

**THE MML DIFFERENCE:  
SUPPLEMENTAL NEWBORN SCREENING BY TANDEM  
MASS SPECTROMETRY (MS/MS)  
#82594**

## **BACKGROUND**

Currently, there are over 30 biochemical genetic disorders (inborn errors of metabolism: IEMs) that can be identified in the first days of life and that can be minimized through proper treatment and medical attention. The goal of newborn screening programs is to identify those conditions for which early intervention can prevent mortality, morbidity, and life-long disability. In many cases, simple changes in diet and nutrition can permit the child to lead a functional life.

Over 4,000,000 screens are performed annually in the United States. Screening is performed by analysis of diagnostic markers in blood spots collected on filter paper on the second day of life. One of the biggest challenges for state programs is deciding which markers to include in their screening program. Currently, the markers tested by state-mandated programs across the United States vary from testing as few as 4 disorders to more than 30. Additionally, most state testing is performed using immuno- and enzyme assays, which provide limited disease detection.

With MS/MS, a large number of IEMs including fatty acid, organic acid, and amino acid disorders, can be tested simultaneously from a single blood spot specimen. This technology currently identifies IEM in 1:4000 newborns

screened. However, because most newborn screening laboratories lack the expertise necessary to perform and interpret MS/MS results, few states have taken full advantage of this new technology.

Growing public awareness of these new diagnostic capabilities among parent support groups and health care providers fostered the creation of alternative testing to supplement state screening programs. These supplemental MS/MS newborn screening options are not yet widely available. Mayo introduced #82594 Supplemental Newborn Screening by Tandem Mass Spectrometry (MS/MS) in 2001, to enable parents to electively test their newborns for a wide variety of IEMs not covered in their state's mandated program. Subsequently, Mayo has expanded its program to include other IEMs, performing more than 30,000 supplemental newborn screens this year, with a projected volume for 2005 of over 100,000 screens. (See list of diseases attached.)

## **PATIENT CARE INFORMATION**

### *Test Utility*

- ◆ Presymptomatic detection of IEM disorders for which early treatment can prevent or reduce morbidity and mortality.

- ◆ Expanded screen detects critical diseases not targeted by all state-mandated newborn screening programs.

### *Impact on the Patient and Family*

- ◆ Potential for a healthy, normal life.
- ◆ Early diagnosis allows genetic counseling of families and in most cases the option of prenatal diagnosis in subsequent pregnancies.
- ◆ Accurate results reduce parental anxiety and long-term detrimental effects.<sup>1</sup>

### *Benefits of the Test*

- ◆ Improves prognosis by timely diagnosis of treatable diseases before the onset of symptoms.
- ◆ Bridges the gap between state and private testing, reducing exposure to litigation.
- ◆ Mayo's low false-positive rate minimizes the clinical, sociologic, and economic costs of false-positive results.<sup>2,3</sup>

## **HEALTH CARE ECONOMICS**

- ◆ Improved false-positive rates lower overall costs, resulting in fewer follow-up expenses such as:
  - laboratory testing
  - avoidable clinical events including
    - emergency department visits
    - hospital admissions
    - laboratory and medical staff time
- ◆ Projected savings of \$36,400,000 annually in the United States.<sup>4</sup>
- ◆ Ohio saved \$4 billion in treatment and institutional costs associated with mental retardation since implementing newborn screening in 1965.<sup>5</sup>

- ◆ Estimated cost per quality-adjusted life year by MS/MS screening of \$5,827 (range, \$736-\$11,419; data presented 2001).<sup>2</sup>
- ◆ Subsequent genetic counseling may reduce future health system (and societal) financial burdens.

## **TECHNOLOGICAL COMPARISON**

### *How Does the Test Compare to Other Tests Offered?*

- ◆ State-of-the-art technology.
- ◆ More sensitive than routine newborn screening methods; >30 additional disorders identified.
- ◆ Fewer false-positives than routine newborn screening methods.

### *How Does the Mayo Test Differ?*

- ◆ Our supplemental screening tests for more diseases than most state programs.
- ◆ Low false-positive rate.\*
- ◆ Extensive familiarity with MS/MS technology.
- ◆ Experience with interpretation of complex metabolic profiles.
- ◆ Laboratory staffed by interdisciplinary team of laboratorians, pediatricians, and geneticists.
- ◆ In-depth clinical knowledge of IEM disorders.
- ◆ Clinical consultation provided for each abnormal case (24/7—only at Mayo).
- ◆ Access to genetic counseling.
- ◆ Rapid turnaround time.
- ◆ Comprehensive follow-up testing available.
- ◆ Initial follow-up tests performed at no charge.

- ◆ Ongoing efforts to further reduce the number of false-positive results.
- ◆ Active research and new test development to expand the scope of testing.

## REFERENCES

1. Waisbren SEP, Albers S, Amato S, et al: Effect of Expanded Newborn Screening for Biochemical Genetic Disorders on Child Outcomes and Parental Stress. *JAMA* 2003;290: 2564-2572
2. Schoen EJ, Baker JC, Colby CJ, et al: Cost-Benefit Analysis of Universal Tandem MS for Newborn Screening. *Pediatrics* 2002;110(4): 781-786
3. CDC Genomics and Disease Prevention: Effect of Expanded Newborn Screening for Biochemical Genetic Disorders on Child Outcomes and Parental Stress. Reviewed by M Walsh. Updated April 15, 2004. Available at: [www.cdc.gov/genomics/hugenet/ejournal/newborn.htm](http://www.cdc.gov/genomics/hugenet/ejournal/newborn.htm)
4. Filiano JJ, et al: Tandem Mass Spectrometry and Newborn Screening: Pilot Data and Review. *Ped Neuro* 2002;26(3):201-204
5. Parents Taking Advantage Of Increased Screening Of Newborns (OH) Associated Press. Dec 28, 2002
6. Isinga RP: Newborn screening with tandem mass spectrometry: Examining its cost-effectiveness in the Wisconsin Newborn Screening Panel. *J Ped* 2002;141(4):524-31
7. Matern D, Magera MJ: Mass spectrometry methods for metabolic and health assessment. *J Nutr* 2001;131: 1615S-20S
8. Matern D: Tandem mass spectrometry in newborn screening. *Endo-crinologist* 2002 Jan-Feb;12(1):50-7
9. Communiqué August 2001: <http://www.mayo.edu/mml/comm/aug2001/aug2001.pdf>
10. Press release [http://www.mayo.edu/comm/mcr/news\\_1653.html](http://www.mayo.edu/comm/mcr/news_1653.html)

## ADDITIONAL READING

- Rinaldo P, Tortorelli S, Matern D: Recent developments and new applications of tandem mass spectrometry in newborn screening. *Curr Op Pediatr* 2004; 16:427-433
- Matern D, He M, Berry SA, Rinaldo P, et al: Prospective diagnosis of 2-methylbutyryl-CoA dehydrogenase deficiency in the Hmong population by newborn screening using tandem mass spectrometry. *Pediatrics* 2003;112:74-78
- Nagan N, Kruckeberg KE, Tauscher AL, et al: The frequency of short-chain acyl-CoA dehydrogenase (SCAD) gene variants in the U.S. population and correlation with the C<sub>4</sub>-acylcarnitine concentration in newborn blood spots. *Mol Genet Metab* 2003;78:239-246

---

\* In 2002, Mayo compared newborn screening results generated by Mayo to those generated at a state laboratory on >5000 newborns. Both laboratories performed similar analytic procedures, yet 14 (60%) of the state's abnormal results were false-positive versus 7 (29%) false-positive results generated by MML. Why were there fewer false positives at MML? The state laboratory reported positive results based on fixed cutoffs and provided no interpretation. MML reviewed each profile and provided a written interpretation based on the observed metabolite pattern and available clinical information (gestational age, diet, birth weight, other risk factors).