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Lessons that newborn screening in the USA can teach us about biobanking and large-scale genetic studies

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Abstract

The intent in establishing newborn screening programs was not to create and sustain a large-scale genetic biobanks. Instead, newborn screening programs were designed as a public health program. As such, they have successfully screened millions of asymptomatic newborns for disease that, undiagnosed and untreated, would cause disability or death. However, historical decisions on retention of residual samples and technological innovation have forced these programs and their proponents to confront the prospect of biobanking and the conduct of large-scale genetic studies. We suggest that the challenges facing newborn screening can provide important lessons for other biobanking and large-scale genetic testing endeavors.

Keywords

biobanking; genetics; newborn screening; screening

Brief overview of newborn screening

In the 1960s, state newborn screening (NBS) programs were established in response to a call for widespread screening for phenylketonuria (PKU), a metabolic disorder caused by a missing or dysfunctional phenylalanine hydroxylase enzyme that impairs the conversion of phenylalanine to tyrosine. PKU causes phenylalanine to accumulate in the blood, cross the blood–brain barrier and cause permanent cognitive impairment. NBS programs were created to identify affected asymptomatic individuals before damage occurs so they can receive preventive treatment. Since the implementation and success of NBS for PKU 50 years ago, screening has been initiated for numerous other disorders [1].

In the USA, screening programs are run by the states, not the federal government. As a result, each state, using its own set of policies and procedures for making these decisions [2,3], decides which disorders its citizens should or should not be screened for as part of the state's program – although now most states eventually add disorders recommended by the

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US Department of Health and Human Services to their screening panels. Certain standards need to be met before a condition can even be considered for addition to a NBS panel, much of which are based loosely on a traditional population screening criteria called the Wilson–Jungner criteria that considers both cost and consequences [4]. First, there has to be an accurate test. Second, the cost of the testing cannot be prohibitive. Third, there has to be evidence that an intervention would improve health outcomes for children confirmed to have a screened condition.

Most NBS tests are performed on whole blood, although there are a few exceptions (e.g., hearing screening and pulse oximetry screening for critical congenital heart disease). The blood is collected from the heel of a newborn and multiple half-inch diameter drops of blood are dried onto a specially manufactured filter paper, creating several spots – generally between three and five – on the paper. Sample punches, usually approximately one-eighth of an inch in diameter, are then taken from a spot and used for testing [5]. Prior to tandem mass spectrometry (MS/MS), most new laboratory tests required the use of an additional ‘punch’ from the blood spot.

In addition to being a state-run public health program, NBS is legally required. As a result, testing does not require parental consent, although most states permit parents to opt-out without punitive action. In order to opt-out, however, parents must be informed enough to know about and exercise that option [6,7]. Few states require healthcare providers to explain the purpose of testing, and few parents have more than a cursory understanding of the NBS process [7]. In fact, few are aware that their babies have even been tested [8]. As a result, parents are sometimes caught by surprise when told that their child has screened positive for a condition on the panel [9]. Such suboptimal education and communication have created challenges for activities both within and outside the program's clinical screening activities.

Residual blood spots: storage & use after NBS

NBS programs were created solely as public health programs. By their very nature, however, they can create huge biorepositories of blood samples from all newborns in the USA. As a result, the state-mandated screening tests may not be the ‘end of the road’ for the blood spots. Over the years, many states have chosen to save rather than discard the residual blood spots (RBS) from NBS cards [3,7]. However, states have different mandates and policies regarding the storage and use of RBS, with 55% storing RBS for <5 years and 45% storing for >21 years [10,11]. Reasons for RBS storage have included retesting of specimens, use of specimens for quality assessment/quality control of existing NBS tests [12], development of new NBS tests, reconfirmation of NBS results, legal proof of testing or forensic studies [13,14]. Availability of RBS for non-NBS-related research use varies across states [10,11].

As early as 1996, the potential for NBS RBS to be a useful biobank of genetic material for each baby born in the USA was acknowledged and envisioned [13]. While the ability to extract and analyze DNA from dried blood spots has dramatically increased the potential utility of these dried blood spots for both NBS testing within the program and research outside the NBS program [15,16], the yield and quality of the DNA varies based on the storage conditions [13]. Medicine has a long tradition of using ‘leftover’ biomedical specimens (e.g., blood, DNA, organs and tissues) for research [17], and the ethical issues raised by the use of stored biomedical specimens – especially those that pertain to the use of specimens for genetic studies – are not new [18]. However, the situation in NBS presents unique lessons for biobanking and large-scale genetic studies.

Lessons learned from NBS & RBS use

Lesson 1: clearly distinguish between clinical & research endeavors

‘Therapeutic misconception’, a well-established phenomenon in medical ethics, describes a situation in which individuals overestimate the benefits or underestimate the risks associated with a specific research study [19,20]. The use of pilot studies in NBS may provoke such ‘therapeutic misconception’ among parents. Despite calls from the American Academy of Pediatrics [21] and March of Dimes for NBS that is more evidence-based and in accordance with federal recommendations [1], historically, most states added disorders to their NBS panels with minimal, if any, large-scale population-based studies of testing [22]. The institution of an evidence-based review assessment of candidate disorders for NBS disorders by the Secretary's Advisory Committee on Heritable Disorders in New-borns and Children is an attempt to remedy this trend [23].

As technological advances augment our ability to test for additional disorders, there has been a call for research studies that go beyond smaller scale clinical trials [24,25]. However, ethicists have raised concern about the public's enthusiasm for screening for disorders that is offered as part of pilot projects [26] – screening for disorders not officially part of the state panel to generate data to guide decisions about official adoption – without full comprehension of the risks and benefits associated with screening. For example, in situations where consent for participation in pilot projects has been clearly separated from the screening for the rest of the disorders, uptake rates are much lower than when presented alongside disorders that are regularly screened [27]. These data raise concern that parents may perceive these pilot disorders to have the same risk–benefit profile of mandated disorders.

Apart from overestimating benefits of pilot programs, the public may underestimate the benefit of clinical NBS and confuse it with RBS research use. Specifically, concerns have been raised that this will lead the public to refuse clinical NBS for their child because they perceive it as experimental [28]. This seems a legitimate concern [29]. While there are no published data to substantiate this, conflation of the issues of screening and research to the lay public by prominent new sources are unsettling [101].

Steps have been taken to improve the education of parents on these issues, while preserving the benefits of both NBS and research. For example, Michigan is one of the few states that recommends a separate consent process for use of RBS be conducted after the collection of the NBS specimen. The goal of separating these discussions is to make a clear distinction between screening and research in parents' minds. Additional work to ensure that the consent interaction (e.g., dialogue, forms) is clear and informative is active and ongoing [30]. Admittedly, this is an open-ended type of consent, as opposed to informed consent, as it is impossible for the parents to know all the possible research that could be conducted in the future [31,102].

When NBS programs engage in both public health/clinical activities and research there is a risk that the public will conflate the activities and end up misconstruing public health/clinical activities as research and *vice versa*. We do not think that NBS programs should discontinue pilot programs and RBS storage and use because of this potential threat. However, we do recommend that programs take steps to clarify that the aims and risks/benefits of these endeavors are different. At the same time, NBS programs should aggressively monitor refusal rates for NBS to ensure that parents are not refusing a potentially life-saving screen for their child because of a simple misunderstanding.

The lesson here for biobanking and other large-scale genetic studies is that failure to effectively distinguish between clinical and research endeavors can threaten the core mission. Although education and communication are among the most challenging processes to optimize, they are likely to be the most fruitful.

Lesson 2: establish & codify ownership in a transparent manner

Who owns the RBS specimens? The answer is often unclear. Even members of state NBS advisory committees are confused [32]. Some might argue that they belong to the state, since the state collected them and stores them, while others would contend that because the RBS were mandatorily collected for NBS and not research, the state does not have *carte blanche* ownership of them. Many state laws are ambiguous and most states do not have laws that address storage and use of RBS [10]. Of those that do, only four decree that the RBS becomes the property of the state, while ten others give state health departments the authority to decide the fate, but not explicit ownership, of those specimens [10].

Not surprisingly, this ambiguity has led to two recent lawsuits, in Texas and Minnesota, that have alleged inappropriate storage and use of RBS. The lawsuit in Texas claimed that storage and use of RBS violated citizens' Fourth Amendment rights (i.e., protection from unreasonable search and seizure), while the lawsuit in Minnesota argued that the practice violated an existing law that required consent be obtained before genetic testing. In both cases, the plaintiffs prevailed. The pretrial settlement of the Texas case and the ruling of the Minnesota case have resulted in the destruction of millions of blood spots in each state [33,34]. Understandably, the outcomes of these two lawsuits have generated substantial anxiety from other states about both the vulnerability and the legality of their stored RBS.

Of note, each state destroyed all of the blood spots, and it is not clear whether parents were offered the option to have their child's blood spot returned to them. It is possible that some parents would have preferred to save their child's blood spot because of its potential future clinical value. For example, the blood spot has been used to identify an undiagnosed metabolic disorder in infants who died suddenly of unknown causes.

By contrast, Michigan provides an example of a state that has gone to great lengths to clarify ownership and maximize transparency. The Michigan BioTrust for Health (BioTrust) represents a collaboration between the Michigan Department of Community Health (MDCH), local universities and research institutes [35]. The BioTrust was established in 2008 using the 'charitable trust model' [36]. As such, the Michigan Department of Community Health serves as the trustee of the specimens, who is legally responsible for using the specimens for the benefit of the donor – in this case the public. Since MDCH's mission is to promote public health, research with RBS should clearly demonstrate the potential to improve the health of the public.

As the trustee of the specimen, MDCH is responsible for directing the NBS program, which provides the specimens, providing institutional review board oversight of research projects, and serving as an honest broker [35]. In this latter capacity, MDCH "acts as the intermediary between the specimen source (biobank) and the research investigator" [37] and is responsible for assigning and maintaining the linkages between specimens and identifiable data. Multiple layers of oversight exist: a Community Value Advisory Board serves as a voice for the lay public and provides guidance on sensitive issues (e.g., cultural, historical and religious) that are of importance to the larger community; a Scientific Review Board reviews all submitted research proposals to ensure that they have scientific merit [35].

We believe that given the mandatory nature of NBS, parents should be considered 'owners' of their child's blood until they transfer ownership or stewardship over to another entity. For

biobanks outside of the NBS context, professional and governmental organizations argue that the donors retain ownership. The courts, however, disagree, and have ruled on multiple occasions that universities own the specimens of the biobank [38–41].

Regardless of the decision as to who owns the specimens, we strongly recommend that biobanks codify and establish ownership of their specimens with their donors – and that they do so in a way that is transparent and acceptable to their donors. We are not suggesting that donors must approve all studies, but argue for a clear contract that specifies whether the samples remain the property of the collecting entity, or whether ownership be transferred to other entities such as another academic institution, a pharmaceutical firm or a state or federal government entity, and whether donors can have their specimens removed from the biobank or destroyed. Use of a charitable trust model for biobanks would help clarify ownership issues and provide more regulatory oversight and privacy safeguards, while fostering trust and participation [31].

Lesson 3: people view DNA-based research as ‘different’ from other types of research – especially if the government is involved

For decades, states have been storing and using RBS [11]. Such specimens were used primarily for two purposes – quality assurance and new test development. Other uses have included population-based studies of risk exposures such as environmental toxins and infectious agents [13]. Some research unrelated to NBS did occur. Often it examined *in utero* exposure to environmental compounds – research questions that blood specimens from state birth cohorts collected over multiple years seemed well-positioned to answer [42]. While such RBS research did not trigger much controversy, the potential to conduct research on the DNA contained within RBS seems to have become a ‘game-changer’ for the public. Despite the fact that most genetic research did not involve whole-genome sequencing – and so would not make the samples readily identifiable to the researcher – the ability to conduct genetic research on RBS has provoked public ire and sparked debate regarding the storage and use of RBS for research purposes [43,44].

Not surprisingly, there is a range of public opinion on these matters. Some individuals fear that RBS research is a mechanism for government control of its citizens. One writer described the situation as “Big Brother in one of its worst incarnations” [45]. Others feared that the government would use RBS for eugenic purposes [103]. One mother worried that “the government has [her] baby's DNA” [101]. Others support such research as a valuable public health resource [29].

The potential for genetic-based research on RBS leads directly to the third and most important lesson of NBS in the genomic era – the assumption that the public views all specimen-based research through one lens is naive. Biobanks and large-scale genetic studies should be frank and honest with donors about the potential use of their specimens for genetic research and any collaboration with government-sponsored programs. They should also have rigorous privacy protections in place to reassure the public that data from research studies will not be released to a third party or used in a discriminatory manner.

Lesson 4: people prefer to be asked ‘permission’ for use of their children's biomedical specimens

It is very likely that states did not perceive research with DNA to be any different than previous research – only research that focused on a different chemical entity within the RBS. Meanwhile, the achievements of the Human Genome Project only made RBS a more valuable scientific commodity. For most states, DNA-based research – especially on de-identified samples – was likely seen as an incremental expansion of existing policies, rather

than entry into another research and public policy domain. That view is clearly wrong. Parents want to be informed about the potential for their children's RBS to be used for research; they want to be allowed to consent or refuse [46,47]. In a nationally representative survey of parents, parents expressed a wish to be asked permission before use of their child's RBS for research, regardless of whether it was used for genetic research or not [46].

The plaintiff in the Texas lawsuit stated that “if they'd asked me if I would consent for this blood to be used for specific medical research. I would have probably said yes” [45]. A survey of a nationally representative sample suggests that the not asking permission to use the RBS for research may be a more significant barrier to participation than the use of RBS for DNA-based research [46]. Specifically, the study found that if permission was asked, more than three-quarters of respondents were willing to allow DNA-based research. However, in situations where permission was not sought, over half were very unwilling to have their specimens used.

Since the technology of genetic testing is changing rapidly, it is difficult to know what sort of testing will be done in the future. As a result, it is not clear what it would mean, exactly, for parents to give permission for future research. Lengthy documents written in dense ‘legalese’ and detailing every possible future study will likely not empower parents. Instead, the best approach might be one that allows parents to ‘opt in’ or ‘opt out’ within a charitable trust model, as the BioTrust does [35]. The consent is not a lengthy document, it is a brochure that provides important frequently asked questions about NBS. Parents then sign on the NBS card granting permission for their newborn's RBS to be used in potential future research through the BioTrust [104]. In addition, since the decision is initially made on behalf of the child, once the child turns 18 years old he/she can request that their specimen be removed from the BioTrust. Research suggests that the public is in support of such a consent model [48].

Whether in an opt-out or opt-in process, parents should be asked for their consent (or dissent) for storing their newborn's blood specimens for potential use in research studies. Given the volume of specimens and the constraints on state budgets, we recommend that RBS only be used for internal NBS program quality improvement and control activities unless parental permission has been obtained. Biobanks outside of NBS should still consider obtaining consent for storage and use of biological samples for research – even if not required by the Common Rule, as in the case of de-identified samples. BioVu, the biobank at Vanderbilt University (TN, USA), provides a useful example of a biobank of de-identified samples that has obtained permission from and attempted to educate potential donors about their biobank [49].

Future perspective

A few lessons for biobanks and other large-scale genetic studies can be gleaned from NBS programs' experience with RBS storage and use. First, to avoid ‘therapeutic misconception’, testing for research purposes must be clearly distinguished from testing for clinical purposes.

Second, biobanks need to establish clear guidelines as to who owns the specimens and should consider the use of a charitable trust model for this. Third, programs must respect and address the strong feelings that some portion of the public has about the use of their specimens for genetic research. Finally, consent or permission for research should be simple, transparent and give donors the right to opt-in or opt-out, regardless of the research regulatory requirements. We believe the implementation of these lessons will help biobanks and large-scale genetic studies function more efficiently, effectively and harmoniously with participants and with the public.

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Executive summary

Newborn screening & residual blood spot storage & use

- The mission of newborn screening (NBS) programs is not to create large-scale genetic biobanks, but to screen asymptomatic newborns for diseases that, undiagnosed and untreated, would cause disability or death.
- NBS programs' storage of residual blood spot specimens and the potential to use specimens for research have sparked controversies and challenges that may provide useful lessons for biobanks and large-scale genetic testing endeavors.

Lesson 1: clearly distinguish between clinical & research endeavors

- Failure of biobanks to effectively distinguish between clinical and research activities can confuse participants and lead to decreased participation.

Lesson 2: establish & codify ownership in a transparent manner

- Biobanks must clearly establish ownership of specimens with donors. A charitable trust model provides an opportunity to do so in a manner that safeguards privacy, oversees regulatory issues and fosters public trust.

Lesson 3: people view DNA-based research as 'different' from other types of research – especially if the government is involved

- DNA-based research is a sensitive public policy topic that must be acknowledged and respected. Government involvement in DNA-based research can provoke fear and distrust.

Lesson 4: people prefer to be asked 'permission' for use of their children's biomedical specimens

- Biobanks should consider obtaining consent or permission from donors for storage and use of de-identified samples even if the Common Rule does not require it.

Future implications

- Beyond the requirements of regulatory guidelines, biobanks should respect the strong feelings that the public has about the use of their biological specimens for genetics research.