Bobby Jindal
GOVERNOR

Bruce D. Greenstein
SECRETARY

State of Louisiana

Department of Health and Hospitals
Office of the Secretary

July 13, 2011

The Honorable Joel T. Chaisson, II, President
Louisiana State Senate
P.O. Box 94183, Capitol Station
Baton Rouge, LA 70804-9183

The Honorable Jim Tucker, Speaker
Louisiana State House of Representatives
P.O. Box 94062, Capitol Station
Baton Rouge, LA 70804-9062

The Honorable Kay Katz, Chairwoman
House Health and Welfare Committee
Louisiana State House of Representatives
P.O. Box 44486, Capitol Station
Baton Rouge, LA 70804-4486

The Honorable Willie L. Mount, Chairwoman
Senate Health and Welfare Committee
Louisiana State Senate
P.O. Box 94183, Capitol Station
Baton Rouge, LA 70804-9183

Dear President Chaisson, Speaker Tucker, and Honorable Chairs:

In response to House Concurrent Resolution No. 187 (HCR 187) of the 2009 Regular Session, the Louisiana Department of Health and Hospitals (DHH) submits the enclosed report. HCR 187 requested that DHH create a pilot program to screen newborns for Severe Combined Immunodeficiency Disorder (SCID). The resolution further requested that DHH submit a report to the House and Senate committees on health and welfare that recommends whether SCID testing warrants permanent inclusion in the state's newborn screening program. SCID is a primary immunodeficiency disorder that causes premature death, usually in the first few months of life.

DHH began pilot testing for SCID in October 2010. Testing concluded in April 2011. Over 32,000 blood samples were tested for SCID, and none of those samples tested positive for SCID. DHH has determined that more samples are needed to fully assess the value of adding testing for immunodeficiency disorders to the Louisiana Newborn Heel Stick Screening Panel. DHH will continue to assess the feasibility and value of continuing sampling of newborns for SCID, and will closely monitor the results of SCID testing in other states as well to determine if the test should be permanently added in Louisiana.

Thank you for allowing us to present information to you regarding the SCID pilot screening program. Kathy Kliebert, DHH's deputy secretary, is available to discuss this report with you should you have any questions or comments. Please feel free to contact her at (225) 342-7092 with any questions or comments that you may have.

Sincerely,

Bruce D. Greenstein
Secretary

DEPARTMENT OF HEALTH AND HOSPITALS

PILOT TESTING FOR SEVERE COMBINED IMMUNODEFICIENCY DISORDER (SCID)

REPORT PREPARED IN RESPONSE TO HCR 187 OF THE 2009 REGULAR SESSION

JULY 2011

Contact:
Louisiana Department of Health and Hospitals
Takeisha Davis, M.D., M.P.H.
Office of Public Health
1450 L&A Road, Metairie, LA 70001
504-219-4402
Takeisha.Davis@la.gov

EXECUTIVE SUMMARY

Severe Combined Immunodeficiency Disorder (SCID), commonly referred to as "bubble boy disease," is a primary immunodeficiency disorder that causes premature death, usually in the first few months of life. Death usually occurs because affected children cannot fight off common childhood infections due to the lack of a functioning immune system. SCID affects approximately one in 100,000 infants. With early detection, SCID can be cured with a bone marrow transplant. This treatment has a 95 percent success rate. Infants born and undiagnosed with SCID and other immunodeficiency disorders may not live to see their first birthday without intervention and treatment.

As requested by House Concurrent Resolution 187 of the 2009 Regular Session, the Louisiana Department of Health and Hospital's Office of Public Health (OPH) conducted a pilot screening program for the detection of SCID in newborns. This pilot testing is being conducted to assess the feasibility of adding testing for immunodeficiency disorders to the Louisiana Newborn Heel Stick Screening Panel (L.R.S. 40:1299 et seq and LAC 48: V.6303) that screens for 28 genetic conditions.

Pilot testing for this disorder began on October 1, 2010. Testing is provided by the Wisconsin State Laboratory of Hygiene at the University of Wisconsin-Madison through funding from the National Institutes of Health and with support from the Centers for Disease Control and Prevention and the Jeffrey Modell Foundation. Testing is conducted by using the same bloodspots that are submitted for the current Louisiana Newborn Heel Stick Screening Panel. Once the Louisiana's State Public Health Laboratory completes testing for the current panel, a blood spot is punched from the sample and sent to the Wisconsin State Laboratory for the T-Cell Receptor Excision Circles Assay, which is the methodology used to screen for SCID and other immunodeficiency disorders.

Follow-up of presumptive positive cases are performed by a staff person from the Research Institute for Children at Children's Hospital in New Orleans. The Institute is funded by the Jeffery Modell Foundation and is under the guidance of the OPH Genetic Diseases Program. The physicians of infants with a presumptive positive result are contacted and a recommendation of a referral to the Jeffrey Modell Diagnostic Center for Immunodeficiencies in New Orleans for further evaluation and treatment is made.

Sufficient funding was procured to test 32,016 samples, beginning October 2010 through April 30, 2011. The samples have been sent to the Wisconsin State Laboratory to screen for T-Cell deficiencies disorders. Of the 32,016 samples, 671, or 2.1 percent, required repeat testing.

The results of the repeat testing on the 671 samples indicated that 70 percent of the newborn infants were within normal limits. Another 30.2%, or 203 infants, required a second newborn screening sample to be collected. Lastly, 1.2% percent or nine samples went for confirmation using flow cytometry testing. While none of the nine samples were confirmed to be a true SCID case, one infant was confirmed to have Jacobsen syndrome. To date, the false positive rate for this test is 0.66%, and there have been no confirmed cases of SCID. This false positive rate is largely due to the high premature birth rate of 12-13% in Louisiana. With an increase in the volume and long-term screening of SCID in newborns, this false positive rate should decrease. The current guideline from the Wisconsin State Laboratory of rescreening samples of 40 T cell excision circles (TRECs) or below is conservative in hopes of not missing a case. So far, it has been shown that true SCID cases show results of zero to very small TRECs. Therefore, the reduction in the false positive rate for SCID should decrease with the increase in population based screening as well as a less conservative bar for confirmation testing.

PILOT TESTING FOR SEVERE COMBINED IMMUNODEFICIENCY DISORDER

DESCRIPTION OF T CELL DISORDERS AND WHY TESTING IS IMPORTANT

Primary immunodeficiency diseases (PIDD) are genetically determined as disorders of a person's host defenses that affect one or several components of the immune system. An important group of PIDD affects the number and function of T-lymphocytes, which are essential to providing cellular immunity against infections that rarely occur in normal individuals. Collectively, they are called T cell deficiencies, or deficiencies of cellular immunity. The most severe forms affect very young children and are called severe combined immunodeficiencies (SCID). Perhaps the most well known patient affected by SCID was David Vetter, who was known as the "Boy in the Plastic Bubble". Vetter was kept alive by extreme protective measures, but died when he came out of the protective bubble and was exposed to infection.

There are many different genetic defects that can cause SCID. Almost all these conditions have in common the fact that the gene defect that causes a malfunction of the immune system does not cause a recognizable abnormality by itself. These patients become clinically ill when they develop infections, which typically occur after three months of life.

When recognized early in life, even before infections begin, T cell deficiencies can be cured through bone marrow transplantation with a 95 percent success rate. However, awareness of PIDD is often lacking and as a result, many patients are left undiagnosed and untreated for their immunodeficiency. These patients may require multiple, prolonged and generally unsuccessful treatments for their infections, causing great distress to their families and high costs within the health care system.

Neonatal screening for T cell deficiencies was initiated in Wisconsin in 2008, followed by Massachusetts in 2009. Currently, six states are screening for T cell deficiencies which is recommended by several national organizations. Louisiana began a pilot study for T cell deficiencies in October 2010.

THE INITIATION OF PILOT TESTING IN LOUISIANA

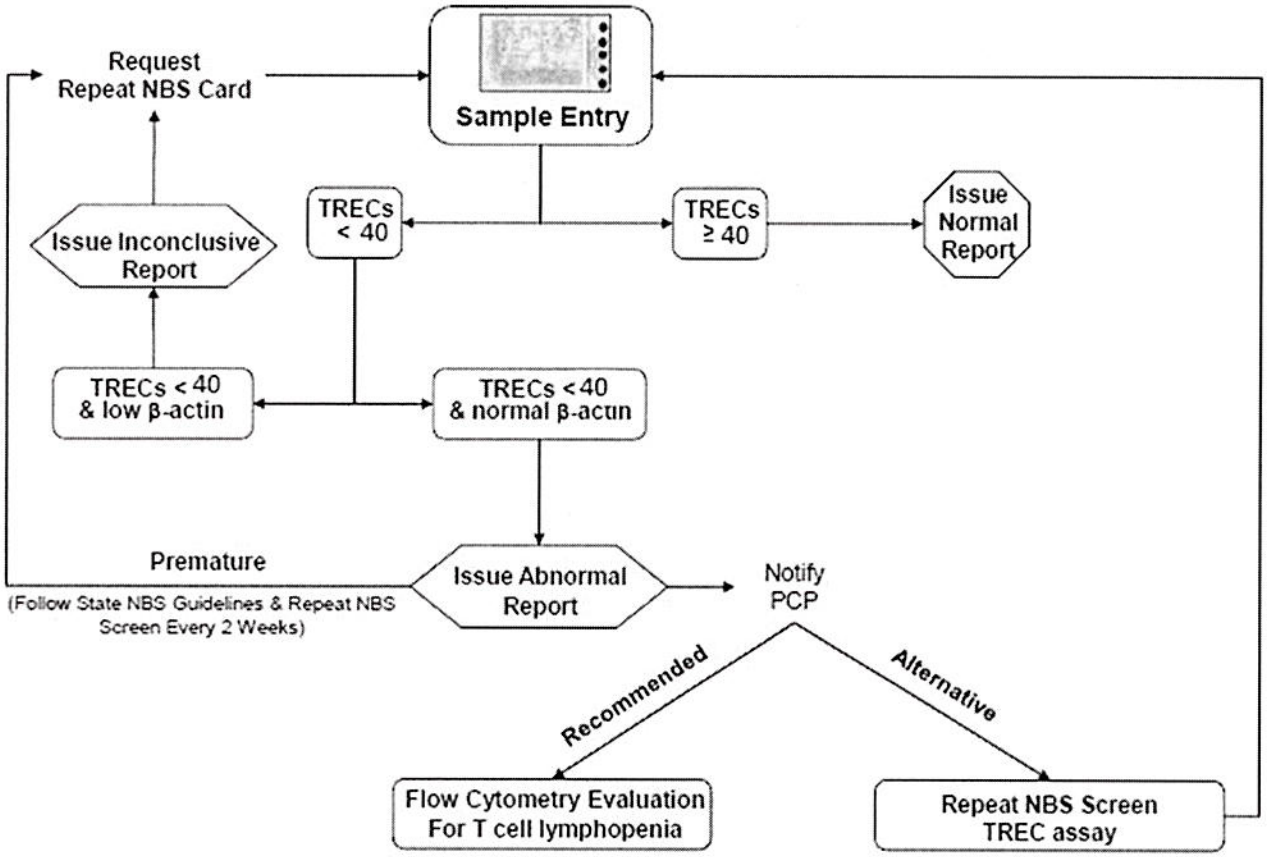
Pilot testing for SCID in Louisiana was the result of several efforts taking place at the same time. As HCR 187 of the 2009 Regular Session of the Louisiana Legislature was being voted on, physicians from the Jeffrey Modell Diagnostic Center for Primary Immodeficiencies at Children's Hospital were applying for funding from the National Institutes of Health (NIH) to perform testing in Louisiana. In November 2009, the Jeffrey Modell Diagnostic Center for Primary Immunodeficiencies sponsored a neonatal screening workshop to discuss the importance of screening for PIDD and funding opportunities. Noted researchers in the field of immunodeficiencies and officials from federal health departments such as the Centers for Disease Control and Prevention (CDC) and NIH were presenters.

The newborn screening testing labs in Wisconsin and Massachusetts were awarded funding from NIH to do pilot testing to assist Louisiana and Puerto Rico respectively with testing. Both programs offered to perform pilot testing for Louisiana. The Wisconsin State Laboratory was chosen based on the number of tests performed and the methodology used to perform the testing.

TESTING PROCESS AND FOLLOW-UP PROTOCOL

Newborn screening for T cell deficiencies is performed by measuring the quantities of DNA that are shed during T cell maturation. A complete absence or extremely low numbers of functional mature T cells is a feature found in the majority of SCID cases. This feature has recently been used to successfully screen neonates for T cell deficiencies by measuring the numbers of T cell excision circles (TRECs). DNA structures that are produced during normal T cell development are called TRECs.

The interpretation of T cells in newborn screening is expressed as quantities of TRECs. If the number of TRECs detected are below a certain level, that child is referred for further testing to assess T-cell development. Louisiana follows the recommendations of the Newborn Screening Laboratory of the Wisconsin State Laboratory of Hygiene. This laboratory established criteria for action which is illustrated in the following flow chart:



A sample that has a value of ≥ 40 is considered to be within normal limits for a newborn and no further action is required. For a sample that has a value < 40, the sample is repeated in duplicate. If the sample is repeatedly < 40 (i.e. at least 2 of the 3 results are < 40), the sample requires further action. This further action either requires a second blood spot to be collected or further confirmation testing.

An additional newborn screening sample is requested from the following options:

1. The TRECs value is < 40 and the β-actin is low in the sample. These results are considered inconclusive.

2. The TRECs value is < 40, normal β-actin levels are present in the sample, and the newborn is premature. In this case the flow chart recommends the newborn be screened every two weeks.
3. Two or three TREC values for the sample are between 25 and 40.

Samples that require further confirmation testing are samples where all three TREC values are < 25.

Referral, Consultation, Evaluation & Treatment

An abnormal TREC result is communicated to the delivery hospital and/or the primary care or designated referral physician to inform them of the newborn screening results, ascertain current status, and determine if there is a history of SCID in the family. If a physician is not available to receive this call and the newborn has left the hospital, the family is contacted directly. A result that prompts this action is a sample that has all three TREC values < 25. One of two basic actions will then be recommended depending on the gestational age of the newborn:

1. If the newborn is premature, additional newborn screening samples will be requested every 2-3 weeks until TRECs normalize. The gestational age of a newborn is recorded at the time of obtaining the newborn screening sample. If TRECs remain low by 37 weeks of gestational age, further testing and/or referral to an immunologist is recommended (see next).

2. If the newborn is a term baby with low TREC results, the primary care physician will be contacted and offered two options for action:

    - Obtain a whole blood sample for a complete blood count (CBC) with differential and flow cytometry at a laboratory capable of the following: enumeration of CD3+ T cell CD4+ T helper cells, CD8+ T suppressor cells, CD19+ B cells, CD16/56+ NK cells and CD45 RA+ ad CD45RO+ cells. The latter subpopulations are essential to determine thymic function. A copy of the test results will be requested regardless of the outcome of the test. If this second tier test show T cell lymphopenia (or low percentage of naïve CD4 or CD8 T cells), referral to an immunology center for further evaluation, diagnosis and treatment is indicated.

    - Refer directly to an immunology center for evaluation rather than perform the initial immunological evaluation locally. This option will be encouraged if the newborn does not appear to be clinically healthy or if the TREC count is very low.

    The family will not be contacted directly unless the primary care physician requests it or if a primary care physician is not available. At this point, contact with the family will be done by one of the immunologists on a list provided to the primary care physician (see list of immunologists and referral centers, below).

Referral Summary for Confirmed Low TREC Results

1. Confirmatory testing: CBC with differential and flow cytometry capable of analyzing lymphocyte subpopulations to include CD45RO+ and CD45RA+ cells.

2. Advanced immunology evaluation: lymphocyte proliferation and identification of molecular abnormality is recommended to be done by clinical immunologists identified and listed below.

Referral Information, Centers and Clinical Immunologists

New Orleans

1. **Jeffrey Modell Diagnostic Center (JMC) for Immunodeficiencies at Children's Hospital. The JMC team can be reached by calling 504-896-9589 during working hours and 504-899-9511 after hours requesting to talk to the fellow on call for Allergy/Immunology. The JMC staff includes:**

Dimitriades, Victoria, MD
Jeffrey Modell Diagnostic Center
Asst Professor of Pediatrics
Department of Pediatrics
LSU Health Sciences Center
at Children's Hospital
RIC Bldg. - Room 4228
200 Henry Clay Ave
New Orleans, LA 70118
Phone: 504-896-9589
Fax: 504-896-9311
Vdimit@lsuhsc.edu
Varsen@lsuhsc.edu

Paris, Kenneth, MD, MPH
Jeffrey Modell Diagnostic Center
Asst Professor of Pediatrics
Department of Pediatrics
LSU Health Sciences Center
at Children's Hospital
RIC Bldg. Room 4228
200 Henry Clay Avenue
New Orleans, LA 70112
Phone: 504-896-9589
Fax: 504-896-9311
Kparis@lsuhsc.edu

Sorensen, Ricardo, MD
Jeffrey Modell Diagnostic Center
Professor of Pediatrics
Department of Pediatrics
LSU Health Sciences Center
at LSU Pediatrics,
Children's Hospital
200 Henry Clay Avenue
New Orleans, LA 70118

Phone: 504-896-2723
Fax: 504-896-9311
Rsoren@lsuhsc.edu
Website: http://www.jmcenterneworleans.org

2. **Tulane University Department of Pediatrics**
   El Dahr, Jane Maronay, MD
   Professor of Clinical Pediatrics
   Clinical Professor of Medicine
   Chief, Section of Pediatric Immunology, Allergy and Rheumatology
   Department of Pediatrics
   Tulane University Medical School
   1430 Tulane Avenue (SL-75)
   New Orleans, Louisiana 70112-2699
   jeldahr@tulane.edu

Baton Rouge

Dimitriades, Victoria, MD
Asst Professor of Pediatrics
Department of Pediatrics
LSU Health Sciences Center
Children's Hospital Outpatient Clinic
720 Connell Park Lane
Baton Rouge, Louisiana 70809
Phone: 504-896-9589
Fax: 504-896-9311
Varsen@lsuhsc.edu

Lafayette

Paris, Kenneth, MD, MPH
Asst Professor of Pediatrics
Department of Pediatrics
LSU Health Sciences Center
Children's Hospital Outpatient Clinic
1211 Coolidge Blvd
Burdin Riehl Building
Lafayette, Louisiana 70503
Phone: 504-896-9589
Fax: 504-896-9311
kparis@lsuhsc.edu

Shreveport

Bahna, Sami, MD, DrPH
Louisiana State University Health Sciences Center
Professor of Pediatrics & Medicine
Chief, Allergy/Immunology Section
1501 Kings Highway
Shreveport, LA 71130-3832

Phone: 318-675-7625
Fax: 318-675-8815
Website: http://www.sh.lsuhsc.edu/allergyimmunology

Stem cell transplantation (bone marrow or cord blood) in Louisiana is available at Children's Hospital in New Orleans through the clinical immunologists at Children's Hospital: Dimitriades, Paris and Sorensen.

SUPPORT FOR SCID TESTING

National screening for T cell deficiencies has been recommended by a number of relevant national organizations. Most importantly, on February 1, 2010, the U.S. Department of Health and Human Services, Secretary's Advisory Committee for Heritable Disorders in Newborns and Children (SACHDNC) unanimously agreed to recommend that SCID be added to the universal newborn screening programs conducted by state public health agencies. This resolution was endorsed by the American College of Medical Genetics (ACMG), which wholeheartedly supports the Federal Advisory Committee's recommendation that SCID be added to the uniform newborn screening panel developed by ACMG in 2005.

The ACHDNC recommendation had been preceded by the Public Policy Council of the American Pediatric Society & Society for Pediatric Research and the Association of Medical School Pediatric Department Chairs. These recommendations were developed, in collaboration with the American Pediatric Association's Advocacy and Public Policy Committee, at a major public policy plenary symposium that has implications for national health care, investments in pediatric research, education, and training of the current as well as next generation of pediatricians and pediatric subspecialists. This jointly sponsored 2009 state of the art plenary session contemplated implications for pediatrics, such as testing for genetic diseases – i.e., newborn screening.

The Louisiana Newborn Screening Advisory Committee (LANSAC) was created in response to LAC 48.V.19. It is composed of members who are knowledgeable about medical genetic disorders, with representation from all three medical schools in the state. Disciplines that are represented include Pediatrics, Neonatology, Genetics, Hematology, Endocrinology, and Pulmonlogy. The purpose of LANSAC is to assist OPH in developing standards for the implementation of newborn screening rules and to make recommendations for the addition of new conditions to the panel.

During a committee meeting in February 2009, the committee recommended pilot screening for SCID. In a subsequent ad hoc meeting in January 2011, the committee expressed its favor for the addition of SCID to the current newborn screening panel. The latter is dependent on budget appropriations for the additional staffing and equipment needed to allow SCID to be added to the established Louisiana Newborn Heel Stick Screening Panel. The advisory committee is in agreement that screening for SCID is important as well as providing funding to perform this screening.

COST ASSOCIATED WITH CONTINUING SCID TESTING

SCID occurs in approximately one out of 100,000 births. This pilot study only covered 32,016 samples. Additional funds are needed to continue the pilot study to test and follow-up on enough infants to reach a large enough sample size to validate the pilot. It is estimated that at least 100,000 samples would have to be tested to validate the pilot.

- Genetic Diseases Program – The DHH Genetic Diseases Program performs follow-up on 28 genetic conditions recommended by the ACMG. The division of work is currently among four staff persons who also perform additional duties such as lead investigations and filing for medical reimbursements. Follow-up consists of receiving reports from the laboratory, notifying the proper medical provider, making a referral for immunologic evaluation, determining if an infant was seen by a specialist and ascertaining a final diagnosis. It is estimated that at least 400 infants will have a presumptive positive result as a result of SCID testing. A minimum of $80,000 per year would be needed to cover the salary and the benefits package and other allocated costs to hire an employee to perform this duty. Additional funds may be needed to contract with pediatric immunologists as medical consultants.

- Louisiana's State Public Health Laboratory – The DHH Public Health lab would need approximately $400,000 in startup costs to purchase the equipment, reagents and hire staff to perform this testing. The lab currently has limited space for adding equipment to perform new tests. The current external funding for providing SCID testing ended April 30, 2011. In order to continue to provide this testing to the state and to validate the pilot, laboratory funding would need to be secured to cover startup costs.

CONCLUSION AND RECOMMENDATIONS

As requested by House Concurrent Resolution 187 of the 2009 Regular Session, the Louisiana Department of Health and Hospital's Office of Public Health (OPH) conducted a pilot screening program for the detection of SCID in newborns. This pilot testing was conducted to assess the feasibility and value of adding testing for immunodeficiency disorders to the Louisiana Newborn Heel Stick Screening Panel (L.R.S. 40:1299 et seq and LAC 48:V.6303) that screens for 28 genetic conditions.

Funding was provided from NIH to Wisconsin State Laboratory to test samples from Louisiana. From October 1, 2010, to April 30, 2011, a total of 32,016 samples have been sent to the Wisconsin State Laboratory to screen for T-cell deficiencies disorders. Of the 32,016 samples, 671 or 2.1 percent required repeat testing. However, there were no confirmed cases of SCID identified through this pilot study. The pilot study only covered 32,016 samples, and it is estimated that at least 100,000 samples would have to be tested to validate the pilot.

It is recommended that SCID screening be continued should DHH-OPH receive additional funding to continue the pilot program and follow-up on a large enough sample size of infants to validate the pilot. In addition, regardless of whether additional funds are secured, it is also recommended that DHH-OPH remain abreast of the results of SCID testing in other states to determine if the addition of this screen to the Louisiana Newborn Heel Stick Screening Panel should be recommended to the legislature in the future.

Acknowledgments

Authors:

Dr. Takeisha Davis, Medical Director, Region 1, Office of Public Health – DHH
Dr. Catherine Evans, Public Health Laboratory, Office of Public Health – DHH
Cheryl Harris, Genetic Disease Program, Office of Public Health – DHH

Louisiana Department of Health and Hospitals

Bruce D. Greenstein, Secretary
Kathy Kliebert, Deputy Secretary
Jerry Phillips, Undersecretary
J.T. Lane, Chief of Staff
Christine Peck, Legislative and Governmental Relations Director

ENROLLED

Regular Session, 2009

HOUSE CONCURRENT RESOLUTION NO. 187

BY REPRESENTATIVE GARY SMITH

A CONCURRENT RESOLUTION

To urge and request the Department of Health and Hospitals to create a pilot screening program for the detection of Severe Combined Immunodeficiency Disorder (SCID) in newborns, to develop the pilot program in consultation with the Centers for Disease Control, the American College of Medical Genetics, and other relevant experts to be chosen at the discretion of the secretary of the Department of Health and Hospitals, and to urge that the program utilize a testing procedure paid for by the parents of the newborn that screens for the presence of the genetic mutation causing SCID, and, if there is a positive screening result, develop a test to confirm the result and follow up with the affected parents of the newborn, and to report on the results of the pilot program to the House Committee on Health and Welfare and the Senate Committee on Health and Welfare no later than April 1, 2011.

WHEREAS, SCID is a life-threatening syndrome in which a person's adaptive immune system is severely impaired; and

WHEREAS, persons with SCID are extremely vulnerable to ordinary infections, and viruses that are minor for persons without SCID are often deadly for persons who have SCID; and

WHEREAS, SCID is detectable through genetic testing, and early detection of this disorder is vital to ensure the survival of those persons with SCID.

THEREFORE, BE IT RESOLVED that the Legislature of Louisiana does hereby urge and request the Department of Health and Hospitals to create a pilot screening program for the detection of SCID in newborns, to develop the pilot program in consultation with the Centers for Disease Control, the American College of Medical Genetics, and other relevant experts to be chosen at the discretion of the secretary of the Department of Health and Hospitals, and to urge that the program utilize a testing procedure that screens for the

presence of the genetic mutation causing SCID, and, if there is a positive screening result, develop a test to confirm the result and follow up with the affected parents of the newborn.

BE IT FURTHER RESOLVED that the pilot screening program shall be offered as an optional test and shall be made available to the parents of every newborn for a two-year period commencing on July 1, 2010. During the pilot period, all costs associated with the testing procedure and any further testing to confirm a positive result shall be paid by the parents of the newborn.

BE IT FURTHER RESOLVED that prior to the end of the two-year pilot period, but no later than April 1, 2011, the Department of Health and Hospitals shall report to the House Committee on Health and Welfare and the Senate Committee on Health and Welfare the following:

(1) Whether testing warrants permanent inclusion in the newborn screening program.

(2) Whether it is cost-effective for the state to cover the test through Medicaid.

BE IT FURTHER RESOLVED that a copy of this Resolution be transmitted to the secretary of the Department of Health and Hospitals.

SPEAKER OF THE HOUSE OF REPRESENTATIVES

PRESIDENT OF THE SENATE