**Review**

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# Current and future perspective of newborn screening: an Indian scenario

DOI 10.1515/jpem-2015-0009
Received January 9, 2015; accepted May 22, 2015; previously published online July 18, 2015

**Abstract**

**Background:** Newborn screening comprises a paramount public health program seeking timely detection, diagnosis, and intervention for genetic disorders that may otherwise produce serious clinical consequences. Today newborn screening is part of the health care system of developed countries, whereas in India, newborn screening is still in the toddler stage.
**Method:** We searched PubMed with the keywords newborn screening for metabolic disorders, newborn screening in India, and congenital disorder in neonates, and selected publications that seem appropriate.
**Results:** In India, in spite of the high birth rate and high frequency of metabolic disorders, newborn screening programs are not part of the health care system. At Union Territory, Chandigarh in 2007, newborn screening was initiated and is currently ongoing for three disorders, that is, congenital hypothyroidism, congenital adrenal hyperplasia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Prevalence of these disorders is found to be 1:1400 for congenital hypothyroidism, 1:6334 for congenital adrenal hyperplasia, and 1:80 for G6PD deficiency.
**Conclusion:** Mandatory newborn screening for congenital hypothyroidism should be implemented in India, and other disorders can be added in the screening panel on the basis of region-wise prevalence. The objective of this review is to provide insight toward present scenario of newborn screening in India along with recommendations to combat the hurdles in the pathway of mandatory newborn screening.

**Keywords:** child disability; dried blood spot; inborn errors of metabolism; neonatal; newborn screening; phenylketonuria.

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## Introduction

Online Mendelian Inheritance in Man database describes over 6000 inherited disorders. A subset of these disorders, known as inborn errors of metabolism (IEM), induces metabolic disturbances in neonates, which if not timely identified and intervened may lead to neurological damage, physical disability, and even death of the neonate. Infants born with these potentially devastating disorders can be spared from early death and mental retardation by a population-based newborn screening (NBS) program. NBS is a process where newborns are subjected to a simple blood test, 24–48 h after birth, for detection of genetic disorders. NBS is a complete program that consists of many components such as education of parents and health care providers, filter paper card screening, follow-up of abnormal results, confirmation of diagnosis, case management, and program evaluation (1). Coordination between each component is required for its successful implementation. Universal NBS program for metabolic disorders has been described a triumph of modern medicine, aiding in early diagnosis and treatment. Recently, NBS was named one among the top 10 great public health achievements by the Center for Disease Control and Prevention (CDC) (2). Screening newborns has become an integral part of neonatal evaluation in developed countries, and millions of newborns per year are screened through this program for a number of disorders. The health policies in India initially

focused on measures to reduce infant mortality rate, but recently, NBS has been introduced in mainstream health care. The Ministry of Health and Family Welfare launched the child health screening and early intervention service, Rashtriya Bal Swasthya Karyakram (RBSK), under the umbrella of National Rural Health Mission (NRHM) to provide care to children aged 0–18 years (3). Disorders included in the screening panel are listed in Table 1. The rationale of the program is to improve the overall quality of life of children through early detection of birth defects, deficiencies, development delays, diseases, and disability. Chandigarh administration has taken a lead in this direction and implemented the NBS program in 2007 at Government Medical College and Hospital, Sector-32, Chandigarh (GMCH-32). All the newborns born at GMCH-32 are being screened for three disorders, namely, congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), and glucose-6-phosphatedehydrogenase (G6PD) deficiency, and this year, Chandigarh administration has expanded this program to other major hospitals of the region as well.

## Important milestones in NBS

The concept of NBS was introduced in the 1960s when Dr. Guthrie proposed bacterial inhibition assay (BIA) for phenylketonuria (4–6). Later on in 1970s, with the development of immunoassays for thyroid function, CH was also included in the NBS panel (7, 8). Discovery of stable DNA from dried blood spot (DBS) in the mid 1980s guided us toward development of molecular-based confirmatory tests for various disorders (9, 10). Recently, it was shown that single-nucleotide polymorphism analysis can be done on unamplified genomic DNA obtained from DBS (11, 12). Revolution in NBS occurred with the introduction of the mass spectrometry (MS) technique. MS/MS technology had made possible the detection of 30 or more metabolic disorders in a single run with high sensitivity and specificity (13). Currently, NBS programs are successfully running worldwide, but there exists a non-uniformity in the screening panel. Keeping in view the non-uniformity in the number and type of metabolic disorders screened, the Maternal and Child Health Bureau and the American College of Medical Genetics took initiative to outline a uniform NBS panel (14). Efforts done by these two institutes led to the formation of the Recommended Uniform Screening Panel. Key factors in the assessment of a particular disorder include availability of a screening test, scientific evidence available, level of understanding of the natural history of the condition supporting epidemiology data, and presence of an effective treatment. On the basis of these parameters, conditions are categorized into core and secondary conditions. With time, NBS has been dramatically evolved from a simple BIA to complex methodologies like gas chromatography mass spectrophotometry, MS/MS, microarray, and next-generation sequencing. This

**Table 1:** Screening panel introduced by RBSK.

| | |
|---|---|
| **Defects at birth** | **Deficiencies** |
| Neural tube defect | Anemia especially severe anemia |
| Down syndrome | Vitamin A deficiency (Bitot spot) |
| Cleft lip and palate/cleft palate alone | Vitamin D deficiency (rickets) |
| Talipes (club foot) | Severe acute malnutrition |
| Developmental dysplasia of the hip | Goiter |
| Congenital cataract | |
| Congenital deafness | |
| Congenital heart diseases | |
| Retinopathy of prematurity | |
| **Childhood diseases** | **Developmental delays and disabilities** |
| Skin conditions (scabies, fungal infection, and eczema) | Vision impairment |
| Otitis media | Hearing impairment |
| Rheumatic heart disease | Neuromotor impairment |
| Reactive airway disease | Motor delay |
| Dental caries | Cognitive delay |
| Convulsive disorders | Language delay |
| | Behaviour disorder (autism) |
| | Learning disorder |
| | Attention deficit hyperactivity disorder |
| Congenital hypothyroidism, sickle cell anemia, beta thalassemia (optional) | |

NBS panel now goes beyond the analysis of blood spot, and we are expecting more breakthroughs in this field in the foreseeable future.

## An NBS picture in India

The Indian Academy of Pediatrics celebrated the golden jubilee of the commencement of its NBS program in 2013, but still the concept of NBS in India is very young. NBS was started in India when other developed countries had designed their policies and mandated NBS. In few states in India, discrete private and government sectors are running their own programs. As a large population-based study has not been done in India, a clear picture regarding exact prevalence of metabolic disorders is not available. However, some information regarding incidence of metabolic disorders in India are available.

In India, the first NBS program was carried out in 1980 in Bangalore, where 1, 25,000 newborns were screened for various metabolic disorders (15). This study revealed that disorders like hyperphenylalaninemia, tyrosinemia, glycinemia, and maple syrup urine disease (MSUD) are prevalent in our population and mainly responsible for mental retardation. A multicentric study was carried out by the Indian Council of Medical Research (ICMR) in 1991 at Bangalore, Bombay, Delhi, and Lucknow to determine the extent and pattern of genetic causes of mental retardation. In this study, it was reported that metabolic defects are responsible for mental retardation in 65 patients out of 1314 patients screened (16). In another expanded study conducted in Hyderabad, 18,300 newborns were screened for amino acid disorders, CH, CAH, biotinidase deficiency, G6PD deficiency, galactosemia, and cystic fibrosis. The results revealed high prevalence of CH followed by CAH and hyperhomocystenemia (17). These studies showed that majority of the cases of mental retardation may be attributed to our inability to detect metabolic disorders in early infancy. Disorders that are potential candidates for NBS in India are as follows.

### Congenital hypothyroidism

CH is the major preventable cause of mental retardation in India. Signs and symptoms of hypothyroidism are often minimal at birth, so clinical diagnosis can be made through NBS. On account of delay in diagnosis and treatment, affected children gradually develop mental retardation. In 2007, ICMR introduced a multicentric program in five states of the country to confirm the incidences of CH and CAH in India. This large pilot study screened a huge number of newborns in Delhi (north), Chennai (south), Kolkata (east), Mumbai (west), and Hyderabad (central). The study has been completed successfully, but the data are still unpublished. Screening programs carried out so far in India to detect incidence of CH are listed in Table 2. All these studies showed that the prevalence of CH is high in India when compared to its worldwide prevalence (1:3000 to 4000) (25–27). In a country like India, where birth rate is very high, this high prevalence underlines the need for nationwide screening for CH.

### Congenital adrenal hyperplasia

According to a screening survey conducted by All India Institute of Medical Sciences, New Delhi, out of 63 cases with ambiguous genitalia, 38% were diagnosed with CAH (28). Few studies also showed that the simple virilizing (SV) type of CAH was more prevalent than the salt wasting (SW) type and affected mostly females. In a study conducted on 29 CAH patients in a tertiary health care center in South India, 76% of CAH patients were female and 24% were male. The SV type was seen in 81% of the women, whereas the SW type was predominant in boys (85%) (29). Similar results were obtained in the study published by Marumudi et al. from North India. Out of 62 patients under study, 50 were SV and 12 were SW, with the majority being female (30). Screening programs carried out to detect incidence of CAH in India are listed in Table 3. High incidence of CAH in these studies indicates the need to screen newborns for CAH. Hence, it is advisable that CAH be added to core screening panel along with CH for early identification and intervention.

**Table 2:** NBS for CH in India.

| Authors and year | No. of babies screened | Incidence | Frequency |
|---|---|---|---|
| Desai et al., 1987 (18) | 12,407 | 1:2481 | 0.04% |
| Desai et al., 1994 (19) | 25,224 | 1:2804 | 0.03% |
| Devi and Naushad, 2004 (17) | 18,300 | 1:1700 | 0.1% |
| Sanghvi and Dewakar, 2008 (20) | 2872 | 1:500 | 0.2% |
| Kaur et al., 2010 (21) | 6813 | 1:3400 | 0.02% |
| Kumar et al., 2014 (22) | 19,800 | 1:1042 | 0.1% |
| Kapil et al., 2014 (23) | 613 | 1:22 | 4.5% |
| Shriram et al., 2014 (24) | 30,514 | 1:900 | 0.1% |

**Table 3:** NBS for CAH in India.

| Authors and year | No. of babies screened | Incidence | Frequency |
|---|---|---|---|
| Devi and Naushad, 2004 (17) | 18,300 | 1:2575 | 0.03% |
| Kaur et al., 2010 (21) | 6813 | 1:6813 | 0.01% |
| Shriram et al., 2014 (24) | 30,514 | 1:2000 | 0.1% |

## Glucose-6-phosphate dehydrogenase deficiency

In India annually 390,000 children are born with G6PD deficiency (31). In the absence of NBS for the same, these infants are at a greater risk of hemolytic anemia. Four hundred different variants and 90 different mutations of this disease are known globally; in India, among them G6PD Mediterranean (563 C→T) is the most common type followed by G6PD Kerala-Kalyan (949 G→A) and G6PD Orissa (131 C→G) (32). The "Heel to Heal" program conducted by the Goa government also showed high prevalence of G6PD deficiency; 33 newborns out of 27,578 screened were identified with G6PD deficiency (33). All the studies showed different prevalence of G6PD deficiency in our population, which vary according to caste, tribe, and ethnic group, which was nevertheless high. Screening programs carried out to detect incidence of G6PD deficiency in India are listed in Table 4.

## Congenital metabolic disorders

Other metabolic disorders like amino acid disorders, organic acidemias, and fatty acid disorders are not frequently studied because they require special and advanced techniques like MS and high-performance liquid chromatography. High initial cost of these systems limits the use of these methods for NBS. Also, high level of expertise is required for sample preparation, system operation, and interpretation of data. As a result, few reports are available regarding the incidence of these disorders in India. Screening programs carried out to detect prevalence of these metabolic disorders are listed in Table 5.

**Table 4:** NBS for G6PD deficiency in India.

| Authors and year | No. of babies screened | Frequency | Male | Female |
|---|---|---|---|---|
| Verma et al., 1990 (34) | 1000 | 3.9% | 5.0% | 2.8% |
| Pao et al., 2005 (35) | 2479 | 2.0% | 2.8% | 1.1% |
| Dash et al., 2005 (36) | 490 | 17.5% | – | – |
| Kaur et al., 2010 (21) | 6813 | 0.8% | – | – |
| Mohanty et al., 2014 (37) | 191 | 16.7% | 20% | 11.3% |

## Congenital hearing loss

Congenital hearing loss is another disorder that is being progressively identified in increasing prevalence in India. According to the survey conducted by the National Sample Survey Organization in 2001, 6.3% of Indians are suffering from significant hearing loss. Of these, a large percentage is children between the ages of 0 and 14 years (43). It is indeed a big challenge to provide education, training, and employment to this large population. Negative impact of sensorineural hearing loss on language acquisition and speech can be minimized if hearing aid is provided in the prelingual phase. Screening programs carried out to detect frequency of congenital hearing loss are listed in Table 6. In order to prevent deafness due to a congenital cause, a pilot project was initiated by the National Programme for Prevention and Control of Deafness in 2006, in 25 districts of 10 states and 1 union territory. It has been proposed to expand the program to 200 districts under the 12th Five Year Plan (43). In developed countries, newborn hearing screening is a well-established program, but it has yet to gain foothold in India.

## Congenital heart diseases

Congenital heart diseases (CHDs) are other disorders recently added to the panel of NBS in developed countries. In India, frequency of 7.8% was observed for CHDs in a study conducted by Vaidyanathan et al. in 2011 on 5487 babies in Kerala (49). High frequency observed in the study strongly emphasized the need for more pilot projects on screening of CHDs.

Few pilot studies and plenty of published data with some survey have been done since the beginning of NBS in India, but there is a need to extemporize the current scene of NBS. At present in India, NBS is not mandatory in the health care system, but it should be mandatory in view of the high prevalence of preventable diseases. Strikingly, 12,000 babies are saved by the NBS program in the United

**Table 5:** NBS for other metabolic disorders in India.

| Authors and year | No. of babies screened | Disorder screened | Cases found | Frequency |
|---|---|---|---|---|
| Kaur et al., 1994 (38) | 2560 | Amino acid disorders | 157 | 6.1% |
| Muranjan and Kondurkar, 2001 (39) | 366 (patients with IEM) | Organic acidemias | 32 | 8.7% |
| Radha et al., 2006 (40) | 607 | Hyperhomocysteinemia | 52 | 8.6% |
| Nagaraja et al., 2010 (41) | 3550 | IEM | 113 | – |
| | | | Amino acid disorders: 61 | 1.7% |
| | | | Organic acidemias: 47 | 1.3% |
| | | | Fatty acid oxidation: 05 | 0.1% |
| Narayanan et al., 2011 (42) | 420 | Organic acidurias | 45 | – |
| | | | Methylmalonic aciduria: 15 | 3.6% |
| | | | Propionic aciduria: 16 | 3.8% |
| | | | MSUD[a]: 13 | 3.1% |
| | | | Isovaleric aciduria: 01 | 0.2% |

[a]Maple syrup urine disease.

**Table 6:** NBS for congenital hearing loss in India.

| Authors and year | No. of babies screened | Technique used | Frequency |
|---|---|---|---|
| Nagapoornima et al., 2007 (44) | 1769 neonates (1490: not at risk; 279: at risk) | OAE[a] | High risk 0.1%<br>Not at risk 0.04% |
| Paul, 2011 (45) | 10,165 | OAE+ABR[b] | Nursery: 0.1%–0.3%<br>ICU: 2%–4% |
| Mishra et al., 2013 (46) | 1101 | OAE+ABR | 1.08% |
| Rai et al., 2013 (47) | 610 | Proportion test | 0.8% |
| Augustine et al., 2014 (48) | 9448 | ABR | 0.3% |

[a]Otoacoustic emissions. [b]Auditory brain-stem response.

States, whereas in India every year, around 25 million births take place, but how many children are diagnosed by IEMs is unknown.

## NBS at a glance in Chandigarh

The NBS program at Chandigarh was started in 2007 with the objective to know the exact prevalence of common metabolic disorders in this region and to develop policies and protocols to initiate NBS in a government setup. After reviewing the literature, a panel of three disorders, namely, CH, CAH, and G6PD deficiency, was prepared. Universal heel prick method was adopted for sample collection between 24 and 48 h of birth after pre-test counseling of the parents on the necessity and benefits of screening. The total number of newborns screened until December 2014 is 25,395 out of 28,272 born at GMCH-32. Coverage of neonates under the NBS program is 89%. The remaining 10% who did not undergo screening include still born (4%), refusal (0.1%), LAMA (left against medical advice) (0.1%), early discharge (2.3%), and NICU admission (3.2%). Incidence of disorders screened in our study is

- Congenital hypothyroidism – 1:1400
- Congenital adrenal hyperplasia – 1:6334
- G6PD deficiency – 1:80 with a higher prevalence in males than in females.

The NBS program at Genetic Centre, GMCH-32, has been evolving over a period of years, and after refinements and re-refinements in sampling collection, sample analysis, and follow-up, we have successfully reduced the false-positive rate. NBS deals with rare disorders, and benefits cannot be easily shown without very large studies; therefore, we are extending the NBS program to other government hospitals of Union Territory, Chandigarh. Along with this, we are planning to add more disorders in the screening panel, namely, galactosemia, phenylketonuria, and biotinidase deficiency.

## Future perspective of NBS in India

The aim of NBS is prevention of child illness. Today, NBS is the most widely used public health initiative known to prevent genetic disorders in developed countries. The current debate over NBS revolves around certain questions:

- What conditions should be added to the screening panel?
- Should infants be screened for a condition only when effective treatment is available?
- Should secondary benefits to family and society be given weight?
- How can we assess the specific benefits and risks before adding a new condition for screening?
- How cautious should we be when the benefits of screening are uncertain?

However, in India, debate is about: Is NBS required in India or not? (50). If we consider the available data, about 25 million births annually take place in India, of which 800,000 are born with congenital malformations, 25,000 with metabolic disorders, 350,000 with G6PD deficiency, and 15,000 with CH (51). Available data strongly emphasize on the need of routine NBS in India.

At present, NBS is not routinely done in mainstream health care in India. The program is still confined to a few centers and projects. At this point in time, emphasis should be on developing policies and protocols to initiate the NBS program nationwide for disorders that if not treated timely produce deleterious effects on the health of the newborn. In a developing country like India, it is impractical to screen newborns for many disorders at this stage. Only disorders in the screening panel for which confirmatory tests are available and there is direct cost-benefit should be included, as this is highly relevant from the socio-economic aspect. Different screening programs conducted in India showed high prevalence of CH; therefore, in the initial stage, focus should be on nationwide implementation of NBS for CH because if no intervention is done in early infancy, it can lead to irreversible impairment of neurocognitive function. Also for confirmed cases of CH, economically viable therapeutic measures are available. Once the NBS program for CH is implemented, we can extend the panel by adding more disorders depending on their prevalence.

This is the time to develop policies and protocols to introduce NBS in our health care system, at least for treatable metabolic disorders. Any center running NBS should consider the following points:

(i) NBS program to be made responsive to recognized needs in the Indian setting.
(ii) Objectives to be defined as early as possible.
(iii) Promotion of equity and access for entire population.
(iv) Overall benefits should outweigh the risks.

These fundamental points must be addressed to ensure the successful implementation and outcome of the NBS program in India.

## Recommendations for successful implementation of NBS program in India

- Implementation of NBS in a country like India where birth rate is quite high, attaining 100% coverage is a difficult task in itself. Problems like high proportion of home deliveries and early discharge from hospitals due to the massive load of deliveries make the situation worse. In order to successfully implement the NBS program, these problems must be taken care of by generating awareness and knowledge about the NBS program among general public, medical professionals, auxiliary nurse midwives, and Anganwadi workers.
- The already existing infrastructure in terms of laboratories and manpower should be strengthened with the minimal budget required, and DBS samples from neighboring states can be sent to already existing laboratories for analysis.
- Cost can be further decreased if custom duty on the import of equipments and consumables is decreased.
- To successfully establish the NBS program, there will be high initial cost, which includes charges for laboratories establishment and testing. There will be an additional expenditure on data management, family notification, follow-up, and confirmatory testing. Continuous funding and a better research system are required to realize the short- and long-term benefits of NBS. Development of infrastructure could be taken care of by the central government through NRHM and RBSK scheme along with contributions by state governments, interested NGOs, corporate sectors, and willing families.
- With the help of CDC and National Accreditation Board for Testing and Calibration Laboratories, quality control of the NBS program can be assured. Quality of program can also be ensured by crosschecking the samples from one laboratory by other.

- With around 25 million annual birth rate, more true-positive cases will be detected as the detection rate improves. For these cases, timely counseling, treatment, and rehabilitation will be necessary.
- For confirmatory testing, nodal or sub-nodal centers can be created in a zone-wise manner, and samples from nearby regions can be sent to these centers.
- For management of confirmed cases, coordination with the already existing team of doctors and paramedical staff involved in NBS shall be recommended through Web networking and other sources of communication.
- Research should be promoted on setting up of uniform protocols and development of new therapies.
- All regions of India are not equipped with a dedicated laboratory for NBS; in these regions, new laboratories can be created in coordination with already existing laboratories.
- With establishment of the NBS program in various regional centers, there will be an increase in the number of false-positive cases, and this can be mitigated through quality testing, high detection rate, and trying to minimize false positives. In order to reduce anxiety and keep the belief of the general population in the need for NBS, proper pre- and post-test counseling should be done.
- Just screening without follow-up and treatment will not fulfill the objective of NBS. "Special clinics" should be constituted in each state to help pediatricians in treating confirmed cases. A special clinic should consist of at least a biochemist, a metabolic specialist, a geneticist, an endocrinologist, and a nutritionist.
- Many metabolic disorders such as MSUD, phenylketonuria, isovaleric acidemia, disorders of leucine metabolism, urea cycle disorders, etc. require dietary treatment. Special medical food is indispensable for treatment of these disorders. At present, these special diets are not commercially available in India; patients have to import these diets. These diets are, however, very expensive and not afforded by majority of patients. Therefore, efforts should be made to develop formulas to prepare these diets in India.

## Conclusion

NBS is aimed at timely identification of disorders that affect neonates so that irreversible damage can be prevented. Challenges faced by the NBS program in India can be resolved by starting the program in a planned manner, and focus should be on technical, medical, and logistic support. Nationwide NBS program should be started for CH, as its prevalence is quite high in India. Once the program picks its pace, experience gained by different laboratories can be applied to the development of policies for sustainability of the NBS program. Awareness is the most important component of NBS and must be started in the very first step before development of infrastructure. After successful implementation of the NBS program, focus should be on the extension of screening panel according to the prevalence of various disorders, establishment of new laboratories, management of sick neonates, and development of new therapies.

**Acknowledgments:** The authors would like to acknowledge the complete financial assistance extended by Chandigarh, Union Territory Administration for this study. We also thank Dr. Deepak Chawla and Dr. Suksham Jain neonatologists, GMCH-32, for management of positive cases of CH, CAH and G6PD deficiency.

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