Neonatal screening

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Neonatal screening (NS) is a medical act in the context of preventive medicine aimed at the early identification of infants affected by certain conditions that threaten their life and long-term health, for which a timely intervention can lead to a significant reduction of morbidity, mortality and associated disabilities. It emerged three decades ago in the context of prevention of mental retardation. Since then, around 600 inborn metabolic disorders have been described and technological progress has been impressive; nevertheless only around 5% of the disorders have been the object of NS. The most frequently cited reasons for the limitation are low prevalence and the lack of treatment. The tandem mass spectrometry has come in place in recent years across the globe, expanding NS to include several disorders of intermediary metabolism. This has shown, in addition to a prevalence much higher than previously thought, the benefits of early detection. The present work is a review of NS, not only from the point of view of technological/medical achievements, but also considering other factors which will affect specific disease selection, according to the social and organizational infrastructure that may expand the borders of NS.

Key words: neonatal screening, newborn screening, genetic screening, screening

Introduction and Principles of Neonatal Screening

Screening is the application of a test to people who are as yet asymptomatic, with the purpose of classifying them with respect to their likelihood of having a particular disease. The procedure itself does not diagnose illness and those who test positive require further diagnostic procedures.

Neonatal screening (NS) is a public health activity, in terms of secondary prevention, aimed at the early identification of infants affected by certain conditions-genetic, metabolic, infectious-that threaten their life and long-term health, for which a timely intervention can lead to a significant reduction of morbidity, mortality and associated disabilities.

It is a pediatric practice based on civic values of reciprocity, mutuality and solidarity and a medicosocial contract which must assure universal and equitable access. The informed participation of parents, the protection of confidentiality and integration of follow-up and treatment services are essential. In order to safeguard these ethical principles, as well as to ensure benefits for newborns, neonatal screening must be supported by a government decision, centrally planned, and financed by the state according to national health goals, with wide coverage and at no expense[1,2].

Public Health Considerations and Historical Background

The first two-thirds of the twentieth century had been characterized by achievements in the control of infectious and nutritional diseases resulting in an important reduction of infantile mortality. In developed countries epidemics of contagious diseases have been replaced as the leading cause of mortality and morbidity and as the major consumer of health care resources by congenital anomalies, developmental and learning disabilities and common chronic diseases of adulthood and aging[3]. In Europe, congenital/genetic defects also remain the more important cause of death and disabilities in children[4].

Neonatal screening emerged in the 1960s in the USA and Europe in the context of mental retardation, contributing decisively to its

development the discovery of phenylketonuria (PKU) by A. Fölling, the method developed by H. Bickel for its successful treatment and the idea of R. Guthrie to collect blood on filter paper, demonstrating that dried blood paper spots were analytically suitable for the detection of PKU with a bacterial inhibition assay. The introduction of neonatal screening for PKU represented the first population-based genetic screening and signaled the introduction of genetic testing into public health programs.

After Nearly 40 Years of Neonatal Screening, Where Are We?

Dried blood spots (DBS) had became a "gold" specimen allowing determination of

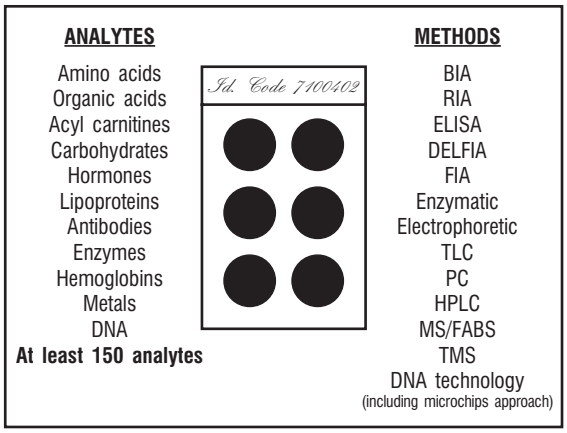

Fig. 1. Analytes that have been determined in dried blood samples collected on filter paper, and more frequently employed screening methods. Abbreviations: BIA, Bacterial Inhibition Assay; RIA, Radioimmunoassay; ELISA, Enzyme-linked Immunoassay; DELFIA, Delayed Europium-linked Fluorescence Immunoassay; TLC, Thin Layer Chromatography; PC, Paper Chromatography; HPLC, High Performance Liquid Chromatography; MS/FABS, Mass Spectrometry/Fast Atom Bombardment Mass Spectrometry; TMS, Tandem Mass Spectrometry.

an impressive number of analytes with a great variety of analytical methods (Fig. 1). The analytical test to be used for neonatal screening must be safe, specific, sensitive, with a good positive-predictive value and a very low number of negative results (or none), of low cost and applicable to DBS. But it must also be recognized that the whole laboratory analytical procedure has very high requirements of quality assurance. There are pre-and post-analytic components which are a major part of a neonatal screening program and must be integrated in the quality assurance program (QAP) laboratory, such as specimen collection and delivery, data collection and registration, timing from birth to beginning of treatment of positive cases and communication with parents/professionals. Follow-up of the whole procedure and education are vital components.

Neonatal screening is a system comprised of many professionals with expertise in many different areas of medical care: nurses, laboratory technicians, clinical biochemists, pediatricians, neuropediatricians, social workers, obstetricians, medical geneticists, and genetic counselors. Through long-term follow-up of patients/families, including reproductive aspects, the neonatal screening program becomes interdisciplinary.

Since the early 1960's our capability to interpret and diagnose inherited metabolic diseases (IMD) has greatly increased. The Metabolic and Molecular Bases of Inherited Disease (MMBID), the book which encompasses the progress of knowledge on inherited disease, described 78 entities in its 1st edition from 1960, and around 600 in its 8th edition from 2001 (MMBID 8)[5]

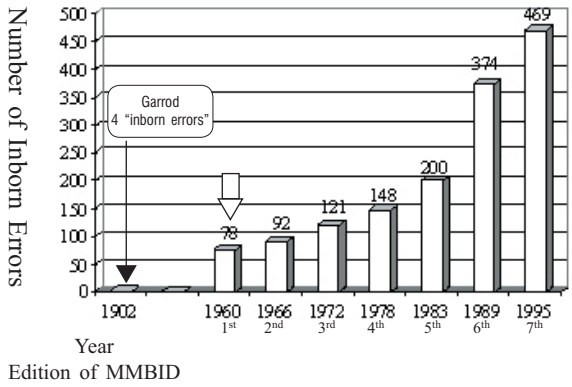

Fig. 2. Graphic representation of the exponential increase in our capability to interpret and diagnose inherited metabolic disorders (IMD). The illustration is based on the rapidly expanding book, "The Metabolic and Molecular Bases of Inherited Disease", the MMBID, which encompasses the progress in new knowledge on IMD. Data source, Jemenez-Scanchez G, Childs B, Valle D[6]. The arrow indicates the beginning of neonatal screening.

(Fig. 2)[6]. The onset of clinical symptoms of IMD is mainly pediatric (Fig. 3). They are overwhelming and often lethal diseases, and life span is reduced. In two-thirds of IMD, death occurs before the age of 10 years in 30% of entities, and in 20% between 10-30

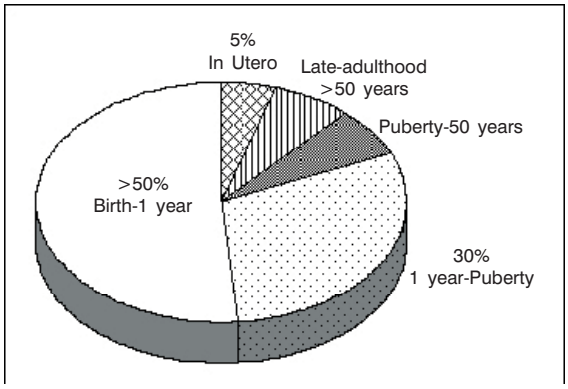

Fig. 3. Age of onset of clinical symptoms of inborn metabolic disorders. Drawing based on the analysis made by Jimenez-Sanchez G, Childs B, Valle D, in the 8th edition of MMBID[6] about conditions described in its precedent edition (MMBID 7).

years. Seventy percent of phenotypes involve more than one anatomical and functional system and the nervous system is affected in 43% of the cases. Most phenotypes compatible with prolonged survival are associated with handicaps that limit access to schooling and work[6]. Nevertheless, only a maximum of 5% of IMDs have been the object of neonatal screening programs, and the bulk of diagnosis mainly relies on the index of clinical suspicion and coordinated access to the biochemical genetics and molecular genetics services.

The few conditions (metabolic and non-metabolic) that had been the object of neonatal screening programs are listed in Table I. Among IMDs, there is universal agreement on PKU and congenital hypothyroidism (CH) and, depending on the national or regional programs, a rather high acceptance of hemoglobinopathies, classical galactosemia, maple syrup urine disease (MSUD), biotinidase deficiency, homocystinuria and congenital hyperplasia (CAH), with less consensus for cystic fibrosis (CF) and tyrosinemia. A new technology has emerged in recent years, the tandem mass spectrometry (TMS), which expands neonatal screening to an important group of disorders of intermediary metabolism (Table II).

To Screen or Not to Screen? Decision Criteria

Current criteria on neonatal screening is based on principles outlined by Wilson & Young and the World Health Organization[8]:

a) Severe morbidity/mortality if the disease is not diagnosed in the neonatal period.

b) A timely medical intervention can lead to a significant reduction of morbidity, mortality and associated disabilities.

c) Prevalence of the disease is relatively high (>1 in 10,000-15,000 newborns).

d) There is an analytical test fulfilling criteria of sensitivity, specificity and low cost.

Nevertheless, the final decision will rely on many additional considerations, including local circumstances, priorities and appraisal of benefits. In evaluating decision criteria it is useful to consider some examples. Figure 4 compares decision criteria in two Mediterranean countries (Italy and Spain) that share many coincident, social, demographic and cultural traits. They also had a similar number of

Table I. Conditions Most Commonly Included in Neonatal Screening Programs

Inherited metabolic diseases	Other conditions
PKU	Endocrine
Hemoglobinopathies	CH
Galactosemia	Infectious
MSUD	HIV (sometimes blinded)
Biotinidase deficiency	Toxoplasmosis
Homocystinuria	Tumors
Tyrosinemia	Neuroblastoma
CAH (21 hydroxylase deficiency)	Ambiental toxicity
Cystic fibrosis	Lead exposure
DMD	
Hypercholesterolemia	
MCAD	
G-6-phosphate dehydrogenase deficiency	
α-1 antitrypsine deficiency	

Abbreviations: PKU: Phenylketonuria; MSUD: Maple syrup urine disease; CAH: Congenital adrenal hyperplasia; DMD: Duchenne muscular dystrophy; MCAD: Medium chain acyl-CoA dehydrogenase; CH: Congenital

Table II. Approximately 30 Diseases Which Can Be Detected By Tandem Mass Spectrometry (TMS)

4-Dienoyl-CoA reductase Deficiency	Hypermethioninemia
2-Methylbutyryl-CoA dehydrogenase deficiency	Isobutyryl-CoA dehydrogenase deficiency
3-Hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG)	Isovaleric acidemia (IVA)
β-Ketothiolase deficiency	Long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)
3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)	**Maple syrup urine disease (MSUD)**
3-Methylgutaconyl-CoA hydratase deficiency	**Medium chain acyl-CoA dehydrogenase** deficiency (MCAD)
5-Oxoprolinuria	Methyl malonic acidemia (MMA)
Argininemia	**Malonic acidemia**
Argininosuccinic aciduria (ASA)	Multiple CoA carboxylase deficiency
Carnitine/Acylcarnitine translocase deficiency	Nonketotic hyperglycinemia (NKH)
Carnitine palmitoyl transferase deficiency type II (CPT-II)	**Phenylketonuria (PKU)**
Citrullinemia	Propionic acidemia (PA)
Glutaric acidemia type I (GA-I)	Short-chain acyl-CoA dehydrogenase deficiency (SCAD)
Glutaric acidemia type II (GA-II)	Trifunctional protein deficiency
Homocystinuria	Tyrosinemia type I, II and III
Hyperammonemia, hyperornitinemia, homocitrullinuria syndrome (HHH)	**Very-long-chain acyl-CoA dehydrogenase** deficiency (VLCAD)

For 11 disorders (those in black) TMS screening is diagnostic and disease specific. For 21, screening is diagnostic, but not disease specific, because similar or even identical patterns of abnormalities can be caused by different enzyme deficiencies; additional follow-up testing is required[7].

PKU : phenylketonuria.
CH : congenital hypothyroidism.
CF . cystic fibrosis.
CAH : congenital adrenal hyperplasia.
GAL : galactosemia.
AA : aminoacidopathies.
BD : biotinidase deficiency.
G6PD : glucose-6-phosphate dehydrogenase.

Fig. 4. Graphic representation of decisions regarding neonatal screening within Italy and Spain. The number of regional/autonomous governments that have decided to screen for each disorder is expressed in % of the total number of regions within the respective countries. Data source, references[9,10].

regions with a political organization allowing independent decisions in matters of public health. In both countries there was universal agreement in favor of screening for PKU and CH, but the decision to screen for galactosemia and CF had been adopted in more regions in Italy than in Spain, while screening for CAH was more frequent in Spain. Moreover, in Spain there were eight regions which historically screened for amino acid disorders with paper or thin layer chromatography, sometimes also in the urine. Nevertheless, specific diseases are not defined in their respective programs, which nowadays would be inadvisable for a neonatal screening program. There are four diseases which are screened in only one region: galactosemia (Spain), biotinidase deficiency (Spain), hemoglobinopathies (Spain) and glucose-6-phosphate dehydrogenase (Italy)[9,10].

Figure 5 gives the example of a country, the United States, with very distinct traits. The entirety of States within the U.S. show universal agreement for PKU and CH, but

PKU : phenylketonuria.
CH : congenital hypothyroidism.
GA : galactosemia.
Hb : hemoglobinopathies.
CAH : congenital adrenal hyperplasia.
BD : biotinidase deficiency.
MSUD: maple syrup urine disease.
HCys : homocystinuria.
CF : cystic fibrosis.
MCAD: medium chain acyl-CoA dehydrogenase.
Tyr : tyrosinemia.
G6PD : glucose-6-phosphate dehydrogenase.

Fig. 5. Graphic representation of decisions regarding neonatal screening in the United States. The number of States within the US that have decided to screen for each disorder is expressed in % of the total number of States. Data source, references[2,11]. Additional disorders that can be screened by tandem mass spectrometry are not represented in the Figure; nevertheless, 23 States are using or introducing this technology as a pilot[11].

90% of States also include galactosemia and hemoglo-binopathies, and around 40% screen for CAH, biotinidase deficiency and MSUD. On the contrary, CF has, at least at the moment, a low acceptance (10%)[2-11].

Hemoglobinopathies screening is justified in the USA due to its high prevalence in populations of Afro-Caribbean origin, but perhaps in some Mediterranean countries, for other epidemiological reasons, we should reconsider its implementation in the future. Concerning galactosemia, prevalence is low (around 1/40,000), and available evidence suggests that although screening may result in earlier diagnosis and limit early morbidity and mortality[12,13], it probably has no effect on long-term complications[14]. It is therefore one example of a controversial issue. While a majority of states within the USA screen for galactosemia, as do Australia and a number of European countries, a majority of pediatricians in of the UK and in Spain feel that through clinical vigilance, galactosemia can be diagnosed in an acceptable time and thus, screening is unnecessary.

Cystic fibrosis is another example of controversy and diversity in decision criteria. Table III summarizes arguments in favor of and against screening for this disease. The ability of neonatal screening to alter long-term prognosis has not been conclusively proven, but there is evidence gathering strength that could be decisive: early detection prevents malnutrition and alleviates or prevents chronic lung disease[15], and this represents a

Table III. Decision Criteria on Neonatal Screening: Controversy Surrounding CF

In favor	Against
Frequent	3-5% false negatives
Life-threatening	1.14% false positives
Safe, simple, effective tests	*Parental stress associated with false+
NBS enables:	**Detects carrier status in minors
Avoidance of delayed diagnosis	Difficulties for a curative treatment
Avoidance of misdiagnosis	
Appropriate and timely genetic counseling	
It could be cost-effective in the short-term (adverted cost in the first years > cost of NBS)	

*** Early detection prevents malnutrition and alleviates or prevents chronic lung disease.

* True for any disease. ** Not a new problem (Hemoglobinopathies). *** Reference (15).
NBS: newborn screening, CF: cystic fibrosis.

direct and worthy benefit for the child. Some countries such as Australia have consolidated the inclusion of CF in the neonatal screening program. In Europe, some years ago, pilots were started in some regions within several countries, i.e. France, Italy, Spain and the UK. More recently, health care authorities from the UK[17] and from France have decided to implement screening in their respective national neonatal screening programs.

Where Are We Going? Will We Expand Neonatal Screening?

Tandem mass spectrometry (TMS) expands neonatal screening to several disorders in amino acid, fatty acid oxidation and organic acid metabolism (Table II). TMS-NS can even improve detection of PKU. The ratio phenylalanine/tyrosine is a very specific and sensitive marker, and its use can prevent early discharge. Moreover, this method gives fewer PKU false positives, which is very important in decreasing the stress of the parents, and, on the other hand, generates cost savings to offset technological costs.

A high sensitivity (95.54%) and specificity (99.67%) for the TMS extended screening has been reported with a total positive-predictive value of 11.52% and a combined prevalence of 1: 2,336[17]. Comparing with rates of cases clinically detected, TMS-NS could increase the number of patients identified each year from 50% to 100%[18]. Some cases have an associated risk of sudden death (MCAD), and in this sense, TMS-NS is not only potentially useful for treatment and counseling but can also save lives.

It is also true, however, that TMS-NS requires formal long-term studies and definition of which diseases will be included in the programs. The sensitivity, specificity and positive predictive value vary depending on the disease[17]. The number of false negatives is still not known. Patients with MCAD detected by TMS-NS might have different mutations which are not found in cases later based on clinical findings[19]. The spectrum of disorders detected by TMS-NS differs from that of those detected clinically, and it is not possible to know which of them might become symptomatic. Moreover, effective therapies for all the conditions TMS-NS can detect have not been developed uniformly.

Nevertheless, it must be recognized that children diagnosed after manifestation of clinical disease present high mortality and morbidity (they are often diagnosed after threatening acute metabolic crises). The outcome can often be improved by early treatment. Parents report significantly less stress with an early diagnosis than when it is reached after a long and distressing period of uncertainty. It can therefore be considered that TMS-NS can provide substantial benefits to the patients and their families[20].

Further discussion of TMS-NS should include two of the classic arguments against NS for any IMD: the low prevalence and lack of curative treatment.

Certainly, it is true that only around 20% of IMDs have a prevalence over 0.0001, with a prevalence of less than 0.00001 for the remaining 80%, which are qualified as "rare disease". But there is also an increasing awareness that cumulatively, these IMDs are much more common than currently believed. In fact, the rate of cases of IMD reported with expanded TMS-NS is very high: 1:4000 in newborns from North Carolina, Pennsylvania, Ohio and Louisiana[21], 1:8000[17] and the above mentioned 1:2336[18] in Germany, 1:3322 in Belgium[22] and 1:13379 in Australia[23], where the combined incidence together with CH, galactosemia and CF reaches 1 affected child in 800. Currently TMS-NS is also being implemented as a pilot in some regions within Italy, Portugal, France, and the UK and has been regularly used or implemented as a pilot within 23 States of the USA[11].

Concerning the lack of curative treatment, we can consider the interesting analysis made by Treacy et al.[24] on IMD described in the MMBID[7]. According to that report, response to treatment was complete in 12% of IMD, and there was no response in 34%. However, in more than half (54%) there was a partial response, which justifies some intervention. We are aware that unless one is prepared to recognize these disorders, they will often be undiagnosed or misdiagnosed, and often the diagnosis is reached at an advanced stage of the disease. TMS-NS provides an early diagnosis and facilitates an early intervention, so that "partial benefits" can become "substantial benefits".

Another emerging fact is that if TMS-NS is implemented, it will be necessary to establish a much closer collaboration among neonatal screening services, biochemical genetics services and metabolic clinicians, because we must now consider not only the question "to screen or not to screen?" but also "to fight or not to fight?" against severe IMD.

New Horizons

Development of the ethical, legal and social frameworks will be very important. Facts, such as the varying degree of effectiveness of therapies, the detection of the heterozygote status in minors (hemoglobinopathies, cystic fibrosis) or the high value of leftover dried blood spots as an unbiased population sample together with the stability of DNA on this spot, raise the debate on the mandatory or voluntary nature of the programs, the protection of confidentiality, the informed consent/dissent of parents as well as the policy of storage and access to the sample for research[25-27]. The development of educational aspects of the programs will be the key to achieve a true shared decision-making.

Technological progress is a non-stop process and there is a growing demand for expanding the range of disorders to be screened. Certainly the supply of blood is limited, but from the concept "one test one disease" we are moving to "one test many diseases" (tandem mass) and in the future from "one sample or punch one disease" to "one sample a whole spot extraction" (solvent for small molecules, buffer for proteins/steroids, DNA extraction); the inclusion of urine spots could also allow new detection[28].

Demonstrated benefits of early detection and treatment will give support to new candidates: Smith-Lemli-Opitz syndrome, X-linked adrenoleukodystrophy, Krabbe and other lysosomal diseases, disorders of creatinine metabolism, congenital defects of glycosylation, and Wilson's disease (3-6 months of age). New genetic tests could include pre-symptomatic susceptibility screening whereby the benefit to the neonate is not immediate: Type-I diabetes, hemochromatosis, and other diseases later in life. The inclusion of diseases for which treatment or symptom prevention may not exist can be considered, if benefits of knowing are proven and are considered sufficient, i.e. provide the family with an opportunity for counseling regarding future pregnancies (Duchenne muscular dystrophy).

Other programs designed to serve infants in the neonatal period such as newborn hearing screening could be connected to newborn heel-stick screening programs in an integrated and coordinated model.

Addition of new IMDs should utilize the existing dried blood spot specimen, and integrate the analytical perfor-mance (QAP) of existing NS programs. Additions should include diseases which have a prevalence sufficient to warrant public health attention, provide measurable benefits to the newborn being tested and consider that benefits to identified infants should outweigh the costs of the NS program.

Final decision will relay on what kind of benefits we consider: curative, palliative, informative, preventive, anticipatory. In fact, the use of NS is shifting towards a wider concept, which includes quality of life issues and psychological benefits to the parents, to the siblings and to the community. Specific disease selection will depend on achievements in technological, clinical, epidemiological and basic research; the social, ethical, legal and organizational framework; and the policy analysis or planning. Public participation (general, parent/patient groups, professionals) in medical policy-making will be key to the issue of NS and genetic screening in general.

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