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# Screening of Newborns for Disorders with High Benefit-Risk Ratios Should Be Mandatory

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## Introduction

Newborn screening was initiated due to its potential to prevent severe disabilities; it has the ability to save lives through early diagnosis and treatment.<sup>1</sup> Today, over 98% of the 4 million newborns born annually in the United States are tested for more than 30 treatable genetic, metabolic, endocrine, and infectious diseases within the first week of life.<sup>2</sup> The emergence of new technologies and the ability to screen for increasing numbers of disorders have led to a broad expansion of disorders on newborn screening panels. While many disorders on expanded panels adhere to traditional screening guidelines, which recommend screening for disorders that are serious or life-threatening, treatable, and have well-understood stages of disease (Table 1), others do not. Inclusion of “non-traditional” disorders has raised the important question about the role of parental consent in newborn screening.

Many states retain the leftover newborn screening cards, also known as residual dried blood spots (DBS), to use for various purposes such as quality assurance and research, often without the knowledge of parents. This practice, which has been criticized to be a violation of genetic privacy law,<sup>3</sup> has been challenged in two state courts by parents whose primary concern was the “...unclear and undisclosed state policies regulating storage and use of their infant’s leftover newborn screening sample...”<sup>4</sup> The result of these litigations has been impactful, such that the Newborn Screening Saves Lives Act 2014 was signed into law, and revisions to the Federal Policy for the Protection of Human Subjects (the Common Rule, 1991) have been proposed, further driving the conversation towards improving newborn screening and DBS policies related to transparency. Thus, it is imperative to continue the discussion about the role of parental consent in newborn screening.

This paper summarizes Dr. Wasserstein’s presentation as part of a point-counterpoint discussion at the Thomas Pitts Memorial Lectureship in Medical Ethics in October 2013, which focused on Ethical and

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Table 1

**Wilson and Jungner Classic Screening Criteria<sup>6,3</sup>**

1. The condition should be an important health problem.
2. An accepted treatment with a recognized disease exists.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the populations.
7. The natural history of the condition (at all stages) should be adequately understood.
8. There should be an agreed policy on whom to treat.
9. The cost of case-finding (including diagnosis and treatment) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be an on-going process and not a "once and for all" project.

Legal Issues in Pediatrics. Our assigned position, that screening of newborns for disorders with high benefit-risk ratios should be mandatory, opposed Dr. Norman Foster's position that parental consent should always be required for newborn screening.

This position paper will review the role of parental informed consent in newborn screening and residual DBS retention, bringing in our own pragmatic, real-life experience directing a large newborn screening referral program, (MW) and as researchers in a pilot newborn screening program that requires parental informed consent (NK, DCM, MW). We present an overview of newborn screening and its expansion, followed by a review of some of the ethical concerns related to newborn screening and residual DBS retention. We then lay out the arguments for and against requiring parental consent including a review of practical experiences using different consent models in pilot studies. We conclude with a discussion and recommendation of what we believe to be an appropriate role of informed consent in this rapidly evolving era of newborn screening.

## Newborn Screening

### History

Newborn screening is an integral public health program that tests infants shortly after birth for conditions that can cause disability or death if left undetected and untreated.<sup>5</sup> These state-run services facilitate early

detection, diagnosis, and treatment of rare disorders, thereby reducing mortality and morbidity.

Newborn screening began in the 1960s with a single disorder, phenylketonuria (PKU). With early diagnosis and pre-symptomatic treatment, a child with classic PKU can effectively be prevented from developing profound mental retardation. Classic PKU is a model of "traditional" newborn screening disorders. These traditional disorders generally conform with the Wilson and Jungner criteria,<sup>6</sup> which provide guidelines to decide if a disease is an appropriate candidate for population-wide screening (Table 1).<sup>7</sup> For the first four decades of newborn screening, most widely screened disorders, such as congenital hypothyroidism, maple syrup urine disease, and biotinidase deficiency shared similar characteristics with PKU in terms of being serious or life-threatening in infants, and having effective, generally low risk treatments that are most beneficial when initiated pre-symptomatically; they are examples of high benefit-risk ratio disorders.<sup>8</sup>

### Expansion of Newborn Screening

Expansion of screening panels was limited by technology until the introduction of tandem mass spectrometry (MS/MS) in the 1990s, which permitted detection of many diseases using the same DBS sample with minimal extra effort or cost.<sup>9</sup> While the ultimate goal of expansion was to benefit greater numbers of infants through early diagnosis of additional treatable diseases, expansion was accompanied by significant challenges and controversies stemming mainly from the key question: which disorders are appropriate for newborn screening, and which are not.

Today, the Advisory Committee on Heritable Disorders in Newborns and Children and the Secretary of the US Department of Health and Human Services work together to establish national guidelines for screening known as the Recommended Uniform Screening Panel, or RUSP, and as of February 2016 they recommend that states screen for 33 core and 26 secondary conditions.<sup>10</sup> It is important to note that each state develops its own newborn screening program and holds the right to choose which diseases to include on their newborn screening panels, how to best inform and educate parents about the diseases on their panel, and how to provide their policies on how residual DBS are used and stored.

The development and evolution of newborn screening technologies, coupled with tremendous stakeholder support for the program, has contributed to the breadth of disorders now seen on expanded newborn screening panels. Most panels now include diseases ranging from more traditional disorders that have a high benefit from

early detection, such as PKU, to those that have unclear benefits either because they may not be particularly harmful (e.g., short chain acyl-CoA dehydrogenase deficiency) or because there might not be an available treatment (e.g., Type A Niemann-Pick); to those for which screening might be beneficial, but the treatment itself carries a significant risk (e.g., early infantile Krabbe disease treated with bone marrow transplantation) (Table 2). In addition, some states include disorders that may manifest later in life rather than in the newborn period (e.g., some lysosomal storage diseases). These represent unique and unprecedented challenges associated with expanded newborn screening.

*Parental Consent Models Currently in Use*

A comprehensive review of newborn screening laws within the United States found that all programs have statutes that mandate or allow for newborn screening, but consent requirements vary by state. Over 45 programs allow for parents to opt-out of routine screening if it conflicts with their religious beliefs and/or other reasons, while five programs do not allow for refusals on any grounds.<sup>11</sup>

Potter et al. evaluated different consent models of newborn screening and worldwide found that four simplified models cover most existing practices:<sup>12</sup>

1. *Mandatory model:* Parents have no authority and are not part of the decision-making process.
2. *Opt out model:* Parents have the authority to refuse the screening but no decision-making is actually required for newborn screening to be done (e.g., Netherlands, most Canadian provinces, and the majority of US states).
3. *Informed compliance model:* Parents have the authority to decide to have their baby screened by giving written or verbal consent

(e.g., France). The high acceptance rate from this model suggests newborn screening may be presented in a way that makes it seem like it's not actually a choice.<sup>13</sup>

4. *Informed choice model:* Parents have decision-making authority and are required to give consent. This model includes the expectations that parents will be fully informed about newborn screening (e.g., the United Kingdom).

*Dried Blood Spot Collection and Residual Retention*

Within 24-72 hours of birth, virtually every baby has a heel stick performed, which begins the newborn screening process. This heel stick is taken by a health care professional and blood is spotted onto a piece of filter-paper card and dried before being sent to the state newborn screening laboratory for testing. After the DBS card is used to screen for the panel of diseases, most states store the residual sample from one month to indefinitely, depending on state policies.<sup>14</sup> The main uses of these residual blood spots are for internal laboratory operations such as quality control and improvement, and development of advanced methodologies.<sup>15</sup> They can also be used for research studies including but not limited to the development of new tests to screen for more disorders, public health studies to better understand conditions in the general population, to investigate the effects of environmental exposures, and basic scientific studies to better understand the causes of birth defects, cancer, or chronic disease.<sup>16</sup> Other uses can include testing to assist in identifying a missing or deceased child and testing to provide additional medical information, at the family's request.<sup>17</sup> Regulations regarding DBS are inconsistent across states, no different from newborn screening practices.

A review of state laws by Lewis et al. from 2008-2009 found that 20 states addressed retention and/or

Table 2  
Spectrum of Disorders on Expanded NBS Panels

Risk Ratio	Characteristics	Examples
<b>High benefit-risk ratio</b>	<ul style="list-style-type: none"> <li>• Serious, life-threatening disorders</li> <li>• Early diagnosis and treatment is essential</li> <li>• Established, relatively low risk treatment</li> <li>• Significant mortality or morbidity if not diagnosed as easily as possible</li> </ul>	<ul style="list-style-type: none"> <li>• Phenylketonuria</li> <li>• Congenital Hypothyroidism</li> <li>• Classic galactosemia</li> <li>• Biotinidase deficiency</li> </ul>
<b>Unknown benefit-risk ratio</b>	<ul style="list-style-type: none"> <li>• May or may not be life-threatening</li> <li>• May have later-onset presentation</li> <li>• May not have established therapy</li> </ul>	<ul style="list-style-type: none"> <li>• Short chain acyl CoA dehydrogenase deficiency</li> <li>• Carnitine palmitoyl transferase II deficiency</li> <li>• 3-Methylcrotonyl CoA carboxylase deficiency</li> </ul>
<b>High benefit/high risk</b>	<ul style="list-style-type: none"> <li>• Serious, life-threatening disorders</li> <li>• High risk treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Krabbe disease</li> <li>• X-linked adrenoleukodystrophy</li> </ul>

use of residual DBS and 13 states addressed only the use of information related to DBS, while the other 17 states and the District of Columbia had no such laws.<sup>18</sup> While most states de-identify samples for quality assurance and research use, few states require parental consent to use DBS for research, and in four states the DBS become state property.<sup>19</sup> Several states require approval from an Institutional Review Board for non-

### Ethical Concerns

#### *Benefits of Newborn Screening and DBS Retention*

Newborn screening, arguably one of the most successful public health programs, has saved lives and prevented severe disabilities through early diagnosis and pre-symptomatic treatment. Tens of thousands of infants have been diagnosed with PKU and other potentially disabling or fatal diseases through

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quality assurance research on DBS and some states allow parents to request that their infants' residual DBS are destroyed and not used for research, which assumes that parents are educated and informed about newborn screening and the use of DBS.

In 2011, the Department of Health and Human Services announced a proposal to review and enhance the Common Rule, which has been in place since 1991.<sup>20</sup> This landmark regulation ensures ethical practices and protects the safety of individuals who participate in research.<sup>21</sup> Under the original rule, the use of de-identified residual DBS from newborn screening was ethical without consent as the specimens were assumed to be medical waste rather than human subject research. However, since DNA is a personal identifier and can be sequenced from all blood samples, true de-identification is nearly impossible, so research conducted on these samples may be considered human subject research requiring informed consent under the proposed revisions to the Common Rule. In fact, under the recently revised Newborn Screening Saves Lives Reauthorization Act of 2014, federally funded DBS research is considered human subject research that requires parental consent.<sup>22</sup> Newborn screening programs are now tasked with implementing informed consent strategies for use and storage of their states' DBS if they are being used for federally funded research.

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In addition to the obvious and undeniable health benefits, newborn screening has other significant benefits, such as preventing the diagnostic odyssey. The vast majority of newborn screening disorders are extremely rare and would likely go undiagnosed for months or years, losing valuable time for treatment while creating anxiety and expense. Pre-symptomatic diagnosis through newborn screening can prevent this anxiety as well as the costs associated with seeking a diagnosis for unexplained symptoms.<sup>23</sup> In addition, early diagnosis through newborn screening permits parents to use this information as a reproductive and family planning decision-making tool, if they choose to do so.<sup>24</sup> While these are not traditional goals of newborn screening, the benefits are nonetheless significant.

According to Blout et al., newborn screening produces overall benefits to society, permitting knowledge about a particular disorder such as incidence, natural history, phenotypic spectrum, and optimal treatment algorithms, thereby allowing more individuals who are affected with these disorders to benefit from this information.<sup>25</sup> For example, screening for

elevated phenylalanine, originally intended to detect classic PKU, identified variant forms of this disorder, enabling us to better understand this disease and optimize treatment. Long-term follow-up studies of children identified with this disorder through newborn screening defined the risks associated with poor adherence to the restricted diet and enabled the development of therapeutic guidelines. Given the rarity of these disorders, one can argue that organized natural history studies and clinical trials are nearly impossible; therefore, newborn screening is an essential component to learning the unknown factors associated with these disorders.

DBS retention and use for quality assurance provides significant benefit by improving the precision and accuracy of testing thus decreasing false-positive and false-negative results, which in turn reduces overall anxiety for parents and allows newborn screening programs to run at their highest possible standards.<sup>26</sup> Moreover, the use of DBS is essential to the continual advancement of early diagnosis and treatment of disease, leading to improved population health outcomes. DBS have also been shown to be very useful outside the scope of newborn screening. As briefly mentioned above, DBS can be helpful in identifying certain environmental exposures experienced by mothers such as exposures to pesticides, harmful drugs, perfluorinated compounds and infectious organisms among others, and have proven useful for forensic purposes in cases where parents would like to get more information after the unexplained death of a child.<sup>27</sup> Thus, in addition to being an invaluable quality assurance tool, DBS use presents a wide range of research opportunities that promotes continued public health development and success.

#### *Risks of Newborn Screening and DBS Retention*

One risk of newborn screening is false-positive results. Botkin et al. state that tandem MS/MS is estimated to generate nine false-positive results for every true-positive, as cutoff thresholds are generally set low to avoid missing affected infants.<sup>28</sup> They argue that these false-positive results not only lead to unnecessary costs and parental anxiety, but can also cause long-term concerns and distress over the health of unaffected children, and in some cases could lead to unnecessary treatments that might be harmful for the child.<sup>29</sup>

The risks caused by over-diagnosis and over-treatment has been brought up in the context of PKU screening where, in the initial years of screening, some children were identified with milder forms of the disorder and were started on restrictive diets, an intervention that was later recognized as being unnecessary and potentially dangerous.<sup>30</sup> Norman Fost claims that these errors in PKU testing caused

brain damage and even death in some infants;<sup>31</sup> however, a subsequent study conducted found that there was insufficient evidence of such harm.<sup>32</sup> Importantly, modern rapid turnaround time for lab results, significant advances in the field of metabolic nutrition, and improved understanding about human metabolism together reduce the risk of potential harm from erroneous over-treatment for diseases like PKU. Despite this progress, there will continue to be risk involved in screening for new diseases where the phenotypic spectrum is not fully understood prior to the onset of screening.

There are also potential risks associated with screening for mild or “later onset” diseases that may not manifest for years after screening, such as some of the lysosomal storage disorders. By including disorders that may not present until adulthood, newborn screening provides medical information that may not be relevant as a pediatric disease, and might be considered to be a significant and anxiety-provoking “burden of knowledge” to some families. This risk is related to the ambiguity of being a “patient in waiting”, i.e., patients that have test values outside the normal range but do not meet the criteria for a clear-cut disease. Parents of such patients might either become overprotective and overstressed or underestimate the seriousness of their child’s condition, which would make it hard to monitor the patient.<sup>33</sup> Screening for these disorders may also have implications for the newborn screening system as a whole, from money and time being directed towards babies who may not develop disease for decades after diagnosis, to the diagnosing physician who may lose patients to follow-up because they lack clear signs and symptoms of the disease.

As screening technologies and genetic testing continue to advance, there are ever-increasing risks associated with insufficient understanding of a disorder, which is relevant to many disorders on the expanded panel. This is exemplified by the detection of infants at high risk for later-onset forms of Krabbe disease in New York, which has been screening for this disorder since 2006. This later-onset phenotype, initially believed to constitute only 10-15% of all Krabbe cases, may be even more common than early-onset phenotype based on the numbers of New York infants found to be at risk.<sup>34</sup> This will require years or even decades of follow-up to determine how many, if any, of these children will express the phenotype. Prior to the initiation of newborn screening for Krabbe disease, physicians had limited information about how to predict disease onset, rate of progression, and the optimal treatment for this later-onset phenotype.<sup>35</sup> This lack of knowledge about the disease can result in the inability

to provide an accurate prognosis, which can be frightening to families with a high-risk child.

The detection of genetic diseases, as well as the retention and use of personal genomic information in the form of DBS, have been stated to cause worry or anxiety over the possibility of discrimination and eugenics.<sup>36</sup> A report showed that over 19 million people had their medical information breached since 2009.<sup>37</sup> Fear of discrimination and lack of confidentiality is especially a concern when one considers the inconsistent regulations of DBS storage and use. Laws regarding use of the residual blood samples are uneven and their potential use without parental consent is significant.<sup>38</sup> In fact, the Departments of Health in Minnesota and Texas were sued by families who alleged that the retention and use of the samples without parental knowledge or consent was an illegal search and seizure.<sup>39</sup> The Texas lawsuit led to the destruction of 5.3 million blood samples that were collected and stored without the consent of parents; and even though the Minnesota case was initially dismissed in district court, the Minnesota Supreme Court ruled in 2011 that "...the use of the blood spots and/or test results for anything other than the initial screening was not explicitly authorized in statute."<sup>40</sup> This ruling resulted in 1.1 million DBS samples and test results to be destroyed, and prompted the Minnesota Legislature to change its statutory language regarding the short-term storage and use of DBS and test results, as well as requiring the use of a written informed consent for long-term storage and use.<sup>41</sup> These lawsuits underscore the public's concerns about genetic privacy, and also suggest that a lack of communication and education about the use of DBS may have contributed to a sense of public mistrust.

*Blurred Lines: Clinical Care versus Clinical Research*  
Distinguishing clinical care from clinical research can be challenging, and is a relevant discussion point in the context of ethical concerns in newborn screening. The goals of both are grounded in similar philosophies: to provide the best care for patients while ensuring their safety and protection from undue harm.

The primary goal of screening for a particular disorder is to improve clinical care. However, mandatory newborn screening may be initiated for rare disorders before critical items are understood, such as natural history and optimal treatment. In other words, "going live" with newborn screening for a particular disorder effectively teaches us about the disease as infants are diagnosed, treated, and followed. Thus, one can reasonably argue that the goals of newborn screening are not only to provide clinical care by diagnosing and treating children, but also to learn from the experi-

ence, therefore creating a better system. This gathering of knowledge, while not the primary purpose of newborn screening, is arguably a form of clinical research, and is another reason to continue the discussion about informed consent.

### **The Pros, Cons, and Practicality of Parental Informed Consent in Newborn Screening**

One argument for requiring parental consent is that by mandating newborn screening, we are undermining the autonomy of parents and their right to make decisions regarding their children.<sup>42</sup> Parents are considered to have the absolute right to make decisions regarding their children's health if there is no evidence of neglect or abuse.<sup>43</sup> These choices are reflected through informed consent, which is an essential legal right in the health care system. When it comes to health care decisions, it has been acceptable to override this right when it is assumed that the patient would have consented if they had a better understanding.<sup>44</sup> Fost claims that this argument should not be used for genetic diseases since they entail more than minimal risk and they represent value choices and reflect parents' beliefs.<sup>45</sup> Although informed consent gives parents their right to autonomy and privacy, Blout et al. argue that the principle of beneficence gives states the right to impose on parental autonomy if there is evidence that the broader public benefit of newborn screening outweighs individual rights.<sup>46</sup> Given the undeniable benefits of newborn screening for high benefit-ratio conditions as described above, we agree with Blout's position that the principle of beneficence overrides parental individual rights in the screening for these life-threatening but treatable conditions.

In addition, there are concerns relating to whether informed consent and parental education is truly possible in the context of newborn screening. An ideal informed consent for newborn screening would contain, at minimum, educational materials explaining the screening process, the specific diseases on the panel, newborn screening policies as well as information about the use and retention of residual samples. It would also include a means to ensure that parents comprehend the information before making a decision, and a clear method to communicate the decision to the testing laboratory.<sup>47</sup> According to Howell, requiring consent is not a simple issue since it obligates a clear explanation of the tests that are being performed as well as the consequences of refusing the screening.<sup>48</sup>

Practical issues also require consideration. There are countless demands competing for the parents' attention, such as learning basic baby care and how to breast feed, decision-making about circumcision and cord blood banking, filling out birth certificate

forms, etc. — an undeniably hectic time. The reality is that education and informed consent about newborn screening is one of the lowest priorities for overwhelmed new parents. Other obstacles include language and educational barriers, and personnel expenses. Thus, ensuring that appropriate education is provided and that parents are making truly informed decisions is at best a challenge, and at worst a near impossible task.

### Exploring Different Informed Consent Models in Pilot Newborn Screening Studies

Pilot newborn screening programs are research studies designed to examine the suitability of a disorder for inclusion on a mandated panel. Since the informed consent process in research studies is usually formal and standardized, pilot studies are appropriate models to evaluate how informed consent might work in newborn screening, and which model might be most useful. Experience can be gained from the pilot MS/MS study in California (CA), which used a full informed consent model.<sup>49</sup> Although 90% of parents consented to participate, only about half of families were approached because the majority of hospitals who participated (79%) only offered screening to a fraction of their parents, and 21% of hospitals chose not to participate at all.<sup>50</sup> The most stated reason for not offering the MS/MS screening to parents was because the increased “burden on hospital staff.” Another barrier for this model included delays in implementation as some hospitals chose to conduct their own ethics review which took time and decreased the enrollment time of this already short 18-month study.<sup>51</sup>

Massachusetts (MA) currently uses an informed compliance method for its severe combined immunodeficiency and MET pilot studies. Hospital staff discusses the study with parents, and asks them whether they would like to participate. They report a remarkable consent rate of >99%,<sup>52</sup> which reflects an extraordinary model of communication and/or one that has been able to remove the main barriers other pilot studies face that use different, possibly more extensive, informed consent models.

In New York, we are conducting a pilot newborn screening for lysosomal storage disorders in conjunction with the New York State Newborn Screening Program. In our study, the informed consent process is done on the maternity ward right after the new baby arrives. Our consenting model, similar to that recommended by the Bioethics and Legal Work Group of the Newborn Screening Translational Research Network,<sup>53</sup> is a waiver of written consent with documentation of verbal assent to participate. We have multiple educational materials including multilingual

brochures, a website, streaming videos, and posters. An on-site coordinator discusses the study in person with each family, answers questions, provides written materials and contact information, and asks the parents if they are interested in participating. This method yields a daily uptake rate of >80%, but it is a very labor intense and expensive way to inform parents.

Analyzing the efficiency, cost, and enactability of the different models of consent and their differing consent rates will permit us to evaluate the role of, and barriers to, informed consent and education in newborn screening, with the ultimate goal of refining and optimizing the process.

### Our Proposal: Screening for High Benefit-Risk Ratio Disorders Should Always Be Mandatory

#### *Undeniable Benefit*

High benefit-risk ratio disorders are serious life-threatening conditions where early diagnosis and treatment is essential to prevent significant mortality and morbidity, and that have a relatively safe treatment that can be monitored and individualized for each patient. Based on our experience caring for infants diagnosed with rare metabolic disorders through newborn screening, we listed examples of high benefit-risk ratio disorders in Table 2. Mandatory newborn screening for high benefit-risk ratio disorders has prevented disability and death by identifying asymptomatic infants and starting them on treatment. For children with disorders like PKU, hypothyroidism, MCAD and biotinidase deficiency, the health benefits of early detection are so profound that it would be unethical to deny newborns from being screened for these conditions.<sup>54</sup>

#### *Potential Dangers of Parental Refusal*

Parents' refusal to screen their babies for these disorders may lead to their death or disability. Although reports from the CA pilot study suggest that few parents would refuse screening for these disorders,<sup>55</sup> and that informed consent could still lead to a high consent rate,<sup>56</sup> it is vital to consider that over time, infants will be missed because of parental refusal of screening (Table 3). These assumptions are based on the uptake rates ranging from 80-99% in pilot programs and the reported incidence of each condition. In our opinion, parental refusal to have their infant screened for a serious, treatable, low risk disorder that is on a newborn screening panel, whether it is due to lack of understanding, mistrust, lack of information, or other reasons may result in significant harm, serious disability, or death. These are wholly unacceptable outcomes; thus, it is essential that screening for high benefit-risk ratio conditions continue to be mandated.

*The Role of Informed Consent in Newborn Screening*  
 The discussion of the role of informed consent in newborn screening belongs not with high benefit risk-ratio conditions, which should always be mandatory, but should be limited to those disorders with uncertain benefit-risk ratios and those with high benefit-high risk ratios (Table 2). In most states, if parents want to refuse newborn screening they can only refuse all conditions listed on the screening panel, and do not have the option to run certain tests while refusing others.<sup>57</sup> The MA model uses a two-tiered system that includes a mandated panel plus an informed compliance model for pilot studies. The President’s Commission report

considered for newborn screening, it is essential that a formal evaluation is undertaken first to define current impediments and develop novel ways to work around them in order to make the process user-friendly, relevant, and implementable.

*Fostering Trust through Education*

Despite there being educational components built in to all newborn screening programs, there still seems to be a significant lack of public awareness about newborn screening and residual DBS retention.<sup>59</sup> It is understandable why some parents might feel a sense of mistrust about the newborn screening and

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DBS retention process if they feel as though it was being done without their knowledge. A study done by Botkin et al. showed that most parents, when informed about newborn screening, favor the use of blood spots for research,<sup>60</sup> highlighting how better education and communication is critical. Educating parents is a challenging process that includes identifying the appropriate timing and location for this discussion. Clearly, current

on newborn screening advocates for such two-tiered models where screening is mandatory for some conditions with high benefit-risk ratios while permission is required for disorders with uncertain benefit-risk ratios.<sup>58</sup>

While mandatory screening for high benefit-risk ratio conditions should always be performed, giving parents an option to decide if they want their child to be screened for diseases that have unclear benefit-risk ratios and those that are high benefit-high risk is reasonable. This would give parents the right to refuse screening for diseases they believe are unnecessary or harmful to know about. Giving parents an option to decide about the storage and use of the DBS for research purposes is also reasonable. However, we feel strongly that if any type of informed consent is to be

methods of newborn screening education are not as effective as they could be; therefore, a comprehensive evaluation of the most effective and practical methods to deliver this information are needed. Qualitative research methodologies such as focus groups can be used in order to identify the best methods of communication with parents and to provide recommendations to providers.<sup>61</sup> Moreover, we need to assess how much information should be given to parents to make sure they have enough understanding to make an informed decision. According to studies by Davis et al., parents want concise information about newborn screening and its benefits, when to expect results, possible need for retesting and the meaning of a positive result.<sup>62</sup>

Table 3

**Potential Number of Infants Missed Due to Parental Refusal If Informed Consent Were to Be Required over a 5-Year Period, Based on Pilot Newborn Screen Consent Rates of 80 to 99%**

	<b>Missed PKU</b>	<b>Missed CH</b>	<b>Missed Galactosemia</b>
If 1% refuse	20	50	4
If 20% refuse	400	1000	67

Based on annual US birth rate of ~4 million, PKU incidence of 1 in 10,000, congenital hypothyroidism incidence of 1 in 4,000, and classic galactosemia incidence of 1 in 60,000

It is important to evaluate different communication strategies, focusing on who should discuss this information and when it is best absorbed, how much information to give, and how to provide this educational information to parents. The effectiveness of different options can then be tested.

## Conclusion

Newborn screening has played a groundbreaking role in the diagnosis and treatment of rare disorders. The modern era of rapidly evolving screening and genomic technology has revitalized the discussion about whether newborn screening, and DBS retention should be mandatory or subject to parental choice. The role of parental choice was recently addressed in the Newborn Screening Saves Lives Reauthorization Act of 2014, which now mandates parental informed consent for federally funded DBS research. However, the mandatory vs. elective nature of newborn screening itself continues to be the subject of discussion.

We opine that screening for disorders with high benefit-risk ratios reduces morbidity and mortality and is an essential part of infant health care and should continue to be mandatory. The immediate and life-saving benefit of screening for these diseases is undeniable. The life-threatening risks of missing affected infants because of parental refusals are too great.

We also feel that if informed consent is to be discussed in the context of newborn screening, the discussion belongs more appropriately with diseases with uncertain benefit risk ratios or that have higher treatment risks. Ideally, initial screening for these types of disorders should occur through a research pilot program in order to carefully collect data to provide evidence about whether the disorders should or should not be part of mandated panels.

Regardless, it is clear that that parental education and open communication play a vital role in the continued success of newborn screening programs. Evaluating how to optimize these interactions is crucial, and should be a prime focus of future newborn screening research.

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