AUTHORIZATION TO LEND AND REPRODUCE THE THESIS

As the sole author of this thesis, I authorize Brown University to lend it to other institutions or individuals for the purpose of scholarly research.

Date: ____________________________  ____________________________

Abhilash Gazula, Author

I further authorize Brown University to reproduce this thesis by photocopying or other means, in total or in part, at the request of other institutions or individuals for the purpose of scholarly research.

Date: ____________________________  ____________________________

Abhilash Gazula, Author
The Relevance of Newborn Screening to India: A Systematic Review

Newborn Screening in the Indian Setting: Recommendations and Challenges

By
Abhilash Gazula
B.S., University of Michigan, 2015

Thesis
Submitted in partial fulfillment of the requirements for the Degree of Master in Public Health in the Brown University School of Public Health

PROVIDENCE, RHODE ISLAND
MAY 2017
This thesis by Abhilash Gazula is accepted in its present form by the Brown University School of Public Health as satisfying the thesis requirements for the degree of Master of Public Health.

Date:________________  ___________________________

Dr. Susan Cu-Uvin, MD, Advisor

Date:________________  ___________________________

Dr. Adam Sullivan, PhD, Reader

Date:________________  ___________________________

Patrick M. Vivier, MD, PhD
Director, Master of Public Health Program

Approved by the Graduate Council

Date:________________  ___________________________

Andrew Campbell, Dean of the Graduate School
Preface and Acknowledgements

This thesis would not have been possible without the guidance and support of my thesis advisor, Dr. Susan Cu-Uvin, and my reader, Dr. Adam Sullivan. Thank you for making yourselves available to answer all my questions and for providing me the support I needed to take on this ambitious project. Additionally, thank you trusting me and providing me with the independence I needed to complete this project. I am grateful for your honest and constructive feedback at every step and for pushing me to become a better academic.

Additionally, I would like to thank the Center for Evidence Synthesis in Health and everyone there for your immense support and guidance. Thank you for not only supporting me in my endeavors but for providing the resources necessary for me to learn the methodology for conducting a systematic review as a part of my thesis. You have helped me become a stronger researcher and professional.

Finally, I would like to thank Dr. Stephen McGarvey. You have served as a mentor to me over the past two years and without your guidance none of this would have been possible. It is because of your support that I have been able overcome multiple hurdles along the way and become not only a better researcher and writer, but a teacher myself. Working with you has not only improved my skills and broadened my talents, but has truly been one of the highlights of my time at Brown.
Table of Contents

The Relevance of Newborn Screening to India: A Systematic Review

Introduction .................................................................................................................. 2

The early phase of Newborn Screening ........................................................................ 2
The Modern Age of Newborn Screening ....................................................................... 5
Guiding Principles of Newborn Screening as a Public Health Program ....................... 6
Newborn Screening in the Indian Context .................................................................... 7

Key Questions ................................................................................................................ 8

Methods ........................................................................................................................ 8

Conditions ..................................................................................................................... 8

Literature Search ........................................................................................................... 9

Study Selection .............................................................................................................. 9

Data Extraction ............................................................................................................. 10

Data Synthesis .............................................................................................................. 10

Results .......................................................................................................................... 11

Hemoglobin Conditions .............................................................................................. 11

Sickle cell anemia (SS) ................................................................................................. 12
Sickle cell/Beta-Thalassemia (S/Th) ............................................................................ 12
Sickle cell/Hemoglobin C disease (Hb S/C) .................................................................. 13
Hemoglobin C disease (Hb C) ...................................................................................... 14
Hemoglobin E/β-thalassemia disease (Hb E/β-thal) .................................................... 14
Various Hemoglobinopathies ...................................................................................... 14
Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD) ........................................... 15

Amino Acid Conditions ............................................................................................... 16

Phenylketonuria (PKU) ............................................................................................... 16
Tetrahydrobiopterin deficiency .................................................................................... 16
Maple Syrup Urine Disease (MSUD) ........................................................................... 17
Homocystinuria (HCY) ............................................................................................... 17
Citrullinemia, Type I (CIT) ........................................................................................ 18
Citrullinemia, Type II (CIT II) .................................................................................... 18
Argininosuccinic acidemia (ASA) ................................................................................. 18
Tyrosinemia, type I (TYR I) ....................................................................................... 19
Tyrosinemia, type II (TYR II) ..................................................................................... 19
Tyrosinemia, type III (TYR III) ................................................................................... 19
Pyroglutamic acidemia (5-OXO) ................................................................................. 19
Carbamoyl phosphate synthetase deficiency (CPS) ..................................................... 20
Hyperornithinemia-Hyperammonemia-Homocitrullinuria syndrome (HHH) ............... 20
<table>
<thead>
<tr>
<th>Condition</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperornithine with Gyrace Deficiency (Hyper ORN)</td>
<td>20</td>
</tr>
<tr>
<td>Argininemia (ARG)</td>
<td>21</td>
</tr>
<tr>
<td>Hypermethioninemia (MET)</td>
<td>21</td>
</tr>
<tr>
<td>Benign Hyperphenylalaninemia (H-Phe)</td>
<td>21</td>
</tr>
<tr>
<td><strong>Fatty Acid Oxidation Conditions</strong></td>
<td>21</td>
</tr>
<tr>
<td>Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)</td>
<td>22</td>
</tr>
<tr>
<td>Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)</td>
<td>22</td>
</tr>
<tr>
<td>Long-chain 3-OH acyl-CoA dehydrogenase deficiency (LCHAD)</td>
<td>23</td>
</tr>
<tr>
<td>Short-Chain Acyl-CoA Dehydrogenase Deficiency (SCAD)</td>
<td>23</td>
</tr>
<tr>
<td>Medium/Short-Chain L-3 Hydroxyacyl-CoA Dehydrogenase Deficiency (M/SCHAD)</td>
<td>23</td>
</tr>
<tr>
<td>Trifunctional Protein Deficiency (TFP)</td>
<td>24</td>
</tr>
<tr>
<td>Carnitine Uptake Defect (CUD)</td>
<td>24</td>
</tr>
<tr>
<td>Carnitine Acylcarbinine Translocase Deficiency (CACT)</td>
<td>24</td>
</tr>
<tr>
<td>Carnitine Palmitoyltransferase I Deficiency (CPT-IA)</td>
<td>25</td>
</tr>
<tr>
<td>Carnitine Palmitoyltransferase Type II Deficiency (CPT-II)</td>
<td>25</td>
</tr>
<tr>
<td>Glutaric Acidemia, Type II (GA2)</td>
<td>26</td>
</tr>
<tr>
<td>Medium-Chain Ketoacyl-CoA Thiolase Deficiency (MCAT)</td>
<td>26</td>
</tr>
<tr>
<td>2,4 Dienoyl-CoA Reductase Deficiency (DE RED)</td>
<td>26</td>
</tr>
<tr>
<td><strong>Organic Acid Conditions</strong></td>
<td>27</td>
</tr>
<tr>
<td>Isovaleric Acidemia (IVA)</td>
<td>27</td>
</tr>
<tr>
<td>Glutaric Acidemia, Type I (GA1)</td>
<td>27</td>
</tr>
<tr>
<td>3-Hydroxy-3-Methylglutaric Aciduria (HMG)</td>
<td>28</td>
</tr>
<tr>
<td>Multiple Carboxylase Deficiency (MCD)</td>
<td>28</td>
</tr>
<tr>
<td>Malonic Acidemia (MAL)</td>
<td>28</td>
</tr>
<tr>
<td>Methylmalonic Acidemia due to Mutase Deficiency (MUT)</td>
<td>29</td>
</tr>
<tr>
<td>Methylmalonic Acidemia caused by Cobalamin disorders A and B (cblA, B)</td>
<td>29</td>
</tr>
<tr>
<td>Methylmalonic Acidemia with Homocystinuria (CBL C, D, F)</td>
<td>30</td>
</tr>
<tr>
<td>3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)</td>
<td>30</td>
</tr>
<tr>
<td>Propionic Acidemia (PROP)</td>
<td>30</td>
</tr>
<tr>
<td>Beta-Ketothiolase Deficiency (BKT)</td>
<td>31</td>
</tr>
<tr>
<td>Glycogen Storage Disease Type II (GSD II) /Pompe Disease</td>
<td>31</td>
</tr>
<tr>
<td>Isobutarylglucuroninuria (IBG)</td>
<td>31</td>
</tr>
<tr>
<td>2-Methylbutyryl-CoA Dehydrogenase Deficiency (2MBG)</td>
<td>32</td>
</tr>
<tr>
<td>3-Methylglutaconic Aciduria (3MGA)</td>
<td>32</td>
</tr>
<tr>
<td>2-Methyl-3-Hydroxybutyric Acidemia (2M3HBA)</td>
<td>32</td>
</tr>
<tr>
<td><strong>Endocrine Conditions</strong></td>
<td>33</td>
</tr>
<tr>
<td>Congenital Hypothyroidism (CH)</td>
<td>33</td>
</tr>
</tbody>
</table>
Newborn Screening in the Indian Setting: Recommendations and Challenges

Introduction .................................................................................................................. 47
History of Newborn Screening .................................................................................... 47
Newborn Screening in the Indian Context .................................................................... 48
Guiding Principles of Newborn Screening as a Public Health Program .................... 49
Recommendations and Challenges for Newborn Screening in India ......................... 51
Conclusions .................................................................................................................. 54

Figure 1 .......................................................................................................................... 55
Table 1 ........................................................................................................................... 56
Table 2 ........................................................................................................................... 57
Table 3 ........................................................................................................................... 57
Table 4 ........................................................................................................................... 58
Table 5 ........................................................................................................................... 59
Table 6 ........................................................................................................................... 59
Table 7 ........................................................................................................................... 60
Table 8 ........................................................................................................................... 61
Table 9 ........................................................................................................................... 61
Table 10 ......................................................................................................................... 62
Appendix A .................................................................................................................... 63
References ..................................................................................................................... 65
The Relevance of Newborn Screening to India: A Systematic Review

Abstract

**Objectives:** Newborn screening (NBS) is a public health measure aimed at the earliest possible detection and management of inborn errors of metabolism to prevent infant mortality and long-term morbidity. While NBS is a mandatory program in many countries, no such program exists in India, despite its clear relevance. To aid the establishment of an NBS program in India, this systematic review analyzes current data to determine which disorders may be relevant to the Indian population.

**Data sources:** We searched MEDLINE from January 1, 2000 to December 12, 2016.

**Review methods:** We included studies with primary or modeled birth prevalence data on at least one of 69 congenital disorders identified for analysis. Systematic reviews of birth prevalence estimates were also included.

**Results:** 41 studies met inclusion criteria for the review. Upon review we recommend 12 disorders for inclusion on and Indian NBS panel: sickle cell anemia (Hb SS), sickle cell/beta-thalassemia (Hb S/Th), sickle cell/hemoglobin C disease (Hb S/C), hemoglobin E/beta-thalassemia disease (Hb E/Th), various hemoglobinopathies, glucose-6-phosphate dehydrogenase deficiency (G6PD), isovaleric acidemia (IVA), methylmalonic acidemia, cobalamin deficiency (cblA, B), propionic acidemia (PROP), congenital hypothyroidism (CH), nonsyndromic congenital hearing loss, and hyperhomocysteinemia.

**Conclusions:** Overall, the strength of evidence for determining the importance of various congenital disorders to the Indian setting is weak. Additionally, there are numerous challenges to address. First, research must be done to determine and confirm the prevalence of numerous disorders to create a program that best serves the Indian population. Second, the specific cost structure of a NBS program in India while taking into consideration the need for subsidies and assistance to allow for complete accessibility. Third, it is crucial that the issue of accessibility to both treatment and the program itself is addressed immediately, or NBS in India will fail to serve as a true population health measure accessible to the entirety of the population. Finally, we encourage Indian physicians and pediatricians to not only lay out what an effective NBS program would look like in India from their perspective.
Introduction

The early phase of Newborn Screening

Newborn screening (NBS) is a term used to describe the various tests that can be used within the first few days of life. When properly and timely used, NBS can have a significant impact on preventing serious health outcomes and even death. NBS began with phenylketonuria (PKU), an inherited disorder marked by increased phenylalanine levels in the blood.\(^1\) In 1934, Ivar Asbjørn Følling, a Norwegian physician who concentrated his work in metabolism and physiology, was visited by Borgny Egeland. Mrs. Egeland had two young children who had been born healthy but had since developed intellectual disabilities; she had noticed a strong odor coming from her son’s urine since he was about a year old.\(^2\)–\(^4\) Determined to find a cause for both the emerging mental retardation and the peculiar odor, Mrs. Egeland had her children seen by numerous physicians, none of which could find an explanation for the condition. One of these physicians referred Mrs. Egeland to Følling, due to his expertise in metabolism.\(^2\)–\(^4\) Over the course of many weeks, Følling obtained multiple urine samples (over 20L worth) and tested them multiple times, eventually determining that the substance causing the strange odor was phenylpyruvic acid. Hypothesizing that the presence of the chemical was the cause for the condition, Følling requested that physicians near Oslo test the urine of other patients. Upon collecting the urine samples of over 400 institutionalized patients, Følling identified 8 additional individuals who also had phenylpyruvic acid in their urine. Følling noted that these patients also had similar features and impairments compared to Mrs. Egeland’s children. This condition eventually became to be known as phenylketonuria (PKU) and is still referred to as Følling’s disease in the region.\(^2\)–\(^4\)

Years later in 1953, Bickel and colleagues were able to show that a simple dietary phenylalanine restriction in patients could reduce the development of symptoms.\(^4\)–\(^6\) In 1957, Centerwall and colleagues developed a diaper screening test based on Følling’s work with urine tests. Centerwall’s test made it far easier to collect and send samples for diagnosis, even allowing for physicians to perform the test in their office. While it was implemented in several health clinics in the Los Angeles area, it ultimately proved to be less than optimal.\(^4\)–\(^7\) Two years later in 1959, Robert Guthrie, a physician and microbiologist, developed an effective test for PKU. He proved that whole blood can be effectively taken, absorbed, and dried on filter paper and then tested for various biochemical markers, thus fathering NBS as we know it.\(^4\)–\(^13\)
Upon obtaining his MD and PhD in bacteriology, Robert Guthrie began his career as a cancer scientist at the Roswell Park Cancer Institute in Buffalo, NY. It was during this time that Guthrie’s second son was born with an undiagnosed developmental delay, motivating him to pursue work in preventing developmental disabilities. The birth of his niece, and her diagnosis of PKU 15 months later in 1958 brought Guthrie’s attention to the treatment of mental disabilities. Guthrie was active in the Buffalo Chapter of the New York State Association for Retarded Children and it was here that he met Dr. Robert Warner, director of the new Children’s Rehabilitation Center at Buffalo Children’s Hospital. Over the course of many meetings, Guthrie described his interest in preventing developmental disabilities due to congenital disorders. Warner explained the need for a simple, rapid, and accurate way to test phenylalanine levels in PKU patients. Guthrie was convinced to transfer from the cancer institute to the Buffalo Children’s Hospital by Warner and Dr. Mitchell Rubin, chief of pediatrics at the children’s hospital. It was here that Guthrie developed his blood test for PKU, a method that has gone on to be used in NBS programs for a variety of conditions globally.

Prior to his work on PKU, Guthrie had developed a filter paper that could be used to test for the metabolites circulating in a patient’s blood using their serum. This would be then used in conjunction with a bacterial inhibition assay (BIA) to test for the presence of various metabolites. Guthrie was able to develop a method modifying his previous work in order to detect the levels of phenylalanine in an infant’s blood. Guthrie cultured Bacillus subtilis on an agar medium with a phenylalanine antagonist to inhibit bacterial growth, and so when blood soaked filter paper cut from dried blood spots are placed on the agar, the amount of excess phenylalanine can be determined by the amount of bacterial growth. Guthrie’s test was initially intended to monitor blood phenylalanine levels in patients on a low phenylalanine diet, he soon determined that it could be used as a screening test to prevent the onset of symptoms in patients with PKU. However, the original cancer test utilized serum, a process far too lengthy and complicated to be useful for routine screening. Guthrie tested the filter paper using whole blood and prove it was just as efficacious, and so NBS was born.

Mass population screening trials and initiatives began soon after. In 1961, Guthrie and his colleagues began a mass screening program. Within 2 years they had collected at tested over 400,000 bloodspots from American newborns and had identified 39 cases of PKU. In 1962, Erie County, New York began
screening newborns, detecting their first case of PKU after screening over 800 neonates. At about the same time, the Maternal and Child Health Division of the US Children’s Bureau (what is now the Health Resources and Services Administration (HRSA)) provided funding for a national trial of Guthrie’s screening test, including a comparison to the current ongoing urine-based screening, eventually proving that it was in fact the most effective for detecting PKU. Soon after, the Massachusetts Department of Health began pilot testing Guthrie’s test and by 1963 became the first state to mandate screening. From then on, Guthrie became a staunch advocate for universal screening. He spent that year training technicians from all over the country and soon became involved with various professional organizations, driving the public health effort in both the US and abroad that would lead to many screening mandates over the next decade. In fact, by the end of the decade, 45 states had passed a screening mandate.

The following decades saw many improvements to NBS programs, beginning with the consolidation of testing laboratories. The first decade of screening was characterized by a small fragmented network of hospitals and both private and publicly funded labs screening locally born infants. Many states soon consolidated their screening programs into state public health laboratories and regional testing centers for 3 reasons: phenylalanine on dried blood spots was stable enough to be mailed to testing centers; it was believed that high volume testing of actual cases of a disease within a reasonable time frame improve the quality of laboratory proficiency testing; and the integration of testing and follow-up were more efficient when centralized. Additionally, in the late 1960s in collaboration with St Joseph’s Hospital in Los Angeles, Robert Phillips developed the Phillips Punch Index Machine. The machine allowed for 4 small samples to be punched simultaneously from a single dried blood spot, and then mechanically distributed each sample to a separate vessel for testing. The punch machine significantly reduced the time and labor required for multiple sample preparation, driving the expansion of NBS globally.

The next two decades were characterized by an expansion of NBS programs to include numerous other disorders, the first of which was congenital hypothyroidism (CH). The technological advances during the late 1960s and early 70s in combination with the much greater prevalence of CH compared to PKU allowed CH to be much more cost-effective than PKU, leading it to be quickly included on panels nationally. However, CH wasn’t simply another disorder, but introduced the concept of two-tier testing, allowing for increased specificity as well as cost-effective screening for many disorders that may have been
otherwise been left out of NBS programs. Two-tiered screening in the US involved a combination of assays for thyroxine (T₄) and thyrotropin (otherwise known as thyroid stimulating hormone (TSH)), both of which are at decreased circulating levels in newborns with typical CH screened at 1-3 days. However, at the time the test was developed, it was both too expensive to screen both hormones in all samples but also testing a single hormone insufficient to provide acceptable sensitivity. By first measuring a single hormone (typically T₄ in the United States) and then measuring the other (TSH) in all samples below a certain value off T₄, screening programs could not only achieve an acceptable level of specificity and sensitivity, but greatly reduce the cost of screening. With the introduction of the automated punching machine and CH testing, it became far easier and necessary (to utilize all the samples collected and punched) to include additional disorders, especially if they required no additional resources. And as soon as 5 disorders were included, it was only logical to consider eight, and so on and so forth. Screening for disorders such as hemoglobinopathies, galactosemia, and maple syrup urine disease (MSUD)—the tests for the latter two of which were also developed by Guthrie and his colleagues—were rapidly added among countless others.

The Modern Age of Newborn Screening

Beginning in the early 1990s, NBS began to evolve into the form we know it today. It all started with the introduction of tandem mass spectrometry (MS/MS) to NBS. With the ability to screen over 30 amino acid, organic acid, and fatty acid disorders simultaneously, MS/MS improved both the cost-effectiveness and efficiency of NBS programs. MS/MS essentially improved the cost-effectiveness and efficiency of two-tiered testing by analyzing multiple metabolites simultaneously. Initially, state programs were reluctant to adopt the technology due to its high instrumental start-up cost (over 400,000 when it was first introduced, the lack of experienced personnel trained to interpret results as well as the time and money required to train them, and the lack of a research mission in most state NBS programs. Nevertheless, by the mid-2000s, almost every state had adapted MS/MS as part of their NBS program.

The late 90s and early 2000s also saw the beginning of efforts to create a uniform national panel for all NBS programs. To address the political barriers to NBS expansion and access, the HRSA funded the American Academy of Pediatrics (AAP) to create an NBS Task Force. The Task Force was meant to review issues and challenges surrounding state NBS programs and make recommendations. A year later,
the Task Force issued a report outlining a national agenda for improving NBS programs. In response to the Task Force report, the HRSA contracted the American College of Medical Genetics (ACMG) to recommend a uniform screening panel for US NBA programs. Upon evaluation of 84 conditions, the ACMG identified 29 core conditions and 25 secondary targets—disorders that may be diagnosed as a result of testing for the core conditions, but otherwise lack the evidence necessary to be classified as a core condition. The ACMG report was then sent to the US Secretary of Health and Human Services after acceptance by the Secretary’s Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children, and was then adapted into the US Recommended Uniform Screening Panel (RUSP). Two years later, on April 24, 2008, US President George W. Bush signed into law the Newborn Screening Saves Lives Act of 2007 (Pub.L. 110-204; NBSSLA). The Act amended the Public Health Services Act to establish grants concerning newborn screening as well as created a mandate and funding to establish the NBS clearinghouse in cooperation with Genetic Alliance. Since, the RUSP has not only been used as a model by state NBS programs across the US, but by countries around the world.

**Guiding Principles of Newborn Screening as a Public Health Program**

There are several guiding principles that were important in establishing NBS. As programs around the globe expanded to include numerous diseases, NBS panels became extremely diverse, with PKU and CH the only real constants. However, both states and nations looked to the Wilson-Jungner criteria to determine which disorders to place on their individual NBS panels.

In 1968, Wilson and Jungner proposed a set of criteria for including a disorder in a population screening program. These conditions include: (i) that the disorder should be an important public health issue, (ii) there should be a sufficient knowledge of the natural history of the disease, (iii) there should be a reliable and simple (and cost-effective) test for the disorder that is acceptable to the population, (iv) symptoms should not manifest at birth or be detectable during a routine examination during the post-natal period (i.e. the child should be asymptomatic at the time of screening), (v) there is an effective treatment available for the disorder, and (vi) a delay in the diagnosis will cause undue harm.

Additionally, at the patient level, NBS typically functions based on the principle of dissent instead of the more common consent. As such, screening is done in all cases unless parents specifically object on a case by case basis. Working in the opposite manner of informed consent, where screening would be only
done in cases where parents explicitly agree to the process, dissent has been used to ensure higher rates of compliance and screening.\textsuperscript{4,13,34}

**Newborn Screening in the Indian Context**

While NBS is a mandatory public health program in many countries, including the United States, no such program exists in India.\textsuperscript{35–38} However, NBS has an immediate relevance to the Indian scenario. India’s annual crude birth rate is 20.7 births per 1000 population,\textsuperscript{39} and approximately 900 children are born daily in the Indian capital territory of Delhi alone—equating to at least 1-2 children with an inborn metabolic disorder daily in Delhi alone.\textsuperscript{35} Additionally, the WHO recommends that countries with an infant mortality rate under 50 deaths/1000 population offer genetic services,\textsuperscript{36} and with an infant mortality rate of 44 deaths/1000 population, it is due time NBS is introduced in India.\textsuperscript{39}

There is demand for NBS among Indian healthcare professionals and academics. Numerous studies have been published on the topic\textsuperscript{34–37,40} and as recently as 2015, the President of the Indian Academy of Pediatrics recommended the adoption of NBS in India in the Indian Journal of Pediatrics.\textsuperscript{36} The past decade has seen the advent of private pilot programs for NBS in major metropolitan areas, including two large multi centric studies in Hyderabad and New Delhi, however, the results have been primarily inconclusive.\textsuperscript{34,35,38}

It could be argued that until recently, NBS wasn’t relevant as a national health priority in India, as it is only relatively recently that India has experienced the epidemiologic transition—a demographic and epidemiological theory first described by Abdel Omran in 1971.\textsuperscript{41} At a basic level, the epidemiologic transition argues that as societies develop, the causes of morbidity and mortality shift from infectious diseases to chronic diseases—which in the case of NBS are inborn errors of metabolism.\textsuperscript{41} This is not to say that chronic diseases do not exist earlier, but that they are significantly overshadowed by the consequences of infectious disease.\textsuperscript{41} Up until the past decade, health policy measures in the country have targeted general mortality and the infectious disease burden—both of which are still of serious concern—instead of disability.\textsuperscript{35} These policies have been largely successful, lowering infant mortality rates immensely,\textsuperscript{39} but this decrease has likely been offset by an increase in disability.\textsuperscript{35} It is only in recent years that India has begun to see a shift from mortality and morbidity due to infectious diseases to those caused by chronic and genetic conditions.\textsuperscript{36}
Therefore, this study looks to determine the disorders which are relevant to an Indian NBS panel and make recommendations for an Indian NBS program. With various companies marketing NBS panels to India, it is important to determine what disorders India would benefit from being on an NBS panel. As such, this study seeks to assess the relevance of various congenital disorders to the Indian setting, and make recommendations for a NBS panel that considers the needs and limitations of the Indian population. We seek to do this through an assessment of disease frequency and a systematic review, with the goal of providing Indian professionals, physicians, and government with a concrete plan and next steps for establishing a national NBS program.

Key Questions

Key question 1: What is the specific birth prevalence of congenital disorders in the Indian population at the national level and how does this prevalence compare to that in the United States?

Key question 2: What congenital disorders are relevant to the Indian setting in the context of Newborn Screening? How are these disorders relevant in terms of:

a. Birth prevalence, both absolute and relative to the US
b. Availability of a therapy
c. Natural history of disease

Methods

Conditions

Conditions included in this analysis were taken from both the Recommended Uniform Screening Panel (RUSP)—a nationally recommended list of conditions for NBS published by the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) of the Department of Health and Human Services (DHHS)\(^1\)—and PerkinElmer’s StepOne Panel\(^2\)—a privately developed panel used by many state programs and marketed to developing countries such as India.\(^3,4\) Both panels were combined to create a list of 69 conditions (see Appendix A). 4 conditions—Hyperalimentation, Medium-chain triglyceride oil administration, Presence of Ethylenediaminetetraacetic acid (EDTA) anticoagulants in
blood specimen, and treatment with benzoate, pyvalic acid, or valproic acid—were excluded for not being congenital/inborn disorders. Synonyms and keywords for all 69 conditions were then identified from Baby’s First Test, the US NBS Clearinghouse which was established as a part of the Newborn Screening Saves Lives Act of 2008.32,45 BabysFirstTest.org was chosen to identify keywords synonymous with the disorders due to all info coming from various academic sources (mainly the US National Library of Medicine (NLM) as well as its purpose of serving as both an academic and public source of information. As such, it was believed that Baby’s First Test would be a sufficient source of terms that would be used in research articles.

**Literature Search**

A literature search of studies in MEDLINE was conducted on December 12, 2016. The search included terms for all disorders included in the study as well as MeSH terms for all disorders when available, a validated pediatric search modified to constrain the search to newborns and neonates, disease incidence, India, the United States, and Newborn Screening. The search was limited to studies published after 2000. This search was created with the help of two experience librarians.

**Study Selection**

Abstracts were screened using Abstrackr, a computerized screening program developed by Brown University’s Center for Evidence Synthesis in Health (CESH) to automate the screening of abstracts for eligible articles for full text screening.46 Abstracts were single screened with the assistance of Abstrackr. Full-text articles were retrieved for all articles screened in at the abstract level.

At the abstract level, studies were considered eligible if they were about one of the 69 conditions and mentioned either, neonates or newborn screening. Studies were excluded if they were explicitly about validation or the tests themselves with no indication of incidence or prevalence data. Studies with populations explicitly not in the US or India were excluded. Non-English studies were also excluded. All review articles were included at the abstract level.

At the full-text level, studies were only included if they explicitly had extractable incidence or prevalence data on one or more of the disorders included. Incidence data was required to be primary or estimated through mathematical models, reviews were excepted. Papers reporting an aggregate incidence
for groupings such as “amino acid disorders” or “fatty acid oxidation disorders” were excluded as the data would have no pertinence to deciding which specific disorders should be included in a state NBS program.

**Data Extraction**

Data from each included study was extracted a single time. Relevant data extracted included: publication information, disorder, neonates diagnosed with a particular disorder, total neonates screened, incidence/prevalence, and study design. Disorders were defined as according to Appendix A. When applicable, data was aggregated by simple pooling to create an overall incidence for a disorder. Data from systematic reviews were only extracted when presented in tables and not solely in narrative, this was done by returning to the primary study. Incidence/prevalence data was converted to birth prevalence per 100,000 births.

**Data Synthesis**

All included studies were summarized in summary tables (see below) that report birth prevalence and any important characteristics of the study or study population. The purpose of these summary estimates was only to compare reported estimates of birth prevalence. Birth prevalence was estimated by a mean weighted by the total number of neonates screened.

All disorders were also summarized by a narrative review of information from the Newborn Screening Clearing House and National Library of Medicine pages. This was done to provide insights when incidence data was not available and to describe subtleties not captured by incidence or prevalence information, such as risk among subgroups and availability of treatment, that may be relevant to determining the importance of each disorder as an important public health issue.

If frequency data for the Indian setting was available and exceeded the frequency reported in the NLM or US studies, then disorders were recommended for an Indian NBS panel. This was done because if a disease with a certain frequency is classified as high enough to warrant inclusion on the US panel, then it should be high enough to warrant inclusion on an Indian panel. This is especially true given the US has a population of approximately 320 million and India one the size of over 1.3 billion, meaning that the same frequency will mean a larger number of neonates affected when comparing India to the US. Otherwise, disorders were determined as relevant by the research team based on populations effected and available information.
Results

The literature search yielded 4157 citations. From these 457 articles were screened in for retrieval and full-text review. 357 articles were irretrievable at the time of the study, and of the remaining 100 articles, 23 were screened in.\(^{47-69}\) Of those 23 articles, 2 were systematic reviews\(^ {56,66}\) which yielded an additional 18 studies.\(^ {38,65,70-85}\) As such, a total of 41 studies are included in this review (Figure 1).

The remaining 77 studies were rejected for not meeting eligibility criteria. 50 studies had no relevant incidence or prevalence data for a congenital disorder, 10 studies had incidence or prevalence data for study populations not in the US or India, 6 studies were cost-analyses with no prevalence or incidence data modeled or presented in an extractable format, 4 studies were case reports, 4 studies presented incomplete information that was not extractable, 2 studies were purely about the validation of the screening test and did not present any primary frequency data, and 1 study was in a non-English language.

Of the 41 studies included in this review, there are 33 prospective cohort studies, 2 retrospective cohort studies, 2 modeling studies, 2 reviews, and 1 systematic review. 1 study qualified as both a systematic review and a prospective cohort study by reviewing data on numerous diseases as well as presenting the preliminary results of a primary screening study. Studies were only qualified as a systematic review if they explicitly described a systematic literature search in their methodology. 19 studies contained data for the US and 22 studies contained data for India. 13 studies reported demographic variables for the study population. The most common demographics reported were age at screening, neonate sex, and race/ethnicity.

The results section is divided by inborn disorder, reporting the birth prevalence estimate per 100,000 births determined by this review as well as a narrative description of each disorder. The disorders are grouped in the following manner: Hemoglobin conditions, Amino Acid conditions, Fatty Acid Oxidation conditions, Organic Acid conditions, Endocrine conditions, Cystic Fibrosis, Other Conditions, Congenital Heart Disease, Congenital Hearing Loss, and Congenital Liver Defects.

Hemoglobin Conditions

Of the 7 hemoglobin conditions included in this review, we recommend 6 of them to be included on an Indian NBS panel. These conditions are: Sickle Cell Anemia (Hb SS), Sickle Cell/beta-Thalassemia (Hb S/Th), Sickle Cell/Hemoglobin C disease (Hb S/C), Hemoglobin E/Beta-Thalassemia (Hb E/Th),
Various Hemoglobinopathies, and Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD) (see Table 10). Descriptions of these conditions and their associated evidence identified in this review are presented below.

**Sickle cell anemia (SS)**

Sickle cell anemia (Hb SS) is a group of disorders categorized by a point mutation in the β-globin gene. This mutation results in the incorrect folding of the β-globin of hemoglobin, resulting in a more rigid and sickle-shaped red blood cell. These abnormal cells degrade far more rapidly than normal red blood cells, leading to anemia. Additionally, these abnormal cells may get stuck in smaller blood vessels, due to their odd shape and rigid nature, causing pain and organ damage, especially in the lungs, kidneys, spleen, and brain. Prior to the onset of NBS and comprehensive care, a 20% mortality rate was observed in children during the first 10 years of life. When untreated, sickle-cell can lead to chronic pain, organ damage, and infection, causing undue morbidity and mortality. Due to NBS, symptoms and complications are greatly reduced, however, there is no known cure.

Two studies were identified that contained data for Hb SS, both for the US. Hoppe et al. (2013) estimated a birth prevalence of 8.9 cases of Hb SS per 100,000 births, based on prospective cohort study of over 5 million Californian infants screened from 2001 to 2011. Michlitsch et al. (2009) estimated a birth prevalence of 8.5 cases of Hb SS per 100,000 births, based on a prospective cohort study of approximately 4.5 million neonates, screened over the course of 8.5 years. The weighted mean birth prevalence for Hb SS in the United States was calculated to be 8.7 per 100,000 births (see Table 1).

No studies were identified containing frequency data for the Indian setting. However, sickle cell disease is identified to be common among individuals of Indian descent. As such, we recommend that sickle cell anemia (Hb SS) be included on a NBS panel for the Indian Setting (see Table 10).

**Sickle cell/Beta-Thalassemia (S/Th)**

β-thalassemias are a group of disorders characterized by a decreased or absent ability to produce the β-globin chain of hemoglobin, resulting in a reduced number of red blood cells (RBCs). Prior to the onset of screening and treatment, beta-thalassemias were characterized by early mortality, but with early detection and treatment through blood transfusions. Sickle cell/Beta-thalassemia is characterized by the inheritance of a trait for both sickle-cell anemia and beta-thalassemia, resulting in both the production of a reduced
number of RBCs as well as a production of some sickle-shaped RBCs. As such, individuals experience both the symptoms of sickle cell anemia and β-thalassemia, requiring treatment with pain medication and blood transfusions. Early detection and effective treatment allows for the management of symptoms and avoidance of early mortality.

Two studies were identified that contained frequency data for Hb S/β-thalassemia in the US. Hoppe et al. (2013) estimated a birth prevalence of 2.8 cases per 100,000 births and Michlitsch et al. (2009) estimated a birth prevalence of 2.2 cases per 100,000 births. The estimated birth prevalence for Hb S/β-thalassemia in the US was calculated to be 2.2 cases per 100,000 births (see Table 1).

No studies were identified containing frequency data for the Indian setting. While the NLM and studies identified in this review present no frequency data for Hb S/β-thalassemia, both sickle cell anemia and β-thalassemia are common in the Indian population. As such we recommend Hb S/β-thalassemia be added to an Indian NBS panel due to its inheritance pattern being related to both sickle-cell anemia and β-thalassemia (see Table 10).

**Sickle cell/Hemoglobin C disease (Hb S/C)**

Sickle cell/Hemoglobin C disease (Hb S/C) is characterized by the inheritance of traits for both sickle cell anemia and hemoglobin C disease. Hemoglobin C disease is caused by a point mutation in β-globin. Treatment is not typically needed and individuals do not experience symptoms except for mild anemia. Individuals with Hb S/C disease have some cells with a sickle shape like those with sickle cell anemia, but experience less pain due to cells blocking blood vessels. Hb S/C disease can be managed through mild pain medication and blood transfusions.

This review identified two studies with frequency data for Hb S/C disease in the US. Hoppe et al. (2013) estimated a birth prevalence of 4.8 cases per 100,000 births and Michlitsch et al. (2009) estimated a birth prevalence of 4.4 cases per 100,000 births. The estimated birth prevalence for Hb S/C in the US was calculated to be 4.6 cases per 100,000 births (see Table 1).

No studies were identified containing frequency data for the Indian setting. Both the NLM and studies identified by this review present no frequency for both Hb S/C disease and hemoglobin C disease. However, we recommend this disease may be added to an Indian NBS panel due to sickle cell trait being common in the Indian population (see Table 10).
**Hemoglobin C disease (Hb C)**

Hemoglobin C disease is caused by a point mutation in β-globin and is typically associated with no symptoms other than occasional mild anemia. Individuals with hemoglobin C disease often need no treatment. Both the NLM and articles identified by this review present no frequency data for Hb C disease in either the US or India. We do not recommend Hb C disease for an Indian NBS panel.

**Hemoglobin E/β-thalassemia disease (Hb E/β-thal)**

Hb E disease is the second most common hemoglobin variant after Hb S. While the homozygous variant is typically benign, Hb E is often inherited with other variants, with the coinheritance of Hb E and β-thalassemia often associated with severe anemia. In some cases, Hb E/β-thalassemia can be so severe that it requires transfusions from birth, and if left untreated, could result in death.

This review identified 2 studies with frequency data for Hb E/β-thalassemia in the US. Hoppe et al. (2013) estimated a birth prevalence of 0.9 cases per 100,000 births and Michlitsch et al. (2009) estimated a birth prevalence of 0.8 cases per 100,000 births. The estimated birth prevalence for Hb E/β-thalassemia in the US was calculated to be 0.9 cases per 100,000 births (see Table 1).

No studies were identified containing frequency data for the Indian setting. However, Hb E/β-thalassemia is identified as being present at some of the highest frequencies in Southeast Asia, including India. Given this information and the potential life-threatening nature of this disorder in infancy, we recommend that this disease be given priority on an Indian NBS panel (See Table 10).

**Various Hemoglobinopathies**

The remaining hemoglobinopathies (disorders such as Hb H and alpha-thalassemias) fall under the label of various hemoglobinopathies on the RUSP. These disorders can range from life-threatening to asymptomatic, but occur at a much rarer frequency individually than the others listed here. Like the other hemoglobinopathies, treatment, when required, typically involves blood transfusions and pain medication.

This review identified 2 studies with frequency data for various other hemoglobinopathies in the US. Hoppe et al. (2013) estimated a birth prevalence of 21.8 cases per 100,000 births and Michlitsch et al. (2009) estimated a birth prevalence of 31.6 cases per 100,000 births. The estimated birth prevalence for various other hemoglobinopathies in the US was calculated to be 26.2 cases per 100,000 births (see Table 1).
Both the NLM and articles identified by this review present no frequency data for various other hemoglobinopathies disease in the Indian setting.\cite{126} We do not recommend this disorder for an Indian NBS panel at this time. However, if this group of disorders is detected secondarily by tests conducted for the other hemoglobinopathies listed here (see Table 10).

**Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD)**

Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD) is an inherited condition that causes a defect in the enzyme glucose-6-phosphate dehydrogenase, resulting in premature cell death in RBCs (hemolysis). Individuals with this disorder experience hemolytic anemia, which in some cases can lead to jaundice, kidney failure, or death. G6PD is typically treated with dietary supplementation, medication, and blood transfusion.\cite{95,96} G6PD is more common in males due to it being x-linked.\cite{95,96}

This review identified a single study with frequency data for G6PD in the US. Nock et al. (2011) estimated a birth prevalence of 11,141.6 cases of G6PD per 100,000 births based on a prospective cohort study of 1095 male neonates born in University Hospital, Cleveland, Ohio.\cite{63} However, this is most likely an overestimate affected by the small sample size and exclusively male sample.

In contrast, this review identified 6 studies with frequency data for G6PD in India. Birth prevalence estimates for G6PD of 1248.3, 3900, 2016.9, 17,551, 807.3, and 16,753.9 cases per 100,000 were given by Kaur et al. (2016), Verma et al. (1994), Pao et al. (2005), Dash et al. (2005), Kaur et al. (2010), and Mohanty et al. (2014), respectively.\cite{56,73,77–80} Kaur et al. (2016) was a systematic review that also provided primary data from an ongoing screening study of infants born in Chandigarh, India from 2007 to 2014.\cite{56} The remaining studies were prospective cohorts of Indian neonates identified from this systematic review.\cite{73,77–80} The estimated birth prevalence for G6PD in India is 2387.7 cases per 100,000 births (see Table 1). Given this data we recommend G6PD be placed on an NBS panel for India, given that using the 2012 annual birth-rate of over 25.6 million births,\cite{39} we would expect to see over 600,000 cases of G6PD annually (see Table 10).
Amino Acid Conditions

Of the 17 amino acid conditions included in this review, we recommend none of them for an Indian NBS panel. Descriptions of these conditions and their associated evidence identified in this review are presented below.

Phenylketonuria (PKU)

Phenylketonuria (PKU) is a disorder characterized by a decreased ability to metabolize the amino acid phenylalanine. If left untreated, phenylalanine can build up in the blood, leading to brain damage and even death. However, if detected and treated early, individuals and avoid symptoms and complications and live health lives. The condition can be easily treated with a phenylalanine restricted diet and, in some cases, a BH4 supplement.\textsuperscript{1,97}

This review identified 2 studies with frequency data for PKU in the US. Hinton et al. (2014) estimated a birth prevalence of 4.3 cases of PKU per 100,000 births based on a 4-state prospective cohort study that screened over 1.2 million neonates over the course of 3 years.\textsuperscript{53} Zytkovicz et al. (2001) estimated a birth prevalence of 14 cases of PKU per 100,000 births based on a prospective cohort study of neonates born in New England.\textsuperscript{69} The estimated aggregate birth prevalence for PKU in the US is 5.9 cases per 100,000 births (see Table 2).

This review identified no articles containing frequency data for India. According to Baby’s First Test and the NLM, PKU is common is the Northern European populations and Ashkenazi Jews.\textsuperscript{1,97} We do not recommend adding PKU to an NBS panel, until further data comes forth.

Tetrahydrobiopterin deficiency

Tetrahydrobiopterin (BH4) deficiencies are a group of disorders characterized by a reduced level of BH4, leading to altered levels of various substances, including phenylalanine, and neurotransmitters. Due to BH4’s relation to phenylalanine, BH4 often presents similarly to PKU, with symptoms including brain damage.\textsuperscript{98} There are two types of BH4 deficiency, biopterin defect in cofactor biosynthesis (BIOPT-BS) and biopterin defect in cofactor regeneration (BIOPT-REG). BIOPT-BS affects the enzymes which are utilized to produce BH4 while BIOPT-REG affects the enzymes utilized for the recycling of BH4. Both of these disorders result in decreased levels of BH4 in the body.\textsuperscript{99,100}
This review identified no articles that contain frequency data for BH 4 deficiency. However, the NLM and NBS clearing house identify BH4 deficiency as an extremely rare disease affecting less than one in one million newborns. As such, we do not recommend adding BH4 deficiency to a NBS panel for India.

**Maple Syrup Urine Disease (MSUD)**

Maple Syrup Urine Disease (MSUD) is characterized by a reduced ability to break down the amino acids leucine, isoleucine, and valine, leading a build of these molecules in the blood. As a result, the urine of individuals affected has a distinctive sweet odor, giving the condition its name. Those affected may seem normal at first, but rapidly develop symptoms, often including severe brain damage, and in some cases seizures or coma. If left untreated, individuals often die within the first 5 months.

This review identified 2 studies with frequency data for MSUD in the US. Hinton et al. (2014) estimated a birth prevalence of 0.5 cases per 100,000 births and Zytkovicz et al. (2001) estimated a birth prevalence of 0.8 cases per 100,000 births. The estimated birth prevalence for the US is 0.5 cases per 100,000 births (see Table 2).

This review identified a single study containing frequency information for MSUD in India. Narayanan et al. (2011) estimated a birth prevalence of 3095.2 cases per 100,000 births based on a prospective cohort of Indian neonates. Narayanan et al. was from Kaur et al. (2016), a systematic review (see Table 2).

However, given the small sample size of Narayan et al. of 420 neonates, and the fact the MSUD is most common in Ashkenazi Jews and French-Canadians, we do not recommend adding this disorder to an Indian NBS panel.

**Homocystinuria (HCY)**

Homocystinuria (HCY) is characterized by a decreased ability to metabolize the amino acid methionine, leading to a build of methionine in the blood. Affected individuals experience a variety of severe symptoms affecting the central nervous system, muscles, and cardiovascular system. Individuals who are treated early can go on to live healthy lives. This review identified no articles with frequency data for HCY in either the US or India. However, both the NLM and NBS clearinghouse identify as HCY as common in individuals of Irish, Germanic, and Norwegian descent. As such, we do not recommend HCY for an Indian NBS panel.
**Citrullinemia, Type I (CIT)**

Citrullinemia, type I (CIT) is an inherited disorder that results in a build up of ammonia in the blood due to the body’s reduced ability to convert it to urea. While infants appear normal at birth, they soon become lethargic, feed poorly, and experience vomiting and seizures. If left untreated, infants often lose consciousness and may soon die.105,106

This review identified a single study with frequency data for CIT in the US. Hinton et al. (2014) estimated a birth prevalence of 0.2 cases per 100,000 births53 (see Table 2). However, no articles were identified with frequency data for India. Additionally, neither the NLM or NBS clearinghouse identifies a frequency of CIT in the Indian setting.105,106 As such, we do not recommend CIT for an Indian NBS panel.

**Citrullinemia, Type II (CIT II)**

Citrullinemia, Type II (CIT II), is a condition characterized by a decreased or absent ability to make citrin, an essential protein in cell metabolism and liver function. CIT II typically affects the nervous system, causing confusion, memory loss, abnormal behavior, seizures, and coma, and is often life-threatening.106,107

This review identified no articles containing frequency data for CIT II in the US or India. The NLM and NBS clearinghouse identifies CIT II as occurring primarily in the Japanese population.106,107 As such, we do not recommend CIT II for an Indian NBS panel.

**Argininosuccinic acidemia (ASA)**

Argininosuccinic acidemia (ASA) is a disorder characterized by a decreased ability to produce arginine, leading to a build-up of argininosuccinic acid and ammonia in the blood. Infants with ASA may experience lethargy, developmental delays, seizures, coma, and in some cases death. Early treatment and lifelong management through a restricted diet and supplements.108,109

This review identified 2 studies presenting frequency data for ASA in the US and none that presented frequency data for India. Hinton et al. (2014) estimated a birth prevalence of 0.3 cases per 100,000 births and Zytkovicz et al. (2001) estimated a birth prevalence of 1.2 cases per 100,000 births.53,69 The estimated birth prevalence for the US is 0.4 cases per 100,000 births (see Table 2). Additionally, neither the NLM or NBS clearinghouse identify a frequency for ASA in India.108,109 As such, we do not recommend ASA for an Indian NBS panel.
Tyrosinemia, type I (TYR I)

Tyrosinemia, type I (TYR I) is characterized by an inability to metabolize the amino acid tyrosine, causing a build-up in the blood and tissues. Infants with TYR I experience failure to thrive (failure to gain weight and grow at a normal rate), occasional jaundice, and possible liver and kidney failure. In severe cases, children experience neurological problems, abdominal pain, and respiratory failure. If left untreated, affect children rarely live past age 10.\textsuperscript{110,111} This review identified no articles with frequency data for TYR I in either the US or India. Additionally, the NLM and NBS clearinghouse identify TYR I as a rare disease primarily found in individuals of French-Canadian descent.\textsuperscript{110,111} As such, we do not recommend TYR I for an Indian NBS panel.

Tyrosinemia, type II (TYR II)

Tyrosinemia, type II (TYR II) is characterized is a decreased ability to metabolize tyrosine. TYR II is a milder form than TYR I, with onset in early childhood. Children affected experience eye pain and redness, photosensitivity, thick and painful calluses on the palms and soles of the feet, as well as developmental delay in 50% of children. Early detection and treatment can prevent severe symptoms and complications.\textsuperscript{110,112} This review identified no articles with frequency data for TYR II in either the US or India. Additionally, the NLM and NBS clearinghouse identify TYR II as a rare disease primarily found in individuals of Arab and Mediterranean descent.\textsuperscript{110,112} As such, we do not recommend TYR II for an Indian NBS panel.

Tyrosinemia, type III (TYR III)

Tyrosinemia, type III (TYR III) is the rarest form of tyrosinemia and a mild form of the disease. Infants with TYR III typically experience intellectual disabilities, seizures, and intermittent ataxia.\textsuperscript{110,113} This review identified no articles with frequency data for TYR II in either the US or India. Additionally, the NLM and NBS clearinghouse identify TYR III as an extremely rare disease, with only a few cases having ever been reported worldwide.\textsuperscript{110,113} As such, we do not recommend TYR III for an Indian NBS panel.

Pyroglutamic acidemia (5-OXO)

Pyroglutamic acidemia (5-OXO) is a disorder characterized by the inability to produce glutathione, an essential molecule in functions ranging from energy production to DNA replication. 5-OXO typically
results in hemolytic anemia and in severe cases, bacterial infection, and various neurological symptoms. Early detection and proper treatment can help alleviate symptoms and prevent severe complications. This review identified no articles with frequency data for 5-OXO in either the US or India. Additionally, the NBS clearinghouse identify 5-OXO as an extremely rare disease, with only 70 cases having ever been reported worldwide. As such, we do not recommend 5-OXO for an Indian NBS panel.

**Carbamoyl phosphate synthetase deficiency (CPS)**

Carbamoyl phosphate synthetase deficiency (CPS) is a metabolic disorder that causes a build-up of ammonia in the blood due to the lack of the enzyme carbamoyl phosphate synthetase I. Infants with CPS experience lethargy, poor feeding, vomiting, developmental delays, seizures, coma, and in some cases, death. Early detection and treatment in the newborn period are important to avoid severe symptoms. This review identified no articles with frequency data for CPS in either the US or India. Additionally, the NBS clearinghouse identify CPS as an extremely rare disease. As such, we do not recommend CPS for an Indian NBS panel.

**Hyperornithinemia-Hyperammonemia-Homocitrullinuria syndrome (HHH)**

Hyperornithinemia-Hyperammonemia-Homocitrullinuria syndrome (HHH) is characterized by the inability to process and remove ammonia, leading to a build-up of ammonia in the blood and tissues. Infants with HHH experience developmental delays, learning disabilities, and muscle spasms. Early detection and treatment help prevent serious complications of HHH. This review identified no articles with frequency data for HHH in either the US or India. Additionally, NBS clearinghouse identify HHH as an extremely rare disease, with fewer than 100 cases having ever been reported worldwide. As such, we do not recommend HHH for an Indian NBS panel.

**Hyperornithine with Gyrate Deficiency (Hyper ORN)**

Hyperornithine with Gyrate Deficiency (Hyper ORN) is characterized by the inability to metabolize ornithine, resulting in progressive vision loss. In some cases, early treatment may prevent or delay serious outcomes. This review identified no articles with frequency data for hyper ORN in either the US or India. Additionally, the NLM and NBS clearinghouse identify hyper ORN as an extremely rare disease, with fewer than 200 cases having ever been reported worldwide. As such, we do not recommend hyper ORN for an Indian NBS panel.
**Argininemia (ARG)**

Argininemia (ARG) is characterized by the inability to metabolize arginine, leading to a buildup of ammonia in the body. Infants with ARG may experience developmental delays, muscle spasms, intellectual disabilities, seizures, and ataxia. Onset of symptoms typically occurs at age 3.\textsuperscript{119,120}

This review identified a single study with frequency data for ARG in the US. Zytkovicz et al. (2001) estimated a birth prevalence of 1.2 cases per 100,000 births\textsuperscript{69} (see Table 2). This review identified no studies with frequency data for ARG in the Indian setting. Additionally, both the NLM and NBS clearinghouse identify house as a rare disease, occurring in one in every 300,000 to 1,000,000 individuals.\textsuperscript{119,120} As such, we do not recommend ARG to be included in an NBS panel for the Indian setting.

**Hypermethioninemia (MET)**

Hypermethioninemia (MET) is a disorder characterized by the inability to metabolize the amino acid methionine. Often, individuals with MET are asymptomatic, but they may experience learning delays and muscle weakness.\textsuperscript{121,122}

This review identified a single study with frequency data for MET in the US. Zytkovicz et al. (2001) estimated a birth prevalence of 0.8 cases per 100,000 births\textsuperscript{69} (see Table 2). This review identified no studies with frequency data for MET in the Indian setting. Additionally, neither the NLM or NBS clearinghouse identify house as a rare disease, occurring in one in every 300,000 to 1,000,000 individuals.\textsuperscript{121,122} As such, we do not recommend MET for an Indian NBS panel.

**Benign Hyperphenylalaninemia (H-Phe)**

Benign Hyperphenylalaninemia (H-Phe) is a mild form of PKU that is characterized by a decreased metabolism for phenylalanine and is typically asymptomatic. The NBS clearinghouse identifies H-Phe as a rare condition affecting less than 75 out of every one million births.\textsuperscript{123} Additionally, this review identified no studies with frequency data for H-Phe for either the US or India. As such, we do not recommend H-Phe for an Indian NBS panel.

**Fatty Acid Oxidation Conditions**
Of the 13 fatty acid oxidation conditions included in this review, we recommend none of them for an Indian NBS panel. Descriptions of these conditions and their associated evidence identified in this review are presented below.

**Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)**

Medium-chain acyl-CoA dehydrogenase deficiency (MCAD) is a condition characterized by the inability to metabolize some fats. Newborns with MCAD often experience symptoms during infancy or early childhood, included lethargy, hypoglycemia, and vomiting. Serious complications include, seizures, difficulty breathing, liver problems, brain damage, coma, and in some instances, sudden death. If caught early and treated, individual can live healthy lives.\(^{124,125}\)

This review identified a single study with frequency data for MCAD in the US. Hinton et al. (2014) estimated a birth prevalence of 6 cases per 100,000 births\(^53\) (see Table 3). This review identified no studies with frequency data for MCAD in the Indian setting. Additionally, both the NLM and NBS clearinghouse identify MCAD as common in individuals of Northern European descent.\(^{124,125}\) As such, we do not recommend MCAD for an Indian NBS panel.

**Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)**

Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD) is a condition characterized by the inability to metabolize certain fats, particularly during periods of fasting. Newborns with VLCAD often experience symptoms such as hypoglycemia, lethargy, and muscle weakness. Serious complications include liver abnormalities, life-threatening heart problems, brain damage, and death. Symptoms for VLCAD typically present during infancy or early childhood, however, occasionally, milder symptoms present in adolescence or adulthood. If detected and managed early, individuals with VLCAD can lead healthy lives.\(^{126,127}\)

This review identified a single study with frequency data for VLCAD in the US. Hinton et al. (2014) estimated a birth prevalence of 1.4 cases per 100,000 births\(^53\) (see Table 3). This review identified no studies with frequency data for VLCAD in the Indian setting. Additionally, neither the NLM and NBS clearinghouse identify a frequency for VLCAD in India.\(^{126,127}\) We do not recommend VLCAD for an Indian NBS panel.
**Long-chain 3-OH acyl-CoA dehydrogenase deficiency (LCHAD)**

Long-chain 3-OH acyl-CoA dehydrogenase deficiency (LCHAD) is a condition characterized by the inability to metabolize certain fats. Infants with LCHAD typically experience difficulty feeding, lethargy, hypoglycemia, hypotonia, liver problems, and retina abnormalities. Later in life, individuals may experience muscle pain, atrophy, and peripheral neuropathy. Serious complications include heart problems, breathing difficulties, coma, and sudden death. Early treatment can help prevent the severe complications of LCHAD.\(^{128,129}\)

This review identified a single study with frequency data for LCHAD in the US. Hinton et al. (2014) estimated a birth prevalence of 0.1 cases per 100,000 births\(^5\) (see Table 3). This review identified no studies with frequency data for LCHAD in the Indian setting. Additionally, both the NLM and NBS clearinghouse identify LCHAD as common in individuals of Finnish descent.\(^{128,129}\) As such, we do not recommend LCHAD for an Indian NBS panel.

**Short-Chain Acyl-CoA Dehydrogenase Deficiency (SCAD)**

Short-chain acyl-CoA dehydrogenase deficiency (SCAD) is a condition characterized by the inability to metabolize certain fats. Infants with SCAD may experience vomiting, hypoglycemia, lethargy, poor feeding, failure to thrive, hypotonia, seizures, developmental delays, and microcephaly. Occasionally, individuals do not experience symptoms until childhood, in which case problems related to muscle weakness and wasting are more common.\(^{130,131}\) This review identified no articles with frequency data in either the US or India. Additionally, the NBS clearinghouse and NLM identify no frequency for SCAD specific to India.\(^{130,131}\) As such, we do not recommend SCAD for an Indian NBS panel.

**Medium/Short-Chain L-3 Hydroxyacyl-CoA Dehydrogenase Deficiency (M/SCHAD)**

Medium/Short-Chain L-3 Hydroxyacyl-CoA Dehydrogenase Deficiency (M/SCHAD) is a condition characterized by the inability to metabolize certain fats. Infants with M/SCHAD may experience poor appetite, vomiting, diarrhea, lethargy, hypotonia, liver problems, hypoglycemia, and hyperinsulinism. Infants are also at risk for serious complications such as seizures, life-threatening heart and respiratory complications, and sudden death. Most individuals live life completely asymptomatic.\(^{132,133}\) This review identified no articles with frequency data in either the US or India. Additionally, the NBS clearinghouse
and NLM identify M/SCHAD as an extremely rare condition.\textsuperscript{132,133} As such, we do not recommend M/SCHAD for an Indian NBS panel.

**Trifunctional Protein Deficiency (TFP)**

Trifunctional protein deficiency (TFP) is a condition characterized by the inability to metabolize certain long-chain fatty acids due to an inadequate supply of mitochondrial trifunctional protein. Newborns with TFP may experience difficulty feeding, lethargy, hypoglycemia, hypotonia, and liver abnormalities. There is also a high risk for developing serious complications such as heart problems, breathing difficulty, coma, sudden death. Individuals who experience an onset of symptoms later in life may experience hypotonia, muscle pain, atrophy, and peripheral neuropathy.\textsuperscript{134,135} This review identified no articles with frequency data in either the US or India. Additionally, the NBS clearinghouse and NLM identify TFP as an extremely rare condition.\textsuperscript{134,135} As such, we do not recommend TFP for an Indian NBS panel.

**Carnitine Uptake Defect (CUD)**

Carnitine uptake defect (CUD) is a disorder in which carnitine—an amino acid important in fatty acid metabolism—cannot be transported into tissues, leading to a decreased ability to metabolize fats. Infants with CUD may experience encephalopathy, cardiomyopathy, confusion, vomiting, muscle weakness, and hypoglycemia. Affected individuals range from being asymptomatic to experiencing heart failure, liver problems, coma, and sudden death. Early treatment can help prevent serious complications and allow those affected to live healthy lives.\textsuperscript{136,137}

This review identified a single study with frequency data for CUD in the US. Hinton et al. (2014) estimated a birth prevalence of 0.9 cases per 100,000 births\textsuperscript{53} (see Table 3). This review identified no studies with frequency data for CUD in the Indian setting. Additionally, both the NLM and NBS clearinghouse identify CUD as common in individuals of Japanese descent.\textsuperscript{136,137} As such, we do not recommend CUD for an Indian NBS panel.

**Carnitine Acylcarnitine Translocase Deficiency (CACT)**

Carnitine acylcarnitine translocase deficiency (CACT) is a condition characterized by the inability to metabolize long-chain fatty acids. Infants with CACT may experience breathing problems, seizures, arrhythmia, hyperammonemia, hepatomegaly, and cardiomyopathy. Affected individuals typically have hypoketotic hypoglycemia. Early treatment can help prevent the severe outcomes of CACT.\textsuperscript{138,139} This
review identified no articles with frequency data in either the US or India. Additionally, the NBS clearinghouse and NLM identify it as a rare condition with less than 30 reported cases. As such, we do not recommend CACT for an Indian NBS panel.

**Carnitine Palmitoyltransferase I Deficiency (CPT-IA)**

Carnitine palmitoyltransferase I deficiency (CPT-IA) is a disorder characterized by the inability to metabolize long-chain fatty acids. Infants with CPT-IA typically have symptoms such as hypoketotic hypoglycemia, hepatomegaly, liver malfunction, and elevated blood carnitine. Individuals with CPT-IA are at risk for nervous system damage, liver failure, seizures, coma, and sudden death. Early detection and treatment can prevent the serious complications of CPT-IA. This review identified no articles with frequency data in either the US or India. Additionally, the NBS clearinghouse and NLM identify CPT-IA as a rare condition affecting less than 50 individuals worldwide. As such, we do not recommend CPT-IA for an Indian NBS panel.

**Carnitine Palmitoyltransferase Type II Deficiency (CPT-II)**

Carnitine palmitoyltransferase type II deficiency (CPT-II) is a disorder characterized by the inability to metabolize long-chain fatty acids. CPT-II has 3 forms: a lethal neonatal form, a severe infantile hepatocardiomuscular form, and a myopathic form. The lethal neonatal form of CPT-II results in respiratory failure, seizures, liver failure, cardiomyopathy, arrhythmia, and hypoketotic hypoglycemia. Those affected by the lethal neonatal form typically have structurally abnormal brain and kidneys and rarely live past the first few months of life. The severe infantile hepatocardiomuscular form affects the liver, heart and muscles and typically involves hypoketotic hypoglycemia, seizures, hepatomegaly, cardiomyopathy, and arrhythmia. Individuals with this form of CPT-II are also at risk for liver failure, nervous system damage, coma, and sudden death. Timely detection and treatment can help prevent the serious complication of this form of CPT-II. The myopathic form of CPT-II is the mildest form of the disease characterized by pain and weakness associated with the breakdown of muscle tissue as well as myoglobinuria, causing the urine to have a distinct red or brown color. In some cases, this can result in severe kidney damage and even kidney failure. Individuals with this form of CPT-II typically experience symptoms in recurrent episodes and are asymptomatic between episodes. Individuals with this form of CPT-II can lead healthy lives if treated early.
This review identified no articles with frequency data in either the US or India. Additionally, the NBS clearinghouse and NLM identify CPT-II as an extremely rare disease, with less than 350 cases being reported worldwide.\textsuperscript{142,143} As such, we do not recommend CPT-II for an Indian NBS panel.

**Glutaric Acidemia, Type II (GA2)**

Glutaric acidemia, type II (GA2) is a disorder characterized by the inability to metabolize proteins and fats. GA2 typically presents as a metabolic crisis—a condition characterized by weakness, poor feeding, decreased activity, and vomiting due to acidosis and hypoglycemia brought on by stressors such as childhood illness—which may in some cases be life-threatening. In severe cases, infants may be born with physical abnormalities, such as brain malformations, hepatomegaly, dilated cardiomyopathy, cysts, kidney malformations, unusual facial features, and genital abnormalities. In its mildest form, individuals experience muscle weakness in adulthood. For some individuals, early detection and management can prevent severe outcomes.\textsuperscript{144,145} This review identified no articles with frequency data in either the US or India. Additionally, the NBS clearinghouse and NLM identify GA2 as an extremely rare disease.\textsuperscript{144,145} As such, we do not recommend GA2 for an Indian NBS panel.

**Medium-Chain Ketoacyl-CoA Thiolase Deficiency (MCAT)**

Medium-chain ketoacyl-CoA thiolase deficiency (MCAT) is a disorder characterized by the inability to metabolize some fats. Infants with MCAT experience symptoms such as vomiting, dehydration, metabolic acidosis, liver dysfunction, and rhabdomyolysis. Severe complications include breathing problems, coma, and death.\textsuperscript{146} This review identified no articles with frequency data in either the US or India. Additionally, the NBS clearinghouse and NLM identify MCAT as an extremely rare disease.\textsuperscript{146} As such, we do not recommend MCAT for an Indian NBS panel.

**2,4 Dienoyl-CoA Reductase Deficiency (DE RED)**

2,4 Dienoyl-CoA reductase deficiency (DE RED) is a condition characterized by the inability to metabolize certain fats. Symptoms include, respiratory failure, failure to thrive, developmental delay, and lactic acidosis. This review identified no articles with frequency data in either the US or India. Additionally, the NBS clearinghouse and NLM identify DE RED as an extremely rare disease, with only 2 cases ever being reported thus far.\textsuperscript{147} As such, we do not recommend DE RED for an Indian NBS.
Organic Acid Conditions

Of the 17 organic acid conditions included in this review, we recommend that 3 of them be placed on an Indian NBS panel. These conditions are: Isovaleric Acidemia (IVA), Methylmalonic Acidemia – Cobalamin Deficiency (cblA, B), and Propionic Acidemia (PROP) (see Table 10). Descriptions of these conditions and their associated evidence identified in this review are presented below.

Isovaleric Acidemia (IVA)

Isovaleric Acidemia (IVA) is a disorder characterized by the inability to metabolize the amino acid leucine. Symptoms can range from mild to life-threatening. Symptoms initially include poor feeding, vomiting, seizures, lethargy, failure to thrive, and developmental delays. Sometimes more severe symptoms present in the first few days of life, including seizures, coma, and death. With timely treatment, children can go on to live healthy lives.\textsuperscript{148,149}

This review identified a single study containing frequency information for IVA in the US. Hinton et al. (2014) estimated a birth prevalence of 0.3 cases per 100,000 births\textsuperscript{53} (see Table 4). This review identified a single study containing frequency information for IVA in India. Narayanan et al. (2011) estimated a birth prevalence of 238.1 cases per 100,000 births.\textsuperscript{82} Narayanan et al. was from Kaur et al. (2016), a systematic review\textsuperscript{56} (see Table 4). Given that IVA is tested in the US and that it is far more prevalent in India than in the US, we recommend IVA for an Indian panel.

Glutaric Acidemia, Type I (GA1)

Glutaric Acidemia, Type I (GA1) is a condition in which the body is unable to metabolize the amino acids lysine, hydroxylysine, and tryptophan, leading to a build-up of these compounds and their intermediate breakdown products in the blood. As a result, individuals could experience brain damage, especially to the basal ganglia, a part of the brain that controls movement. Other symptoms include intellectual disability, macrocephaly, bleeding in the brain or eyes that can be mistaken for child abuse, decreased muscle tone, and movement issues such as spasms, jerking, and rigidity. With proper treatment and diet management, those with GA1 can lead healthy lives.\textsuperscript{150,151}

This review identified a single study containing frequency data for IVA in the US. Hinton et al. (2014) estimated a birth prevalence of 0.8 cases per 100,000 births\textsuperscript{53} (see Table 4). This review identified no studies containing frequency data for GA1 in India. Additionally, both the NLM and NBS clearinghouse
identify GA1 as occurring primarily in the US Amish population, the Ojibway Native American population in Canada, and those of Swedish descent.\textsuperscript{150,151} As such, we do not recommend GA1 for an Indian NBS panel.

**3-Hydroxy-3-Methylglutaric Aciduria (HMG)**

3-Hydroxy-3-Methylglutaric Aciduria (HMG) is a condition where the body cannot properly metabolize the amino acid leucine and cannot properly produce ketones, a type of molecule used for energy production during periods of fasting. Infants with HMG usually experience symptoms within the first year of life, including: vomiting, diarrhea, dehydration, lethargy, hypotonia, hypoglycemia, metabolic acidosis, and in some cases, respiratory issues, convulsions, coma, and death. Early detection and treatment can help prevent the serious complications of HMG.\textsuperscript{152,153} This review identified no studies containing frequency data for HMG in India or the US. Additionally, both the NLM and NBS clearinghouse identify HMG as a rare disease with fewer than 100 known cases worldwide.\textsuperscript{152,153} As such, we do not recommend HMG for an Indian NBS panel.

**Multiple Carboxylase Deficiency (MCD)**

Multiple carboxylase deficiency (MCD) is a disorder characterized by the decreased activity of enzymes that utilize biotin for energy production. Infants with MCD typically have difficult feeding, respiratory issues, skin rash, alopecia, and lethargy. Early detection and lifelong management with biotin supplements can prevent the complications of MCD. If left untreated, infants may experience developmental delays, seizures, and coma.\textsuperscript{154,155} This review identified no studies with frequency data for MCD in either India or the US. Additionally, the NLM and NBS clearinghouse identify no frequency data specific to India.\textsuperscript{154,155} Thus, we do not recommend MCD for an NBS panel in India.

**Malonic Acidemia (MAL)**

Malonic acidemia (MAL) is a condition where the body is unable to metabolize certain fats for energy production. Infants with MAL experience developmental delays, hypotonia, seizures, diarrhea, vomiting, hypoglycemia, and cardiomyopathy. With a restricted diet and medication, infants can go on to live a healthy life.\textsuperscript{156,157} This review identified no studies with frequency data for MAL in the US or India. Additionally, both the NLM and NBS clearinghouse identify MAL as an extremely rare disease with less
than 30 cases being reported worldwide.\textsuperscript{156,157} As such, we do not recommend MAL for an Indian NBS panel.

**Methylmalonic Acidemia due to Mutase Deficiency (MUT)**

Methylmalonic acidemia (MMA) due to mutase deficiency (MUT) is a type of MMA characterized by the inability to metabolize the amino acids methionine, threonine, isoleucine, and valine as well as cholesterol, leading up to a build-up of methylmalonic acid. This is due to a decreased amount of the enzyme methylmalonyl CoA mutase or because of the inability to produce functional copies of the enzyme. Infants with MUT may experience vomiting, dehydration, hypotonia, developmental delays, lethargy, hepatomegaly, and failure to thrive. In the long-term, infants may experience difficulty feeding, intellectual disabilities, chronic kidney disease, and pancreatitis. Without treatment, MUT may lead to coma and death.\textsuperscript{158,159}

This review identified a single study with frequency data for MUT in the US. Hinton et al. (2014) estimated a birth prevalence of 1.1 cases per 100,000 births\textsuperscript{53} (see Table 4). This review identified no studies with frequency data for India. Additionally, neither the NLM nor NBS clearinghouse identify frequency data for MUT in India.\textsuperscript{158,159} As such, we do not recommend MUT for an Indian NBS panel.

**Methylmalonic Acidemia caused by Cobalamin disorders A and B (cblA, B)**

MMA caused by Cobalamin disorders A and B (cblA, B) is a type of MMA similar to MUT, where methylmalonyl CoA mutase is non-functional. In cblA, B, at least one of the two enzymes involved in the conversion of vitamin B\textsubscript{12} to Adenosylcobalamin, a coenzyme required for the proper functioning of methylmalonyl CoA mutase, are non-functional or present in decreased level. Infants with cblA, B experience symptoms similar to those experienced by infants with MUT.\textsuperscript{158,160}

This review identified a single study with frequency data in cblA, B for the US. Hinton et al (2014) estimated a birth prevalence of 0.3 cases per 100,000 births\textsuperscript{53} (see Table 4). This review identified a single study containing frequency information for cblA, B in India. Narayanan et al. (2011) estimated a birth prevalence of 3571.4 cases per 100,000 births.\textsuperscript{52} Narayanan et al. was from Kaur et al. (2016), a systematic review\textsuperscript{56} (see Table 4). Given that cblA, B is tested in the US and that it is far more prevalent in India than in the US, we recommend cblA, B for an Indian panel.
Methylmalonic Acidemia with Homocystinuria (CBL C, D, F)

MMA with Homocystinuria (cblC, D, F) is similar to both MUT and cblA, B. In cblC, D, F, additional enzymes involved in adenosylcobalamin synthesis are dysfunctional. As such, infants experience symptoms similar to those experienced in MUT.\textsuperscript{158,161} This review identified no studies with frequency data for cblC, D, F in either the US or India. Additionally, the NLM and NBS clearinghouse do not identify any frequency data specific to India.\textsuperscript{158,161} As such we do not recommend cblC, D, F for an Indian NBS panel.

3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)

3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC) is a condition where the body is unable to metabolize leucine. Infants with 3MCC experience symptoms such as difficulty feeding, recurrent vomiting and diarrhea, lethargy, and hypotonia. If caught and managed early, serious complications can be avoided and children can lead healthy lives, however, if left untreated, infants may experience developmental delays, seizures, and coma.\textsuperscript{162,163}

This review identified a single study containing frequency data for 3MCC in the US. Hinton et al. (2014) estimated a birth prevalence of 3.1 cases per 100,000 births\textsuperscript{53} (see Table 4). No studies with frequency data for India were identified. Additionally, both the NLM and NBS clearinghouse identify no specific frequency for India.\textsuperscript{162,163} As such, we do not recommend 3MCC for an Indian NBS panel.

Propionic Acidemia (PROP)

Propionic acidemia (PROP) is a disorder characterized by the inability to metabolize various fats and proteins. Newborns with PROP experience poor feeding, vomiting, loss of appetite, hypotonia, and lethargy within the first couple of days of life. Occasionally, PROP progresses to more serious symptoms such as heart abnormalities, seizures, coma, and death. With proper management, the early complications of PROP can be avoided.\textsuperscript{164,165}

This review identified a single study with frequency data for PROP in the US. Hinton et al (2014) estimated a birth prevalence of 0.2 cases per 100,000 births\textsuperscript{53} (see Table 4). This review identified a single study containing frequency information for PROP in India. Narayanan et al. (2011) estimated a birth prevalence of 3809.5 cases per 100,000 births.\textsuperscript{92} Narayanan et al. was from Kaur et al. (2016), a systematic review\textsuperscript{56} (see Table 4). Given that PROP is tested in the US and that it is far more prevalent in India than in the US, we recommend PROP for an Indian panel (see Table 10).
**Beta-Ketothiolase Deficiency (BKT)**

Beta-Ketothiolase Deficiency (BKT) is a disorder characterized by the inability to metabolize the amino acid isoleucine or ketones, intermediary products of lipid metabolism. Neonates with BKT typically experience symptoms within the first two years of life including vomiting, dehydration, respiratory difficulty, lethargy, and seizures. Newborns may also experience ketoacidotic attacks leading to coma.\(^{166,167}\) This review identified no studies with frequency data for BKT in both the US and India. Additionally, both the NLM and NBS clearinghouse identify BKT as a rare disease with an unknown frequency.\(^{166,167}\) Therefore, we do not recommend BKT for an NBS panel for India.

**Glycogen Storage Disease Type II (GSD II) /Pompe Disease**

Glycogen Storage Disease Type II (GSD II), also known as Pompe Disease, is a disorder where a build-up of glycogen due to the deficiency of an enzyme responsible for the breakdown in the lysosome, causing damage in muscle and nervous tissues. There are 3 types of Pompe disease: classic infant-onset, non-classic infant onset, and late-onset. In classic infant-onset Pompe, symptoms including myopathy, hypotonia, hepatomegaly, heart defects, failure to thrive, and respiratory problems present in the first few months of life. If untreated, classic infant-onset Pompe causes death from heart failure within the first year of life.\(^{168,169}\) Non-classic infant-onset Pompe is characterized by delayed motor skills, progressive muscle weakness, and cardiomegaly in the first year of life. While individuals do not typically experience heart failure, the muscle weakness may lead to serious breathing complications, leading most children to only live into early childhood.\(^{168,169}\) In late-onset Pompe, symptoms may not present until late childhood, adolescence, or adulthood and are typically milder and less likely to affect the heart than in both the infantile-onset forms of Pompe. Most individuals with late-onset Pompe experience progressive muscle weakness that may eventually lead to respiratory issues, and in some cases failure.\(^{168,169}\) This review identified no studies containing frequency data for Pompe disease in the US or India. Additionally, both the NLM and NBS clearinghouse do not identify a specific frequency for Pompe in India.\(^{168,169}\) As such, we do not recommend Pompe for an Indian NBS panel.

**Isobutarylglucinuria (IBG)**

Isobutyrylglycinuria (IBG) is a disorder characterized by the inability to metabolize the amino acid valine. Neonates with IBG are typically asymptomatic, however, some individuals develop symptoms such
as dilated cardiomyopathy, hypotonia, anemia, low blood carnitine, and developmental delays. With early treatment, most individuals can lead healthy lives. This review identified no studies with frequency data for IBG in either the US or India. Additionally, both the NLM and NBS clearinghouse identify IBG as an extremely rare disease with less than 30 known cases worldwide. As such, we do not recommend IBG for an Indian NBS panel.

2-Methylbutyryl-CoA Dehydrogenase Deficiency (2MBG)

2-Methylbutyryl-CoA Dehydrogenase Deficiency (2MBG) is a condition where the body is unable to properly metabolize the amino acid isoleucine. Most infants with 2MBG are typically asymptomatic. However, a small portion of infants experience symptoms such as poor feeding, lethargy, vomiting, and in serious cases, difficulty breathing, seizures, and coma. With proper treatment, individuals with 2MBG can live healthy lives. This review identified no studies with frequency data for 2MBG in either the US or India. Additionally, both the NLM and NBS clearinghouse identify 2MBG as common in people of Hmong descent but as otherwise a rare condition. As such, we do not recommend 2MBG for an Indian NBS panel.

3-Methylglutaconic Aciduria (3MGA)

3-Methylglutaconic Aciduria (3MGA) is a disorder where the function of the mitochondria is impaired, leading to a build-up of 3-methylglutaconic acid and 3-methylglutaric acid in the blood and urine. Infants with 3MGA experience symptoms such as psychomotor delay, speech delays, dystonia, spastic quadripareisis, and optic atrophy. Children later go on to develop leukoencephalopathy, contributing to more severe neurological symptoms such as dysarthria and ataxia. This review identified no studies with frequency data for 3MGA in both the US and India. Additionally, both the NLM and NBS clearinghouse identify 3MGA as an extremely rare condition with less than 20 cases having been reported worldwide. As such, we do not recommend 3MGA for an Indian NBS panel.

2-Methyl-3-Hydroxybutyric Acidemia (2M3HBA)

2-Methyl-3-Hydroxybutyric Acidemia (2M3HBA) is a condition characterized by the inability to metabolize valine, leucine, and isoleucine. Infants with 2M3HBA may experience symptoms such as metabolic acidosis, hypoglycemia, hypotonia, seizures, retinal degeneration, hearing loss, and developmental delays ranging from mild to severe. Early diagnosis and treatment have been proven to be
Endocrine Conditions

Of the two endocrine conditions included in this review, we recommend that Congenital Hypothyroidism (CH) be added to an Indian NBS panel (see Table 10). Descriptions of these conditions and their associated evidence identified in this review are presented below.

**Congenital Hypothyroidism (CH)**

Congenital Hypothyroidism (CH) is a condition where the body is unable to produce enough thyroid hormone due to a partial or complete loss of function of the thyroid gland, a smaller or absent thyroid gland, or in some cases, when the gland is abnormally located. Thyroid hormone plays a key role in the regulation of growth, brain development, and metabolism. Infants with CH experience symptoms such as lethargy, difficulty feeding, intellectual disabilities, failure to thrive, and hypotonia. CH can be treated simply with oral thyroid supplements.\(^{178,179}\)

This review identified no studies with frequency data for CH in the US. However, this review identified 9 studies with frequency data for CH in India. 8 of these studies\(^{38,70-76}\) were prospective cohorts of Indian neonates identified from Kaur et al. (2016),\(^{56}\) a systematic review. Kaur et al. (2016) also presented primary data of prospective cohort of 25,395 neonates from Chandigarh, India. As such, this review estimated a total birth prevalence of CH for India of 93 cases per 100,000 births (see Table 5). Given this data we recommend CH be placed on an NBS panel for India, given that using the 2012 annual birth-rate of over 25.6 million births,\(^{39}\) we would expect to see over 23,000 cases of CH annually (see Table 10).

**Congenital Adrenal Hyperplasia (CAH)**

Congenital Adrenal Hyperplasia (CAH) is a series of disorders where there is an excessive production of androgens and an insufficient production of cortisol. There are 3 types of CAH: salt-wasting, simple virilizing, and non-classic CAH. Both salt-wasting and simple virilizing CAH are the classic type and are
associated with an early growth spurt but an overall shorter adult height. Additionally, individuals may experience decreased fertility and females may experience excessive hair growth, male pattern baldness, and irregular menstruation. Infants with the salt-wasting form of CAH lose large amounts of salt in their urine, which can be especially life-threatening in infancy. Individuals may also experience poor feeding, weight loss, dehydration, and vomiting. In classic CAH, female infants may also have ambiguous genitalia while males have normal genitalia, but the testes may be smaller. In individuals with non-classic CAH, females may experience male pattern baldness, irregular menstruation, and decreased fertility while males may experience beard growth earlier than normal and have smaller testes. Some individuals may be completely asymptomatic. With timely treatment, children can have normal development and live healthy lives. This review identified no studies with frequency data for the US, however 4 studies containing frequency data for India were identified. Birth prevalence estimates of 38.3, 14.7, 49.2 and 15.8 cases per 100,000 live births were estimated by Devi and Naushad (2004), Kaur et al. (2010), Shriram et al. (2014), and Kaur et al. (2016), respectively. Kaur et al. (2016) was a systematic review that also presenting primary data from a prospective cohort of Indian neonates studied from 2007-2014 in Chandigarh, India. The remaining studies were prospective cohorts of Indian neonates identified in Kaur et al. (2016). The total estimated birth prevalence for CAH in India is 33.4 cases per 100,000 births (see Table 5). Given that using the 2012 annual birth-rate of over 25.6 million births, we would expect to see approximately 8,550 cases of CAH annually. Given this data and the fact that both the NLM and NBS clearinghouse identify CAH as less common in individuals of Asian descent, we do not recommend CAH be placed on an NBS panel for India.

**Cystic Fibrosis**

Cystic Fibrosis (CF) is a disorder of the mucus glands, causing an excess production of abnormally thick and sticky mucus that builds-up causing progressive damage to the respiratory system and chronic problems in the digestive system. In the respiratory tract, the mucus can clog the airways and lead to bacterial infections, causing chronic coughing, wheezing, inflammation, and over time, fibrosis. In the digestive system, mucus may build-up and block the intestine or build up in the pancreas, blocking the
pancreatic duct and reducing both the production of insulin and the ability of digestive enzymes to reach
the intestine. As a result, infants with CF may experience diarrhea, malnutrition, poor growth, and weight
loss. In adolescence and adulthood, the shortage of insulin caused by blockage of pancreatic ducts can
cause cystic fibrosis-related diabetes mellitus. If left untreated, CF is a fatal childhood disease, however,
with proper treatment, individuals can live well into adulthood, albeit with chronic respiratory, digestive,
and reproductive issues. Men with CF have congenital bilateral absence of the vas deferens, a condition
where the vas deferens are blocked by mucus and unable to properly develop, leading to infertility. Women
with CF may experience complications during pregnancy.

This review identified a single study containing frequency data for CF in the US. Kharrazi et al. (2015)
estimated a birth prevalence of 34.1 cases per 100,000 births based on a prospective cohort of 2,573,293
Californian neonates screened from July 2007 to June 2012. This review identified no studies containing
frequency data for India. Additionally, both the NLM and NBS clearinghouse identify CF as most common
in Caucasian populations. As such, we do not recommend CF be placed on an NBS panel for India.

Other Conditions

Of the 8 conditions classified as “other” in this review, we recommend that Hyperhomocysteinemia be
included on an Indian NBS panel (see Table 10). Descriptions of these conditions and their associated
evidence identified in this review are presented below.

Biotinidase Deficiency (BIOT)

Biotinidase deficiency (BIOT) is a disorder where the body is unable to utilize dietary biotin (also
known as vitamin B7). Infants can experience symptoms ranging from mild to severe, including seizures,
hypotonia, respiratory issues, skin rashes, alopecia, candidiasis, and developmental delays. Lifelong
treatment with biotin supplements can prevent complications from developing and improve those that have
already developed. This review identified no studies with frequency data for the US or India.

However, both the NLM and NBS clearinghouse identify BIOT as common in individuals of European,
Turkish, Saudi Arabian, and Japanese descent. As such, we do not recommend BIOT for an Indian
NBS panel.
**Classical Galactosemia (GALT)**

Classical Galactosemia (GALT) is one type of galactosemia, a disorder characterized by the inability to metabolize galactose, a component of lactose. If not treated promptly, individuals with GALT develop life-threatening symptoms within the first few days of life. Infants with GALT may experience symptoms such as difficulty feeding, lethargy, failure to thrive, jaundice, liver damage, abnormal bleeding, sepsis, developmental delays, cataracts, speech difficulties, and intellectual disability. Additionally, females with GALT may develop an early loss of function in the ovaries. When treated early, children with GALT can go on to live healthy lives.186,187 This review identified no studies with frequency data for GALT in either the US or India. Additionally, the NLM and NBS clearinghouse identify GALT as occurring primarily in individuals of Irish descent.186,187 Therefore, we do not recommend GALT for an Indian NBS panel.

**Galactoepimerase Deficiency (GALE)**

Galactoepimerase deficiency (GALE) is another form of galactosemia due to the dysfunction of the enzyme galactose epimerase. Neonates with GALE typically experience much milder symptoms than those with GALT, such as cataracts, however, in some cases, severe complications including delayed growth and development, intellectual disabilities, liver disease, kidney problems, and death may occur. Proper treatment can allow children with GALE to live healthy lives.187,188 This review identified no studies with frequency data for GALE in either the US or India. Additionally, both the NLM and NBS clearinghouse identify GALE as most common in African Americans.187,188 As such, we do not recommend GALE for an Indian NBS panel.

**Galactokinase Deficiency (GALK)**

Galactokinase deficiency (GALK) is the third type of galactosemia caused by the dysfunction of the enzyme galactose kinase. Infants with GALK experience symptoms ranging from mild to severe including cataracts, delayed growth and development, intellectual disabilities, liver disease, and kidney problems. When the condition is diagnosed and treated early, children with GALK can live healthy lives.187,189 This review identified no studies containing frequency data for GALK in the US and India. Additionally, both the NLM and NBS clearinghouse identify GALK as a rare disease with no specific frequency for India.187,189 As such, we do not recommend GALK be placed on an NBS panel for India.
Severe Combined Immunodeficiency (SCID)

Severe Combined Immunodeficiency (SCID) is an X-linked disorder of immune system that occurs primarily in males (also known as bubble boy disease). Children with SCID have a severely compromised immune system and are subject to recurrent and persistent infections. Infants with SCID often develop chronic diarrhea, thrush, and skin rashes while also growing slower than other children due to their poor health. Without proper treatment, children with SCID typically do not live past infancy. 190, 191

This review identified 7 studies containing frequency data for SCID in the US. Birth prevalence of 49.3, 2.1, 2, 1.7, 50.6, 1.7, and 2.1 cases per 100,000 births were estimated by Baker et al. (2010), Buckley (2012), Kwan et al. (2013), Kwan et al. (2014), van der Spek et al. (2015), and Vogel et al. (2014), respectively. 49, 51, 58 - 60, 66, 67 Buckley (2012) and Kwan et al. (2014) were both reviews that presented results of several US NBS screening programs. 51, 59 Van der Spek (2015) was a systematic review that presented an aggregate estimate of SCID prevalence in the US based on multiple cohorts of US neonates. 66 The remaining studies were all prospective cohorts of US neonates. 49, 58, 60, 67 We estimate a birth prevalence for SCID for the US of 2.2 cases per 100,000 births.

This review identified no studies with frequency data for India. Additionally, both the NLM and NBS clearinghouse identify SCID as more common in the Navajo Apache population and individuals of Turkish descent. 190, 191 As such, we do not recommend SCID for an Indian NBS panel.

Mucopolysaccharidosis, Type I (MPS I)

Mucopolysaccharidosis, Type I (MPS I) is a disorder characterized by the inability to properly metabolize some complex sugars, causing them to build up in the cells. Infants with MPS I are often asymptomatic at birth except for an umbilical hernia or an inguinal hernia, however, symptoms ranging from mild to severe present within the first couple of years of life. Children with MPS I experience symptoms such as macrocephaly hydrocephalus, heart valve irregularities, hepatosplenomegaly, macroglossia, enlarged vocal cords, sleep apnea, clouding of the cornea, hearing loss, recurrent ear infections, short stature and joint deformities, dysostosis multiplex, carpal tunnel, spinal stenosis in the neck, developmental delays or even regress, and possible death due to airway obstruction or heart disease. Children with the severe form of the disease may not live past late childhood while those with the milder form can typically live into adulthood. 192, 193 This review identified no studies with frequency data for either
the US or India. Additionally, the NLM and NBS clearinghouse identify as a rare disease with no specific frequency for India.192,193 As such, we do not recommend MPS I for an Indian NBS panel.

**Adrenoleukodystrophy (ALD)**

Adrenoleukodystrophy (ALD), also known as X-linked adrenoleukodystrophy, is a disorder that occurs primarily in males where the body cannot metabolize very long chain fatty acids, leading to their build-up in the body. ALD mainly affects the adrenal glands and nervous system leading to demyelination, damage to the adrenal cortex causing adrenocortical insufficiency, weakness, weight loss, skin changes, vomiting, and coma. There are three forms of ALD: a childhood cerebral form, adrenomyeloneuropathy type, and Addison disease only.194,195 Children with the cerebral form experience symptoms beginning in early childhood such as learning disabilities and behavioral problems that worsen over time, vision problems, difficulty swallowing, poor coordination, and impaired adrenal gland function. The rate at which symptoms progress is variable but individuals with the cerebral form typically only live a few years after the onset of symptoms.194,195 Individuals with the adrenomyeloneuropathy type do not develop symptoms until adulthood. Typically, these symptoms include paraparesis, urinary and genital tract disorders, behavioral problems, and in severe cases, brain damage and nervous system disorders leading to early death.194,195 Those with Addison disease only experience adrenocortical insufficiency as the sole symptom, beginning in adolescence or early adulthood. In rare cases, those with ALD develop psychiatric disorders and dementia in adolescence or early adulthood. This review identified no studies with frequency data for ALD in the US or India. However, both the NLM and NBS clearinghouse identify ALD as a common disease globally, regardless of race or ethnicity, occurring in 1 in 17,000 individuals and more frequently in males.194,195 Given this information and the 2012 annual birth rate of over 25.6 million births,39 we would expect approximately 1500 cases of ALD annually in India. Additionally, the treatment for ALD is minimal and research is still on-going.194,195 Therefore, we do not recommend ALD be placed on an NBS panel for India.

**T-Cell Lymphopenia**

T-cell lymphopenia is a disorder characterized by abnormally low levels of T-cells, in the absence of any immune deficiency condition, HIV infection, or chemotherapy, resulting in a T-cell count similar to those seen in AIDS patients. As such, affected individuals develop recurrent and persistent infection, which
may not only retard growth but result in early mortality. Without effective treatment, most individuals do not live past infancy or early childhood.\textsuperscript{196}

This review identified 5 studies with frequency data for T-cell lymphopenia in the US. Birth prevalence of 4.2, 5, 12.7, 15.7, 11.7 cases per 100,000 births were estimated by Buckley (2012), Kwan et al. (2013), Kwan et al. (2015), van der Spek et al. (2015), and Vogel et al. (2014), respectively.\textsuperscript{\textasciitilde51,58-60,66,67} We estimate an aggregate birth prevalence for T-cell lymphopenia in the US of 11.5 cases per 100,000 births (see Table 7).

This review identified no studies with frequency data for India. Additionally, the NBS clearinghouse identifies the frequency for T-cell lymphopenia as unknown.\textsuperscript{196} As such, we do not recommend T-cell lymphopenia for an Indian NBS panel.

**Hyperhomocysteinemia**

Hyperhomocysteinemia is a disorder characterized by an abnormally high level of homocysteine in the blood.\textsuperscript{197} Infants with hyperhomocysteinemia are at an elevated risk for cardiovascular disease,\textsuperscript{198,199} renal disease,\textsuperscript{199} Alzheimer’s disease,\textsuperscript{200} and dementia.\textsuperscript{201} If left untreated, individuals may experience stroke or death. Hyperhomocysteinemia can be treated with B\textsubscript{6}, B\textsubscript{9}, and B\textsubscript{12} supplements.\textsuperscript{202}

Hyperhomocysteinemia was not identified by any of the panels reviewed to determine disorders to be analyzed, however, it was identified as prevalent by of the studies included in the review.\textsuperscript{56,81} Radha et al. (2006) estimated a birth prevalence of 8566.7 cases per 100,000 births based on a cohort of 607 Indian neonates.\textsuperscript{81} Radha et al. (2006) was identified in Kaur et al. (2016), a systematic review.\textsuperscript{56} Given this information, we recommend hyperhomocysteinemia for an Indian NBS panel (see Table 10).

**Critical Congenital Heart Disease (CCHD)**

Critical congenital heart disease (CCHD) refers to a group of life-threatening heart defects that require intervention within the first few days of life. These defects can range from arrhythmias to structural abnormalities in the heart and from mild to severe, requiring multiple open heart surgeries. Most of these conditions have a life-long impact on patients. Infants with CCHD may appear asymptomatic at during the first few days of life but symptoms such as a heart murmur, tachypnea, hypotension, hypoxemia, and cyanosis become apparent soon after. If left untreated, CCHD may cause shock, coma, and death. However,
with timely treatment and diagnosis, most live long and healthy lives. Some individuals may have related health issues later in life such as reduced stamina during exercise and increased risk of arrhythmias, heart failures, cardiac arrest, stroke, and premature death. CCHDs can be detected early by pulse oximetry, a test that measures the level of oxygen in the blood before they leave the neonatal nursery.\textsuperscript{203,204}

This review identified 5 studies with frequency data for CCHD in the US. Birth prevalence estimates of 150.9, 74.1, 2745.4, 169.3, and 1113.4 cases per 100,000 births were given by Ailes et al. (2015), Bradshaw et al. (2012), Johnson et al. (2014), Peterson et al. (2013), and Wright et al. (2014), respectively.\textsuperscript{47,50,\textit{55,64,68}} Ailes et al. (2015) was a modeling study using a Monte-Carlo Simulation and the calculated 2000-2005 CCHD US prevalence to simulate the US 2012 birth cohort and estimate the prevalence of CCHD in this cohort.\textsuperscript{47} Peterson et al. (2013) was another modeling study that used the 2011 US birth cohort to estimate the prevalence of CCHD.\textsuperscript{64} Both Bradshaw et al. (2012) and Wright et al. (2014) were prospective cohorts of 6745 and 988 US neonates, respectively,\textsuperscript{50,68} while Johnson et al. (2014) was a retrospective cohort of 7030 US neonates.\textsuperscript{55} We estimate an aggregate birth prevalence for CCHD in the US of 162.4 cases per 100,000 births (see Table 8).

This review identified no studies with frequency data for CCHD in India. Additionally, both the NLM and NBS clearinghouse identify no specific frequency information for CCHD in India.\textsuperscript{203,204} As such, we do not recommend CCHD be placed on an NBS panel for India.

\textit{Hearing Loss}

Nonsyndromic congenital hearing loss is the partial or total loss of hearing that is not associated with other symptoms or due to a separate disorder. Hearing loss can either occur in a single ear (unilateral) or both (bilateral) and can range from mild to profound in degree. The term “deafness” is often used to refer to severe-to-profound hearing loss. Additionally, hearing loss may be progressive, worsening in severity as a patient ages. Most types of nonsyndromic hearing loss are sensorineural, indicating a permanent loss of hearing due to damage of the inner ear. Less commonly, nonsyndromic hearing loss is conductive, indicating changes in the middle ear. Some forms involve both the middle and inner ears. With early identification and intervention, children with nonsyndromic hearing loss are less likely to experience
challenges with cognitive development, language, and social skills. Hearing loss is typically screened for prior to discharge.205,206

This review identified a single study with frequency information for nonsyndromic congenital hearing loss in the US. Mehl et al. (2002) estimated a birth prevalence of 196.3 cases per 100,000 births based on a prospective cohort of 148,240 Colorado neonates screened from 1992-199961 (see Table 9).

This review identified 7 studies with frequency data for India. 4 of these studies55,83–85 were prospective cohorts of Indian neonates identified by Kaur et al (2016), a systematic review.56 Augustine et al. (2014) was a prospective cohort of 9448 Indian neonates born from January to November 2010, in Christian Medical College, Vellore, Tamil Nadu, India.48 Augustine et al. (2014) was identified in our search as well as by Kaur et al. (2016).56 The remaining two studies were prospective cohorts of 415 neonates born in Rajasthan, India from March to October 201152 and 2534 neonates born from February 2012 to January 2015.65 This review estimates an aggregate birth prevalence of 1562.8 cases of nonsyndromic congenital hearing loss per 100,000 births for India (see Table 9). As such, given that hearing loss is screened for in the US and that our birth prevalence estimate for India is approximately 8-fold higher than that for the US, we recommend hearing loss be added to an Indian NBS panel (see Table 10).

**Congenital Liver Defects**

Congenital liver defects are a rare group of disorders that usually block the bile or biliary ducts, structures that play important roles in digestion. As a result, children may experience symptoms such as malnutrition, poor growth, weight loss, jaundice, stomach pain, and failure to thrive among others. If left untreated, children could suffer liver damage and death. Treatment depends on the type of defect, but may include surgery or even transplant in certain cases. With proper treatment, individuals can often live long and healthy lives.207 This review identified no studies with frequency data for congenital liver defects in either the US or India. Additionally, congenital liver defects are considered a rare disease.207 As such, we do not recommend congenital liver defects be added to an Indian NBS panel.
Discussion

This review identified a total of 41 studies containing pertinent frequency data for at least one of the 69 conditions identified for analysis in both the Recommended Uniform Screening Panel (RUSP) and PerkinElmer’s StepOne Panel. Of the studies identified, 33 were prospective cohort studies, 2 were retrospective cohort studies, 2 were modeling studies, 2 studies were reviews, 1 was a systematic review, and 1 study was classified as both a systematic review and a prospective cohort study.

Of the 69 disorders identified for analysis, we identified frequency data for 30 diseases in total, 26 in the US and 9 in India. Generally, the strength of evidence for determining the importance of various congenital disorders to the Indian setting is weak. Few studies report frequency data for congenital disorders in India, and of the disorders with reported frequency data, most were only reported by a single study. Only 4 disorders had frequency data identified by several studies: Glucose-6-phosphate dehydrogenase deficiency (G6PD) (see Table 1), congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH) (see Table 5), and nonsyndromic congenital hearing loss (see Table 10).

Based on the frequency data identified by this review and those presented by both the United States National Library of Medicine as well as the Newborn Screening Clearinghouse, we recommend a total of 12 disorders for a preliminary NBS panel in India (see Table 10). Of these 12 disorders, 6 were conditions affect hemoglobin. While 4, of these conditions (Hb SS, Hb S/β-thalassemia, Hb S/C, and Hb E/β-thalassemia) had no frequency data report by the studies included in this review, they were described as common in the southeast Asian populations, and specifically in the Indian population. As such, despite the lack of data, we felt that it important to include these disorders on an Indian NBS panel. On the other hand, while there were no studies reporting frequency data for various hemoglobinopathies, we recommend that given the number of hemoglobinopathies that are already included on the panel, that any others that may be identified at no additional cost or labor as secondary findings also be included on the panel. The remaining 7 disorders were all based on a combination of birth prevalence estimates derived from studies included in this review as well as considering population information, such as that used to determine the relevance of the hemoglobinopathies included on this panel. 1 of the disorders included in our recommendations was not present on either the RUSP or PerkinElmer’s StepOne Panel. Hyperhomocysteinemia was reported to have a birth prevalence of 8566.7 cases per 100,000 births by
Radha et al. (2010) a prospective cohort study of 607 Indian neonates identified by Kaur et al. (2016), a systematic review. Due to its high prevalence and identification by two studies assessing the frequency of congenital disorders in India, we felt that hyperhomocysteinemia should be added to preliminary NBS panel for India. Additionally, it is important to note that over half of the disorders here are simply included because birth prevalence data was simply available. However, had data been available for numerous additional diseases, further considerations would be necessary for determining not only what diseases to include on the panel, but in what order to add them.

Cost is a significant consideration when not only implementing an NBS program, but when adding additionally tests. Thus, a new program may only be able to afford adding 5 or 10 studies to an initial panel, especially when considering the initial cost required to begin an NBS program. For example, in a 2015 presentation to HRSA’s Discretionary Advisory Committee on Heritable Disorders in Newborns and Children, Scott Grosse, a CDC health economist, elucidated the cost of introducing a new set of disorders to an NBS screening program, using the specific example of lysosomal storage disorders. The cost structure of a single disorder is complex. It involves laboratory costs—including staffing, equipment, reagents, space, and utilities—short-term follow-up, and downstream costs such as clinical follow-up from screening through diagnosis and long-term management of identified disorders. Assuming there are 100,000 births annually in the region/state covered by our NBS program, and that there are 1.2 screens per infant (accounting for the occasional secondary and confirmatory screen), we would need to purchase approximately 3 MS/MS instruments and the required supplementary equipment, costing approximately $1.2 million. Additionally, the annual costs of a program can run high. The sheer labor costs for running a program of such size could be as high as $340,000, while the cost of upkeep may be upwards of $330,000 (including the cost of depreciation, general maintenance, and lab upgrades). The costs of the tests themselves also of concern, as the cost to screen each disorder may range anywhere from $5-8 with an additional $1 cost per test for the reagents, accruing to a total annual cost of at least $600,000. Therefore, in our scenario, the initial cost for an NBS program would be $1.2 million with an additional annual cost of $1.27 million. While these figures are specific to lysosomal storage disorders in the US, it is fair to assume that the cost of an NBS program in India would be similar for any disorder being added to the program. Additionally, it is important to note that NBS is an economy of scale, and as such, as more disorders are
added and more infants are tested, the actual cost of the program decreases over time. Nonetheless, cost is an important consideration for not only determining what tests to add to an Indian panel, but also about the practicality of an NBS program in India. While NBS is unequivocally overdue in India, much work still needs to be done to assess what the actual cost of NBS would be in the Indian context. A cost analysis was out of the scope of this study; however, we do recommend that one be done to assess how to practically implement an NBS program in India.

An additional issue to consider is the availability and accessibility of treatment. NBS serves no purpose if treatment is unavailable for diagnosed disorders. In fact, providing parents with a screening program with no way to act upon the information will result in undue stress considering positive screening results. As such, one of the most important steps of rolling out an NBS program is ensuring that treatment is available in the immediate area for parents to access if they are faced with a positive screen. However, perhaps a larger issue in the context of India is accessibility. First of all, 68.84% of India’s 1.3 billion people live in a rural setting while 61% of births occur outside of the hospital setting. The majority of Indian newborns may not have an interaction with a healthcare professional within the crucial period for NBS. As a result, it is important that an NBS program not only involves more traditional providers, but is also developed in a way that keeps these individuals in mind in terms of both access to screening but also in terms of management and follow-up. Subsequently, poverty in India is of serious concern. According to the World Bank, in 2011, 21.2% of India’s population was living on a purchasing power of less than $1.90 a day. However, it is important to note that while the poverty rate is set at $1.90 a day, the actual threshold to properly access NBS—due to both being able to pay for tests but also to maintain lifelong disease management—could in fact be far higher, resulting in a significantly larger portion of the population unable to access an NBS program. This is then further compounded by the structuring of healthcare payment in India. Unlike in the US or UK, where the cost of NBS is covered by insurance, the cost of healthcare in India is paid for out of pocket by each patient. As such, not only must patients deal with their personal financial barrier, but worry about being able to afford treatment, if it is available in the first place.

Additionally, in 2015, 27.8% of individuals aged 15 or older in India were illiterate, creating a further barrier to access. Of greater concern, however, is health literacy. While 72.2% of the population meets the basic literacy threshold, it is unknown what portion is health literate, and would therefore be able to
properly interact with and absorb information surrounding NBS and the subsequent test results they are presented with. As such, a large portion of the population is unequipped to access an NBS program either due to financial barriers or literacy rates. As a result, without the proper infrastructure and support, an NBS program in India will be unsuccessful in serving as a true population health measure and in reducing the morbidity and mortality of congenital disorders in India.

This review has several limitations. First, several studies were irretrievable at the time of this study due to a lack of resources. These studies may have contained pertinent frequency information, therefore decreasing both the robustness of our prevalence estimations for various disorders as well as our conclusions. In addition, we were unable to double screen or extract studies, therefore introducing possible bias to our findings. However, this was most likely minimal and likely did not have much of an effect on our conclusions.

In light of this review, we would like to conclude with the following recommendations. First and foremost, additional research must be done to determine and confirm the prevalence of numerous congenital disorders through both active and passive population surveillance systems in order to create a NBS program that best serves the Indian population. Second, cost analyses and research must be done to determine the specific cost structure of an NBS program in India and the burden both to the state and the patient. The cost-structure of an NBS program in India should involve subsidies and assistance to allow the entirety of the population to access and utilize this crucial public healthy measure. Third, it is crucial that the issue of accessibility to both treatment and the program itself is addressed immediately, or NBS in India will fail to serve as a true population health measure accessible to the entirety of the population. Finally, we encourage Indian physicians and pediatricians to not only lay out what an effective NBS program would look like in India but also to comment on the panel recommended in this paper.
Newborn Screening in the Indian Setting: Recommendations and Challenges

Abstract

Since its inception in the US in the 1960s, newborn screening has become an integral public health measure in many countries, reducing infant mortality and morbidity through the early detection and management of inborn errors of metabolism. Nevertheless, while newborn screening is a mandatory program in countries such as the US and the UK, no such program exists in India despite its immediate relevance to the country. We discuss recommendations for a national newborn screening program in India including a preliminary panel. However, there are still major challenges facing the implementation of a newborn screening program in India and much work must be done to assess how to tackle issues such as cost and accessibility.
Introduction

Newborn screening (NBS) is a public health measure aimed at the earliest possible detection and subsequent treatment and management of various disorders, primarily metabolic in origin, in an effort to prevent serious complications and health outcomes. NBS is not a confirmatory diagnosis, but instead a method for detecting abnormalities of concern to warrant timely investigation and management. NBS allows for the detection of disorders that if not caught early, may lead to serious disease sequelae and in some cases, early mortality. Guidelines recommend that NBS be done within the first 24-72 hours of the postnatal period and prior to discharge or that children born at home be brought in for screening within the first couple of days. Massachusetts first introduced mandatory screening for Phenylketonuria (PKU) in 1963, NBS has since expanded into a universal public health measure around the globe screening for numerous disorders, due to various technological and methodological advances. In this paper, we discuss the history of the NBS, its guiding principles, and NBS in the Indian context, including recommendations for a national program and specific concerns and relevance to India.

History of Newborn Screening

NBS is a relatively young population-health measure. Robert Guthrie developed a screening test for Phenylketonuria (PKU), after his niece was diagnosed with the disease. Guthrie developed a screening test based on dried blood spots absorbed onto filter paper, facilitating mass screening for PKU due to the medium’s stability and ease of use. Guthrie’s work was crucial to establishing NBS as an essential population health measure around the world. In the past five decades, technology has progressed and numerous additional disorders were added, NBS would become mandatory across the US and many other countries around the world. It wasn’t until the late 1990s and early 2000s that NBS developed into the program it is today.

In the early 1990s, the introduction of tandem mass spectrometry (MS/MS) changed the landscape of NBS globally. Up until this point, while doubtlessly an essential intervention, NBS was characterized by labor and time as rate-limiting factors. Each disorder required a specialized test to detect relevant biomarkers, all of which required a piece of blood-soaked filter paper. The introduction of the Phillips Punch Index Machine in the late 1960s significantly reduced the time and labor requirements for multiple sample preparation, allowing NBS to expand into a true population health measure. However, it wasn’t
until the introduction of MS/MS technology that labs were able to expand NBS to test for multiple disorders concurrently in a matter of hours. MS/MS allowed NBS programs to screen over 30 amino acid, organic acid, and fatty acid disorders simultaneously, improving both the cost-effectiveness and efficiency of NBS programs globally.4,13,23–28

In the US, the late 1990s was the beginning of the universally recommended national panel. The Health Resources and Services Administration (HRSA) of the US Department of Health and Human Services, funded the American Academy of Pediatrics (AAP) to create an NBS Task Force to review issues and challenges surrounding state NBS programs. Soon after, the task force issued a report outlining an agenda and guidelines for improving NBS programs in the US.4,13,29 These AAP guidelines are currently referenced globally. In response to the task force report, the HRSA contracted the American College of Medical Genetics (ACMG) to recommend a uniform screening panel for the US. In 2006, upon evaluation of 84 conditions, the ACMG recommended 29 core conditions and 25 secondary disorders (those that can be identified as a consequence of testing for the core condition but lacking the evidence to classify them as core conditions) as part of the US Recommended Uniform Screening Panel (RUSP).13,30,31 Two years later, on April 24, 2008, US President George W. Bush signed into law the Newborn Screening Saves Lives Act of 2007 (Pub.L.110-204; NBSSLA). The Act amended the Public Health Services Act to establish grants concerning newborn screening as well as created a mandate and funding to establish the NBS clearinghouse in cooperation with Genetic Alliance.13,32 Since, every state in the US has adopted the RUSP in some form as part of their universal NBS program.

Newborn Screening in the Indian Context

While NBS is a mandatory public health program in many countries, including the United States, no such program exists in India.35–38 However, it is clear that NBS has an immediate relevance to the Indian scenario. India’s annual crude birth rate is 20.7 births per 1000 population,39 and approximately 900 children are born daily in the Indian capital territory of Delhi alone—equating to at least 1-2 children with an inborn metabolic disorder daily in Delhi alone.35 Additionally, the WHO recommends that countries with an infant mortality rate under 50 deaths/1000 population offer genetic services,36 and with an infant mortality rate of 44 deaths/1000 population, it is due time NBS is introduced in India.39
There is a clear demand for NBS among healthcare professionals and academics. Numerous studies have been published on the topic and as recently as 2015, the President of the Indian Academy of Pediatrics recommended the adoption of NBS in India in the Indian Journal of Pediatrics. Thus, there has been a true desire to show that NBS works in the Indian context. The past decade has seen the advent of private pilot programs for NBS in major metropolitan areas, including two large multi-centric studies in Hyderabad and New Delhi, however, the results have been primarily inconclusive. While there has been a consensus that congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), glucose-6-phosphate dehydrogenase deficiency (G6PD), and hearing loss are important disorders that should be screened for, knowledge on the remaining multitude of possible screening targets is still sparse. There still has been no attempt at a true population-level screening program, with current attempts taking the form of prospective observational studies at the hospital level.

It could be argued that until recently, NBS wasn’t relevant as a national health priority in India, as it is only relatively recently that India has experienced what is called the epidemiologic transition. The epidemiologic transition is a demographic and epidemiological theory first described by Abdel Omran in 1971. At a basic level, the epidemiologic transition argues that as societies develop, the causes of morbidity and mortality shift from infectious diseases to chronic diseases—which in the case of NBS are inborn errors of metabolism. This is not to say that chronic diseases do not exist earlier, but that they are significantly overshadowed by the consequences of infectious disease. Until the past decade, health policy measures in the country have targeted general mortality and the infectious disease burden—both of which are still of serious concern—instead of disability. These policies have been largely successful, lowering infant mortality rates immensely, but this decrease has likely been offset by an increase in disability. It is only in recent years that India has begun to see a shift from mortality and morbidity due to infectious diseases to those caused by chronic and genetic conditions.

**Guiding Principles of Newborn Screening as a Public Health Program**

In 1968, Wilson and Jungner proposed a set of criteria for including a disorder in a population screening program. These conditions include: (i) that the disorder should be an important public health issue, (ii) there should be a sufficient knowledge of the natural history of the disease, (iii) there should be a reliable and simple (and cost-effective) test for the disorder that is acceptable to the population, (iv)
symptoms should not manifest at birth or be detectable during a routine examination during the post-natal period (i.e. the child should be asymptomatic at the time of screening), (v) there is an effective treatment available for the disorder, and (vi) a delay in the diagnosis will cause undue harm. In 2004, Devi and Naushad proposed some additional criteria specific to India and the developing world: (i) screening should be done if only a specific treatment is available and accessible, (ii) sample collection should be simple, and (iii) transportation of samples for testing should be easy.

Most disorders considered for NBS in India meet these criteria, as the Wilson-Jungner criteria were the standards used to determine their inclusion in NBS programs around the globe. Most if not all diseases have a well-known natural history and are targets because not only would any significant delay in diagnosis or management result in serious health complications, but without NBS, they would be detected too late. Additionally, each of these disorders have been added to panels with the understanding that there is an available treatment. With the adaption of MS/MS technology tests have only become more reliable and cost-effective. Finally, NBS has been done using dried blood spots since Guthrie’s work in the 60’s. As such, sample collection is simple and quick heel stick and transportation can be done through normal mail due to the stability of dried blood spots. What is yet to be determined is the importance of various disorders as public health issues specific to India.

Of additional consideration is the role that government plays in NBS programs. Traditionally, NBS is a state run program mandated at either the regional or the national level. However, the Indian Ministry of Health has yet to show any interest in NBS. At a minimum, the Ministry of Health needs to fund research to understand disease epidemiology within India and needs to set minimum standard guidelines for NBS programs, similar to the RUSP and ACMG report. Additionally, either the central government or individual regional governments must take responsibility for establishing NBS programs as true population health measures, and move them past the small-scale, hospital-level measures they are in India today.

Of final consideration are the critical issues of communication and parental consent or dissent. Currently, almost all NBS programs operate around the principle of informed dissent, where screening is done in all cases unless parents specifically object on a case by case basis. Working in the opposite manner of informed consent, where screening would be only done in cases where parents explicitly agree to the
process, dissent has been used to ensure higher rates of compliance and screening. Where there are debates around the which of the two processes is more ideal, one must be chosen for Indian programs. Additionally, communication is key when instituting an NBS program. It is expected that health literacy around NBS in the general population is low, especially in populations of lower socio-economic status. Proper and timely communication of why blood is being collected, what it will be used for, results, and what they mean are all critical to not only ensure parent compliance, but to ease the stress of a new and unfamiliar process. Access to information in a way that will not only help parents manage conditions their children are diagnosed with but also to ease the stress associated with the various results is key to the success of an NBS program.

**Recommendations and Challenges for Newborn Screening in India**

At this point in time, India does not have a NBS program, but it is critical one is established soon. The first step requires determining which disorders should be included on an NBS panel specific to India. To consider this, we conducted a systematic review to determine the relevance of 69 disorders to India based on identified birth prevalence across studies as well as understood prevalence among specific populations. 41 studies were included in our review, containing frequency data for 9 out of 69 of the diseases identified in this review. However, based on the data identified as well as the frequency information presented by the US National Library of Medicine and Newborn Screening Clearinghouse, we recommend a total of 12 disorders for a preliminary NBS panel in India (see Table 1). Generally, we found that the strength of evidence for determining the importance of various congenital disorders to the Indian setting is weak. Few studies reported frequency data for congenital disorders in India, and of the disorders with reported frequency data, most were only reported by a single study. Only 4 disorders had frequency data identified by several studies: Glucose-6-phosphate dehydrogenase deficiency (G6PD), congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), and nonsyndromic congenital hearing loss. Of note, 1 of the disorders included in our recommendations was not initially identified among the original 69. Hyperhomocysteinemia was reported by two studies in our review with a birth prevalence of 8566.7 cases per 100,000 births. As a result, we felt that hyperhomocysteinemia should be added to preliminary NBS panel for India. Additionally, we recommend that additional disorders be added on a case by case basis, after determining the specific birth prevalence of each individual disorder. Finally, given the heterogeneity
of India, we highly recommend customizing panels regionally based on epidemiologic data and varying risk factors across regions. It would be expected that there will be natural variations in the prevalence of various disorders given the natural histories of local populations across the country.

One of the most important steps after determining relevant disorders for an NBS panel is creating and managing the necessary infrastructure as well as associated costs. In most countries, blood samples are taken on filter paper in local hospitals and are then sent to regional screening laboratories for testing. It is at these regional laboratories that samples are tested and results are interpreted, which are then communicated back to pediatricians and obstetricians. It is then the role of the physician to communicate the results to parents, discuss next steps, and develop treatment plans when necessary. In countries such as the US and UK, all of these laboratories utilize the MS/MS method of testing. As such, there is much work to be done in the Indian setting.

First and foremost, labs need to be created, funded, and staffed. This difficult task involves the long-term leasing or purchase of sufficient space, typically in metropolitan centers with both the infrastructure and skilled personnel available for support. Additionally, skilled personnel must be trained to not only prepare and run samples but to interpret the results. We predict that the largest cost and barrier is the acquisition and maintenance of MS/MS technology. Without a doubt, MS/MS technology is the most efficient and cost-effective solution for screening in the long-term, considering its ability to screen over 30 metabolites simultaneously, the requirement for a single sample preparation, and its efficient use of labor. However, MS/MS technology is not without its drawbacks. The initial cost of MS/MS per lab is estimated to range somewhere from thousands to tens of thousands of US dollars. Additionally, there are only a handful of labs with an existing capacity to utilize MS/MS for NBS in India currently, meaning that the initial cost for a national program would be immense.

Additionally, there is a significant cost associated with NBS for the patient. Given India’s healthcare finance structure, the majority of screening costs would come out of the pockets of parents not to mention the costs of treatment, especially for disorders requiring life-long management. As such, there needs to be a model for subsidizing or assisting parents with costs, otherwise, NBS will never be able to succeed as a population health program that serves individuals regardless of status.
An additional issue to consider is the availability and accessibility of treatment. Additionally, while financial barriers are undoubtedly serious concern, availability and accessibility of treatment may be a larger issue. NBS serves no purpose if treatment is unavailable for diagnosed disorders. In fact, providing parents with a screening program with no way to act upon the information will result in undue stress considering positive screening results. As such, one of the most important steps of rolling out an NBS program is ensuring that treatment is available in the immediate area for parents to access if they are faced with a positive screen. Moreover, it is important that accessible treatments are also acceptable to the local population. As such, in collaboration with physicians and community workers, treatments such as restricted diets, need to be adapted to be both culturally and socially acceptable to local communities.

However, perhaps a larger issue in the context of India is accessibility. First of all, 68.84% of India’s 1.3 billion people live in a rural setting while 61% of births occur outside of the hospital setting. The majority of Indian newborns may not have an interaction with a healthcare professional within the crucial period for NBS. A true effort must be made to ensure that this large portion of the population is reached. We advocate for partnerships with and involvement of community health workers and more traditional health workers, such as midwives, who both understand local communities and have an established trust to be a part of the NBS program to reach those infants born out of the healthcare system. We argue that the involvement of these individuals is crucial to not only the success of an NBS program, but to ensuring that there is a real impact on infant morbidity and mortality.

Subsequently, poverty in India is also a serious concern. According to the World Bank, in 2011, 21.2% of India’s population was living on a purchasing power of less than $1.90 a day. However, it is important to note that while the poverty rate is set at $1.90 a day, the actual threshold to properly access NBS—due to both being able to pay for tests but also to maintain lifelong disease management—could in fact be far higher, resulting in a significantly larger portion of the population unable to access an NBS program. This is then further compounded by the structuring of healthcare payment in India. Unlike in the US or UK, where the cost of NBS is covered by insurance, the cost of healthcare in India is paid for out of pocket by each patient. As such, not only must patients deal with their personal financial barrier, but worry about being able to afford treatment, if it is available in the first place. Additionally, in 2015, 27.8% of individuals aged 15 or older in India were illiterate, creating a further barrier to access. Of greater
concern, however, is health literacy. While 72.2% of the population meets the basic literacy threshold, it is unknown what portion is health literate, and would therefore be able to properly interact with and absorb information surrounding NBS and the subsequent test results they are presented with. As such, a large portion of the population is unequipped to access an NBS program either due to financial barriers or literacy rates. As a result, without the proper infrastructure and support, an NBS program in India will be unsuccessful in serving as a true population health measure and in reducing the morbidity and mortality of congenital disorders in India.

Finally, awareness of NBS among both the general population and professionals must be improved to bolster the success of a national program. A 2007 survey done in Bangalore found the many healthcare professionals are not aware of the bloodspot test developed by Robert Guthrie. 79% of obstetrician and 62% of pediatricians were not aware of the test, 49% of neonatologists were skeptical of the benefits of NBS and believed that it was only warranted in high risk cases, and most professionals were pessimistic about its benefits and the outcomes of treated children. Additionally, 95% of nurses and 99% of the general public did not know what NBS was. For NBS to work, awareness among both professionals and the public is necessary.

Conclusions

NBS is an important yet challenging public health measure for India moving forward. We recommend an initial panel of 12 conditions to begin, with systematic and customized expansion after. However, India faces many challenges in regards to finances and logistics, and will only be able to move forward with the cooperation of professional groups and the public. Further research needs to be done to truly understand the prevalence of these disorders in India as well as to assess the true cost of NBS in India.
Figure 1. Literature Flow Diagram

Citations retrieved from MEDLINE (January 1, 2000 – December 12, 2016) (n = 4157)

Excluded (n = 3700)
- Did not meet broad eligibility criteria per title and abstract

Articles identified for full-text retrieval (n = 457)

Excluded (n = 434)
- Irretrievable (n = 357)
- No relevant data (n = 50)
- Non-English (n = 1)
- Validation study (n = 2)
- Cost-analysis (n = 6)
- Wrong population (n = 10)
- Case reports (n = 4)
- Not extractable (n = 4)

Included Studies:
- 23 included after full-text screening
- Additional 19 studies identified in included reviews
Table 1: Birth Prevalence Estimates for Hemoglobin Conditions

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Total screened</th>
<th>Cases identified</th>
<th>Birth prevalence per 100,000</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sickle cell anemia (Hb SS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoppe 2013 [*]</td>
<td>5419093</td>
<td>483</td>
<td>8.9</td>
<td>US</td>
</tr>
<tr>
<td>Michlitsch et al. 2009 [*]</td>
<td>4505000*</td>
<td>381</td>
<td>8.5</td>
<td>US</td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, India†</em></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, US‡</em></td>
<td>8.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sickle-cell/Beta-Thalassemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoppe 2013 [*]</td>
<td>5419093</td>
<td>151</td>
<td>2.8</td>
<td>US</td>
</tr>
<tr>
<td>Michlitsch et al. 2009 [*]</td>
<td>4505000*</td>
<td>97‡</td>
<td>2.2</td>
<td>US</td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, India†</em></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, US‡</em></td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sickle-cell/Hemoglobin C Disease (Hb S/C)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoppe 2013 [*]</td>
<td>5419093</td>
<td>259</td>
<td>4.8</td>
<td>US</td>
</tr>
<tr>
<td>Michlitsch et al. 2009 [*]</td>
<td>4505000*</td>
<td>197</td>
<td>4.4</td>
<td>US</td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, India†</em></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, US‡</em></td>
<td>4.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemoglobin E/Beta-Thalassemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoppe 2013 [*]</td>
<td>5419093</td>
<td>51</td>
<td>0.9</td>
<td>US</td>
</tr>
<tr>
<td>Michlitsch et al. 2009 [*]</td>
<td>4505000*</td>
<td>34§</td>
<td>0.8</td>
<td>US</td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, India†</em></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, US‡</em></td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Various hemoglobinopathies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoppe 2013 [*]</td>
<td>5419093</td>
<td>1182</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michlitsch et al. 2009 [*]</td>
<td>4505000*</td>
<td>1422</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, India†</em></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, US‡</em></td>
<td>26.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glucose-6-Phosphate Dehydrogenase Deficiency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaur et al. 2016**</td>
<td>25395</td>
<td>317</td>
<td>1248.3</td>
<td>India</td>
</tr>
<tr>
<td>Verma et al. 1994††</td>
<td>1000</td>
<td>39</td>
<td>3900</td>
<td>India</td>
</tr>
<tr>
<td>Pao et al. 2005††</td>
<td>2479</td>
<td>50</td>
<td>2016.9</td>
<td>India</td>
</tr>
<tr>
<td>Dash et al. 2005††</td>
<td>490</td>
<td>86</td>
<td>17551</td>
<td>India</td>
</tr>
<tr>
<td>Kaur et al. 2010††</td>
<td>6813</td>
<td>55</td>
<td>807.3</td>
<td>India</td>
</tr>
<tr>
<td>Mohanty et al. 2014††</td>
<td>191</td>
<td>32</td>
<td>16753.9</td>
<td>India</td>
</tr>
<tr>
<td>Nock et al. 2011</td>
<td>1095</td>
<td>122</td>
<td>11141.6</td>
<td>US</td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, India†</em></td>
<td>2387.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, US‡</em></td>
<td>11141.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** *Total screened is calculated from the assumption that 530,000 neonates are screened annually for 8.5 years (Jan 1998 - June 2006) Michlitsch 2009; †calculated mean weighted by total screened; ‡Cases consisting of Sickle beta plus thalassemia (Hb Sβ+) and Sickle beta zero thalassemia (Hb Sβ0); §Cases consisting of Hb E/β0 and Hb E/β+; ||Cases consisting of Hb C/β thalassemia, Hb S/E, Hb S/HPFH, Hb S/variant, Alpha thalassemias, Hb H disease, Hb H Constant Spring, Hb Bart's (hydrops fatalis), Beta thalassemia, and Hb D/β thalassemia; ¶Cases consisting of Hb S-HPFH, Hb S-Leopore, Hb S/O-Arab, Hb β0, Hb C β0, Hb D β0, Hb C β+, Hb H, Hb H w/ E trait, hb H w/ Hb EE, hb H-Constant Spring, Hb H w/ other variants, Hb H w/ SS, Hydrops fetalis, Hb EE, Hb CC, Hb C-HPFH, and heterozygous variants (i.e. trait carriers); **systematic review; ††study pulled from Kaur et al. 2016 reference
### Table 2: Birth Prevalence Estimates for Amino Acid Conditions

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Total Screened</th>
<th>Cases Identified</th>
<th>Birth prevalence per 100,000</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenylketonuria (PKU)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>58</td>
<td>4.3</td>
<td>US</td>
</tr>
<tr>
<td>Zytkovicz et al. 2001</td>
<td>257000</td>
<td>36</td>
<td>14</td>
<td>US</td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, India</em></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, US</em></td>
<td>5.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maple Syrup Urine Disease (MSUD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narayanan et al. 2011†</td>
<td>420</td>
<td>13</td>
<td>3095.2</td>
<td>India</td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>7</td>
<td>0.5</td>
<td>US</td>
</tr>
<tr>
<td>Zytkovicz et al. 2001</td>
<td>257000</td>
<td>2</td>
<td>0.8</td>
<td>US</td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, India</em></td>
<td>3095.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, US</em></td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Citrullinemia Type I (CIT)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>2</td>
<td>0.2</td>
<td>US</td>
</tr>
<tr>
<td><strong>Argininosuccinic acidemia (ASA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>4</td>
<td>0.3</td>
<td>US</td>
</tr>
<tr>
<td>Zytkovicz et al. 2001</td>
<td>257000</td>
<td>2</td>
<td>1.2</td>
<td>US</td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, India</em></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Estimated birth prevalence per 100,000, US</em></td>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Argininemia (ARG)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zytkovicz et al. 2001</td>
<td>257000</td>
<td>2</td>
<td>1.2</td>
<td>US</td>
</tr>
<tr>
<td><strong>Hypermethioninemia (MET)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zytkovicz et al. 2001</td>
<td>257000</td>
<td>2</td>
<td>0.8</td>
<td>US</td>
</tr>
</tbody>
</table>

**Notes:** *calculated mean weighted by total screened; †extracted from Kaur et al. 2016, a systematic review*

### Table 3: Birth Prevalence Estimates for Fatty Acid Conditions

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Total Screened</th>
<th>Cases Identified</th>
<th>Birth Prevalence per 100,000</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>80</td>
<td>6</td>
<td>US</td>
</tr>
<tr>
<td><strong>Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>19</td>
<td>1.4</td>
<td>US</td>
</tr>
<tr>
<td><strong>Long-chain 3-OH acyl-CoA dehydrogenase deficiency (LCHAD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>1</td>
<td>0.1</td>
<td>US</td>
</tr>
<tr>
<td><strong>Carnitine uptake deficiency (CUD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>12</td>
<td>0.9</td>
<td>US</td>
</tr>
</tbody>
</table>
Table 4: Birth Prevalence Estimates for Organic Acid Conditions

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Total Screened</th>
<th>Cases Identified</th>
<th>Birth Prevalence per 100,000</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isovaleric acidemia (IVA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narayanan et al. 2011*</td>
<td>420</td>
<td>1</td>
<td>238.1</td>
<td>India</td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>4</td>
<td>0.3</td>
<td>US</td>
</tr>
<tr>
<td>*Estimated birth prevalence per 100,000, India†</td>
<td></td>
<td></td>
<td>238.1</td>
<td></td>
</tr>
<tr>
<td>*Estimated birth prevalence per 100,000, US†</td>
<td></td>
<td></td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Glutaric acidemia type I (GA1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>11</td>
<td>0.8</td>
<td>US</td>
</tr>
<tr>
<td>Methylmalonic acidemia due to mutase deficiency (MUT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>15</td>
<td>1.1</td>
<td>US</td>
</tr>
<tr>
<td>Methylmalonic acidemia, cobalamin disorders (cblA, B)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narayanan et al. 2011*</td>
<td>420</td>
<td>15</td>
<td>3571.4</td>
<td>India</td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>4</td>
<td>0.3</td>
<td>US</td>
</tr>
<tr>
<td>*Estimated birth prevalence per 100,000, India†</td>
<td></td>
<td></td>
<td>3571.3</td>
<td></td>
</tr>
<tr>
<td>*Estimated birth prevalence per 100,000, US†</td>
<td></td>
<td></td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>42</td>
<td>3.1</td>
<td>US</td>
</tr>
<tr>
<td>Propionic acidemia (PROP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narayanan et al. 2011*</td>
<td>420</td>
<td>16</td>
<td>3809.5</td>
<td>India</td>
</tr>
<tr>
<td>Hinton et al. 2014</td>
<td>1343696</td>
<td>2</td>
<td>0.2</td>
<td>US</td>
</tr>
<tr>
<td>*Estimated birth prevalence per 100,000, India†</td>
<td></td>
<td></td>
<td>3809.5</td>
<td></td>
</tr>
<tr>
<td>*Estimated birth prevalence per 100,000, US†</td>
<td></td>
<td></td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

Notes: *extracted from Kaur et al. 2016, a systematic review; †calculated mean weighted by total screened
### Table 5: Birth prevalence estimates for Endocrine Conditions

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Total Screened</th>
<th>Cases Identified</th>
<th>Birth Prevalence per 100,000</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital Hypothyroidism (CH)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaur et al. 2016*</td>
<td>25395</td>
<td>18</td>
<td>70.9</td>
<td>India</td>
</tr>
<tr>
<td>Desai et al. 1987†</td>
<td>12407</td>
<td>5</td>
<td>40.3</td>
<td>India</td>
</tr>
<tr>
<td>Desai et al. 1994†</td>
<td>25224</td>
<td>9</td>
<td>35.7</td>
<td>India</td>
</tr>
<tr>
<td>Ramadevi &amp; Naushad 2004†</td>
<td>18300</td>
<td>11</td>
<td>60.1</td>
<td>India</td>
</tr>
<tr>
<td>Sanghvi and Dewakar 2008†</td>
<td>2872</td>
<td>6</td>
<td>208.9</td>
<td>India</td>
</tr>
<tr>
<td>Kaur et al. 2010†</td>
<td>6813</td>
<td>2</td>
<td>29.4</td>
<td>India</td>
</tr>
<tr>
<td>Kumar et al. 2014†</td>
<td>19800</td>
<td>19</td>
<td>96</td>
<td>India</td>
</tr>
<tr>
<td>Kapil et al. 2014†</td>
<td>613</td>
<td>28</td>
<td>4567.7</td>
<td>India</td>
</tr>
<tr>
<td>Shriram et al. 2014†</td>
<td>30514</td>
<td>34</td>
<td>111.4</td>
<td>India</td>
</tr>
<tr>
<td><strong>Estimated birth prevalence per 100,000, India‡</strong></td>
<td></td>
<td></td>
<td>93</td>
<td></td>
</tr>
<tr>
<td><strong>Estimated birth prevalence per 100,000, US‡</strong></td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** *systematic review; †study pulled from Kaur et al. 2016; ‡calculated mean weighted by total screened

| **Congenital Adrenal Hyperplasia (CAH)** |                |                  |                               |            |
| Kaur et al. 2016*         | 25395          | 4                | 15.8                          | India      |
| Ramadevi & Naushad 2004†  | 18300          | 7                | 38.3                          | India      |
| Kaur et al. 2010†         | 6813           | 1                | 14.7                          | India      |
| Shriram et al. 2014†      | 30514          | 15               | 49.2                          | India      |
| **Estimated birth prevalence per 100,000, India‡** |                |                  | 33.4                          |            |
| **Estimated birth prevalence per 100,000, US‡** |                |                  | N/A                           |            |

**Notes:** *Cystic Fibrosis and Cystic Fibrosis Transmembrane Conductance Regulator protein-related metabolic syndrome cases

### Table 6: Birth Prevalence Estimates for Cystic Fibrosis

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Total Screened</th>
<th>Cases Identified</th>
<th>Birth Prevalence per 100,000</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kharrazi et al. 2015</td>
<td>2573293</td>
<td>878*</td>
<td>34.1</td>
<td>US</td>
</tr>
</tbody>
</table>

**Notes:** *Cystic Fibrosis and Cystic Fibrosis Transmembrane Conductance Regulator protein-related metabolic syndrome cases
### Table 7: Birth Prevalence Estimates for Other Conditions

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Total Screened</th>
<th>Cases Identified</th>
<th>Birth Prevalence per 100,000</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe Combined Immunodeficiency (SCID)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baker et al. 2010*</td>
<td>71000</td>
<td>35</td>
<td>49.3</td>
<td>US</td>
</tr>
<tr>
<td>Buckley 2012†</td>
<td>960049</td>
<td>20</td>
<td>2.1</td>
<td>US</td>
</tr>
<tr>
<td>Kwan et al. 2013</td>
<td>993724</td>
<td>20</td>
<td>2</td>
<td>US</td>
</tr>
<tr>
<td>Kwan et al. 2014§</td>
<td>3030083</td>
<td>52</td>
<td>1.7</td>
<td>US</td>
</tr>
<tr>
<td>Kwan et al. 2015</td>
<td>7900</td>
<td>4</td>
<td>50.6</td>
<td>US</td>
</tr>
<tr>
<td>van der Spek et al. 2015</td>
<td></td>
<td></td>
<td>3150000</td>
<td>53</td>
</tr>
<tr>
<td>Vogel et al. 2014</td>
<td>485912</td>
<td>10</td>
<td>2.1</td>
<td>US</td>
</tr>
<tr>
<td><strong>Estimated birth prevalence per 100,000, India</strong></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Estimated birth prevalence per 100,000, US</strong></td>
<td>2.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T-cell lymphopenia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buckley 2012†</td>
<td>960049</td>
<td>40</td>
<td>4.2</td>
<td>US</td>
</tr>
<tr>
<td>Kwan et al. 2013</td>
<td>993724</td>
<td>50</td>
<td>5</td>
<td>US</td>
</tr>
<tr>
<td>Kwan et al. 2015</td>
<td>7900</td>
<td>1</td>
<td>12.7</td>
<td>US</td>
</tr>
<tr>
<td>van der Spek et al. 2015</td>
<td></td>
<td></td>
<td>3150000</td>
<td>494</td>
</tr>
<tr>
<td>Vogel et al. 2014</td>
<td>485912</td>
<td>57**</td>
<td>11.7</td>
<td>US</td>
</tr>
<tr>
<td><strong>Estimated birth prevalence per 100,000, India</strong></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Estimated birth prevalence per 100,000, US</strong></td>
<td>11.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hyperhomocysteinemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radha et al. 2006††</td>
<td>607</td>
<td>52</td>
<td>8566.7</td>
<td>India</td>
</tr>
</tbody>
</table>

**Notes:** *preterm and full-term births; †narrative review of US pilot screening studies by state; §narrative review of 11 diff programs across US; ‖aggregate result of review across 11 US cohorts and one Taiwanese cohort; ¶ calculated mean weighted by total screened; **cases of idiopathic T-cell lymphopenia and non-SCID with T-cell impairment; ††extracted from Kaur et al. 2016, a systematic review*
Table 8: Birth Prevalence Estimates for Critical Congenital Heart Defects

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Total Screened</th>
<th>Cases Identified</th>
<th>Birth Prevalence per 100,000</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ailes et al. 2015*</td>
<td>3,952,937</td>
<td>5,965</td>
<td>150.9</td>
<td>US</td>
</tr>
<tr>
<td>Bradshaw et al. 2012</td>
<td>6,745</td>
<td>5</td>
<td>74.1</td>
<td>US</td>
</tr>
<tr>
<td>Johnson et al. 2014</td>
<td>7,030</td>
<td>193†</td>
<td>27.45.4</td>
<td>US</td>
</tr>
<tr>
<td>Peterson et al. 2013</td>
<td>3,957,304</td>
<td>6,700‡</td>
<td>169.3</td>
<td>US</td>
</tr>
<tr>
<td>Wright et al. 2014</td>
<td>988</td>
<td>11§</td>
<td>1113.4</td>
<td>US</td>
</tr>
</tbody>
</table>

*Estimated birth prevalence per 100,000, India|| N/A

Notes: *mean estimate of nonsyndromic CCHD cases based on a simulated 2012 US birth cohort and calculated 2000-2005 US CCHD prevalence using a Monte Carlo Simulation; †CCHD cases from live births, prenatal diagnoses, and those transferred to Brigham and Women’s Hospital for suspected or confirmed cases of CCHD. Neonates in the NICU were excluded. ‡Timely and late detections of CCHD; §pulse oximetry failures, not confirmed CCHD cases; ||calculated mean weighted by total screened.

Table 9: Birth Prevalence Estimates for Nonsyndromic Congenital Hearing Loss

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Total Screened</th>
<th>Cases Identified</th>
<th>Birth Prevalence per 100,000</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augustine et al. 2014*</td>
<td>9,948</td>
<td>39</td>
<td>412.8</td>
<td>India</td>
</tr>
<tr>
<td>Gouri et al. 2015</td>
<td>415</td>
<td>18</td>
<td>4337.3</td>
<td>India</td>
</tr>
<tr>
<td>Nagapoornima et al. 2007†</td>
<td>1,769</td>
<td>3‡</td>
<td>169.6</td>
<td>India</td>
</tr>
<tr>
<td>Paul 2011†</td>
<td>10,165</td>
<td>325§</td>
<td>3197.2</td>
<td>India</td>
</tr>
<tr>
<td>Mishra et al. 2013 †</td>
<td>1,101</td>
<td>12</td>
<td>1089.9</td>
<td>India</td>
</tr>
<tr>
<td>Rai et al. 2013 †</td>
<td>610</td>
<td>5</td>
<td>819.7</td>
<td>India</td>
</tr>
<tr>
<td>Sharma et al. 2015</td>
<td>2,534</td>
<td>5</td>
<td>197.3</td>
<td>India</td>
</tr>
<tr>
<td>Mehl et al. 2002</td>
<td>14,8240</td>
<td>291</td>
<td>196.3</td>
<td>US</td>
</tr>
</tbody>
</table>

*Estimated birth prevalence per 100,000, India 1562.8

Notes: *Also identified in Kaur et al. 2016, a systematic review; †extracted from Kaur et al. 2016, a systematic review; ‡both high risk and low risk cases; §cases from both nursery and NICU; ||calculated mean weighted by total screened.
Table 10: Recommended Newborn Screening Panel for India

<table>
<thead>
<tr>
<th>Disorder</th>
<th>India Birth Prevalence per 100,000</th>
<th>US Birth Prevalence per 100,000</th>
<th>Reasoning/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle Cell Anemia (Hb SS)</td>
<td>N/A</td>
<td>8.7</td>
<td>Identified to be common among individuals of Indian descent [38, 40]</td>
</tr>
<tr>
<td>Sickle Cell/Beta-Thalassemia (Hb S/Th)</td>
<td>N/A</td>
<td>2.2</td>
<td>Identified to be common among individuals of Indian descent [38, 40, 42]</td>
</tr>
<tr>
<td>Sickle Cell/Hemoglobin C Disease (Hb S/C)</td>
<td>N/A</td>
<td>4.6</td>
<td>Identified to be common among individuals of Indian descent [43]</td>
</tr>
<tr>
<td>Hemoglobin E/Beta-Thalassemia Disease (Hb E/Th)</td>
<td>N/A</td>
<td>N/A</td>
<td>As secondary disorder due to hemoglobinopathies already included on this panel. This set of disorders should be included if they incur minimal additional labor and cost.</td>
</tr>
<tr>
<td>Various Hemoglobinopathies</td>
<td>N/A</td>
<td>26.2</td>
<td>Estimated birth prevalence of 2387.7 cases per 100,000 births, leading to an estimated 600,000 annual cases in India.</td>
</tr>
<tr>
<td>Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD)</td>
<td>2387.7</td>
<td>11141.6</td>
<td>Estimated birth prevalence of 238.1 cases compared to that of 0.3 cases per 100,000 births in India and the US, respectively.</td>
</tr>
<tr>
<td>Isovaleric Acidemia (IVA)</td>
<td>238.1</td>
<td>0.3</td>
<td>Estimated birth prevalence of 3571.4 cases compared to that of 0.3 cases per 100,000 births in India and the US, respectively.</td>
</tr>
<tr>
<td>Methylmalonic Acidemia, Cobalamin Deficiency (cblA, B)</td>
<td>3571.4</td>
<td>0.3</td>
<td>Estimated birth prevalence of 3809.5 cases compared to that of 0.2 cases per 100,000 births in India and the US, respectively.</td>
</tr>
<tr>
<td>Propionic Acidemia (PROP)</td>
<td>3809.5</td>
<td>0.2</td>
<td>Estimated birth prevalence of 93 cases per 100,000 births, leading to an estimated 23,000 annual cases in India.</td>
</tr>
<tr>
<td>Congenital Hypothyroidism (CH)</td>
<td>93</td>
<td>N/A</td>
<td>Not initially identified for analysis in this review but identified as prevalent in India by one of the studies included [Radha 2006]. Birth prevalence of 8566.7 cases per 100,000 births.</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>8566.7</td>
<td>N/A</td>
<td>Estimated birth prevalence of 1562.8 cases compared to that of 196.3 cases per 100,000 births in India and the US, respectively.</td>
</tr>
<tr>
<td>Nonsyndromic Congenital Hearing Loss</td>
<td>1562.8</td>
<td>196.3</td>
<td></td>
</tr>
</tbody>
</table>
Appendix A.

I. Hemoglobin Conditions
   a. Sickle cell anemia (SS)
   b. Sickle/Beta-Thalassemia (S/Th)
   c. Sickle/Hemoglobin C disease (S/C)
   d. Hemoglobin C disease (Hb C)
   e. Hemoglobin E disease (Hb E)
   f. Hemoglobinopathies
      g. Glucose-6-Phosphate Dehydrogenase Deficiency

II. Amino Acid Conditions
   a. Phenylketonuria (PKU)
   b. Tetrahydrobiopterin deficiency
      i. Biopterin Defect in Cofactor Biosynthesis
      ii. Biopterin Defect in Cofactor Regeneration
   c. Maple Syrup Urine Disease (MSUD)
   d. Homocystinuria (HCY)
   e. Citrullinemia, Type I (CTI)
   f. Citrullinemia, Type II
   g. Argininosuccinic acidemia (ASA)
   h. Tyrosinemia type I (TYR1)
   i. Tyrosinemia, Type II
   j. Tyrosinemia, Type III
   k. Pyroglutamic academia (5-OXO)
   l. Carbamoyl phosphate synthetase deficiency
   m. Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome
   n. Hyperornithine with Gyrate Deficiency
   o. Argininemia
   p. Hypermethioninemia
   q. Benign Hyperphenylalaninemia

III. Fatty Acid Oxidation Conditions
   a. Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
   b. Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
   c. Long-chain 3-OH acyl-CoA dehydrogenase deficiency (LCHAD)
   d. Short-Chain Acyl-CoA Dehydrogenase Deficiency (SCAD)
   e. Medium/Short-Chain L-3 Hydroxyacyl-CoA Dehydrogenase Deficiency (M/SCHAD)
   f. Trifunctional protein deficiency (TFP)
   g. Carnitine uptake defect (CUD)
   h. Carnitine Acylcarnitine Translocase Deficiency (CACT)
   i. Carnitine Palmitoyltransferase I Deficiency (CPT-IA)
   j. Carnitine Palmitoyltransferase Type II Deficiency (CPT-II)
   k. Glutaric Acidemia, Type II (GA2)
   l. Medium-Chain Ketoacyl-CoA Thiolase Deficiency (MCAT)
   m. 2,4 Dienoyl-CoA Reductase Deficiency (DE RED)

IV. Organic Acid Conditions
   a. Isovaleric acidemia (IVA)
   b. Glutaric acidemia type I (GA1)
   c. Hydroxymethylglutaric aciduria/HMG-CoA lyase deficiency (HMG)
   d. Multiple carboxylase deficiency (MCD)
   e. Malonic Acidemia (MAL)
   f. Methylmalonic acidemia due to mutase deficiency (MUT)
   g. Methylmalonic acidemia cblA and cblB forms: cobalamin deficiency (CBLA, B)
   h. Methylmalonic Acidemia with homocystinuria
   i. 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
j. Propionic acidemia (PROP)
k. Beta-Ketothiolase deficiency (BKT)
l. GSD II Glycogen Storage Disease Type II (Pompe)
m. Isobutarylglucinuria (IBG)
n. 2-Methylbutyryl-CoA Dehydrogenase Deficiency (2MBG)
o. 3-Methylglutaconic Aciduria (3MGA)
p. Beta(β)-Ketothiolase Deficiency (BKT/βKT)
q. 2-Methyl-3-Hydroxybutyric Acidemia (2M3HBA)

V. Endocrine Conditions
   a. Congenital hypothyroidism (CH)
   b. Congenital adrenal hyperplasia (CAH)

VI. Cystic Fibrosis (CF)

VII. Other Conditions
   a. Biotinidase deficiency (BIOT)
   b. Classical galactosemia (GALT)
   c. Galactoepimerase Deficiency
   d. Galactokinase Deficiency
e. Severe Combined Immunodeficiency (SCID)
f. Mucopolysaccharidosis Type I
g. Adrenoleukodystrophy
h. T-cell Related Lymphocyte Deficiencies

VIII. Congenital Heart Disease (CCHD)

IX. Congenital Hearing Loss

X. Congenital Liver Defects
References


65


70. Desai MP, Colaco MP, Ajgaonkar AR, et al. Neonatal screening for congenital hypothyroidism in a


133. Baby’s First Test. Medium/Short-Chain L-3 Hydroxyacyl-CoA Dehydrogenase Deficiency.


152. Baby’s First Test. 3-Hydroxy-3-Methylglutaric Aciduria. babysfirsttest.org.
Baby's First Test. 2


National Institutes of Health, U.S. National Library of Medicine. isobutyryl


Baby's First Test. 2-Methylbutyrylglycinuria. babysfirsttest.org.


