

# Health Information Exchange in Relation to Long-Term Follow-Up Data System in Newborn Screening Program: General Overview and the Saudi Status

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## Keywords

Newborn screening program · Long-term follow-up data system · Health information exchange · Centralized registry system · Saudi Arabia

## Abstract

**Background:** Newborn screening program (NBS) is a vital public health service aiming to prevent morbidity, mortality, and disability through early detection and intervention. The service is a complex system that requires proper communication between its different constituents. The advent of technology in this field represented by the existence of robust analytical diagnostic tools which allow for rapid analysis of many rare congenital disorders along with the accelerated revolution of health information technology is a capstone towards improvement of an individual's life quality and patient safety enhancement. **Summary:** Effective screening program requires an effective system that delivers results in timely manner, tracks those who are affected, and shares long-term outcomes at population level. Recently, more focus has been placed on the implementation of long-term follow-up (LTFU) data systems as an effective tool for continuous evaluation of the efficacy of NBS program. The ability to communicate health information using health information exchange system (HIE) is very essential to effective

implementation of any LTFU plan. **Key Messages:** This review explores other programs' experience in the impact of implementing HIE system in relation to LTFU data system in the era of NBS program and the importance of having a well-established collaboration infrastructure. Also, and at a glance, the current status of the Saudi National NBS program in the context of health informatics and barriers faced towards implementation of successful LTFU data system in relation to HIE is highlighted. Future trends may involve incorporating genomic data to LTFU system allowing for the application of the newly emerged personalized medicine era.

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## Introduction

Newborn screening program (NBS) aimed for preventing disability, morbidity, and mortality rates through early detection of a spectrum of rare genetic disorders, hence allowing for early intervention and management of affected cases [1]. The program is a complex system that needs a proper communication between its different components, which include laboratory, courier services, diagnosis confirmation, different hospitals, physician, nurses, pharmacy, nutritionist, public health practitio-

ners, genetic counselors, and families. The effectiveness of program performance requires continuous evaluation throughout all its components and this can be supported by implementation of a comprehensive short-term follow-up (STFU) system composed of education, screening, diagnosis, and referral as well as long-term follow-up (LTFU) data system focusing on treatment and care management of cases [2]. STFU data system starts once blood samples are collected till test results are released and confirmed cases are referred to specialty clinic for treatment. In other terms, one could say that the type of information acquired by STFU data system includes coverage rate (percentage of population screened), sensitivity and specificity of screening test, age at diagnosis, time of follow-up initiation, and time of treatment initiation, whereas LTFU data system focuses on the period after diagnosis confirmation and looks after the continuity of quality improvement of services provided to cases, evidence-based treatment, monitoring the health outcomes of cases overtime, and the generation of new knowledge [3, 4].

Although STFU is an important component in NBS program evaluation, more focus is emerging on the importance of implementing LTFU data system as a tool to evaluate the efficacy of NBS program. A guideline published in 2013 by the Clinical and Laboratory Standards Institute defines NBS LTFU as “All of the activities that should occur after a patient is diagnosed and subsequently confirmed with a condition. It may include care coordination, assuring the availability of evidence-based treatment, continuous quality improvement, and new knowledge discovery, as well as periodic assessment of the clinical outcomes in affected individuals” [5].

While advancement in NBS technology represented in the introduction of a reliable high-throughput screening analytical tool “tandem mass spectrometry” allows for screening a large number of genetic metabolic disorders using a single dried blood spot [6], also associated advancement in information technology in terms of the presence of software that can be customized to the clinical need allows for better coordination and data mastering, hence improving patient safety [7].

An effective screening program requires an effective system that delivers results in a timely manner, tracks those who are affected, and shares long-term outcomes at population level. The ability to communicate health information using health information exchange system (HIE) is very essential to the effective implementation of any LTFU plan. This requires a proper coordination between all those sharing patient data [8]. In Saudi Arabia, despite the fact that NBS program was established more

than 15 years ago, there is yet no unified system/legislation in place for LTFU data management and sharing of confirmed cases. Because of the high prevalence of cases in Saudi Arabia, one of the highest worldwide (1 in 1,034 newborns screened) [9], establishing a good collaboration infrastructure allowing aggregating and sharing long-term outcomes of detected conditions is much needed.

This review aims to explore the importance of LTFU data aggregation of cases and preview other programs' experience in the impact of implementing HIE in relation to LTFU data system in the area of newborn screening program as well as the importance of having a well-established collaboration infrastructure. The other goal is to briefly describe the current setting of the Saudi National NBS program in the context of health informatics and barriers faced towards implementation of successful LTFU data system in relation to HIE and share some recommendations towards successful implementation of unified Saudi National Newborn Screening Health Information System (SNNSHIS).

## Methods

Electronic search using PubMed and Google Scholar was conducted to search for articles related to the experience of implementing health information exchange and LTFU data system in newborn screening program and its impact on health care quality in general and patient safety in particular. The key words used in this search were [Newborn screening program and (health information exchange or informatics or long term follow up data system) and (Saudi Arabia)]. To add more relevant articles to this review, cross-referencing was accomplished and any relevant articles to this topic were retrieved. In all selected articles, the findings were listed and identified. Only English-language articles were included.

## Results

A total of 22 relevant articles were retrieved. Based on countries' experience on the impact of using LTFU data systems and preparation of HIE infrastructure in newborn screening programs, the findings are summarized below.

### *Impact of LTFU Data System Implementation in the NBS Programs*

LTFU phase starts from the moment of initial diagnosis and referral of cases is made. Due to the rarity of these disorders, this system allows to aggregate population-

based data about the developmental health outcome of patients with specific conditions and allows to evaluate intervention over the years, thereby providing a determination of best practice in regards to treatment strategies [2]. Herein we listed examples of fruitful impacts of LTFU implementation in countries such as Japan, France, and the USA.

#### Japan

For instance, in Japan and since the start of NBS program in 1977, an LTFU study on phenylketonuria patients was conducted and showed through accumulated data that IQ is inversely related to blood phenylalanine levels and found that blood levels of phenylalanine decreased when using the newer restricted dietary treatment guidelines. Also, the same study was able to compare IQ levels of patients with different diseases to reach for a conclusion that patients with MSUD disease have the lowest level of IQ [10].

#### France

Similarly, in France, longitudinal follow-up data since the establishment of NBS program for more than 30 years provide information about epidemiology of PKU, sensitivity of screening procedure, treatment strategies, and patient outcome. The study showed that PKU patients entered primary school at the same age of controls but later than controls in secondary schools where developmental delay was evident in the oldest patients [11].

#### United States of America

Additionally, many NBS programs in the USA established LTFU data systems. For example, the California Genetic Disease Screening Program (GDSP) had established in 2005 a web-based screening information system (SIS) that integrates both STFU and LTFU data records. The LTFU system meant to assess care provided to affected children over a 5-year period. Since 2007, metabolic centers start collecting LTFU data annually on each resolved case by using an Annual Patient Summary (MCAPS) data screen that is integrated to SIS. Preliminary results showed a decline in hospitalization rate for each year of life for some diseases, no deteriorations in skill acquisitions, and a decrease in emergency visits for most cases diagnosed with MCAD [12]. Likewise, New England developed LTFU data system using the Massachusetts centralized state-based comprehensive NBS program. The preliminary result showed that subspecialists see the majority of children with cystic fibrosis or sickling hemoglobinopathies as they grew unlike children with

metabolic conditions where subspecialists do not see them frequently as they age. One major benefit impact of collecting centralized data is the ability to monitor and trace if patients are no longer followed up at one center and transfer or chose to obtain care at another center and also the use of established communication to distribute information for quality improvement [13]. As well, New York State department of health (NYSDOH) in September 2008 had implemented an LTFU surveillance and tracking system by record linkage of newborn screening data to an existing administrative database (i.e., vital records, hospital discharge, early intervention, and birth defect registry). Linkage between records was accomplished through using common identifiers in matching different databases such as last name, gender, and date of birth. This system, besides its ability to match large data sets, proves to be cost-effective, inexpensive, and efficient. The system successfully allows for better health-outcome assessment of affected children as well as to assess health care service utilization [14].

#### *Building Capacity of Well-Coordinated Collaboration Infrastructure*

There is no doubt that establishing a well-coordinated collaboration between different entities involved in the program will result in undeniable benefits in research and development of those rare disorders particularly in development of therapeutic guidelines. Given the fact of the rarity of these disorders, collaboration between different parties allows accessing a large scale of data resources such as biobanks and data warehouse, hence having sufficient patient population to conduct well-designed research allowing for better clinical outcome evaluation and more understanding about the natural history of these disorders, thereby providing an evidence-based approach to treatment strategies that provides a high benefit-risk ratio in disease management [15].

The Newborn Screening Translational Research Network (NBSTRN) and Rare Diseases Clinical Research Network (RDCRN) are examples of two programs that provide an existing collaborative multicentered infrastructure to support rare diseases research and share longitudinal data to help understand rare diseases progress, hence developing improved approaches for diagnosis and treatment [15–18]. The NBSTRN also offers tools for researchers such as informed consent templates, disease registries, state NBS profiles, and consultation on planning pilot studies [18]. Their research activity is focused on understanding the natural history of the disorders, which leads to the development of proper pharmaceutical

drug treatment or nutritional intervention. For example, the RDCRN's Urea Cycle Disorder Consortium in collaboration with other collaborators successfully developed Raviciti treatment intended for the management of some urea cycle disorders that cannot be managed by protein-restricted diet or amino acid supplements alone in patients aged 2 years and older [15]. Another fruitful collaboration example is the Inborn Errors of Metabolism Collaborative (IBEMC), where it was successful to establish the Inborn Errors of Metabolism Information System (IBEM-IS), which is a data collection system that gathers information on diagnosis, treatment, and long-term outcomes of affected patients from 30 centers in 21 different states in the USA. The first patient enrollment was in 2007 and the primary aim of such establishment is to support decision-making by gathering information and to impact care and clinical management of affected patients. In an attempt to increase the sharing of uniformed data, IBEMC had collaborated with NBSTRN [19]. The IBEM-IS has been used to describe the outcomes of 37 children with 3-methylcrotonyl-CoA carboxylase deficiency as well as outcomes and genotype-phenotype correlation of 52 patients with very-long chain acyl CoA dehydrogenase deficiency [20, 21]. The alliance between different collaborators aiming to capture longitudinal information of each affected patient and linking them to a larger data set in order to assess and share health outcomes and create a platform for national research can be looked at as a means of health information exchange [15].

#### *HIE in Relation to LTFU in Newborn Screening Programs*

Effective implementation of any LTFU plan in NBS programs requires the ability to communicate and share long-term health information through information exchange with all the stakeholders involved in the program. HIE allows the transformation of health-related data among many parties and in conjugation with LTFU activities, which assures the long-term availability of updated health information of patients as they grow and will definitely support NBS program prime objectives [8]. Benefits include evaluation of patients on long-term treatment and outcomes from a population health perspective, thus improving individual health in particular and community health in general, availability of evidence-based medicine, ensuring best care quality, and completion of long-term monitoring data by accessibility of information in many locations (i.e., emergency departments, primary care physician's office, among different

hospitals, pharmacies, and specialist physicians) as well as reducing cost through avoidance of test repetitions upon patient mobility from one health care institute to another [8, 22].

Successful implementation of HIE in NBS programs requires development of unified terminology and vocabulary used throughout different laboratory databases and registries. Building up an interoperable platform among all participants in the program is a very crucial step. In the USA, much progress has been made in the last 5 years in the development of HIE. National guidelines for reporting newborn screening results have been created by joint efforts of many newborn screening stakeholders. The guidance include comprehensive Logical Observation Identifiers Names and Cods (LOINC) panel and an example annotated HL7 message that states can use as a template to develop their specifications for transmitting electronic NBS result messages [23]. In summary, the developed standardized guidance for electronic reporting of NBS results using nationally accepted vocabulary and electronic messaging standards includes: (1) LOINC, which contains standard codes for identifying laboratory tests and other clinical measures, (2) SNOMED CT (Systematized Nomenclature of Medicine – Clinical Terms), an international terminology standard for systematically specifying symptoms and diagnoses, (3) UCUM (Unified Code for Units of Measure), which specifies the units for a given test or measure in a standard, machine-readable format, and (4) HL7 (Health Level 7), which specifies the standards for electronic messaging [24]. The National Library of Medicine (NLM) and Health Resources and Services Administration (HRSA) in 2009 created a LOINC panel that covered all of the conditions included in the Recommended Uniform Screening Panel (RUSP). NLM played a role in reviewing several state NBS programs test HL7 messages and refined the LOINC panel and HL7 messaging guidance as per their feedback. Additionally, NLM keep updating and refining this guidance as new conditions are added to the NBS RUSP. The HRSA/NLM HIT guidance for NBS was published on the NLM NBS website (<http://newbornscreeningcodes.nlm.nih.gov>) [24, 25]. Furthermore, NLM worked with Regenstrief Institute to create a LOINC panel with codes for dietary monitoring of conditions diagnosed on NBS. This was achieved through collecting information from state as well as international NBS programs regarding conditions monitored by dried blood spot and key analytes used for their monitoring [24]. Despite the presence of some challenges towards implementing NBS in the context of HIT by state programs as lack of funding and HIT expertise,

**Table 1.** List of disorders included in the national newborn screening program

List of disorders included in the national newborn screening program	
Aminoacidopathies	Phenylketonuria Maple syrup urine disease
Urea cycle disorders	Citrullinemia Argininosuccinate lyase deficiency
Organic acid disorder	Propionic acidemia Methylmalonic acidemia Glutaric acidemia type-I Isovaleric acidemia 3-Methylcrotonyl-CoA carboxylase deficiency 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency Beta-ketothiolase deficiency
Fatty acid oxidation defects	Medium-chain acyl CoA dehydrogenase deficiency Very long chain acyl CoA dehydrogenase deficiency
Carbohydrate disorder	Galactosemia
Endocrine disorder	Congenital hypothyroidism Congenital adrenal hyperplasia
Vitamin responsive disorder	Biotinidase deficiency

incorporating NBS LOINC codes and HL7 messaging for NBS based on the HRSA/NLM guidance to the laboratory instrument and information systems vendors as PerkinElmer, OZ Systems, and Natus Neometrics eases pace of adoption of HIT by state NBS programs [24].

#### *Current Status and Overview of the Saudi National NBS Program in the Context of Health Informatics*

Despite the fact that Saudi Arabia is one of the pioneers among Arab countries to implement comprehensive NBS program, since its establishment in August 2005 [9, 26], published data or information provided regarding the current setting of this program in the context of health information system is scant. Thereby, our second goal here is to briefly highlight the current setting of program, pinpoint some of existing gaps, and recommend means to overcome obstacles towards establishment of successful Saudi National Newborn Screening Health Information System (SNNSHIS).

#### *Saudi NBS Program Setting*

Apart from some private hospitals, the program covers almost all of the country's health care providers. As indicated in the Ministry of Health (MOH) portal, program coverage reached 97% among all governmental maternity and children's hospitals across the kingdom (183/188) [27]. Legislations of mandating screening test and covering test

expenses by insurers are in place. Currently, the program offers screening of 17 different rare genetic metabolic and endocrine disorders (shown in Table 1). The current situation of the program can be described as decentralized by means that screening service provision involves multiple parties (i.e., MOH, King Faisal Specialists Hospital, National Guard Health Affairs, Military Hospitals, and some private hospitals) that lack systematic network coordination. All service providers share the same workflow that starts once blood is collected from the newborns 24–72 h after birth and sent to the laboratory for analysis. Once received, the newborns' demographics are entered into the Laboratory Information Management System (LIMS), analysis is conducted, and result reports are generated after 24–48 h and sent to the client's referral hospitals through secure portals. In case of positive results, new sample(s) is/are requested for retesting and diagnosis confirmation [9]. In the current setting, unfortunately, there is neither unified software used in the screening sites nor a common database for screening results sharing. Every screening site has their own database which is not connected to any other site. The screening sites permit their own clients to access their data result through a secure portal. Until now, there is no designated authority to collect confirmed cases from screening sites at a national level. Every laboratory designates an authorized person to report their own positive cases. In brief there is a need of national guidelines stating legislations to

standardized approaches regarding NBS data management, hence facilitating the establishment of a centralized confirmed cases registry. Of note, the latest available representative multicenter large cohort published data estimate overall prevalence of 16 different screened disorders included in panel at the time of publishing, as 1 in 1,043 newborn are screened, which is one of the highest worldwide [9]. This is attributed to the high rate of consanguineous marriages, which ranged between 51 and 56% [28, 29].

#### Challenges towards Establishment of LTFU System in Saudi Arabia

Effective NBS program is not merely a diagnostic confirmation; it is rather a long-term process that requires a proper coordination and communication among all involved parties (i.e., laboratory, courier services, nurses, physicians, pharmacists, genetic counselors, different hospitals, nutritionists, coordinators, public health practitioners, and families) [8]. Appreciating this fact leads to the recognition of a major challenge in the current system, which is the lack of proper systematic coordination between different health care providers. To date there is neither a national genetic disease registry nor LTFU in Saudi Arabia. The LTFU data system is a missing component in the current program setting. This system will allow aggregation of population-based data, hence helping in evaluating intervention by assessing affected children's health outcomes. Also, it allows waving cost/benefit of disorders involved in the panel.

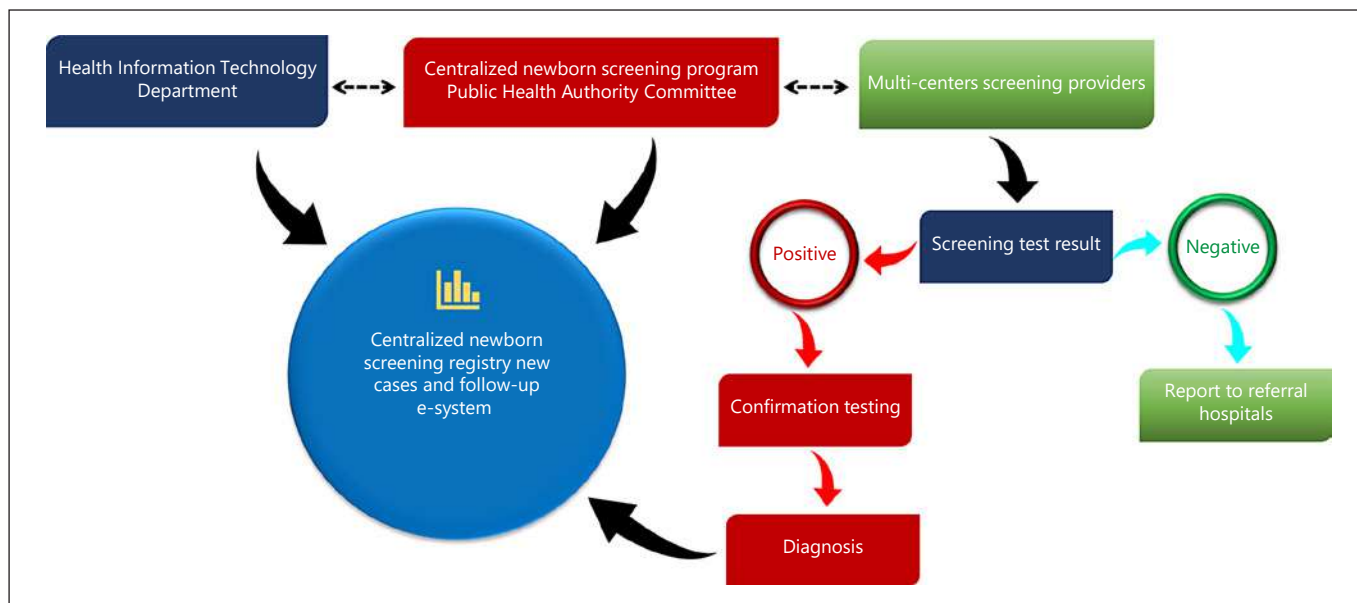
The ability to build up interoperable SNNSHIS in the kingdom that allows sharing longitudinal health outcomes of cases among all service providers is a vital capstone in the success of the program. Given this fact, the creation of a health information exchange platform that allows for health information communication is much needed for the successful establishment of LTFU data system. This mission can be achieved by considering implementation of the unified Electronic Health Record project (EHR) that was approved in 2008 by the Saudi Health Council. Many studies highlight promising adoption rates of EHR implementation by many health care providers such as National Guard Health Affairs, King Faisal Specialist Hospital and Research Center, and other health care facilities [22, 30, 31].

#### Discussion and Conclusion

Newborn screening is a public health system that shows its vast adaption of advancement in health information technology. A secured flow of patient information

among multi data users along with the availability of LTFU data of patients that traces any changes in their health outcome over years will surely be a capstone in any successful NBS program. LTFU of individuals with congenital conditions gained attention as a key component of the newborn screening system to enhance its effectiveness. However, challenges and barriers towards its proper implementation do exist. For instance, in the USA, Hoff et al. had reported that half of NBS programs were not engaged in any type of LTFU activity. Main barriers were financial constraints, problems in communication with providers treating patients, and lack of practices in comprehensive quality assurance. Variability within the US programs in the implementation of LTFU and absence of LTFU systems components in some US newborn screening programs were challenges that impose the need to standardize or create uniform LTFU policies and guidelines that guide programs to unify practice across clusters of disorders [32]. Other literature had also stated challenges faced by US NBS programs in performing ongoing evaluation and quality assurance in relation to LTFU data for affected newborns. The results reflect that more than half of survived programs reported no collection of LTFU data and a lot of variety exists in the types of LTFU data collected across those programs performing LTFU data collection. Also, lack of technology use in many state NBS programs collecting LTFU data was reported. Again, these findings emphasize the need for unified data collection practices and policies in relation to quality assurance, program evaluation, and cost-benefit analysis across state NBS programs [33].

Efforts to identify potential data elements and data sources to create a framework that can be used for assessing outcomes for the health and well-being of children identified through state NBS programs have been designed by the US Department of Health and Human Services Discretionary Secretary of Health and Human Services' Advisory Committee on Heritable Disorders of Newborns and Children (ACHDNC) through their Follow-Up and Treatment Subcommittee (FUTR). Members of the FUTR, in consultation with other stakeholders, identified potential data elements and measures to be applied to each screened condition within the Recommended Uniform Screening Panel (RUSP). The data elements and measures will vary by condition [34, 35]. This framework is envisioned as a system approach to standardize assessment of outcomes and for continuous improvement of the US NBS program. However, barriers do exist towards its implementation. For example, inconsistency of case definitions as well as variable formats and variations



**Fig. 1.** Cost saving system approach toward establishment of a centralized newborn screening registry of confirmed cases. HSEN or newborn screening hearing loss and critical congenital heart defects program e-systems implemented by MOH can be utilized by newborn screening service providers for entry of any new cases and update case status of LTFU data elements.

of codes in data sources are challenging aspects [35]. A means to overcome this obstacle is the use of health information technology (HIT) standards such as those developed by HL7 (Health Level Seven) [36] and LOINC (Logical Identifier Names and Codes) [37] coding to unify field formatting, labeling, and value coding as to facilitate automatic data mining from different data sources [35].

Despite some of the challenges that may appear in terms of continuity of collaborators to collect data and integration among different databases, future application of HIE in relation to LTFU data will result in improving program timeliness and ensure treatment effectiveness, thus enhancing the quality of patient care services.

In Saudi Arabia, recognizing pitfalls of the current setting is the first milestone towards implementation of successful SNNSHIS. Lack of systematic network collaboration and proper coordination between different entities involved in the program as well as unavailability of centralized national genetic disease registry are main barriers. However, with the futuristic 2030 vision of the country and the support of the Ministry of Health that identified e-Health as a strategic objective, we believe that the chances of implementing LTFU system in conjugation with HIE is promising. This is attributed to the fact of the high rate of Electronic Health Record system (EHR) adoption in Saudi Arabia [30].

In alignment with the countries' e-Health transformation strategy adopted by MOH, we thought of sharing some recommendations that may guide concerned stakeholders to the development of an effective system allowing registration of every diagnosed new case, hence improving program timeliness and treatment effectiveness and enhance the quality of patient care services. These recommendations are summarized in Figure 1 and include empowering the presence of centralized authoritative and administrative newborn advisory committee within the Saudi Health Council, Public health authority (Weqaya) or MOH particularly with the current decentralized approach of the program. This committee should involve as many stakeholders as service provider representatives involved in the newborn screening process and establishing coordination with the health information technology department at MOH. This step will facilitate the development of centralized SNNSHIS and aid coordination and communication between different stakeholders involved in this process.

This advisory committee shall form a taskforce concerned in setting up elements required for the establishment of a comprehensive SNNSHIS that contains required components of both short- and long-term follow-up data. This step is vital not only to allow for proper evaluation of treatment and health outcome of affected

children but also helps in providing accurate and precise information regarding prevalence, mortality rate, and survival rate of these disorders as well as estimating coverage rate in addition to easing estimation of disability-adjusted life year (DALY). Also, to enhance newborn screening for precision public health particularly with the advent of new technologies such as genomic and related “omics” that convey detailed information about the human body, one could think of incorporating genomic data to this system, which will allow for application of the newly emerged era, that is, personalized medicine. The aggregated data will provide an evidence-based decision of which therapeutic strategy can be precisely fit and benefit individual patients [15, 38].

Till the establishment of this NNSHIS, which is cost and time intensive, one could think of utilizing the successful example of the implementation of the Health Electronic Surveillance Network (HESN) application developed by MOH that permits hospitals all over the kingdom to register new communicable diseases through secure access to health care providers [39]. Expanding this application to include non-communicable diseases including screened disorders and mandating all hospitals to register new cases is a means of centralizing newborn data in a cost-saving fashion. Another option is to take advantage of the existing e-system used by MOH for the registration and follow-up of newborn screening hearing loss and critical congenital heart defects program [40].

This review has the limitation of using only PubMed and Google scholar and not utilizing other powerful search databases such as Cochrane and Embase, which may result in missing some relevant articles reflecting other nations’ experience in the impact of using LTFU data system in newborn screening program. Using PubMed and Google scholar did not show any articles from Saudi Arabia in this regard.

Future direction may aim toward establishment of a comprehensive child health information system in which the NBS results are integrated to immunization records. Also, with the advances in genomic technology, LTFU may capture information about genotype (i.e., genetic mutation causing disorder) allowing for better understanding of phenotype/genotype correlation of various genetic disorders and contributing to aiding precision medicine concept. Once this system is completed nationally, it can be expanded and upgraded to regional then international level through establishing collaborations with other parties sharing the same interest. Sharing aggregated meaningful data through future application of HIE in relation to LTFU data with other different ethnic

groups will give the true disorder’s prevalence worldwide. Also, it will promote research efforts to foster more knowledge about adverse events of specific medications and lead to best global evidence-based practice in terms of treatment used and proper medical interventions.

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## Conflict of Interest Statement

The authors have no conflict of interest to declare.

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## Author Contributions

Lujane AlAhaidib contributed to literature search and content drafting. Ali AlOdaib critically revised the content of this review.

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