Newborn screening conditions: What we know, what we do not know, and how we will know it

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Abstract: Expanding newborn screening beyond that for phenylketonuria was always the goal of Guthrie once phenylketonuria screening was on solid ground. He succeeded in this effort to an extent, adding screening for galactosemia, maple syrup urine disease, and homocystinuria. Screening for congenital hypothyroidism, congenital adrenal hyperplasia, biotinidase deficiency, and a few additional disorders was added by others over the years. However, a very large expansion of covered metabolic disorders eluded Guthrie despite his best efforts. This required a new screening technology, tandem mass spectrometry, which was not available until recently. Now, almost all developed newborn screening program use tandem mass spectrometry to cover the 29 metabolic disorders recommended for coverage by the American College of Medical Genetics and additional secondary disorders. The results have in some cases been spectacular in preventing or greatly reducing the burden of disease imposed by many of the screened disorders. However, expanded newborn screening has also brought problems that need to be addressed. These include lack of knowledge about the natural history of some of the disorders, absence of effective preventive therapy for others, identification of seemingly benign disorders or benign variants of severe disorders, and the resulting parental anxiety. To address these and other issues brought by expanded newborn screening, a national effort led by the American College of Medical Genetics has been developed. This effort known as the Newborn Screening Translational Research Network seeks to stimulate research, advocate pilot screening programs for proposed new additions to screening, and develop a protocol-based systematic long-term follow-up of infants identified in expanded screening programs. Upon the outcome, this critical effort will depend on the health and well-being of children throughout the United States. ***Genet Med* 2010:12(12):S213–S214.**

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New opportunities present new challenges. This is true for all of life's endeavors and is certainly true for newborn screening (NBS). In fact, it has always been true for NBS, dating from its inception in 1962 for a single metabolic disorder, phenylketonuria (PKU).[1] Although we now understand much about PKU, far less was then known, and, as a result, Guthrie had to overcome substantial opposition before universal NBS was accepted.[2] However, once NBS for PKU was accepted came expansion. First was the addition of galactosemia, then maple syrup urine disease, and homocystinuria.[3] Once again, these were rare disorders for which specific diagnosis and treatment were still in their infancies.[4,5] In fact, NBS has invariably served as the major stimulus for rapidly expanding our basic and clinical understanding of these disorders.

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This story was repeated as disorders were added—congenital hypothyroidism, congenital adrenal hyperplasia, and biotinidase deficiency. Perhaps, the single exception was sickle cell disease, which was almost as well understood when added to NBS as now.[6] Nevertheless, screening for sickle cell was really screening for hemoglobinopathies, and identification of so many of the latter has opened up a new window into the myriad of hemoglobin variants.

The recent very major expansion of NBS, made possible by tandem mass spectrometry, is a continuation of this story but greatly magnified by the enormity of the expansion at a single time. Although previous expansions in newborn screening added one or very few disorders, the recent expansion has added 30–40 or more disorders (the number of disorders included in NBS depends on how a "disorder" is considered. For instance, some programs consider NBS for PKU to encompass all the hyperphenylalaninemias as a single disorder, whereas other programs consider PKU to be one of several hyperphenylalaninemic disorders [viz., mild PKU, mild hyperphenylalaninemia, DHPR deficiency, etc.], each counted separately), and little more is known about the disorders identified in this expansion than about the disorders added in the past. Moreover, the categories of the disorders added, those of fatty acid oxidation, of organic acids, and of the urea cycle, are complicated biochemically, clinically, and therapeutically. Many have only quite recently been described.

This is not to say that expanded NBS was unjustified or has not been beneficial. To the contrary, when it began there was good reason to believe that many of the disorders led to severe and irreversible damage that presymptomatic treatment could ameliorate or prevent. Studies of outcome from expanded screening have supported this belief. Notable are the reports from Australia[7] and Germany.[8] Based on these reports and the experience of some state programs in the United States, the American College of Medical Genetics in 2006 recommended that all NBS programs increase coverage to 29 core disorders while recognizing that in the process of screening for the core disorders a number of additional metabolic disorders, called "secondary targets," would also be identified.[9] Currently, expanded screening covers newborns in all states and the District of Columbia.[10]

As in all medical advances, however, there is "no free lunch." Expanded screening has problems that need to be addressed. False-positive results and the occasional false-negative result are realities, although they are amazingly infrequent given the number of conditions covered and the number of babies screened.[11] A much more troubling problem, however, is our lack of definitive information about the natural history of several disorders that are encountered in screening with relative frequency but which previously were only rarely reported. Two examples are short-chain acyl-CoA dehydrogenase deficiency, a fatty acid oxidation disorder, and 3-methylcrotonyl-CoA carboxylase deficiency, an organic acid disorder. Although short-chain acyl-CoA dehydrogenase deficiency has been reported in association with clinical problems, the overwhelming majority of affected infants identified by screening have been asymptom-

atic.[12] The same has been true for 3-methylcrotonyl-CoA carboxylase deficiency.[13] Even more important is the uncertainty as to clinical effects of the mild variants of serious disorders identified in screening. Notable disorders in this category are the mild variants of very long-chain acyl-CoA dehydrogenase deficiency,[14] isovaleric acidemia,[15] and citrullinemia.[16] It is likely that every disorder has a mild variant that is far less dire than the "parent" disorder and may even be benign.

In fact, mild variants and the resulting uncertainty about their effect have always been a large part of NBS. When screening began, it was believed that any infant with an increased level of phenylalanine had PKU and would become retarded unless dietary therapy was introduced soon after birth. However, investigations showed that "PKU" was really composed of different degrees of hyperphenylalaninemia[17] and that there was a frequent mild form, called mild hyperphenylalaninemia, which we now know is benign and does not require treatment.[18] The story was repeated when screening for galactosemia was introduced; the mild variant known as the Duarte/galactosemia genetic compound, once considered significant, is likely benign.[19,20]

A national effort is required to answer these and many other questions about expanded NBS, including the effect of treatment, because no one program or even region can acquire enough cases of these rare disorders to provide definitive answers. Work toward this effort began with recognition by the Maternal and Child Health Bureau of the Health Resources and Services Administration of the need for long-term follow-up (LTFU) of NBS. This effort is now supported by the National Institute of Child Health and Human Development with funding to the American College of Medical Genetics to develop the Newborn Screening Translational Research Network (NBSTRN) in which LTFU of NBS is a central mission. The NBSTRN includes stimulation of research, advocacy of pilot screening programs for proposed new additions to screening, and a protocol-based systematic LTFU of the infants identified in screening programs. To accomplish the goal, the NBSTRN will need to bring together large collaborative systems of the type developed so successfully by the National Cancer Cooperative groups.[21] Most importantly, it will need to take advantage of the Maternal and Child Health Bureau-funded Regional Collaboratives to provide information about the identified infants as they develop through childhood, adolescence, and even into their adult years.

It is of vital importance that NBS laboratories, health providers, and specialty clinics know which disorders are important and require immediate attention and which disorders, including variants of known serious disorders, are much less important. Health providers and clinics must know which treatments are effective and which are noneffective. The health and well-being of children throughout the United States depend on the outcome of the NBSTRN. It must succeed.

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