Open Access

OBM Genetics

Original Research

Newborn Screening Programs: Next Generation Ethical and Social Issues

Karine Sénécal [1,*], Brigid Unim [2], Bartha Maria Knoppers [1]

1. Centre of Genomics and Policy, Department of Human Genetics, McGill University, Montréal, Québec, Canada; E-Mails: karine.senecal@mcgill.ca; bartha.knoppers@mcgill.ca
2. Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy; E-Mail: brigid.unim@uniroma1.it

* **Correspondence:** Karine Sénécal; E-Mail: karine.senecal@mcgill.ca

Academic Editors: Joanne Traeger-Synodinos and François Rousseau

Special Issue: Genetic Screening

OBM Genetics
2018, volume 2, issue 3
doi:10.21926/obm.genet.1803027

Received: October 19, 2017
Accepted: July 12, 2018
Published: August 15, 2018

Abstract:

The benefits of neonatal screening programs are undeniable: children's lives are saved, and disease burden and morbidity alleviated. Without a doubt, « classical » neonatal screening programs are in the best interests of newborns. Indeed, those screening programs are recognized among the ten most important public health achievements. However, newborn screening programs raise ethical, legal and social challenges. For example, which criteria should govern whether or not to include a disease in the list of screened conditions? Is it equitable that there is great variability in the number and types of diseases screened from one neonatal screening program to another? What should be the consent procedure and/or the notification process to parents? Should carrier status for a recessive disorder be communicated to parents? What are the practices surrounding the collection, retention and potential secondary use of residual blood spots? Are these practices ethically sound? Moreover, in recent years, one of the biggest challenges of newborn screening programs has become the availability of a new technology: the arrival of next-generation sequencing technologies, such as whole genome sequencing, at a decreasing cost. This sequencing approach offers the possibility to use genomics tools in a public health setting—to provide

"precision" public health. However, there remain issues related to disease prediction, notably: the identification of certain genetic factors could impact other family members. In addition to such medical information, whole genome sequencing also has the potential to reveal genetic variations of uncertain or completely unknown significance, and information about non-health traits, which may affect the parent-children relationships as well as the family dynamic.

The goal of this manuscript is, first, to describe the key challenges associated with the use of genomic sequencing technologies into the public health umbrella of newborn screening programs. Secondly, we will discuss the positions and statements published in the last decade surrounding genomic sequencing technologies in newborn screening programs. We will demonstrate that, given the diversity of positions and stakeholders involved, a centralized and unique vision may be premature—albeit needed—at the international level. More specifically, we urge for immediate deliberation by the WHO on the policy challenges raised by the potential introduction of genomic sequencing in newborn screening programs. We believe that now is the time to reach an international consensus based on public health ethics and law as well as evidence-based outcomes.

Keywords

Newborn screening; public health; screening programs; next-generation sequencing; whole genome sequencing; ethics; policies; social issues

1. Introduction

As a concept, public health ensures the continuous monitoring of the health of populations as well as the protection of health and prevention of disease. Along with other surveillance measures and programs, public health agencies have adopted a long tradition of screening programs for identifying asymptomatic individuals at increased risk or in the early stages of disease to reduce potential morbidity or mortality. From the late 1960s, a set of resources and activities called newborn screening (NBS) programs (now part of public health) have been deployed to: identify asymptomatic newborns affected by a rare metabolic disease, genetic disorder or other severe disability; confirm diagnosis, and subsequently, treat those affected. Formerly, screening was limited to diseases that were well-known, that required immediate medical intervention to avoid irreversible damage, and for which effective treatments were available. NBS programs were consistent with the ethical principles for screening programs set out by Wilson and Jungner in Principles and Practice of Screening for Disease (1968) [1]. These 'classical' criteria can be summarized as follows:

"a population screening program (whether for children or for adults) has been considered justifiable only if the targeted condition is an important health problem, whose natural history is well-understood, and whose symptoms are amenable to early intervention and effective treatment. Accordingly, the mere availability of a reliable test would not justify routine screening for a condition, unless such screening could be shown to provide direct medical benefit to those

who test positive for the condition. In short, the moral focus of newborn screening has been what is good for the infant [the best interest of the child]" [2].

Based on the premise that newborn screening is considered to be in the best interests of the individual child, NBS have been carried out for decades worldwide [3]. The Centres for Disease Control and Prevention recognized that NBS was among the ten most important public health achievements [4]. Nevertheless, despite its benefits, NBS raises some ethical, legal and social challenges —notably with regards to the variety of specific disorders screened for, educational information and consent practices, genetic counseling, long-term follow-up procedures, as well as storage and secondary use of residual blood spots (initially collected). To contextualize, we will briefly explain those challenges. NBS programs are being challenged by new, complex and contested policy dilemmas regarding the possible introduction of whole genome sequencing (WGS) into newborn screening programs (I). We then scope the emergence of differing norms to address these challenges (II), and finally, encourage a position statement to be adopted by an international organization such as the World Health Organization (III).

2. Challenges to NBS Programs

2.1. Expansion of "Screenable" Conditions

Since the year 2000, technological innovations such as tandem mass spectrometry (MS/MS) have expanded the number of screenable diseases, and augmented the feasibility of the screening process [3, 5-7]. This was notably the case in North America (e.g. in the United States [8] and in several Canadian provinces [3] and in Europe [9]. As a result, debate arose around the objectives, rationale and decision making criteria governing NBS [2, 10-12]. In particular, there was debate concerning which conditions should be included in NBS programs. Specifically:

"In 2008, the President's Council on Bioethics published a report about newborn screening scrutinizing the [American College of Medical Genetics and Genomics (ACMG)]'s recommended uniform screening panel. While the Council did not explicitly criticize the expansion of screening, it did express some doubt about the ACMG's methods for doing so. The Council noted that the ACMG's loosened screening criteria for the secondary panel effectively expanded the number of conditions that could be included in the newborn screening panel in the future. Rather than limiting screening to conditions that were treatable, as Wilson and Jungner recommended, the ACMG instead expanded screening to include conditions that simply could be tested for using multiplex platforms" [13].

Thus, the conventional criteria for assessing the pertinence of screening for a specific condition were overlooked, expanding the list and thereby affecting the nature of consent to be provided.

2.2. Consent Challenges

Originally, consent to NBS was generally implied (i.e. the information about the screening was given to the parents, and the screening test was performed in the absence of opposition) The implicitness of consent was even mandatory in certain USA states, as it was clearly in the immediate benefit of the asymptomatic newborn to be identified before the symptoms and harms materialized. Thus, perhaps unsurprisingly, morbidity and mortality were reduced [14]. However, the argument justifying implicit consent became less convincing with the expansion of the number

of conditions included under NBS [13]. In addition, adding screening for recessive disorders to the list meant the possible revelation of the carrier status of a child and, indirectly, the carrier status of at least one of the parents. Carrier status of the child also has implications for the parents and for their own reproductive risks [14], so concerns were raised about the type of consent required.

Indeed, one of the concerns in the ongoing debate is how to involve parents in the consent process for NBS [14]. On the one hand, the principle of respect for autonomy is operationalized in the process of informed consent, on the other hand, moving away from a notification of NBS with possible parental opt-out to an explicit consent in the context of childbirth may decrease the number of children screened and so affect their health rights (e.g. United Nations Convention on the Rights of the Child, s. 24 [15]. The most serious aspect of NBS that raised issues however was that of the retention and the secondary uses of residual blood spots.

2.3. Storage and Secondary Uses

Newborn screening involves a needle prick to the baby's heel, soon after birth. A few drops of blood are placed on filter paper (Guthrie card) that preserves the sample for laboratory screening. Once screening is completed, the remaining samples are usually stored, to allow future confirmatory diagnosis and re-testing as needed, and to ensure quality control within the NBS program. The storage of bloodspots for these purposes is generally well accepted, as these uses are linked to the primary purpose of the initial collection [16, 17]. The issue resides in further storage and use for purposes unrelated to the initial collection.

The Guthrie cards represent an unmatched and unbiased resource for genetic research and public health surveillance, and sometimes for non-medical purposes (e.g. for the identification of disaster victims [18, 19] and for forensic uses) [20]. Genetic research using residual blood specimens (RBSs) is limited only by the amount of residual dried blood remaining on the card [21]. Even today, NBS programs are best characterized as either lacking policies or as inconsistent regarding the storage for other uses or research use of RBSs and the need to obtain consent or not [22] for these additional purposes. Additionally, there is inadequate transparency and communication about informed consent to such storage and potential future uses, as we will see in the next paragraphs, to say nothing of public health emergencies.

Since traditional NBS programs are usually operated in the best interests of the child without explicit written consent, storage and secondary uses of RBSs are now subject of intense debate [21], as evidenced by a series of lawsuits in 2009, 2010 and 2012 in the United States (Texas, Michigan, and Minnesota) and Canada (British Columbia). The underlying motive for these lawsuits was the fact that parents were unaware of storage for uses beyond the needs of the NBS program, that there was violation of privacy, failure to obtain adequate informed consent and misrepresentation [20]. In the same period, the ACMG published a 2009 Position Statement on Importance of Residual Newborn Screening Dried Blood Spots [22]. In 2010, the Institute of Medicine of the National Academies of the USA followed with a report entitled "Challenges and opportunities in using residual NBS samples for translational research" [21]. The latest report underscored concerns about current practices regarding the storage and secondary research uses of RBSs [23].

In some cases, future use in research and the possibility of opting-out for long-term storage or such future research are not reported for NBS programs. As Gene Watch UK summarized:

"[t]he system now used [in UK] for consent, which is proposed to continue, involves gaining broad consent from the mother to all future use when the blood spot is taken. This means that if a mother agrees to (one or all of) the tests to protect her baby's health, she cannot refuse the permanent retention of the blood spot or its use for any type of research in the future. This is unethical because it effectively forces mothers to agree to research on their child's behalf, knowing that refusal could jeopardise their baby's health" [24].

Thus, implied or presumed consent to this NBS program becomes the functional equivalent of consent to storage and possible research use. In that sense, the lawsuits concerning storage and further secondary uses, as well as the expansion of the number of screened diseases, provide an opportunity to revisit the practices on information given to parents about screening and their consent, if appropriate, for storage. Moreover, international organizations determine, harmonize or at a minimum should take a position on the approaches regarding the information to be given to parents.

In addition to storage and future research use of RBSs, another challenge is the issue of the current practice regarding consent to the use of the next-generation sequencing technologies, such as WGS, as costs decrease. As stated by Laberge and Burke in this special issue, "this growing technological capacity drives interest in new opportunities for genetic screening" [25]. The introduction of WGS raises the possibility to use genomics tools in a public health setting and to offer a "precision" public health.

3. Whole-Genome Sequencing in NBS?

Next-generation sequencing reveals the sequence of nucleotides of part or of the entire genome of an individual [26]. Its rapid development has considerably reduced the cost and the time required to sequence the whole genome (WGS). Reportedly, sequencing an individual's complete genome will eventually cost under one thousand dollars [27]. The availability of WGS is changing the current practice of medicine and public health by facilitating more accurate and, while at the same time, cost-effective genetic testing [28]. Some commentators predict that the earliest applications of WGS will be restricted to public health settings, such as NBS programs [29]. Others estimate that in ten or twenty years from now, all newborns will have their genomes sequenced [30]. However, this positive perspective is not unanimous. Indeed, many authors emphasize the challenges associated with the potential use of WGS in NBS and have underlined "some major concerns such as clinical analysis, result, storage of sequencing data, and communication of clinically relevant mutations to pediatricians and parents, along with their ethical, legal, and social implications" [31]. There are also concerns about the lack of evidence of benefit of screening for most disorders that could be screened for with WGS. Many of the "results" generated by the WGS will be variants of uncertain or unknown significance. What can be done with this kind of "result"? What will be the effect of revealing this kind of information, for example, in the relationship between the parent and their child, and other societal risks such as employment or insurability? As a result, several academic and professional organizations have begun discussing the issues raised by the possible introduction of WGS into NBS programs [32, 33].

3.1. Benefits and Risks

A 2008 report by the United States President's Council on Bioethics describes the use of WGS in NBS programs as an appropriate and "inevitable end-point in the development of personalized medicine" [34]. Indeed, some have argued that every (or almost all) detectable conditions should be screened for at birth. For them, such screening would be the most effective way to increase the understanding for diseases that are rare, poorly understood, and currently untreatable, to find eventually treatments [2, 34]. The USA National Institutes of Health launched a funding opportunity in 2012 and invited applications to explore the implications, challenges and opportunities associated with the possible integration of genomic sequencing in NBS [35]. Included among the research projects that have been financed is a pilot that, amongst other objectives, explores the potential of genomic sequencing (whole-exome sequencing - WES) as a method of NBS for disorders currently screened for, as well as others not currently screened for but may benefit the newborns. The value of additional information provided by WES in NBS was studied by researchers, as well as the interest of parents in receiving such more broad information than the results usually available from NBS programs [36]. These indicators suggest that there is a real possibility that WGS or other genomic sequencing approaches could eventually be used in NBS programs. Moreover, it has been proposed that the NBS would be the best setting for WGS, as everyone could benefit from personalized medicine (i.e. prevention and treatment) during their live time [34]. However, this prospect raises many ethical, legal, social issues, as well as policy concerns [37].

The National Institutes of Health–funded "The Genome Sequence-Based Screening for Childhood Risk and Newborn Illness Project", referred to as the BabySeq project, a randomized controlled trial evaluating the benefits and potential harms of providing WES or WGS results to families of newborns and their physicians. More specifically, the researchers studied the psychological and social impact of WES or WGS and compared it with standard care (i.e. "standard" NBS programs), with parents of newborns who are placed into the intensive care unit and parents of newborns who did not need placement in the neonatal intensive care unit. Newborns within each cohort were randomly assigned to receive standard NBS or NBS and genomic sequencing. BabySeq explored the psychosocial impact on the family in taking into consideration the perceptions of child vulnerability, parent–child bonding, and self and/or partner blame. Although using WGS may be especially useful for the diagnosis of sick newborns, the BabySeq Project explored the interest and outcomes of sequencing newborns and found that while sequencing has utility for diagnosing sick infants, it may not yet be ready to replace standard tests for broad population screening.

Researchers and others have described other challenges beyond the technical aspects of WGS testing. Such challenges include participant recruitment, dealing with unexpected findings, and returning information about carrier status [38]. Thus, in addition to amplifying the traditional issues raised by screening programs, and NBS programs more specifically [39] (e.g. notably with regards to consent, counselling, storage, and future uses of dried blood spots), WGS in NBS also raises additional policy concerns about willingness to participate in this kind of screening, the challenges associated with return of results and secondary findings (or variants of unknown significance) to family and (eventually) to children as they grow, the duty to reanalyze the data with the development of new knowledge.

3.2. Return of Results and Secondary Findings

Were WGS to be applied in NBS programs, one of the challenges would not only be to digest and properly interpret the large amount of genetic data generated by WGS (a "genomic tsunami"), but also to delineate which information should be communicated or not to the parents. As Goldenberg and Sharp emphasize, "returning genetic results that do not require immediate medical action or results for which clinical implications are unclear may create unwanted psychosocial burdens on parents". Professional guidelines (such as national pediatric society or genetic association) generally recommend genetic testing in minors only when it provides health benefits during childhood; for example when established, effective and important medical treatment can be offered before the child reaches adulthood [40, 41]. The reason justifying this position is that genetic testing of minors should usually wait until the person is mature enough to make an informed decision. This reflects the conscientious attention given so far in the clinical setting before offering genetic tests, where special attention is paid to respect of personal autonomy, the importance of pre- and post-test counselling, and the confidentiality of genetic information. If all children were screened in the context of NBS programs, how would their data be treated? Should the data be given to their parents or paediatricians? Should the data be stored and given to them when they reach legal majority (however defined) [42]? As the Presidential Commission for the Study of Bioethical Issues points out in their October 2012 report, "whole genome sequencing in children raises a number of unique issues with regard to fully informed decision making" [43]. Dealing with such a huge mass of sequence data raises a new set of ethical and legal challenges relating to: the rights of parents to access the genetic information of their children, the best interests of the child, the right to know and not to know, privacy rights, the informed consent and counselling issues, psychological impact of knowing information that could only become relevant (or not) much later in life, impact on family relations, responsibility towards blood relatives, the duty to recontact, and the duty to follow of healthcare professionals as well as the possible liability of government or physicians. In order to meet these challenges, several groups or organizations have adopted position statements on the potential use of WGS in NBS programs.

4. Policy Positions on the Potential Use of WGS in NBS

4.1. International Position Statements

To date, two Recommendation documents have been published at the International level. Both of them have been written by groups of experts and subsequently endorsed by professional groups in the international and European arena. First among these documents was the "Genomic Newborn Screening: Public Health Policy Considerations and Recommendations" (2017) of the Paediatric Task Team of the Global Alliance for Genomics Health. The second document, titled "Statement on the Continued Importance of Targeted Approaches in NBS Programs", was published in 2015. It was endorsed by several international organizations (i.e. the European Society of Human Genetics, the P3G International Paediatric Platform; the Human Genome Organisation; and the PHG Foundation). These two documents adopted a similar approach with regards to the possible integration of WGS in newborn screening programs: they both recommended that, at this time and to the extent possible, screening methods remain targeted to

minimize secondary findings. Moreover, the 2015 Statement re-emphasized the importance of targeted approaches in NBS programs [44]. It stated that the "responsible use of genome sequencing within a public health program such as NBS should not be technology-driven, but rather be adopted on the basis of its public health potential". Thus, at this time, it recommended a targeted approach: the goal of using WGS in NBS should be the identification of gene variants bound to a higher risk of preventable of treatable conditions, for which treatment has to start in the newborn period or in early childhood. Regarding the storage of the WGS information of newborns for future health care purposes, this prospect was ruled premature in the 2015 Statement of Principles. However, it also recognized that policy makers need to consider uses of WGS informations to improve public health and research, and the issue of the potential to identify individuals and their relatives [44]. In addition to this Statement, the international normative documents also scored important points concerning the potential use of WGS in NBS programs. For example, the GA4GH Pediatric Task Team claims, in is Public Health Policy Considerations and Recommendations, that more research is needed to resolve outstanding health policy and ethical issues before the use of genomic sequencing could be implemented for NBS (recommendations 7-8). A substantial ethical and policy concerns raised in the context of populational pediatric screening programs is the return of incidental genomic findings. Hence, the 2015 Statement already mentioned had argued that even in the case of a targeted approach, there remains a need for new models of informing parents [44]. Information should be included about the possibility of finding unsolicited results and give appropriate explanation on which kind of information to report to the newborn's parents, the potential storage and research uses of the RBSs and data.

Although it is interesting to see that the recommendations adopted a similar approach, both policy documents were developed by a group of experts and were circulated and endorsed by a variety of organizations. It would be useful if other organizations in the international scene evaluate the benefits and risks associated with the possible use of WGS in NBS programs. States will require advice from international organizations in order to adopt reasonable and harmonized positions.

4.2. European Position Statements

At the European level, caution is also in order. In this regard, the European Union Network of Experts on Newborn Screening (EUNENBS) [45] warns against over-optimistic expectations or premature decisions based on partial evidence with regards to new technical possibilities for screening. The EUNENBS considers that a "major challenge when facing the possibilities to expand NBS programs is the balancing of pros and cons. All forms of screening raise certain social and ethical concerns" [45]. According to the Network, screening should only occur when it is clinically relevant, and a responsible per-disease evaluation is needed. However, it also recognizes that it is difficult to define the threshold for whether screening of a disorder is clinically relevant or not. Similarly, the European Society of Human Genetics (ESHG) had already adopted (in addition to the 2015 international Statement on the Continued Importance of Targeted Screening document [44]), other principles relevant to the potential use of WGS in a population screening context. Indeed, its earlier 2013 Recommendations on "Whole-genome Sequencing in Health Care" [28] declared that the issue with genomic sequencing will soon no longer be which target-diseases to include in the test panel, but which should be excluded by a selective analysis of WGS. Presumably, the

challenge will be to avoid a broader scope not based on the rigorous evaluation of clinical utility and other screening criteria. The ESHG takes the position that using WGS requires "a justification in terms of necessity (the need to solve a clinical problem) and proportionality (the balance of benefits and drawbacks for the patient)" [28]. It defines a screening program "as the offer of medical testing to persons without symptoms or other indications that would make such testing clinically necessary" [author's emphasis] [28], NBS clearly falls within this definition. The prospect of the introduction of the WGS into the NBS clearly does not meet these criteria. In the same vein, the European Commission and the EuroGentest adopted in 2013 a Joint Research Centre Scientific and Policy Report on Genetic Testing Offer [46]. According to this report, the use of genomic sequencing to analyse an individual's complete genotype or predisposition to disease should not be a tool for NBS programs or other populational screening programs at this stage. Finally, the ESHG underlined another issue: the use of genomic sequencing in NBS programs may reveals information that will only be relevant later in life, and so jeopardizes the right of the child's to decide if he or she want to know this information, when he or she will be mature enough to do so [28].

In short, in both the international and European arena, a relatively uniform consensus is emerging according to which it is not justified to use WGS or other genomic sequencing methods in NBS programs. However, many of those organizations also recognized that while this position is valid now, it may change with time. Some go further and identify key issues that should be addressed before genome sequencing could potentially be incorporated into NBS programs. Are those international normative and European position statements adequate to guide national positions? As we will see in the next section, national positions—like the international and European positions described above— have adopted "at this time" position indicating possible future revisions. As recently demonstrated by the authors of a systematic review and a Delphi consensus process [47] with regards to the transformation of screening principles (articulated by Wilson and Jungner in 1968 about wide-population screening programs), there is "a lack of coordinated progression among subsequent sets of screening principles and limited acknowledgement of other related work" [47]. Perhaps it is time for international guiding organizations like the World Health Organization, UNESCO and the International Newborn Screening Organization to articulate consistent minimum criteria or principles to guide the eventual implementation of genomic sequencing in national newborn screening programs.

4.3. National Positions

Similar to the international and European initiatives, several countries have made recommendations in regard to the potential use of WGS in NBS programs. For example, the United Kingdom [29, 48], The Netherlands [49, 50], Italy [51] as well as the United States [2, 26] have produced reports that also reject the implementation of WGS in NBS programs, although some specify that this position is only valid for now and likely to change over time [26, 29, 48].

As early as 2005, the UK's Human Genetics Commission issued a report, entitled "Profiling the Newborn" [48]. It discarded the implementation of large scale genetic profiling in NBS programs; mainly due to lack of cost-effectiveness of this approach.

Five years later, a monitoring report of the Health Council of Netherlands of 2010 also took position on genomic sequencing and explained that:

"genome-wide screening appears to have more disadvantages than potential advantages for the parties involved at this time. Offering such screening as part of standard healthcare cannot currently be justified" [49]. Addressing more specifically the question of the potential use of WGS in NBS programs, the authors of the Netherlands report emphasized that "the question becomes not only whether parents can oversee the Pandora's box they are opening, but also whether they have the right to make that decision for their children" [49].

Yet, in 2015, the Health Council of The Netherlands published a new set of recommendations for Neonatal Screening [50]. Generally speaking, this Committee emphasized the health gains for the newborn as the goal of screening programs and states thereby is justifying a proactive approach to screen newborns if an effective treatment exists. The Committee also underlined the disadvantages of NBS screening for untreatable conditions: "screening for untreatable conditions in children can be considered an infringement on their right to an open future earlier knowledge of a condition may overshadow the first period with the newborn; the literature describes this as loss of the 'golden years'" [50]. Irrespective, the Committee stated that targeted screening at the level of DNA is recommended for actionable conditions that couldn't be diagnosed on the basis of the concentration of a specific metabolic product in the heel prick card. Finally, as with the international and European positions presented above, the Health Council of The Netherlands will review the possibility of expanding the neonatal screening program over the upcoming years, while considering both its scientific and social aspects [50].

In Italy, a 2017 Position statement on exome sequencing of infants in critical condition [51] details the criteria for possible genomic sequencing in NBS programs:

"Currently, integration of [next-generation sequencing] NGS in newborn screening is not feasible due to the high cost of genomic sequencing and difficulties in interpretation of the results. It takes weeks to report the results of NGS and NGS has to be reliably performed with DNA extracted from the dried blood specimen necessary for newborn screening. Moreover, a major challenge would be the bioinformatics required, analyzing the vast amount of data in the context of rare or novel nucleotide changes. However, with the further decrease in costs for WES or WGS, the improvement of bioinformatic techniques and once the technical issues (analytical and bioinformatics), ethical and legislative issues (e.g. communication of results, data ownership), economic issues (cost of analysis and computational, costs for data storage) and data security (adequate encryption systems) are resolved, it is expected that the NGS method can be utilized in neonatal screening programs" [unofficial translation] [51]."

In the USA, the potential use of WGS into NBS programs has garnered less consensus. In 2008, the President's Council of Bioethics foresaw the use of WGS in NBS programs as an inevitable endpoint. However, it recommended that "when differential diagnosis of some targeted disorders entails detection of other poorly understood conditions that would not otherwise be suitable candidates for NBS , such results need not be transmitted to the child's physician and parents" [2]. Also, it added that we should "[r]eject any simple application of the "technological imperative," i.e., the view that screening for a disorder is justified by the mere fact that it is detectable via multiplex assay, even if the disorder is poorly understood and has no established treatment. There should be no presumption that multiplex screening platforms are to be used in full profile mode" [2].

Similarly, current guidelines are also divergent or, at least, unclear. On the one hand, the 2013 American Academy of Pediatrics (AAP) and ACMG Policy Statement on Ethical and Policy Issues in

Genetic Testing and Screening of Children [40] did not mention WGS. Yet, in 2012, the ACMG had explicitly stated that WGS should not be used as a first-tier approach for NBS [26]. It is surprising that this position was not reaffirmed in the later Joint Statement that specifically addressed the subject of NBS [40]. More surprising still is the fact that such an influential organization as the AAP has not considered WGS, even though this technology is now used at many levels (clinic, research, direct-to-consumer, etc.). In contrast, the National Institutes of Health (NIH) funded various studies under the Genomic Sequencing and Newborn Screening Disorders research program in 2013 [33] in regards to: i) genomic sequencing and analysis; ii) research related to patient care; and iii) the ethical, legal and social (ELSI) implications of using genomic information in the newborn period.

5. Conclusion

While there has been some clarification concerning the need to obtain parental consent for the ongoing storage or research uses of NBS [50], there is little doubt that newborn screening programs around the world are in flux. Indeed, together the issues of the implicit consent of parents to collection founded on the best interests of the child, the number of conditions being screened for, storage and research uses, the gradual introduction of NGS technologies and the issue of the return of results and secondary findings, all lean towards a united effort to revisit the Wilson and Jungner WHO criteria – soon to be 50 years old! Although these criteria were revisited for the genomic age in 2008 by certain authors attempting to adapt the criteria to better fit the genomic era [12], the advent of NGS mandates revisiting the principles and practices that govern genetic screening in the international arena. To date, they have served us well but renewed international consensus on the basic tenets is critical. We can also learn from some of the current pilot studies on WGS as well as from the use of WGS in paediatric intensive care or in families with children with rare disorders—in these recent contexts did the introduction of WGS in NBS create insurmountable ELSI barriers?

Despite the challenges raised by the use of WGS in paediatrics [52], it is primordial to continually assess the risks and benefits for newborns, parents, the family and society as a form of anticipatory governance [53]. We also need to take into consideration the potential impact on the resources of public health systems and that genetic screening test for newborns are now being offered by private companies directly to the consumer [54]. As explained by Laberge and Burke in this special issue: “interest in commercially available tests by patients and prospective parents drives the use of these tests, which in turn may influence professional practice” [25].

In short, we have seen that various stakeholders are beginning to provide recommendations regarding the use of WGS in paediatrics. Now is the time to: 1) reach an international consensus based on public health ethics and law, as well as evidence-based outcomes; and 2) distinguish the use of WGS in the clinical/research setting from that of public health programs. It is also important to better understand the potential risks and benefits of sequencing newborns in public health, by studying for example its psychosocial risks for family dynamics over time [52]. Although the public health benefit of newborn screening programs is irrefutable, psychosocial aspects, equity and programmatic challenges need to be addressed, to say nothing of quality assurance. How to ensure we act in the best interests of all newborns in shaping the international paediatric norms for the next 50 years? We call on the WHO to convene and to act!

Acknowledgments

The authors would like to thank Seydina Touré for his help in reviewing the manuscript.

Author Contributions

All authors contributed to the review of the literature and policies, writing and editing of the manuscript.

Funding

This work was supported by the Canada Research Chair in Law and Medicine (Canadian Institutes for Health Research/CRC), the Ministère de l'Économie, de la Science et de l'Innovation du Québec, PSR-SIIRI-850 (Canada); the Fonds de recherche du Québec – Santé, the Quebec Network of Applied Genetic Medicine (RMGA), the PRECeDI project (Marie Skłodowska-Curie Research and Innovation Staff Exchange (RISE), Grant agreement no: 645740).

Competing Interests

The authors declare that no competing interests exist.

References

1. Wilson J, Jungner G. Principles and practice of screening for disease. J R Coll Gen Pract. 1968; 16: 318.
2. The President's Coucil on Bioethics. The changing moral focus of newborn screening: An ethical analysis by the president's council on bioethics. Bioethics. 2008.
3. Wilson K, Kennedy SJ, Potter BK, Geraghty MT, Chakraborty P. Developing a National Newborn Screening Strategy for Canada. Health Law Rev. 2010; 18: 31-39.
4. Centers of Disease Control and Prevention (CDC). Ten Great Public Health Achievements—Worldwide, 2001-2010. Mmwr Morb Mortal Weekly Rep. 2011; 60: 814-818.
5. Kerruish NJ, Robertson SP. Newborn Screening: New Developments, New Dilemmas. J Med Ethics. 2005; 31: 393-398.
6. Wilcken B, Wiley V, Hammond J, Carpenter K. Screening newborns for inborn errors of metabolism by tandem mass spectrometry. N Engl J Med. 2003; 348: 2304.
7. Centers of Disease Control and Prevention (CDC). Impact of expanded newborn screening--United States, 2006. MMWR Morb Mortal Weekly Rep. 2008; 57: 1012-1015.
8. National Newborn Screening and Genetics Resource Center (NNSGRS). U.S. National Screening Status Report -- updated 9/20/04. Genet Mol Biol Microbiol. 2004.
9. Cornel M, Rigter T, Weinreich S, Burgard P, Hoffmann GF, Lindner M, et al. Newborn Screening in Europe; Expert opinion document. Eur J Hum Genet. 2014; 22: 12-17.
10. Botkin JR. Research for newborn screening: developing a national framework. Pediatr. 2005; 116: 862-871.
11. Grosse SD, Boyle CA, Kenneson A, Khoury MJ, Wilfond BS. From public health emergency to public health service: the implications of evolving criteria for newborn screening panels. Pediatr. 2006; 117: 923-929.

12. Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bull World Health Organ. 2008; 86: 317.
13. Council for Responsible Genetics. Newborn screening in America: Problems and policies. 2012; 8.
14. Ross LF, Saal HM, David KL, Anderson RR. Technical report: ethical and policy issues in genetic testing and screening of children. Pediatr. 2013; 15: 321-321.
15. United Nations Human Rights. Convention on the Rights of the Child. 1989.
16. Rothwell EW, Anderson RA, Burbank MJ, Goldenberg AJ, Lewis MH, Stark LA, et al. Concerns of newborn blood screening advisory committee members regarding storage and use of residual newborn screening blood spots. Am J Public Health. 2011; 101: 2111-2116.
17. Bombard Y, Miller FA, Hayeems RZ, Carroll JC, Avard D, Wilson BJ, et al. Citizens' values regarding research with stored samples from newborn screening in Canada. Pediatr. 2012; 129: 239-247.
18. Hartman D, Benton L, Morenos L, Beyer J, Spiden M, Stock A. The importance of Guthrie cards and other medical samples for the direct matching of disaster victims using DNA profiling. Forensic Sci Int. 2011; 205: 59-63.
19. Hartman D, Drummer O, Eckhoff C, Scheffer JW, Stringer P. The contribution of DNA to the disaster victim identification (DVI) effort. Forensic Sci Int. 2011; 205: 52-58.
20. Knoppers BM, Avard D, Sénécal K, Harris JR, Haugan A, Budinljøsne I. Newborn screening programmes: emerging biobanks? Nor Epidemiol. 2012; 21: 163-168.
21. Institute of Medicine. Challenges and Opportunities in Using Residual Newborn Screening Samples for Translational Research - NCBI Bookshelf. National Academies Press. 2010.
22. ACMG. Position Statement on Importance of Residual Newborn Screening Dried Blood Spots. 2009.
23. Botkin JR, Goldenberg AJ, Rothwell E, Anderson RA, Lewis MH. Retention and research use of residual newborn screening bloodspots. Pediatr. 2013; 131: 120-127.
24. Gene Watch. Keeping Blood Spots from Newborn Babies, UK. Gene Watch UK. 2006.
25. Laberge AM, Burke W. Avoiding the technological imperative: Criteria for genetic screening programs. 2017; 1.
26. ACMG. Points to consider in the clinical application of genomic sequencing. Genet Med Offic J Am Coll Med Genet. 2012; 14: 759-761.
27. Dondorp WJ, De Wert GM. The 'thousand-dollar genome': an ethical exploration. Eur J Hum Genet. 2013; 21: S6.
28. Van El CG, Cornel MC, Borry P, Hastings RJ, Fellmann F, Hodgson SV, et al, on behalf of the ESHG Public and Professional Policy Committee. Whole-genome sequencing in health care. Eur J Hum Genet. 2013; 21: 580.
29. Wright DC. Next steps in the sequence: the implications of whole genome sequencing for health in the UK: PHG Foundation. 2011.
30. Berg JS, Agrawal PB, Bailey DB, Beggs AH, Brenner SE, Brower AM, et al. Newborn sequencing in genomic medicine and public health. Pediatr. 2017; 139: 1-13.
31. Yang L, Chen J, Shen B. Newborn screening in the era of precision medicine. Translational Informatics in Smart Healthcare: Springer. 2017; 47-61.

32. Tarini BA, Goldenberg AJ. Ethical issues with newborn screening in the genomics era. Annu Rev Genomics Hum Genet. 2012; 13: 381-393.
33. Goldenberg AJ, Sharp RR. The ethical hazards and programmatic challenges of genomic newborn screening. Jama. 2012; 307: 461-462.
34. Collins F. The language of life: DNA and the revolution in personalised medicine: Profile Books. 2010.
35. National Institute of Child Health and Human Development. Genomic Sequencing and Newborn Screening Disorders (U19). NIH. 2012.
36. National Institue of Health (US Department of Health and Human Services). NIH program explores the use of genomic sequencing in newborn healthcare 2013. Available at: Accessed November. 2014; 4: 23.
37. Frankel LA, Pereira S, McGuire AL. Potential psychosocial risks of sequencing newborns. Pediatrics. 2016; 137: S24-S29.
38. Heger M. Newborn Sequencing Projects demonstrate successes, challenges, of widespread implementation. Genome Web. 2017; 1: 1.
39. Friedman JM, Cornel MC, Goldenberg AJ, Lister KJ, Sénécal K, Vears DF. Genomic newborn screening: public health policy considerations and recommendations. BMC Med Genom. 2017; 10: 9.
40. American College of Medical Genetics and Genomics (ACMG), American Academy of Pediatrics (AAP). Ethical and policy issues in genetic testing and screening of children. Pediatr. 2013; 131: 620-622.
41. Canadian Paediatric Society (CPS) Position Statement – Guidelines for genetic testing of healthy children. Paediatr Child Health. 2003; 8: 42-45.
42. Institue of Medicine of the National Academies. Integrating large-scale genomic information into clinical practice: workshop summary: National Academies Press. 2012; 51.
43. Presidential Commission for the Study of Bioethical Issues. Privacy and progress in whole genome sequencing. Washington (DC): 2012.
44. Howard H, Knoppers B, Cornel M, Wright Clayton E, Sénécal K, Borry P. endorsed by the European Society of Human Genetics; the P3G International Paediatric Platform; the Human Genome Organisation; & the PHG Foundation(2015). Whole-genome sequencing in newborn screening? A statement on the continued importance of targeted approaches in newborn screening programmes. Eur J Hum Genet. 2015; 23: 1593-1600.
45. Cornel M, Rigter T, Weinreich S, Burgard P, Hoffmann GF, Lindner M. Newborn screening in Europe - Expert Opinion Document. EU Tender – Evaluation of population newborn screening practices for rare disorders in Member States of the European Union. 2012.
46. European Commission EuroGentest. European workshop on genetic testing offer in Europe. 2013.
47. Dobrow MJ, Hagens V, Chafe R, Sullivan T, Rabeneck L. Consolidated principles for screening based on a systematic review and consensus process. Can Med Assoc J. 2018; 190: E422-E429.
48. Human Genetics Commission. Profiling the newborn: a prospective gene technology? 2005.
49. Dondorp W, de Wert G. (Health Council of The Netherlands). The 'thousand-dollar genome': an ethical exploration, Monitoring Report Ethics and Health, 2010/2. The Hague: Centre for Ethics and Health. 2010.

50. Health Council of The Netherlands. [New recommendations for the Dutch neonatal screening programme. A report from the Health Council of the Netherlands]. Ned Tijdschr Voor Geneesk. 2015; 159: A9115.
51. Società Italiana di Pediatria (SIP), Società Italiana di Neonatologia (SIN), Società Italiana Malattie Genetiche Pediatriche e Disabilità (SIMGePeD), Società Italiana di Genetica Umana (SIGU). Intersociety policy statement on the use of whole-exome sequencing in the critically ill newborn infant. Ital J Pediatr. 2017; 43: 100.
52. Leslie AF, Stacey P, Mcguire AL. Potential Psychosocial Risks of Sequencing Newborns. Pediatr. 2016; 137: S24.
53. Ozdemir V, Husereau D, Hyland S, Samper S, Salleh MZ. Personalized Medicine Beyond Genomics: New Technologies, Global Health Diplomacy and Anticipatory Governance. Curr Pharmacogenomics Person Medicinenom. 2009; 7: 225-230.
54. Borry P, Sénécal K, Knoppers BM. Do It Yourself Newborn Screening. Jama Pediatr. 2016; 170: 523-524.