COLORADO
Department of Public Health & Environment

To: Members of the State Board of Health

From: Dr. Emily Travanty, PhD, Scientific and Deputy Division Director, Laboratory Services Division

Through: Scott Bookman,
Division Director, Laboratory Services Division

Date: September 18, 2019

Subject: **Request for Rulemaking Hearing**
Proposed Amendments to 5 CCR 1005-4, *Newborn Screening and Second Newborn Screening* with a request for a rulemaking hearing to be set for November 20, 2019

NOTE: This rulemaking modifies the composition of the newborn screening panel and the screening algorithm for the second newborn screening panel.

In preparation for a Public Rulemaking Hearing, please find copies of the following documents:

a) Proposed Amendments to 5 CCR 1005-4,
b) Statement of Basis and Purpose and Specific Statutory Authority,
c) Regulatory Analysis, and
d) Early Stakeholder Engagement

The Colorado Newborn Screening Program (CONBSP) provides initial and second newborn screening for 35 rare genetic and metabolic conditions. Dried blood spot (DBS) specimens are collected by a birthing facility, or a physician, nurse, midwife, or other health professional attending a birth outside a birthing facility or a newborn well child appointment, who submit the specimens to the department for testing in the Laboratory Services Division (LSD). The CONBSP screens approximately 123,000 specimens per year collected from newborns born in Colorado. Newborns identified at risk through screening are connected to contracted follow-up specialists who guide the newborn's family and primary care provider (PCP) on appropriate next steps. Each year, the CONBSP identifies approximately 80-100 newborns with one of the conditions on the screening panels, i.e. there are approximately 80-100 true positive screening results per year across all conditions screened.

Here, the department is proposing two changes to the current rule:

1) Adding Spinal Muscular Atrophy (SMA) due to homozygous deletion of exon 7 in Survival Motor Neuron (SMN1) gene to the newborn screening panel
2) Including Phenylketonuria (PKU) in the list of conditions on the second newborn screening panel which follow a limited, rather than population-wide, screening algorithm

Importantly, for change (2), the entire population will still be screened for PKU on the initial screen. For the second newborn screen, the department is proposing alignment of the

screening workflow for PKU with the current screening workflow for Biotinidase Deficiency (BIO), Classical Galactosemia (GALT), and Cystic Fibrosis (CF).

The rule changes are proposed in response to three factors:

1) the CDPHE regularly reviews national recommendations for newborn screening,
2) stakeholders of the CONBSP advocated for the inclusion of additional conditions on Colorado's newborn screening panels, and
3) the CONBSP continually strives to improve the efficiency and cost-effectiveness of its screening algorithms.

Thank you for your consideration.

STATEMENT OF BASIS AND PURPOSE
AND SPECIFIC STATUTORY AUTHORITY
for Amendments to
5 CCR 1005-4, Newborn Screening and Second Newborn Screening

Basis and Purpose.

The *Newborn Screening and Second Newborn Screening* rules perform the following functions:

a) Define key terms,
b) Establish procedures for the collection and submission of blood spot specimens for testing,
c) Establish procedures for laboratory testing, reporting, and follow-up services for newborn screening and second newborn screening,
d) Establish requirements for quality control and education, and
e) List conditions covered by the newborn screening and second newborn screening panels.

Together, these definitions, procedures and requirements establish roles and responsibilities, for the genetic and metabolic testing portion of Colorado's Newborn Screening Program.

The following changes to the rules are being proposed:

1) **Proposed Change for Initial Screening**
The Department proposes the addition of one new condition, Spinal Muscular Atrophy (SMA) due to homozygous deletion of exon 7 in the SMN1 gene, in Section 2.4 of the rules. All references to SMA that follow refer to Spinal Muscular Atrophy due to homozygous deletion of exon 7 in Survival Motor Neuron 1 (SMN1) gene.

SMA is a family of neuromuscular conditions with outcomes ranging from premature infantile death to diminished motor capabilities starting in adulthood[1,2,3]. Nearly 95% of all SMA cases are due to homozygous deletion of exon 7 in SMN1[1]. Importantly, there is a relatively inexpensive and highly specific molecular test to identify this specific form of SMA. Moreover, as a targeted molecular test, the SMA screening assay has high clinical value meaning a screen positive result is likely a true positive result. The high clinical value of the test also minimizes the burden of false positives on the population[4]. At present there are two FDA-cleared treatments of SMA, Spinraza and Zolgensma[5]. Because motor neurons do not regrow, it is important to begin treatment as early as possible, making SMA a strong candidate for newborn screening. Recent studies have demonstrated better outcomes with earlier treatment[6].

At the national level, the Health and Human Services (HHS) Secretary maintains the Recommended Uniform Screening Panel (RUSP), which serves as guidance, but not a mandate, to state public health programs on the composition of newborn screening (NBS) panels. The HHS Secretary is advised by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) on the composition of the RUSP. SMA was added to the RUSP in July 2018. The RUSP is a national recommendation which is reviewed by individual states. A state-by-state assessment is important for a number of reasons including:

- Votes by the ACHDNC are almost never unanimous, reflecting uncertainty even within the expert panel convened to assess the condition's appropriateness for population-wide newborn screening.
- The ACHDNC assigns a rating to assess the magnitude and certainty of net benefit from population-wide newborn screening, which is rarely 'high' even for conditions added to the RUSP[7].
- The demographics of the state's population may differ significantly from those of the national population, potentially leading to much different levels of disease prevalence in a state versus national population.
- Different states have different capacities to treat patients and to cover the costs of treatment.

Of the 35 conditions included in Colorado's initial newborn screening panel, six (phenylketonuria, hypothyroidism, abnormal hemoglobins, galactosemia, cystic fibrosis, biotinidase deficiency) are identified in statute. The remainder have been added by the Board of Health when the board has determined that Section 25-4-1004(1)(c), C.R.S. has been satisfied. To support the Board's review, the department utilizes the four criteria delineated at Section 25-4-1004(1)(c), C.R.S. when evaluating whether the Department should recommend the condition for inclusion on the newborn screening panel through Board of Health rulemaking.

Section 25-4-1004(1)(c), C.R.S., reads:

> The state board shall use the following criteria to determine whether to test infants for conditions that are not specifically enumerated [in statute]:
>
> (I) The condition for which the test is designed presents a significant danger to the health of the infant or his family and is amenable to treatment;
>
> (II) The incidence of the condition is sufficiently high to warrant screening;
>
> (III) The test meets commonly accepted clinical standards of reliability, as demonstrated through research or use in another state or jurisdiction; and
>
> (IV) The cost-benefit consequences of screening are acceptable within the context of the total newborn screening program.

Below, the department evaluates the suitability of this form of SMA for population-wide newborn screening in Colorado using the four (4) criteria in Section 25-4-1004(1)(c), C.R.S. Based upon prior discussions by the Board, the Department has taken proactive measures to secure the resources needed to implement the proposed condition prior to making the recommendation to the Board of Health. When securing funding, the Department has consistently communicated that it is the Board of Health's decision as to whether the proposed condition will be added.

The Department's analysis of SMA relative to the criteria outlined in statute is summarized in the table below. Additional analysis and supporting documentation is provided following the table.

Summary of Analysis for Population-wide Newborn Screening for Spinal Muscular Atrophy (SMA)		
Statutory Language		**CDPHE Findings**
Criterion 1.	The condition for which the test is designed presents a significant danger to the health of the infant or his family and is amenable to treatment	• SMA can result in **premature death of a newborn** • FDA-cleared Treatments: 2 (Spinraza, Zolgensma)
Criterion 2.	The incidence of the condition is sufficiently high to warrant screening	• Prevalence Estimate: 1:7,000 to 1:24,000 • Expected Cases Per Year in CO: **3 to 9**
Criterion 3.	The test meets commonly accepted clinical standards of reliability, as demonstrated through research or use in another state or jurisdiction	• Assay development with **guidance from CDC** • Estimated Positive Predictive Value: 95-100% • States currently screening for SMA: **NY, MN, UT** • States with pilot studies: MA, WI, GA, NC • States approved to screen but not yet implemented: KS, MO, AR, IL, IN, MI, OH, WV, PA, VA, MD, NH
Criterion 4.	The cost-benefit consequences of screening are acceptable within the context of the total newborn screening program	• Colorado Medicaid already covers Spinraza and Zolgensma • Cost-benefit analysis completed assuming newborns with SMA will be treated • WA NBS estimates **~$35,000 in additional costs per year** for treatment of a newborn with late as opposed to early diagnosis* • Better outcomes for newborns treated sooner (Nurture vs Endear trial data)

*Personal communication courtesy of Dr. John Thompson, Director, and Megan McCrillis, Health Services Consultant, at the Washington Department of Health

Criterion I: The condition for which the test is designed presents a significant danger to the health of the infant or his family and is amendable to treatment

Spinal Muscular Atrophy is the name of a family of neuromuscular conditions characterized by the loss of motor function resulting in varying degrees of muscular atrophy and weakness[1,2,3]. The most common form of SMA is caused by homozygous deletion of exon 7 in the SMN1 gene[3], and it is this specific form of SMA that is proposed for screening of newborns in Colorado.

The extent of muscle loss for an individual with homozygous deletion of exon 7 in SMN1 varies significantly leading to five different types of SMA based upon functional milestones achieved and age of death without treatment, as summarized in **Table 1.1**. SMA is a condition with a wide range of clinical consequences, because another gene, SMN2, is able to make small quantities of the protein made by the SMN1 gene. The greater the amount of SMN2 in the individual, the more SMN2 can compensate for lack of protein produced by the SMN 1 gene. The number of copies of the SMN2 gene in each individual varies from 0 to 8 copies, leading to different clinical outcomes of SMA based upon the number of SMN2 genes in the affected individual. Thus, there is a relatively good correlation between the SMN2 copy number and the clinical complexity of SMA, where a higher copy number of the SMN2 gene is generally associated with better clinical outcomes[8].

Table 1.1. Activity-based Classification System for SMA

SMA Type	Age of Onset	Highest Motor Activity	Natural Age of Death
0	Prenatal	Respiratory Support	<1 Month
1	0-6 Months of Age	Never Sits	<2 Years
2	<18 Months of Age	Sits, but Never Stands Alone	Adult
3	>18 Months of Age	Stands Alone, Walks Unassisted	Adult
4	>21 Years of Age	Walks Unassisted During Adulthood	Adult

The table lists the characteristics of the five types of SMA based upon clinical presentation (Courtesy of Dr. Julie Parsons and Melissa Gibbons, Neuromuscular Clinic at Children's Hospital of Colorado).

As documented in **Table 1.1**, the consequences of SMA include premature death for more than one type of SMA, demonstrating there is a significant danger to the health of the infant for this condition. At present, most newborns with SMA are identified when they present with symptoms during development. Unfortunately, irreversible damage has occurred during the time it takes symptoms to emerge. While treatment can prevent or minimize further loss of motor function, the previous neuromuscular damage remains, leading to significant ancillary medical expenses, such as durable medical equipment. Newborn screening would allow presymptomatic identification of newborns with SMA, thereby allowing for preservation of motor function at higher levels[6]. It is possible to detect SMA with prenatal screening, but prenatal screening for SMA is not available through a population-wide public health program.

At this time, there are two treatments for SMA approved by the U.S. Food and Drug Administration (FDA): Spinraza and Zolgensma. Spinraza is an oligonucleotide-based treatment that must be administered throughout the lifetime of the patient to maintain beneficial effects. Zolgensma is a gene-therapy based approach that might require only one treatment during the patient's lifetime. Both treatments are expensive. For Spinraza, the cost of drug alone is $750,000 during the first year of treatment, and $375,000 for each subsequent year. There are also significant costs associated with administration of the Spinraza, which is provided intrathecally and requires the use of anesthesia in a newborn. The list price of Zolgensma is $2.1 million.

The Department recognizes that patient costs are relevant to *Criterion I* (amendable to treatment) and *Criterion IV*. Related, it is important to understand the implications to public insurance (Health First Colorado- Colorado's Medicaid Program), see Colorado Department of Health Care Policy and Financing (HCPF) Letter of Support. Importantly, Spinraza was added to HCPF's formulary in March 2018 and established criteria for Zolgensma coverage in July 2019.

Thus, children born with SMA in Colorado today are often receiving treatment when they present with clinical systems later in life. Clinical trials have demonstrated improved outcomes for children when they begin treatment before clinical symptoms of SMA present as compared to those children who start treatment after clinical symptoms emerge[4,6,9].

Criterion II: The incidence of the condition is sufficiently high to warrant screening

The department uses the word "incidence" in this analysis for consistency with statutory language. The department acknowledges that the prevalence is preferred in situations where the size of the total population, in this case conceptuses, is unknown[10].

SMA is the most common genetic cause of death in children under two years of age[3]. To evaluate whether the incidence of SMA is sufficiently high to warrant screening in Colorado, several resources were reviewed including published data from the scientific literature, various state data sources, and data from a specialty clinic in Colorado as summarized in **Table 1.2**. In **Table 1.3**, the number of cases of SMA in Colorado was compiled by a specialty clinic according to the individual's birth year.

Table 1.2. Summary of Data Sources Reviewed to Estimate Incidence of SMA

Data Source	Population	Frequency
Sugerman et al.[11]	U.S. Pan-ethnic Population	1/11,000
ACHDNC Evidence-based Review Group for SMA[4]	Various	1/7,000 to 1/11,000 (See Table 2 on p. 20 of the ACHDNC Evidence Review Group's report)
Neuromuscular Clinic/Children's Hospital of Colorado	Colorado Newborns†	1/21,600 (2007-2018; see Table 3 below)
Colorado Responds to Children with Special Needs (CDPHE's Center for Health and Environment Data)	Colorado Residents	1/24,000 (2016-2018; ICD10-CM G12.0 only—Type 1 only)

†*Some newborns born in Colorado counties bordering other states may be seen at clinics in other states.*

Table 1.3. SMA frequency data organized by newborn's birth year and by clinical type of SMA for newborns born in Colorado.

Year Born	Cases of SMA (Types 0-3)	Number of Live Births in CO
2018	2	63,455*
2017	1	64,382
2016	4	66,599
2015	0	66,581
2014	3	65,830
2013	4	65,007
2012	1	65,187
2011	7	65,055
2010	1	66,355
2009	3	68,628
2008	6	70,031
2007	5	70,809

Total	**37**	**797,919**

*These data were provided by the Neuromuscular Clinic at Children's Hospital of Colorado courtesy of Dr. Julie Parsons and Mellissa Gibbons. *Value provided by Center for Health and Environmental Data.*

The Department has not included Type 4 SMA are not included in Department's assessment of this criterion as Type 4 SMA typically presents in early adulthood (>21 years of age). This type of SMA exceeds the scope of the CONBSP which serves newborns through 365 days of the child's birth.

Based upon the data available the department projects that 3-9 Colorado newborns will screen positive for SMA each year. Over the 35 conditions covered by the current CO NBS panel, there are 80-100 true positives per year, putting SMA in the range of occurrence observed with other conditions presently screened.

Criterion III: The test meets commonly accepted clinical standards of reliability, as demonstrated through research or use in another state or jurisdiction

In 2015, Taylor, Lee and colleagues published a method that allows for simultaneous screening of SMA and Severe Combined Immunodeficiency (SCID)[12]. The process of screening for multiple conditions using a single sub-sample of a DBS specimen is referred to as multiplexing. (See **Technical Note 1** for more details of sampling from dried blood spot specimens.) The ability to multiplex SMA screening with existing workflow for SCID screening significantly reduces the cost and complexity of adding SMA to a newborn screening panel. Others have published similar multiplex approaches for SCID and SMA[3].

One objective quality measure of a clinical test is the positive predictive value (PPV) of the test, which is calculated as the percentage of true positive cases divided by the total number of screen positive results, i.e. true positives plus false positives. Tests with a high PPV have greater clinical value than tests with a low PPV, as the likelihood of a true positive is greater for a test with a high PPV as compared to a test with a low PPV.

Beginning in November 2018, CONBSP staff began working collaboratively with scientific experts from the U.S. Centers for Disease Control and Prevention (CDC) to develop a multiplexed screening assay for SCID and SMA, as part of a grant award from the CDC to the CONBSP (1 NU88EH001320-01-00). Importantly, the PPV for nearly all approaches to SMA screening used to date is extremely high. According to the **Impact on Public Health Systems** portion of the ACHDNC's Evidence Review Group Report[4], "SMA screening methods have high (100%) positive predictive value and no false positives have been reported to date…". The Department assumed a PPV of 95-100% when performing its analysis as new data may become available as more states implement SMA newborn screening. At present, four (4) states have implemented population-wide NBS for SMA, while another four (4) states have ongoing pilot studies and another twelve (12) states have adopted but not yet implemented NBS for SMA.

Criterion IV: The cost-benefit consequences of screening are acceptable within the context of the total newborn screening program

There are four categories of costs:

A. The laboratory costs of adding SMA screening are estimated below

B. Additional expenses associated with the Department contracting with medical experts to provide follow-up services for SMA,
C. Confirmatory testing and genetic tests to assess SMN2 copy number, and
D. Treatment of individuals diagnosed with SMA, i.e. treatment of true positives.

A. Laboratory Costs for Adding SMA Screening

The CONBSP has anticipated the likelihood of adding new conditions to the newborn screening panel based upon two factors: 1) guidance available at the national level through the RUSP and 2) stakeholder advocacy for the addition of new conditions. To aid with the expenses of adding new screening conditions, the department's Executive Director increased the newborn screening fee in Colorado from $92/child to $111/child on July 1, 2018. In addition, the CONBSP applied for a series of grant and contract funds available from public and private sources: the CDC (public) and the CDC Foundation (private). Funding awards in the amount of $250,000 per year for 2 years (CDC) and $200,000 (CDC Foundation) have been or will be used to offset the cost of implementing population-wide screening for SMA. Importantly, both funding agencies are aware that the Board of Health, and not the CONBSP, will make the final decision on the appropriateness of newborn screening for SMA.

Since receiving the funding awards, the COBNSP has taken several steps to study and prepare for population-wide screening of SMA, should it be approved by the Board of Health. First, in the course of replacing equipment used to screen current conditions, the CONBSP purchased new instruments (real-time polymerase chain reaction (rtPCR) system) and equipment that have the capacity to screen for SMA. The instruments were delivered in December 2018, and the program is in the process of validating these instruments for clinical testing. Second, the CONBSP has been collaborating with expert scientists at the CDC since November 2018 with the aim of developing and validating a multiplex rtPCR assay for simultaneous screening of SCID and SMA. CONBSP staff have been trained on a SCID-SMA assay development, have developed a Colorado-specific assay, and initiated a validation study in the summer of 2019. In addition, using only funds from a CDC grant, the CONBSP filled a term-limited scientist position with a staff member with extensive clinical molecular biology experience to work primarily on the development of the SCID-SMA assay. This scientist participated in the New York Newborn Screening Laboratory's New Disorders Workshop held in July 2019.

Finally, the CONBSP participated in the Association of Public Health Laboratories' (APHL) Molecular Assessment Program (MAP) in June 2019. Under this program, experts in molecular biology and newborn screening visit state newborn screening programs to evaluate current practices and make recommendations for strengthening molecular testing. Experts participating in the visit come from the CDC, APHL, and from other state newborn screening or public health programs.

A combination of funding sources including CDC Grant funds, CDC Foundation funds, APHL/Immune Deficiency Foundation funds and NBS Cash Fund will be used for the following: 1) updating the CONBSP's Laboratory Information Management System (LIMS) with the multiplexed assay for SCID-SMA, 2) replacing the robotic arms used in the CONBSP's molecular suite, 3) providing salary support for current CONBSP staff to assist with validation studies, conduct staff training, and prepare standard operating procedures, as well as 4) monitor activity performed by contracted medical experts for follow-up services.

Table 1.4 below provides estimates for startup and continuing costs. The costs of these items are covered with a mix of funds from grants, contracts, and the Newborn Screening and Genetics Counseling Cash Fund.

Table 1.4. Estimates of Startup and Recurring Costs for Population-wide Newborn Screening for SMA

Item	Startup or Recurring	Cost
LIMS Modification	Startup	$15k-30k
Equipment Modernization		
rtPCR Instruments	Startup	~$100k
Robotic Arms	Startup	~$100k
DNA Purification	Startup	~$30k
2nd-Tier Test (digital PCR)	Startup	~$55k
Laboratory Staff (FTE)	Recurring (0.2 FTE)	$1,000/month
Reagents		
Validation	Startup	$20k
Daily Screening	Recurring	$2,500/month

B. Follow-up Services Costs Tied to Adding SMA Screening

The CONBSP uses a Connect-to-Care model for providing follow-up services for all of the conditions on its newborn screening panel. Under this model, newborns who screen positive are either screened again or connected to medical experts who provide guidance on next steps to the newborn's family and primary care provider (PCP). The CONBSP conducted a Request for Information (RFI) in December 2018 to determine whether there were appropriate medical experts in Colorado for SMA. There is at least one qualified provider able to provide specialty care should the Board of Health decide to approve newborn screening for SMA. At this time, it is not possible to estimate the cost of the specialty care contract for SMA. Over the past two years, the CONBSP has used a competitive bid process to award follow-up contracts for several disorders on the current panel. In general, the use of a competitive process has reduced the cost of follow-up services for the CONBSP, suggesting the cost of follow-up services for SMA might be similar to existing follow-up contracts for other conditions. The unknown cost of the follow-up contract is one source of uncertainty in our analysis. Funding for this contract will come from the NBS Cash Fund. Importantly, the PPV of the SMA screening assay is very high, so there should be very few false positives.

C/D. Patient and Family Costs including Confirmatory Tests and Treatment

The Department recognizes that patient costs are relevant to *Criterion I* (amendable to treatment) and *Criterion IV*, see discussion above. From other follow-up contracts, the CONBSP has data on the cost of genetic counseling and in-person visits with specialists.

Families with children affected by SMA face direct and indirect financial consequences, such as the costs of confirmatory testing, treatment and supportive care, and loss of economic productivity. Confirmatory genetic tests typically cost between $800 and $2,000. If SMA is added to the newborn screening panel, confirmatory testing costs would constitute follow-up services as described in the rule and thus, the confirmatory testing costs would be covered by the newborn screening program and services would be provided through the connection to care model with contracted follow-up providers. Additional health care expenses for individuals with SMA include respiratory treatment with bi-level positive airway pressure support,

orthopedic management of scoliosis and other deformities, and nutritional support[6]. As described above, the two FDA-cleared treatments for SMA, Spinraza and Zolgensma, are expensive. Parents and family members of affected children often serve as primary care givers, which reduces or eliminates their ability to continue working.

Treatment has been shown to provide significant benefits, especially when started presymptomatically[6]. Because Spinraza and Zolgensma have been cleared relatively recently, the long-term outcomes of treatment are not yet well defined. However, in the most severe forms of SMA, types 0, 1, and 2, it is clear that life expectancy is increased for the child. With time, long-term analysis will also reveal the amount, if any, of net savings generated through presymptomatic treatment of SMA as compared to SMA treated after clinical signs present. Presumably, the greater amount of motor function preserved in children treated presymptomatically will preserve greater levels of function, leading to less dependence on expensive supportive care.

2) **Proposed Change for Second Specimen Screening**

Section 25-4-1004.5(3), C.R.S. requires second specimens be submitted for Phenylketonuria (PKU). This is communicated in the rule at Section 3.3.1. Section 25-4-1004.5(3)(b), C.R.S., authorizes the Board to promulgate exceptions to the necessity for a second specimen test. The Department requests 3.3.1 Phenylketonuria (PKU) be added to the list of conditions with exceptions at Section 3.2.2.2.

Section 25-4-1004.5(3), C.R.S. requires,

(a) Infants born in the state of Colorado who receive newborn screening pursuant to section 25-4-1004 (1) must have a second specimen taken to screen for the following conditions:
   (I) Phenylketonuria;
   (II) Hypothyroidism;
   (III) Galactosemia;
   (IV) Cystic fibrosis; and
   (V) Such other conditions as the state board may determine meet the criteria set forth in Section 25-4-1004 (1)(c), C.R.S. and require a second screening for accurate test results.

(b) The state board is authorized to promulgate rules and standards for the implementation of the second specimen testing specified in this subsection (3), including:
   (I) Identification of those conditions for which a second specimen shall be required;
   (II) The age of the infant at which the second screening may be administered;
   (III) The method by which the parent or parents of a newborn shall be advised of the necessity for a second specimen test;
   (IV) The procedure to be followed in administering the second specimen test;
   (V) Any exceptions to the necessity for a second specimen test and the procedures to be followed in such cases; and
   (VI) The standards of supervision and quality control that shall apply to second specimen testing.

The CONBSP regularly conducts reviews of data collected over years of screening to determine whether clinical outcomes justify the maintenance of current practices. Such regular reviews

are important in light of the program's collective efforts to improve clinical outcomes, to improve the clinical value of our screening results, to perform testing timely, to incorporate new technology, and to identify cost savings. In 2018, CONBSP staff conducted a comprehensive review of our current workflow for second screening of phenylketonuria (PKU). Results of the program's analysis are summarized below. This analysis was presented to clinical specialists at the Children's Hospital Inherited Metabolic Disease (IMD) Clinic on October 25, 2018 and to the broader Colorado newborn screening stakeholder community at a meeting of the Colorado Newborn Screening Stakeholders' Committee on January 29, 2019. The specialists at the IMD Clinic currently serve as the contracted follow-up specialists to the CONBSP for screen positive PKU results.

To assess the clinical impact of the population-wide screening for PKU on second screen specimens, CONBSP staff reviewed five years of screening data (2013-2017). Data for the second PKU screen results and clinical outcomes are summarized in **Table 2.1** and **Table 2.2**.

Table 2.1. Five Year Review of Second PKU Screening Results.

Parameter	Value	Percentage
Total Number of Second Screen Specimens Tested	349,000	
Screen Positive Result (First biochemical run)	2,473	0.71% (% of total specimens)
Screen Positive Result (Second biochemical run)	142	5.7% (% of specimens with Screen Positive result on first biochemical run)
Screen Positive Result (First MS/MS run)*	42	1.7% (% of specimens with Screen Positive result on first MS/MS run)

*See **Table 2.2** for additional breakdown of results for specimens with a screen positive result on the first MS/MS run.

Table 2.2. Breakdown of Outcomes for 42 Specimens with Screen Positive Results on First MS/MS Run.

Parameter	Value	Percentage
Total Specimens with Screen Positive Result on Second Screen (First MS/MS run)	42	
Patients with PKU Screen Positive Result on Initial Screening Specimen	19	45% (% of total specimens)
Patients with No Initial Screen Results for PKU	2	4.8% (% of total specimens)
Patients from Specialty Care Centers/Neonatal Intensive Care Units with other Elevated Amino Acids	19	45% (% of total specimens)
Screen Negative Results on Initial Newborn Screening Specimen (Both Patients Diagnosed with Hyperphenylaninemia)	2	4.8% (% of total specimens)

As shown in **Table 2.1**, the biochemical assay for measuring phenylalanine has poor reproducibility as less than 6% of specimens which were positive on a first run later repeated as positive on a second run for the biochemical assay. In the workflow of the CONBSP, the

current method of measuring phenylalanine on second screen specimens is a poor fit for population-wide screening. As indicated in **Table 2.2**, during the five years reviewed, only two patients with a clinical condition were identified due to population-wide screening for PKU on second screen specimens. Importantly, both patients were diagnosed with hyperphenylalaninemia (HyperPHE), which is not a screening target of the CONBSP, but rather an incidental finding due to the distribution of phenylalanine levels in the population. While patients with HyperPHE are evaluated and monitored by staff at the IMD Clinic, typically they are not treated. The data also demonstrate the CONBSP's ability to reduce false positives through the use of second-tier testing, i.e. the MS/MS test eliminates many of the screen positive results from the biochemical assay.

The data indicates there is minimal clinical risk associated with moving second PKU screening from population-wide screening to a limited approach that aligns with the three other second specimen screening exceptions to population wide screening (Biotinidase Deficiency (BIO), Classical Galactosemia (GALT), and Cystic Fibrosis (CF)). Further, cost-benefit analysis using a data set with five years of second screening for PKU justifies the change in workflow. Specifically, the CONBSP spent more than $500,000 on second screens for PKU over those five years, but did not identify a single new case of PKU based on second screen results. A detailed description of the costs can be found in the Regulatory Analysis at #3.

At present, a PKU screen is ordered for every second screen specimen when it arrives in the laboratory, and its unique identifier is entered into the laboratory information management system (LIMS). Under the proposed change, whether a second screen PKU is ordered would be decided by the LIMS after second screen specimens are linked to initial newborn screening specimens. Under the proposed rule, the second screen for PKU will occur if: 1) there was a screen positive result for PKU from the initial specimen screen, 2) the initial specimen was collected within the first 24 hours of the newborns life as the PKU result may be artificially low in this circumstance, 3) the initial specimen was unsatisfactory, or 4) a second screen specimen cannot be linked to an initial screen (in this circumstance the full complement of screening from the initial screening panel would be ordered, including PKU).

Screening Workflow

Additional details of the screening workflow, including the process of punching sub-samples, **Figure 1,** have been included in **Technical Note 1**. The current and proposed workflow and clinical interpretive logic for screening of initial and second screen specimens for PKU are provided in **Technical Note 2**. See **Figure 4** for more details of the proposed workflow. See **Figures 5**, **6**, and **7** for more details about the reference ranges and disease values for patients with PKU.

Technical Note 1: Punching or the Process of Sub-sampling a Dried Blood Spot Specimen

The CONBSP analyzes a type of specimen called a dried blood spot (DBS). DBS specimens are collected on filter paper-based collection kits supplied to submitters by the program. On each collection card, submitters are asked to collect at least five large DBS specimens. Each DBS is approximately 12mm in diameter. At the CONBSP's laboratory, the DBS specimens are sub-sampled using mechanical punchers. Each sub-sample is approximately 3mm in diameter. To begin screening for both initial and second newborn screening specimens, a single sub-specimen or punch, is taken for every test performed. In general, when the results from the first run of a test are screen positive, the test is repeated in duplicate, i.e. two new sub-

samples are prepared and tested separately. The final clinical interpretation is then based on the average of the second two sub-samples.

Figure 1. Punching sub-samples from dried blood spots. This photo shows the monitor of a computer connected to a punching station in the CONBSP Laboratory. Four (4) sub-samples or punches have been taken from the third DBS specimen from the left, and the green numbered circles on the second DBS specimen from the left indicate the location of three sub-samples about to be punched. For the first run of a first-tier test on an initial or second newborn screening specimen, blood from a single punch is tested. In contrast, two punches are taken for the repeat run of a specimen with screen positive results on the first run.

Technical Note 2: Testing Workflow and Clinical Interpretive Logic for Initial and Second Newborn Screening for PKU

The initial and second newborn screening methodologies differ for PKU. At present, in Colorado, all initial newborn screening specimens and all second newborn screening specimens are screened for PKU. For historic reasons, different screening methodologies and testing algorithms are used for the initial and second newborn screening for PKU. Specifically, for initial newborn screening specimens, tandem mass spectrometry (MS/MS) is the only method used to screen for PKU, **Figure 2**. In contrast, for second newborn screening specimens, the CONBSP uses two tiers of testing with a biochemical assay as the first tier of testing and MS/MS as the second-tier of testing. Note that second-tier tests are performed only when results from the first-tier test are screen positive, **Figure 3**. While the workflow and clinical interpretive logic for initial newborn screening for PKU follow those of other amino acidemias, the workflow and clinical interpretive logic for second newborn screening for PKU are more complex, leading to consumption of larger amounts of the dried blood spot specimens and greater complexity of coding within the LIMS. This raises the risk that dried blood spot (DBS) specimens will be completely consumed before testing is completed. In such circumstances, none of the screening results are reported and a new specimen is requested, creating further burden on the CONBSP and the broader newborn screening system. The workflow proposed here for second screen PKU screening uses significantly less specimen, making successful completion of all testing more likely.

Figures 2 and **3** illustrate the current versions of the workflows and clinical interpretive logic for initial and second screening of PKU, respectively. **Figure 4** illustrates the proposed workflow and clinical interpretive logic for second screening of PKU.

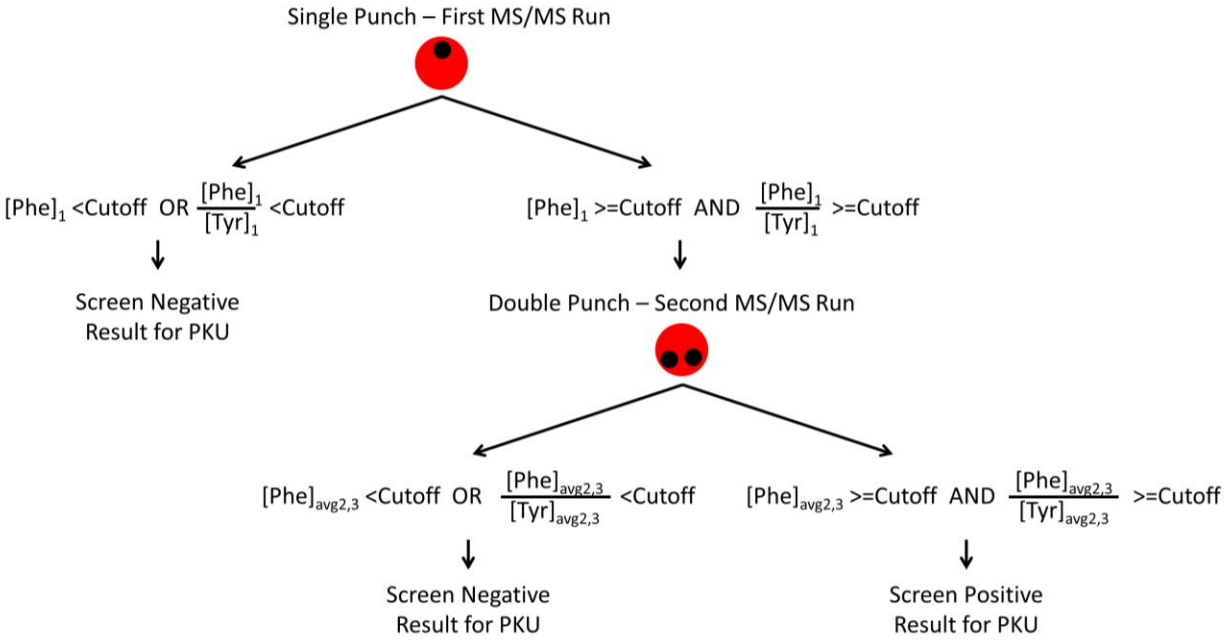

Figure 2. Current PKU Workflow: Initial Newborn Screening Specimen. For an initial newborn screening specimen, screening for PKU is performed by tandem mass spectrometry (MS/MS). For the first MS/MS run, a single punch is taken from a single dried blood spot specimen (DBS). [See **Technical Note 1** for more information about punching of DBS specimens.] Two results, the concentration of phenylalanine ($[Phe]_1$) and the ratio of the concentration of phenylalanine to the concentration of tyrosine ($[Phe]_1/[Tyr]_1$), are compared to separate cutoff values. The value of $[Phe]_1$ is referred to as an analyte value, and the value of the ratio of $[Phe]_1/[Tyr]_1$ is referred to as a ratio. If the value of either the analyte or ratio is less than the respective cutoff, then the result is reportable as screen negative. If values of both the analyte and the ratio are greater than or equal to the respective cutoff, then a second MS/MS run is performed, this time using two new punches from the DBS specimens. The results from the second two punches are averaged, and then interpreted using logic similar to that used for the first MS/MS run. That is, if the average value of either the analyte, $[Phe]_{2,3}$, or the ratio, $[Phe]_{2,3}/[Tyr]_{2,3}$, is below the relevant cutoff, the specimen result is screen negative for PKU; however, if the average value of both the analyte and the ratio is greater than the relevant cutoffs, the specimen result is screen positive for PKU.

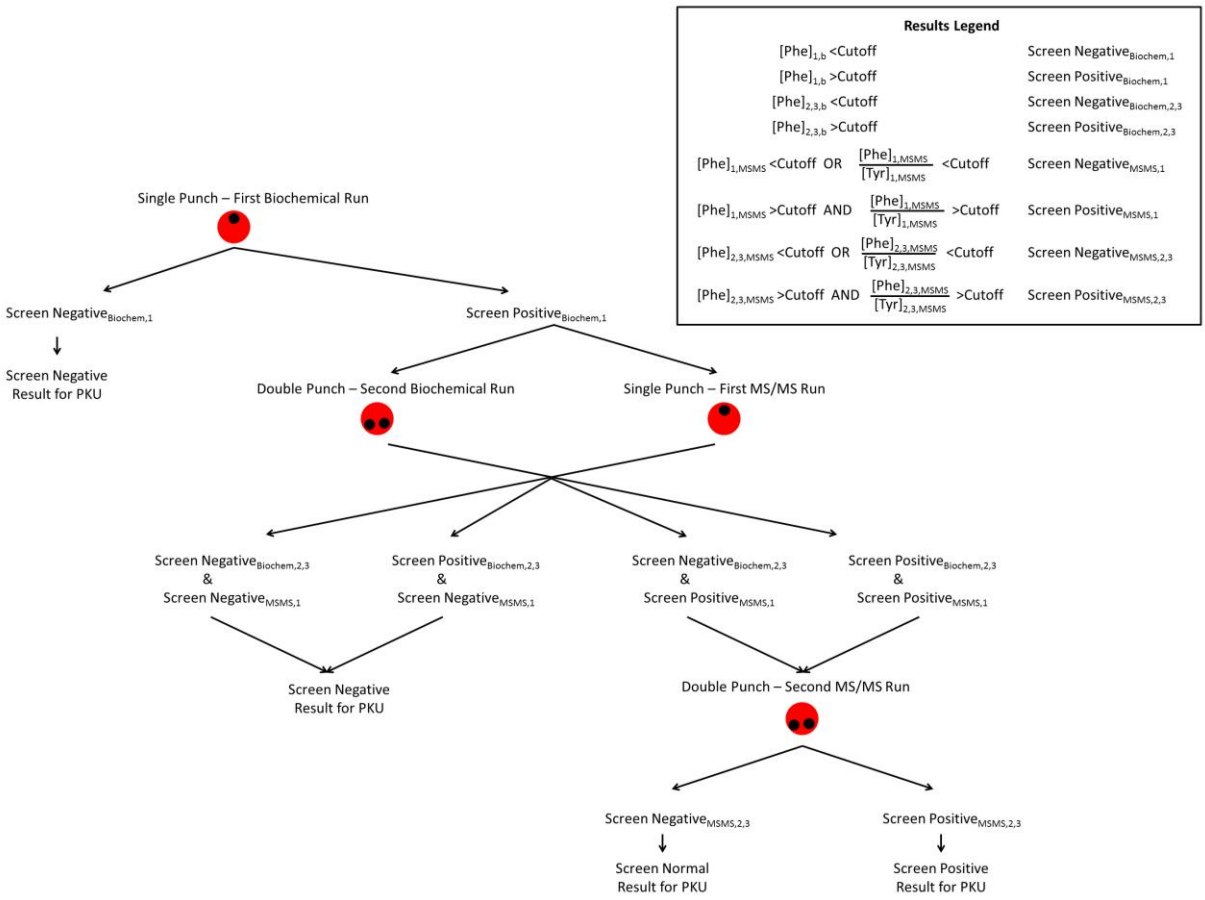

Figure 3. Current PKU Workflow: Second Newborn Screening Specimen. For a second newborn screening specimen, screening for PKU is performed first using a biochemical assay to measure the concentration of phenylalanine in the specimen. For the first run of the biochemical assay, a single punch is taken from a single dried blood spot specimen (DBS). [See **Technical Note 1** for more information about punching of DBS specimens.] The concentration of phenylalanine ($[Phe]_{1,b}$) from the biochemical assay is compared to a cutoff value. If the value of $[Phe]_{1,b}$ is less than the cutoff, then the result is reportable as screen negative. If the value of $[Phe]_{1,b}$ is greater than or equal to the cutoff, then two additional tests are performed: 1) a second run of the biochemical assay using two additional punches and 2) a first run of tandem mass spectrometry (MS/MS) using one additional punch. The clinical interpretive logic then gives precedence to the MS/MS results, such that result is reported as screen negative if the MS/MS result is screen negative, and MS/MS is repeated if the MS/MS result is screen positive for PKU regardless of the biochemical results in either case. When a second MS/MS run is performed, the testing algorithm calls for two new punches from the DBS specimens. The results from the second two punches are averaged, and then interpreted solely on the basis of the second MS/MS run. [See **Figure 2.** PKU Workflow: Initial Newborn Screening Specimen for additional details on the interpretation of MS/MS results.] Thus, the current workflow consumes up to five punches just to reach a conclusion on the screening status of PKU.

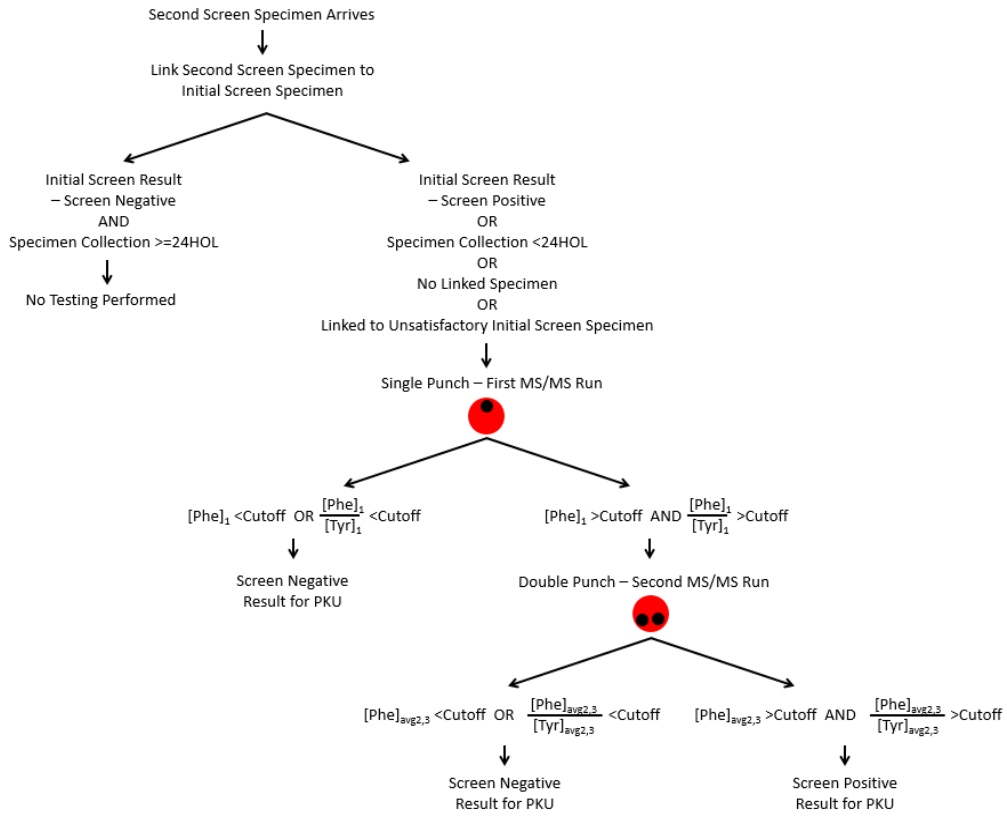

Figure 4. Proposed PKU Workflow: Second Newborn Screening Specimen. If the Board of Health adopted the proposed rule change regarding second screening of PKU, screening for PKU on second specimens would take place after second screen specimens were linked to their initial screens, allowing automation in the laboratory information management system (LIMS) to assess the PKU results from the initial screen as well as the newborn's age at collection of the initial specimen. So long as the initial PKU screening result was screen negative and the initial screening specimen was collected from a newborn of at least 24 hours of life (24HOL), then no additional PKU screening would be performed on the second screen specimen. If the initial PKU screening result was screen positive or the age of the newborn at collection was less than 24 hours of life or null (not connected to an initial screening specimen) or the initial specimen was unsatisfactory, then the second screen specimen would be screened for PKU using tandem mass spectrometry (MS/MS). The workflow and clinical interpretive logic of the subsequent MS/MS screening would be identical to the current workflow for initial screening of PKU, **Figure 2**. The proposed workflow for PKU is nearly identical to the process used for three other conditions on the second screen panel: Biotinidase Deficiency (BIO), Classical Galactosemia (GALT), and Cystic Fibrosis (CF).

Technical Note 3: Comparison of CONBSP's Reference Range Data with International Peer Laboratories, and Review of Analyte and Ratio Measurements for True Positive Cases of PKU

As part of the CONBSP's regular review of data, we now include analysis using Mayo's Collaborative Laboratory Integrated Reports (CLIR)[12], which supersedes the Region 4 Stork

Project (R4S)[13]. Both CLIR and R4S represent international efforts to compare newborn screening data and to optimize clinical interpretive logic. As part of the CONBSP's participation in CLIR, program staff uploaded approximately 42,000 sets of de-identified reference data, taken from newborns born in 2018 with all normal newborn screening results. For the analysis here, CONBSP staff examined three factors: 1) the reference range of phenylalanine (see **Figure 5**), 2) the distribution of phenylalanine concentrations in true positive PKU cases (see **Figure 6**), and 3) the distribution of the ratios of phenylalanine to tyrosine in true positive PKU cases, **Figure 7**).

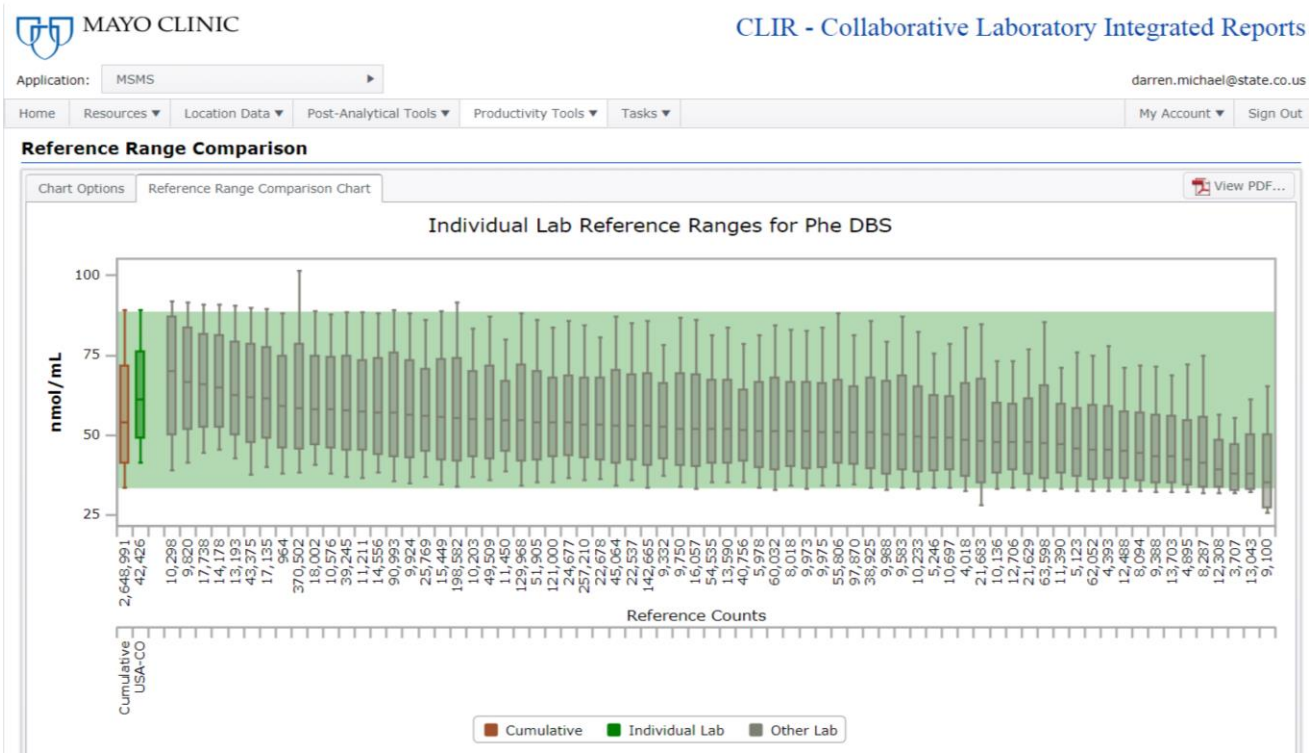

Figure 5. The figure shows reference range data for phenylalanine concentration in dried blood spot specimens. Cumulative data are on the far left, while data from the CONBSP are second from the left. Each boxplot represents data from one laboratory. The number of specimens per laboratory is indicated under the respective boxplot. The horizontal line in each boxplot indicates the laboratory's median value, while the boundaries of the rectangle represent the 25th percentile and 75th percentile. The whiskers extend up to 1.5 times the length of the box to represent the far edge of the population. The reference range for the CONBSP overlaps with the project's reference range, suggesting that data for phenylalanine concentration in CLIR from disease cases will have relevance to the CONBSP, as shown in **Figure 6**.

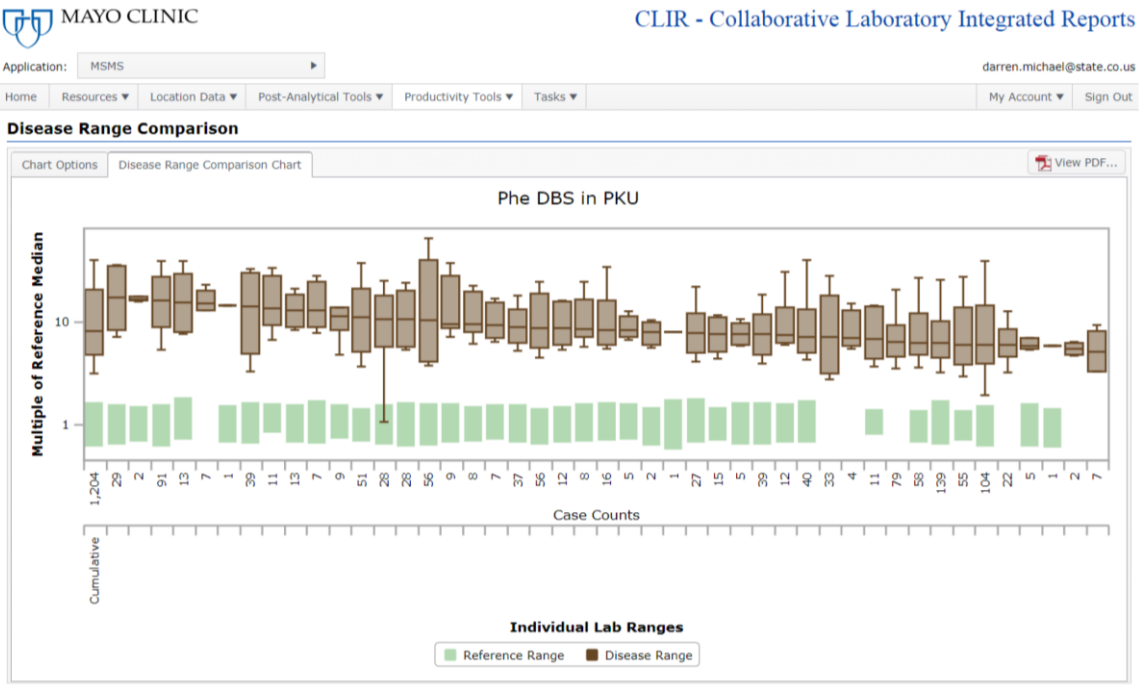

Figure 6. The distribution of phenylalanine concentration in dried blood spot specimens from newborns with PKU and reference populations. The green boxes at the bottom of the plot show the reference range data for phenylalanine concentration in DBS specimens from various newborn screening laboratories across the world, while the brown boxes and whiskers at the top show the distribution of phenylalanine from true positive patients from across the world. Importantly, the y-axis is on a log scale indicating the significant difference between the typical PKU patient and a newborn from the reference range. The limitation of population-wide screening is demonstrated by the downward whisker from laboratory #28. It would not be practical to set a cutoff value low enough to detect the disease case from laboratory #28 with the lowest phenylalanine concentration.

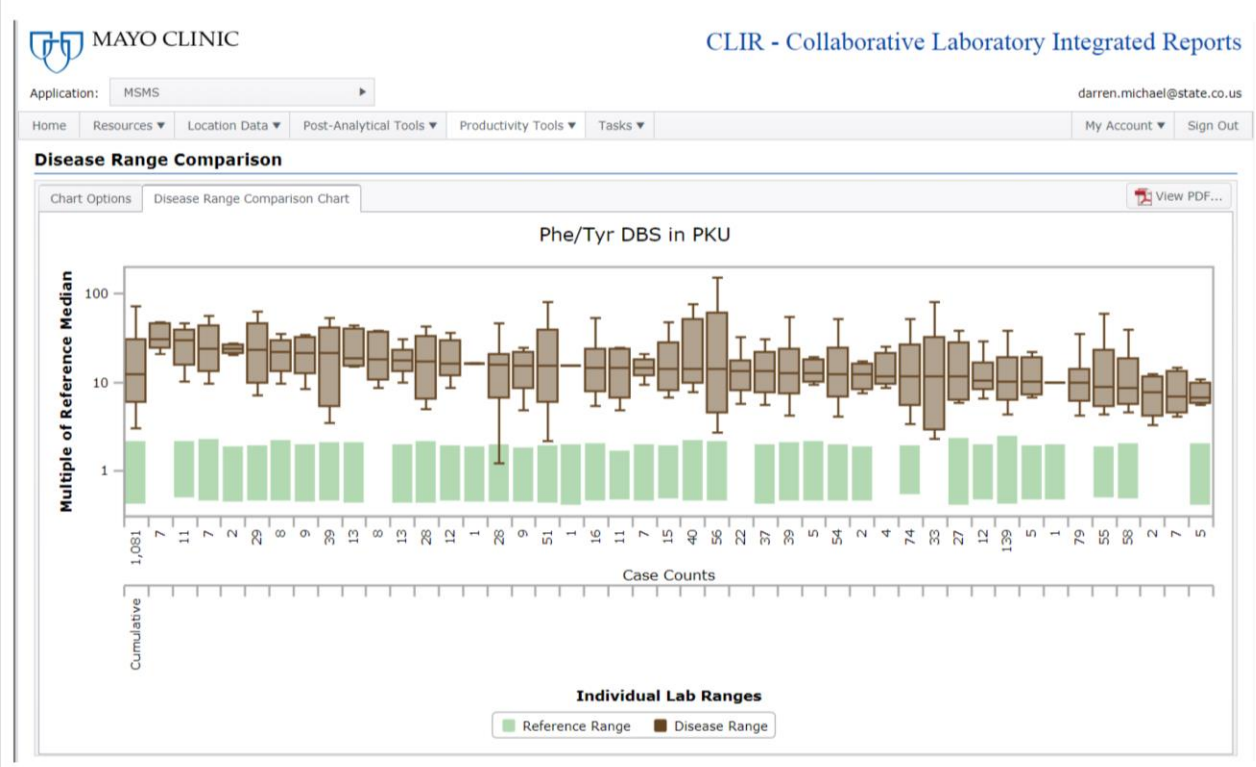

Figure 7. The distribution of ratios of phenylalanine concentration to tyrosine concentration in dried blood spot specimens from newborns with PKU and reference population. The values of the ratio for the reference range are shown in green near the bottom of the figure, and the values for true positive cases are shown in brown at the top of the figure. The y-axis is on a log scale to highlight the significant differences between the reference range and the true positives. The data for laboratory #28 highlight, again, the limitations of population-wide screening.

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Specific Statutory Authority.

These rules are promulgated pursuant to the following statutes: Sections 25-4-1004(1)(c)(I-IV) and 25-4-1004.5(3), C.R.S.

Is this rulemaking due to a change in state statute?

_____ Yes, the bill number is _____. Rules are ___ authorized ___ required.

___X___ No

Does this rulemaking include proposed rule language that incorporate materials by reference?

_____ Yes ___ URL

___X___ No

Does this rulemaking include proposed rule language to create or modify fines or fees?

_____ Yes
___X___ No

Does the proposed rule language create (or increase) a state mandate on local government?

__X_ No.

- The proposed rule does not require a local government to perform or increase a specific activity for which the local government will not be reimbursed;
- The proposed rule requires a local government to perform or increase a specific activity because the local government has opted to perform an activity, or;
- The proposed rule reduces or eliminates a state mandate on local government.

REGULATORY ANALYSIS
for Amendments to
5 CCR 1005-4, Newborn Screening and Second Newborn Screening

1. A description of the classes of persons affected by the proposed rule, including the classes that will bear the costs and the classes that will benefit from the proposed rule.

Group of persons/entities Affected by the Proposed Rule	Size of the Group	Relationship to the Proposed Rule Select category: C/S/B
CDPHE's Laboratory Services Division Newborn Screening Program	~14	C
Colorado's Newborns	~63,400/yr	B
Parents/Families of Colorado's Newborns	~500,000	B
Birthing Facilities	~100	S
Physicians identified on NBS demographic slips	~4,000	S/B
Midwives	~150	S
Pediatricians and Family Medicine Physicians	~5,000[15]	S/B
Patient Advocacy Groups, e.g. March of Dimes, Cure SMA	~5	S
Adult Patients with Rare Diseases	~500,000[16]	S
Clinical Specialists currently contracted with CDPHE to provide follow-up services	~20	C/S
Large Reference Laboratories	~2	S
Colorado Department of Health Care Policy and Financing		S

15. *Colorado Physician Workforce Profile* **2016** Association of American Medical Colleges.
16. *Genetic and Rare Diseases Information Center* U.S. Department of Health and Human Services accessed at https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases on 6/21/2019.

While all are stakeholders, groups of persons/entities connect to the rule and the problem being solved by the rule in different ways. To better understand those different relationships, please use this relationship categorization key:

C = individuals/entities that implement or apply the rule.
S = individuals/entities that do not implement or apply the rule but are interested in others applying the rule.
B = the individuals that are ultimately served, including the customers of our customers. These individuals may benefit, be harmed by or be at-risk because of the standard communicated in the rule or the manner in which the rule is implemented.

2. To the extent practicable, a description of the probable quantitative and qualitative impact of the proposed rule, economic or otherwise, upon affected classes of persons.

Economic outcomes
Summarize the financial costs and benefits, include a description of costs that must be incurred, costs that may be incurred, any Department measures taken to reduce or eliminate these costs, any financial benefits.

C: The Department will incur costs related to the proposed rule. These costs are identified in the Statement of Basis and Purpose and #3 below.

Please describe any anticipated financial costs or benefits to these individuals/entities.

S: There are no costs to health care facilities and providers submitting specimens as this portion of the process is unchanged. There may be some minimal cost savings if additional specimens are not needed for PKU second specimen testing. The Department of Health Care and Policy may incur additional costs; this is discussed in #3 below.

B: Patients and families will incur treatment costs when the newborn screen result for SMA is positive. These costs are detailed in the Statement of Basis and Purpose. There may be some minimal cost savings if additional specimens are not needed for PKU second specimen testing. Fewer false positives reduces unnecessary medical appointments and the costs associated with confirmatory testing.

Non-economic outcomes

Summarize the anticipated favorable and non-favorable non-economic outcomes (short-term and long-term), and, if known, the likelihood of the outcomes for each affected class of persons by the relationship category.

S: Pediatricians and family medicine physicians will benefit from timely detection and connection to medical experts when serving a child with an SMA screen positive result.

Advocacy organizations, parents and adult patients with rare genetic conditions might see the addition of SMA as a sign of the state's awareness of rare disorders and the state's willingness to help populations at risk.

Reference laboratories and other screening programs benefit from shared learning of operations and the clinical interpretation of results.

B: Newborns will benefit from improved quality of life when connected to care in a timely manner. The parents of newborns will benefit from a screening method with a high positive predictive value as there will be few false positives associated with SMA screening.

3. The probable costs to the agency and to any other agency of the implementation and enforcement of the proposed rule and any anticipated effect on state revenues.

A. Anticipated CDPHE personal services, operating costs or other expenditures:

As discussed in the Statement of Basis and Purpose, with the multiplexed approach to SMA screening, the Department will incur approximately $350,000 in one-time costs (setting up the Laboratory Information Management System (LIMS), algorithm validation, equipment [see table below]) and $3,500 in monthly on-going expenditures.

Item	Startup or Recurring	Cost
LIMS Modification	Startup	$15k-30k
Equipment Modernization		
rtPCR Instruments	Startup	~$100k
Robotic Arms	Startup	~$100k
DNA Purification	Startup	~$30k
2nd-Tier Test (digital PCR)	Startup	~$55k
Laboratory Staff (FTE)	Recurring (0.2 FTE)	$1,000/month
Reagents		
Validation	Startup	$20k
Daily Screening	Recurring	$2,500/month

The simplification of the second screen for PKU will reduce CONBSP operating costs. The CONBSP uses a kit for a biochemical assay to measure phenylalanine concentration in second screen specimens. The program spends an average of $9,400/month or $112,800/year on these phenylalanine kits. Over the five years reviewed, the CONBSP spent $564,000 on biochemical assay kits for population-wide screening of PKU on second screen specimens. Approximately 500 second screen specimens per year were reflexed to MS/MS testing based on elevated phenylalanine levels as measured by the biochemical assay, see Statement of Basis and Purpose, **Table 2.1**. Each specimen evaluated by MS/MS consumes $8.25 of reagents, leading to an annual cost of $4,125 for the additional MS/MS testing triggered by population-wide second screen measurement of phenylalanine. Over five years, the reflex MS/MS testing added $20,625 to the CONBSP's operating budget. Thus, the total five-year cost for reagents alone was $584,625 for population-wide screening of PKU on second-screen specimens. The change in workflow for second screening of PKU will decrease the number of false positive results for second screen specimens that is triggered by the complex and tiered testing algorithm used at present. This reduces the Department's need for contracted follow-up services for PKU. In addition, calling for the resubmission of specimens due to running out of usable dried blood spots, reduces staff workload. The workload reductions are minimal. Any significant change in the CONBSP's workflow requires a change in the laboratory information management system (LIMS); while modifying LIMS for PKU is necessary to implement the proposed rule, it is anticipated that the long-term maintenance of PKU second specimen screening will be less intensive than the current algorithm. The CONBSP anticipates that the changes to the LIMS required by the change in second-screen testing for PKU will be covered by its annual maintenance fee. Similar changes to the LIMS have taken 1-3 months to implement

Some new costs will arise due to the rescreening for PKU of second screens linked to initial specimens collected before the newborn reached 24 hours of life. CONBSP staff used data from a quality improvement project to estimate that roughly 5% of initial specimens are collected before 24 hours of life. With an annual volume of approximately 70,000 initial screen specimens, the CONBSP estimates 3,500 of the initial specimens would be collected before the newborn reached 24 hours of life, triggering a rescreen of PKU by MS/MS on the second screen specimen. The additional MS/MS testing would add approximately $29,000 to the operating budget. This estimate should be treated as an upper limit of the true value, as some of the initial specimens collected before the newborn reached 24 hours of life would flag for a different condition detected by MS/MS, thereby triggering a rescreen of all conditions

identified using MS/MS, i.e. the costs of rescreening these specimens is already part of the CONBSP's annual operating budget.

Anticipated CDPHE Revenues:

For the addition of SMA, CDPHE has received funding from the Centers for Disease Control and Prevention (CDC) and CDC Foundation to aid with implementing population-wide newborn screening for SMA. The addition of a condition presently on the RUSP but not yet implemented in Colorado would satisfy the requirements of both funding opportunities. A small portion of the CDC Foundation funding is dependent upon successful addition of SMA to the state's newborn screening panel. Importantly, both funding agencies are aware that the authority to add conditions rests with the Board of Health. Recurring expenses will be supported by the Newborn Screening and Genetic Counseling Cash Fund (NBS Cash Fund). As communicated in the Statement of Basis and Purpose, the fee is set by the Executive Director. The fee is currently $111.00. This fee is paid by the named submitter of an initial newborn screening specimen.

B. Anticipated personal services, operating costs or other expenditures by another state agency:

The FDA approved treatments for SMA are expensive and many of the children diagnosed with this disorder require health care coverage under Medicaid. Health First Colorado, the State Medicaid Program, is already covering these costs for children that are diagnosed following clinical presentation of symptoms, therefore additional costs associated with treatment therapy is not anticipated. Additionally, early identification and treatment prior to clinical presentation of symptoms will reduce irreversible nerve damage and thereby reduce ongoing costs associated with ancillary medical expenses.

Anticipated Revenues for another state agency: NA

4. A comparison of the probable costs and benefits of the proposed rule to the probable costs and benefits of inaction.

For addition of SMA, the startup costs are significant, as those costs include replacing aging equipment and performing validation studies for a new multiplexed assay. However, the recurring expenses for SMA are quite low relative to other conditions, due to multiplexing with the SCID screening assay. Newborns identified presymptomatically are likely to experience better outcomes. Parents of affected children will likely experience less hardship if their children are treated presymptomatically.

If the screening panel is kept the same, the CONBSP will not incur new expenses, and it will not increase its workload. On the other hand, it will not achieve the aims of its funding awards, which might impact the CONBSP's ability to raise new funds in the future. If SMA is not added, affected newborns will be identified later in life, and costs might be higher for insurers such as Medicaid due to poor outcomes when treatment is started later in life.

For adjusting the second screening of PKU, the CONBSP should experience a significant reduction in expenses, as well as reduction in the number of false positives, leading to improved clinical value of testing.

If the screening algorithm for PKU remains constant, the CONBSP will continue to spend more than $100,000/year on reagents for a test that has not demonstrated clinical value over the last five years.

Along with the costs and benefits discussed above, the proposed revisions:

___ Comply with a statutory mandate to promulgate rules.
___ Comply with federal or state statutory mandates, federal or state regulations, and department funding obligations.
___ Maintain alignment with other states or national standards.
___ Implement a Regulatory Efficiency Review (rule review) result
_X_ Improve public and environmental health practice.
_X_ Implement stakeholder feedback.
___ Advance the following CDPHE Strategic Plan priorities:
___ Advance CDPHE Division-level strategic priorities.

The costs and benefits of the proposed rule will not be incurred if inaction was chosen. Costs and benefits of inaction not previously discussed include:

N/A

5. A determination of whether there are less costly methods or less intrusive methods for achieving the purpose of the proposed rule.

The department is not aware of less costly approaches that could be implemented in a timely manner for either proposed rule change. By implementing a multiplexed, laboratory developed test for screening of SCID and SMA, the CONBSP is selecting an efficient and cost-effective approach to newborn screening. The changes to second screen workflow for PKU screening are also made with a focus on improving the clinical value of our testing, while minimizing risk of false negative results.

6. Alternative Rules or Alternatives to Rulemaking Considered and Why Rejected.

Alternatives:

For the addition of SMA, the department also considered keeping its newborn screening panel in its current form. This would mean newborns with SMA who could benefit most from early diagnosis of SMA would not be identified through newborn screening. Families which are aware of the risks posed by SMA could opt for prenatal screening or commercial newborn screening. However, this would work against the department's focus on health equity. Children identified with SMA through the natural progression of the disease are still likely to be treated, so newborn screening is not likely to inflate treatment costs for the broader healthcare system. In fact, because children who start treatment earlier generally have better outcomes than those who start treatment later, it is possible the overall costs of care will be lower for children treated sooner, as the preservation of motor neuron function can reduce the child's reliance on medical interventions or equipment to maintain quality of life.

For the proposed change in workflow and clinical interpretive logic for second screening of PKU, the department considered leaving the process as is and also performing MS/MS testing on every second screen specimen. The cost-benefit analysis highlights the significant expense associated with the current method. Moreover, the current process wastes DBS material unnecessary, thereby increasing the risk that screening will not be completed on a specimen. The cost of performing MS/MS on every second screen would exceed $500,000/year with the current MS/MS method. The CONBSP cannot afford this workflow at this time.

7. To the extent practicable, a quantification of the data used in the analysis; the analysis must take into account both short-term and long-term consequences.

Please refer to the Statement of Basis and Purpose.

STAKEHOLDER ENGAGEMENT
for Amendments to
5 CCR 1005-4, Newborn Screening and Second Newborn Screening

State law requires agencies to establish a representative group of participants when considering to adopt or modify new and existing rules. This is commonly referred to as a stakeholder group.

Early Stakeholder Engagement:
The following individuals and/or entities were invited to provide input and included in the development of these proposed rules:

Organization	Representative Name and Title (if known)
Colorado Department of Healthcare Policy and Financing	Dr. Tamaan Osbourne-Roberts, Chief Medical Officer
Colorado Department of Healthcare Policy and Financing	Michelle Miller, Chief Nursing Officer
Children's Hospital of Colorado/Neuromuscular Clinic	Dr. Julie Parsons
Children's Hospital of Colorado/Neuromuscular Clinic	Melissa Gibbons
Cure SMA	Michelle Pritekel
Cure SMA	Janet Mulay
Cure SMA	Loree Mulay Weisman
Cure SMA	Taylor Hickerson
Hemoglobinopathies Follow-up Clinic	Donna Holstein Dr. Kathy Hassell
Congenital Hypothyroidism Follow-up Clinic	Dr. Aristides Maniatis
Congenital Adrenal Hyperplasia Follow-up Clinic	Dr. Jennifer Barker
Children's Hospital/Inherited Metabolic Disease Follow-up Clinic	Dr. Peter Baker
Children's Hospital/Severe Combined Immunodeficiency Follow-up Clinic	Dr. Cullen Dutmer
Pediatrician (Western slope region)	Dr. Patrice Whistler
Pediatrician (Colorado Springs)	Dr. Ted Maynard
Laboratory Services Division staff	Dr. Emily Travanty Dr. Darren Michael Greg Bonn Cory Porter Abena Watson-Siriboe Tyrone Holt Kristin Viart Molly Maskrey Dinh Tran Kendra Jones Jian Abbuehl
Mother of Child with MPS-1	Christine Tippett
Wyoming DoH	Christina Taylor Carleigh Soule
Mother of Child with MCADD	Kay Kelly
Children's Hospital/ Inherited Metabolic Disease Follow-up	Dr. Janet Thomas

Clinic	
Biogen	Ritchard Engelhardt
Biogen	Dr. Keri Kasun
Biogen	Tami Sova
Biogen	Amy Redhair
Patient	Lori Wise
University of Colorado Hospital (UCH)	Dr. Mary Kohn
Children's Hospital/Inherited Metabolic Disease Follow-up Clinic	Dr. Shawn McCandless
Unknown	Sherri Casas
University of Colorado Hospital	Ann Behring
Children's Hospital of Colorado	Kevin J.D. Wilson
Children's Hospital/ Inherited Metabolic Disease Follow-up Clinic	Erica Wright
Unknown	Jolene Hamann
Unknown	Katie Hamann
Unknown	Emily McLaughlin
Children's Hospital of Colorado	Dr. Chris Rausch
Banner Health	Ginger Fast
NewSTEPs	Sarah McKasson
Children's Hospital/ Inherited Metabolic Disease Follow-up Clinic	Dr. Austin Larson
Children's Hospital/ Inherited Metabolic Disease Follow-up Clinic	Dr. Johan Van Hove
Children's Hospital/ Inherited Metabolic Disease Follow-up Clinic	Amanda Bawcom
Children's Hospital/ Inherited Metabolic Disease Follow-up Clinic	Lauren Noll
Children's Hospital/ Inherited Metabolic Disease Follow-up Clinic	Curtis Coughlin
Children's Hospital/ Inherited Metabolic Disease Follow-up Clinic	Janell Kierstein
Children's Hospital/ Inherited Metabolic Disease Follow-up Clinic	Leighann Sremba
Children's Hospital/ Inherited Metabolic Disease Follow-up Clinic	Casey Burns
Children's Hospital/ Inherited Metabolic Disease Follow-up Clinic	Sommer Gaughan

A variety of early stakeholder engagements were conducted.

- The upcoming rulemaking process was discussed at a series of presentations by Dr. Darren Michael given in Grand Junction on January 31, 2019 and February 1, 2019. Flyers with details regarding our online stakeholder survey (see below) were prepared to distribute to attendees of events in Grand Junction.

- The Department discussed proposed changes to the Colorado newborn screening panel with representatives from the Colorado Department of Healthcare Policy and Financing (HCPF) from 2/21/2019 through 8/30/2019.

- The Department conducted a regular series of internal meetings with representatives from Executive Leadership Team, as well as several divisions including the Prevention Services Division, the Center for Health and Environmental Data, and the Laboratory Services Division.

- The Department also conducted quarterly meetings of the Colorado Newborn Screening Stakeholders Committee (CONBSC) on January 29, 2019, March 26, 2019, and June 25, 2019.

    - At the January 29, 2019 meeting, a portion of the meeting was set aside to discuss the rulemaking process with stakeholders, as well as to review the process for considering new conditions for addition to or removal from the Colorado newborn screening panel. The four statutory requirements used by the Board of Health were also reviewed. A timeline for anticipated rulemaking in 2019 was presented, and stakeholders were shown a preview of the online survey discussed below.

    - At the March 26, 2019 meeting of the CONBSC, the agenda included a 'Clinical Care' segment featuring an extended discussion of SMA. Dr. Tamaan Osbourne-Roberts, Chief Medical Officer of HCPF, attended the meeting and explained HCPF's approach to providing data to the CONBSP. Dr. Julie Parsons and Melissa Gibbons from Children's Hospital of Colorado provided an overview of the SMA focusing on four items: 1) Genetics of SMA, 2) Natural History of SMA, 3) Current and Future Treatments of SMA, and 4) Follow-up Care for Children Identified through NBS. Attendees were then allowed to ask questions of Dr. Osbourne-Roberts, Dr. Parsons, and Ms. Gibbons.

    - At the June 25, 2019 meeting of the CONBSC, Dr. Darren Michael presented an update on the rule making process for adding SMA to the screening panel and the proposed changes to PKU testing. During the public comments portion of the agenda, Tami Sova from Biogen (maker of Spinraza) shared information about drug function and Biogen's overall analysis of the impact of treatment on families and patients with SMA.

Summary of Stakeholder Survey

The CONBSP also conducted an online survey of newborn screening stakeholders from January 2019 through June 2019. During this period, eight-two stakeholders responded to a range of questions about the appropriateness of adding four different conditions to the Colorado newborn screening panel. Responses to individual questions are summarized below.

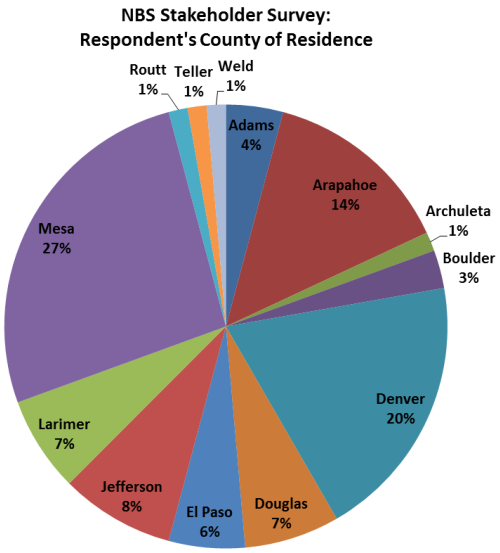

Figure 8. Stakeholders were asked to identify their county of residence.

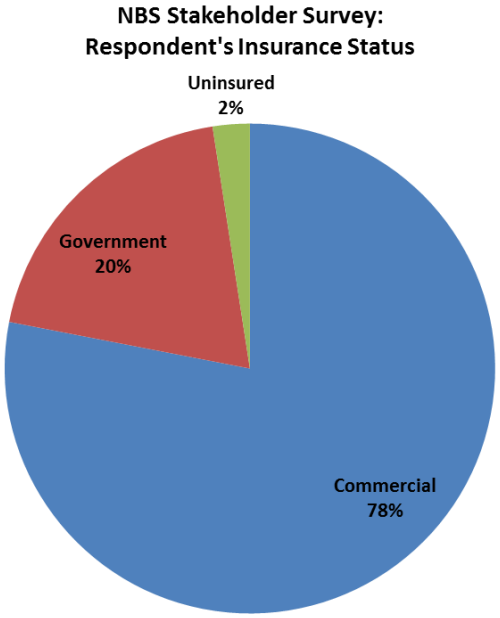

Figure 9. Stakeholders were asked to identify the type of health insurance they use, if any. A small number of respondents indicated multiple types of insurance.

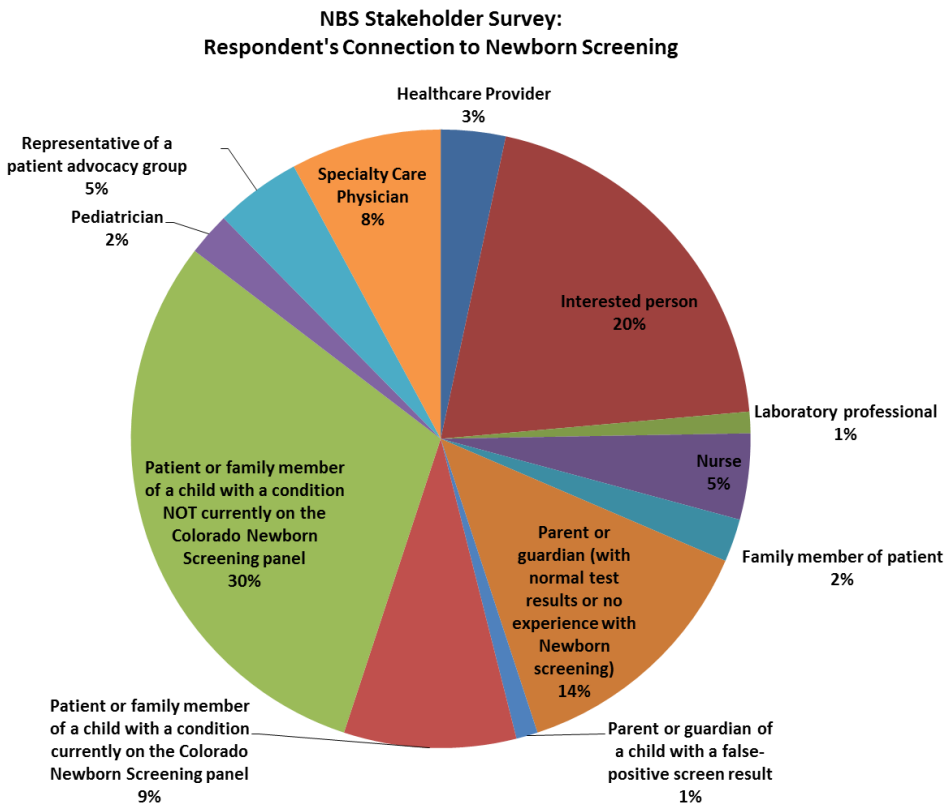

Figure 10. Stakeholders were asked to identify their relationship to newborn screening. Respondents were allowed to provide more than one answer for this question.

Stakeholder feedback that led to prioritization of RUSP recommendations

Should the following condition be added to the Colorado Newborn Screening panel?	Yes	No	Uncertain
Pompe Disease	56 (70.9)	1 (1.3)	24 (30.4)
Mucopolysaccharidosis Type 1	51 (65.4)	1 (1.3)	27 (34.6)
X-linked Adrenoleukodystrophy	49 (62.8)	1 (1.3)	28 (35.9)
Spinal Muscular Atrophy	77 (96.3)	1 (1.3)	2 (2.5)

Stakeholder feedback on the appropriateness of population-wide newborn screening in Colorado for four different conditions that are not currently on the newborn screening panel but for which there is a RUSP recommendation and stakeholders have expressed some interest in exploring whether inclusion in the Colorado panel is appropriate. The strong stakeholder support for the addition of SMA influenced the CONBP's decision to focus on SMA for the present rulemaking. The CONBSP will continue to work with stakeholders on the other three conditions included in the survey to determine, which, if any, are appropriate for newborn screening in Colorado, as well as continue to review the appropriateness of the conditions for which screening is currently required.

Stakeholder Group Notification

The stakeholder group was provided notice of the rulemaking hearing and provided a copy of the proposed rules or the internet location where the rules may be viewed. Notice was provided prior to the date the notice of rulemaking was published in the Colorado Register (typically, the 10th of the month following the Request for Rulemaking).

__X_ Not applicable. This is a Request for Rulemaking Packet. Notification will occur if the Board of Health sets this matter for rulemaking.

____ Yes.

Summarize Major Factual and Policy Issues Encountered and the Stakeholder Feedback Received. If there is a lack of consensus regarding the proposed rule, please also identify the Department's efforts to address stakeholder feedback or why the Department was unable to accommodate the request.

No major factual or policy issues were encountered.

Please identify the determinants of health or other health equity and environmental justice considerations, values or outcomes related to this rulemaking.

This rulemaking will provide population-wide newborn screening for SMA. By conducting screening for SMA through a public health program, the department is promoting health equity for SMA screening. Under the department's current model of providing follow-up services, newborns who screen positive, as well as their families and PCP's, are connected timely to appropriate medical experts who can guide families and PCP's on appropriate next steps. An overarching aim of newborn screening is to provide affordable population-wide screening to all newborns, as well as to connect those infants at risk quickly to specialized care.

By evaluating the effectiveness of the current approach to second screens for PKU, the department is meeting its mandate to provide newborn screening in the most efficient and cost-effective manner possible. By reducing the CONBSP's screening expenses for PKU without significantly increasing the risk of a false negative PKU result, the department is freeing resources of the CONBSP to strengthen other aspects of the program, which should benefit all newborns screened under the program.

Overall, after considering the benefits, risks and costs, the proposed rule:

Select all that apply.

	Improves behavioral health and mental health; or, reduces substance abuse or suicide risk.	X	Reduces or eliminates health care costs, improves access to health care or the system of care; stabilizes individual participation; or, improves the quality of care for unserved or underserved populations.
	Improves housing, land use, neighborhoods, local infrastructure, community services, built environment, safe physical spaces or transportation.		Reduces occupational hazards; improves an individual's ability to secure or maintain employment; or, increases stability in an employer's workforce.
	Improves access to food and healthy food options.		Reduces exposure to toxins, pollutants, contaminants or hazardous substances; or ensures the safe application of radioactive material or chemicals.

X	Improves access to public and environmental health information; improves the readability of the rule; or, increases the shared understanding of roles and responsibilities, or what occurs under a rule.		Supports community partnerships; community planning efforts; community needs for data to inform decisions; community needs to evaluate the effectiveness of its efforts and outcomes.
	Increases a child's ability to participate in early education and educational opportunities through prevention efforts that increase protective factors and decrease risk factors, or stabilizes individual participation in the opportunity.		Considers the value of different lived experiences and the increased opportunity to be effective when services are culturally responsive.
X	Monitors, diagnoses and investigates health problems, and health or environmental hazards in the community.		Ensures a competent public and environmental health workforce or health care workforce.
	Other:_____ _____		Other:_____ _____

COLORADO
Department of Health Care Policy & Financing

1570 Grant Street
Denver, CO 80203

August 26, 2019

Scott Bookman, Administrative Director
Laboratory Services Division
Colorado Department of Public Health and Environment
8100 Lowry Boulevard
Denver, CO 80230-6923

RE: Proposed Amendments to 5 CCR 1005-4, *Newborn Screening and Second Newborn Screening*

Dear Mr. Bookman:

The Colorado Department of Health Care Policy and Financing (the Department), is pleased to express our support for the addition of Spinal Muscular Atrophy (SMA) to the Colorado Department of Public Health and Environment's (CDPHE) Newborn Screening (NBS) panel.

The mission of the Department is to improve health care access and outcomes for the people we serve while demonstrating sound stewardship of financial resources. We aim to deliver high quality health care to the residents of Colorado through the administration of the Medicaid and Child Health Plan Plus programs, as well as a variety of other programs for Colorado's low-income families, the elderly and persons with disabilities. Early detection and treatment for rare conditions like SMA is of utmost importance to the Department and aids the Department in achieving our mission. The Department fully supports CDPHE and the addition of SMA to the NBS panel.

The Department looks to forward to further collaboration with CDPHE on the NBS program.

Sincerely,

Kim Bimestefer
Executive Director
Colorado Department of Health Care Policy & Financing

DEPARTMENT OF PUBLIC HEALTH AND ENVIRONMENT

Laboratory Services Division

NEWBORN SCREENING AND SECOND NEWBORN SCREENING

5 CCR 1005-4

Adopted by the Board of Health on _____; effective _____.

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SECTION 2: NEWBORN SCREENING REQUIREMENTS FOR NAMED SUBMITTERS

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2.4 List of Conditions for Newborn Screening

The Laboratory shall conduct screening tests for the following conditions:

2.4.1 Phenylketonuria

2.4.2 Congenital Hypothyroidism

2.4.3 Hemoglobinopathies

2.4.4 Galactosemia

2.4.5 Cystic Fibrosis

2.4.6 Biotinidase Deficiency

2.4.7 Congenital Adrenal Hyperplasia

2.4.8 Medium Chain Acyl-CoA Dehydrogenase Deficiency

2.4.9 Very Long Chain Acyl-CoA Dehydrogenase Deficiency

2.4.10 Long-Chain L-3-Hydroxy Acyl-CoA Dehydrogenase Deficiency

2.4.11 Trifunctional Protein Deficiency

2.4.12 Carnitine Acyl-Carnitine Translocase Deficiency

2.4.13 Short Chain Acyl-CoA Dehydrogenase Deficiency

2.4.14 Carnitine Palmitoyltransferase II Deficiency

2.4.15 Glutaric Acidemia Type 2

2.4.16 Arginosuccinic Acidemia

2.4.17 Citrullinemia

2.4.18 Tyrosinemia

2.5.19 Hypermethionemia

2.4.20 Maple Syrup Urine Disease

2.4.21 Homocystinuria

2.4.22 Isovaleric Acidemia

2.4.23 Glutaric Acidemia Type 1

2.5.24 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency

2.4.25 Multiple Carboxylase Deficiency

2.4.26 3-Methylcrotonyl-CoA Carboxylase Deficiency

2.4.27 3-Methylglutaconic Aciduria

2.4.28 Methylmalonic Acidemias

2.4.29 Propionic Acidemia

2.4.30 Beta-Ketothiolase Deficiency

2.4.31 Carnitine Uptake Defect

2.4.32 Arginase Deficiency

2.4.33 Malonic Acidemia

2.4.34 Carnitine Palmitoyltransferase Deficiency 1a

2.4.35 Severe Combined Immunodeficiency

2.4.36 Spinal Muscular Atrophy due to homozygous deletion of exon 7 in Survival Motor Neuron 1 gene

SECTION 3: SECOND NEWBORN SCREENING REQUIREMENTS FOR NAMED SUBMITTERS

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3.2.2.2 Section 25-4-1004.5(3)(b)(V), C.R.S. allows exceptions to testing of second newborn screening specimens. Second newborn screening specimen testing is not required for the conditions identified at 3.3.1, 3.3.4, 3.3.5 and 3.3.6 unless: an unsatisfactory specimen was submitted for an initial newborn screening specimen; a~~n abnormal~~ screen positive result was obtained on an initial newborn screening specimen from the same newborn; ~~or~~ there is no record of a satisfactory initial newborn screening specimen submission, or; for 3.3.1 only, the initial newborn screening specimen from the same newborn was collected before 24 hours of life.

3.3 List of Conditions for Second Newborn Screening

The Laboratory shall conduct screening tests for the following conditions:

3.3.1 Phenylketonuria

3.3.2 Congenital Hypothyroidism

3.3.3 Hemoglobinopathies

3.3.4 Galactosemia

3.3.5 Cystic Fibrosis

3.3.6 Biotinidase Deficiency

3.3.7 Congenital Adrenal Hyperplasia

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