UPDATES ON IMPLEMENTATION OF SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY, CRITICAL CONGENITAL HEART DISEASE, AND POMPE DISEASE

JELILI OJODU, MPH, ASSOCIATION OF PUBLIC HEALTH LABORATORIES
MARCI SONTAG, PHD, COLORADO SCHOOL OF PUBLIC HEALTH
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**APHL Vision**
A healthier world through quality laboratory systems.

**APHL Mission**
Shape national and global health outcomes by promoting the value and contributions of public health laboratories and continuously improving the public health laboratory system and practice.

**NewSTEPs Vision**
Dynamic newborn screening systems have access to and utilize accurate, relevant information to achieve and maintain excellence through continuous quality improvement.

**NewSTEPs Mission**
To achieve the highest quality for newborn screening systems by providing relevant, accurate tools and resources and to facilitate collaboration between state programs and other newborn screening partners.
BACKGROUND
The Foundation for SCID Newborn Screening

Immune deficiencies, infection, and systemic immune disorders

Development of a routine newborn screening protocol for severe combined immunodeficiency

Maw B. Baker, MD, William J. Grossman, MD, PhD, Ronald H. Lammig, PhD, Gary L. Hoffman, BS, Charles D. Bivings, DPhil, Daniel F. Kutryc, MD, Michael F. Ogles, BS, Thomas J. Lathem, BS, Murray L. Kitchin, MD, PhD, and John M. Routes, MD, MS

Medline and MedWorld, Inc.

Background: Severe combined immunodeficiency (SCID) is characterized by the absence of functional T and B cells. Without early diagnosis and treatment, infants with SCID die from severe infections within the first year of life. Objective: To determine the feasibility of detecting SCID in newborns by quantifying T-cell receptor excision circles (TRECs) from dried blood spots (DBS) on newborn screening (NB) cards.

Methods: DNA was extracted from DBS on NB cards, and real-time quantitative PCR (RT-qPCR) was used to determine the number of TRECs. Positive controls consisted of DBS from a 1-month-old T-B- NK patient with SCID and whole blood specimens collected de novo from T-cell-deficient patients. Results: The mean and median numbers of TRECs from 576 deidentified DBS were 867 ± 79, respectively, per 3.2-mm punch (n = 3; whole blood). Two samples failed to amplify TRECs on initial analysis; all but 1 demonstrated normal TRECs and their amplification on retooling. No TRECs were detected in either the SCID or neonatal T-cell-deficient samples, despite the presence of normal levels of T cells.

Conclusions: The use of RT-qPCR to quantitate TRECs from DNA extracted from newborn DBS is a highly sensitive and specific screening test for SCID. This assay is currently being used in Wisconsin for routine screening for SCID.

Avery Ch. Immunol 2005;134;523-7.

Key words: Dried blood spots, Amplimers assay of transplant, newborn screening, routine quantitative PCR, severe combined immunodeficiency, T-cell receptor excision circles.

The goal of newborn screening (NBS) is to identify pregancyneurodevelopmental disorders with potentially serious or fatal disorders that can be successfully treated, leading to significant reductions in morbidity and mortality. The 45-year history of NBS demonstrates that it is an extremely successful and cost-effective public health intervention and provides useful information to the field of preventive medicine.1 Routine NBS began in the 1960s, with a disorder, phenylketonuria, and grew to a panel of 29 conditions as recommended by the American College of Medical Genetics.2 As knowledge of the causes of genetic disorders increases, detection technologies advance, and better treatment regimens emerge, more diseases will be added to the NBS panel.

Severe combined immunodeficiency (SCID) was recognized as a disorder that meets the criteria for inclusion in NBS in a Center for Disease Control and Prevention conference entitled "Applying Public Health Strategies to Primary Immunodeficiency Diseases." ACR
diagnosis includes infants who are asymptomatic at birth, acute medical consequences without treatment, availability of confirmatory tests and effective treatment, and improved outcomes with early intervention. The National Advisory Committee of Heritable Disorders in Newborns and Children has selected SCID as the focus of the pilot project using a unique approach as a primary key.

The New England Newborn Screening Program evaluated and validated a multiplex TREC assay in which both the TRECs allohydro and an internal control are acquired from a single punch and run in the same reaction. Massachusetts then implemented a statewide pilot SCID NBS program. The authors describe the rationale for a pilot NBS SCID program, a comprehensive strategy for successful implementation, the screening test algorithm, the screening follow-up algorithm and preliminary experience based on statewide screening in the first year. The Massachusetts experience demonstrates that SCID NBS is a program that can be implemented as a population-based test with minimal risk of false positives.

Introduction

Severe combined immunodeficiency (SCID) arises as a combination of genes in the expression of primary immunodeficiency (PID). SCID is particularly common for immunodeficiency in the list of conditions subject to neonatal screening.

Guidelines for implementation of population-based newborn screening

Anne Marie Carrion, Jane E. Blake, Yong-Yun Pan, Francois J. Duson, Luiz B. Nascimento, Mark S. Pastores, H. Cary Mowbray, Ellen R. Roy, Alfredo Damalma, Indrani Saha, Hager R. Ettin

Received: 22 January 2011 Revised: 26 March 2011 Accepted: 1 April 2011 Published Online: 20 May 2011

Abstract: Severe combined immunodeficiency (SCID) is a Primary Immune Deficiency that is under consideration for population-based newborn screening (NBS) by many NBS programs, and has recently been recommended for inclusion in the US Uniform panel of newborn screening conditions. A network of SCID NBS programs, the National Immunodeficiency Surveillance Network (NISN), has been established to promote the implementation of SCID NBS as a part of standard NBS protocols. Aims: To evaluate whether SCID NBS is feasible and enables routine detection of SCID in newborns.

The New England Newborn Screening Program participated in the NISN and validated a multiplex TREC assay in which both the TRECs and an internal control are acquired from a single punch and run in the same reaction. Massachusetts then implemented a statewide pilot SCID NBS program. The authors describe the rationale for a pilot NBS SCID program, a comprehensive strategy for successful implementation, the screening test algorithm, the screening follow-up algorithm and preliminary experience based on statewide screening in the first year. The Massachusetts experience demonstrates that SCID NBS is a program that can be implemented as a population-based test with minimal risk of false positives.

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Introduction

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Addition to the RUSP: February 2010

February 25, 2010

The Honorable Kathleen Sebelius
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Sebelius:

The Advisory Committee on Heritable Disorders in Newborns and Children (the Committee) is charged with advising the Secretary of the Department of Health and Human Services in areas relevant to heritable conditions in newborns and children including newborn and child screening, counseling, and health care services for newborns and children having or at risk for heritable disorders.

The Health Resources and Services Administration’s (HRSA) Maternal and Child Health Bureau (MCHB) commissioned the American College of Medical Genetics (ACMG) in 2001 to convene an expert panel to outline a process of standardization of outcomes and guidelines for state newborn screening programs, including a recommended uniform panel of conditions to include in state newborn screening programs. The ACMG expert panel was asked to conduct an analysis of the scientific literature on the effectiveness of newborn screening and gather expert opinion to delineate the best evidence for screening specified conditions and develop recommendations focused on newborn screening, including but not limited to the development of a uniform condition panel. It was expected that the analytical endeavor and subsequent recommendations be based on the best scientific evidence and analysis of that evidence. Upon review of the final ACMG report it

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children
5500 Fisher’s Lane, Room 18A19
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www.hrsa.gov/heritabledisorderscommittee

When developing its recommendations to the Secretary, the Committee considers the nature of the science itself underlying the potential additions of the technologies and the heritable conditions to the RUSP.

It is with these issues in mind that the Committee recommends a tiered approach to the screening of SCID and related T-cell related lymphocyte deficiencies.

- The addition of SCID to the uniform panel, and related T-cell lymphocyte deficiencies to the list of secondary targets as a comprehensive entity, with the understanding that the following activities will also take place in a timely manner.
  - The National Institutes of Health shall fund surveillance activities to determine health outcomes of affected newborns with any T-cell lymphocyte deficiency receiving treatment as a result of prospective newborn screening;
  - The Health Resources and Services Administration shall fund the development of appropriate education and training materials for families and public health and health care professionals relevant to the screening and treatment of SCID and related T-cell lymphocyte deficiencies.
  - The Centers for Disease Control and Prevention shall develop and distribute to performing laboratories suitable dried blood spot specimens for quality control and quality assurance purposes.

This is the first condition determined to be ready for addition to the Committee’s Recommended Uniform Screening Panel since 2005. It is a milestone for this Committee and represents the success of the Committee’s evidence review system. Thank you for your consideration of this important topic.

Sincerely yours,

R. Rodney Howell, M.D.
Chairperson
Challenges in SCID NBS Implementation

Approval/Legislation
  – Funding
  – Priorities

Laboratory
  – Equipment/Work flow
  – Training
  – Technical Challenges and Analysis

Follow-up and Clinical
  – Availability of Immunologists
  – Developing Relationships

Education
  – Staff
  – Leadership
  – Clinicians
  – Community/Advocacy
PROGRESS IN SCID IMPLEMENTATION
2014

SCID Screening Status
- Not Screened
- Universally Screened

State Screening Status Count

Not Screened

Universally Screened

Number of States

NewSTEPs
A Program of the Association of Public Health Laboratories™
SCID Technical Assistance

- Funding Opportunities
- CDC Technical Assistance and Trainings
- Monthly Call: NBSTRN/NewSTEPs
- Technical Assistance In-Person Meeting (July 2015)
- 12 Grantees awarded up to $150,000/year for two years from APHL for SCID Implementation
- Resources shared on www.nbstrn.org and www.newsteps.org
SCID Grantees

- Educational Resources
- Technical Assistance
- Molecular Screening Capacity
- In-House Screening
- Expert Advisors
- Clinical Referral Networks
- Algorithm Development
SCID Updates

FDA allows marketing of the first newborn screening test to help detect Severe Combined Immunodeficiency

For Immediate Release

December 15, 2014

Release

The U.S. Food and Drug Administration today allowed marketing of the EnLite Neonatal TREC Kit, the first screening test permitted to be marketed by FDA for Severe Combined Immunodeficiency (SCID) in newborns.
Stay Connected with NewSTEPs
To find out how to remain connected with NewSTEPs via social media and the listserv please click here. Join us to engage in peer to peer information exchange about newborn screening activities.

About NewSTEPs
The Newborn Screening Technical assistance and Evaluation Program (NewSTEPs), funded through a cooperative agreement to the Association of Public Health Laboratories (APHL) by the Genetic Services Branch of the Health Resources and Services Administration (HRSA), provides quality improvement initiatives, an innovative data repository and technical resources for newborn screening programs.
Measuring the Impact of SCID NBS

- NewSTEPs Repository
  - Count newborns identified by NBS with SCID
SCID Summary

• 72% of newborns in the U.S. are born in states with universal screening for SCID.
• By the end of 2016, 86% of newborns in the U.S. will be born in states offering universal screening for SCID.
• Universal screening for SCID is influenced by a dynamic environment.
Critical Congenital Heart Disease (CCHD)
Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective study in 39 821 newborns

Anne de Wette Granelli, cardiac sonographer; Margareta Wennemo, obstetrician; Kenneth Sandberg, consultant neonatologist; Mats Mellander, consultant paediatric radiologist; Carina Bejmer, consultant obstetrician; Leif Ingvar, consultant obstetrician; Monika Ericsson, consultant obstetrician; Niklas Segerdahl, consultant paediatrician; Annika Agren, research nurse; Birgitta Marie Erlanson-Ekman, consultant obstetrician; Jan Sunnergardh, consultant paediatric radiologist; Mario Ventura, consultant neonatologist; Ingridzis Oslams, professor of paediatric cardiology

Objective: To evaluate the use of pulse oximetry to screen for early detection of life-threatening congenital heart disease.

Design: Prospective screening study with a newborn pulse oximetry before discharge from well-baby nurseries in West Götaland. Cohort study comparing the detection rate of duct dependent circulation in West Götaland with that in other regions not using pulse oximetry screening. Deaths at home with undetected duct dependent circulation were included.

Results: 39,821 screened babies born between 1 July 2004 and 31 March 2007. Total duct dependent circulation cohort: West Götaland 936 (2.3%), other regions 872 (2.2%). Male outcome measures Sensitivity, specificity, positive and negative predictive values, and likelihood ratio for detection of duct dependent circulation in West Götaland (936/39,821) were: Sensitivity 0.998, Specificity 0.996, Positive predictive value 0.998, Negative predictive value 0.996, and Likelihood ratio for detection of duct dependent circulation in West Götaland were: Sensitivity 0.998, Specificity 0.996, Positive predictive value 0.998, Negative predictive value 0.996, and Likelihood ratio 0.998.

Conclusions: Introducing pulse oximetry screening in West Götaland resulted in only 2.3% echocardiograms with normal cardiac findings for every true positive case of duct dependent circulation. The high rate of life-threatening congenital heart disease was 936/39,821 (2.3%) in other regions versus 5.78% (2.3%) in West Götaland (P < 0.001). Overall, 0.998 in West Götaland and 0.996 in other regions. Deaths at home with undetected duct dependent circulation were included.

Setting: All 5 maternity units in West Götaland and the supranational referral centre for neonatal cardiac surgery.

Participants: 39,821 screened babies born between 1 July 2004 and 31 March 2007.

BACKGROUND: Although newborn screening for congenital heart disease (CHD) was recommended by the US Health and Human Services’ Advisory Committee on Heritable Disorders in Newborns and Children to promote early detection, it was denied by the Secretary of the HHS as not ready for adoption pending an implementation plan from HHS agencies.

OBJECTIVE: To develop strategies for the implementation of a safe, effective, and efficient screening.

METHODS: A work group was convened with members selected by the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children, the American Academy of Pediatrics, the American College of Cardiology Foundation, and the American Heart Association.

RESULTS: On the basis of published and unpublished data, the work group made recommendations for a standardized approach to screening and diagnostic follow-up. Key issues for future research and evaluation were identified.

CONCLUSIONS: The work-group members found sufficient evidence to begin screening for low blood oxygen saturation through the use of pulse-oximetry monitoring to detect CHD in well-baby and intermediate care nurseries. Research is needed regarding screening in special populations (eg, at high altitudes and to evaluate service infrastructure and delivery strategies (eg, telemedicine) for nurseries without on-site echocardiography. Public health agencies will have an important role in quality assurance and surveillance. Central to the effectiveness of screening will be the development of a national technical assistance center to coordinate implementation and evaluation of newborn screening for CHD. Pediatrics 2011;127:e193-e1967

ABSTRACT

Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective study in 39 821 newborns

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Addition to the RUSP: September 2011

September 21, 2011

R. Redsky Howell, M.D.
Committee Chairperson
Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children
5600 Fishers Lane, Room 18A19
Rockville, MD 20857

Dear Dr. Howell:

As indicated in my letter to you on April 20, 2011, I determined that the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children’s (SACHDNC) recommendations pertaining to the addition of Critical Congenital Heart Disease (CCHD) screening to the Recommended Uniform Screening Panel (RUSP) were not yet ready for adoption. Consequently, I referred the SACHDNC’s recommendations to the Interagency Coordinating Committee on Screening in Newborns and Children (ICC) for additional review and input regarding implementation. I asked the ICC to review the evidence gaps described by the SACHDNC and propose a plan of action to address, identification of effective screening technologies, development of diagnostic procedures, public, and strengthening service infrastructure.

As you know, congenital heart disease affects approximately 1 in 1000 live births, one quarter of which could be detected and potentially treated by measuring blood oxygen saturation. Given this reality and the available information on the effectiveness of screening, I have decided to adopt the SACHDNC’s first recommendation to add CCHD to the RUSP. In addition, I am requesting that the SACHDNC collaborate with the Health Resources and Services Administration (HRSA) to complete a thorough evaluation of the potential public health impact of universal screening for CCHD, as required by the authorizing statute, section 1111 of the Public Health Service Act (42 U.S.C. § 300b-18(b)(4)).

I have decided to adopt the SACHDNC’s first recommendation to add CCHD to the RUSP.

I would like to commend the SACHDNC on your success in creating and implementing an external scientific evidence review process for rare conditions that incorporates systematic evidence-based and peer-reviewed recommendations. I am encouraged by the emerging evidence base for the utility of early diagnosis and detection of CCHD via measurement of blood oxygen saturation, as well as the momentum and commitment that is evidenced at the state and federal levels to support implementation and investigation of successful screening programs. While we collectively engage in the remaining work that needs to be completed, HHS will continue to encourage states, health care facilities, and individual clinicians to provide this screening and contribute to the knowledge base in this important area.

I am committed to advancing screening for CCHD, and I appreciate the contributions of the SACHDNC in assisting HHS and states to explore ways to enhance newborn and child screening to improve the health of infants born in the United States.

Sincerely,

Kathleen Sebelius

[Signature]
Challenges and Opportunities
CCHD NBS Implementation

• Approval/Legislation
  – Funding
  – Priorities

• Point of Care Testing
  – Equipment/Work flow in hospitals
  – Training/Education of nursery staff
  – Determining best algorithm

• Special populations
  – NICUs
  – Home births
  – High Altitude
  – Rural areas/lack of cardiology support
Unique Challenges and Opportunities
CCHD NBS Implementation

• Data Collection
  – State authority to collect data
  – Mechanisms to collect data
  – Hospital time and buy-in to report data
  – Defining minimum data set
  – Funding for surveillance
  – Quality assurance/Quality control

• Birth Defects Registry
  – Partner to collect long-term follow-up data
  – Identify false negatives

• Education
  – Staff
  – Leadership
  – Clinicians
  – Community/Advocacy
CCHD Screening Progression
2012

CCHD Screening Stats
- Not Screened
- Universally Screened

State Screening Status Count

NewSTEPs
A Program of the Association of Public Health Laboratories™
MMWR Summarizes CCHD Experience in U.S.

- Data Collection:
  - States that have implemented/planning to implement CCHD screening
    - 24 current data collection,
    - 14 future data collection
    - 13 no plans for data collection
  - Types of data collection:
    - Aggregate data collection only
    - Pass/fail results on all newborns
    - O₂ saturation results on all newborns
    - O₂ saturation results on failed newborns only

Critical congenital heart defects (CCHD) occur in approximately two of every 1,000 live births (1). Newborn screening provides an opportunity for reducing infant morbidity and mortality (2,3). In September 2011, the U.S. Department of Health and Human Services (HHS) Secretary endorsed the recommendation that critical congenital heart defects be added to the Recommended Uniform Screening Panel (RUSP) for all newborns (4). In 2014, CDC collaborated with the American Academy of Pediatrics (AAP) Division of State Government Affairs and the Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs) to assess states’ actions for adopting newborn screening for CCHD. Forty-three states have taken action toward newborn screening for CCHD through legislation, regulations, or hospital guidelines. Among these 43, 32 (74%) are collecting or planning to collect CCHD screening data; however, the type of data collected by CCHD newborn screening programs varies by state. State mandates for newborn screening for CCHD will likely increase the number of newborns screened, allowing for the possibility of early identification and prevention of morbidity and mortality. Data collection at the state level is important for surveillance, monitoring of outcomes, and evaluation of state CCHD newborn screening programs.
Mechanisms to collect CCHD NBS Data

- Electronic Birth Certificate
- Birth defects registry
- Hospital electronic medical record
- Dried blood spot card
- Paper forms
- Health level-7 messaging; automatic file transfer
Stay Connected with NewSTEPs

To find out how to remain connected with NewSTEPs via social media and the listserv please click here. Join us to engage in peer to peer information exchange about newborn screening activities.

About NewSTEPs

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Measuring the Impact of CCHD NBS

- NewSTEPs Repository
  - Count newborns identified by NBS with CCHD

### Diagnostic Workup

- **Primary Screening Targets**
  - Hypoplastic left heart syndrome
  - Pulmonary atresia with intact septum
  - Tetralogy of fallot
  - Total anomalous pulmonary venous return
  - Transposition of the great arteries
  - Tricuspid atresia
  - Truncus arteriosus

- **Secondary Screening Targets**
  - Coaractation of the aorta
  - Double outlet right ventricle
  - Ebstein anomaly
  - Interrupted aortic arch
  - Single ventricle

- Birth Defects Registries
Technical Assistance Webinars

- Initiated by NYMAC Regional Genetics Collaborative (New York and Mid-Atlantic Region)
- Responsibility transferred to NewSTEPs in 2013
- Recorded and transcribed, (available at www.newsteps.org)
POMPE
I accept the DACHDNC recommendation to add Pompe disease to the RUSP.
Pompe Screening in the US

Missouri begins Pilot Testing 1/11/2013
ACHDNC recommends Pompe be added to the RUSP, sends letter to Sec. of HHS 6/2/2013
Sec. of HHS interim response to ACHDNC, ICC to review 1/27/2014
New York begins Universal Screening 10/1/2014
Sec. of HHS recommends Pompe to be added to RUSP 3/2/2015
Illinois begins Universal Screening 6/1/2015
Missouri begins Universal Screening 8/3/2015

10/1/2014
NY - 33 referrals ~210,000 births
8/15/2015
MO - 107 referrals ~210,150 births
7/31/2015

Screening Methodologies:

NY – FIA MS/MS + Molecular
IL – LC MS/MS moving towards FIA MS/MS
MO - Digital microfluidics fluorescent assay

Pompe and Other LSD Activities in the US

Pilot/Research Study

• Missouri
  – Pompe + 3 LSDs by digital microfluidics
  – Krabbe, Niemann Pick A/B by stand-alone fluorometry (in validation)

• Wisconsin
  – NIH funded Pompe NBS pilot study
  – NBS for 6 LSDs bill introduced: Krabbe, Fabry, Pompe, Niemann–Pick, Gaucher, MPS-1
Pompe and Other LSD Activities in the US

• New York
  – NIH funded Pompe NBS pilot study
  – Pilot testing (Four NY City hospitals: Fabry, Gaucher, Niemann-Pick A/B, MPS-1)
  – Live screening: Krabbe, Pompe
• Washington
  – Pompe, Fabry and Gaucher
  – De-identified samples, FIA-MS/MS + molecular
  – Recently expanded to include 3 more LSDs
Digital microfluidics fluorescent assay

Tandem mass spectrometry assay
# Future Pompe Screening

<table>
<thead>
<tr>
<th>Status of Pompe Screening</th>
<th>NBS Program</th>
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<tr>
<td>Required but not fully implemented</td>
<td>New Jersey</td>
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<tr>
<td></td>
<td>Kentucky</td>
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<tr>
<td></td>
<td>Texas</td>
</tr>
<tr>
<td></td>
<td>Michigan</td>
</tr>
<tr>
<td>Being considered, not yet approved</td>
<td>Colorado</td>
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<td>Ohio</td>
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Challenges in Pompe NBS Implementation

- Progression of disease – late onset
- Cost of treatment
- Recently added to RUSP
- Dedicated instrumentation
- LIMS software
- Staffing
Timeline of adding to state panel

General Process for Adding Conditions

State(s) consider condition(s), design and execute studies, provide study data

- Condition is added to the RUSP
- State decides to add or not to add condition (6 months to 1 year)
- State changes rules/statutes (6 months to 1 year)
- State obtains funding (1 to 3 years)
- State conducts implementation or pilot (1 to 3 years)
Public Health Impact Assessment

• **Past:** Limited and lack of formal public health impact assessments conducted prior to recommending the addition of CCHD, SCID and Pompe to the RUSP.

• **Present:**
  – MPS-1 Public Health Impact Assessment: Complete
  – X-ALD Public Health Impact Assessment: Complete

• **Future:** Public Health Impact remains a key component of assessment when evaluating additional conditions to be added to RUSP.