Newborn Screening for Metabolic Disorders: How Are We Doing, and Where Are We Going?

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Owing to technological advances during the last decade, there has been a paradigm shift in the way that we diagnose patients with inherited metabolic disease. The introduction of tandem mass spectrometry (MS/MS),7 a technology with sufficient analytical sensitivity to measure metabolic biomarkers in small blood spot samples, has allowed us to shift from what was initially a diagnosis made after or during acute metabolic decompensation into an era in which diagnosis is made immediately in the newborn period. In this environment, the diagnosis of certain metabolic diseases frequently precedes the onset of symptoms, giving physicians an opportunity to prevent many of the catastrophic events that used to occur. To this point, disorders such as medium-chain acyl-CoA dehydrogenase (MCAD) deficiency now rarely initially present as the acute-onset liver failure that was previously seen in unscreened and consequently undiagnosed patients. Clinical outcomes for MCAD deficiency are now excellent, and data on some of the other screened disorders are starting to show the benefit of early diagnosis.

Diagnostic technology continues to increase in its capability to provide early diagnosis of increasing numbers of these metabolic diseases as more biomarkers become identified. In this Q&A, 5 leading thinkers in the field provide their insights into where we presently stand in this area and where we might be headed in the future.

Has there been a positive impact on patient care as a result of early diagnosis and implementation of the American College of Medical Genetics (ACMG) recommended-screening disorders?

Piero Rinaldo: The implementation of the ACMG uniform panel has had a positive impact at multiple levels. The consistency of the panel has virtually eliminated the discrepancies between neighboring states, often a cause of heartbreaking events where parents have experienced significant morbidity and mortality of their child that would not have happened if their child had been born just across the state border. Given the 99% implementation of the primary targets by US programs, today it is almost irrelevant where a baby is born. Another positive outcome has been a much greater awareness that—with almost no exception—the analytes detected by MS/MS are not unique to a single, better-known condition but often entail a complex differential diagnosis. Collaboration and data sharing have also improved, creating an environment better suited for evidence-based clinical validation.

Bridget Wilcken: There is no all-encompassing answer to this question. A positive impact on patient care can mean many things—earlier diagnosis, more-appropriate treatment in specialized centers, and, most importantly, an improved outcome. But it also means that...

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7 Nonstandard abbreviations: MS/MS, tandem mass spectrometry; MCAD, medium-chain acyl-CoA dehydrogenase; ACMG, American College of Medical Genetics; NBS, newborn screening; PKU, phenylketonuria; CH, congenital hypothyroidism; SCID, severe combined immunodeficiency; CF, cystic fibrosis; APHL, Association of Public Health Laboratories; HRSA, Health Resources Services Administration; LSD, lysosomal storage disease; TREC, T-cell excision circle; BIA, bacterial inhibition assay.
the benefits should outweigh the harms—again a difficult call, as one is comparing different things. There is no doubt that screening has resulted in earlier diagnosis for most patients, and it is very likely that eventually there will be more appropriate treatment in experienced metabolic centers. Benefit for patients with disorders on the new expanded list has been demonstrated clearly for MCAD deficiency and glutaric aciduria type 1, and for all disorders taken together, and we have assessed this when patients and controls have been 6 years old. But the ACMG recommendations do include disorders that are now thought to be benign or nearly so, and additionally but unavoidably, screening detects patients with mild forms of significant disorders. This not only dilutes the real benefit (screen-detected patients may have mild disease and so do well, producing an apparent benefit) but may also cause harm because of unneeded treatment. Well-designed observational outcome studies are needed. Randomized controlled trials will not be possible now because of both the rarity of individual disorders and the currently perceived benefit.

Kenneth Pass: Absolutely! There are numerous accounts of life-saving interventions as a result of using positive newborn screening (NBS) results to initiate prompt and effective therapies. These are most often seen in the fatty acid and acyl-carnitine disorders now identified through the use of MS/MS. These disorders are not apparent on a physical exam, as is true of most NBS disorders, but can lead very quickly to a metabolic crisis situation. Moreover, it is without question that the quality of life for these infants has been improved by the timely intervention resulting from NBS. This was apparent from the beginning of NBS testing for phenylketonuria (PKU) and is especially true for one of the more common conditions in all panels: congenital hypothyroidism (CH). Untreated, CH can result in profound mental retardation and physical manifestations. Once a newborn is identified, therapy is easy and effective. Among the 60+ conditions in today’s NBS panels, only severe combined immunodeficiency (SCID) can be completely cured through bone marrow transplantation. However, none would argue that morbidity can be greatly reduced for most of these disorders, notably CH, cystic fibrosis (CF), PKU, and sickle cell disease.

Michael Watson: When the ACMG was contracted to assess 80+ conditions in 2002 to determine their appropriateness for NBS, there was significant interstate variability in what was screened. There is now near uniformity among the states in screening for a core set of conditions, and a federal advisory committee (Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children) coordinates a central review of evidence for conditions being considered for addition to or subtraction from the uniform panel of conditions. There was limited patient care guidance (e.g., practice guidelines) and research related to the conditions to which screening was directed. Clinical histories of the conditions were poorly developed, due to the rarity of the conditions and a lack of systems that would allow for the aggregation of information about cases found in NBS that were distributed around the country. This is a critical need as we invariably learn much about the range of phenotypes associated with a genetic condition until cases are identified in a general and large population setting. In response to federal legislation in the Newborn Screening Saves Lives Act, the Eunice Kennedy Shriver National Institute for Child Health and Human Development has sponsored an evolving research program (the Newborn Screening Translational Research Network) that focuses on new technologies, treatments, and a broad range of research related to NBS and the conditions that are candidates for addition to NBS programs.

Furthermore, there was significant variability between states in the performance characteristics of the screening tests (i.e., analytical and clinical sensitivity and specificity, and predictive values of screening results). There are now programs that facilitate interlaboratory comparison and improvement of NBS (Region 4 Stork) that complement the CDC’s Newborn Screening Quality Assurance Program and that have worked toward minimizing the number of families that are unnecessarily alarmed by notification of a screen-positive result is an important outcome.
Ronald Wanders: Absolutely! However, in the Netherlands we don’t screen for all of the disorders recommended by the ACMG. In 2007, NBS for inborn errors of metabolism was expanded from 1 disorder (PKU) to 14 disorders, including, among others, MCAD, various disorders of long-chain fatty acid oxidation, galactosemia, biotinidase deficiency, and maple sugar urine disease. The Dutch screening program already included CH and adrenal genital syndrome. In addition to the inclusion of 13 new inborn errors of metabolism, screening for sickle cell anemia and thalassemias was included in 2007, and CF was included in 2011. There were some initial problems with the expanded screening program, mainly due to the screening tests used and cutoff values, but these were quickly overcome.

Have there been any unanticipated findings or negative impacts on patient care as a result of the implementation of these guidelines?

Piero Rinaldo: There is still no consensus among experts and providers of NBS services about the clinical justification of including in the recommended panel a few secondary targets with a poorly defined natural history. Having said that, the only way to settle such issues is to gather the evidence over an extended period of time and then consider the need for revisions of the recommended panel on the basis of objective evidence, not subjective opinions.

Bridget Wilcken: There have certainly been some. The inclusion in the ACMG list of very rare disorders whose clinical significance was unknown seems to have been unwarranted. With hindsight, it would have been better to support a few excellent centers that could include certain disorders, with parental consent, on an explicit research basis. This would have avoided distressing parents of babies with very rare disorders who may have been put on difficult and possibly harmful diets (low valine diet, for example, in isobutyryl-CoA dehydrogenase deficiency) for something that turns out to be apparently benign. Such babies have also been labeled for life as having a disorder. Astonishingly, the recommended list includes, in its secondary targets, one disorder that has been recorded only once. This requires a marker not used for other disorders and so was entirely unnecessary. Many screening programs are worried about the increased number of false-positive tests, but some studies show that where these are well managed and parents have accurate information, there is much more tolerance of such results. But false-positive results and, worse, those that indicate a disorder of uncertain clinical significance always have some negative impact.

Kenneth Pass: Regrettably, yes. As with any population-based program (the US tests over 4 million babies each year), unanticipated things can happen. One of the more common impacts is the inability to locate a child who has a positive screening result. Despite great efforts on the part of the program’s follow-up unit, it is sometimes impossible to locate a family, because of having nothing to work with except incorrect information provided to the NBS program. This can also occur when the initial specimen is not suitable for testing and the program is unable to locate the family for rescreening. In both instances, the newborn can fail to get appropriate medical care.

Introduction of testing for CF also brought unanticipated changes in the operation of the national CF centers. Before NBS for CF, these centers were presented only with infants (or toddlers) who were sick and not otherwise diagnosable. In many instances, the CF center was the last resort in a long search for a diagnosis. With the addition of NBS for CF, asymptomatic infants were arriving for diagnostic workup. It was quickly realized that these NBS referrals could not be seen on a clinic day when sick children were also seen. Thus, a new day exclusively for NBS referrals had to be adopted. Additionally, the centers now had to deal with CF carriers, rather than the affected infants they were accustomed to seeing. This caused a major reorganization of their diagnostic protocols.

A decade or more after beginning NBS for PKU, the first indications of a problem arose when children born to mothers with PKU were themselves severely disabled, but not with PKU. Their birth defects were primarily related to the development and function of the heart. Intensive investigation led to the unexpected condition of maternal PKU, in which increased concentrations of phenylalanine in a mother not using the strict diet were teratogenic to the unborn fetus. Many of these women were unaware that they had PKU, since they had been “off diet” for many years. With extensive education programs and a closer involvement of the obstetric community, it was possible to identify these soon-to-be-mothers so that they could resume their PKU diet.

Michael Watson: As discussed above, our understanding of genetic diseases is typically biased by their modes of ascertainment until those at risk can be identified in a general population setting and their outcomes under-
stood. The range of phenotypes of the conditions tends to broaden as the true clinical histories of the conditions are captured. Some have considered the need to constantly improve our knowledge bases to be a negative impact of screening. However, it is a necessary and critical step in developing our understanding of the diseases. It is difficult to determine how much knowledge about a disease is sufficient to begin NBS. For rare diseases, more is always better. In the ideal world, these sorts of large population-based studies of diseases would be done before formal introduction of the condition into NBS programs. However, for conditions with incidences in the 1 per 50,000 to 100,000 range, very large population-based studies would be required. As is apparent from the Orphan Drug Act, the real issue boils down to determining how much premarket data are needed before the introduction of a test and the types of systems that have to be in place to support postmarket surveillance that ensures the availability of data needed to continuously reassess decisions made after test introduction.

**Ronald Wanders**: Yes, there were indeed some surprises. One example was the outcome of screening for homocystinuria, which was done only on the plasma methionine concentration. A very high incidence of false-positive screening results was found on one of the Dutch neonatal intensive care units. This was due to the use of a specific high-methionine parenteral amino acid mixture. Screening for homocystinuria was stopped in 2010 as it became clear that this method had not resulted in any true-positive screening results and thus may have led to false-negative results. We hope to reinitiate screening for this disorder later this year with a screening method based on the plasma homocysteine concentration. In addition, we detected completely novel clinical presentations of mitochondrial trifunctional protein deficiency.

**Has implementation created additional burden on laboratory or clinical services?**

**Piero Rinaldo**: If additional burden occurs, it is a direct consequence of poor performance, which is avoidable. High false-positive rates and low positive predictive values are almost always related to a failure to rely on all potentially informative markers for a given condition and inadequate reliance on profile interpretation and pattern recognition.

**Bridget Wilcken**: In New South Wales, Australia, we investigated the burden produced over the 8 years from 1998–2006, after screening 730,000 babies. Our system is highly integrated, and almost all metabolic patients attend a single center. All follow-up testing is performed through that center also. For outpatient appointments, 13% were for patients with disorders detected by NBS (excluding PKU). An estimate of the real increase in work was 3% to 10%. For laboratory services, only 401 samples were referred for evaluation, less than 1% of the metabolic laboratory’s total. The situation would be very different elsewhere if there were less integration, but overall, I believe the extra burden would be small, especially as experience with the new screening grows. In any case, most patients affected by clinically significant disorders would present soon for clinical and laboratory care.

**Kenneth Pass**: Yes. With the introduction of MS/MS as a screening tool, a totally unfamiliar testing platform that was expensive and required laboratory renovations and highly trained technicians was required. Most laboratories were unfamiliar with the technology and needed training before widespread introduction. This training was provided through a joint effort of the Association of Public Health Laboratories (APHL), the Health Resources Services Administration (HRSA), and the CDC, as was done previously when screening for sickle cell disease was introduced universally through the new (at that time) technology of isoelectric focusing. Furthermore, with use of the MS/MS technology, the number of conditions in the screening panel grew from 8 in most programs to almost 60 in some programs. This has placed an unusual burden on the clinical community, since each screen-positive infant must be evaluated to confirm or correct the screening results. This had also been a problem when screening for CF was added to the screening panel. With the introduction of MS/MS technology in the screening laboratory, additional efforts were needed from the clinical community of biochemical geneticists and metabolic specialists, because many of these 30+ conditions could not be identified with the customary clinical techniques used by pediatricians. Certainly, initial therapy for this group of disorders by a pediatrician presented obstacles of knowledge and time. The ACMG, with funding from the HRSA, developed a set of Fact Sheets that clearly outlined the initial steps needed for this group of newborns on their first meeting with their pediatrician. These are now included with the NBS report by programs in the US.

**Michael Watson**: The burden isn’t as much a function of the numbers of patients identified by expanded NBS as it is one of a severely limited biochemical genetic and clinical genetics disease provider workforce. NBS doesn’t create “new” patients but does identify additional people who won’t turn out to be patients. However, the “new” patients typically present before serious complications develop and so are usually more readily
treatable than would be a seriously disabled patient. One would hope that many of the patients who would otherwise present for diagnosis after clinical symptoms develop would ultimately be seen by those trained in their diagnosis, but unfortunately they often aren’t. Tales of the diagnostic odyssey that many of these patients experience are not uncommon, but it is clear that the benefits of early identification and treatment outweigh the alternative.

An additional burden on providers is also related to the performance characteristics of the screening tests themselves. There is significant variability across the country in the clinical sensitivity and predictive values of the screening tests. Programs have been developed that seek to minimize the number of screen positives that won’t be true positives, and significant progress has been made in shifting this balance to the benefit of both the providers who see the patients and the families that must enter into the healthcare system for evaluation.

**Ronald Wanders:** Definitively yes. One of the consequences of expanded NBS has been that laboratories are confronted with diagnostic activities that have to be performed right away, not only during the day but also on weekends, simply to establish whether a patient with a positive screening result is truly affected or not. The number of emergency admissions to the centers for metabolic disorders in the Netherlands increased significantly. Although most individuals who tested positive later proved to be false positives, all referred newborns should initially be treated as patients while waiting for the results of the full diagnostic workup.

**Do you anticipate further expansion to include additional conditions, and if so, which ones?**

**Piero Rinaldo:** Thankfully, further expansion will be driven, at least in the US, by a well-defined process of evidence review under the auspices of the Health and Human Services Secretary Advisory Committee on Inherited Disorders in Newborns and Children. Conditions are nominated and vetted on the basis of the severity of the condition, the availability of sensitive and specific screening tests (including second-tier tests), and the availability and efficacy of treatment modalities. After the inaugural addition of SCID to the uniform panel, many other conditions detectable by the analysis of dried blood spots have come under consideration. Lysosomal storage diseases (LSDs) are widely debated and accordingly are under intense scrutiny, but there are others where the treatment modalities may indicate a great potential from early intervention. Some of them may leapfrog better-known conditions toward inclusion in the panel. Some of these “dark horses” are Wilson disease, X-linked adrenoleukodystrophy, disorders of creatine metabolism, remethylation disorders (for example, methylene tetrahydrofolate reductase deficiency), familial hypercholesterolemia, and Friedreich ataxia, just to name a few.

**Bridget Wilcken:** It is inevitable that there will be further expansion. New treatments suggest new candidate disorders. So do new marker compounds and new technology, as well as new ideas on what is an acceptable aim for NBS. Firstly, I imagine that there will be quite an expansion of screening for LSDs as specific treatments become available. Current treatments are particularly expensive, and this causes some ethical concerns about opportunity costs. There is also concern about the possibility of simply stretching out the life span, but with diminishing quality, for some LSD disorders. This has certainly been shown for infantile Pompe disease, where there is a clear survival benefit of early treatment for some, but which may not be long-lasting. Mutation-specific treatments (for example read-through of stop codons, exon skipping, pharmacological chaperones) are exciting and will certainly lead to new screening. A prime candidate here would be Duchenne muscular dystrophy, for which there has been a screening test available for over 30 years and for which a likely benefit has been shown in early trials of read-through of stop codons for those with such a mutation. Primary DNA testing is going to be readily possible as the price of sequencing plummets downwards, and many disorders suggest themselves. Specific disorders such as long QT syndrome would be easy to deal with, but very broad screening would have equally broad problems.

**Kenneth Pass:** Without a doubt. Currently many programs are evaluating the addition of screening for SCID. The HRSA Advisory Committee on Heritable Disorders in Newborns and Children has recommended that SCID become a part of the core panel of disorders, meaning universal screening in the US for SCID is likely to be adopted rapidly. Results from nationwide pilot studies to evaluate SCID screening in an NBS laboratory, sponsored by the National Institute of Child Health and Human Development and the CDC, will provide valuable information for programs adding SCID to their panels in the near future. Interestingly, the currently accepted screening method for detecting SCID is a molecular test using real-time PCR, although multiplex bead immunoassays that appear to offer increased sensitivity and specificity have been reported. Use of the T-cell excision circle (TREC) assay would be the first time in which DNA is used as the primary biomarker by NBS. This, once again, will introduce a new technology to the screening programs, real-time PCR to detect TRECs in the Guthrie spot. The CDC,
Ronald Wanders: Yes. The advisory board for NBS on metabolic disorders has recently advised the inclusion of propionic and methylmalonic aciduria into the screening program. This advice will subsequently be discussed in the general perinatal screening committee, and we hope to have a positive response later this year. There is also discussion of including screening for mucopolysaccharidosis I and Pompe disease. However, more studies are needed before the advisory board will put this on their agenda.

Michael Watson: This is no doubt the case. The goal of many investigators and disease-advocacy groups has been the development of a low-cost screening test that can presymptomatically identify those at risk for a high-burden condition for which a treatment can significantly alter outcomes. Since the publication of the recommended uniform NBS panel in 2005, a federal advisory committee, the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children, was formed, and systems for nominating conditions for consideration with subsequent evidence-based reviews have been put into place. Nine conditions or phenotypes have been considered, including Fabry disease, Krabbe disease, and hemoglobin H disease, and SCID and critical cyanotic congenital heart disease have been recommended for addition to the screening panels. More conditions are in the queue for evaluation. The pipeline of treatments already in clinical trials for many of these types of conditions is also filling, so the expectation is that these programs will continue to expand.

Over the next decade, will the present technology continue to be the primary tool for NBS, or will alternative array-based molecular techniques take precedence?

Piero Rinaldo: NBS in the future is likely to be a combination of a few multiplex assays on 3 parallel platforms: MS/MS, bead-based immunocapture assays, and some type of array-based molecular technique. A key factor in defining what NBS will be in future times actually comes from the extent to which broad-based parental carrier screening will become an accepted standard of care. Furthermore, it is likely that future expansions will still be carried out on a regional basis, not state by state, as is done currently in most instances.

Bridget Wilcken: I believe that the present technology will dominate, overall, in the next decade. Prominent new technologies coming sooner rather than later might include digital microfluidics and some aspects of next-generation metabolic profiling. As to some form of array-based molecular techniques, I think and hope that everyone will proceed cautiously. Various molecular techniques can be applied to NBS. One new example might be an array to detect huge numbers of mutations for CF screening as a second-tier test. This could be good, but inevitably laboratories would be swamped with gene variants in combinations of uncertain significance, as well as detecting even more carriers, with the problems that would ensue. As a first-tier test, this would be overwhelming. Similarly, whole-genome sequencing will become very cheap, and NBS may seem a seductive target. It would be difficult to keep away from detecting risk factors of unclear predictive value for adult-onset disease, and carriers of serious or lethal disorders would be detected very commonly. The need for genetic counseling could be expected to increase exponentially. I hope assays related to function will continue to dominate for a while.

Kenneth Pass: Possibly. Historically, technology has been the driving force for the expansion of NBS panels. Indeed, the initiation of NBS as a public health program was made possible by the development of the bacterial inhibition assay (BIA) for PKU by Dr. Robert Guthrie in the early 1960s. Before the BIA, screening for PKU was based on testing for ketones in the wet diapers of infants. This was done in hospitals, clinics, and doctors’ offices in an uncoordinated manner, with less than optimum coverage for the newborn population. The BIA and use of a special filter paper for collecting a specimen (also proposed by Dr. Guthrie) that could be sent through the mail made centralization of testing possible. These are now known as Guthrie specimens in his honor. These 2 procedures provided the framework by which NBS programs became established in public health laboratories in the US and the foundation upon which most US programs now operate.

With the completion of the full sequencing of the human genome, there was great anticipation that molecular markers (genes) would replace today’s use of serum biomarkers, such as thyroxine and phenylalanine. Several reports had previously shown DNA could easily be extracted from the Guthrie spot and analyzed successfully for genetic markers. All that was needed was a technology to allow the testing of hundreds of Guthrie spots each day. During the wait for this new
speedy technology, studies have disputed the one-gene, one-product hypothesis because of many factors, among which imprinting, small interfering RNAs, and pseudogenes present especially difficult technical problems for a screening laboratory. Interestingly, the NBS community has begun evaluating systems that can reveal several biomarkers simultaneously, much as MS/MS had done previously, but with less-demanding immunoassays. With multiplex bead arrays, a pattern of biomarkers descriptive of conditions such as CH and CF can be identified. Thus, the ambiguity of today’s use of a single biomarker and/or single-gene analysis for a condition may be avoided.

**Michael Watson:** Present technologies based on the functional outcomes of genetic abnormalities as reflected in metabolic imbalances or altered protein structures remain powerful tools for NBS. Many genetic abnormalities at the molecular level are associated with significantly variable expression of the disease phenotype and with variability in disease penetrance. However, as the costs of targeted microarrays and whole-genome analysis technologies continue to drop, a point at which they become the first tier of an NBS algorithm may arrive. Proteomic arrays that may better reflect functional outcomes of genetic abnormalities and be more predictive of disease development will also continue to evolve. The critical issue will be how we develop the systems that enable well-controlled and well-organized clinical trials of these technologies in an environment of NBS to ensure their safe and effective evaluation.

**Ronald Wanders:** Difficult to judge, but I believe that at least for the next decade the current technology will continue to be the primary tool for NBS of inborn metabolic diseases. Since the full clinical value of techniques such as whole-exome sequencing remains unclear, use of these techniques for NBS cannot currently be predicted.

**Are the ACMG recommendations universally followed?**

**Piero Rinaldo:** Is 99% implementation in the US of the uniform panel good enough? I think so!

**Bridget Wilcken:** It is clear that the ACMG recommendations have had a big impact, not only in the US but also around the world. I believe that outside the US people involved in NBS consider the ACMG recommendations carefully but are usually not following them closely.

**Kenneth Pass:** Well, yes and no. All states now screen for the core panel of 30 conditions, with the exception of SCID, for which screening has been established only in Wisconsin, Massachusetts, California, and New York. One could expect SCID to be added soon by all US programs. Detailed information concerning the status of NBS programs in the US can be found on the CDC and APHL websites. Certainly, given adequate resources, all programs would add a new condition following its recommendation by the Advisory Committee. Regrettably, that is not the situation today.

**Michael Watson:** Uniformity in screening for the ACMG and Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children recommended panels of core or primary conditions to which laboratory-based screening is targeted has greatly improved across the states. More recently recommended conditions, such as SCID and critical congenital cyanotic heart disease, are at various stages of assessment, mandate, and introduction into screening by many states, a process now facilitated by national programs that allow for broad collaboration among early adopter states to more rapidly develop robust data on particular conditions during pilot testing. There is greater variability in whether particular states include the secondary conditions that also may be associated with the markers for the primary target disease. There is also some variability in whether states screen for conditions beyond those in the recommended panels, such as toxoplasmosis, hyperammonemia/hyperornithinemia/homocitrullinemia and glucose-6-phosphate dehydrogenase deficiency. Hopefully, those scientists in states for which screening for these conditions has been taking place will develop data that will allow the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children to evaluate them for further consideration for addition to nationally recommended panels.

**Ronald Wanders:** No. In the Netherlands, as in most European countries, the selection of diseases to be included in NBS programs is done independently of the ACMG recommendations. For the expansion of the NBS program in 2007 in the Netherlands, the Health Council, an independent scientific advisory body, provided the government with advice about which diseases to include. This advisory board consists of medical doctors, ethicists, clinical geneticists, legal advisors, and patient organizations. Currently, the separate disease-specific advisory boards, such as the one on inborn errors of metabolism, can also advise about inclusion of a disease.

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