Condition Review Updates

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Advisory Committee on Heritable Disorders in Newborns and Children
5/12/2017

Condition Review Workgroup (CRW)

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COST ANALYSIS WORKGROUP (CAWG)

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Outline

- Consumer-Friendly Summaries (5m)
- Revisions to the Condition Review Procedures (15m)
  - Added Cost Assessment Methods (10m)

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Summary of current status based on continuous updates and prior presentations

Consumer-Friendly Summaries

- Single summary version of condition review reports
- Target Audience: General public *(e.g., all parents, clinicians, policymakers, state newborn screening programs)*
- Plain Language (reading level ≤8th grade)
- Executive summary (1 page)
- Summary (≤10 pages)
- Modeled after AHRQ and other consumer summaries

Consumer-Friendly Summaries – Main Sections

- Title: Newborn Screening for <*condition*>: A Summary of the Evidence and Advisory Committee Decision
- Executive Summary (stand alone)
- About this Summary
- Understanding the Condition
- Finding Newborns who Have <*condition*>
- Treatment for <*condition*>
- Does Early Diagnosis or Treatment Help Patients with <*condition*>?
- Public Health Impact
- Helpful Information

Newborn Screening for X-linked Adrenoleukodystrophy

A Summary of the Evidence and Advisory Committee Decision

Report date: 14 October 2015

HRSA Maternal & Child Health

This summary was prepared under a contract to Duke University from the Maternal and Child Health Bureau of the Health and Resources and Services Administration (Contract Number: HHSH250201500002I/HHSH25034003T).

EXECUTIVE SUMMARY

This summary reviews the information that the federal advisory committee used when deciding whether to recommend adding X-linked adrenoleukodystrophy (X-ALD) to the Recommended Uniform Screening Panel.

About the condition

X-ALD is a rare genetic disorder caused by a change in a single human gene. X-ALD affects 6 out of every 100,000 children, with boys more severely affected than girls. X-ALD can cause problems with the adrenal glands, brain, and spinal cord. There are different types of X-ALD, and some types can be treated. Delaying or missing treatment in these types of X-ALD may cause death during childhood.

Detecting X-ALD in newborns

Newborn screening for X-ALD can happen along with routine newborn screening for other conditions during the first few days of life. Newborn screening for X-ALD measures levels of a specific fatty acid in the blood. This process uses the same dried blood droplets already collected for screening of other disorders. Newborns with high fatty acid levels are at higher risk for X-ALD. Doctors refer these newborns to specialists for confirmatory and diagnostic testing. Testing confirms that almost all newborns with high fatty acid levels have either X-ALD or another serious health condition.

Treatment for X-ALD

There is no cure for X-ALD. Available treatments include cortisol replacement (for adrenal problems) and human stem cell transplantation (for brain problems). There is no treatment for the spinal cord problems caused by X-ALD.

Early monitoring and treatment improve health outcomes of children with X-ALD.

Public Health Impact

Researchers believe that screening all newborns in the United States each year for X-ALD would increase the number of people identified with X-ALD and improve their chances of survival.

As of 2016, the federal government recommends that state newborn screening programs include X-ALD. At the time of the report, 1 state screened newborns for X-ALD and 3 more had requirements to start. Most other states estimated that screening for X-ALD could begin 1 to 3 years after funding became available.

ABOUT THIS SUMMARY

What is newborn screening?

Newborn screening is a public health service that can change a baby's life. Newborn screening involves checking all babies to identify those few who look healthy but who are at risk for one of several serious health conditions that benefit from early treatment.

Some serious health problems occur even when a baby looks well and may delay diagnosis of the condition. Delays can make treatment less effective. Screening babies early is important to find those at risk and help them get the best possible care. Newborn screening programs have saved the lives and improved the health of thousands of babies in the United States in recent decades.

Who decides what screening newborns receive?

In the United States, each state decides which conditions to include in its newborn screening program. To help states determine which conditions to include, the federal government provides a list of conditions for recommended screening. We call this list the Recommended Uniform Screening Panel (RUSP).

Progress in screening and medical treatments can lead to new opportunities for newborn screening. It may make sense to add new conditions to the RUSP. To learn more about how this happens, see **Box A**.

What will this summary tell me?

In 2014, the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) considered adding a condition called X-linked adrenoleukodystrophy (X-ALD) to the RUSP. This summary presents key information the committee used to make its decision. It will answer these questions:

- What is X-ALD?
- How do we screen newborns for X-ALD?
- How is X-ALD treated?
- Does early diagnosis or treatment help patients with X-ALD?
- How would newborn X-ALD screening affect the health of the country?
- What is the status of newborn X-ALD screening in the US?

Box A: Adding a Condition to the RUSP

The first step of adding a condition to the RUSP involves nominating the condition to a committee, called the ACHDNC. If this committee accepts the nomination, it asks medical and research experts to gather information describing how effectively we can identify and treat the condition. The experts organize this information into a report. The committee examines the report, then makes a recommendation to the head of the Department of Health and Human Services. This person decides whether to add the condition to the RUSP.

UNDERSTANDING THE CONDITION

What is X-ALD?

X-ALD is a rare genetic disorder. People with X-ALD have a change in a single gene called ABCD1. Normally, this gene makes a protein that helps the body break down types of fats, known as very long chain fatty acids (VLCFAs). In people with X-ALD, the ABCD1 gene does not work properly. When the ABCD1 gene does not work properly, VLCFAs build up in the body and cause health problems.

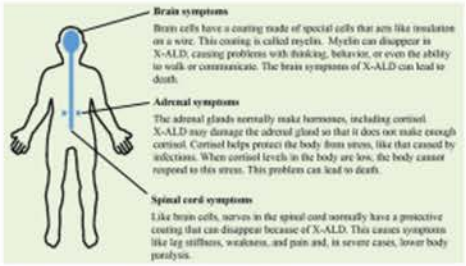
How common is X-ALD?

- X-ALD is a rare disorder that affects 6 out of every 100,000 children.
- About 40% of affected children are boys. Girls with the genetic change causing X-ALD do not always develop the disorder.

What kinds of health problems does X-ALD cause?

X-ALD can damage the adrenal glands, brain, and spinal cord (Figure 1).

Figure 1: Symptoms of X-ALD



X-ALD symptoms can look different in different people, even for people with the same change in the ABCD1 gene. Boys typically have more severe symptoms than girls.

Are there different types of X-ALD?

Doctors classify X-ALD into 3 types based on symptoms:

- **Adrenocortical insufficiency**: People with this type of X-ALD have adrenal gland problems only.
- **Cerebral ALD**: People with this type have problems affecting the brain. Many also have problems with their adrenal glands. This is the most serious type of X-ALD. It affects 1 out of every 2 or 3 people with X-ALD and is most common in young boys.
- **Adrenomyeloneuropathy**: People with this type of X-ALD have spinal cord problems. They may also have problems with their adrenal glands.

When do X-ALD symptoms develop?

The timing and type of problems caused by X-ALD vary between different people. However, large surveys of people with X-ALD can tell us when certain symptoms of X-ALD are most likely to arise.

Age	Symptom	Details
Birth	No symptoms	• X-ALD is present at birth, but most babies with the disorder have no visible symptoms. Parents and doctors cannot tell by looking if a baby has X-ALD.
Childhood	Adrenal symptoms	• Most boys with X-ALD develop these symptoms during childhood or adolescence. They can begin during the first year of life and usually happen during childhood. They can occur before other X-ALD problems. The risk for these symptoms is lifelong.
	Brain symptoms	• These symptoms usually appear between ages 2 and 10 years in boys with cerebral ALD. They get worse quickly. Without treatment, many boys lose the ability to walk and talk and can die within 3 years.
Adulthood	Spinal cord symptoms	• These symptoms appear in the 30s or 40s. • Girls with the genetic change causing X-ALD may never develop symptoms. If they do, symptoms typically do not develop until mid- to late adulthood.

Without newborn screening, the average delay between a child's first symptoms and a diagnosis of X-ALD is almost 10 years.

FINDING NEWBORNS WHO HAVE X-ALD

How do we screen newborns for X-ALD?

Newborn screening for X-ALD can happen along with other routine newborn screening in the first few days of life. Most newborn screening begins when a doctor or nurse collects a few drops of blood from a baby's heel and dries them onto a special piece of paper. The hospital sends this sample to the state's newborn screening laboratory. The laboratory checks the blood for many disorders.

To screen for X-ALD, laboratories use a machine called a tandem mass spectrometer to measure how much of the VLCFA (fatty acid) is in the blood spots. High levels of VLCFAs mean a higher risk for X-ALD.

When a newborn has high VLCFA levels, the baby needs more tests. The baby's doctor may refer the newborn to a specialist to tell for sure if the baby has X-ALD.

How well does screening for X-ALD work?

Experts believe that X-ALD screening identifies the following:

- All boys at risk for X-ALD.
- Some children who do not have X-ALD but who do have other serious health problems that also raise VLCFA levels.
- Some girls with X-ALD. Screening does not identify all girls with X-ALD, because some of these girls do not have high VLCFA levels at birth.

What happens after a newborn screens positive for X-ALD?

Doctors refer newborns with positive X-ALD screens for more testing. This testing involves measuring VLCFAs in the blood to confirm the diagnosis. Doctors may test whether there is a change in the ABCD1 gene. They also might run other tests, like measuring how well the adrenal gland works or taking pictures of the brain with a special scanner known as magnetic resonance imaging (MRI).

Problems caused by X-ALD usually do not happen in very young children. Therefore, doctors carefully monitor patients after diagnosis to see if they need treatment. This monitoring includes checking the adrenal function and taking pictures of the brain once or twice each year. People with X-ALD require monitoring for problems throughout their life.

What are some of the benefits and risks of newborn X-ALD screening?

Benefits	Risks
• Earlier symptom monitoring.	• Newborns with X-ALD may not show symptoms for years or decades. • Some babies who screen positive may not actually have X-ALD.
• Earlier treatment.	• Earlier exposure to treatment risks.
• More time to plan for the future.	• More anxiety about the future.
• Health counseling and family planning for family members.	• Sometimes, people do not want to know genetic risks. Some families do not like to share health information.
• Reassurance for the families of babies who do not screen positive for X-ALD.	• In some cases, girls with X-ALD do not screen positive for the disorder. Screening would offer false reassurance for these girls.

TREATMENT FOR X-ALD

How is X-ALD treated?

There is no cure for X-ALD. Treatments focus on treating the problems caused by the disorder.

- **Cortisol Treatment**

  Cortisol treatment helps with the adrenal gland problems of X-ALD. People whose adrenal glands do not make enough cortisol may take cortisol by mouth or, if they are very sick, in other ways. During times of stress or illness, these people need more cortisol than their bodies can make. When people with X-ALD have adrenal problems, they need cortisol treatment for their whole life. Cortisol treatment does not help with the brain or spinal cord problems caused by the disorder.

- **Hematopoietic Stem Cell Transplantation (HSCT)**

  HSCT can slow down or even stop the brain problems from worsening in X-ALD. HSCT treatment is also called a "bone marrow transplant." HSCT replaces the bone marrow in a patient with the bone marrow from a donor who does not have X-ALD. The new bone marrow makes blood cells with a working ABCD1 gene and protein for breaking down VLCFAs. HSCT is not suitable for all children with X-ALD – only those with brain symptoms. HSCT does not help with the adrenal gland or spinal cord problems caused by X-ALD.

What are the risks of treatment for X-ALD?

Cortisol therapy is safe. People receiving cortisol therapy have careful adrenal and treatment monitoring to make sure that their treatment is appropriate.

HSCT therapy has several risks. The first step in HSCT is to wipe out a patient's bone marrow. Medicines for this step can cause side effects. Until the new bone marrow is working, patients also have a high risk for infection. Sometimes, the new bone marrow cells can attack the patient; this problem can usually be treated with medicines. Because of these risks, HSCT can lead to death. The risk of death depends on many things, like how well the donor and patient bone marrow match. Families offered a transplant for their child should talk to special transplant doctors about whether this treatment is right for their child.

Does early diagnosis or treatment help patients with X-ALD?

Researchers have not yet determined exactly how much **early diagnosis** from newborn screening improves health for patients with X-ALD.

However, early diagnosis before symptoms develop allows **early monitoring and treatment** – and early monitoring and treatment lead to better outcomes for people with X-ALD. Babies diagnosed early, like after a relative develops X-ALD, have fewer brain problems and longer lives than similar babies not diagnosed early.

- **Early monitoring**
  X-ALD symptoms are unpredictable and arise at different times for different people. Early monitoring gives patients the best chance of detecting and treating symptoms as soon as they arise.
- **Early cortisol treatment**
  Although we do not know how much early cortisol treatment helps in X-ALD, early cortisol treatment works in other disorders that cause adrenal problems. Delaying cortisol treatment in X-ALD may cause worse symptoms.
- **Early HSCT treatment**
  HSCT works better in patients with mild brain symptoms. HSCT is risky, so only boys with clearly worsening brain symptoms receive this treatment. Early monitoring by specialists is the best way to identify boys who can benefit from HSCT.

Box B: Where Can I Learn More?

Follow the links below to learn more about information from this summary.

- To learn more about nominating conditions to the RUSP, visit the Nominate a Condition website.
- To read the full X-ALD evidence report, visit the Nominated Conditions website.
- To read the ACHDNC decision about adding X-ALD to the RUSP, visit the Nominated Conditions website.
- To learn more about X-ALD, visit the National Institutes of Health X-ALD website.
- To learn more about the genetics of X-linked diseases, read this book chapter.
- For more patient support and advocacy resources, visit these websites:
  - ALD Connect
  - The Adrenoleukodystrophy Foundation
  - CLIMB: Children Living with Inherited Metabolic Diseases
  - National Organization for Rare Disorders: Adrenoleukodystrophy

PUBLIC HEALTH IMPACT

How would newborn X-ALD screening affect the health of the country?

Screening all 4 million newborns in the United States each year for X-ALD would do the following:

- Increase the number of people diagnosed with X-ALD from about 92 to about 143 each year.
- Increase the number of people with X-ALD who survive without serious disability by about 37 each year.
- Prevent about 18 deaths due to X-ALD each year.

What is the status of newborn X-ALD screening in the US?

Advisory Committee Decision

In September 2014, X-ALD was nominated to the RUSP. The committee that provides recommendations on the RUSP accepted the nomination. The committee then asked medical and research experts to prepare a report describing how well we can identify and treat X-ALD in newborns.

Based on the report, the committee voted to recommend adding X-ALD to the RUSP. In 2016, the head of the United States Department of Health and Human Services recommended that all newborns receive X-ALD screening.

States Screening for X-ALD

- At the time of the report, 1 state screened newborns for X-ALD. Three more had requirements to start.

States Offering Screening	States with Requirements to Start Screening
New York	California, Connecticut, New Jersey

- Most other states estimated that newborn X-ALD screening could begin 1 to 3 years after funding became available.
- Before states can begin screening, they need the right equipment. They also must make sure that the screening process works correctly. Finally, they need to develop a follow-up program for babies at high risk for X-ALD.

HELPFUL INFORMATION

Glossary

Term	Definition
ABCD1	The gene responsible for causing X-ALD.
Adrenocortical insufficiency	A type of X-ALD in which the adrenal glands do not produce enough hormones.
Adrenomyeloneuropathy	A type of X-ALD in which people have spinal cord symptoms.
ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children. The committee that oversees the RUSP.
Cerebral ALD	A type of X-ALD in which people have brain symptoms. This type is the most severe and primarily affects children.
HSCT	Hematopoietic stem cell transplantation. A type of therapy for X-ALD that can provide the body with a working copy of the ABCD1 gene. Also called a bone marrow transplant.
MRI	Magnetic resonance imaging. A special scanner that takes pictures of the brain.
Myelin	A coating on brain cells that can disappear in X-ALD. This causes problems with thinking, behavior, and the ability to walk and communicate.
RUSP	Recommended Uniform Screening Panel. The list of conditions for which the federal government recommends newborn screening.
Tandem mass spectrometer	A machine that measures substances in dried blood spots.
VLCFAs	Very long chain fatty acids. The substances in food that people with X-ALD cannot break down.
X-ALD	X-linked adrenoleukodystrophy. A rare genetic disorder that affects the adrenal glands, spinal cord, and brain.

Source

The information in this summary comes from the report *Newborn Screening for X-Linked Adrenoleukodystrophy (X-ALD): A Systematic Review of Evidence* (14 October 2016), commissioned by the ACHDNC. The report reviewed evidence on X-ALD screening and treatments in children through July 2015. It included both published and unpublished research. To see a copy of the report, visit this website.

Changes to the Condition Review Process

- Compliance with legislative mandates
- Facilitate ACHDNC decision-making process

Legislative Mandate

Newborn Screening Saves Lives Reauthorization of 2014 *(enacted March 2015):*

- The ACHDNC shall
  - "…evaluate public health impact, ***including the cost***, of expanding newborn screening."

  - "Deadline for review. —For each condition nominated…, the Advisory Committee shall review and vote on the nominated condition ***within 9 months*** of …referr[ing] the nominated condition to the condition review workgroup.''

Cost Assessment of NBS Expansion

- **Objective(s)**:

  Primary: To inform ACHDNC decision-making about costs to expand newborn screening

  Secondary: To inform state newborn screening programs

- **Framework**: Budget Impact Analysis (modified)
  - Focus on fiscal impact to payer to add health intervention
  - Guiding principles, parameters, and approach

Budget Impact Analysis –Elements & Parameters

Key Element	Application to Assessing Cost of NBS Expansion
Framework	Budget Impact Analysis (modified)
Payer Perspective	State PH NBS *Laboratory*
Intervention Mix	• Adding newborn screening for condition to existing screening panel infrastructure • ST Follow up of presumptive positive screens (not including diagnosis)
Time Horizon	Year 1 – Start up Years 2-5 – Implementation (if needed to annualize costs)
Cost Data Source(s)	*Primary*: State NBS Laboratories *Secondary*: Other pilot programs, researchers, vendors
Ranges and Alternative Values for Uncertainty	Cost Variability by a) State, b) Condition, c) Other (screening method, purchase v lease, funding stream, etc.)
Cost Estimates	• Cost per specimen to add the condition under consideration • Total costs per 100,000 (prorated) for Start-up Year • Ranges of cost estimates, with context/assumptions (if >1 state) • Narrative description of context and assumptions

NBS Cost Assessment – Primary Costs

Cost estimates - required

State Public Health Lab Costs	Description
EQUIPMENT	Direct purchase or lease. Reagent Rental Agreement (RRA)
CONSUMABLES	supplies, reagents Reagent. Rental Agreement (RRA)
OTHER LAB EXPENSES	If not already included; maintenance, repairs, installation, reporting/LIMS
LABOR – LAB & FU	FTEs, by position, salary + fringe
OVERHEAD (INDIRECT COSTS)	Space/building, utilities

NBS Cost Assessment – Secondary Costs

- Variability in costs included in state NBS laboratory budgets
- Secondary costs = costs that vary widely across states, may skew cost estimates
- Included in assessment with Assumptions and Context narrative information
- Secondary cost examples:
  - Confirmatory Testing/Referrals
  - Follow up for genetic counseling
  - Longer-term follow up – care and monitoring

Assumptions, Cost Drivers, Context

- State annual birth cohort (range ~6,000 - ~500,000)
- Variations in number of specimens per baby (e.g., Texas does two per baby)
- State budget vs. NBS cost structure – who pays for what?
- Timing is Everything
  - *Start-up Year*
    - Purchases vs. Leasing/rental agreements
    - Funding source – fed-funded pilot vs. state-funded start-up
    - Post start-up period to Screening efficiencies
  - *State Political Context, Advocacy and Appropriations*
- And all the other sources of variation
  - different screening algorithms, in-house vs. outsource contractor labs, proximity to specialized services, the condition itself

Cost Assessment of Expanding NBS

	Main Cost Assessment Steps	Information Source(s)
1	**Determine validated screening procedures for high-throughput screening for the target condition, including laboratory set up, start-up and implementation.**	Nomination package review Published Evidence Interview(s) with states/programs conducting population-based screening
2	**Identify states which have considered expansion/conducted initial cost estimates**	Public Health System Impact state survey, add response option to Q1.
3	**Complete the NBS Expansion Cost Estimation Tool**	
	a. Gather cost estimates and assumptions from states/programs conducting pilots or population-based screening, or states/programs which have conducted initial cost estimates	In-depth follow up interviews with states identified in PHSI survey, or other programs • Cost estimation inputs • Cost input Assumptions & Context
	a. Calculate costs (total and cost per infant) to expand newborn screening for participating states/pilot programs	Synthesis of cost information on spreadsheet, identify assumptions and context for each estimate
	a. Review cost estimates across states, identify and collect any missing information	Follow up interviews or email with states/programs as needed
4	**Summarize Cost Estimate Information**	
	a. Cost estimate ranges, anchored with alternative scenarios/assumptions with each estimate	Review of NBS expansion cost estimation tool and interview information
	a. Summarize assumptions and context of cost estimate findings	Review of NBS expansion cost estimation tool and interview information
5	**Incorporate summaries of cost assessment (6 and 7) into Condition Review Report (PHSI section, summary)**	

NBS Expansion Cost Estimate Tool

Specimens annually: = *x*

Platform *(MSMS, DMF, POC, other)* _____

NBS LABORATORY - DIRECT COSTS

EQUIPMENT	
Option: Reagent Rental Agreement (RRA)	
Option: Direct equipment purchase	
Expected Life	
Service agreement if not included	
CONSUMABLES	
Disposable supplies (pipettes, etc.)	
Reagents	
OTHER LAB EXPENSES	
LABOR - TOTAL FTES (*x*)	

Lab Personnel	FTEs	SAL	FB
Follow-Up			

CONFIRMATORY TESTING REFERRALS	
Contract costs with genetic referral center(s)	
OVERHEAD /INDIRECT COSTS	

Initial Pretest Results

NBS LABORATORY - DIRECT COSTS				STATE A	STATE B
Specimens tested annually:				100,000	180,000
Platform *(MSMS, DMF, POC, other)*				DMF	MSMS w/ UPLC
Reagent Rental Agreement (RRA)				$ 400,000	$ 1,300,000
Number of conditions tested using platform				4	6
CONSUMABLES				$ N/A	$ 200,000
OTHER LAB EXPENSES				$ -	$ 30,000
LABOR				$ -	$ 461,000
Lab Personnel	FTEs	SAL	FB (36.4%)	$ 167,560	
OVERHEAD /INDIRECT COSTS				$ Not reported	$ 250,000
Total Laboratory				$ 560,000	$ 2,241,000
Cost/Specimen and Cost/Specimen/Condition				**$5.60, $1.40**	**$12.45, $2.08**

Cost Pretest -- Added States

NBS LABORATORY - DIRECT COSTS				STATE C	STATE D
Specimens tested annually:				80,000	98,000
Platform *(MSMS, DMF, POC, other)*				MSMS w/ UPLC	MSMS w/ UPLC
Reagent Rental Agreement (RRA)				$ 286,517	
Equipment purchase – annual cost (assume 8 years)					$ 1,800,000 $ 360,000
Number of conditions tested using platform				1	5
CONSUMABLES				$ N/A	$ 780,000
OTHER LAB EXPENSES				$ -	$ 150,000
LABOR				$ -	$ 269,596
Lab Personnel	FTEs	SAL	FB (36.4%)	$ 124,000	
Supervisor	0.75				
Lab Tech	0.75				
OVERHEAD /INDIRECT COSTS				$ 177,868	$ 23,454
Total Laboratory				$ 631,885	$ 1,433,050
Cost/Specimen and Cost/Specimen/Condition				**$7.90, $7.90**	**$14.63, $2.44**

Challenges in Assessing Costs

- Limited time for collecting data
- NBS programs do not have cost data available for us in the way we need it (but that is not their job)
- Estimates will mostly represent early adopters
- Cost variability not predictable
- State NBS laboratories face privacy issues that limit what they can share with us
- Alternative estimation will be needed for point-of-care or other non-dried blood spot specimens
- If no U.S. *state* has started screening or planning to screen
- Changes in vendor pricing, FDA-approvals, new screening technology that are ongoing

Condition Review - Evolution of Component Parts

Components	Description	Main Information Sources	Year Added to CRs
Systematic Evidence Reviews	Net benefits of early detection, diagnosis, and treatment (on individual, family)	Published literature Grey literature	2006/2008
		Unpublished Data (if needed)	2012 – Pompe
		Unpublished Data & Analysis (if needed)	2013 – present (MPS I, XALD)
Public Health Impact – Population	Net benefits of newborn screening on population-level health	Published literature – major health outcomes Decision analysis modeling	2011 – piloted with Hyperbili 2012 – present
Public Health Impact – NBS system	Feasibility of population-based screening Readiness of states to expand screening	Screening procedures Survey of all NBS programs Interviews with states mandated to screen	2012 – piloted with Pompe 2013 - present
		Costs to expand screening	2013 –cost pilot MPS I 2016 - present

Summary of Completed Reviews – Timing

CONDITION	Nom to HRSA mm/yy	NPWG Pres mm/yy	AC Vote for SER (mm/yy)	CRW Preliminary Update (mm/yy)	CRW Final Report (mm/yy)	AC Vote - RUSP (mm/yy)	HHS Vote - RUSP (mm/yy)	SER	DA	PHSI	Unpub datal	Completion Time (in months)
X-ALD	09/13	10/13	01/14	02/15; 05/15	08/2015	08/2015	02/2016	SER	DA	PHSI	Unpub datal	**20**
MPS I	02/12	04/12	05/12	09/13; 01/14	02/15	02/2015	02/2016	SER	DA	PHSI	Unpub datal	**21** *[started 5/13, after Pompe]*
Pompe Disease	02/12	04/12	05/12	09/12	05/13	05/2013	03/2015	SER	DA	(PHSI)	Unpub datal	**12** *PHSI pilot*
Critical Congenital Heart Disease	10/09	--	01/10	05/10	09/10	09/2010	09/2011	SER	--	--	--	**8**
Hyperbilirubinemia	07/09	--	01/10	01/11	01/12	(NO) 01/2012	--	SER	(DA)	--	--	**24** *DA pilot*
Hemoglobin H Disease	04/09	--	09/09	01/10	05/10	(NO) 05/2010	--	SER	--	--	--	**8**
Krabbe Disease	01/08	--	8/08	05/09	09/09	(NO) 09/2009	--	SER	--	--	--	**13**
Pompe Disease (1)	10/07	--	01/08	08/08	10/08	(NO) 10/2008	--	SER	--	--	--	**9**
Severe Combined Immunodeficiency	09/07	--	01/08	11/08	02/09	01/2010	02/2010	SER	--	--	--	**13**

Condition Review - Target Timing by Component

CR Components	Description	Main Information Sources	Timing								
			Q1 (M1–M3)			Q2 (M4–M6)			Q3 (M7-M9)		
Systematic Evidence Reviews (SER)	Net benefits of early detection, diagnosis, and treatment on individual	Published literature *Pilot programs/States*	X	X	X	X	X	X			
		Grey literature, Unpublished evidence			X	X	X	X			
		Analysis				X	X	X	X		
Public Health Impact – Population	Net benefits of newborn screening on population-level health	Published literature – major health outcomes Decision analysis modeling		X	X	X	X	X	X	X	X
Public Health impact – NBS system	Feasibility of population-based screening, Readiness of states to expand screening	Screening procedures Survey of all NBS programs Interviews with screening states			X	X	X	X	X		
		Costs to expand screening			X	X	X	X	X	X	

Major Process Changes Planned - Overview

- Restructure Procedures with Short-term Reporting Objectives
- Anchor Points for Reporting Objectives
  - TEP Meetings
  - ACHDNC Meetings
- Prioritize information gathering activities
- Start as early as possible

Condition Review REPORTING OBJECTIVES			
TQ0 Month 0	AC Meeting - Nomination/Request for Review		
TQ1 (Month 3)	**AC Meeting - Condition Review Presentation 1**	**SER**	**DA**	**PHSI**
Scope of Review, Key Questions	☑		
Preliminary Search Results/PRISMA	☑		
Pilot Screening Overview	☑	☑	☑
Draft Decision Analysis Structural Model		☑	
Draft Screening Fact Sheet			☑
Draft list – Screening States			
Technical Expert Panel (TEP) Members	☑	☑	☑
TEP 1 Input	☑	☑	☑
TQ2 (Month 6)	**AC Meeting – Condition Review Presentation 2**	**SER**	**DA**	**PHSI**
Review of Evidence Assessment of quality	☑		
Major outcomes of interest	☑	☑	
Rev Decision Analysis Structural Model		☑	
Key Studies for Decision Model		☑	
Screening Fact Sheet & Webinar			☑
PHSI Surveys, Interviews Update			☑
TEP 2 Input	☑	☑	☑
TQ3 (Month 9)	**AC Meeting – Condition Review Presentation 3**	**SER**	**DA**	**PHSI**
Summary of Evidence and Quality	☑		
TEP 3 Input	☑	☑	☑
Decision Analytic Model		☑	
PHSI Survey results			☑
PHSI Follow up Interview summaries			☑
Cost Assessment Results			☑

Potential Risks for Delays

- Procedure Revisions – Untested
- Availability of Evidence
- Nature of Population – based Pilot
- Condition – specific complexities
- Major risks for delays –
  - Systematic Evidence Review – majority must done in Q1 to inform other components
  - Decision Analysis Model –
    - Complex, multi-step modeling procedures
    - Dependent on available evidence, TEP guidance
  - Costs / Public Health System Impact –
    - Dependent on states which have estimated
    - Dependent on states to share information

Other Changes – Proposed and Planned

- Leverage preliminary evidence from Nomination Package
  - Work with HRSA and the ACHDNC when a Nomination Package is in process
    - Supported in legislation
    - Jumpstart to SER
    - Nomination form revisions proposed
- Gather pilot screening program information early in process
  - Interviews and collaboration with states/pilot screeners
- Establish cut-off point for new evidence for current review
  - Published/in press
  - Unpublished data
  - Analysis of unpublished data
- Integrate Cost Assessment Methods within Public Health System Impact Procedures
- Incorporate summaries that address specific ACHDNC decision criteria

Facilitate ACHDNC Decision-Making Process

ACHDNC Decision-Making Criteria

- ❑ Evidence for Clinical Effectiveness/Net benefit
  - ✓ Magnitude/Strength of Evidence
  - ✓ Certainty of Evidence
- ❑ Public Health Impact
  - ✓ Feasibility and Readiness to Expand Screening
  - ✓ Cost of Expanding Screening

Planned Summary Reporting to Inform AC Decisions

- Magnitude and Certainty of Evidence
  - (total # of studies, quality/risk of bias assessments of individual studies and body of evidence)
- Projected Population-level Health Impact
  - (point estimates, confidence intervals, sensitivity analyses as data allow)
- Public Health System Impact
  - Feasibility of population-based screening (demonstrated validity, screening results)
  - Readiness of states to expand screening (Prepared, Developmental readiness, Unprepared)
  - Estimated costs to expand ($ per screen, Total $ per 100,000, as available)

Questions?

Thank you!

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