel review methodology, the way health benefits are weighed against harms, and the socioeconomic–political environment all play a role” (Vallance et al. 2008). How evidence is interpreted depends on the review team: governmental agencies/offices may have more stringent criteria for evidence than experts in the field of NBS who, in contrast, tend to accept lower levels of evidence for studies on rare disorders [“good enough” evidence for a policy decision (Moyer et al. 2008)]. Marked

Table 1 Compilation from the literature of items that require attention in the implementation process of new or expanded newborn screening (NBS) programs

Impact of uncertainty	Families	Parental stress while awaiting results (control test, diagnostic result) ;meaning of results: false positive (nondiseases), true positive, false negative
		Anxiety raised by information that can be difficult to understand and interpret (believe their child is sick in case of false positive disorders vs biochemical variants)
		Reliability of diagnostic methods to confirm a (true/false) positive screen (e.g., sweat test)
		Lack of knowledge regarding definitive manifestations, long-term outcomes of children identified through screening (clinical heterogeneity within a single biochemical condition)
		Nonacceptance of a diagnosis in the absence of symptoms (explain the need of therapeutic measures although the child is asymptomatic)
Impact of knowledge	Families	Reactions to early diagnosis (including the benefit to parents by removing the stress of a delayed diagnosis)
		Effects on the parent–child relationship (medicalizing the child's life, parental overprotectiveness)
		Repercussions on reproductive decision making
		Life-style decisions
		Internet odyssey
Stigmatization	Families	Genetic discrimination by third parties (including insurance subscription and employment prospects)
		Isolation, exclusion from social community (school, leisure time with friends, affective life)
		Unexpected identification of carrier status, disclosure of such information about family members, misleading communication regarding the clinical significance of carrier status
		Determination of misattributed parentage (nonpaternity)
Consent	Families and health care professionals	Implicit consent or explicit informed consent or dissent (right to refuse testing)
		Cultural position against screening
		Uptake of screening (valuable health care service)
		Timing of patient education (a consensus exists for information integrated into prenatal care)
		Professional roles regarding the provision of patient education
Professional knowledge gap	Health care professionals	Professional education (initial and continuing)
		Guidelines and protocols for case management
		Availability of trained metabolic disorder specialists
Social impacts	Society	Accessibility and equity
		Choice between mandatory and voluntary programs
		Legal issues of bioethic laws
		Societal roles in health care planning and biomedical research
		Possibility of eugenics (myth of the perfectly designed baby)
Economic impacts	Society	Laboratory expenses
		Cost of short-term follow-up services , program management, long-term follow-up services, case management, family support beyond diagnosis, genetic counselling, nutritional counselling (formula foods) or treatment
		Cost of orphan drugs
Research and evaluation	Health care system and society	Lack of evidence-based data
		Provision of services
		Storage of samples and their use for research
		Difficulty to imagine/consider randomized controlled trials
		Difficulty of cost-effectiveness studies
Organizational aspects	Health care system	Reorganization in regard to inevitable budget constraint
		Centralization: concentration on supraregional NBS laboratories, new structure for confirmatory testing and reorganization of clinical centers (reference centers) might be necessary to provide the same quality of services to all babies in a country
		Integration of screening programs in national plan for rare diseases
		Timely availability of screening results and tracking system
		Technical: maintenance and quality assurance
		Professional: availability, interdependence, and expertise
		Integrated system: development and sustainability (life-long management)

differences of opinion were apparent even for well-documented conditions (Pollitt 2006). Finally, "as with other areas of medicine, conflict of interest can influence decision makers" (Vallance et al. 2008).

Parent's groups (advocacy groups) can influence choices. Hiller et al. (1997) stated that whereas professionals have technical expertise, they are no better qualified than the lay public to make political and moral decisions!

The Wilson and Jungner principles have to be revisited in regard to medical advances (Wilcken 2003; Pollitt 2006; Pollitt 2007; Dhondt 2007a). The incidence of a disease is a less compelling criterion when the disorder can be detected at no additional cost with multiplex technology, but inclusion of diseases for which there is no effective treatment remains questionable. In 2000, a report by the American Academy of Pediatrics stated that a condition is a good candidate for NBS only if "the treatment for the condition is effective when initiated early, accepted among health care professionals, and available to all screened newborns." In 2008, the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes (Council of Europe 2008) reaffirmed that approval of a screening program "may only be given after independent evaluation of its ethical acceptability and fulfilment of (the following) specific conditions…..(C) appropriate preventive or treatment measures in respect of the disease or disorder which is the subject of the screening, are available to the persons concerned."

Many national committees have developed their own criteria. However, "many of the final judgements remain qualitative and thus basically subjective" (Pollitt 2007). Such considerations explain variation of MS/MS screening panels between countries, some of them having decided to screen only for MCADD (in addition to PKU) (Bodamer et al. 2007; Pollitt 2009). A harmonized policy (at least in Europe) regarding screening for rare diseases is highly desirable (Bodamer et al. 2007). In fact, how does one explain to the parents of a child with brain damage caused by one of the screenable diseases that, if the child had been born in an adjoining country, he or she would have been screened and treated for the disorder and would be developing normally?

Criteria for the choice of a screening technology

The choice of technology can also be controversial. Looking for a phenotype has well known limits (choice of cutoff, two-tier strategies, primary and secondary targets with MS/MS); on the other hand, genotype determination that is sometimes considered a more reliable approach has several other limitations (carrier recognition, lack of genotype to phenotype correlation, undesirable discovery of nonpaternity) (Dhondt 2007b). The use of MS/MS has introduced a number of new problems. Two modes of MS/MS testing can be used: nontargeted analysis, in which a large number of metabolites are analyzed (known as full profile testing or multiple reaction monitoring); and targeted analysis, including identification and quantification of preknown metabolites or metabolite classes (known as selective reaction monitoring) (Ceglarek et al. 2009). Selective monitoring means using the multiplex platform to target only those conditions deemed appropriate for screening. In contrast, the full-profile approach means making maximum use of the information-gathering powers of the technology without regard to the distinction between appropriate and inappropriate target conditions. In addition, the full-profile mode increases the risk of incidental detection of abnormal conditions, for which the clinical significance of a positive screening result is very much in doubt. The use of stored data following multiplex screening (e.g., m/z ratios from MS/MS not routinely selected for screening) that can be retrospectively interpreted is often not considered. The availability of stored data is an opportunity for retrospective diagnosis if a child dies (search for an etiology of sudden death). In 2005 (Bodamer et al. 2007), German health authorities decided to limit the number of disorders to be detected by MS/MS to ten and decided that all results of analytes not needed for this purpose must be suppressed or deleted immediately after analysis.

Health care issues

Expansion of screening programs requires a complex infrastructure (to support testing, counselling, education, treatment, and follow-up). Consequently, economic aspects cannot be ignored and can explain limited expansions, especially if the principle of equitable access to the program is maintained. The survey made by Feuchtbaum et al. (2006) noted that lack of funding was a major barrier to MS/MS screening implementation. In some countries, such as the United States (http://savebabies.org/screening_info.html), the concept of the supplemental newborn screen has been chosen as an addition to the routine NBS, including an extra sample and an extra cost.! The cost of treatment (orphan drugs) has also to be considered (Stewart 2006; McCabe et al. 2005). The treatment of some lysosomal storage disorders, which can be added to the panel of screened conditions (Meikle et al. 2006; Matern 2008), is extremely expensive, especially when efficient enzyme replacement therapy is available. The decision of a health care system as to whether or not to fund treatments is not easy: "even if the drugs were 100% effective, the question remained whether they produced enough benefit to justify their cost, given other claims on resources" (Burls et al. 2005).

Ethical issues

Global principles

Ethical principles have been periodically adapted to medical advances (Table 2). With expanded programs, new ethical questions have emerged: risks of discrimination or stigmatization (program targeted to subpopulation), respect for autonomy of persons to make their own decisions, parental anxiety resulting from a false positive test (especially when reporting to parents screening results for untreatable conditions identified as byproducts of screening), worries about medicalization of the neonatal period.

Benefits of screening programs might be redefined, including family and societal considerations, such as reproductive decisions (antenatal diagnosis), life-style decisions—and NBS as an appropriate tool of biomedical research, which benefits society as a whole by increasing our knowledge of rare diseases. In such a context, availability of an effective treatment would no longer be an absolute prerequisite. The cultural acceptability of NBS is also a point that needs professional and public debate. In fact, paradoxical (and unexpected) attitudes have been observed. This can be illustrated by the example of newborn hearing screening. Some deaf people are against screening for hearing defects (Levy 2002; Bauman 2005), although screening for deafness is usually perceived as a major public health objective. During a pilot study aimed at establishing the efficacy of detection and intervention, the French National Deaf Federation (Fédération Nationale des Sourds de France) appealed to the French National Ethical Committee (Comité Consultatif National d'Ethique, avis 103 2008), which stated that "there is a cultural identity in being born deaf and we should not destroy that cultural identity by preventing children from being born deaf"; and that "the screening should not be systematically performed at the neonatal period in regard to the risk of over medicalization of deafness."

Consent

In ethical terms, the role of the consent process is to safeguard patients' autonomy; however, a recent study showed that many patients have limited knowledge of the legal implications of signing or not signing consent forms (Akkad et al. 2006). Written consent is usually not required for the majority of NBS tests, especially tests of proven validity and utility (Laberge et al. 2004) or when the law requires that all neonates be tested (mandatory programs). Conversely, if benefits or potential risks are balanced, consent has to be collected (Matsuda 2003; Huang and Lin 2003; Liebl et al. 2002). The risk that alarming families may reduce their compliance with screening tests seems low. Liebl et al. (2002) reported high compliance in an expanded MS/MS-based NBS program despite required written parental consent, thanks to an appropriate strategy to provide adequate information to parents and professionals. Informed consent means, indeed, to provide understandable information. Today, it is believed that parents are willing to assume their responsibility; however, it is difficult to be sure that parents are not inundated with a flood of medical information that can alter a proper decision, and that they can read and understand such medical information. The American Academy of Pediatrics 2000 stated the importance of ensuring that the material is written at an appropriate literacy level (Fant et al. 2005).

Genetic screening and bioethics

Specific ethical considerations are linked to the use of DNA tests that can be perceived as an intrusion in the genetic characteristics of an individual. Consequently, written consent seems necessary with incorporation of DNA tests into the screening strategy (e.g., CF) or an obligation when bioethic laws are explicit (Dhondt 2005). Genetic tests may inadvertently identify newborn infants who, although not affected by the condition, carry a gene for it. It has been often stated that identification of healthy carrier infants is

Table 2 Some milestones in medical ethics and reports focused on genetic diagnosis/screening

Time period	Milestone
410 BC	*Primum non nocere* (Hippocrates): The Hippocratic Oath requires physicians to benefit their patients according to their best judgment
1968	Principles and practice of screening for disease (Wilson and Jungner 1968)
1979	Principles of Biomedical Ethics (Beauchamp and Childress 1979)
1979	The Belmont report (1979): Basic ethical principals in medical research
2005	Universal Declaration on Bioethics and Human Rights (adopted by UNESCO's General Conference)
2008	Additional protocol to the Convention on Human Rights and Biomedicine concerning genetic testing for health purposes (Council of Europe Treaty Series - No. 203 2008)
2008	The changing moral focus of newborn screening: an ethical analysis by the President's Council on Bioethics (2008)

seen by some health professionals as undesirable because of its potential for unjustified anxiety about the health of the newborn (Lewis et al. 2006). The information of a carrier status can also raise fears of stigmatization (misuse by insurers, employer), fears that are evident in many ethnic minorities (labeling a person or family as having undesirable characteristics) (Dhondt 2007b; De Montalembert et al. 2005). In practice, not all NBS programs inform parents of carrier results. With the introduction of CF screening using DNA technology, the French National Ethical Committee was asked to give advice, which they published in 2007 (Comité Consultatif National d'Ethique, avis 97 2007): "disclosure of the genetic carrier status is not recommended." However, since retention of information can be perceived as unethical, it has been suggested that DNA testing should be replaced by a two-tiered strategy, with a first screen for elevated immunoreactive trypsinogen and subsequent analysis of pancreatitis-associated protein (Sarles et al. 2005).

Conclusion

It is difficult to think of any arguments against screening for conditions in which there is clear proof that early intervention is effective in preventing serious complications. Things start to become slightly more complicated as the range of tests being offered increases and new technologies become available. The analysis of the US Council on Bioethics concluded that: "the prudent course is to reaffirm that the primary goal of newborn screening is to provide direct medical benefit to children affected by serious disease, and that mandatory newborn screening can be justified only when there is convincing evidence that the benefits for the infant of screening and treatment outweigh the risks and burdens (President's Council on Bioethics 2008). Regarding disorders for which there is not yet confirmation of benefit, it may be prudent to recommend pilot screening and to have a mechanism that can be used to adapt or even to stop a program. It is also important to consider NBS as a component of national rare disease plans in order to ensure universal access to confirmatory tests, clinical care, and treatment (French National Plan for Rare Diseases 2005–2008 (2004).

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