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ON TREATABILITY: CONSIDERATIONS OF TREATMENT IN THE CONTEXT OF NEWBORN SCREENING

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Newborn screening is one of the most vigorous expressions of public health genetics. In the United States, for example, more than four million newborns are screened shortly after birth for one or more genetic diseases, in addition to screening for non-genetic conditions.

A central and fascinating aspect of newborn screening is the concept of 'treatability'. The concept of treatability, especially in the context of newborn screening, is often poorly defined. In this presentation, I would like to review the notion of treatability in newborn screening as it was considered, both with intent and by inference, in three key documents of the newborn screening literature.

Most persons have a preconception of the concept of treatability. In general, treatability is usually thought of as the quality of being treatable or, more concretely, responsiveness to medical, surgical or psychotherapeutic modalities. These definitions, in turn, have several implications, including: (1) the individual with the abnormal phenotype is the one being treated; (2) there is sufficient knowledge regarding key aspects of the condition or the abnormal phenotype to allow for treatment; (3) there is a (desired) response to the treatment; (4) the response can be defined or described; and (5) some phenotypes are untreatable.

The above definitions and associated implications of the concept of treatability suggest some of the complexity of the concept of treatability but, nonetheless, do not speak to many other fundamental aspects of this topic – especially as applied to newborn screening.

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Overall, key questions in discussing the treatability of any clinical condition include: (1) What is the purpose and who are the subjects of the treatment? (2) What is known regarding the natural history of the condition when untreated? (3) How is response to treatment defined? (4) What is the evidence base regarding the effectiveness, limitations, and acceptability of the treatment? (5) What is the minimal acceptable evidence base, who decides this, and by what process?

In terms of the first of the above questions, one can readily recognize that there can be multiple purposes of treatment. The objective of treatment, for example, might be preventing the development of severe sequelae of a condition in the entirety of the cohort or limiting, but not preventing, some clinical consequences of a condition in a particular cohort. Treatment in other contexts might consist of the provision of material supports to a family or affected individual or in still other contexts might consist of education or counseling, either for an affected individual or one or more members of a family. Thus, there are markedly different ways to conceptualize the purpose of treatment. A specific newborn screening program might even have – either with intent or unintentionally – multiple purposes for the treatment of different conditions. The recognition of multiple possible objectives of treatment is a necessary first step in the planning of any medical screening or treatment program.

It is equally essential to know what is actually known about the natural history of the condition when it is not treated and to have a clear understanding of how one can define an effective response to treatment. An understanding of the evidence base regarding the effectiveness, limitations and acceptability of the treatment is necessary for the success of any screening program. Moreover, the process of gathering, evaluating and formalizing the data comprising the evidence base on these issues is another vital aspect of the development of any clinical treatment program. Taken together, these are the elemental issues in discussing treatability in any clinical condition.[1]

It is important to recognize that there are some differences regarding the treatment of conditions detected by newborn screening programs and the treatment of other types of clinical conditions. Some of these differences are absolute, but most are relative. First, the conditions currently detected in newborn screening programs are uncommon to rare and are extremely diverse. Thus, many current newborn screening programs screen for some congenital infectious condi-

[1] Wylie Burke et al., *Defining Purpose: A Key Step in Genetic Test Evaluation*, 9 GENETICS MED. 675, 675 (2007); Virginia A. Moyer et al., *Expanding Newborn Screening: Process, Policy, and Priorities*, 38 HASTINGS CENTER REP. 32 (2008).

tions (e.g., toxoplasmosis), congenital endocrine disorders (e.g., congenital hypothyroidism), congenital metabolic diseases (e.g., phenylketonuria), and congenital developmental anomalies (e.g., some types of congenital hearing deficit). These are very diverse types of clinical conditions in terms of their underlying pathogenetic mechanisms. Further, it follows that the treatments of these conditions are not the dominion of any single clinical specialty. Instead, the successful treatment of clinical conditions detected through most newborn screening programs requires, among others, expertise of endocrinologists, specialists in infectious disease, specialists in medical genetics and metabolism, and specialists in hearing disorders.

There are two other aspects of treatment of persons with conditions detected by newborn screening programs that differ, in a relative sense, from the treatment of persons with many other types of clinical conditions. These are that the treatment of conditions detected through newborn screening programs often must be implemented immediately after their detection and that the treatments are lengthy and, sometimes, lifelong.

Keeping this framework in mind, the concept of treatability in newborn screening programs should also be considered from an historical perspective. There are approximately 25 national and international documents that discuss or promulgate the conceptual and operational framework of newborn screening programs. I will discuss the concepts of treatability in three of these documents, although all of them have something to say about treatability and each is interesting and instructive. The particular parameters to be reviewed include: how these documents conceptualize the purpose of treatment; the notion of what is known about phenotype and natural history; what they have to say about evidence base; and how these issues are considered in a policy-making context.

The first document that I will discuss, authored by a committee from the American Academy of Pediatrics in 1965, is important as it is historically the earliest of the documents to consider the fundamental elements of newborn screening.[2] The authors of that document note eight major criteria that relate to whether or not a disorder should be included in newborn screening effort; three of the criteria directly relate to the notion of treatability. These are: (1) "[d]oes the seriousness of the disorder justify screening?"; (2) "[i]s therapy for the disease in question available?"; and (3) "[a]re there acceptable medical

[2] Committee on Fetus and Newborn, *Screening of Newborn Infants for Metabolic Disease: Committee on Fetus and Newborn*, 35 PEDIATRICS 499 (1965).

facilities prepared to confirm diagnosis and consult about the institution of therapy?"[3]

Although the document is brief, only three pages, it is rich with both direct statements and implications pursuant to the issues of treatability of conditions detected through newborn screening programs. The document is unambiguous that the primary objective of treatment is treatment of the newborn (and, by inference, not any other party). The document indicates that the condition to be screened for must be one that is clinically serious for the affected child if that child does not undergo treatment, although there is no definition of "seriousness". Similarly, a definition of treatment is not provided, although a medical approach is implied. The authors of the document also indicate that there must be an adequate evidence base regarding the eight parameters, although what comprises an adequate evidence base is also undefined.

Further, the authors of the document acknowledge that there needs to be an intact medical system for the delivery of treatment. The document does not include specific detail of the components, administration, or the quality control of that system. Moreover and by inference, the authors endorse an expert-dominant and non-inclusive model of public health policy-making; they do not acknowledge the existence of any other potential models of how newborn screening policy could be constituted.

Finally, the authors recognize that newborn screening is a dynamic area of medicine. This recognition is important since information in technology, science, and medicine relevant to newborn screening is always advancing and the new knowledge will have ramifications for screening and treatment. Consequently, newborn screening policies and programs need to be re-visited in a systematic manner. However, the authors of this document do not describe a process for systematically re-evaluating newborn screening medicine and programs.

The second document of this review is one of the most influential treatises on screening in medicine, the work of Wilson and Jungner.[4] This document does not specifically address the topic of newborn screening but, rather, concerns general population screening. It is arguably the most cited and influential document shaping past and current newborn screening programs. It includes ten criteria for all screening programs, seven of which directly relate to various aspects

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[3] *Id.* at 499.

[4] World Health Organization [WHO], *Principles and Practice of Screening for Disease*, Public Health Papers No. 34 (1968) (J.M.G. Wilson & G. Jungner).

of the notion of treatability. These are: (1) "[t]he condition ... should be an important health problem"[5]; (2) "[t]here should be an accepted treatment for patients with recognized disease"[6]; (3); "[f]acilities for diagnosis and treatment should be available"[7]; (4) "[t]here should be a recognizable latent or early symptomatic stage"[8]; (5) "[t]he natural history of the condition, including development from latent to declared disease, should be adequately understood"[9]; (6) "[t]here should be an agreed policy on whom to treat as patients"[10]; and (7) "[t]he cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole."[11]

When one crystallizes the key elements of this long document, Wilson and Jungner make clear that the primary objective of treatment should be the treatment of the screen-positive individual. They further state that the condition to be treated must be of significance to the individual and the community. How these are weighed is not explicated but the authors note that this decision making should include a cost analysis. They do not provide a definition of treatment, although a medical approach is implied. Their discussion of treatment, in contrast to other documents in the field, specifically includes the need to avoid doing harm to persons who are screened and are not in need of treatment. Wilson and Jungner state that an evidence base is needed for many of the ten parameters of screening programs but they, too, are not specific regarding the meaning of an adequate evidence base.

Wilson and Jungner acknowledge the importance of an integrated medical system for therapy to be effective although detail regarding the components, administration and quality control of the system is not specified. They do not discuss or endorse particular models of public health policy-making, although one can safely infer three components of any model they would approve: (1) the need for an adequate evidence base for any policy; (2) individual and community outcomes measures; and (3) the need for periodic re-evaluation of policies and programs.

The third document that I will discuss is that authored by the American College of Medical Genetic Newborn Screening Expert

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[5] *Id.* at 26.
[6] *Id.*
[7] *Id.*
[8] *Id.*
[9] *Id.* at 27.
[10] *Id.*
[11] *Id.*

Group.[12] This document has been both influential and controversial. The authors set forth 12 principles that relate to the function of newborn screening programs and whether a disorder should be included in a newborn screening effort, of which seven directly relate to the concept of treatability. They include: (1) "[n]ewborn screening policy development should be driven primarily by the interests of affected newborns, with secondary consideration being given to the interests of unaffected newborns, families, health professionals, and the public"; (2) "[n]ewborn screening is more than testing[, but also] a coordinated comprehensive system consisting of education, screening, follow-up contact, diagnosis, treatment and management, and program evaluation"; (3) "[t]he medical home and the public and private components of the screening programs should be in close communication, to ensure confirmation of test results and appropriate follow-up evaluation and care of identified newborns"; (4) "[r]ecommendations about the appropriateness of conditions for newborn screening should be based on evaluation of scientific evidence and expert opinion"; (5) "[t]o be included as a primary target condition in a newborn screening program, a condition should meet the following minimal criteria ... and there [should be] demonstrated benefits of early detection, timely intervention, and efficacious treatment of the condition"; (6) "[c]entralized health information data collection is needed for longitudinal assessment of disease-specific screening programs"; and (7) "[p]ublic awareness, coupled with professional training and family education, is a significant program responsibility that must be part of the complete newborn screening system."[13]

Although the stated primary objective of treatment is treatment of the screen-positive individual, the scoring system devised by the ACMG Newborn Screening Expert Group allows for an expanded notion of treatment, including even minimally effective treatment for the screen-positive newborn or no direct treatment of the screen-positive baby but, instead, supports for the family. Furthermore, the scoring system allows for the possibility that some very rare disorders could receive a high score, so prevalence is no longer a dominant issue for inclusion in a screening program as it had been for the preceding newborn screening policies.

The ACMG Newborn Screening Expert Group desired an evidence base for many of the parameters noted above and, in contrast to prior attempts to construct newborn screening policy, set out in writ-

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[12] Michael S. Watson, et al., *Newborn Screening: Toward a Uniform Screening Panel and System – Executive Summary*, 117 PEDIATRICS S296 (2006).

[13] *Id.* at S298.

ing the nature of the extant evidence base. However, due to the scarcity of data from controlled studies on these rare disorders there was heavy reliance on expert opinion in assessing the appropriateness of the various conditions for possible inclusion in newborn screening efforts. The authors acknowledged the importance of a comprehensive and intact program in order for the therapy to be effective. They also acknowledged the value of a cost-effectiveness analysis but the latter was limited in detail and did not acknowledge that the costs of any newborn screening effort should be considered in the larger context of the entirety of the public health enterprise.

The ACMG Newborn Screening Expert Group endorsed an inclusive model of public health policy-making. They included persons with different types of expertise in the construction of their document. However, the methodology used in creating that work has been strongly criticized. There have been concerns of narrow representation of diverse perspectives and expertise of the participating experts, narrow representation of the diversity of consumers, and concerns of conflicts of interests. These concerns are particularly significant in the context of a process characterized by an especially disproportionate reliance on expert opinion.[14]

Their model of policy-making, like that of Wilson and Jungner, acknowledged a need for an adequate evidence base coupled with both individual and community outcomes measures. And they similarly acknowledged that the field of newborn screening is dynamic and, as a consequence, there is a need to re-visit programs and policies.

CONCLUSIONS

There are several general conclusions that can be ascertained about treatability in newborn screening from the analysis of these three documents. Clearly, there is a longstanding recognition, dating more than 40 years, of a need for a strong evidence base for all aspects of newborn screening policies. This includes having an evidence base for issues pertaining to treatment. Unfortunately, the development and use of an evidence base has been challenging, although there are recent and sincere efforts to try to remedy this.

In terms of the types of treatments, one can make several conclusions and interesting speculations. It is apparent and not unexpected,

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[14] Marvin Natowicz, *Newborn Screening – Setting Evidence-Based Policy for Protection*, 353 NEW ENG. J. MED. 867, 868-870; *see also* Jeffrey R. Botkin, et al., *Newborn Screening Technology: Proceed with Caution*, 117 PEDIATRICS 1793, 1795 (2006).

for example, that there has been an evolution of treatments for conditions detected by newborn screening. In the earliest years of newborn screening, in the time of screening for just phenylketonuria and hypothyroidism, the treatments were exclusively medically based (i.e., implementation of a special diet and hormone replacement, respectively). But the types of treatment have expanded to include surgical approaches, too (e.g., one of the treatments for certain types of congenital hearing deficit is cochlear implantation). In the not-too-distant future, various types of cell transplantation therapies and molecular genetic therapeutics will likely become established therapeutic modalities for some disorders detected by newborn screening programs. The acceptance of counseling, education and support as the sole or major treatment for some diagnosed conditions, a much broader notion of treatment, is less clear and is an issue of considerable controversy at the present time.[15]

In the past, therapy for most disorders detected through newborn screening programs was primarily single modality therapy. This is largely the case at the present time as well. For example, the mainstay of treatment for congenital hypothyroidism is the provision of thyroid hormone and the primary treatment for many of the organic acidemias and aminoacidopathies is the provision of a specific diet. However, with the increasing recognition that even simple monogenic disorders often have a multiplicity of other interacting determinants that construct the final phenotype, such as modifier genes and environmental factors, it is apparent that single modality treatment is not the way that many of these conditions will be treated; rather, multiple treatment modalities will be used, sometimes from the time of diagnosis and in many instances there will be sequential use of different treatments as the individual ages and the phenotype morphs.

In addition, while the genetic conditions detected through current newborn screening programs are monogenic disorders, newborn screening may evolve to include screening for some disorders that have a multifactorial mode of determination, although screening for selected multifactorially determined conditions is controversial at the present time. If this occurs, there will be a significant likelihood of multimodal treatment for some of the multifactorially determined conditions since, by definition, there are multiple determinants of the phenotype and, therefore, multiple potential targets for therapeutic

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[15] *See generally* Donald B. Bailey, Jr., et al., *Changing Perspectives on the Benefits of Newborn Screening*, 12 MENTAL RETARDATION & DEVELOPMENTAL DISABILITIES RES. REVIEWS 270 (2006) (discussing historical and current public perceptions of benefits of newborn screening).

interventions. Moreover, as multimodality treatment becomes important for many monogenic and, possibly, multifactorially determined conditions, there will be an increased challenge to develop an adequate evidence base regarding treatment effectiveness. It is challenging to develop a good evidence base when one is dealing with uncommon or frankly rare disorders; this challenge will be magnified, however, if there are multiple treatment regimens that are deemed important for the care of the diagnosed individuals.

The three documents reveal different fundamental objectives. The earlier documents maintained that the target of newborn screening is the newborn and that the type of condition to be screened must be one that has an effective treatment and that has a reasonably high prevalence.[16] These perspectives have been recently challenged.[17]

The three documents also differ in several ways regarding the process of decision making about key issues in newborn screening including, but not limited to, issues relating to treatability. For example, the policies for newborn screening programs noted in the earlier documents, including guidelines for inclusion of specific disorders to be screened for, appear as more or less absolute principles. Notwithstanding the lack of comprehensive definition and consequent subjectivity of many of these guidelines, they have, nonetheless, functioned as relatively rigorous guideposts. However, the disease scoring system developed by the ACMG Newborn Expert Group constitutes a challenge to previous guidelines of newborn screening and represents a shift regarding how the decision making process concerning the suitability of a condition for inclusion in a newborn screening program is done.[18]

The decision making process regarding treatability and other key issues of newborn screening differ in the three documents in other ways as well. Decision making regarding public health policy in newborn screening began as an expert-dominant process that was mainly non-inclusive. Thus, a group of experts in pediatric medicine from the American College of Pediatrics met in 1965 and determined

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[16] Committee on Fetus and Newborn, *supra* note 2; World Health Organization, *supra* note 4.

[17] Watson et al., *supra* note 12.

[18] *See generally* Scott D. Grosse, et al., *From Public Health Emergencies to Public Health Service: The Implications of Evolving Criteria for Newborn Screening Panels*, 117 PEDIATRICS 923 (2006) (discussing the shift to more moderate benefits including voluntary screening programs and allowing for parental choices). *See also* Michael S. Watson, *Current Status of Newborn Screening: Decision-Making About the Conditions to Include in Screening Programs*, 12 MENTAL RETARDATION & DEVELOPMENTAL DISABILITIES RES. REVIEWS 230 (2006) (comparing criteria of scoring systems in the United States and several other countries).

basic principles for the operation of newborn screening; individuals with expertise in public health policy making, epidemiologists, diverse members of the general public and other relevant personnel were not included in that panel. While the decision making process in newborn screening continues as an expert-dominant process, it has also become more inclusive in some instances. The ACMG Newborn Expert Group, for example, included professionals with a variety of expertise and some consumers. Yet, important and controversial issues remain. In addition to a need for inclusion of all relevant professional expertise, there are two other unsolved concerns. These are: (1) how to meaningfully include the diverse perspectives of the general public, and (2) the (controversial) role of the commercial sector in the newborn screening policy making process.[19] Overall, the issue of which parties should have "a seat at the table" is, arguably, the most fundamental issue in newborn screening policy making.

All three documents highlight the importance of an intact system of care for the successful treatment of individuals with conditions detected through newborn screening programs. However, it is clear that there is a global insufficiency and maldistribution of professionals and other key resources relating to effective treatment of the disorders that are detected by newborn screening programs. This, coupled with increased screening, portends increased inequality of access to the benefits of an ideally functioning newborn screening program, both within our nation and internationally.

Finally, most newborn screening policy making bodies, including those that authored the documents under consideration, have not rigorously considered the detection and treatment of conditions in newborn screening in the context of the larger public health enterprise. There are a multitude of important public health needs, yet resources to effectively deal with these needs are limited.[20] Newborn screening programs, like all public health initiatives, need to be viewed in a

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[19] Elaine H. Hiller et al., *Public Participation in Medical Policy-Making and the Status of Consumer Autonomy: The Example of Newborn-Screening Programs in the United States*, 87 AM. J. PUB. HEALTH 1280, 1280 (1997); Catherine F. Ard & Marvin R. Natowicz, *A Seat at the Table: Membership in Federal Advisory Committees Evaluating Public Policy in Genetics*, 91 AM. J. PUB. HEALTH 787, 787 (2001); Sarah E. Gollust et al., *Community Involvement in Developing Policies for Genetic Testing: Assessing the Interests and Experiences of Individuals Affected by Genetic Conditions*, 95 AM. J. PUB. HEALTH 35, 35 (2001); Marvin R. Natowicz & Catherine Ard, *The Commercialization of Clinical Genetics: An Analysis of Interrelations Between Academic Centers and For-Profit Clinical Genetics Diagnostics Companies*, 6 J. GENETIC COUNSELING 337, 338 (1997).

[20] Mary Ann Baily & Thomas H. Murray, *Ethics, Evidence, and Cost in Newborn Screening*, 38 HASTINGS CENTER REP. 23, 23-4 (2008).

more global context whereby we are mindful of both the significance and complexity of public health needs and the resources that can be used to address these challenges.