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Expanded Newborn Screening in South India: A Nine-Year Evaluation of Programme Uptake, Recall, and Diagnostic Yield

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Abstract

Background

Expanded newborn screening (ENBS) plays a crucial role in the early detection of congenital genetic, metabolic, and endocrine disorders, enabling timely interventions to reduce morbidity and mortality. In India, the screening, prevention, and management of Inborn Errors of Metabolism (IEM) are yet to be fully integrated into the national healthcare system. The aim of this study was to evaluate the feasibility, screening uptake and coverage, recall rates, and diagnostic yield of ENBS in a tertiary care centre in South India.

Methods

This retrospective observational study included 28,175 newborns screened between 2016 and 2024 using an ENBS panel covering 54 disorders. Screening data were analyzed for annual programme uptake, screening coverage, recall rates, confirmatory testing, confirmed diagnoses, diagnostic yield, and clinical follow-up.

Results

Among 86,947 live births, 28,175 newborns underwent ENBS, corresponding to an overall screening coverage of 32.4%. Screening uptake increased from 5.1% (n=435) in 2016 to 42.1% (n=3,979) in 2024. A total of 401 infants were recalled for further evaluation (recall rate 1.4%; n=401). A total of 94 newborns were confirmed to have screened disorders, corresponding to an overall diagnostic yield of 0.3% (1 in 299 screened newborns). Congenital hypothyroidism was the most frequently detected disorder (46 cases), followed by G6PD deficiency (37 cases). Additional confirmed diagnoses included congenital adrenal hyperplasia (n=2), cystic fibrosis (n=3), fatty acid oxidation disorders (n=3), organic acid disorders (n=2), and amino acid disorders (n=1). Positive predictive value varied across conditions, with the highest observed for G6PD deficiency. Most confirmed cases received timely genetic/metabolic counseling, appropriate treatment, and follow-up.

Conclusions

Over nine years, implementation of ENBS in a tertiary-care setting was associated with a substantial increase in screening uptake and enabled the identification of clinically important and potentially treatable disorders with a relatively low recall rate. These findings demonstrate the potential feasibility and clinical utility of expanded newborn screening in India and support the development of structured newborn screening and follow-up pathways within maternal and child healthcare services.

Categories: Genetics, Pediatrics, Internal Medicine
Keywords: diagnostic yield, expanded newborn screening, feasibility, inborn errors of metabolism, neonate, recall rate

Introduction

Expanded newborn screening (ENBS) enables early detection of congenital, metabolic, and endocrine disorders, reducing morbidity, mortality, and long-term disability through timely intervention and structured follow-up. Metabolic disorders, including inborn errors of metabolism (IEM), though individually rare, collectively affect 1 in 1,000-5,000 live births globally [1]. In India, the reported incidence is approximately one in 1,000 newborns [2]. The prevalence of metabolic disorders varies across different states, with Bihar having high prevalence of congenital hypothyroidism (10.2 per 1,000) and congenital adrenal hyperplasia (16.0 per 1,000), West Bengal had higher rates of G6PD deficiency (146.7 per 1,000) and phenylketonuria (8.2 per 1,000), Delhi had high prevalence of biotinidase deficiency (8.5 per 1,000) and Hyderabad had high prevalence of galactosemia (3.89 per 1,000) [3]. The incidence of inherited metabolic disorders detected through expanded newborn screening varies considerably across countries and

populations [4]. Reported incidences include approximately 1 in 8,557 newborns in Japan, 1 in 7,030 in Taiwan, 1 in 13,205 in South Korea, and 1 in 2,200 in Germany [5]. In China, substantial regional variation has been reported, with estimates ranging from approximately 1 in 1,683 to 1 in 8,304 newborns [6].

Congenital anomalies and inherited metabolic disorders are the third leading cause of neonatal mortality in India, influenced by consanguinity, high birth rates, limited genetic counselling, and improved diagnostics. In India, selected state-level initiatives have begun screening for limited conditions, but comprehensive national integration is lacking [3]. The Indian Academy of Paediatrics strongly advocates inclusion of newborn screening in our public health policy.

Evidence across the globe shows that IEM incidence varies widely, and while many high-income countries have established ENBS as a public health priority, implementation remains inconsistent in low- and middle-income settings [7]. India has region-specific newborn screening initiatives, but lacks a centrally mandated Universal Newborn Screening program, primarily due to infrastructural constraints, shortages of trained human resources, sociocultural barriers, and inequities in access [8].

The present study aimed to assess the feasibility, parental acceptance, screening coverage, recall rates, and diagnostic yield of ENBS over nine years at a tertiary care centre. This study was conducted in a single centre and provides programme-level evidence in a population that was screened voluntarily.

Materials And Methods

This retrospective observational study was conducted at Fernandez Hospital, Hyderabad, India, a tertiary care center with a level three Neonatal Intensive Care Unit over a nine-year period from January 2016 to December 2024. This study protocol was reviewed and approved by the Institutional Ethics Committee, Institutional Review Board, and Fernandez Foundation with EC Reference No.21_2022. Written and informed consent was obtained from the parents or guardians to perform and report the extended newborn screening test. No data that identifies the patient has been mentioned.

All neonates who underwent ENBS during the study period were included. Neonates who have not undergone ENBS and those who succumbed before sample collection were excluded. Participant identification and data retrieval were carried out using the hospital laboratory database.

The primary objective is to estimate the detection rate of endocrine disorders (congenital hypothyroidism and congenital adrenal hyperplasia), cystic fibrosis, and inborn errors of metabolism (amino acid, organic acid, and fatty acid oxidation disorders) among neonates undergoing ENBS. The secondary objective is to evaluate parental acceptance of ENBS and determine the neonatal recall rate among screened neonates.

Screening procedure

ENBS was offered to all newborns after 48 hours of life. Neonates discharged before 48 hours were counselled and screened during their follow-up outpatient visit. For neonates admitted to the neonatal intensive care unit (NICU), screening was performed once they were clinically stable and established on full enteral feeds. Parents were counseled regarding the screening program, provided with an information brochure, and written informed consent was obtained prior to sample collection. Capillary blood samples were collected by heel prick onto standardized filter paper cards. In cases of inadequate or unsatisfactory specimens, repeat sampling was performed. Dried blood spot (DBS) samples were analyzed using immunoassay and tandem mass spectrometry (MS/MS).

The ENBS programme comprised a panel of metabolic, endocrine and other inherited disorders. Screening was performed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and DELFIA-based biochemical assays, according to the analyte and condition. The MS/MS component included amino-acid and acylcarnitine profiling, while DELFIA-based assays included thyroid-stimulating hormone (TSH), 17-hydroxyprogesterone (17-OHP), immunoreactive trypsinogen (IRT), total galactose, glucose-6-phosphate dehydrogenase (G6PD) activity, and biotinidase activity.

The MS/MS screening panel included amino-acid markers such as phenylalanine, tyrosine, leucine/isoleucine, methionine, citrulline, ornithine, and arginine, together with a broad acylcarnitine profile (C0-C18 species). The conditions, corresponding screening analytes and analytical methods as well as acylcarnitine and amino acid analytes tested and reference ranges, were also included. Screening cut-offs were analyte- and assay-specific laboratory reference limits. A result exceeding the relevant screening threshold was considered screen-positive and prompted repeat screening and/or appropriate confirmatory investigations, depending on the analyte and clinical context. Abnormal TMS screening profiles were further evaluated using urine liquid chromatography-tandem mass spectrometry (LC-MS/MS), where indicated. Screening results were not considered diagnostic in isolation.

Particular attention was given to factors such as age at collection, feeding status, prematurity, low birth weight, transfusion, total parenteral nutrition, illness, medications, and specimen collection or handling

that may influence newborn screening results.

Recall and follow-up procedures

Newborns with borderline or abnormal screening results were recalled for repeat testing. Families were contacted by telephone, email, postal letter, or, when necessary, through a home visit. Infants with normal results on repeat testing were reassured and discharged from further follow-up.

The recall rate was defined as the proportion of infants requiring repeat or confirmatory testing following a borderline or abnormal screening result, expressed as a percentage of the total number of infants screened.

Parents of neonates with persistently abnormal results were informed of the findings and counselled regarding the need for confirmatory investigations. Confirmation of suspected cases was performed through targeted biochemical analyses of the abnormal metabolites identified on screening, followed by appropriate molecular genetic testing, including exome sequencing and/or deletion-duplication analysis, as indicated. In confirmed cases of hypothyroidism, technetium thyroid scintigraphy and thyroid ultrasonography were performed to determine the underlying etiology. Newborns with confirmed diagnosis were enrolled in regular follow-up and managed according to established clinical protocols.

The conditions screened, initial screening tests, and corresponding confirmatory diagnostic methods are summarized in Table *1*, and acylcarnitine and amino acid analytes tested and reference ranges are represented in Table *2*.

SLNo	Condition screened	Parameter tested	Principle	Cutoff values	Confirmatory test
1	Congenital hypothyroidism	nTSH	Time-resolved fluoroimmunoassay	>20 µU/ml	Serum TSH, free T4, free T3
2	Cystic fibrosis	IRT	Time-resolved fluoroimmunoassay	>65 µg/ml	CFTR gene mutation analysis
3	Congenital adrenal hyperplasia	17 OHP	Time-resolved fluoroimmunoassay	>30nmol/ml	CYP21A2 deletion, duplication and sequencing
4	G6PD Deficiency	G6PD	Oxidation test	<1.5 units/gmHb	G6PD quantitative assay by spectrophotometry and G6PD gene testing
5	Galactosemia	TGAL	Fluorescent galactose oxidase method	>15mg/dl	Exome sequencing

TABLE 1: Conditions included in the expanded newborn screening (ENBS) panel, primary screening assays, and confirmatory diagnostic evaluations.

nTSH: neonatal thyroid-stimulating hormone; IRT: immunoreactive trypsinogen; G6PD: glucose-6-phosphate dehydrogenase; 17-OHP: 17-hydroxyprogesterone; CFTR: cystic fibrosis transmembrane conductance regulator; TGAL: total galactose

Acyl carnitine analytes	Reference ranges (µmol/L)
Free carnitine (C0)	7 - 125
Acetylcarnitine (C2)	1.5 - 80
Propionylcarnitine (C3)	< 6.3
Malonylcarnitine+3-OH-butyrylcarnitine (C3-DC+C4-OH)	< 0.45
Butyrylcarnitine (C4)	< 1.7
Methylmalonylcarnitine (C4-DC)	< 1.29
Isovalerylcarnitine (C5)	< 1
3-methylcrotonylcarnitine (C5:1)	< 0.9
Hexanoylcarnitine (C6)	< 0.95

3-OH-isovalerylcarnitine (C5-OH)	< 0.9
Octenoylcarnitine (C8:1)	< 0.7
Octanoylcarnitine (C8)	< 0.6
Decadienoylcarnitine (C10:2)	< 0.22
Decenoylcarnitine (C10:1)	< 0.45
Decanoylcarnitine (C10)	< 0.65
Glutarylcarnitine (C5DC)	< 0.6
Dodecenoylcarnitine (C12:1)	< 0.51
Dodecanoylcarnitine (C12)	< 0.54
Tetradecadienoylcarnitine (C14:2)	< 0.13
Tetradecenoylcarnitine (C14:1)	< 0.8
Myristoylcarnitine (C14)	< 1.2
3-OH-Tetradecenoylcarnitine (C14-OH)	< 0.2
Hexadecenoylcarnitine (C16:1)	< 1.4
Palmitoylcarnitine (C16)	< 10
3-OH-hexadecanoylcarnitine (C16-OH)	< 0.1
Octadecadienoylcarnitine (C18:2)	< 0.73
Octadecenoylcarnitine (C18:1)	< 7
Stearoylcarnitine (C18)	< 4
3-OH-octadecenoylcarnitine (C18:1OH)	< 0.1
3-OH-stearoylcarnitine (C18OH)	< 0.1
Amino acid analytes	**Reference ranges (µmol/L)**
Glycine	< 745
Alanine	74 -613
Valine	41- 233
Leucine - isoleucine	26 - 250
Methionine	1 - 54
Citrulline	5 - 60
Phenylalanine	21 - 155
Tyrosine	17 - 250
Ornithine	< 239
Arginine	< 50

TABLE 2: Acyl carnitine and amino acid analytes.

Acyl carnitine and amino acid analytes were assessed using tandem mass spectrometry. Reference ranges are expressed in µmol/L. Clinical/whole exome sequencing was performed as applicable.

Statistical analysis

Data were entered into Microsoft Excel (Microsoft Corp., Redmond, WA) and analysed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY). Categorical variables were summarized as frequencies and percentages. The annual screening coverage was calculated as the proportion of live-born neonates who underwent ENBS among all live births during each study year and expressed as a percentage.

The diagnostic yield (detection rate) for each screened disorder was calculated as the number of confirmed cases divided by the total number of newborns screened and reported both as a percentage and as 1 in N screened newborns. The recall rate was defined as the proportion of screened newborns who required repeat testing or confirmatory evaluation following an initial positive screening result. The positive predictive value (PPV) was calculated as the proportion of recalled newborns who were confirmed to have the disorder after diagnostic evaluation. Screening outcomes, including screen-positive cases, confirmed cases, false-positive cases, loss to follow-up, and molecular diagnoses, were summarized descriptively. Infants who were screen-negative on initial ENBS testing were not followed up, so false negatives cannot be accurately calculated.

Results

During the study period from January 2016 to December 2024, the study center recorded 86,947 live births. Of the 86,947 live births during the study period, all were eligible for newborn screening, and the programme was offered universally to all newborn infants. A total of 28,175 newborns underwent ENBS, including 23,526 term and 4,649 preterm infants, corresponding to an overall screening coverage of 32.4% (n=28,175) of total live births (95% CI: 32.1-32.7%). The number of newborns eligible for ENBS, consented and underwent ENBS each year, the number of newborns who declined ENBS, and the number of newborns who missed screening because of logistical issues like missing follow-up after postnatal discharge, change in address, or personal reasons are represented in Table *3*.

SL NO	Year	Newborns eligible for ENBS	Declined ENBS	ENBS done	Missing due to Logistical/clinical Reasons
1	2016	8,578	7,575	435	568
2	2017	8,891	6,798	1,111	982
3	2018	9,305	4,803	2,419	2,083
4	2019	10,457	4,234	4,371	1,852
5	2020	9,831	3,627	3,452	2,752
6	2021	9,586	3,262	3,836	2,488
7	2022	10,889	3,891	4,376	2,622
8	2023	9,952	3,051	4,196	2,705
9	2024	9,458	3,619	3,979	1,860
	Total	86,947	40,860	28,175	17,912

TABLE 3: Annual numbers of newborns eligible for ENBS, whose guardians declined screening, who underwent screening, or who missed screening due to clinical or logistical reasons

ENBS: expanded newborn screening

Screening was voluntary and contingent on parental consent, which contributed to incomplete coverage in the program's early years. The uptake of ENBS increased over time; in 2016, only 5.1% (n=435) of newborns were screened, whereas by 2024, coverage had risen to 42.1% (n=3,979) of all newborns delivered at the centre. Figure *1* illustrates the annual number of live births and the proportion of neonates screened through ENBS during the study period.

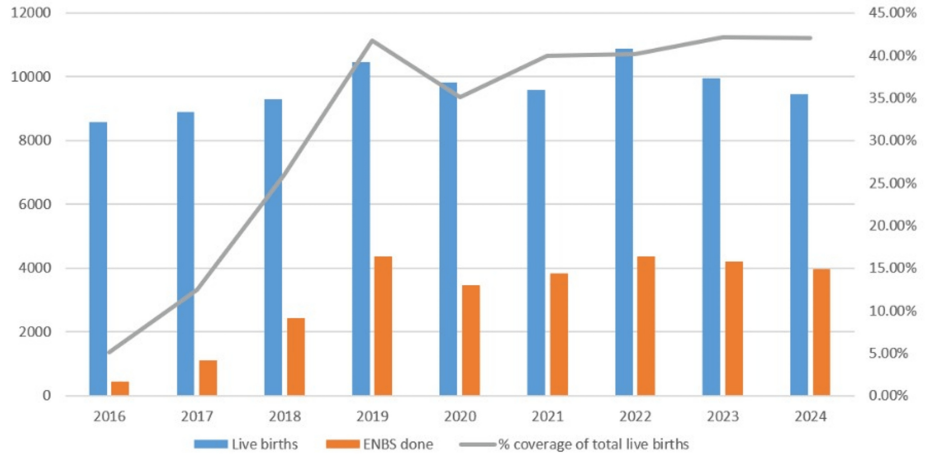


FIGURE 1: Annual number of live births and the proportion of neonates who underwent ENBS during the study period.

ENBS: expanded newborn screening

Of 479 neonates who were initially positive, a total of 401 neonates were recalled for further evaluation, and 78 could not be recalled for different reasons, such as neonates not being brought to follow-up postnatal visits, not being able to contact their parents due to an address change, parents not willing to do repeat testing, and parents not being approachable due to a change in telephone numbers (recall rate: 1.4% (n=401) (95% CI: 1.29-1.56%). Of the 401 recalled newborns with an initial positive ENBS result, 387 underwent confirmatory testing, whereas 14 did not undergo confirmatory testing due to different reasons, such as being lost to follow-up, death of the infant before confirmatory testing could be done, or parents refusing further diagnostic evaluation. Among those evaluated, 94 were confirmed to have a screened disorder, and 293 were false positives. The positive predictive value (PPV) among newborns with confirmatory testing was 24.3% (n=94) (95% CI: 20.3-28.8%). Of 28,175 neonates screened, 94 were diagnosed with endocrine disorders like congenital hypothyroidism, congenital adrenal hyperplasia, and conditions such as cystic fibrosis and metabolic disorders including amino acid, organic acid, and fatty acid oxidation disorders. The diagnostic yield attributable to metabolic/genetic disorders (excluding CH, G6PD) was 1 in 2561 (0.04%), while there was an overall diagnostic yield of 1 in 299 screened newborns, corresponding to a detection rate of 0.3% (94) (95% CI: 0.27%-0.40%). Nine (9.5%) among 94 confirmed cases had a history of consanguinity. Demographic characteristics of confirmed cases are represented in Table *4*.

SL NO	Demographic characteristics	No. of confirmed cases (n)	%
1	Age at diagnosis		
	< 1 year	80	85.1%
	>1 year	14	14.9%
2	Gender		
	Male	55	59%
	Female	39	41%
3	Term	78	83%
	Preterm	16	17%
4	Consanguinity		
	Yes	9	9.5%
	No	85	90.5%
5	Siblings affected		
	Yes	6	6.4%
	No	88	93.6%

TABLE 4: Demographic characteristics of confirmed cases

A total of 72 (0.2%) neonates screened positive for congenital hypothyroidism (CH); 69 (0.2%) were recalled for confirmatory testing, of whom 46 (0.2%) were confirmed to have CH. The detection rate of CH was 1 in 612 screened neonates, with a recall rate of 0.2% (n=69). The underlying etiologies included dyshormonogenesis (n=33), thyroid aplasia (n=6), ectopic thyroid (n=6), and thyromegaly (n=1).

A total of 128 (0.4%) neonates had immunoreactive trypsinogen (IRT) levels >65 µg/mL; 108 (0.4%) were recalled and underwent repeat testing. Of these 108 infants recalled, normal IRT levels were found in 90 infants and abnormal IRT levels were found in 18 infants. Among 18 infants with abnormal IRT levels on repeat testing, three were confirmed to have cystic fibrosis (CF) by genetic testing, corresponding to a detection rate of one in 9,391 screened neonates; among the remaining 15 infants who did not undergo confirmatory testing, 13 infants remained clinically healthy on follow-up until three years of age, while two died in early infancy, but the cause of death is not known. A total of 90 neonates who had normal IRT values on repeat testing and 13 infants who remained clinically healthy on follow-up contributed to 103 false positive cases.

A total of 25 (0.08%) neonates had elevated 17-hydroxyprogesterone (17-OHP) levels, of which 19 (recall rate 0.06%) were recalled for confirmatory testing. Two (0.007%) infants (one male and one female) were confirmed to have congenital adrenal hyperplasia (CAH), corresponding to a detection rate of one in 14087 screened neonates.

Around 49 (0.2%) neonates had low glucose-6-phosphate dehydrogenase (G6PD) activity (<1.5 U/g Hb), of whom 41 (0.1%) were recalled (recall rate 0.1%), and 37 (0.1%) were confirmed to have G6PD deficiency, yielding a detection rate of one in 761 screened neonates. Molecular confirmation was obtained in two cases, as several parents declined genetic testing because of the perceived mild nature of the condition and the feasibility of clinical monitoring. Twenty-three (62.1%) affected infants developed neonatal hyperbilirubinemia and were managed with phototherapy.

Only 10 (0.04%) of the 28,175 screened neonates had elevated total galactose levels (>15 mg/dL). Out of 10 neonates with a positive screen for galactosemia, all 10 neonates were recalled, and repeat testing for total galactose levels was done. Repeat testing in these 10 neonates showed normal total galactose levels, and no case of galactosemia was confirmed.

A total of 73 (0.3%) neonates screened positive for amino acid disorders, of which 53 (0.2%) were recalled for repeat testing (recall rate 0.2%). Around 0.2% (n=49) had normal results on repeat testing. One (0.003%) infant underwent genetic testing and was confirmed to have tyrosinemia type III, corresponding to a detection rate of one in 28,175 screened neonates, while three (0.001%) infants were lost to follow-up.

A total of 115 (0.4%) neonates had positive initial screens for organic acid disorders, of whom 95 (0.3%) were recalled (recall rate 0.3%); 84 (0.3%) had normal repeat test results. Two infants were diagnosed with 3-methylglutaconic aciduria and propionic acidemia, respectively, corresponding to an overall detection rate of one in 14,087 screened neonates. Three families declined further testing, and six infants were lost to follow-up. Seven (0.02%) neonates screened positive for fatty acid oxidation disorders, of whom three (0.01%) were confirmed on further evaluation, corresponding to a detection rate of one in 9,391 screened neonates.

The screening outcomes for metabolic disorders are summarized in Table 5, while the recall rates and detection rates for each disorder are presented in Table 6.

S. No	Metabolic disorder	Number of neonates with positive screen; n (%)	Total number of neonates recalled; n (%)	Confirmed cases; n (%)	False Positive	Lost to follow up/ neonatal death/ refused further evaluation; n (%)	Among confirmed cases			
							Term; n (%)	Pre-term; n (%)	Male; n (%)	Female; n (%)
1	Congenital hypothyroidism	72 (0.2%)	69 (0.2%)	46 (0.2%)	23 (0.08%)	0	40 (87%)	6 (13.0%)	15 (32.7%)	31 (67.3%)
2	Cystic fibrosis	128 (0.4%)	108 (0.4%)	3 (0.01%)	103 (0.4%)	2 (0.007%)	3 (100%)	0	3 (100%)	0
3	Congenital adrenal hyperplasia	25 (0.08%)	19 (0.06%)	2 (0.007%)	17 (0.06%)	0	1 (50%)	1 (50%)	1 (50%)	1 (50%)
4	G6PD deficiency	49 (0.2%)	41 (0.1%)	37 (0.1%)	4 (0.01%)	0	29 (78.4%)	8 (21.6%)	35 (94.6%)	2 (5.4%)
5	Galactosemia	10 (0.04%)	10 (0.04%)	0	10 (0.04%)	0	0	0	0	0
6	Amino acid disorder	73 (0.3%)	53 (0.2%)	1 (0.003%)	49 (0.2%)	3 (0.01%)	1 (100%)	0	0	1 (100%)
7	Organic acid disorder	115 (0.4%)	95 (0.3%)	2 (0.007%)	84 (0.3%)	9 (0.03%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)
8	Fatty acid disorder	7 (0.02%)	6 (0.02%)	3 (0.01%)	3 (0.01%)	0	3 (100%)	0	0	3 (100%)
	Total	479 (1.7%)	401 (1.4%)	94 (0.3%)	293 (1.0%)	14 (0.04%)	78 (83%)	16 (17%)	55 (59%)	39 (41%)

TABLE 5: Screening outcomes for disorders included in the ENBS panel.

S.No	Condition screened	Number of newborns screened during study period (n)	Neonates with positive screen; n (%)	Neonates recalled; n (%)	Neonates who could not be recalled; n (%)	Recall rate	Confirmed cases among recalled cases; n (%)	Recalled neonates who did not undergo confirmatory test due to lost to follow up/ neonatal death/ refused further evaluation; n (%)	Consanguinity; n (%)	Diagnostic yield; n (%)
1	Congenital hypothyroidism	28,175	72 (0.2%)	69 (0.2%)	3 (0.01%)	0.2	46 (0.2%)	0	5 (10.8%)	1:612 (0.2%)
2	Cystic fibrosis	28,175	128 (0.4%)	108 (0.4%)	20 (0.07%)	0.4	3 (0.01%)	2 (0.007%)	1(33.3%)	1:9391 (0.01%)
3	Congenital adrenal hyperplasia	28,175	25 (0.08%)	19 (0.06%)	6 (0.02%)	0.06	2 (0.007%)	0	1 (50%)	1:14087 (0.007%)
4	G6PD Deficiency	28,175	49 (0.2%)	41 (0.1%)	8 (0.03%)	0.1	37 (0.1%)	0	2 (5.4%)	1:761 (0.1%)
5	Galactosemia	28,175	10 (0.04%)	10 (0.04%)	0	0.04	0	0	0	0
6	Amino acid disorder	28,175	73 (0.3%)	53 (0.2%)	20(0.07%)	0.2	1 (0.003%)	3 (0.01%)	0	1:28175 (0.003%)
7	Organic acid disorder	28,175	115 (0.4%)	95 (0.3%)	20(0.07%)	0.3	2 (0.007%)	9 (0.03%)	0	1:14087 (0.007%)
8	Fatty acid disorder	28,175	7 (0.02%)	6 (0.02%)	1 (0.004%)	0.02	3 (0.01%)	0	0	1:9391 (0.01%)
	Total	28,175	479 (1.7%)	401 (1.4%)	78 (0.3%)	1.4	94 (0.3%)	14 (0.04%)	9 (9.5%)	1:299 (0.3%)

TABLE 6: Recall rates and diagnostic yield of disorders detected through ENBS

Table 7 presents the positive predictive value (PPV) of newborn screening for different disorders, with G6PD deficiency showing the highest PPV of 90.2% and amino acid disorders having the lowest PPV at 2.0%.

S. No	Condition screened	Diagnostic yield; n (%)	True positive; n (%)	False positive; n (%)	Positive predictive value; n (%)
1	Congenital hypothyroidism	1:612 (0.2%)	46 (66.7%)	23 (33.3%)	66.7% (n=46)
2	Cystic fibrosis	1:9391 (0.01%)	3 (2.8%)	103 (97.2%)	2.8% (n=3)
3	Congenital adrenal hyperplasia	1:14087 (0.007%)	2 (10.5%)	17 (89.5%)	10.5% (n=2)
4	G6PD Deficiency	1:761 (0.1%)	37 (90.2%)	4 (9.8%)	90.2% (n=37)
5	Galactosemia	0	0	10 (100%)	-
6	Amino acid disorder	1:28175(0.003%)	1 (2%)	49 (98%)	2.0% (n=1)
7	Organic acid disorder	1:14087 (0.007%)	2 (2.3%)	84 (97.7%)	2.3% (n=2)
8	Fatty acid disorder	1:9391 (0.01%)	3 (50%)	3 (50%)	50.0% (n=3)
	TOTAL	1:299 (0.3%)	94 (24.3%)	293 (75.7%)	24.3% (n=94)
	Diagnostic yield of metabolic/genetic disorders (excluding CH, G6PD).	1:2561 (0.04%)			

TABLE 7: True-positive cases, false-positive cases, and positive predictive values for disorders included in the ENBS panel.

Table *8* summarizes the cases confirmed by exome sequencing. Most confirmed cases received appropriate counselling, treatment, and regular follow-up. Figure *2* shows a summary of the outcomes of the newborn screening program.

S No	Clinical features	Gene	Diagnosis	Variant	ACMG classification	Criteria applied	Inheritance and zygosity
1	Bilateral pulmonary parenchymal infiltrates, lower gastrointestinal obstruction, and jejunal atresia with meconium plug.	CFTR	Cystic fibrosis (OMIM#219700)	c.1521_1523del (p.Phe508del)	Pathogenic	PS1, PM2, PM4, PM5, PP5	Autosomal recessive and homozygous
2	Failure to thrive, mild anemia, jaundice, hepatomegaly	CFTR	Cystic fibrosis (OMIM#219700)	c.1029del (p.Cys343Ter)	Pathogenic	PVS1, PM2, PM3, PP5	Autosomal recessive and compound heterozygous
				c.1500_1503delinsAAATG (p.Thr501AsnfsTer3)	Likely pathogenic	PVS1, PM2	
3	Jaundice	CFTR	Cystic fibrosis (OMIM#219700)	c.1393-1G>A (3' splice site)	Pathogenic	PS1, PM2, PM4	Autosomal recessive
4	Ambiguous genitalia, hyperpigmentation of labioscrotal folds with rugosity, with no gonads palpable; vaginal and urethral openings were present.	CYP21A2	Congenital adrenal hyperplasia due to 21-hydroxylase deficiency	c.293-13C>G	Pathogenic	PM2, PM3, PS3, PP5	Autosomal recessive and homozygous
5	Child exhibited poor feeding, dull activity, hyponatremia, hyperkalaemia, elevated renin, elevated aldosterone.	CYP21A2	Congenital adrenal hyperplasia due to 21-hydroxylase deficiency	c.293-13C>G	Pathogenic	PM2, PM3, PS3, PP5	Autosomal recessive and homozygous

6	Neonatal jaundice	G6PD	G6PD deficiency	c.1388G>A (p.Arg463His)	Pathogenic	PS3, PL1, PM5, PP2, PP3, PP5	Autosomal recessive and homozygous
7	Asymptomatic	G6PD	G6PD deficiency	c.949G>A (p.Glu317Cys)	Likely pathogenic	PM1, PM2, PP2, PP3, PP5	Autosomal recessive and homozygous
8	Asymptomatic	HPD	Tyrosinemia, type III(OMIM#276710)	c.75G>A (p.Trp25Ter)	Pathogenic	PVS1, PM2, PS4, PP5	Autosomal recessive and homozygous
9	At 98 hours of life, baby had encephalopathy, hypoglycemia, poor feeding, lethargy, laboured breathing, and succumbed	PCCA	Propionic acidemia (OMIM#606054)	c.1500_1503delinsAAATG (p.Thr501AsnfsTer3)	Likely pathogenic	PVS1, PM2	Autosomal recessive and homozygous
10	Neonatal jaundice, metabolic acidosis, hypoglycemia, dull activity, and generalized hypotonia.	SERAC1	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome (OMIM-714739)	c.1643_1646dup (p.Leu550SerfsTer19)	Pathogenic	PVS1, PM2, PM3, PP5	Autosomal recessive and homozygous
11	Baby had apneic episodes, hypoglycaemia, hypocalcaemia, refractory lactic acidosis, encephalopathy, and cardiac dysfunction. Succumbed on Day 5	HADHA	Isolated deficiency of long-chain 3- hydroxyl-CoA dehydrogenase (OMIM#609016); Mitochondrial trifunctional protein deficiency-1 (OMIM#609015)	c.180+1G>C (5' splice site)	Likely Pathogenic	PVS1, PM2	Autosomal recessive and homozygous
12	Child is normal and is on carnitine supplementation	SLC22A5	Carnitine deficiency, systemic primary (OMIM#212140)	c.629A>G (p.Asn210Ser)	Pathogenic	PM1, PM2, PM3, PS3, PP2, PP5,	Autosomal recessive and homozygous

TABLE 8: Disorders with confirmed molecular diagnoses established by exome sequencing.



FIGURE 2: Figure summarizing the outcomes of the newborn screening program.

Discussion

This nine-year study evaluated the feasibility and outcomes of ENBS in a tertiary care centre. Among 28,175

newborns screened, the overall diagnostic yield of ENBS was 0.3% (n=94), with congenital hypothyroidism and G6PD deficiency accounting for many confirmed diagnoses.

This study demonstrated marked improvement in screening uptake and acceptability, with a recall rate of 1.4% (n=401), although overall coverage was limited to 32.4% (n=28,175). Recall rates, though variably defined, were typically 0.05-2% in established MS/MS panels. A low recall rate may reflect an efficient screening algorithm. However, it may also reflect relatively stringent cut-offs or protocol differences. The feasibility and acceptability of ENBS could be enhanced by implementing it as a public health program by addressing existing infrastructure and accessibility barriers.

National and international guidelines recommend universal screening for congenital hypothyroidism and hearing loss due to high prevalence and clear benefits of early treatment, while congenital adrenal hyperplasia, G6PD deficiency, and hemoglobinopathies are screened selectively [7]. In India, G6PD deficiency is most common, followed by congenital hypothyroidism and adrenal hyperplasia. Expanded newborn screening is limited by cost, workforce, and follow-up challenges. Programs like Rashtriya Bal Swasthya Karyakram (RBSK) [9], Unique Methods of Management and Treatment of Inherited Disorders (UMMID) [10], Organisation for Rare Diseases India (ORDI), and Rare Disease Clinics contribute to national policy and support newborn screening, raise genetic awareness, enable early diagnosis, and provide structured management, guiding the expansion of rare disease initiatives in national health programs [11].

The study highlights favourable parental acceptance and awareness of ENBS in a tertiary care setting in India and provides supportive evidence for strengthening screening services within existing maternal and child health programs.

In India the prevalence of CH ranges from 1:722 to 1:2835, whereas the global incidence is approximately 1 in 2000 live births [12,13]. In this study, the detection rate of CH among screened newborns was 1 in 612, with a 0.2% (n=69) recall rate. Age-specific TSH cut-offs reduce false positives [14]. Routine neonatal screening, including for low-birthweight and preterm infants, is recommended. Genetic evaluation helps differentiate transient from permanent CH, guiding appropriate therapy.

In the present study, the frequency of CF within the screened cohort was 1 in 9,391 newborns. The incidence is within the Asian range but higher than many earlier Indian reports [15,16]. This may reflect improved detection through expanded newborn screening. The recall rate was 0.4% (n=108), which is lower than most reports. Of 108 infants with persistently high IRT, only three (0.01%) had molecular confirmation of CF, highlighting relatively high false-positive rates using the IRT-based screening. The use of second-tier testing or genetic analysis may improve specificity [17]. These findings support including CF in routine newborn screening where its burden may be underestimated.

Congenital adrenal hyperplasia (CAH) was confirmed in two of the 28,175(0.007%) screened newborns, corresponding to a frequency of 1 per 14,087 screened neonates. The recall rate was 0.06% (n=19). Among confirmed cases, 50% (n=1) were male neonates with the salt-wasting (SW) type, and 50% (n=1) were female neonates with the simple virilizing (SV) type. In a South Indian tertiary centre, 76% (n=22) of CAH patients were female, and 24% (n=7) were male; the SW form was seen in 81% (n=18) of females and 85% (n=6) of males [18]. Several other Indian studies report variable CAH incidence and phenotype [19]. The worldwide incidence ranges from 1 in 14,000 to 1 in 18,000 live births [20]. Studies indicate a higher incidence in India than globally, highlighting the need for universal newborn screening for early diagnosis and timely treatment, especially of life-threatening salt-wasting forms. In a multicentre Indian cohort of 315 clinically confirmed CAH cases, pathogenic variants were detected in 94.3% (n=297) of patients. CYP21A2 deletions (36.2%), the intron 2 splice-site variant c.293-13A/C>G (i2g) (29.6%), and the p.Gln319* variant (11.3%) were the predominant genetic alterations, collectively accounting for 77.1% of all detected variants [21].

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked recessive disorder affecting ~400 million people, particularly in India, and can cause prolonged neonatal jaundice or haemolytic anemia, making early diagnosis essential. In India, the reported incidence ranges from 2% to 27.9%. The global estimate is 443 million people in 2021, with the highest burden in South Asia [22]. In this study, the recall rate was 0.1% (n=41), with a detection rate of 1 in 761 (0.1%) among screened newborns, which is higher than many previous reports, and two cases had a genetic diagnosis. Early screening enables reduction of haemolytic complications.

Galactosemia, caused by GALT deficiency, impairs galactose metabolism. Indian newborn screening studies show variable results ranging from no confirmed cases to 1 in 10,300 and 1 in 41,027 neonates [14, 23]. Its incidence in Western countries is 1 in 30,000-60,000 live births, while in India, about 4% of neonates with cholestasis may have the disorder [24].

Porta et al. screened 1,123,909 newborns, recalling 8,991. Confirmatory testing identified 31 cases, 13 of which were classic galactosemia [25]. In the present study of 28,175 Indian newborns, the recall rate was 0.04% (n=10), with no confirmed cases. Although galactosemia screening yields high false positives, its potential lethality justifies consideration.

Phenylketonuria (PKU) is the most common amino acid disorder. Newborn screening enables early dietary intervention. Across Asia, incidence ranges from 1 in 17,000 to 26,000. In India, Kommalur et al. reported PKU in 1 of 20,513 newborns [23] alongside other amino acid disorders. Hong Kong screened 125,688 newborns (2015-2022), finding amino acid disorders (AAs) in 1 in 6,983, mostly citrullinemia type 2 [26]. In the present study of 28,175 newborns, there was one confirmed case per 28,175 screened newborns (recall 0.2%, n=53).

The detection rate of organic acid disorders (OADs) was 1 in 14,087 among screened newborns, with a recall rate of 0.3% (n=95). Population-based incidence data for organic acidemias in India are lacking. However, in a large North Indian cohort reported by Sunita et al., 293 of 394 patients with suspected OADs had molecular confirmation, with glutaric acidemia type I and methylmalonic acidemia emerging as the most common disorders. 16 genes were identified, of which 25% (n=4) were novel variants [27]. In a study conducted by Narayanan et al. in South India, 420 cases clinically suspected to have organic aciduria were screened, of which 45 cases (10.7%) were found to have organic acidurias, including 15 cases of methylmalonic aciduria, 16 cases of propionic aciduria, 13 cases of MSUD, and one case of isovaleric aciduria diagnosed [28]. A 10-year study in China (2014-2023) screened 693,797 newborns and identified 69 OAD cases (1:10,055) [29]. Incidence rates in Germany, Taiwan, Japan, and South Korea ranged from 1 in 10,000 to 1 in 31,000 [5]. Additional regional studies in the U.S., China, Hong Kong, and Germany show variable prevalence [30]. MMA is globally common, while GA-1 is more frequent in certain European and Amish populations [31].

Three (0.01%) cases of fatty acid oxidation disorders (FAODs) were identified among 28,175 screened newborns (three in 28,175), with a recall rate of 0.02% (n=6). The incidence varies from 0.9 to 4.9 per 100,000 in Asians, but the exact incidence in India is not known [32]. In Southeastern China, 36 FAOD cases were identified among 210,913 newborns (1:5,859), with primary carnitine deficiency most common [33]. A multicentre study in Belgium reported medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency as the predominant FAOD (75.9%; n=41) [34]. The reported incidence worldwide ranged from 1 in 9,000 to 1 in 111,000, with MCAD being the most frequent [35].

Overall, AA, OADs, and FAOD distribution is heterogeneous globally due to genetic background, consanguinity, screening strategies, diet, and healthcare access. The relatively higher frequency within our cohort highlights the importance of expanded newborn screening for early diagnosis and improved outcomes [5].

DBS-based biochemical newborn screening is designed to be highly sensitive, making false positives more common than false negatives, as missing affected infants is more harmful. Causes of false positives include prematurity, low birth weight, illness, or transient metabolite elevations. Some assays, such as T-cell receptor excision circles (TRECs) for SCID, are particularly prone to false positives due to immature immune systems. Second-tier testing and informative biomarkers improve positive predictive value and reduce unnecessary recalls [36]. False negatives may occur if samples are collected too early or in mild/subtle disease forms, e.g., partial GALT deficiency in galactosemia or mild FAOD/amino acid disorders.

Genetic NBS can supplement biochemical screening, reduce false positives, and ease parental anxiety. Genome-based NBS poses challenges due to cost, data interpretation, storage, incidental findings, and anxiety. Its benefits are maximized when symptom-driven, ethnically guided, and integrated with local genetic architecture [37]. However, genomic screening is not a replacement for conventional NBS.

The strength of our study lies not in the description of individual disorders but in demonstrating the feasibility, acceptance, diagnostic yield, and operational challenges of implementing expanded newborn screening over a prolonged period in a tertiary-care setting in India.

The limitations of this study include its single-centre design, which may not be representative of the broader population, and incomplete screening coverage due to voluntary participation. Additional limitations were loss to follow-up for some infants after initial screening, as well as the absence of evaluation of long-term clinical outcomes and cost-effectiveness of the screening program. Screening coverage was limited to 32.4% (n=28,175) of live births because participation was voluntary. Therefore, the findings should not be interpreted as population-based incidence estimates. The reported frequencies represent detection rate and diagnostic yield within the screened cohort.

Conclusions

This nine-year experience demonstrates the feasibility of ENBS in a tertiary-care setting and its ability to identify treatable disorders at an early stage, and provides data on the uptake, recall rates, and diagnostic yield of ENBS. This study demonstrates a marked increase in parental acceptance and screening uptake over a nine-year period, supporting the operational feasibility of ENBS programs and identifying challenges related to follow-up, recall compliance, and confirmatory testing that need to be addressed for successful large-scale implementation. This study supports the strengthening and integration of newborn screening services within existing maternal and child health programs to facilitate early diagnosis and intervention for inherited metabolic disorders.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Ethics Committee, Institutional Review Board, Fernandez foundation issued approval EC Reference No.21_2022. This study protocol was reviewed and approved by Institutional Ethics Committee, Institutional Review Board, Fernandez foundation with EC Reference No.21_2022. . **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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