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Newborn Screening in the 21st Century

From the Editors and Authors:

Since our last Update on Newborn Screening in 1998, there has been significant expansion of newborn screening programs in various regions of the country, mostly to include metabolic disorders identifiable by tandem mass spectrometry. States in our region are just now starting to expand their programs. The Summer 2005 *Genetic Drift* provides an update on newborn dried blood spot screening (NBS). Specifically, this *Genetic Drift* issue explains for health care providers the new laboratory techniques (tandem mass spectrometry or MS/MS) used to screen for a large number of metabolic disorders, provides a brief and simple description of the main categories of disorders that can be identified by MS/MS, and differing ethical views on newborn screening expansion. Some of the views expressed in the articles differ from those of the Editors or other Authors. However, it is important to present different viewpoints of this important public health service to the readers to allow them to recognize the challenges we face in this genomic age.

At the national level, the American College of Medical Genetics (ACMG) has issued a comprehensive report supporting the expansion and uniformity of newborn screening panels among different States. This report presents one of the rare evidence-based recommendations in favor of screening neonates for additional disorders. A brief summary of the criteria used to identify disorders to be included in newborn screening programs and a list of the disorders identified is also provided in this issue of *Genetic Drift*.

Newborn screening programs are probably one of the best examples on how advances in genetic research can be translated into medical care and preventive medicine. Newborn screening can work well only if there is a close collaboration between the public health sector, laboratory medicine, metabolic specialists, and the medical home of affected patients. It is our hope that the concepts presented in this issue will provide an opportunity for all of us to realize our shared goals and support further collaboration to promote the health of all newborns.

Lastly, the Teratogen Hot Topic for this issue is on the statin medications used to treat hypercholesterolemia. Currently all statins are FDA category X, meaning not to be used during pregnancy.

This issue was spearheaded by Rebecca Anderson, RN, BS (UT) and Nicola Longo, MD, PhD (UT), with additional contributions from Randy Heidenreich, MD (AZ), Marzia Pasquali, PhD (UT), Jeffrey Botkin, MD, MPH (UT), Joseph Martinec (TX) and Dee Quinn, MS, CGC (AZ). Senior Editor is Carol Clericuzio, MD (NM).

In This Issue

Newborn Screening Then and Now

Nearly seven years have passed since the *Genetic Drift* last dealt with newborn screening. While there are many new considerations, the following review and update of the topics in the previous edition seems timely and relevant.

Alternative use of newborn screening blood spots still remains an issue for programs. It is clear that these blood spots represent a "treasure-trove" of population genetic information. Yet, genetic population studies are not the goal when these specimens are initially obtained, and the vast majority of states do not obtain consent from parents for such uses. Additionally, there is significant variation in the amount of time newborn screening spots are stored and in the methods used to store them. No consensus exists among the many programs regarding research use of newborn screening spots and it will likely take a national consensus to help guide programs.

Newborn screening for cystic fibrosis is more widely accepted by the medical community as beneficial. Screening is presently done or planned to be implemented on all or selected patients in 13 states. It is very likely that with the passage of time, more and more states will implement CF screening. The long-term implications of such screening, from patient outcome to family planning, will become more evident over time.

Early mother and infant hospital discharge is still a concern but less so than before. With the passage of federal legislation, most mothers and infants are now staying in the hospital at least 24 hours. This change, in conjunction with improvement in newborn screening technology, has helped reduced the concern that inadequate time has passed for infants to accumulate metabolites in order to detect tested diseases. Many states have also implemented a second screen taken at a variable time after discharge to improve disease detection. Still, some patients are discharged early or infants in hospitals have screens obtained by nursing staff on a schedule (for example, at 8:00 AM) regardless

of the time of birth. The opportunity for a false negative or positive newborn screen remains ever present.

Carrier detection for all diseases, particularly the hemoglobinopathies, is an unintended consequence of newborn screening programs which must be addressed. Many programs exist from state to state to try and deal with the counseling needs of identified patients, but the number of patients can easily overwhelm the programs ability to provide effective counseling. This will continue to be an issue well into the future.

There is one inescapable conclusion about newborn screening: one need only look at the outcome of patients with phenylketonuria and hypothyroidism to conclude that early detection and treatment of these disorders is a mission accomplished!

Contributed by Randy Heidenreich, MD (AZ)

Expanded Newborn Screening by Tandem Mass Spectrometry (MS/MS)

Introduction

Newborn screening is a public health activity aimed at the early identification of conditions for which timely intervention can lead to the elimination or reduction of mortality, morbidity, and disabilities. Its efficiency and effectiveness is dependent upon the smooth integration of sample collection, laboratory testing, follow-up, diagnosis, timely treatment, and tracking of outcomes. All of these components make newborn screening a program, rather than a simple medical test.

Newborn screening tests performed by each state are not uniform. Most state programs now include screening for phenylketonuria (PKU), congenital hypothyroidism, galactosemia, and sickle cell disease. Some newborn screening programs include congenital adrenal hyperplasia, homocystinuria, maple syrup urine disease, biotinidase deficiency, and tyrosinemia. Technology, instrumentation, and clinical advances over the past several years have led to newborn screening using tandem mass spectrometry (MS/MS), a technique that allows the screening of multiple disorders in the same blood spot collected on the standard newborn screening card. The major categories of disorders detectable by this technique will be discussed here.

Clinical Significance

Tables 1-A, 1-B and 1-C list the disorders identifiable by MS/MS. They are grouped into three main categories depending on the metabolites that are affected or accumulate.

Amino Acid Metabolism

Phenylketonuria is currently screened by all states and will not be discussed here.

Tyrosinemias comprise 3 different disorders, affecting aromatic amino acid metabolism. Type I tyrosinemia is a cause of liver disease leading to cirrhosis and liver cancer. Therapy with a special drug, NTBC, prevents cirrhosis and liver cancer. Type II tyrosinemia leads to skin/corneal ulcerations and, in some cases, mental retardation. Tyrosinemia type III is extremely rare and not yet

well known. All patients with tyrosinemia types 1 and 2 require special diets low in phenylalanine and tyrosine. Treated patients have normal intelligence.

Maple Syrup Urine Disease (branched chain ketoacid dehydrogenase deficiency) results in the accumulation of branched chain amino acids leading to vomiting, brain edema, coma and death. Irreversible brain damage may result if dietary therapy is not initiated early.

Homocystinuria (cystathionine beta synthase deficiency) is a disorder of sulfur amino acid metabolism leading to mental retardation and other complications (lens dislocation, thrombosis). These can be prevented or ameliorated by a diet low in sulfur amino acids and supplemented with high doses of pyridoxine, folic acid, vitamin B12 and betaine.

Citrullinemia, argininosuccinic aciduria, and argininemia are urea cycle defects. The first two can present in newborns as lethargy progressing to coma with severe hyperammonemia. Milder variants of these forms and arginase deficiency present in older children as developmental

AMINO ACID METABOLISM		
ABBREVIATION	**DISORDER**	**DEFECT**
PKU	Phenylketonuria	phenylalanine hydroxylase deficiency and variants
TYR 1	Tyrosinemia type 1	1 fumarylacetoacetate hydrolase deficiency
TYR 2	Tyrosinemia type 2	tyrosine amino transferase deficiency
TYR 3	Tyrosinemia type 3	4-OH-phenylpyruvate dioxygenase deficiency
MSUD	Maple Syrup Urine Disease	branched chain ketoacid dehydrogenase deficiency
HCY	Homocystinuria	cystathionine beta synthase deficiency
CIT	Citrullinemia	arginino succinic acid synthase deficiency
ASA	Argininosuccinic aciduria	arginino succinic acid lyase deficiency
ARG	Argininemia	arginase deficiency
	Hyperprolinemia type 2	pyrroline-5-carboxylate dehydrogenase deficiency

TABLE 1-A. DISORDERS IDENTIFIABLE BY MS/MS SCREENING IN NEWBORNS

delays/mental retardation and spasticity (in arginase deficiency). These disorders are treated with a low-protein diet in addition to special medications (benzoate, phenylbutyrate).

Diagnosis in all cases is confirmed by plasma amino acids and urine organic acids. Enzyme assay or DNA studies further confirm the diagnosis in selected disorders.

Fatty Acid Oxidation

Defects of fatty acid oxidation , such as medium chain acyl CoA dehydrogenase (MCAD) deficiency, are usually silent and become evident only when the body needs energy from fat at times of fasting, infections, or fever. Previously healthy children can become acutely ill and suffer brain injury or death from the very first episode. During episodes, laboratory testing may indicate hypoglycemia and increase in liver function tests with reduced/absent ketones in urine. Other fatty acid oxidation disorders (LCHAD deficiency) can also affect the muscle and the heart with muscle pain and cardiomyopathy. Diagnosis of these disorders is confirmed by measuring urine organic acids, plasma carnitine levels (quantitative), and plasma acylcarnitine profile. DNA testing and enzyme assays are available for further confirmation of most of these conditions. Treatment is dietary and consists of the avoidance of fasting, institution of a low-fat diet (sometimes supplemented with specific types of fat), and carnitine supplementation.

FATTY ACID OXIDATION	
ABBREVIATION	**DISORDER**
MCAD	Medium Chain Acyl CoA Dehydrogenase Deficiency
VLCAD	Very Long Chain Acyl CoA Dehydrogenase Deficiency
SCAD	Short Chain Acyl CoA Dehydrogenase Deficiency
LCHAD, TFP	Long Chain 3-OH Acyl CoA Dehydrogenase Deficiency
CUD	Carnitine uptake defect (OCTN2 carnitine transporter defect)
CPT-1	Carnitine Palmitoyl Transferase I Deficiency
CPT-2	Carnitine Palmitoyl Transferase 2 Deficiency
CACT	Carnitine Acylcarnitine Translocase Deficiency
MAD	Multiple Acyl CoA Dehydrogenase Deficiency

TABLE 1-B. DISORDERS IDENTIFIABLE BY MS/MS SCREENING IN NEWBORNS

Organic Acidemias

Organic acidemias comprise several different conditions leading to the accumulation of organic acids - chemicals produced in the metabolism of amino acids, nucleotides, and fatty acids. Disorders such as propionic acidemia, methylmalonic acidemia, isovaleric acidemia, and multiple carboxylases deficiency can present shortly after birth with refusal of feeding, vomiting, and lethargy progressing to coma. Laboratory evaluation may indicate metabolic acidosis (with low plasma bicarbonate) and hyperammonemia. Therapy consists of special diets restricting the compounds that result in the formation of the abnormal organic acid, supplementation with vitamins specific for each disorder, and carnitine supplements. For some of these conditions, aggressive therapy of infections with IV fluids containing glucose is essential to avoid catabolism and trigger aggravation of clinical symptoms. For all of these disorders, diagnosis is confirmed by measuring plasma amino acids,

urine organic acids, and the plasma acylcarnitine profile. DNA testing, enzyme assay, and complementation studies can provide definitive confirmation of the diagnosis.

Conclusions

Expansion of newborn screening programs to include disorders detectable by MS/MS will allow identification of pre-symptomatic children with disorders affecting amino acid, fatty acid, and organic acid metabolism. Diagnosis is supported by measuring plasma amino acids, urine organic acids, and plasma acylcarnitine profile and is confirmed by enzyme or DNA testing. Therapy should be initiated as soon as possible and usually involves special diets with vitamin/carnitine supplements. In a few cases, specific drugs are available to remove or prevent formation of toxic metabolites.

Contributed by Nicola Longo, MD, PhD (UT)

ORGANIC ACIDS		
ABBREVIATION	**DISORDER**	**DEFECT**
PROP	Propionic Acidemia deficiency	propionyl CoA carboxylase deficiency)
MUT, Cbl A,B	Methylmalonic acidemia	multiple enzymes
IVA	Isovaleric acidemia	isovaleryl CoA dehydrogenase deficiency
2MBG		Methylbutiryl CoA dehydrogenase deficiency
IBG		Isobutyryl CoA dehydrogenase deficiency
2M3HBA	2-Methyl 3-hydroxy butyric aciduria	2-Methyl-3-OH-butyryl-CoA dehydrogenase deficiency
GA I	Glutaric acidemia type 1	(glutaryl CoA dehydrogenase deficiency
3MCC		3-Methylcrotonyl CoA carboxylase deficiency
BKT		3-Ketothiolase deficiency
HMG	3-OH 3-CH3 glutaric aciduria	3-Hydroxy-3-methyl glutaryl CoA lyase deficiency
MCD		Holocarboxylase synthase (multiple carboxylases) deficiency

TABLE 1-C. DISORDERS IDENTIFIABLE BY MS/MS SCREENING IN NEWBORNS

Tandem Mass Spectrometry: Principles and Interpretation of Results

Introduction

Screening for metabolic disorders in newborns began over 30 years ago with assays of phenylalanine on dried blood spots to identify infants with PKU. Technology, instrumentation, and clinical advances over the past several years have led to newborn screening using tandem mass spectrometry (MS/MS or TMS). The advantage of MS/MS compared to traditional screening techniques is that multiple metabolites can be detected simultaneously with one analysis from one blood spot, allowing the identification of several metabolic disorders at once. Two main classes of metabolites are detected by this technique: amino acids and acylcarnitines. Amino acids can identify inborn errors of amino acid metabolism (phenylketonuria, tyrosinemia, maple syrup urine disease, etc.), while the study of the acylcarnitine profile can identify defects of fatty acid oxidation and organic acidemias.

Methodology

A small punch (one-eighth inch diameter) of the blood collected on filter paper provides the sample needed for MS/MS analysis. The sample is then extracted with methanol. After drying, acetonitrile and water are added to the sample that is then injected in the mass spectrometer. A mass spectrometer measures the ratio of the mass (m) of a chemical and its charge (z). For this reason, all molecules are first ionized, usually by electrospray (a process by which molecules are electrically charged). The ions (negatively or positively charged molecules) formed are separated according to their mass to charge ratios. Since most of the ions have one positive charge, their mass to charge ratio corresponds to the mass of the molecules ionized in this process. Two mass spectrometers are used in tandem to separate and analyze mixtures of compounds, such as amino acids or acylcarnitines. This is where the name tandem mass spectrometer (MS/MS or TMS) comes from. After the ions are separated by the first mass spectrometer, they enter the "collision cell" where they are broken down into fragments by collision with a neutral gas. The fragments pass through a second mass spectrometer that separates them according to their mass to charge (m/z) ratio. Each molecule has a characteristic fragmentation pattern and classes of compounds will fragment in a similar way. For example, all acylcarnitines (carnitine conjugated with organic acids or short-, medium-, long-chain fatty acids) generate a fragment of m/z 85. In contrast, after fragmentation all amino acids lose a neutral fragment of m/z 102. The tandem mass spectrometer used for newborn screening is set up to measure only these classes of metabolites (acylcarnitines and amino acids) using the information about their mass and fragmentation pattern. The analysis is very fast (<2 minutes) and suitable for high throughput application such as newborn screening.

Interpretation of Results

Metabolic disorders are caused by a block in a biochemical pathway, causing the accumulation of disease-specific amino acids or acylcarnitines. With traditional newborn screening methods, samples are flagged when the quantity of a measured metabolite is above a certain value (cut-off). With MS/MS several markers are detected at the same time and the interpretation of the results is based heavily on pattern recognition, while the measurement of the concentration of the different metabolites supports the interpretation. The ability to detect multiple metabolites allows the use of ratios of metabolites to define whether an elevated value is due to a metabolic derangement or to the clinical and nutritional status of the newborn. For example, an elevated phenylalanine is suggestive of PKU. In newborns receiving intravenous hyperalimentation,

phenylalanine might also be elevated, leading to a presumptive positive result for PKU if only phenylalanine is measured. The availability of multiple metabolites (in this case other amino acids) allows the calculations of ratios, such as the ratio phenylalanine/tyrosine, which can distinguish between amino acid supplementation (intravenous hyperalimentation) and disease (PKU).

The importance of pattern recognition in the interpretation of MS/MS results is better illustrated by the interpretation of acylcarnitine profiles. Carnitine functions as a shuttle to transport long chain fatty acids inside mitochondria where they undergo metabolism. In this process, the fatty acid is shortened producing acetyl-CoA. In addition to this role, carnitine conjugates with organic acids to facilitate their removal. When one step in the metabolism of fatty acids or amino acids/organic acids is impaired, there is an increase in the corresponding acylcarnitine. MCAD deficiency, a defect in the metabolism of medium chain (6 to 10 carbon atoms) fatty acids, results in an increase in C8-, C6- and C10-carnitine (carnitine conjugated with C8 (octanoic), C6 (hexanoic) and C10 (decanoic) acids). The concentration of C8-carnitine (the marker commonly used for MCAD deficiency in newborn screening programs) is not always higher than the established cut-off. The excessive formation of acylcarnitines in fatty acid oxidation disorders leads to depletion of carnitine resulting in lower concentration of all acylcarnitines and a possible decline of C8-carnitine levels below defined cut-offs. Interpretation of acylcarnitine profiles, therefore, cannot be based only on cut-off values, because acylcarnitines might not be significantly higher than the cut-off value. Further, the same metabolite elevated in MCAD deficiency (C8-carnitine) is elevated in other diseases (Multiple Acyl-CoA Dehydrogenase Deficiency, MADD) or result from drug therapy (valproic acid) or dietary supplements (MCT oils used in special care formulas for premature infants). In the same way that the amino acid profile aids in the detection of true PKU, the full acylcarnitine profile aids in the detection of disorders of fatty acid oxidation and organic acidemias. Ratios of key metabolites, as well as their absolute values, are used to identify true positive results.

While amino acids concentrations do not change significantly with age, acylcarnitine concentrations vary significantly. For most acylcarnitines, their concentrations are highest in the first week of life and decrease rapidly afterwards. Different cut-off values should be established and used for different age groups.

Conclusions

Tandem mass spectrometry can be utilized to pre-symptomatically identify many metabolic disorders. The interpretation of the results requires highly trained personnel familiar with the disorders and the biochemical abnormalities caused by them.

Contributed by Marzia Pasquali, PhD (UT)

The American College of Medical Genetics Draft Report
Newborn Screening: Toward a Uniform Screening Panel and System

Developing a Uniform Screening Panel

In 2002, the Health Resource Service Administration Maternal and Child Health Bureau requested that the American College of Medical Genetics (ACMG) convene an expert group to review available information on newborn screening in order to make recommendations on a uniform screening panel based on the best scientific evidence. The ACMG established the following principles to guide the criteria by which to evaluate conditions and make recommendations:

1. Universal newborn screening is an essential public health responsibility that is critical to improve the health outcome of affected children.
2. Newborn screening policy development should be primarily driven by what is in the best interest of the affected newborn, with secondary consideration given to the interests of unaffected newborns, families, health professionals and the public.
3. Newborn screening is more than a lab test. It is a coordinated and comprehensive system consisting of education, screening, follow-up, diagnosis, treatment, management, and program evaluation.
4. The medical home and the public and private components of the screening programs should be in close communication to ensure confirmation of test results and the appropriate follow-up and care of identified newborns.
5. Recommendations about the appropriateness of conditions for newborn screening should be based on the evaluation of scientific evidence and expert opinion.
6. To be included as a primary target condition in a newborn screening program, a condition should meet the following minimum criteria:
   - It can be identified at a phase (24 to 48 hours after birth) at which it would not ordinarily be clinically detected;
   - There is a test with appropriate sensitivity and specificity;
   - There are demonstrated benefits of early detection, timely intervention and efficacious treatment of the condition being tested.

7. The primary targets of newborn screening should be conditions that meet the criteria listed in #6 above. The newborn screening program should also report any other result of potential clinical significance.
8. Centralized health information data collection is needed for longitudinal assessment of disease-specific screening programs.
9. Total quality management should be applied to newborn screening programs.
10. Newborn screening specimens are valuable health resources. Every program should have policies in place to ensure confidential storage and appropriate use of specimens.
11. Public awareness coupled with professional training and family education is a significant program responsibility that must be part of the complete newborn screening system.

Initially, eighty-four conditions were chosen for consideration. These conditions were chosen for one or more reasons: already screened for, revealed when other disorders screened for, worthy, identified by advocacy groups, part of the differential diagnosis for anther condition. It is important to acknowledge that there is limited scientific evidence available on several of the rare disorders considered. The following criteria were then applied to these conditions: clinical characteristics, sensitivity and specificity of screening, availability of diagnostic tests, treatment and management. Surveys of interested individuals and organizations were conducted and compared with the response of recognized experts. Subsequently an evidence base was established for each condition from reviews of references. The conditions were scored and placed in the following categories:

- Core Panel - High scoring;
- Secondary Targets - Moderately scoring, but part of the differential diagnosis of a high scoring condition; and
- Not Appropriate for Newborn Screening - Low scoring conditions at this time.

Ultimately, 29 disorders were agreed upon and are listed in Table 2 below:

TABLE 2. Uniform Newborn Screening Panel Recommended by the ACMG
Organic Acid Metabolism Disorders ■ Beta-ketothiolase deficiency ■ Glutaric acidemia type I ■ Hydroxymethylglutaric aciduria ■ Isovaleric acidemia ■ 3-Methylcrotonyl-CoA Carboxylase deficiency ■ Methylmalonic acidemia, Cbl A and Cbl B Forms ■ Methylmalonic acidemia, mutase deficiency form ■ Multiple carboxylase deficiency ■ Proprionic acidemia
Fatty Acid Oxidation Disorders ■ Carnitine uptake defect ■ Long-chain hydroxyacyl-CoA dehydrogenase deficiency ■ Medium-chain acyl-CoA dehydrogenase deficiency ■ Trifunctional protein deficiency ■ Very-long-chain acyl-CoA dehydrogenase deficiency
Amino Acid Metabolism Disorders ■ Argininosuccinic acidemia ■ Citrullinemia ■ Homocystinuria ■ Maple syrup urine disease ■ Phenylketonuria ■ Tyrosinemia type I
Hemoglobin Disorders ■ Hb S/Beta-thalassemia ■ HB S/C disease ■ Sickle cell anemia
Others ■ Biotinidase deficiency ■ Congenital adrenal hyperplasia ■ Congenital hypothyroidism ■ Cystic fibrosis ■ Galactosemia ■ Hearing deficiency

Cost-Effectiveness and Future Needs

Newborn screening is a system involving the following components: screening, short-term follow-up, diagnosis, treatment/management, and evaluation (American Academy of Pediatrics, 2000). The ACMG set out to determine the extent to which states have addressed the many components of this system and to recommend performance standards. Quality improvement, appropriate diagnosis and management are considered the primary responsibilities of the system. The components of prenatal education, screening, follow-up, diagnosis, management, and program management were found to be limited and significantly variable among states. It was observed that the state screening programs could benefit from a more robust national role in newborn screening. The ACMG report concluded that most state newborn screening programs improve outcomes and reduce overall costs. The identification of pre-symptomatic individuals at an early time in life can lead to many years over which the benefits accrue and ultimately outweigh the costs.

Reference

American Academy of Pediatrics. 2000. Serving the family from birth to the medical home. Newborn screening: A blueprint for the future - A call for a national agenda on state newborn screening programs. Pediatrics 106:389-422.

Contributed by Nicola Longo, MD, PhD (UT) and Rebecca A. Anderson, RN, BS (UT)

Ethical Issues in Newborn Screening

The traditional ethical issues relevant to newborn bloodspot screening include concerns over risks and benefits of programs, mandatory versus informed consent models, and the management of residual samples. The most pressing ethical issues in 2005 have arisen from the advent of powerful new technologies, primarily tandem mass spectrometry (MS/MS). But it is interesting to note that a very similar set of issues emerged with the very birth of PKU screening in the 1960's. The recognition of the condition as a cause of mental retardation, an understanding of some of the basic pathophysiology, and the invention of a new screening method together fueled enormous excitement. Population screening became feasible, with a tangible prospect of eliminating mental retardation from this cause. Metabolic specialists and lay advocates for those with disabilities successfully pushed for the development of state mandated programs over the initial objections of the medical profession. Many professionals were concerned that not enough was known about PKU to offer a safe and effective treatment. Subsequent events showed that the critics were right, but only to a certain extent. PKU was not well understood, particularly the distinction between PKU and benign hyperphenylalaninemia. A number of healthy children were placed unnecessarily on a restrictive diet resulting in malnutrition and developmental delay. Yet knowledge was gained over time from screening programs that enabled these mistakes to be corrected and children with PKU to benefit from screening.

The development of MS/MS poses the problem of new technology adoption in a particularly difficult and compelling way due to the large number of tests that can be run simultaneously.

States are rapidly implementing MS/MS with the number of newborn screening tests mandated in many states increasing by a factor of 5. As was the case in the 1960's, lay advocacy groups are at the forefront of efforts to expand newborn screening.

The key question is whether we are sufficiently confident that the benefits of population screening outweigh the harms, and that the benefits justify the use of scarce resources for this purpose. The literature documenting the benefits of newborn screening is remarkably thin beyond a few long-standing programs for PKU, congenital hypothyroidism, and hemoglobinopathies. Resources over the past 30 years simply have not been devoted to a comprehensive assessment of programs and their benefits for many conditions on screening panels. Each component of screening programs from sample acquisition to lifetime treatment maintenance has a failure rate that can seriously jeopardize the efficacy of the entire program. The pediatric community was surprised and disappointed to learn after decades of screening that treatment for galactosemia does not prevent developmental delays, although screening almost certainly reduces mortality, albeit to an uncertain degree.

The potential negative impacts of screening programs must be addressed in any ethical analysis of these policy decisions. For example, why is it that we no longer do routine chest x-rays on hospital admissions? Why is it that women in their 30's are not encouraged to get mammograms? The answer is not because these screening approaches offer no potential benefits. The answer is that the negative impacts arising from poor sensitivity and specificity and high cost are too great to make these reasonable approaches to disease identification and early treatment. Population screening is simply not a very effective tool for many conditions.

Negative impacts from screening are several-fold. First, there are the false positive results that are inherent in any screening program in which the specificity is not 100% and the condition is uncommon. The positive predictive values for newborn screening tests range from less than 1% to about 10% (meaning that 90 – 99% of initial positive results are false positive). Chasing down families and children following an abnormal result is a significant expense, but the greater concern is the psychological impact on parents. The literature clearly shows that a subset of parents persist in the belief that their children are not normal following a false positive newborn screening result. A more difficult problem arises from the ability of the technology to detect metabolic variants of unknown significance and to detect children who have very mild forms of the condition who were never destined to become ill. Starting these infants on highly restrictive diets and/or burdensome, costly medications may well cause unnecessary and significant harms to children and families.

Certainly for some conditions, these types of harms will be justified by the benefits of lives saved or disabilities averted. But very little is known about the efficacy of preventive treatment for many conditions on the MS/MS panel. Much of the literature reports results from small numbers of children on different treatment regimens in comparison to historical controls. Theoretically, treatment approaches may make sense but, in the real world, children lack access to expertise, families cannot afford treatments, parents cannot maintain strict regimens over years and, of course, sometimes theories about what might work are wrong. Some advocates of expanded screening claim that this information will only come from large scale screening programs and comprehensive tracking of treated children. This will be the case only if expanded screening is coupled with a national registry and tracking – not the case at the present time.

Healthcare policy is often made without a firm evidence base. However, in this context, the rapid expansion of screening confronts an additional ethical dimension. Newborn screening is mandated in all but a few states. The justification for permitting screening without the informed choice of parents is that the benefits of screening are sufficiently compelling that choice jeopardizes the welfare of children. This justification collapses as screening involves conditions for which the benefits are marginal or speculative. Yet the newborn screening system is not designed to offer informed choice, even though information and education would surely benefit parents and providers as active participants in the system.

The contemporary ethical challenge for newborn screening is to carefully analyze what we know about our many options to best promote the welfare of children. Population screening for a wide spectrum of conditions is not necessarily the most effective use of limited public health resources. Yet the technological imperative is strong. Using our enthusiasm to move forward with research first and constant reassessment later is the best way to build on successes and minimize mistakes in these important programs.

Contributed by Jeffrey R. Botkin, MD, MPH (UT)

Newborn Screening: A Consumer Reflection

Texas, with its 375,000 annual births, is poised to join the apparent march toward the possibly universal use of tandem mass spectrometry (MS/MS) as a newborn screening tool. In the space of little more than 40 years we have experienced a phenomenal expansion of newborn screening, and the consequences have generally been spectacularly positive. My daughter, Annaliese, now 22 and nearing completion of her undergraduate requirements for a bachelors degree in International Business Relations (with a minor in German), is a notable beneficiary of mandatory testing for PKU. While her cousin, now 60 and in her 55th year as a resident of the Denton State School, is a poignant reminder of the risks and costs, both personal and public, of a failure to detect this now highly treatable genetic disorder. Texas Representative Myra Crownover, a sponsor of the House bill which would provide funding for expanded screening, explained part of her motivation by relating the sad events involving an Austin couple and their son, Peter, who has glutaric academia, type 1. One parent is originally from Wisconsin, the other from Pennsylvania. Peter was born in Austin and was therefore tested for only 6 conditions, and most importantly, not for glutaric academia, type 1. Peter was eventually diagnosed with this disorder after a full range of tests but not before he suffered major impairment of his motor skill development. His condition would arguably have been diagnosed much earlier in the home state of either parent where a broader screen is mandated. It is difficult to avoid feeling optimistic about increasing the number of mandatory screened conditions from 6 to 29.

Consumer advocates have been prone to embrace new technology on the theory that all scientific advances are positive. Much of the lobbying for expanded newborn screening has come from consumers and organizations like the March of Dimes. I have participated as a March of Dimes member in the legislative advocacy effort to expand newborn screening in Texas. However, having also served as the chair of the Ethical, Legal and Social Issues Work Group that helped generate the 1999 Report of the American Academy of Pediatrics (AAP) Newborn Screening Task Force, I am aware of the complexity of the issues raised by the embrace of

MS/MS. The AAP report is what the American College of Medical Genetics (ACMG) based its recent recommendation to expand the "primary target" of screened conditions to 29. The ACMG report, issued on March 8, 2005, was open to public comment for the following 60 days. Having experienced the spirited debate that preceded the AAP Report it is difficult to imagine that there is consensus in inclusion of these 29 conditions. Moreover, even if the ACMG recommendation remains unchanged, I think the genetics community needs to periodically re-visit the AAP Report analysis and hold MS/MS up to serious scrutiny. Not even the enthusiastic supporters of MS/MS among genetic services providers portray this technology as being the infallible tool that some consumer groups perceive it to be. Like many technologies, use of MS/MS in newborn screening has both limitations and yet unrecognized consequences. Continuously "testing the test" against the standards set forth in the AAP Report will yield fewer false positives and negatives and contribute to the evaluation of the long-term risks/benefits of MS/MS.

Contributed by Joseph Martinec (TX)

Teratogen Hot Topic: Use of Statins in Pregnancy

Statins (HMG-CoA reductase inhibitors) were developed to treat elevated blood cholesterol levels (see table below). A 2004 update to the National Cholesterol Education Program's clinical practice guidelines on cholesterol management advises physicians to consider new, more intensive treatment options for people at high and moderately high risk for a heart attack. These options include setting lower treatment goals for low density lipoproteins or LDLs ("bad cholesterol") and initiating cholesterol-lowering drug therapy at lower LDL thresholds.

The liver synthesizes approximately 1500–2000mg of new cholesterol each day and an additional 200-400mg is consumed in the diet. Cholesterol is a structural component of cell membranes and a precursor to the production of steroid hormones and bile acids. Most of this cholesterol travels complexed with fatty acids and protein in the form of LDLs. During pregnancy, cholesterol levels normally rise 25-90% and triglycerides rise 300-400%.

In the U.S., maternal age at conception is increasing, thereby increasing the risk for maternal hypercholesterolemia. This trend, taken together with the recently lowered guidelines for desirable serum cholesterol, has raised concerns that increased numbers of reproductive-age women may be taking a statin medication. All of the cholesterol-lowering statin medications are classified by the FDA as category X. Category X drugs are contraindicated for pregnant women

Statins

Brand Name	Generic Name	Average Dose
Mevacor	lovastatin	10-80mg. daily
Lipitor	atorvastatin	10-80mg. daily
Zocor	simvastatin	10-80mg. daily
Prevachol	pravastatin	40-80mg. daily
Lesco	fluvastatin	20-80mg. daily
Crestor	rosuvastatin	5-40mg. daily
*Baycol	cerivastatin	

* Removed from market due to concerns about myopathy.

because the risks to the fetus outweigh benefits to the mother. Category X was assigned because of studies showing adverse reproductive effects in animals and the knowledge that cholesterol is essential to early embryonic development. Additionally, the harmful effects to the mother and infant of discontinuation of statin therapy for pregnancy and lactation are not felt to outweigh the potential teratogenicity to the fetus. It is worrisome that since 50% of pregnancies in the U.S. are unplanned, there is the potential for large numbers of fetuses to be exposed in the early part of pregnancy. One example of a rare clinical situation in which statin therapy may be prescribed during pregnancy is severe familial hypercholesterolemia.

Animal Teratogenicity Data

The majority of animal reproductive data is available on lovastatin, which has been shown to produce skeletal malformations (vertebrae, sternum and ribs) in rats and mice. Higher doses in rats were associated with gastroschisis. Other animal data has shown no ill effects on the fetus.

There are also concerns about the role that cholesterol plays in fetal development. One function of cholesterol is to attach to the Sonic hedgehog (Shh) protein. Shh protein is one of a family of glycoproteins that are known to program development and differentiation of embryonic cells. Animals given inhibitors to cholesterol biosynthesis or to the Shh protein develop holoprosencephaly, a very severe brain malformation in which the brain fails to separate into two hemispheres.

Human Teratogenicity Data

There are currently no prospective, controlled studies looking at statin use by pregnant women. The best human data is summarized below:

> The Worldwide Adverse Experience System (WAES), developed by Merck & Co., collected voluntary reports of outcomes of pregnancy in which lovastatin or simvastatin were used. At the time of publication, 134 exposures with known outcomes were recorded. Nine anomalies were reported with exposure to lovastatin or simvastatin at any time during pregnancy. The overall risk for birth defects was not increased over the background risk. Although the authors did not feel there was a pattern of birth defects, those reported include several skeletal and central nervous system malformations.

> A recent article by Edison and Muenke, 2004, described an uncontrolled case series of reports to the FDA, manufacturers and in the medical literature of statin exposures during pregnancy. Of the 70 cases with known outcomes, there were 31 adverse outcomes: 5 with fetal demise; 22 with structural defects; and 4 with intrauterine growth restriction. Among the 22 patients with structural anomalies, 5 had defects of the central nervous system (2 with holoprosencephaly) and five had limb defects, including two with the VACTERL association (a combination of vertebral, anal, cardiac, tracheoesophageal, renal, radial and other limb defects).

Conclusions

While there is some concerning animal and human reproductive data on the effects of statin exposure during pregnancy, the data are currently inconclusive. Prenatal exposure to statins is not recommended due to these concerns, as well as the limited benefit of treating

hypercholesterolemia in pregnancy. The current human data shows that most statin-exposed pregnancies will result in a normal child, but a small risk cannot be ruled out. The premise raised by Edison and Muenke, that fetal exposure to statins interferes with the Shh pathway and results in adverse effects on the central nervous system and the limbs is worrisome and needs to be addressed with a controlled study.

ADDENDUM:

A member of OTIS (Organization of Teratology Information Services) has submitted a grant to collect data on pregnancies exposed to statins. This study would be similar to the current OTIS sponsored study on Rheumatoid Arthritis and Pregnancy.

To reach OTIS for questions regarding any exposures during pregnancy:

Phone: 1-866-626-6847

Website: www.otispregnancy.org

For the rheumatoid arthritis and pregnancy study:

Phone: 1-877-311-8972

Website: www.raandpregnancy.org

Reference

Edison RJ, Muenke M. Correction: Gestational Exposure to Lovastatin Followed by Cardiac Malformation Misclassified as Holoprosencephaly.[Letter] N Engl J Med 2005;352(26):2759.

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