The Blurred Distinction between Treatable and Untreatable Conditions in Newborn Screening

Donald B. Bailey Jr.
THE BLURRED DISTINCTION BETWEEN TREATABLE AND UNTREATABLE CONDITIONS IN NEWBORN SCREENING

Donald B. Bailey, Jr.†

ABSTRACT

Newborn screening is increasingly possible for conditions that do not have medical treatments that must be provided early in order to be effective. This raises a fundamental question of what information should be disclosed to parents. Historically the potential for treatment has been essential before conditions are included in newborn screening. Here I argue that the distinction between treatable and untreatable conditions is not a clear one and may be less useful in the future. I give examples of treatments that could be used even with “untreatable” conditions, envision a possible future of newborn screening, and suggest research and policy questions that need to be answered quickly so that screening can expand in a rational fashion.

THE BLURRED DISTINCTION BETWEEN TREATABLE AND UNTREATABLE CONDITIONS IN NEWBORN SCREENING

Newborn screening was established in the 1970s in the United States when a screening test and an effective treatment became available for phenylketonuria (PKU). By altering an infant’s diet, the intellectual disability and other developmental problems associated with PKU could be prevented. Since the effects of PKU were irreversible, the treatment had to be provided early in life in order to be effective. This fundamental expectation – that screening should be justified by the need for a known medical treatment that had to be provided early

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in life to be effective – has served as the foundation for what is now a well-established newborn screening program in every state, the goal of which is to identify, shortly after birth, children with conditions in need of immediate treatment.

However, as technology advances and large-scale genetic testing becomes cheaper, new methodologies for detecting conditions will increasingly be capable of simultaneously identifying a large number of conditions, disease states, or risk states that may not have medical treatments currently available. This phenomenon is already a reality in the case of tandem mass spectrometry, a methodology now widely used by newborn screening programs to identify multiple conditions at the same time, and will only grow as technology moves toward microarray or whole-genome analyses. Inevitably this will pose a dilemma regarding the disclosure of results, as articulated by Botkin et al.:

If programs choose only to disclose results on conditions that clearly meet established criteria, then results on the other conditions, and the potential benefits flowing from those results, will be withheld from families and care providers. On the other hand, offering results on a large number of conditions for which there is limited or no evidence of benefit to affected children may cause harm to some children and families and is likely to be a poor use of scarce resources.

In this article, I continue our examination of changing perspectives on the definition of treatment, concepts of benefit, and the standards of evidence needed before a condition is included in newborn screening programs. I suggest that differentiating between treatable

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5 Don Bailey, Newborn Screening for Intellectual Disability: Past, Present, and Future, in 36 INTERNATIONAL REVIEW OF RESEARCH IN MENTAL RETARDATION 1 (Laraine Masters Glidden ed., 2008); Donald B. Bailey, Jr., Newborn Screening for Fragile X Syndrome, 10 MENTAL RETARDATION & DEVELOPMENTAL DISABILITIES RES. REVIEWS 3 (2004); Donald B. Bailey, Jr. et al., Supporting Family Adaptation to Presymptomatic and “Untreatable” Conditions in an Era of Expanded Newborn Screening, 33 J. PEDIATRIC PSYCHOL. 1 (2008); Donald B. Bailey, Jr. et al., Changing Perspectives on the Benefits of Newborn Screening, 12 MENTAL RETARDATION & DEVELOPMENTAL DISABILITIES RES. REVIEWS 270 (2006); Donald B. Bailey et al.,
and untreatable conditions is a dichotomy that will become less useful and less clear in the next generation of newborn screening and genetic testing more broadly. I give examples of four “treatments” that could be used even with “untreatable” conditions. The paper concludes with a set of questions that need to be answered to help inform debates about treatability and benefit.

I. CURRENT CONCEPTS OF TREATMENT AND BENEFIT

Most states currently screen for at least a core set of 29 conditions recommended by a 2006 report developed under the auspice of the American College of Medical Genetics (ACMG). The ACMG report resulted from an extensive deliberation by experts to create a system for scoring diseases or conditions with regard to suitability for newborn screening. Following a rating of more than 80 conditions by experts, ACMG recommended that all states screen for the core conditions and report out 25 additional conditions that would necessarily be identified when testing for the core conditions, even though treatments are not available for all. The report has been enormously influential, as evidenced by the rapid increase in the number of conditions screened since the report was released. The current status of newborn screening in each state is available at http://genes-r-us.uthscsa.edu/nbsdisorders.pdf.

Treatment and benefit figured prominently into the scoring system. Of the possible total of 2100 points, 600 could be earned for the potential efficacy of existing treatments (200), benefit of early intervention to individuals (200), benefit of early identification for family and society (100), and the prevention of mortality (100). Another 400 points could be assigned based on treatment availability, cost, simplicity of therapy, and availability of providers to implement the treatments.

Although the 29 core conditions all have treatments that either prevent death or improve health outcomes, there was a continuum of expert opinion regarding treatment efficacy for each, as evidenced in Figure 1. The figure depicts for each condition the percent of the maximum score that would have been received had all experts agreed

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6 Michael S. Watson et al., Newborn Screening: Toward a Uniform Screening Panel and System, 8 GENETICS MED. (SUPP.) 1S (2006).
that the treatment could prevent all negative consequences of the condition. The ratings ranged from 32% - 85%.

Only four conditions (congenital hypothyroidism, biotinidase deficiency, PKU, and medium chain acyl-CoA dehydrogenase or MCAD) were rated as having treatments that prevent all negative consequences. For example, MCAD is an autosomal recessive disorder, inherited when both parents carry the abnormal MCAD gene. Children with MCAD have a missing or faulty enzyme needed to break down fat. This only becomes a problem, however, if children go without food for more than 10-12 hours. A child with MCAD could look perfectly normal for months, but then develop severe symptoms during the course of an illness such as the flu, when the child may not feel like eating. If not treated quickly, the child can have seizures or die. The primary treatment regimen involves careful monitoring of diet and avoiding fasting. L-carnitine is prescribed to prevent low blood sugar when children have other illnesses. If these procedures are followed, children with MCAD are expected to have normal growth and development.7

However, more than half of the recommended panel of core conditions and most of the secondary targets were considered to have treatments that only prevent “some” of the negative consequences of the condition.8 For example, every state requires or offers screening for propionic acidemia, a rare inherited disorder that affects the body’s ability to break down certain proteins, leading to the buildup of harmful substances in blood and urine. Untreated propionic acidemia can lead to severe neurological damage, coma and death. Treatment usually involves a combination of a low-protein diet, medication treatment, and monitoring to make sure that children eat something every 4-6 hours to prevent a metabolic crisis. Although early treatment significantly reduces mortality and improves health outcomes, children with propionic acidemia typically have a range of health problems, sometimes severe, throughout life.9

7 Gabriella A. Horvath et al., Newborn Screening for MCAD Deficiency: Experience of the First Three Years in British Columbia, Canada, 99 CAN.J. PUB. HEALTH 276 (2008).
8 Donald B. Bailey, Jr. et al., Changing Perspectives on the Benefits of Newborn Screening, 12 MENTAL RETARDATION & DEVELOPMENTAL DISABILITIES RES. REVIEWS 270 (2006).
Although the ACMG report has had a major influence on state policy and practice, it has been criticized for both its methodology and some of its recommendations. Some have expressed concern that the report sets a new precedent by recommending screening for some conditions without sufficient research evidence regarding treatment efficacy and by using new criteria (benefit to family and society) that have not previously been considered in making screening decisions.\(^\text{10}\) These are valid points. The report was not a research review per se and for some conditions there simply have not been adequate longitudinal studies with sufficiently large samples to fully understand the long-term consequences of screening and treatment. Since most of the conditions screened are rare, a national program of coordinated research is clearly needed to answer questions about the real benefits of specific treatments and whether other ethical, legal, and social concerns are valid.\(^\text{11}\)

In the meantime, technology is developing at a rapid pace. Advocacy groups continue to push for expanded screening\(^\text{12}\) and private companies are offering supplementary screening options to families who can afford it. What will be the role of treatability and proven treatment efficacy in this rapidly changing context? What would be the advantages and disadvantages of expanding concept of benefit beyond child health? Would such expansion be welcomed by the public and lead to improved outcomes for children and families, or would it overburden an already stretched system and not achieve the hoped-for benefits?

II. EXPANDING THE RANGE OF POTENTIAL BENEFITS FROM NEWBORN SCREENING

Baily and Murray\(^\text{13}\) argue that newborn screening must be evidenced-based to be ethical, a position generally consistent with virtually all analyses of newborn screening. But sometimes this evidence

\(^{10}\text{Jeffery R. Botkin et al., Newborn Screening Technology: Proceed with Caution, 117 PEDIATRICS 1793 (2006); Marvin Natowicz, Newborn Screening - Setting Evidence-Based Policy for Protection, 353 NEW ENG. J. MED. 867 (2005).}\n
\(^{11}\text{Donald B. Bailey et al., Ethical, Legal, and Social Concerns About Expanded Newborn Screening: Fragile X Syndrome as a Prototype for Emerging Issues, 121 PEDIATRICS e693 (2008).}\n
\(^{12}\text{Diane B. Paul, Patient Advocacy in Newborn Screening: Continuities and Discontinuities, 148 AM. J. OF MED. GENETICS PART C (SEMINARS IN MEDICAL GENETICS) 8 (2008).}\n
\(^{13}\text{Mary Ann Baily & Thomas H. Murray, Ethics, Evidence, and Cost in Newborn Screening: Would Resources Spent on Screening be Better Spent Elsewhere?, 38 HASTINGS CENTER REP. 23 (2008).}\n
can take a long time to develop and it may be virtually impossible to meet some standards of evidence (e.g., multiple random assignment studies, placebo or no-treatment conditions for rare conditions that are life-threatening, longitudinal follow-up studies). An example of the dilemmas created by the expectation for evidence-based decision-making is newborn hearing screening. In 2001 the U.S. Preventive Services Task Force reported that there was insufficient evidence of the efficacy of newborn hearing screening. Nonetheless, advocacy groups continued to push for screening and as a result all states now require or offer newborn hearing screening. A recent update of the task force statement still only gave newborn screening a grade of “B” and concluded that “there is moderate certainty that the net benefit of screening all newborn infants for hearing loss is moderate.”

Data from the ACMG report help draw a distinction between treatment and benefit. Treatment refers to the intervention that is provided, whereas benefit refers to the results obtained when the treatment is provided. It could be argued that the primary standard for newborn screening should not be whether a treatment is available, but rather whether benefit accrues as a result of early identification. Newborn screening should not be conducted if no benefit is anticipated. But what is meant by meaningful benefit and what types of benefit would be considered valid?

The US Preventive Services Task Force emphasizes improved health as the benchmark outcome. But medical treatment of a condition is only one of a number of potential benefits of newborn screening. The history of newborn hearing screening and more recent findings show that parents, advocacy groups, and some clinicians often perceive a wider range of benefits than traditionally considered.

15 Id. at 144.
17 Donald B. Bailey, Jr. et al., Changing Perspectives on the Benefits of Newborn Screening, 12 MENTAL RETARDATION & DEVELOPMENTAL DISABILITIES RES. REVIEWS 270 (2006).
Figure 2 provides some examples of an expanded set of goals for newborn screening that could result in a wide range of benefits for children, families, and society. For children, the benefits could extend beyond reducing mortality and improving physical health. Early intervention could help prevent secondary conditions, enhance developmental outcomes, promote positive emotional development and adaptation, and maximize quality of life. For families, the benefits could include access to potentially important health information, the avoidance of the financial and emotional costs of a lengthy quest to find out what is wrong with their child, and empowerment to advocate more effectively for appropriate services for their child. For heritable disorders, newborn screening would provide timely information about reproductive risks for the parents as well as for extended family members who might also be carriers of the condition. From a societal perspective, newborn screening, even for “untreatable conditions,” could help assure that all families have equitable access to timely health information, that public health services minimize costs and maximize benefits, and that the adverse consequences to society of the lack of universally available health care information are avoided.

How these benefits are considered when evaluating the suitability of conditions for screening is an issue yet to be resolved. Whether this shift would be desirable or not is currently debated. At the end of this paper, I suggest some questions that need to be answered in order to inform this discussion.

III. REVISITING TREATMENTS AND TREATMENT OUTCOMES

A recent report from a national newborn screening advisory committee described four components that would be an essential part of any treatment program: coordinated care through a medical home, evidenced-based treatment, ongoing quality assessment and improvement, and research to discover new knowledge about the conditions screened. Providing even these core components is currently


20 Alex R. Kemper et al., *Long-Term Follow-Up After Diagnosis Resulting from Newborn Screening: Statement of the U.S. Secretary of Health and Human Services’ Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children*, 10 GENETICS MED. 259 (2008).
challenging, and efforts are needed to standardize more broadly the principles recommended in this report.

In a recent paper,21 we expand the concept of follow-up by suggesting four treatments that could be provided for "untreatable" conditions: information, support, surveillance, and intervention. Here I suggest outcomes that could be measured as a result of these treatments.

Information. Newborn screening results in a laboratory report providing information about genetic or metabolic abnormalities. But this report is usually only the first step in a family's quest to understand what the condition is and what it means for their child. Often this involves learning a new vocabulary, meeting new professionals, learning about basic biological processes, and understanding both the certainties and uncertainties associated with a diagnosis. For many parents this information will be confusing and overwhelming, and could lead to misunderstanding, anxiety, or despair. To prevent this from happening, families need to have access to accurate and understandable information. This "treatment" could include brochures, web-based resources, and access to knowledgeable and sensitive professionals. Multiple sources of information should be available in multiple languages. The materials should address common questions that parents have and promote hope and optimism. If families have access to accurate and understandable information, the ultimate benefit will be that families are empowered as participants in informed decision-making.

Support. To deal with complicated genetic information and the challenges inherent in raising a child with a condition that may affect health and development, families need to have emotional and functional assistance from a trusted source. Professionals can provide this when they use family-centered practices that respect family beliefs, values and goals, promote parent-professional collaboration, and focus on a positive outlook and quality of life issues. Also important are the informal support networks – friends and neighbors, religious or community organizations, support groups or parent-to-parent programs, and even virtual communities formed on the internet. When families have emotional and functional assistance from a trusted source, the ultimate benefit will be that families feel supported by professionals and a social network, are optimistic about the future,

and are able to cope with both the adversities and uncertainties associated with their child’s condition.

**Surveillance.** An important component of follow-up is surveillance, in which children participate in periodic screenings or assessments. These could include systematic use of standardized screening tools and clinical observations informed by knowledge of the condition and the range of possible secondary complications. Parent observations and reports should be valued and included as part of the ongoing assessment. When children participate in appropriate and periodic screening or assessments, the ultimate benefit will be that parents are reassured that someone is paying attention to their child’s well-being so that services or treatments will start promptly when needed.

**Intervention.** Treatments and services have historically been key to newborn screening follow-up. Here we refer both to medical treatments as well as non-medical treatments, such as early intervention programs, parent training, and specialized services such as occupational therapy or speech-language therapy. These treatments or services should be based on assessed needs and individualized. A team approach should maximize integration of goals and services, fitting treatments into family routines and maximizing children’s participation in family and community. When children and families receive a wide range of individualized treatments and services, the ultimate benefit is that health, development, and quality of life are maximized, and the primary or secondary consequences of conditions are minimized.

**IV. SUMMARY AND FUTURE DIRECTIONS**

What will be the future of newborn screening and what will be the role of concepts such as treatment and benefit? In Figure 4, I suggest one envisioned future of newborn screening, contrasted with current screening programs. Currently, most newborn screening is not voluntary, rather it is a mandated public health program with limited options for non-participation. Parents are generally told about the program during prenatal visits and get written information about screening in the packet of materials they receive in the hospital, but mostly this is for their information only. States screen for anywhere from 25 to 55 conditions based on state policy and medical need. Follow-up typically consists of medical management, either by the child’s primary physician or a regional disease specialist. These programs are typically evaluated with regard to reductions in morbidity and mortality, and cost effectiveness.

In the near future, perhaps the next 3-5 years, we can expect a number of possible changes in screening. There will likely be a selec-
tive expansion of screening as more genes or other biomarkers are
discovered or new treatments are developed. Some of these may be
offered in the context of voluntary programs with informed consent.
As technology continues to develop, the likelihood of "secondary
targets" will grow, which refers to conditions that were not the
original target of a laboratory test but which are necessarily identified
secondary to the primary intent of screening. There will be increasing
pressure to disclose these results but the benefit of doing so will be
unclear. Hopefully we will see collaboration between the medical
management of identified children and other service systems such as
early intervention community programs. I predict that we will see a
gradual yet consistent shift in the evaluation of newborn screening,
with well-being and benefit defined more broadly and the ability to
help families adapt successfully to information from screening being
one criterion for determining the desirability of screening.

In the next decade, I foresee a radical shift in both the possibilities
and complexities of newborn screening. New technologies will make
whole-genome scans increasingly likely and affordable, opening up
the possibility of detecting hundreds of pieces of health-related infor-
mation at birth. This will force a radical re-examination of the pur-
pose and form of newborn screening, potentially leading to a new
integration of medicine and public health. Informed decision-
making strategies will be needed to help families know about these
possibilities well before birth so that they can make informed deci-
sions about whether and what information they would like. This will
require a re-designed system of comprehensive, coordinated and fam-
ily-centered services. Evaluation issues will become increasingly
complex, and there may be a paradigm shift in expectations for evi-
dence.

If this is a possible future for newborn screening, research and
thoughtful policy discussions will be needed to make sure that we
understand the ramifications of possible changes and how to prepare
for them. Some questions that should be addressed include:

- If the cost of screening becomes irrelevant (or less relevant) or
technology evolves toward whole genome screening possibili-
ties, what role will treatment potential play in decisions about
the disclosure of results?

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22 Scott D. Grosse et al., From Public Health Emergency to Public Health
Service: The Implications of Evolving Criteria for Newborn Screening Panels, 117
PEdiATRICS 923 (2006); Muin J. Khoury et al., Will Genomics Widen or Help Heal
the Schism Between Medicine and Public Health?, 33 AM. J. OF PREVENTive MED.
310 (2007); Muin J. Khoury et al., Quantifying the Health Benefits of Genetic Tests:
The Importance of a Population Perspective, 8 GEneTiCS MED. 191 (2006).
How important is treatability of a condition from the perspective of consumers, the parents who would be the recipients of health-related information?

Would a two-tier system of screening, with some conditions being mandated and others voluntary, be possible or desirable, and how would treatment potential figure in determining which conditions go into which tiers?

Are there ways to quantify expanded benefits to the child, family, or society so that cost-benefit analyses are possible?

What systematic research is needed to assure that the debate over treatability of conditions is, itself, evidenced-based?

Answering these questions earlier rather than later will help assure that decisions with regard to expansion of newborn screening are adequately informed.

Figure 1. Percent of maximum score rating for efficacy of treatments available for the 29 core conditions recommended by the American College of Medical Genetics (Data compiled from tables provided in Watson et al., 2006).
Figure 2. Child, family, and societal goals of newborn screening

**FAMILY GOALS**
- Access potentially important health information
- Avoid financial and emotional costs of "diagnostic odyssey"
- Empower advocacy for appropriate services
- Know about reproductive risks

**CHILD GOALS**
- Reduce mortality
- Improve physical health
- Prevent secondary conditions
- Enhance development
- Promote positive emotional development and adaptation
- Maximize quality of life

**SOCIETAL GOALS**
- Assure equitable access to timely health information
- Minimize costs and maximize benefits of public health services
- Protect individuals from the adverse consequences of health information or the lack thereof
Figure 3. Four types of treatment and their consequences.

<table>
<thead>
<tr>
<th>Information</th>
<th>Support</th>
<th>Surveillance</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Families have access to accurate and understandable information</td>
<td>Families have emotional and functional assistance from a trusted source</td>
<td>Children participate in periodic screening or assessments</td>
<td>Children and families receive individualized treatments or services</td>
</tr>
<tr>
<td>Families are empowered as participants in informed decision-making</td>
<td>Families feel supported by professionals and a social network, are optimistic about the future, and are able to cope with adversities and uncertainties</td>
<td>Parents are reassured that someone is paying attention to their child’s well-being so that services or treatments will start promptly when needed</td>
<td>Health, development, and quality of life are maximized, and the primary or secondary consequences of conditions are minimized</td>
</tr>
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Successful Family Adaptation to Newborn Screening

Figure 4. An envisioned future of newborn screening

<table>
<thead>
<tr>
<th>PRE-SCREENING</th>
<th>SCREENING</th>
<th>FOLLOW-UP</th>
<th>EVALUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOW</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Not voluntary</td>
<td>25–55 conditions screened based on medical need</td>
<td>Medical management by primary care physician or specialist</td>
<td>• Reduced morbidity and mortality</td>
</tr>
<tr>
<td>• Notice given prenatally or in hospital</td>
<td></td>
<td></td>
<td>• Cost-effectiveness</td>
</tr>
<tr>
<td>COMING SOON</td>
<td></td>
<td></td>
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<tr>
<td>Informed consent</td>
<td>Selective expansion</td>
<td>Beginning collaboration with other service systems</td>
<td>• Well-being defined more broadly</td>
</tr>
<tr>
<td>ENVISIONED FUTURE</td>
<td></td>
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<tr>
<td>Informed decision-making</td>
<td>More secondary targets</td>
<td>Comprehensive, coordinated, family-centered system of services</td>
<td>• Family adaptation to information</td>
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<tr>
<td>• Microarrays</td>
<td>• $1,000 genome</td>
<td></td>
<td>• More complex evaluation issues</td>
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<td></td>
<td></td>
<td></td>
<td>• Paradigm shift in expectations for evidence</td>
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