Chapter 3
Newborn Screening in the Era of Precision Medicine

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Abstract As newborn screening success stories gained general confirmation during the past 50 years, scientists quickly discovered diagnostic tests for a host of genetic disorders that could be treated at birth. Outstanding progress in sequencing technologies over the last two decades has made it possible to comprehensively profile newborn screening (NBS) and identify clinically relevant genomic alterations. With the rapid developments in whole-genome sequencing (WGS) and whole-exome sequencing (WES) recently, we can detect newborns at the genomic level and be able to direct the appropriate diagnosis to the different individuals at the appropriate time, which is also encompassed in the concept of precision medicine. Besides, we can develop novel interventions directed at the molecular characteristics of genetic diseases in newborns. The implementation of genomics in NBS programs would provide an effective premise for the identification of the majority of genetic aberrations and primarily help in accurate guidance in treatment and better prediction. However, there are some debate correlated with the widespread application of genome sequencing in NBS due to some major concerns such as clinical analysis, result interpretation, storage of sequencing data, and communication of clinically relevant mutations to pediatricians and parents, along with the ethical, legal, and social implications (so-called ELSI). This review is focused on

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these critical issues and concerns about the expanding role of genomics in NBS for precision medicine. If WGS or WES is to be incorporated into NBS practice, considerations about these challenges should be carefully regarded and tackled properly to adapt the requirement of genome sequencing in the era of precision medicine.

Keywords Newborn screening • Precision medicine • Whole-genome sequencing • Whole-exome sequencing • Genomics

3.1 Introduction

Newborn screening (NBS) is one of the nation's most successful public health programs. In the 50 years since their inception, state-mandated NBS programs have saved thousands of children's lives and prevented disabilities in countless more cases by early identification and treatment of children with phenylketonuria (PKU) or congenital hypothyroidism. The introduction of tandem mass spectrometry in the late 1990s allowed for programs to screen for multiple conditions using a single blood spot. As NBS program has expanded, it can also involve some inherited diseases [1], including cystic fibrosis, sickle cell disease, Duchenne muscular dystrophy, tuberous sclerosis, etc. Secretary's Advisory Committee on Heritable Disorders in Newborns and Children currently recommends that states screen for 31 disorders [2].

Early detection can help families avoid the lengthy and stressful "diagnostic process" involved in finding out what pester their child. While this can be accomplished only for the metabolic and endocrine disorders, there could not be even greater benefit from NBS for genetic disorders in general, including a large scale of non-metabolic genetic disorders. Nowadays, the development of next-generation sequencing (NGS) technologies has substantially reduced both the cost and the time required to sequence an entire human genome. With the prospect of the availability of NGS technologies and consequently the greater facility to conduct whole-genome sequencing (WGS), we could predict that the current practice of medicine and public health will be greatly changed due to more accurate, sophisticated, and cost-effective genetic testing results provided by these technologies [3] (Fig. 3.1).

In the era of precision medicine, accurate clinical information and evidence will be demanded to be used to manage a patient at an individual level or at a community level appropriately [4]. If the sequencing or genome technologies are to be incorporated in NBS program in the future, it can be predicted that this implementation will not only improve diagnosis and management of some disorders at a strong heritable level but also improve the quality of screening for current NBS conditions by providing the predictive value of NBS results [5]. Furthermore, great expectations arise from massive parallel or high-throughput next-generation sequencing. However, although genomics has already revolutionized our knowledge of genetic diseases with molecular pathology and will help us improve personalized diagnosis and individual treatment or prediction for NBS, there are still controversies about the widespread application of WGS in NBS. Concerns have been raised about the

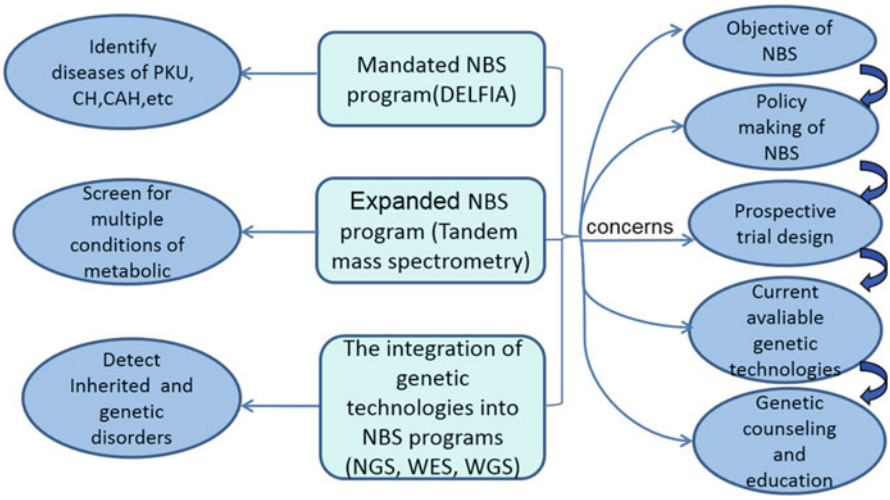

Fig. 3.1 Concerns about NBS in the era of precision medicine. Abbreviations: *PKU* phenylketonuria, *CH* congenital hypothyroidism, *CAH* congenital adrenal cortical hyperplasia

potential impact of WGS on NBS [6–8], for example, the unwanted secondary findings it may reveal, counseling, result interpretation, cost and access to follow-up, etc. When, by whom, and even whether these results should be disclosed is still uncertain. To date, limited research has been performed to assess opinions of using WGS/WES in the newborn period. In this review, we will discuss current critical issues about the potential use of genome sequencing during NBS in the era of precision medicine, including the application of new DNA sequencing technology, its value and policy-making of NBS, prospective trial designs, as well as the clinical, ethical, and psychosocial challenges it poses when applied to newborn screening (Fig. 3.1).

3.2 Objective and Implications of NBS

Overall, NBS is a public health program aimed at the early identification in newborns without symptoms, for which we can take early and timely interventions to eliminate or reduce mortality, morbidity, and disabilities. Nowadays, in some countries, although whole-genome sequencing is not used widely in newborn screening programs, sometimes it only seems as a secondary method to confirm genetic disorders for positive results such as cystic fibrosis or sickle cell disease; in the next decade, experts have predicted that sequencing technologies could be in widespread availability for all healthy newborns [7].

Despite many techniques including current immunoassays (e.g., DELFIA), enzyme assays, and other molecular methods have been applied to analyze the

test procedures in NBS laboratories [9], with the integration of WES or WGS into NBS programs, a great wider range of genetic diseases would be screened [10], which could also provide more accurate information about newborns. Besides, genome sequencing can provide health-related information for NBS, by which newborns could be supplied with the risk prediction about adult-onset disorders. However, the focused goals of NBS would be changed due to the large amount and high complexity of data that are available through genomic screening [6]. In the era of precision medicine, considering the original intention of NBS, we suggest that the application of new sequencing technologies or genome sequence approaches firstly focus on the identification of highly penetrant disease-causing variants, by which we can reach a high risk of preventable or treatable conditions during the newborn and childhood period. Secondly, according to the main objective of NBS, as for those unintended sequencing results of unknown clinical significance that would be troublesome to many families, if the unwanted sequences are not health-related information which go beyond disease-causing risks to the newborn, it should not be considered as critical contexts. It will remain to the genetic counselors to make appropriate interpretation and give proper advisement to the parents. In general, we recommend that NBS should put emphasis on providing benefits including information for the family, by which it will contribute to family health through preparing for the possible progressive disability in the child and giving genetic counseling for family planning and prenatal or preconceptual diagnosis in future pregnancies.

3.3 Policy-Making of NBS for Precision Medicine

Although individual states' methods varied, each state utilized a set of criteria developed by the World Health Organization as well as local legislative input to determine whether a disorder should be included in NBS. Regarding scholars' expertise, evaluation for additions to the recommended uniform screening panel (RUSP) is based on a set of criteria which include the natural history of the condition, availability of screening and diagnostic tests, potential treatment, cost-effectiveness, as well as the analytic validity (test accuracy), clinical validity (ability of the test to predict disease), and clinical utility (ability of the test to lead to improved outcomes) of the screening method used for each condition [11]. Besides, the policy of NBS programs differentiates from one to the other in variant states or countries owing to various structures in health-care systems, available funds, local politics, input from professional groups, parent groups, and the acceptability of general public. In recent years, programs in the European Union (EU) are heterogeneous and aim to identify between 1 and 30 treatable conditions [12]. Nowadays, the number of disorders offered on NBS panels has increased in both North America and Europe [13, 14]. The diversity of number of conditions is large; the policy of screening program in NBS is also based on two models: mandatory and optional. For instance, Canada has no national strategy on NBS,

and there is no mandatory policy but a wide variation between provincial programs. It often includes a certain number of diseases about newborn screening accompanied with information and consent given to parents [15]. In the USA, the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children currently recommends 57 conditions for screening, including 31 core disorders and 26 secondary disorders [16]. By contrast, in some developing countries of Asia Pacific, the conditions of NBS are only focused on PKU and congenital hypothyroidism. Although there is the largest population in India all over the world, NBS is still not a health-care priority [17]. As extended NBS programs were nonexistent in these countries, the diseases offered in NBS did not include a large range of genetic conditions, which will be incorporated when large-scale genomic technologies such as WGS and WES are applied into NBS program.

Concerning the issues that are demanded in precision medicine, the more diseases with effective intervention or treatment and more accurate results a NBS program could detect, the better extension and augmentation of newborn screening would be available. Meanwhile, the goal of newborn screening is primarily to identify diseases in which early treatment is necessary to improve outcome in an efficient and cost-effective manner. As for those diseases of early onset that require immediate medical actions, despite NBS is justifiable as a compulsory, state-supported activity aim to protect the benefit of newborn children by identifying diseases so as to avert a disastrous outcome [18], in some mandatory screening programs, ethical concerns will rise due to timely treatment unavailable. For example, during the early years of mandatory screening, lack of comprehensive insurance coverage for PKU formula left some children with a diagnosis but no means to treat it [19].

In a word, toward accelerating the implementation of NBS program in the era of precision medicine, policy-makers should be prudent while considering whole-genome sequencing of NBS. They should make appropriate policy about screening program, regarding testing platform, assessment criteria, confirmative diagnosis, genetic counseling service, effective treatment, as well as follow-up systems based on principles of cost-effective, accurate, available, and predictive value according to different situations of economic, technology development, education, and social conditions. If genome sequencing technology is to be applied into NBS, firstly, new models of informed consent in the context of NBS will have to be developed. In some scholars' opinions, appropriate model of informed consent can not only increase the information provided as well as the right time with provision but also can maximize participation rates [20]. Secondly, regarding expansion of NBS to incorporate genomic sequencing, policy of NBS should include additional education both in genetic counselors and parents or other relevant stakeholders prior to initiating WGS into NBS. As for the sequencing data, which would be helpful to genetic information of newborns for predictive value, a clear protocol for the safe storage in electronic medical files also should be elaborated. No matter whether the results are analyzed or not, these data should be handled and treated like all clinical information included in patients' medical file and be protected by adequate privacy and confidentiality procedures, which are supported by Heidi Carmen et al. [21].

3.4 Prospective Trial Design of NBS in Precision Medicine Era

In the next decade, we can predict that the application of sequencing technologies in newborns will become a routine part in NBS [8]. However, the approach chosen will depend on the determined goal of the NBS program, and it will also impact on the resulting of practical and ethical issues, including not only benefits but also disadvantages. As stated by Wade et al. [22], only when a clear health-care program has been specified, meaningful assessment including the population target and purpose of testing with P-WGS (pediatric whole-genome sequencing) can be accomplished. In line with the main objective of NBS in precision medicine mentioned above, the primary goal of genome sequencing and other genetic technologies in NBS should be able to identify the gene variants predicting preventable or treatable conditions with high risks, for which treatment has a meaningful intervention in the newborn period or in early childhood. Thus we suggest the trial design be capable of detecting variants and genes with disease-causing which are known to have a high penetrance with effective and appropriate preventive or therapeutic interventions. Also if indications from early diagnosis are lacking or uncertain, screening tests should not be recommended. It is the same to the conditions in which the test is unsuitable or cannot detect those cases despite of predictive advantage [11, 23].

It is expected that when sequencing technologies are sufficiently robust and affordable, we can make the genomes of all newborns (at least part of) sequenced at birth. Although these molecular technologies have the potential tendency to replace current tandem mass spectrometry assays and any additional single-gene tests which could be needed in NBS [6], some scholars considered that WGS should not be used in traditional NBS within the same framework; instead, it should be considered in the setting of pre- and posttest counseling. Also it should not be mandatory, and parental consent should be demanded [8]. And as for endocrine disease, such as congenital hypothyroidism, which is not a genetic condition, it cannot be diagnosed by genome sequencing. Therefore, for the condition not belonging to genetic disease, the present methods of NBS cannot be replaced by sequencing technologies [24].

In the era of precision medicine, the trial design of NBS may include the integration of traditional test and current WGS sequencing panel, which could be performed in a certain prioritized order, for instance, higher-risk individuals receiving higher intensity of screening with the aim of reduced mortality through earlier detection of curable lesions and lower-risk individuals being spared unnecessarily frequent or invasive tests. Besides, the design selection should depend on many—and very different—factors and must concern adequately not only about such characteristics as sensitivity, specificity, and positive and negative predictive value but also demonstration of accurate, exercisable, and beneficial impact of using the test on patients' health or on health-care service according to individualized situation in different states.

3.5 NBS and Current Genetic Technologies

Blood spot cards have been widely used as an alternative sampling method to large epidemiology studies mainly due to their low cost and ease of transportation and storage [25]. Today, great advantages arise from a further technical advancement, represented by massive parallel or high-throughput next-generation sequencing (NGS). In precision medicine, current genetic technologies differ from each other (Table 3.1). As for the newborn screening specimen, it is possible for us to sequence the exome or the entire genome owing to the rapid development of NGS [26]. NGS is based on deep sequencing, which produces billions of short sequences at a time. The recent technologies for the investigation of genomes, transcriptomes, and DNA methylation are revolutionizing our ability to detect mutations of almost all types, from single-nucleotide variation to gene fusion and chromosomal rearrangements. Many studies have confirmed that NGS could dramatically increase the number of disorders identified by newborn screening as well as identify genetic variations (especially through targeted sequencing) that indicate risk of the infant for subsequent development of many disorders. Besides, it can detect the same variations of family members by extension. Microarray expression data (develop from array comparative genomic hybridization, ACGH) were based on the use of probes, which implied a semiquantitative determination of RNA and a partial representation of the human genome, limited to selected genomic features chosen a priori. As for WGS/WES, although the exome is also covered by WGS, WES provides better sequencing coverage of the coding regions and is superior to WGS in finding DNA changes of known medical significance [27]. However, WGS has its own advantages. By covering the genome, WGS identifies not only variations in the coding regions but also sequence variations in noncoding regions that may alter the expression of a gene, substantially increasing the likelihood and comprehensiveness of genetic diagnosis.

Table 3.1 Differences in current genetic technologies in precision medicine

Technology	Percentage of genome sequenced	Descriptions of features	Spectrums of detection
Targeted sequencing	0.005% ~ 0.1% (100 s ~ 1000s of genes)	Based on deep sequencing	Limited genes of target disease
Whole-exome sequencing (WES)	1% (about 25,000 genes)	Provides better sequencing coverage of the coding regions	Capable of finding DNA changes of known medical significance
Whole-genome sequencing (WGS)	100%	Based on covering the whole genome	Variations in the coding regions accompanied by sequence variations in non-coding regions
Array comparative genomic hybridization (ACGH)	Variant (according to selected genomic features chosen priori)	Based on the use of probes, a partial representation of the genome	The presence of copy number variations within the genome

Although NGS can improve personalized diagnosis and personalized therapy along with treatment, in fact, study has noted that DNA test is not a routine part of NBS and that only a very small proportion of babies have a DNA test currently in certain countries [13, 28]. The probable reason was that patients can only afford a limited number of tests due to financial burden and thus do not have the necessary genetic workup and early intervention, while failure to obtain an accurate diagnosis will likely miss a critical time window for clinical management. When molecular testing is given into wide application in NBS, it is anticipated to be frequent to identify more than one disease in one individual. Fortunately, it is possible for us to obtain a relatively comprehensive genetic workup through one assay which can detect not only point mutation but also copy number variations designed for a set of different genes [29]. It has been predicted that as sequencing technologies are getting mature and analysis standards are better defined, WGS seems to ultimately promise a better opportunity for DNA diagnosis, where in a single laboratory test can focus on either a single variant, single gene, or a panel of genes, the exome. Once all of the analytical challenges have been resolved, analysis can also be expanded as needed to cover the entire genome [30]. In the coming years, we will need to expand novel NBS trials that incorporate sequencing and establish shared databases to centralize genomic data for precision medicine.

3.6 The Role of Genetic Counseling and Education in NBS

With the utility of genetic testing in NBS, it can bring more education to primary care providers as well as the benefit obtained during the learning process [31]. The success of a newborn screening system should be measured not only by its capacity to identify potential disorders but also by its ability to communicate results in an effective and sensitive manner. Now most parents have shown interest in genetic screening of their newborns [32]; as stated previously, integration of next-generation sequencing into NBS program could generate incidental findings of uncertain value to parents, children, and clinicians; it is vital for offering appropriate genetic counseling to parents at the appropriate time (Fig. 3.2).

As the clinical phenotype might be apparent at different periods, at birth or within the first weeks or months of life, or maybe later in onset, appearing in childhood or the adult years, it is often difficult to ascertain the correlation between the phenotype and the genotype. As a result, many alterations identified by WGS or WES remain undefined due to the uncertain functional consequence and associated therapeutic implications. In NBS, when screening confronts the prospect of WGS, especially as the context of a public is not in accordance with basic genetic concepts, it is important and challenging for us to transform this into effective action and meaningful outcome [33]. Careful and intelligent planning should be designed; otherwise the consequences could be extremely disruptive to many families. Then who should disclose and interpret the test results? Based on Ulm E's study, it is suggested that the physician–geneticist be selected as the preferred

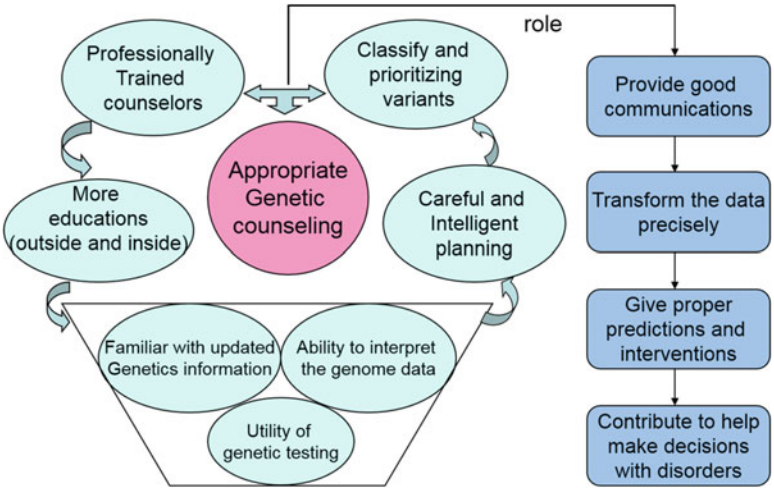

Fig. 3.2 The role of genetic counseling and education in NBS in the era of precision medicine

provider to disclose the result as well as disclose the carrier status and also genetic counselors be chosen most frequently [8].

Interpretation will vary among screening laboratories; when routine genetic screening identifies many more variants than currently known to us, some scholars considered this will derive from the uncertainty of many genetic variants, which will not only continue but likely increase [34]. With the integration of WGS into NBS, it is a major challenge in the application of which in precision medicine for classifying and prioritizing variants identified through integrated genomic analysis [35], and then genetic counselors should be trained professionally and be highlighted of being a well-prepared workforce to interpret and counsel for these results to patients. It was suggested that we need further education and information about the diseases on the panels, their genotypic and phenotypic variation, and the potential for receiving variants of unknown significance [36]. Educational opportunities were emphasized to provide updated information about WGS/WES along with its use in NBS. Typically, we should make policies conformed to a standardized medical model, with which we can obtain genetic information with health implications.

3.7 Future Challenges in NBS Program in the Era of Precision Medicine

3.7.1 Unanticipated Information

Although the numerous sequencing results obtained from genome sequencing are more accurate and robust than that of most current traditional NBS, not all sequencing data result in clear, comprehensible disorder. Mardis has stated that dealing with

the deluge of data generated from WGS or WES is a very redundant task and has been a cost of "the $1000 genome" and "the $100,000 analysis" [37]. Therefore, concerning about the economic cost, the use of WGS or WES in NBS is not suitable due to the limited available public health-care budgets at present. Furthermore, the interpretation of DNA data in a population of healthy newborns is a challenge (Table 3.2). Besides, the genotype–phenotype relationship in metabolic conditions is often not straightforward.

There are several high-throughput sequencing platforms, with many emerging applications for sequencing. These platforms and applications offer different trade-offs of cost, speed, throughput, read lengths, error rates, and bias. Currently, challenges remain in fully characterizing variations in human genomes. Precise and individualized diagnosis is often limited by current knowledge of disease etiologies. The large number of diseases, broad and incompletely understood phenotypic spectrums, and various genetic heterogeneity all contribute to hamper the diagnostic yield. However, ultimately with the maturation of sequencing

Table 3.2 Challenges of integration of WGS/WES into NBS program

Aspects of challenges	Results of influence	Recommended managements
Unanticipated information	Difficult counseling due to inability to interpret DNA data properly	(a) Using publicly available databases
		(b) Being well versed with genomics and computational tools and methodologies
		(c) Developing standards or criteria for analysis and interpretation
Ethical issues	Affecting public trust and privacy, consent, as well as issues about utilizing residual samples for research	(a) Access to care
		(b) Health disparities
		(c) Ownership of genetic information
		(d) The desire or nondesire for public policy must be heavily considered
Social issues	Potential discrimination from insurers and employers and issues of storage of genetic information and subsequent outcomes	(a) Highly selective reporting of findings
		(b) Requirement of informed consent for genetic screening and promise of privacy protection
		(c) Concerning about affordable treatment, follow-up of long-term medical outcomes
Health behaviors or environmental impacts on NBS	Influences on the epigenome owing to dietary, physical, social, chemical, or unknown effects	(a) Early intervention, prevention, and closer monitoring of health behaviors
		(b) Genomic risk profiling and genetic susceptibility prediction

technologies and standardization in analysis, some of these challenges will be resolved [38]. For example, using publicly available (as well as private) databases may be helpful in terms of determining whether these variants have been identified previously. Also it would require a new breed of clinicians with good clinical acumen and are equally well versed with genomics and computational tools and methodologies (Table 3.2).

Study has declared that precision medicine has a significant impact on medical knowledge, and also it will focus on genetic evidence based on medicine with the aim of improving the health of mankind [39]. It can be predictive that genome sequencing will be incorporated into NBS for expanding program; thus developing standards or criteria for analysis and interpretation should be taken into account according to the rationale of being helpful to the precise diagnosis and treatment or predictive value of diseases in newborn or early childhood, along with those conditions onset in adulthood. As for prediction of risk in genetic disorders, parents should be conveyed with the idea that genomic profiling would be a risk test—not a diagnostic test—and the cognition of the limitations of accurate prediction, the putative benefits and drawbacks, and the possible personal, family, and social implications [40].

3.7.2 Ethical and Social Issues of Integration WGS into NBS

It has demonstrated that neonatal dried blood spot samples (DBSS) collected shortly after birth and stored for decades comprise an excellent resource for NGS studies of disease. The integration of WGS or WES into state NBS programs may be appealing given the possibility of sequencing technologies to improve the quality of screening, reduce costs, and open the potential to utilize the programs to screen children for a much wider range of conditions. However, with the expanding of NBS, it will raise a number of ethical, legal, and social issues involving public trust, privacy, and consent as well as broader questions about utilizing residual samples for research. With a positive or uncertain NBS result, it will inevitably cause distress or lingering anxiety to parents, which would be even worse due to counselors' practical inability to interpret all of the WGS data in a clinically useful manner. Besides, another concern about the provision of genetic susceptibility test results involves potential discrimination from insurers and employers [40].

As for the unwanted results brought by WGS/WES, it prefers to select meaningful reporting of the findings prudently in order to reduce the psychic burden of parents. However it would be in contradiction with the rights of the family to be fully informed. Furthermore, there will rise a number of questions through storage of genetic information such as governance and privacy protection associated with the stability and accessibility of the data [41]. For instance, based on Aaron J's study, within a state's NBS program, although there is a high interest in WGS offered as an option at first, when parents were informed that identified data

generated from sequencing might be stored and used in future research, their interest dropped off finally [42]. Also very few parents opt out of current NBS; nevertheless, there will be an influence on universal NBS owing to the requirement of informed consent for genetic screening. So health education challenges are faced not only with the proper interpretation of genomic information but also its disclosure. Concerning about the importance of screening for adult-onset disorders, which was an expanded part in NBS, we recommend NBS programs should be a long-standing public health enterprise and aim at rapid transformation with numerous implications for practice and policy [36]. To improve the quality and maintain the integrity of NBS, it is critical to keep a follow-up of long-term medical outcomes, no matter if the disorders could be provided with affordable treatment or not. To sum up, when implementing these NBS programs for precision medicine, the ethical issues (access to care, health disparities, ownership of genetic information, and the desire or nondesire for public policy) that involve genetics must be heavily considered.

3.7.3 Health Behaviors or Environmental Impacts on NBS

With the development of epigenome, it is viewed that environmental factors including social, chemical, and physical exposures have diverse influences on the phenotypes and could provide individuals with disease risk prediction [36]. As the number of disorders detected by NBS increases, there appear shifts in the types of disorders and in the care provided by NBS programs. A large amount of challenges correlated with public health, ethical, and policy emerged during NBS. PKU is a classic example of this perspective shift. Treatment for PKU requires consumption of a diet with low phenylalanine. However, it was revealed that when the phenylalanine levels in mothers with PKU elevated, there was a tendency of increased risk of having a child with birth defects and cognitive impairment [43]. Based on a public health perspective, the value of genomic information primarily focused on its potential prevention efforts. Thus, a suggestion of phenylalanine-restricted diet was recommended to all women of childbearing age. By genomic risk profiling, participants would be given prediction of genetic susceptibility so as to improve early intervention, prevention, and closer monitoring. Thus, through individual guide of health behaviors and appropriate genetic counseling with different findings, it will contribute equally to human health.

3.8 Conclusion

The opportunity to perform extensive genotyping on DNA extracted from DBSS used in the newborn screening programs has opened new avenues in newborn screening as well as for the study of the genetic influence of many complex

disorders. As the most obvious advantage would be the possibility of identifying virtually any metabolic and non-metabolic genetic disorder in the newborn, the use of genomic sequencing in newborns would represent a new approach to precision medicine. With the potential to provide vast amounts of genome sequencing results about physical and psychological health information at the beginning of life, we face numerous challenges such as clinical analysis, interpretation, and communication of clinically relevant mutations to clinicians and patients. In spite of significant promise and more accurate information, NBS in precision medicine faces with a number of issues—social, ethical implications, stakeholder education, technical (cost and widespread implementation), interpretation and infrastructure (data storage and management), etc.

As public health officials work to come to a conclusion on WGS/WES for newborns, it is important to make cogitative concerns at the forefront of the discussion. In the era of precision medicine, policy-makers should firstly make appropriate NBS policies and trial designs according to the main goal of NBS. Secondly, they need to tackle such challenges as storing vast amounts of sequence data securely, developing genetic counseling techniques for better advisements, educating families and involved stakeholders, acquiring long-term follow-up systems, and establishing ethical standards for the practice as a whole. These challenges will also apply to prenatal and carrier testing initiatives. Before the application of WGS/WES into NBS, the public health community must decide whether the benefits of adding WGS/WES to well-established newborn screening programs outweigh the associated ethical pitfalls in precision medicine.

Coupled with advances in data handling and analysis, genome sequencing is on a path to becoming a standard tool in research and NBS of clinical genetics. In addition, this sequencing technology has prodigious potential for disease diagnostics and in the screening of newborns. We can predict that there will be an inevitable trend about integration genome sequencing into NBS in the era of precision medicine.

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