

**Long-Term Follow-up of Infants Identified
by Tandem Mass Spectrometry
Screening in Oregon, Iowa and Idaho**

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Thanks to the World Wide Web, we live in an information and communication age. At our fingertips we have the latest and most up to date information about almost any subject one can imagine and we can communicate that information instantly with many thousands of people around the world. However, as wonderful as the Internet is, it cannot tell us how all the children and adults with FAO disorders, or any other metabolic disorder, are doing. We don't know how many children are affected, what kinds of treatments they are receiving, whether those treatments are effective, what kinds of problems might be occurring in children over time or how they will do as adults. Basic information needed by every parent, metabolic treatment center and newborn screening programs. We search for journal articles and textbooks; we surf the Net and join various list serves to try and get as many answers as we can, but these answers are always incomplete and out of date. While millions of documents are available on the web regarding common medical conditions, the web pages for metabolic and genetic diseases are scarce. For instance, Google generates 1,000 times more pages regarding "diabetes" (46 million) than MCADD (41 thousand). The irony is that the answers we seek are there, hidden away in the medical records of all our children.

Long-term follow-up is the process of collecting and analyzing information on persons with the same disorder to determine differences and/or similarities in the 'functional outcome'. That is, do affected children grow up, finish school and live independent and productive lives? Do they have complications or disabilities? If so, are these the result of metabolic crises, imperfect treatments, differences in gene mutations, or other unrelated causes? For most metabolic disorders these answers are either unknown or imperfectly understood. One reason for this lack of understanding is that there is no comprehensive long-term follow-up for most metabolic conditions. As a result, it can take years before a complication, such as renal failure in MMA, to come to light and many more years before effective treatments are devised and tested.

Long-term follow-up is difficult and expensive to do. It can take many hours to collect data from a patient's chart, make sure it is accurate, and reported in a format that is confidential and can be compared with other patients. Also, in some cases it is difficult to decide which data should be collected. Some data, such as developmental and educational testing can be impossible to obtain if children are "doing well", as insurance companies and/or parents do not see the need or refuse to pay for it. As a result, the most comprehensive studies, for example the PKU Collaborative Study and the Childhood Cancer Study, require large expenditures of federal money and have taken years to complete. Yet the benefits of those studies have been enormous to families and patients. Childhood leukemia has gone from a death sentence to curable in the space of one generation. In phenylketonuria (PKU) we now know that phenylalanine control is needed well into adulthood and while dietary treatment is better than it was 25 years ago, we must pursue more palatable treatments and a permanent cure. Without the PKU Collaborative studies for both children and pregnant mothers, we would still be discharging patients from clinic at age 6, with the advice that treatment is no longer necessary!

Metabolic treatment staff and parents feel strongly that expanded newborn screening offers the opportunity to identify many infants before their first crisis. We all know from grim experience the damage that can occur as infants struggle for their lives and physicians struggle to make a diagnosis with that initial crisis. We all expect that newborn screening will make a big difference in the outcome of our children. While we campaign for the addition of disorders to the newborn screening in our states or provinces, we must also campaign for a comprehensive long-term follow-up program. Without long-term follow-up the benefits of screening may not be known for another generation and valuable time will be lost.

Most of the disorders covered by tandem mass spectrometry (MS/MS), except for PKU and medium chain acyl-CoA dehydrogenase deficiency, are so rare that comprehensive studies may be years away. We could speed up this process if we could collect data on all the infants now being detected by newborn screening. These data would give us an "early warning system" that would monitor not only health and development, but also would catalog all treatments, laboratory results, complications, frequency and severity of crises, costs, burdens and barriers to appropriate care. If parents, treatment centers and the government worked together these data, collected anonymously, could be pooled and analyzed on a national or even international level, to

give us important insights into what is happening to our children in real time. These data are critical to biochemical and molecular research, the development of clinical studies to improve or evaluate treatments, to advocate for the specialty care and services our children may need and to demonstrate the efficacy of newborn screening.

In 2002, the Center's for Disease Control (CDC) recognizing the need, began a collaborative agreement with Oregon Health & Science University and Iowa State Department of Health to identify which data should be collected and to develop and test a data collection tool for use in the long-term follow-up of children identified by newborn screening with organic acid, fatty acid oxidation and urea cycle disorders. This tool, a database, has now been developed and is being beta tested by entering follow-up data from the infants identified in Iowa, Oregon and Idaho. By the end of 2005, we will have collected data on approximately 75 children (43% have FAO's) in our three states ranging in age from weeks to 3 years. We have a functional database, which could be deployed to any metabolic treatment center or state genetics clinic in the country. We are interested in continuing our work on this project. Important next steps include evaluating the efficiency and costs of data collection methods, addressing confidentiality issues, adding additional metabolic disorders and most importantly continuing to collect data on the babies and children. Parents can help by continuing to advocate for comprehensive long-term follow-up for all children being identified by newborn screening.

Even though we have a small number of children, important data from our work are already coming to light. The first is that the incidence of all the MS/MS disorders in our states is about 1 baby in 3,000 births, three times as many as we expected. In Oregon and Idaho, where every baby is tested at discharge from the hospital and again at about two weeks of age, 10-12 % of our cases have been identified only on the second test! We know that 15% of all cases were symptomatic before the screening results were known and of these, 2 died. Of the surviving infants, 92% are developing normally, although most are too young for formal developmental testing. Soon we shall know how many have developed 'crises' since diagnosis and treatment, and if there is any apparent difference between our states or by disorder in this regard. We want to be able to look at costs of care, not only routine metabolic care, but also emergency care. We want to know who is paying for care and whether there are barriers to getting needed care.

Our dream, ultimately, would be to see the development of a National (International) Metabolic Disease Data Center that could pool data from large numbers of individuals. Such a center could provide valuable information on the incidence of various metabolic conditions and the outcome data needed by parents, treatment centers, newborn screening programs and governments to ensure our children's futures.

Judi Tuerck has worked for the last 26 years as the nurse coordinator for the Metabolic Clinic at Oregon Health & Science University. She has cared for hundreds of children with metabolic disease and their families. She has also worked to follow-up infants with possible metabolic disease found in the NW Regional Newborn Screening Program to ensure prompt treatment. This last year she resigned her position in the clinic to concentrate her efforts on the implementation of expanded screening, long-term follow-up and educational issues relating to newborn screening and metabolic disease. She was asked to present the Long-Term Follow- Up project data to the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children on January 13, 2005. She is a mom and a grandmother.

Sara Copeland is the Medical Director for the Metabolic Program at the University of Iowa and Medical Director for the Iowa Newborn Screening Program. She has been instrumental in the development of the database and invaluable in moving the project forward.