CD Summary

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NEWBORN SCREENING — THIS BABY'S TAKING OFF

"Strange is it, that our bloods, of colour, weight and heat pour'd all together, would quite confound distinction, yet stand off in differences so mighty."[1]

DURING THE NEXT few weeks, the Oregon State Public Health Laboratory (OSPHL) will implement a major expansion of its newborn metabolic screening panel to bring the program in line with evolving national standards of practice.[2,3] Currently, all Oregon infants are screened for six disorders: phenylketonuria (PKU), congenital hypothyroidism, galactosemia, biotinidase deficiency, maple syrup urine disease (MSUD) and hemoglobinopathies (e.g., sickle cell disease). By adopting a new technology—tandem mass spectrometry (MS/MS)—each child can now be screened for an additional 20 metabolic disorders, including fatty acid oxidation (FAO) disorders, organic acid disorders, and additional amino acidopathies. Also, congenital adrenal hyperplasia (CAH) will be added to the screening battery by the end of 2002. Due to the wonders of modern technology, all this can be done using the same collection procedures and sample size currently used.

In 1962, Oregon became the first state to implement statewide screening for PKU. Dr. Robert Guthrie visited the OSPHL from Buffalo, NY, and taught the staff his newly developed method for detecting elevated phenylalanine levels in neonatal dried blood spots. He actually wrote the laboratory method on a paper towel, which unfortunately has been lost to antiquity. Prior to implementing PKU screening, one percent of all admissions to Oregon's Fairview Training Center were for untreated PKU. After PKU screening began, there was never another such admission. For the ensuing 40 years the OSPHL, in partnership with the Oregon Health and Science University (OHSU), has provided early detection, medical consultation, follow-up, and clinical intervention for infants with metabolic disorders to prevent early mortality or lifelong disability. The OSPHL operates the Northwest Regional Newborn Screening Program (currently OR, AK, ID, NV, HI, and three military bases), testing a total of 230,000 samples per year. To date, three million newborns have been screened and over 1,300 affected infants identified (see table). So far, we're unaware of any infant whose metabolic disorder was missed by the program.

TANDEM MASS SPECTROMETRY

In 2001, the Oregon Legislative Assembly authorized the OSPHL to expand routine newborn screening tests to include disorders detectable by MS/MS. This will enable the laboratory to increase the number of metabolic disorders screened for from six to 26, including fatty, amino, and organic acid disorders, while also improving the detection of "current" amino acid disorders (PKU and MSUD). For the detection of abnormal amino acid levels MS/MS will replace Dr. Guthrie's 1960's-era assay and assure more specific and rapid results (three minutes versus two days—really).[4,5]

Infants with FAO disorders lack the ability to oxidize fatty acids necessary for energy production when glucose has run out (e.g., during fasting periods). The most common of these disorders is medium-chain acyl-CoA dehydrogenase deficiency (MCADD), with an incidence of 1:10,000 live births. Approximately one-third of infants with MCADD die during their first crisis, and the surviving two-thirds may have severe brain damage. Postmortem testing of Oregon infants has documented several deaths due to MCADD that could have been prevented by neonatal screening and prompt treatment.

Amino acid disorders are characterized by the absence or reduced activity of enzymes necessary to metabolize certain amino acids. The build-up of these amino acids can cause severe developmental disability, seizures, microcephaly, cerebral palsy, hyperactivity, coma, and death. In addition to PKU and MSUD, infants will now be screened for tyrosinemia and homocystinuria.

Organic acid disorders result in the accumulation of these acids (e.g., propionic, methylmalonic) in blood and urine, disrupting the acid-base balance. All of these disorders can lead to serious mental or physical impairment, including death.

Using MS/MS, at least 25 different disorders can be screened for simultaneously, within just a few minutes. (Reader Alert: Unless you care how MS/MS works, skip to the next section.) MS/MS technology utilizes electrospray ionization to generate a fine spray of charged, ion-carrying droplets that are passed through a gas curtain interface into a mass analyzer that determines the types of molecules present based on their mass-to-charge ratio. The molecules are then fragmented in a collision cell and passed through a second analyzer that identifies the quanti-

Disorders detected through December 31, 2001, based on screening 2,994,620 infants.*

Disorder	No. Detected
Congenital hypothyroidism	740
Phenylketonuria	321
Hemoglobinopathies	129
Galactosemia	57
Congenital adrenal hyperplasia	29
Biotinidase deficiency	25
Maple Syrup Urine Disease	11
Total	1,312**

* Oregon 1,453,939 infants (1962-2001), Alaska 222,175 (1975-83, 1987-2001), Idaho 493,131 (1976-2001), Nevada 474,174 (1978-2001), Montana 165,342 (1975-85), Delaware 72,181 (1992-98), Military bases 35,665 (1991-2001).

** Resist the temptation to calculate incidence; each disorder has a different denominator (no. of infants screened).

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ties of molecules present, thereby generating distinct patterns that reveal abnormal results. The peak for each analyte can be compared to an internal standard to yield both a qualitative and quantitative result. Thus, MS/MS is not really a "screening" method in the traditional sense of high sensitivity/low specificity. Rather, it approaches 100% sensitivity and specificity, even when used in a population-screening situation.

CONGENITAL ADRENAL HYPERPLASIA

The second area of expansion will be the screening of all Oregon infants for congenital adrenal hyperplasia (CAH), which occurs in 1:12,000 live births but shows significant ethnic variation (as high as 1:400 in some Alaska Native groups). CAH is an autosomal recessive error of steroid synthesis which prevents normal production of cortisol. The low level of cortisol induces increased secretions of corticotropins (ACTH), causing adrenal hyperplasia. The most common type of CAH is 21-hydroxylase deficiency, which is tested for in newborn blood spots by immunoassay for elevated levels of 17-hydroxyprogesterone (17-OHP). By four to five months' gestation, diminished cortical production in the adrenal glands stimulates the fetal pituitary gland to produce ACTH and excessive adrenal androgens. The androgens virilize female external genitalia, and male infants may show increased scrotal pigmentation or be asymptomatic. However, in approximately two-thirds of the cases, the 21-hydroxylase deficiency also causes reduced production of mineralocorticoids, which leads to a hypotensive, hyperkalemic, salt-losing crisis with rapid onset of shock and adrenocortical failure within 7–28 days of birth. This "salt-wasting" form of CAH is fatal if not detected and treated promptly. The OSPHL has screened Hawaii and Alaska infants for CAH for several years, and will be adding CAH screening for Oregon by the end of 2002.

IN SUMMARY

Although the Newborn Screening Program will be undergoing these changes in testing methods over the next few months, the fundamental operation of the program will remain unchanged. The two-part and single-filter paper kits will still be available (at an increased cost per kit), and timing for the collection of the first and second samples will stay the same. Five blood collection circles will still provide sufficient sample for the laboratory to perform all screening tests; no additional blood spots will be required. Follow-up services/consultations for abnormal results and disorders will remain unchanged; these will still be provided by metabolic, endocrinology, and hematology specialists at OHSU. The OSPHL will be providing practitioners with more detailed information as the expansion proceeds. If you have questions about the upcoming changes, please contact the Newborn Screening Program at 503/229-5882.

REFERENCES

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2. CDC. Using tandem mass spectrometry for metabolic disease screening among newborns. MMWR 2001;50:1–22.
3. Zytkovicz TH, et al. Tandem mass spectrometric analysis for amino, organic, and fatty acid disorders in newborn dried blood spots: a two year summary from the New England Regional Newborn Screening Program. Clin Chem 2001;47:1945–55.
4. Marshall E. 2001. Fast technology drives new world of newborn screening. Science 2001;294:2272–74.
5. Rinaldo P, Matern D, Bennett MJ. Fatty acid oxidation disorders. Ann Rev Physiol 2002;64:447–502.

What we *meant* to say was...

In *CD Summary* number 5113 (June 18, 2002), the charts for syphilis, gonorrhea, tuberculosis and chlamydiosis were mis-labeled. Instead of reading "reported cases," the y-axis should have been "cases per 100,000," just like the rest of them.

In *CD Summary* number 5109 (April 9, 2002), we had some problems with missing prefixes and poor arithmetic. The prefix correction in the text is capitalized, the corrected totals in the table are in italics. Now it should all make sense.

ASSESSING THE RISK OF RABIES...

Rarely, an animal may bite after deliberately crossing neutral space despite having one or more open avenues of escape—such a bite is called "UNprovoked." In general, unprovoked bites are risky, whereas provoked bites are not.

Animal rabies test results, Oregon 1997–2001

Year	Bat	Cat	Dog	Fox	Other animals
1997	14/116	1/83	0/52	0/6	0/45
1998	6/95	0/95	0/56	0/3	0/49
1999	11/115	1/95	0/45	0/1	1/47[⊗]
2000	8/73	0/79	0/56	1/4	0/4
2001	4/59	0/67	0/46	0/1	0/41
Totals	**43/458 (9%)**	**2/419 (1%)**	***0/255(0.5%)***	***1/15 (0%)***	***1/188[⊗] (0.5%)***

[⊗] Yow! it was a cow!