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NEWBORN SCREENING: TOWARD A JUST SYSTEM

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Abstract

Many characterize America's newborn screening initiatives as the modern-day miracle of our public health systems. Collectively, state programs manage to test the 4 million neonates born every year in the U.S. for at least a minimal number of genetic and metabolic disorders.

These catastrophic diseases, though treatable, are asymptomatic or exhibit no clinical signs in the early neonatal period.[1] *Newborn screening (NBS), then, is the only way to identify the disorders early enough so that treatment can be initiated before it is too late to prevent harm.*[2] *Thanks to post-screening treatment, every year an estimated 3,000 affected infants develop normally instead of succumbing to severe liver disease, physical disability, mental retardation or sudden death.*[3]

My analysis of the ethics of American newborn screening programs (NBSPs) is not a concern about their intrinsic morality. It is concern over the fact that every year more than 2,000 babies die or suffer morbidity[4] *precisely because they were not comprehensively screened. The ethical dilemma plaguing American NBS, then, is that of unequal access to a quality system. Resolving this moral issue is a matter of applying the first principle of justice: "to all equally according to their needs."*[5] *As every infant shares equally in a common human nature and, therefore, experiences the same natural needs for the goods of health, life, and safety, so every newborn is in justice—or by right—entitled to pursue those goods (including quality NBS).*

Here I argue that the cardinal responsibility of state administrators is to develop just screening systems: programs that make it possible for every neonate in every state to have equal access to an advanced, comprehensive and well-coordinated newborn screening system (NBSS).[6]

Part I: Background

America's health-based population screening program—with its current multi-component system of education, follow-up, diagnosis, treatment, and program evaluation—began with the development of a single assay. In 1962, Dr. Robert Guthrie produced the first "simple, sensitive, and inexpensive screening test"[7] for neonates born with a metabolic disorder called hyperphenylalanemia or phenylketonuria (PKU). The latter, a disease most often inherited in an autosomal recessive pattern, involves an inborn error of metabolism (IBEM)[8] that causes a toxic buildup of phenylalanine in the infant's body and, ultimately,

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retardation and death. In the mid-1960s, Massachusetts mandated the first mass NBS program by testing all its infants for PKU. Today all states test for at least PKU, congenital hypothyroidism (CH) and galactosemia (GS).

In the 1990s, laboratory developments produced sophisticated biochemical testing methods such as tandem mass spectrometry (MS/MS).[9] With the capacity to measure for amino acids and acylcarnitines simultaneously in a single, two-minute assay, MS/MS can be used to screen for 20 treatable inborn errors of metabolism (IBEM) and over 30 reportable metabolic disorders. Currently many states utilize MS/MS which, together with high-pressure liquid chromatography and flourometric methods, make it possible to not only screen for IBEM, but also for hematological disorders, endocrinopathies, infectious diseases, and inherited disorders such as cystic fibrosis.[10]

As of June 1, 2005, the March of Dimes reported that 23 states screen for more than 20 of the recommended disorders; 12 states screen somewhere between 10 and 20 disorders; and 15 more states and the District of Columbia screen for less than 10 conditions. As of this writing, Mississippi is the only state that screens for all of the 29 diseases recommended by the American College of Genetic Medicine, the Health Resources and Services Administration (HRSA), the March of Dimes (MOD) and the American Academy of Pediatrics (AAP).

Prior to the newborn's discharge, most NBS tests require a blood specimen, a few droplets of blood drawn from the baby's heel and dried on a piece of absorbent paper. In a well-coordinated NBSS, collecting the blood specimen sets in motion a host of follow-up measures: laboratory analysis of the blood sample; notification of test results to clinicians/parents; repeat diagnostic test for test-positive infants; referral of affected infants to appropriate disease specialists for treatment management; and long-term care support coordinated by the involved primary physician.

Part II: Identifying Weaknesses

Based on NBS studies, I have identified the following design and outcome deficiencies in each of the NBSS components as well as operational weaknesses in the system as a whole.

A. Education

The General Accounting Office reports that there are still a few state programs that do not educate parents about NBS. Of the majority that do, less than one-fourth inform parents of their option to screen for disorders not included in the state-mandated screening panel.[11,12] Most importantly, without uniform guidelines to stipulate content, there is no way, currently, to guarantee thorough NBS education for parents in every state.

NBS information is generally distributed to hospital staff, midwives, pediatricians, primary care providers and local health department staff, with the presumption that the latter will distribute the material to parents. But this dissemination strategy makes it difficult, if not impossible, to track whether the educational materials are ever delivered to parents or whether they adequately understand the disseminated information. Furthermore, only a minority of state

screening programs involve both obstetricians and pediatricians in parental NBS education. And very few programs provide educational information in languages other than English.

More than a few states report that program administrators and some participating health care professionals, particularly primary clinicians, are insufficiently knowledgeable both about the goals and procedures involved in NBS in general and with genetic medicine and the latest genetic tests in particular. Nor has the introduction of mass spectrometry always been accompanied by adequate technical training for both laboratory experts (who are expected to perform the analyses) and medical specialists (who will interpret the large amount of data generated by the blood sample analysis).[13]

B. Screening

Wide variability in the number of diseases screened in each state follows directly from the lack of uniform criteria for screening expansion.[14] Some state programs, for instance, decide to screen for new diseases based on: cost,[15] test availability, and possibility of treatment; others rely on the latest findings of disease research, do not figure in costs, and consider diseases for which there is no documented treatment. Many state programs cannot expand their testing panel to include more than 20 metabolic disorders because they cannot afford the expensive spectrometers needed to screen them.[16]

There are also divergent informed consent practices. Ten states neither notify parents nor procure their consent for screening. Thirty-eight states notify parents but do not ask their consent for the collection of the blood sample. Only 3 states require parents to sign consent forms for NBS.[17]

Forty-eight states allow parents to refuse NBS. Twenty-seven state programs permit parents to refuse screening only for religious reasons, several allow exemptions for any reason. Parents in 5 states are required to give only a verbal notification of refusal to screen when it is for a religious reason, and parents in one state can verbally refuse screening for any reason.[18]

There are no uniform policies specifying the purposes for which residual NBS blood samples can be used[19] or whether the specimens should contain patient identifiers.[20] Although residual specimens are currently being used for research and epidemiological studies, four states' programs do not require researchers to obtain prior approval. Others allow researchers access to the data only upon IRB approval from the state lab or from the state program director. Currently, there is also no consensus amongst state programs about the ethics of using residual NBS samples for forensics purposes.[21]

Some states fund their NBSP, in part or in full, through state tax dollars; others finance their program solely through screening fees. According to one survey, current fees range from ten to sixty dollars, and eight states charge no fee at all. Some programs bundle the cost of genetic counseling, follow-up care, treatment and education into the screening costs; others charge only for laboratory fees.[22]

Twenty-six state NBSPs have advisory committees that include lay membership. Together with other advocacy or community support groups, state advisory committees have raised public awareness of screening for metabolic

and genetic diseases, especially among expectant mothers. In addition, they have exerted political pressure on state health departments to expand and standardize their screening panels.[23]

C. Follow-up

In general, almost all state screening programs are plagued by an unacceptable level of false positive test results, especially in respect to endocrinopathies.[24] Similarly, due to lack of uniform guidelines, programs are also inconsistently successful in avoiding false negatives.[25]

In respect to achieving the needed rapid turn-around time for repeat testing following positive results, some state programs lag far behind others.[26]

Even though many NBS specialists have good reason to argue that repeat testing ought to be universally mandated, only 8 states require that their newborns be screened a second time at a later date. In the other 42 programs, repeat screening is only ordered if the first test was before 24 or 48 postnatal hours.[27]

State NBS notification practices compromise the ability of some parents to actively participate in their child's health care. For instance, in all but 2 state programs, normal screening results are reported to the birth hospital, not to the parents. Then, almost 80% of surveyed pediatricians followed a "no news is good news" rationale in reporting those test results to parents.[28] Fewer than half the states directly notify parents of abnormal results; no state directly notifies parents of normal results.

While each state program keeps a database of its screened newborns in order to track presumptive-positive infants, only two thirds of them are set up for inter-state database networking.[29]

D. Diagnosis

Currently, more than half of America's NBSPs have regulations in place to insure that the diagnostic information they collect is kept confidential.[30] However, the jury is still out on the question at the center of the debate: Do insurance companies have the right to know positive diagnostic test results? Without appropriate access guidelines, there is always the possibility that insurance companies will use NBS diagnostic information to "discriminate in … unacceptable ways."[31] Furthermore, few screening programs have set up a mechanism for educating insurers about the significance of NBS diagnostic results.[32]

Currently, there appears to be no uniform confidentiality guideline stipulating whether parents can withhold their newborn's diagnosis from the primary clinician or whether parents can order the physician not to record the information on the newborn's chart.

State NBSPs vary widely in respect to their provisions for genetic counseling and carrier screening for parents and siblings of an infant diagnosed with a genetic disease. To date, no consensus on best practices has emerged,[33] and there are no national quality assurance standards for the actual counseling services.[34] Disagreements in counseling practice stem from divergent response to pertinent questions. First: How should counseling programs handle carrier

test results that challenge family relationships such as paternity? Second: Is the state screening program responsible for explaining to family members the medical implications of being genetically related to diagnose-positive infants.[35] Third: Should NBSPs inform parents of their carrier status and alert siblings to voluntary carrier screening? Only a minority of state programs provide genetic counseling for parents or siblings who are unaffected carriers.[36,37]

E. Treatment

Some state screening programs neither refer their affected newborns for treatment nor confirm when their care begins. Only 60% of programs annually track affected infants to "ensure continuous access to care, follow-up and support" and to provide "the resources to obtain needed medications and therapies."[38] However, *long-term* treatment management (from infancy through childhood and adulthood)[39] appears to be the weakest link in almost all state programs.[40]

Furthermore, screening programs vary in their ability to connect primary physicians, especially those in rural areas, with clinicians at specialized pediatric centers.

F. Evaluation

There appears to be some limitations within and disparities between state NBSPs regarding the evaluation (continuous oversight and improvement) of their respective systems. To date, only a few screening programs facilitate system excellence by carefully delineating where the activities of each system component begin and end so that the networking of their programs is "seamless and nonduplicative."[41] Not all state NBSPs are consistent about policy formation in respect to quality assurance (QA) standards for all NBS services; to monitoring programs that evaluate whether QA standards are realized; to ongoing improvements in the various parts of the system beyond testing, or to the implementation of duplication-free data collection and networking.

Some sparsely populated states have managed to meet quality assurance standards for testing methods by regionalizing the laboratory component of their NBSSs.[42] A significant number of programs monitor the quality of their screening activities—interpreting complex results as well as tracking diagnostic and treatment service delivery—by purchasing the information-processing technology that facilitates such evaluation.

While most states have advisory committees which recommend ways of achieving system excellence, some have yet to establish this important "public" aspect of program evaluation. Similarly, only a few NBSPs have been built in collaboration with their state's medical or public health professional organizations (e.g., State Maternal and Child Health Program, State Laboratory of Hygiene, State Division of Public Health, Department of Health and Family Services).[43] Furthermore, due to insufficient state-federal cooperation on NBS issues, state screening programs receive limited advice from national advisory committees (ACGM) and national medical (AAP) or public health professional organizations (HRSA, March of Dimes).[44]

NBS studies suggest a link between the non-judicious management of

some state programs and the dearth of uniform quality standards for NBS administration. For example, some screening systems have expanded testing, but have failed to proportionately expand services in downstream system components.[45,46]

Part III: Recommended Resolutions

A. Education

The following national policy guidelines would help to correct the deficiencies threatening the quality of the education component of state programs:

First, *obstetricians should be responsible for parental NBS education in the prenatal period; pediatricians in the postnatal period*. In both phases, the clinicians must reinforce verbal instruction with printed materials. These same clinicians should also provide comparable educational opportunities for non-English speaking parents.

Second, *primary clinicians should be required to discuss specific aspects of NBS with parents*: the importance of having a newborn screened; which diseases are screened by the state, which by private labs; what a normal test results means; what an abnormal test means; the chances of having an affected infant (1 in 1500 births);[47] how and when parents need to respond to a positive test; importance of timely treatment management for affected neonates; and websites (http://genes-r-us.uthscsa.edu/nbsdisorders.pdf) where parents can find more detailed information about NBS in general, individual state programs in particular, and respective parental support and advocacy groups.

Third, *NBS program administrators, obstetricians, pediatricians and their nursing colleagues should be trained in NBS on levels commensurate with their professional involvement*.

- All should be thoroughly acquainted with the nature and goals of a quality NBS program and to what extent their state program has accomplished those goals.
- Primary physicians should, first, understand their respective roles and responsibilities in working toward a quality system and, second, understand the important interface between them and the laboratory and medical specialists involved in diagnosis and treatment.
- Pediatricians must be adequately trained to carry out their duties of initial management following notification of test results: discuss the significance of positive/negative initial screening results; refer the affected infant to appropriate medical centers and subspecialists; coordinate the scheduling of additional tests necessary for a definitive diagnosis, and inform parents of affected newborns about the option of carrier status testing and family genetic counseling.
- Pediatricians must be trained in the basics of human genetics as well as population genetics;[48] have knowledge of the actual tests; be aware of factors that could influence test results (gestational age, early

discharge, diet, and transfusions); and be able to effectively translate technical genetic information into layman's terms so parents can understand it.

Fourth, *genetic specialists involved in NBS diagnosis and treatment must be thoroughly conversant in the etiology, pathophysiology, clinical heterogeneity, and psychosocial issues associated with each of the screened diseases. They should also be required to attend whatever continuing educational opportunities are necessary to maintain their professional competency.*[49]

Fifth, *laboratory technologists must have adequate theoretical and practical training in biochemical testing, especially that of mass spectrometry.*

B. Screening

The following national policy guidelines should help to correct the deficiencies threatening the quality of the screening component of state programs:

First, *the pediatrician (or appropriate health care representative) should notify parents when their newborn's blood specimen is being collected and screened*. (I would argue *against* a policy requiring parental consent for newborn testing. The state has the authority to mandate NBS because it is a safe, simple and beneficial means of carrying out one of its primary responsibilities: protecting the health and welfare of its newborn citizens. In doing so, the state presumes [rightly, in my estimation] that any reasonable person, given the chance, would chose to be screened. In such a context, parental consent is redundant.)

Second, *there are no justifiable grounds for parental refusal of NBS specimen collection and testing*. (I would contend that, in *Douglas County v. Anaya*, the Nebraska Supreme Court put sound legal [and ethical] flesh on the argument that parents do not have a right to refuse NBS for a religious [and, by implication, for any other] reason. The higher court ruled that the screening statute of Nebraska is neutral and of general applicability, that is, it "does not aim to infringe upon or restrict practices because of their religious motivation" and it only incidentally [if at all] imposes burdens on conduct motivated by religious belief. Therefore, the state screening statute is presumptively constitutional and need only have a "rational basis." The reasonable basis—infants "'can grow and develop to be free of a metabolic disease' through a 'blood test administration which is merely a pinprick to the child's heel'"—overcomes the Anaya's constitutional challenge (based in their belief that "life is taken from the body if blood is removed from it and that a person's lifespan may be shortened if blood is drawn").[50]

Third, *every state ought to screen for a uniform set of diseases (Current recommendations: a core panel of 29 [treatable] metabolic and genetic diseases and a secondary panel of 25 reportable disorders for which there are no documented treatments)*.

Fourth, *every state should follow a uniform criteria matrix in adding diseases to their screening pane*. For example: the disease can be detected at a phase when it would not ordinarily be clinically detected; an appropriately sensitive and specific test is available; benefits of early detection include, but are not limited to, treatment of the condition;[51] scientific evidence and expert opinion corroborate screening for the disease(s) in question.

Fifth, *standards for specimen collection should include, first, a consistent, careful technique to ensure an adequate sample and, second, proper documentation from requisition for testing to appropriate processing and follow-up.*[52]

Sixth, *every state screening program should be funded by state tax revenues earmarked for NBS and by affordable uniform screening fees* (covering at least partial costs of education, screening, follow-up, treatment and genetic counseling).

Seventh, *Federal NBS legislation should authorize a national NBS oversight agency to subsidize state screening fees/state tax dollars with federal funding*: facilitating a) the purchase of expensive spectrometers essential to test expansion; b) continuing education for the medical professionals involved in NBS; c) educational materials and services for parents and families; d) long-term support for affected children;[53] and e) payment of screening fees for parents who are poor, uninsured or lack a permanent home. National policy should specify realistic screening fees, relying on the proven cost-effectiveness of NBS where protracted benefits to affected individuals aggregate over costs.[54]

Eighth, *in deciding legitimate uses of residual NBS specimens, the interests of parents and minors must be balanced against those of researchers (the study of medical genetics)*[55] *and forensic experts (the pursuit of law enforcement goals).* If residual blood samples are used for either purpose, proper consent must be obtained from the parent or the patient if they are of age.

Ninth, *screening specimens should be stored in ways consistent with patient privacy* (e.g., using a coding system that prevents researchers from knowing the identity of the newborn but allows authorized individuals to decode a specimen if a future need arises).

C. Follow-up

The following national policy guidelines would help to correct the deficiencies threatening the quality of the follow-up component of state programs:

First, *the level of false positive results must be brought to an acceptable level through mass spectrometry analysis and by designing tests with more specific markers for the detection of the respective diseases,*[56] (particularly congenital endocrinopathies).

Second, *the administration of initial screening and the follow-up of positive tests must be ordered correctly and performed on an appropriate schedule.*

Third, *repeat tests should be mandated for all infants at a specified interval after initial screening.* Mandated repeat testing is necessary because a) newborns tend not to have adequate protein intake by the time of the initial test; b) some infants are transfused prior to the initial screening test; c) some infants receive antibiotics or other interfering substances that could limit the interpretation of results; d) some infants are premature, or e) in the case of heat-damaged specimens, some tests are inadequate or results are inconclusive.

Fourth, *testing laboratories (public and private) should notify primary clinicians of test-positive infants immediately and inform involved clinicians of test-negative infants within 7 days.*

Fifth, *primary clinicians (pediatricians) should promptly report test results to parents verbally and in writing and then discuss their implications*: the chances are good that a test-positive infant does not have the disorder, but more definitive tests need to be scheduled without delay; there is a high probability that a test-negative baby will not evidence the disease later, but parents need to inform the pediatrician immediately when they observe any weakness or developmental delays in their infant.

Sixth, *primary clinicians should follow the "Action Sheet"*[57] *guidelines developed by ACGM for each screened disease to assure an expeditious response to test-positive infants and a step-by-step timely pursuit of diagnosis and treatment.*

D. Diagnosis

I recommend the following national policy guidelines to help correct the deficiencies threatening the quality of the diagnosis component of state programs:

First, *every state NBSP should employ the number of specialists proportionate to the diagnostic demands (testing, analysis) within its system.*

Second, *post-diagnostic genetic counseling and carrier screening for the parents and family of affected newborns must follow appropriate quality assurance standards:* counselors must have adequate genetic and psychosocial training; carrier testing should be available but on a voluntary basis; the best interests of the involved sibling or parent is the driving principle of carrier status screening; potentially untoward information (non-paternity, e.g.) could be withheld as long as the best interests of all others involved are not compromised.

Third, *insurance companies do not have a right to access the genetic information generated by a newborn screening diagnosis.*

Fourth, *parents have the right to instruct the physician not to record positive screening results on the newborn's chart or to request that test results are withheld from the primary physician only if doing so does not compromise the right of the newborn to pursue health and life.*

Fifth, *every state screening program should be a part of a NBS database networking system that tracks affected infants, facilitates genetics research, and avoids needless duplication.*

E. Treatment

The following national policy guidelines would help to correct the deficiencies threatening the quality of the treatment component of state programs:

First, *every state program must refer affected newborns for treatment, confirm when treatment begins and track ongoing treatment including regular access to needed dietary and medicinal therapies.*

Second, *proper uniform referral mechanisms must be in place so that primary physicians, especially in rural areas, can procure treatment for their affected newborn patients with clinicians at specialized pediatric centers.*

Third, *every state screening program should provide long-term treatment management for persons with rare metabolic and genetic diseases.*

F. Evaluation

The following national policy guidelines would help to correct the deficiencies threatening the quality of the evaluation component of state programs:

First, *every state NBS administrator must be adequately trained and required to pursue continuing educational opportunities both in the art of management and in the science of NBS.*

Second, *it is the responsibility of NBS administrators to procure the necessary technological infrastructure for their programs: the most advanced laboratory analysis technology (to efficiently support NBS testing and follow-up) and up-to-date information-processing technology (for effective oversight and evaluation).*

Third, *it is the responsibility of the NBS administrator to procure state/federal funding for the needed information-processing technology and to train the IT experts who will use it to monitor quality, track outcomes and interpret complex results.*

Fourth, *it is the responsibility of the NBS administrator to establish a state advisory committee with a broadly representative membership and to link it to national counterparts.*

Fifth, *it is the responsibility of the NBS administrator to implement national guidelines defining the quality of each system component and their seamless coordination.*

Conclusion

I have argued that the need for uniform NBS policies is evidenced in the fact that, without federal oversight, state NBSPs have expanded sporadically and with uneven quality. But every child's right to quality NBS can only be realized when every state program is equally excellent. I am confident that the formulation of national guidelines like those recommended above and their universal implementation through cooperative state/national administrative agencies would help to shape a NBSS in every state that is advanced, well-balanced, coordinated and, therefore, *just*. Thus, every newborn, in whatever state they reside, will have equal access to quality NBS services.

Endnotes

1 Diseases such as phenylketonuria (PKU), congenital hypothyroidism (CH) and galactosemia (GS), currently screened in every state, can cause infants irreparable damage if left undiagnosed and untreated. Consequently, public newborn screening programs do not *just* screen. They also provide a comprehensive system of education, follow-up, diagnosis, treatment, and program evaluation.

2 Bradford L. Therell, Jr., "U.S. Newborn Screening Policy Dilemmas for the Twenty-First Century," *Molecular Genetics and Metabolism* 74(2001):64, 67.

3 Gatrell Bryant, Kimberly M. Horns, Nicola Longo, Julieanne Schiefelbein, "A Primer on Newborn Screening," *Advanced Neonatal Care* 4(2004): (p. 1 of online copy available at: http://www.medscape.com.viewarticle/493247).

4 "Senator Dodd Introduces Bill to Encourage Newborn Screening for Life-Threatening Disorders," Press Release, August 28, 2002 (http://caresfoundation.org/news_letter/fall02).

5 Mortimer Adler, *Six Great Ideas* (New York: Touchstone) 1990, 164-173, 180, 191.

6 My thesis agrees with a recommendation from the report of the American College of Genetic Medicine: every state ought to screen their newborns for a core panel of 29 conditions and for an additional 25 conditions that "are a part of the differential diagnosis of a condition in the core

panel or are clinically significant and revealed by the screening technology but lack an efficacious treatment." ("Newborn Screening: Toward a Uniform Screening Panel and System," Executive Summary, 23).

7 Bryant, Horns, Longo, Schiefelbein, "A Primer on NBS," 2.

8 Metabolic disorders or IBEM negatively affect the body's ability to produce or break down compounds such as amino acids, organic acids, and fatty acids into smaller substances that the body needs for energy, growth and repair. Amino acids are the building blocks of proteins, and proteins govern somatic cell functions. Before amino acids can do their work, various enzymes must be present. When these enzymes are missing, *amino acidurias* result. Abnormally large quantities of amino acids in the urine or blood have toxic effects on the body and can cause mental retardation. *Organic acidurias* typically occur when a lack of enzymatic activity causes a missing or malfunctioning step in amino acid catabolism (chemical breakdown*). Fatty acid oxidation disorders* results when oxidation, the process that breaks down fatty acids releasing energy crucial for bodily functions, is interrupted due to missing enzymes. Without treatment, infants with FAODs risk coma and death (ARUP, "Supplemental Newborn Screening," found at: //www.arup-lab.com/home/pediatric_testing/sns_faqs.jsp).

With phenylalanemia (PKU), the neonate lacks the enzyme phenylalanine hydroxylase necessary to process the amino acid, phenylalanine, found in almost all food. Accumulated amounts of phenylalanine impairs development of the CNS. Failure to treat this disease results in seizures and severe mental retardation.

In galactosemia (GS) the infant lacks one of three enzymes (galactose-1-phosphate uridyl transferase, galactokinase, or uridine diphosphate-galactose-4-epimerase) required to break down galactose into glucose. Treatment consists of a galactose-free diet. Failure to treat results in "failure to thrive, mental retardation, liver disease, cataracts, and even death from sepsis or bleeding" (Bryant, Horns, Longo, Shiefelbein, "A Primer on NBS," 6).

9 Tandem mass spectrometry tests compounds in the infant's blood called amino acids and acylcarnitines. Amino acids are the building blocks of proteins that become important parts of tissues, muscles, organs, blood. Carnitines transport fats in and out of the cell's energy factory, the mitochondria. An acylcarnitine occurs when a fatty acid attaches to carnitine. Acylcarnitines are identified by the size of the fat molecules attached to it. A mass spectrometer weighs the acylcarnitines present in the infant's blood and reveals how much of any specific acylcarnitine is present. The report produced by mass spec analysis displays vertical lines distributed across a horizontal axis (a mass spectrum) where the vertical lines identify a compound's mass and the height of the line indicates the amount of the compound. MS/MS is very accurate and is able to measure more than one compound simultaneously in a single, 2-minute analysis. More than 30 metabolic disorders can be screened with MS/MS.

A spectrometer is referred to as a *tandem mass* spectrometer because of its two mass analyzers that are separated by a collision chamber. "It requires a few droplets of blood on filter paper. After the specimen is dry, 4 small circular punch-outs are made and prepared. Next, the sample is injected into the spectrometer where it is ionized, sorted, and given a molecular weight (the ratio of the mass of the ions to their charge) in the first analyzer. The ions then enter the collision chamber where they are broken into smaller fragments. The fragments enter the final chamber where they are resorted and weighed. The info detected is then plotted on a histogram for interpretation. This technique can identify and quantify most amino acids and generate an acylcarnitine profile to screen for disorders of fatty acid oxidation and organic acidemias" (Ibid, 5).

10 ACGM Report, "Newborn Screening," 23. Cystic fibrosis can be detected by screening a newborn's dried blood specimen for concentration of immunotrypsinogen. Dr. Paul Fernhoff, medical director of the Department of Human Genetics at Emory University School of Medicine, points out that cystic fibrosis, absent NBS detection, would probably not be diagnosed until the child is from one to three years of age, by which time he/she would have suffered numerous infections and the family would have been frantically looking for a diagnosis. With early detection comes early treatment and a brighter prognosis for the cystic fibrosis patient. (Patricia Guthrie, "Georgia lags in testing newborns," *The Atlanta Journal-Constitution* 7/12/05 [online at http://www.ajc.com/metro/content/metro/atlanta/0705/12screening.html].)

11 U.S. General Accounting Office Report to Congressional Requesters, "Newborn Screening: Characteristics of State Programs," March, 2003 (available at www.gao.gov/cgi-bin/getrpt?GAO-03-449).

12 As Debra Gara responded after losing her baby who died because her rare, but screenable and treatable, disease was not detected: "I'm angry at the state, too, but I'm more angry at the medical profession for not telling me anything (about supplemental screening options). ("Parents Seek Expanded Newborn Testing," Associated Press, April 28, 2003 [http://www.intelihealth.com/IH/ihtPrintWSIHW000/333/8010/363942.html].)

13 Cf. "Save Babies Through Screening Foundation, Inc" (http://www.savebabies.org/NBS/msms-chace.phb).

14 Therell, "U.S. Newborn Screening Policy Dilemmas," 67.

15 Ibid., 71.

16 "Parents Seek Expanded Newborn Testing," Associated Press, April 28,2003 (http://www.intelihealth.com/IH/jhtPrint/WSIHW0000/333/8010/363942.html). Senators Dodd and DeWine are still looking for their colleagues' support for federal legislation that would help fund the MS/MS technology that would facilitate just such expansion.

17 Kenneth D. Mandl, Shlomit Feit, Cecilia Larson and Isaac S. Kohane, "Newborn Screening Program Practices in the United States: Notification, Research, and Consent," *Pediatrics* 109(2002):272.

18 Ibid.

19 Therell, "U.S. Newborn Screening Policy Dilemmas," 67.

20 Mandl, Feit, Larson and Kohane, "Newborn Screening Program Practices, 271.

21 Therell, "U.S. Newborn Screening Policy Dilemmas," 73.

22 Bryant, Horns, Longo, Shiefelbein, "A Primer on NBS," 2.

23 The inspiring precedent for this was the advocacy work of Dr. Guthrie (whose own child was retarded and whose niece had PKU) who "took his screening ideas to groups for the political support needed to move screening ideas into government-run public health institutions." (Therell, "U.S. Newborn Screening Policy Dilemmas," 65.)

24 Abstract: Kwon C. Farrell PM, "The magnitude and challenge of false-positive newborn screening test results," *Archives of Pediatrics & Adolescent Medicine,* July, 2000 in AAP, HRSA's, "A Compendium of Resources," 4.

25 Some state programs report false negatives, for example, in newborns suffering from GS. The infants falsely tested negative because they were tested before they ingested breast milk or formula containing lactose and, consequently, before high levels of galactose were present. (Therell, "U.S. Newborn Screening Policy Dilemmas," 65.)

26 Bryant, Horns, Longo, Schiefelbein, "A Primer on NBS," online copy, 4. A case in point: some state programs report that their test-positive premature infants who are transferred to another medical facility have not been re-tested in a timely fashion, since the system was not appropriately linked to the infant's current health care provider.

27 Ibid., p. 3

28 Ibid., p. 4.

29 Mandl, Feit, Larson and Kohane, "Newborn Screening Program Practices," 269. This means that only two-thirds of state programs have the ability to efficiently track affected infants and their parents in the event of residence change.

30 U.S. GAO, "Newborn Screening: Characteristics of State Programs," 24.

31 Abstract: O'Neill, O. "Genetic information and insurance: some ethical issues," *Philos Tran. R. Soc Lond B Biol Sci* 1997: 352(1357):1087 in AAP, HRSA's "A Compendium of Resources," 46.

32 It is probably safe to assume that insurance providers, like many other lay people, frequently misunderstand the medical distinction between the diagnosis of "unaffected carrier" for a genetic disease and that of "affected carrier."

33 Abstract: Farrell M. "Genetic counseling and risk communication services of newborn screening programs," *Archives of Pediatrics & Adolescent Medicine.* 155(2):120-6, 2001 Feb in AAP, HRSA's "A Compendium of Resources," 60.

34 Ibid.

35 CM Constantin, A Faucett, IM Lubin, "A Primer on Genetic Testing," *Journal of Midwifery & Women's Health,* 50(2005):202.

36 Unaffected carriers for an autosomal recessive disease have a single copy of the defective gene but do not suffer from the effects of the disease. Affected carriers have two copies of the defective gene (one from their mother; the other from their father) and suffer the disease's effects. If both spouses are unaffected carriers for a particular autosomal recessive disease, they have a 25% chance of having a child with two copies of the abnormal gene, a 50% chance of having a child who is an unaffected carrier and a 25% chance of having an unaffected non-carrier child.

37 AAP, "Ethical Issues With Genetic Testing in Pediatrics," *Pediatrics* 107(June, 2001):1451-53.

38 Bryant, Horns, Longo, Schiefelbein, "A Primer on NBS," 11.

39 Therrell, U.S. Newborn Screening Policy Dilemmas, 73. As one physician put it: "What is the value of a public health screening program in which children fall through the cracks? The importance of follow-up NBS treatment management was discussed after a lecture ("Economics of Newborn Screening") delivered by Jean Ann Wright, MD, MBA at the AAP conference presented

on November 1, 2003 at the Hilton New Orleans Riverwalk: *Ethical Issues in Expanding Newborn Screening*.

40 ACMG report, "Newborn Screening," 2.
41 Therell, U.S. Newborn Screening Policy Dilemmas, 72.
42 Ibid., 65.
43 Abstract: Ciske JB. Hoffman G. Hanson K. Annable KM. Wolff J. Litsheim T. Laessig R. Aronson R., "Newborn screening in Wisconsin: program overview and test addition," *Wisconsin Medical Journal* 99 (2):38-42, 2000, Apr in AAP, HRSA's "A Compendium of Resources," 1.
44 ACGM report, "Newborn Screening," 31.
45 Therrell, Dilemmas, 71. NBS administrators sometimes lose sight of the fact that increased testing means a higher volume of presumptive positive lab results, which require more expert laboratory and medical evaluations, which require more specialist personnel for proper diagnosis and treatment.
46 Ibid., 72. Furthermore, not all state systems have successfully negotiated cooperation between their own and private screening programs. In some instances, state administrators have not made sure that, whenever necessary, the state systems are able to absorb the follow-up and treatment services from private testing labs.
47 While the chances that a baby tests positive for one of the 20 recommended disorders are 1 in 1500 births (Cf. www.aboutnewbornscreening.com/faq.htm), the national incidence of the four most frequently tested diseases varies considerably: for congenital adrenal hyperplasia (1:20,000); congenital hypothyroidism (1:3,000); for galactosemia (1:59,000) and hyperphenylalaninemia (PKU) (1:14,000).
48 Therell, Dilemmas, 70.
49 Ibid.
50 Douglas County, Nebraska, appellee, v. Josue Anaya and Mary Anaya, husband and wife, as parents of Rosa Ariel Anaya, a minor child, appellants. On March 25, 2005, the Nebraska Supreme Court denied the Anaya's religious challenge of NBS. There is a similar case working its way through the Federal court system. The ACLU has filed an amicus brief on behalf of Ray and Louise Spiering who are challenging the Nebraska NBS statute based on the Scientology practice of not disturbing newborns for seven days after birth.
51 The MOD gives three reasons for screening reportable diseases with no documented treatments. First, parents who know that their child is suffering from one of these disorders is spared treatment odysseys. Second, they can be on the lookout and advocate for research that might eventually lead to a treatment for their child's disease. Third, the parents can also use the knowledge of their carrier status to make future reproductive plans as well as deciding about genetic testing for siblings of the affected newborn.
52 Bryant, Horns, Longo, Shiefelbein, "A Primer on NBS," 7.
53 This might include monetary support for anything from helping families afford the dietary and medicinal resources for long-term management of a disease to supporting patient transition from child to adult care to providing low-cost phenylalanine formula for PKU newborns.
54 ACGM report, Newborn Screening, 22.
55 O'Neill, O. "Genetic information and insurance: some ethical issues," *Philos Tran. R. Soc Lond B Biol Sci* 1997:352(1357):1087.
56 Abstract: Kwon C. Farrell, "The magnitude and challenge," in Compendium, 4.
57 ACGM report, Newborn Screening, 5.

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