



NEWBORN SCREENING NEWS

The California Newborn Screening Program

Spring 2003

Tandem Mass Spectrometry (MS/MS) Pilot Project Comes to an End - June 13, 2003

Last Day to be Included in the MS/MS Pilot Project is June 13, 2003

At this time, the one-time funding for the MS/MS Pilot Project has been exhausted. The Newborn Screening (NBS) Program will accept specimens with parental consent for MS/MS Screening that have been collected on or before Friday, June 13, 2003.

After June 13, 2003 testing will not be available through the California Program. Parents wishing to have optional supplemental screening for their newborns will need to do so by making arrangements directly with one of the private laboratories offering the screening for a fee, such as Baylor (1-800-4Baylor) or NeoGen (1-866-463-6436). The NBS program will not pay for the supplemental screening. Families with health insurance should check with their insurance company or health maintenance organization regarding coverage.

Please do not offer Tandem Mass Spectrometry Supplemental Screening through the California NBS

Program to any family after June 13, 2003.

Specimens received after that date of collection will only receive routine mandated tests. The mandated NBS Program test for phenylketonuria (PKU), primary congenital hypothyroidism, galactosemia, sickle cell disease and other hemoglobin disorders will not change.

Hospitals and prenatal care providers will soon be receiving a supply of new, updated lavender *Important Information for Parents* booklets. Until that time, we request that you use the original lavender colored *Important Information for Parents* pamphlets or remove the central light purple section and the consent form with the yes/no stickers from the dark purple *Important Information for Parents* booklet for your patients who will deliver their babies after June 13th. If you run out of booklets before your new shipment arrives, you can obtain more by calling (510) 412-1542.

Review of The Tandem Mass Spectrometry Pilot Project

The California Department of Health Services Tandem Mass Spectrometry (MS/MS) Pilot Project began offering MS/MS screening for babies on January 7, 2002.

Assembly Bill 2427 mandated that the Genetic Disease Branch (GDB) conduct a pilot project to study the expansion of the state NBS Program using tandem mass spectrometry. The goal of the MS/MS project was to ascertain which of the 25 disorders detectable by MS/MS have clinical significance, respond to treatment, and therefore warrant inclusion in the mandatory NBS Program. The MS/MS detectable metabolic disorders include disorders of amino acid, organic acid and fatty acid oxidation. Early detection and treatment of these disorders in newborns can prevent serious outcomes such as mental retardation, seizures, coma and death. The GDB has been offering this test at no additional charge to those families who consented to participate. Over 320,000 newborns

have been tested in this supplementary, voluntary pilot project.

MS/MS Project - First 16 Months Experience

In the first 16 months, 309,074 newborns whose parents consented to participation were screened using MS/MS technology for metabolic disorders other than PKU. Of those screened, 425 newborns were referred for follow-up and 41 affected newborns were diagnosed. Twenty-two of the 41 cases were MediCal eligible. Sixteen SCADD/EMA cases were diagnosed. The clinical significance of some of these cases is variable and not well understood but will continue to be evaluated. Two disorders with potentially serious consequences, MMA and MCADD, made up half of the disorders diagnosed. The second most common MS/MS disorder diagnosed in the first year of the pilot project was MCADD, a fatty acid oxidation disorder. The prevalence rate for MCADD was 1 in 20,000 births. Seven out of the eleven infants with MCADD are Hispanic. The

majority of Hispanic families of babies diagnosed with an MS/MS disorder considered Spanish to be their primary language. The third most common disorder diagnosed was MMA, an organic acid disorder, with a prevalence rate of 1 in 32,000. At any given time, there are a significant number of pending cases due to outstanding diagnostic studies. More definitive prevalence rates will be estimated when all of the data have been collected and evaluated.

MS/MS Screen Turn-Around Time

The MS/MS pilot project was designed to enable follow-up and evaluation of data in a centralized, consistent and closely monitored process. The MS/MS screening and follow-up process occurs after the mandatory NBS has been completed on the same specimen. Due to this design, the turn-around time for MS/MS screening results has been longer than it is in the mandatory program. Since the beginning of the MS/MS project, the median screen turn-around time (the time it takes for a newborn screen specimen to be processed from blood collection to MS/MS screen and referral) is 28 days. The laboratory staff has worked hard to decrease the screen turn-around time by adding additional trained staff, adding another mass spectrometer machine, revising analytical measures and updating maintenance schedules. If MS/MS screening were incorporated into the California NBS Program, it is anticipated that the turn-around time would be the same as that of the mandatory NBS (approx. 3 days).

Lab Value Review/Cutoff Changes

As part of the screening and research process, data are monitored and adjustments in lab value ranges are made. Metabolic specialists from across California met with the MS/MS staff in May and October 2002 to discuss changes in cutoffs for lab value ranges. As a result of adjusting cutoffs, the number of babies referred for follow-up has been dramatically reduced.

Hospital Participation

As of January 2003, about 60% of California hospitals were participating in the MS/MS project in contrast to 33% participation when the project began January 2002. The hospitals were offered several options regarding participation in the MS/MS Pilot Project. These included: 1) participation using the state internal review board (IRB) approval, 2) participation using individual hospital IRB review and approval process, 3) distribution of the state-provided materials without any local IRB review, or 4) non-participation. Among the hospitals choosing not to participate, reasons reported include restrictions or requirements of individual hospital IRBs and a concern about staff time required for the consent process.

MS/MS Project - The Future

The MS/MS pilot project is funded by the California NBS Program through June 2003. Laboratory, follow-up, diagnosis, treatment and outcome data are being collected as part of a three year evaluation process supported by HRSA project #1 H46 MC 00199-01. When the research phase is completed, data on prevalence rates for MS/MS detectable disorders will be available along with information on which disorders are most amenable to treatment.

Guidelines are being developed for diagnostic follow-up and treatment of the most frequently identified disorders. The guidelines should be helpful for other states in implementing MS/MS screening and for California whenever MS/MS is incorporated into the mandatory NBS Program.

Thank You

The California Department of Health Services would like to thank the staff at the participating hospitals, NBS Area Service Centers, Metabolic Centers, public health departments, California Children's Services offices and

Cases Detected Through MS/MS Project		January 7, 2002 - May 2, 2003: N = 309,074	
Category	Description	Disorders Identified	Number Diagnosed
Amino Acid Disorders	Caused by the accumulation of amino acids in the blood (e.g., arginine)	Argininemia	1
Organic Acid Disorders	Caused by the toxic buildup of organic acids in the blood (e.g., propionic acid or methylmalonic acid)	Methylmalonic acidemia (MMA)	8
		Propionic acidemia (PA)	2
		3-methylcrotonyl-CoA carboxylase deficiency (3MCC)	2
Fatty Acid Oxidation Disorders	Caused by a defect in the conversion of fats into fatty acids for use as an energy source	Medium chain acyl-CoA dehydrogenase deficiency (MCADD)	11
		Short chain acyl-CoA dehydrogenase deficiency/Ethylmalonic aciduria (SCADD/EMA)	16
		Multiple acyl-CoA dehydrogenase deficiency (MADD or GA-2)	1
Total			41

MCADD

One third of all disorders diagnosed through the MS/MS Pilot Project were MCADD (Medium Chain acyl-CoA Dehydrogenase Deficiency). Persons with this metabolic disorder have a lifelong deficiency in medium chain *acyl-CoA dehydrogenase*, the enzyme that breaks down fats to be converted into energy. Because the fat cannot be used as an energy source, the body relies on glucose for energy needs. During periods of fasting or increased energy demand, (i.e. illness), there is a greater risk for hypoglycemia. Because people with MCADD only have symptoms when their blood sugar level drops, many children are not diagnosed for weeks, months or even years.

What Can Happen: Without information from newborn screening, babies with MCADD may only be diagnosed when a metabolic crisis occurs. Metabolic crisis can occur as a result of fasting - when babies go without feeding for over 8 hours or experience an illness/infection accompanied by vomiting, diarrhea and/or fever. A metabolic crisis can lead to severe hypoglycemia, hyperammonemia, acute encephalopathy, cardiomyopathy, liver failure and, if prolonged, developmental disabilities, coma or death. Metabolic disorders, including MCADD, may be one of the causes of unexplained sudden death in infants and children.

pediatric offices for their dedication, commitment, consultation, availability and advocacy to families involved in the MS/MS follow-up process. We also want to thank all of the parents who agreed to participate in the MS/MS project. Participants in the MS/MS project provide information on how best to incorporate MS/MS screening into the state's mandatory NBS Program. Incorporation of MS/MS screening into the California program would result in early detection and treatment of more metabolic disorders in newborns.

For More Information:

The Department of Health Services, NBS Program's website has added information on MS/MS screening for parents and providers (see website address listed below). There is information about the project, the screening process, potential disorders detected and links to resources, support networks and professional organizations.

MS/MS Project Contact Information

Toll-Free Phone Number: 866-954-2229 (954-BABY)

Email Address: msms@dhs.ca.gov

Website: www.dhs.ca.gov/gdb - click on newborn screening then MS/MS project

Benefits of Newborn Screening: If a baby is diagnosed with MCADD early, the prognosis is excellent. A Metabolic Specialist can regulate the baby's dietary fat intake, prescribe a nutritional supplement and teach parents how to monitor glucose levels and avoid fasting. Hypoglycemic episodes can be prevented with careful monitoring. Parents are advised to call their pediatric care provider when their baby has an illness or infection to avoid problems. Their doctor will initiate immediate intervention if hypoglycemia does occur.

Status of Babies Diagnosed With MCADD Through the MS/MS Pilot Project

Symptoms: The majority (nine out of eleven) of the babies diagnosed with MCADD were asymptomatic when their MS/MS result was reported. One baby had mild hypoglycemia and was in the NICU right after birth and one baby had poor tone and thrush.

Prognosis: All of the babies are currently healthy and have an excellent prognosis. They are continuing to be closely monitored by their primary healthcare provider and a CCS-approved metabolic specialist in their area. The families can receive genetic counseling services, glucose monitoring/nutrition education, and social support from the metabolic center staff.



The Genetic Disease Branch (GDB) which includes the NBS Program and the prenatal Expanded AFP Screening program moved into the new Department of Health Services facility in Richmond in mid-April. Our new address is:

**Genetic Disease Branch
Newborn Screening Section
850 Marina Bay Parkway, F175
Richmond, CA 94804**

We will discontinue use of our Berkeley P.O. box sometime in the near future so please begin using our new address. Unfortunately, we were unable to keep the same telephone numbers.

Important Numbers At Our New Location:

Genetic Disease Branch Main Number (510) 412-1502
Educational Materials Request Line (510) 412-1542
Newborn Screening Results Request Line (510) 412-1541
Newborn Screening Fax Machine (510) 412-1559

Of course, you can always contact your NBS Area Service Center, as those sites were not part of the GDB move. Thank you for your patience. We hope to keep your inconvenience to a minimum.

Errors on Specimen Collection Forms Are Costly to Hospitals and the Newborn Screening Program

Screening newborns prior to 12 hours of age can produce invalid (i.e., false negative) PKU test results. This can cause phenylketonuria to go undetected and untreated in affected babies, resulting in mental retardation. Newborn screening programs have warned hospitals and doctors about the danger of early specimen collection since the inception of newborn screening. Collection of specimens as close to discharge as practical has been the standard recommendation throughout the country. Many states require second specimens for newborns whose specimen is collected at less than 24 hours. California has not supported this practice as it is impractical and not cost effective to re-screen such a large portion of the population, and the method used in California has been shown to be accurate with specimens collected at 12 hours or more. Over the past five years hospitals have been remarkably successful in reducing the percent of newborns whose specimen has been collected prior to 12 hours of age (from approximately 10% in the early 1990's to under 1.5% in 2000); thus making it feasible to institute a second mandatory screen on newborns tested prior to 12 hours of age.

Two years ago the Newborn Screening (NBS) Program instituted a protocol to identify (and hospitals verify) babies truly screened at less than 12 hours of age and rescreen them between 12 hours and six days of age. The protocol has proven to be effective in assuring that all babies are screened at an appropriate time. Additionally, the verification process has revealed that 82% of those tests identified as "early" had actually been collected after 12 hours and did not require retesting. They were initially flagged as "early" due to incorrect or incomplete data entered on the test request forms (TRF) by hospital staff. These errors in documentation are proving to be very costly in that the process of verifying dates/times of birth and collection is very labor-intensive for hospital staff, NBS Area Service Center (ASC) staff, and state NBS Program staff. Moreover, babies whose TRFs have insufficient data to calculate age at collection must be retested. Repeating this invasive procedure on a baby because of poor documentation is obviously not good care.

ASC staff contact hospitals to obtain or verify information regarding infants whose collection forms indicate either that they were screened under 12 hours of age or that their ages at collection cannot be calculated due to erroneous or insufficient data (e.g., missing date or time of birth and/or collection). Hospital staff must investigate each case and arrange for the retesting of those who were truly early and those whose age at collection could not be determined. Most of the newborns will have been discharged, and will have to be brought back to the hospital for specimen collection. ASC staff track the babies to make sure that they are retested.

In July through December, 2002, 3850 babies (1.4% of all babies tested in the state) initially appeared to be either early collections or had insufficient data for age at collection to be calculated. After the facilities reviewed the cases to verify the information, it was determined that 622 babies (0.23% of all babies tested in the state) had truly been collected at less than 12 hours of age, and 54 babies had missing data that could not be captured. These babies had to be retested.

Tips for Assuring the Accuracy of Data Entered on the Test Request Forms

- Fill in *all* the fields on the form and write legibly. Dates and times of birth and specimen collection are necessary to determine age at collection, but **all** the required information is needed.
- When collecting a <12-hour specimen for pre-transfusion testing, check the box "To be transfused" as the reason for early collection. Collect a post-transfusion specimen at least 24 hours post-transfusion and by the 6th day of age, and provide the transfusion date and time on the TRF.
- Review completed TRFs for accuracy and legibility. Make sure noted date of birth precedes the date of specimen collection! Consider assigning a staff member to review all TRFs prior to the specimens leaving the hospital to assure accuracy and completeness.



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