REPORT OF THE
DEPARTMENT OF HEALTH PROFESSIONS ON

The Feasibility and Appropriateness of Expanding Current Required Screening Tests for Newborns

TO THE GOVERNOR AND
THE GENERAL ASSEMBLY OF VIRGINIA

HOUSE DOCUMENT NO. 49

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January 5, 1994

TO: The Honorable Lawrence Douglas Wilder
Governor of the Commonwealth of Virginia

The Members of the General Assembly of Virginia

I am pleased to transmit this report which constitutes the response of the Virginia Department of Health to House Joint Resolution No. 657 of the 1993 Session of the General Assembly of Virginia.

This report offers the results of the Department's study of the feasibility and appropriateness of expanding current required screening tests for newborns to include testing for certain metabolic and other disorders, including Medium Chain Acyl CoA Dehdrogenase Deficiency (MCAD).

Robert B. Stroube, MD, MPH
State Health Commissioner

Enclosure

cc: The Honorable B. Norris Vassar
Acting Secretary of Health and Human Resources

REPORT OF THE

VIRGINIA DEPARTMENT OF HEALTH

ON THE FEASIBILITY AND APPROPRIATENESS OF EXPANDING CURRENT REQUIRED SCREENING TESTS FOR NEWBORNS TO INCLUDE TESTING FOR CERTAIN METABOLIC AND OTHER DISORDERS

TO THE GOVERNOR

AND THE GENERAL ASSEMBLY OF VIRGINIA

DECEMBER, 1993

EXPANDING SCREENING TESTS FOR NEWBORNS

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Executive Summary

More than 95,000 babies born to Virginians each year are screened for seven genetic disorders that may cause mental retardation, hearing loss, developmental disabilities, liver disease or sudden death. The disorders are phenylketonuria, hypothyroidism, galactosemia, homocystinuria, Maple Syrup Urine Disease, biotinidase deficiency and sickle cell disease (Appendix B). Early detection and treatment diminish or eliminate the harmful effects of these disorders.

The 1993 General Assembly passed House Joint Resolution 657 charging the Virginia Department of Health to study the feasibility and appropriateness of expanding currently required screening tests for newborns to include testing for additional metabolic and other disorders, including medium chain acyl coA dehydrogenase (MCAD) deficiency.

Over the past ten years there has been an increasing interest in MCAD deficiency as a cause of one to three percent of cases of sudden infant death syndrome (SIDS). If recognized early and before irreversible problems develop, MCAD deficiency can be treated effectively with glucose and carnitine supplementation and the avoidance of fasting.

However, the technologies are not developed sufficiently to warrant population screening for MCAD deficiency at this time. Also, costs of specialized equipment and personnel are exorbitant relative to other newborn screening tests currently performed.

The study team recommends to the Governor and the Virginia General Assembly:

A. That MCAD deficiency not be added to the currently required screening tests for newborns.

B. That currently required screening tests for newborns not be expanded. Technology that is available for testing certain metabolic and other disorders is not amenable to screening of mass populations.

C. That the Virginia Department of Health study, once a year, the feasibility and appropriateness of expanding currently required screening tests for newborns.

Introduction and Methodology

The 1993 General Assembly passed House Joint Resolution 657 requesting the Virginia Department of Health to study the feasibility and appropriateness of expanding currently required screening tests for newborns to include testing for certain metabolic and other disorders.

This study was staffed by the Division of Children's Specialty Services of the Virginia Department of Health, with participation by representatives of the Health Department's Advisory Board for Genetics, Endocrine, Metabolic and Other Inherited Diseases. The Advisory Board heard testimony from Ms. Carolyn Stamm and the advanced placement students from Virginia Beach, who had initiated the resolution.

A subcommittee of the Advisory Board was selected to conduct the study. This subcommittee had representation from the Medical College of Virginia, Eastern Virginia Medical School, University of Virginia, Division of Consolidated Laboratory Services of the Virginia Department of General Services, and the Division of Women's and Infants' Health of the Virginia Department of Health. Current literature was reviewed by the subcommittee members.

Medium chain acyl coA dehydrogenase (MCAD) deficiency is a disorder of fatty acid oxidation. It is inherited as an autosomal recessive trait and is estimated to occur in 1 in 6,000 to 10,000 births. The disorder usually presents in the first year of life with symptoms such as lethargy, hypotonia, hypoglycemia, coma and, in one-third of the cases, death. Over the past ten years there has been increasing interest in this disorder as a cause of one to three percent of cases of sudden infant death syndrome (SIDS). The disorder, if recognized early and before irreversible problems develop, can be treated effectively with glucose and carnitine supplementation and the avoidance of fasting.

The subcommittee agreed that MCAD deficiency meets the criteria for a disorder suitable for newborn screening in that it is relatively common, has serious clinical consequences if not diagnosed and treated, and can be readily treated. The considerations for implementation into the existing screening programs, however, also include the costs and the availability of the technologies required to diagnose MCAD deficiency.

Current Methodologies and Problem

The current methodologies available for the diagnosis of MCAD deficiency include an enzymatic assay, a DNA diagnostic assay, and organic acid/mass spectrophotometry.

The enzymatic assay is performed on extracts of tissue, such as liver (biopsy or autopsy samples), fibroblasts, etc. The isolation of the tissues requires biopsy or separate blood drawing. The enzyme assay is not possible on dried blood-soaked filter paper samples that are currently used in newborn screening. In addition, the culturing of the cells is laborious and costly and is not readily amenable to screening large populations.

The DNA diagnostic testing is based on the fact that the gene for MCAD deficiency has been cloned and sequenced and it has been determined that, in the general population, about 90% (mostly Caucasian) of the affected individuals have the same molecular mutation (A to G 985 mutation). Therefore, a single molecular probe has been developed that can be used to screen DNA for the mutation from individuals who are suspected of having the disorder. The procedure, unfortunately, requires that the DNA be isolated from the sample, fluorescently or radioactively labeled probes be available, and hybridization be performed on dot-blots or on gels. The procedure is currently time-consuming and costly and, as yet, is not amenable to screening large populations.

The testing was discussed with Dr. Ed McCabe at Baylor College of Medicine in Texas, who is at the forefront of developing the technology for newborn screening with molecular methodologies. He reports that the technology is improving, but automation of the system is not yet available for screening. No states or regions are performing newborn screening for MCAD deficiency using DNA diagnostics at this time.

The organic acid/mass spectrometric assays can be performed on body fluids, such as urine or plasma/serum. The procedures are well established, but various extractions must be performed to prepare the samples prior to testing. Recently, these procedures have been adapted for the determination of appropriate metabolites that are elevated in MCAD deficiency, using the blood-soaked filter papers used in newborn screening. These methods have been developed by Dr. David Millington and his colleagues at Duke University in North Carolina (International Journal of Mass Spectrometry and Ion Processes by Millington et al. 111:211-228, 1991). This method identifies carnitine derivatives of the various organic acids on 25 µl of whole blood spotted onto a filter paper. This method has the advantage that other organic acid disorders, in addition to MCAD deficiency, can be identified on the same screen.

To determine the status of this method for newborn screening, Dr. Millington was contacted. The major disadvantages of the procedure are the preparation of the samples, the cost of the testing and the cost of the equipment that is necessary to perform the testing. He recommended that two mass spectrometry instruments are needed (one for back up in case of mechanical down-time) with a total cost of about $600,000. Two Gilson autosampling processors are required at a cost of about $60,000 for both. For 100,000 tests per year, the machines may last for 5 years and then new machines would have to be purchased. The initial investment for this equipment and accessories (columns and chemicals) is about $750,000. This does not include the salaries of at least two laboratory technologists who are highly trained in mass spectrometry and who can trouble-shoot the equipment, and a third back-up technician. Each MCAD test would cost about $20 to $25 per sample, whereas other current newborn screening tests cost $0.10 to $2.00 per sample.

The equipment and the methods are not being used for newborn screening in North Carolina, but are at McGee Women's Hospital in Pittsburgh, Pennsylvania. Dr. Ed Naylor has contracted with multiple institutions for 12,000 to 15,000 newborn samples. When contacted, Dr. Naylor confirmed the cost of the equipment and the cost of the testing. He stated that several affected patients have been identified by screening. No other states or regions are currently performing newborn screening for MCAD deficiency.

Based on the available information, the subcommittee members assigned to study newborn screening for MCAD deficiency unanimously agreed that it would be premature to begin screening for MCAD deficiency at this time. The costs of equipment and personnel are excessive relative to other newborn screening tests currently performed, and the technologies are not developed sufficiently to warrant population screening now.

Certain other disorders, such as cystic fibrosis and congenital adrenal hyperplasia, are currently being considered for expansion of screening tests. The subcommittee agreed that it is not cost effective to expand the current testing at this time. The test for cystic fibrosis is relatively expensive compared to the current screening tests. The procedure for congenital adrenal hyperplasia is available, but is laborious and costly. There is a high rate of false positives and false negatives for both disorders. Procedures are being refined to improve current methodologies which will be less costly and amenable to screening mass populations.

The subcommittee agreed to review the feasibility and appropriateness of expanding currently required screening tests for newborns once a year, or sooner if new information or data warrant consideration for screening.

Conclusions

The study team recommends to the Governor and the Virginia General Assembly:

A. That MCAD deficiency not be added to the currently required screening tests for newborns because the technologies are not developed sufficiently to warrant population screening for MCAD deficiency at this time. Also, costs of specialized equipment and personnel are exorbitant relative to other newborn screening tests currently performed.

B. That currently required screening tests for newborns not be expanded. Technology that is available for testing certain metabolic and other disorders is not amenable to screening of mass populations.

C. That the Virginia Department of Health study, once a year, the feasibility and appropriateness of expanding currently required screening tests for newborns.

GENERAL ASSEMBLY OF VIRGINIA--1993 SESSION

HOUSE JOINT RESOLUTION NO. 657

Requesting the Department of Health to study the feasibility and appropriateness of expanding current required screening tests for newborns to include testing for certain metabolic and other disorders.

Agreed to by the House of Delegates, February 4, 1993
Agreed to by the Senate, February 16, 1993

WHEREAS, pursuant to § 32.1-65 of the Code of Virginia, every infant born in the Commonwealth must be subjected to screening tests for various inborn metabolic disorders, including biotinidase deficiency, phenylketonuria, hypothyroidism, homocystinuria, and galactosemia, to prevent mental retardation, permanent disability, or death; and

WHEREAS, the Commissioner of Health is directed by statute to establish, in cooperation with local health directors, a voluntary program for the screening of individuals for various genetically related diseases, traits, and inborn errors of metabolism as the Board of Health considers necessary; and

WHEREAS, Medium Chain Acyl CoA Dehydrogenase Deficiency, or MCAD, is a genetic disorder in which a missing or malfunctioning enzyme obstructs the body's conversion of fats to life-sustaining energy; and

WHEREAS, of the 7,000 babies whose deaths were attributed to Sudden Infant Death Syndrome in 1991, an estimated one to three percent were likely due instead to undiagnosed MCAD; and

WHEREAS, early detection of this genetic disorder may reduce future infant deaths; and

WHEREAS, a mass spectrometry machine, such as the model currently being tested at Duke University, provides the capability to screen for MCAD and 19 other diseases with great accuracy through laboratory tests similar to those presently required for newborns in Virginia; and

WHEREAS, further review of MCAD and other recently developed screening techniques is necessary to determine the need for expanding current required tests for newborns in Virginia; now, therefore, be it

RESOLVED by the House of Delegates, the Senate concurring, That the Department of Health study the feasibility and appropriateness of expanding current required screening tests for newborns to include testing for certain metabolic and other disorders. The study shall include, among other things, a review of Medium Chain Acyl CoA Dehydrogenase Deficiency and an examination of mass spectrometry technology and its potential effect on the reduction of death, disease, and disability.

The Department shall submit its findings and recommendations to the Governor and the 1994 Session of the General Assembly in accordance with the procedures of the Division of Legislative Automated Systems for the processing of legislative documents.

APPENDIX B

GLOSSARY OF TERMS

Phenylketonuria (PKU) A defect in the metabolism of the essential amino acid phenylalanine which results in excessive accumulation of phenylalanine and abnormal metabolites in body fluids.

Hypothyroidism A deficiency of thyroid hormone that is usually due to an absent or abnormally developed thyroid gland.

Galactosemia A disorder of carbohydrate metabolism in which galactose cannot be converted to glucose because of missing or deficient enzymes.

Maple Syrup Urine Disease (MSUD)
A disorder of branched-chain ketoacid decarboxylation resulting in high serum levels of leucine, isoleucine, valine and their corresponding ketoacids in blood, urine and cerebral spinal fluid.

Homocystinuria A deficiency of enzyme, cystathionine synthetase, which normally converts methionine to cystine, causing elevated levels of homocysteine, methionine, and metabolites of homocysteine in blood and urine.

Biotinidase Deficiency A disorder of biotin recycling that leads to multiple carboxylase deficiency.

Sickle Cell Disease A disorder involving the protein portion of the hemoglobin molecule. Hemoglobin S is produced when the amino acid valine is substituted for glutamic acid on the beta chain.