COLORADO
Newborn Screening Program
Division of Disease Control and Public Health Response

To: Members of the State Board of Health

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Subject: 2024 Board of Health Rulemaking for Additional Conditions Proposed Amendments to 5 CCR 1005-4, Newborn Screening and Second Newborn Screening

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In preparation for a Public Rulemaking Hearing, the following documents are included in this rulemaking packet:

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 services for 39 conditions. Dried blood spot (DBS) specimens are collected by hospitals, midwives, and pediatricians who submit the specimens for testing to the Colorado State Public Health Laboratory. The CONBSP screens approximately 68,000 newborns in Colorado and Wyoming annually. About 64,000 newborns receive a routine second screen to retest for two conditions: Congenital Hypothyroidism (CH) and Congenital Adrenal Hyperplasia (CAH). Additionally, all previous abnormal results or specimens from a newborn without an adequate amount of blood on the first screen are tested on the second screen.

CONBSP is structured by a connect-to-care model allowing contracted health care specialists to help the newborn's family and primary care provider with the immediate next steps. Each year, the CONBSP identifies approximately 80-100 newborns with one of the conditions on the screening panels. In addition to true positive cases, more than 700 newborns who require confirmatory testing are identified each year. Carriers of hemoglobin trait, immune deficiencies, and other disorders are indicated by newborn screening. True positive newborns may appear healthy. However, newborns who are affected can face severe health issues that are best detected and treated early. Without early intervention, these conditions can lead to

death, disability, and failure to thrive. Early diagnosis allows babies to receive treatment before they start experiencing irreversible damage from their conditions.

The program proposes two changes to the current rule that will bring Colorado's newborn screening panel into alignment with the current conditions on the Recommended Uniform Screening Panel (RUSP). The RUSP is a list of disorders that the Secretary of the Department of Health and Human Services (HHS) recommends for states to screen as part of their state's universal newborn screening (NBS) programs. In addition, the CONBSP requests authorization to test a subset of newborns at increased risk for congenital cytomegalovirus (cCMV) infection. The proposed additions are as follows:

1. Adding Guanidinoacetate methyltransferase deficiency (GAMT) to the universal Colorado newborn screening panel. This disease was added to the RUSP in 2023.
2. Adding Mucopolysaccharidosis Type II (MPS II, Hunter's Syndrome) to the universal Colorado newborn screening panel. This disease was added to the RUSP in 2022.
3. Adding targeted screening for congenital cytomegalovirus (cCMV) infection by testing newborns who do not pass the newborn hearing screen, newborns who do not have a newborn hearing screen completed by day 10 of life, and newborns whose birth weight is in the bottom 10% of the population.

The rule changes are proposed in response to four (4) factors:

1. CDPHE regularly reviews national recommendations for newborn screening and seeks full alignment with the conditions recommended for screening on the RUSP.
2. CDPHE regularly reviews other state programs and best practices.
3. Stakeholders requested expanded testing and data integration.
4. Stakeholders advocated for the inclusion of additional conditions on Colorado's newborn screening panel and targeted testing.

Colorado stakeholders proposed legislation in 2018, House Bill 18-1006, to allow the CONBSP to increase fees and establish funds necessary to build the infrastructure required to align with the RUSP.

Construction allowing for basic laboratory infrastructure to increase newborn screening capabilities is complete. Instrumentation bids for purchase are also complete and the instruments will be purchased if the Board approves this rule package. In July 2023, the Health Resources and Services Administration (HRSA) awarded the program a five-year grant to provide staffing and additional support for the implementation of new disorders. This rulemaking proposes the inclusion of these conditions. The program has already begun early stakeholder engagement to gather feedback on these proposed amendments.

Population-based testing will be initiated in the next 18 months. If these proposed amendments to the rule are adopted, the next three to six months will be focused on testing, evaluating, and purchasing new instrumentation. After adoption of the rule, required laboratory information management system (LIMS) updates and validation will occur. Pilot

studies and final sample testing validations will occur 6-18 months after adoption. The program will use a phased implementation approach with the goal of preparing one disorder for population-based testing by December 2024. It will begin screening for the remaining disorders in the first half of 2025.

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

The Department proposes amendments to this rule that will bring the Colorado newborn screening panel into alignment with the current conditions on the Recommended Uniform Screening Panel (RUSP). In addition, the program's stakeholders requested the addition of targeted screening. The proposed additions are as follows:

- Adding Guanidinoacetate methyltransferase deficiency (GAMT) to the Colorado newborn screening panel.
- Adding Mucopolysaccharidosis Type II (MPSII) to the Colorado newborn screening panel.
- Adding the targeted testing of newborns for congenital Cytomegalovirus (cCMV).

The Newborn Screening and Second Newborn Screening rule performs the following functions:

- Defines key terms,
- Establishes procedures for the collection and submission of blood spot specimens for testing,
- Establishes procedures for laboratory testing, reporting, and follow-up services for newborn screening and second newborn screening,
- Establishes requirements for quality control and education, and
- Lists conditions covered by the newborn screening and second newborn screening panels.

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

For the past 60 years, virtually every one of the more than 3.6 million infants born in the United States each year has undergone newborn screening. Newborn screening is a well-established and proven state public health program that identifies newborns with certain genetic, metabolic, hormonal, and functional conditions. Newborn screening is considered one of the most effective public health campaigns in terms of both cost and prevention. Newborns often appear healthy, but their health may deteriorate quickly without any warning. Approximately one in every 300 newborns in the United States has a condition that can be detected through screening. Thanks to this early detection, infants born with these disorders receive prompt treatment, which can prevent permanent disability, developmental delay, and even death. The Newborn Screening Saves Lives Reauthorization Act continues the systematic evidence-based and peer-reviewed process of determining the federal RUSP, which now serves as the model for state newborn screening programs. The RUSP is a list of disorders that the Secretary of the Department of Health and Human Services (HHS) recommends for states to screen as part of their state universal newborn screening (NBS) programs.

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The CONBSP is proposing two changes to the current rule that will bring the Colorado newborn screening panel into alignment with the current conditions on the RUSP. There is an additional request to provide testing for newborns who do not pass or miss the newborn hearing screen or are in the bottom 10% of the newborn population for birth weight.

Proposed Change for Initial Screening

Of the 39 conditions presently included in the initial newborn screening panel, six (phenylketonuria, hypothyroidism, abnormal hemoglobins, galactosemia, cystic fibrosis, and biotinidase deficiency) are identified in statute. The remainder were added by the Board of Health, in accordance with the criteria in section 25-4-1004(1)(c), C.R.S. The Department undertakes a review when a condition is recommended by the RUSP for inclusion on the newborn screening panel, consistent with the criteria laid out in statute.

In the table below, the Department evaluates the suitability of GAMT and MPS II for population-wide newborn screening in Colorado using the four (4) criteria in Section 25-4-1004(1)(c), C.R.S. and proposes their addition to this rule.

Summary of analysis for population-wide newborn screening for GAMT and MPS II		
Statutory language	**Summary of CDPHE Findings**	
	GAMT	**MPS II**
"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."	Criterion met The condition causes physical damage and/or death. Treatments and medical interventions are available and improve outcomes.	Criterion met The condition causes physical damage and/or death. Treatments and medical interventions are available and improve outcomes.
The test meets commonly accepted clinical standards of reliability, as demonstrated through research or use in another state or jurisdiction.	Criterion met Currently there are multiple screening methods. Screening is performed in four (4) U.S. states or territories. Nineteen additional states are in the process of adding GAMT to their screening panel (as of Dec. 22, 2023).	Criterion met Currently there are multiple screening methods. Screening is performed in four (4) U.S. states or territories. Eleven additional states are in the process of adding MPS II to their screening panel (as of Dec. 22, 2023).

The cost-benefit consequences of screening are acceptable within the context of the total newborn screening program.	Criterion met Ongoing screening costs for the condition are similar to other conditions on the current CONBSP panel.	Criterion met Ongoing screening costs for the condition are similar to other conditions on the current CONBSP panel.

GAMT:

(I) As outlined in Colorado Revised Statute (C.R.S.) Section 25-4-1004, "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."

Guanidinoacetate methyltransferase (GAMT) deficiency is an autosomal recessive condition that prevents the body from making a substance called creatine. Creatine helps the body store and use energy. GAMT is an enzyme that helps make creatine from another substance called guanidinoacetate (GAA). GAMT deficiency means GAMT is present at low levels or does not work correctly. This makes it harder for the body to produce creatine. Without early treatment, low levels of creatine and high levels of guanidinoacetate can damage the brain and muscles, leading to a high consumption of energy within the body. As a result of low creatinine levels, organs do not receive a sufficient amount of energy, leading to global developmental delays (GDD) and intellectual disability. Other signs and symptoms can include hypotonia (decreased muscle tone), seizures, movement disorders, epilepsy, and behavioral problems. Treatment for epilepsy and movement disorder involves a high dose of creatinine that restores the cerebral creatine deficiency. In conjunction, treatment also involves ornithine supplementation and an arginine restricted diet to decrease GAA in the central nervous system. Early intervention and diagnosis can promote healthy neurodevelopmental outcomes. The addition of GAMT to the newborn screening panel can help provide early diagnosis for asymptomatic newborns, helping them achieve healthy neurodevelopmental outcomes.

The severity and age of onset for GAMT differs. Signs of GAMT begin from three to 36 months of age. They may include one or more of the following:

- Frequent seizures or epilepsy
- Delayed sitting or walking
- Delayed speech
- Weak muscle tone
- Uncontrolled movements (tremors or tics)
- Intellectual disability

When GAMT is detected early and proper treatment is started immediately, many babies with the condition are able to live longer lives with improved growth and development. This is why newborn screening for GAMT is so important.

(II) The incidence of the condition is sufficiently high to warrant screening.

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GAMT is estimated to affect one in every 250,000 to 550,000 newborn babies in the United States. Incidence rate of the condition is sufficiently high and comparable to other disorders currently on the CONBSP panel.

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

In January 2023, GAMT was added to the RUSP and currently, platforms already exist that can be used for first tier testing. CONBSP would use the Revvity NeoBase™ 2 test kit for tandem mass spectrometer to test for GAMT alongside other disorders for which the program already tests. The ability to test for other conditions simultaneously using current testing platforms allows for additional cost savings. Four U.S. states are currently testing for GAMT. Nineteen other states authorized testing to begin in 2024 and 2025.

(IV) The cost-benefit consequences of screening are acceptable within the context of the total newborn screening program.

There are four categories of costs described below, the first three of which are incurred by CDPHE. CDPHE will not be increasing its current provider NBS fee of $111 per newborn with the implementation of this testing.

Laboratory costs (CDPHE): The current CONBSP fee and HRSA Propel Grant will support laboratory costs for GAMT. This grant provides funding for initial costs for equipment, LIMS, modification, staffing, and validation testing. The current CONBSP mass spectrometer testing kit and instrumentation can screen for GAMT.

Item	Start-up or recurring	Cost
LIMS Modification*	Start-up	$10,000
Equipment modernization	Start-up	$0
MS/MS*	Start-up	$4,000
Laboratory staff (FTE)*	Start-up (.25 FTE)	$6,000
Laboratory staff (FTE)*	Recurring (0.0 FTE)	$0/month
Reagents	Start-up	$0
Validation*	Start-up	$4,000
Daily screening**	Recurring	$5,420/month

*Based on minimal additional time for multiplexed testing with established methods.
** Based on 65,000 samples per year at $1 per sample.

Costs associated with the Department contracting with medical experts to provide follow-up services for GAMT (CDPHE): CONBSP expects to find one newborn every four years when testing for GAMT, with an average follow-up cost of $1,000-$3,000 per newborn. Annual medical expert costs are expected to be approximately $500.

Costs associated with confirmatory testing and genetic tests to assess GAMT (CDPHE): Follow-up testing cost ranges from $200-$345 per sample. Current contracts with specialists are in place with a similar scope of work.

Costs associated with treatment of individuals diagnosed with GAMT, i.e. treatment of true positives (providers, insurance, families): Early diagnosis and treatment results in improved clinical outcomes and prolonged survival of individuals with GAMT. Once a child is diagnosed, costs for treatment recommended by a medical professional may be covered by insurance. Supplement treatments, though inexpensive and effective, are not covered by every insurance provider. Early diagnosis allows for treatment to begin and limits the effects of the disorder. Delayed care increases costs over the lifetime of the child.

- Current recommended treatments: During treatment of GAMT deficiency, creatine is supplemented daily along with high or low-dose ornithine supplementation. Sodium benzoate may also be provided. In GAMT deficiency, creatine supplementation can restore brain creatine levels and improve neurological status. The average annual cost of daily creatine, ornithine, and sodium benzoate supplementation ranges from $350-$1,250.

Mucopolysaccharidosis type II (MPS II)

(I) As outlined in C.R.S. Section 25-4-1004, "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."

MPS II is an X-linked lysosomal storage disorder (LSD) and the most common type of MPS disorder. In people affected by this disorder, lysosomes – membrane-bound cell organelles that contain digestive enzymes – are unable to break down complex sugars. This results in excess sugars building up, impacting multiple parts of the body. The deficient lysosomal enzyme is iduronate-2-sulphatase (I2S). The excess sugars that build up are referred to as glycosaminoglycans (GAGs). At birth, infants may appear healthy, but can develop signs and symptoms later in life, which is why MPS II has a spectrum of severity. Approximately two-thirds of patients have the severe type of the disorder that is linked with cognitive impairment and progressive cognitive decline, which typically manifests around 20 years of age. Early detection and Enzyme Replacement Therapy can help prevent or delay severe outcomes.

Early signs of MPS II include:

- Soft out-pouching around the belly-button (umbilical hernia) or lower abdomen (inguinal hernia)
- Large head (macrocephaly)

- Enlarged vocal cords causing a hoarse voice
- Recurring upper respiratory infections
- Distinctive facial features that appear “coarse”
- Severe developmental delay and learning disabilities
- Swollen abdomen (due to enlarged liver and spleen)
- Seizures
- Hearing loss
- Frequent ear infections
- Poor vision
- Thick, non-stretchy skin
- Pebble-like white growths on back and upper arms
- Short stature

Life expectancy in MPS II varies. Individuals with early progressive MPS II have progressive cognitive deterioration, progressive airway disease, and cardiac disease usually resulting in death before age 15. Individuals with slowly progressive MPS II can survive into early adulthood with normal intelligence and GAG accumulation affecting other organ systems. The most common causes of death are heart disease or airway obstruction.

(II) The incidence of the condition is sufficiently high to warrant screening.

The severe form of MPS II occurs in about one in 100,000 to 170,000 male newborns. Incidence of MPS II in heterozygous females has been noted, but is extremely rare.

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

In 2022, MPS II was added to the RUSP. There are limited platforms now available for first tier testing. FDA-authorized digital microfluidics and mass spectrometry kits are scheduled for release in 2024. The ability to multiplex, i.e. test for other conditions simultaneously using these testing platforms, allows for additional savings. Currently, MPS II is being tested in four states or territories. Eleven additional states will begin testing in 2024 and 2025.

(IV) The cost-benefit consequences of screening are acceptable within the context of the total newborn screening program.

There are four categories of costs described below, three of which are incurred by CDPHE. CDPHE will not be increasing its current provider NBS fee of $111 per newborn with the implementation of this testing.

Laboratory costs (CDPHE): The NBS cash fund and HRSA Propel grant will support laboratory costs for MPS II. This grant provides funding for initial costs for staffing and reagents through June 2028. The cost estimates below are for the current MPS II method. Additional cost savings would be realized with the authorization of the multiplexed method. Laboratory costs of adding MPS II screening are estimated below.

Item	Start-up or recurring	Cost

LIMS modification*	Start-up	$15k-30k
Equipment modernization	Start-up	$0
Digital Fluidics Systems*	Start-up	$0
Laboratory staff (FTE)*	Start-up (.5 FTE)	$12,000
Laboratory staff (FTE)*	Recurring (0.0 FTE)	$0/month
Reagents	Start-up	$0
Validation	Start-up	$8k
Daily screening**	Recurring	$17,500/month

*Based on 65,000 samples per year at $3.23 per sample.

Costs associated with the Department contracting with medical experts to provide follow-up services for MPS II (CDPHE): CONBSP expects to find one to two newborns every three years when testing for MPS II, with an average follow-up cost of $1,000-$3,000 per newborn. Annual costs for medical experts are estimated to be $1,500.

Costs associated with confirmatory testing and genetic tests to assess MPS II (CDPHE): Genetic testing is provided by the vendor of the first tier testing method at no additional cost. Follow-up enzyme level testing cost ranges from $200-$350 per sample.

Costs associated with treatment of individuals diagnosed with MPS II, i.e. treatment of true positives (providers, insurance, families): Once the child is diagnosed, costs for treatment recommended by a medical professional are covered by public and private insurance. Early diagnosis allows for treatment to begin sooner and limits the effects of the disorder. Any delay of care can lead to increased costs, including financial costs and medical trauma, impacting both infant and family long term.

Recommended treatments:

- Enzyme Replacement Therapy (ERT) - This treatment is administered by intravenous solution (IV) weekly to replace or supplement the missing or low enzymes. ERT is not a cure. It slows progression and may improve growth, joint movement, sleep apnea, respiratory function, pain levels, vision, and liver/spleen enlargement. Estimated costs are $300,000-400,000 per year, plus infusion facility costs.
- Hematopoietic Stem Cell Transplantation (HSCT) - HSCT is the gold standard for treatment of the severe form of MPS II in patients diagnosed and treated before 2-2.5 years old. The estimated cost of this treatment for severe MPS II is $500,000. ERT is often used while waiting for HSCT, then for as long as six months following transplant (approximately one year in total).

- Physical therapy - Physical therapy is a very important part of treating the signs and symptoms of MPS II. Consistent physical therapy early on can help preserve mobility and lessen pain and joint stiffness.
- Surgeries to improve quality of life - Removing the tonsils and adenoids, as well as insertion of ventilating (ear) tubes, can prevent some upper respiratory infections and may reduce hearing loss. Hearing aids may be recommended for some children. Those with mild to severe MPS II may develop a buildup of fluid in the brain (hydrocephalus), and surgery to relieve the pressure inside the skull may be recommended.

Proposed change for targeted screening: cCMV

Cytomegalovirus, or CMV, is the most common infectious cause of birth defects in the United States.[1] Congenital CMV infection (cCMV) occurs when the birthing parent develops an active CMV infection during pregnancy and the baby is infected with CMV. Approximately one in 200 babies is born with cCMV. This means about 300 children are born with cCMV in Colorado each year. Unfortunately, each year, fewer than 30 of these children are diagnosed. Screening newborns for cCMV using the blood spot will improve identification of cCMV.[2,3]

Although CMV is not currently on the RUSP, CONBSP proposes using the blood spot to detect CMV by testing those newborns at highest risk for infection. Because cCMV is a major risk factor for early childhood hearing loss, these rules propose testing any newborn who does not pass the newborn hearing screen. Also proposed for inclusion is any newborn who does not have a hearing screen completed by day 10 of life. This age cutoff allows for screening testing to be completed, allowing for diagnosis prior to day 21 of life. Identification of cCMV before day 21 allows time to identify those infants with cCMV who should be offered antiviral treatment, which should be started before one month of life. In addition, CONBSP will test the blood spot of any newborn with a birth weight lower than 10% of the newborn population. Newborns who are small for gestational age (SGA) and/or admitted to a newborn intensive care unit (NICU) are at increased risk for cCMV.

CONBSP will work with the Newborn Hearing Screening Program, which is a part of the Center for Health and Environmental Data (CHED) within the Colorado Department of Public Health and Environment (CDPHE), to identify newborns who did not pass the newborn hearing screen or did not have a screen completed before day 10 of life. In addition, CONBSP will use demographic data from blood spot cards to identify newborns with a birth weight in the lower 10% of the newborn population (approximately <2500 grams). Results of cCMV testing will be reported to the submitter of the sample on the CONBSP blood spot report. A diagnosis of cCMV will require confirmation by a positive result on a urine CMV PCR test. Through early detection, newborns will have the opportunity for improved health outcomes and prevention of further damage from hearing loss.

Summary of analysis for Targeted newborn screening for cCMV	
Statutory language	**Summary of CDPHE findings**

	cCMV
"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."	Criterion met The condition causes physical damage and/or death. Treatments and medical interventions are available and improve outcomes.
The test meets commonly accepted clinical standards of reliability, as demonstrated through research or use in another state or jurisdiction.	Criterion met Minnesota began universal population based testing using the blood spot in February 2023 and New York began such testing in October 2023. Connecticut will begin such testing in 2025. Fifteen states require each newborn who fails the newborn hearing screening be tested for cCMV.
The cost-benefit consequences of screening are acceptable within the context of the total newborn screening program.	Criterion met Ongoing screening costs for the condition are similar to other conditions on the current CONBSP panel.

(I) As outlined in C.R.S. Section 25-4-1004, "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."

(1) **cCMV presents a significant health risk.**

About 10% of children born with cCMV will have multiple organs affected and a high risk of lifelong problems. This is called "symptomatic cCMV." About 3% of these children will die in the first 28 days of life. Symptoms at birth may include low birth weight, microcephaly, jaundice, rash, hepatomegaly, or splenomegaly.[4] Imaging may show brain injury. Bloodwork may reveal a low platelet count or abnormal liver function. Long-term problems include cerebral palsy, seizures, developmental delays, and blindness. Half to two-thirds of these children will be deaf or hard-of-hearing.

Another 10-15% of children born with cCMV will have only sensorineural hearing loss as a result of the infection.[5-8] Many of these children will also have balance problems.[9-11] Children in this category are labeled as having "asymptomatic cCMV with hearing loss." Some will not pass the newborn hearing screen, while others will have healthy hearing at birth, but then become deaf or hard-of-hearing in the first few years of life.[12,13] cCMV is the most common non-genetic cause of early childhood deafness, accounting for 20% of all cases at birth and 25% by age 4.[14]

Detection of cCMV in newborns will lead to early recognition of early childhood hearing loss and timely intervention. The 2021 World Hearing Report from the World Health Organization emphasizes the benefits of early identification of hearing loss and early intervention.[15] Hearing problems in infancy lead to deficits in speech and language development, delayed social skills, and poor school performance. When untreated or unrecognized until after the critical period for language development before age 2, childhood hearing loss is associated with lower rates of high school graduation and lower lifetime earning potential.[16-18] Research shows that by the time a child with hearing loss graduates from high school, more than $400,000 per child can be saved in special education costs if the child is identified early and given appropriate educational, medical, and audiological services.[19]

The remaining approximately 75-80% of infants with cCMV will never have clinical manifestations, and are labeled "asymptomatic." Note that in 2023 the Council of State and Territorial Epidemiologists (CSTE) developed Standardized Surveillance Case Definitions for Congenital Cytomegalovirus (cCMV) Infection and Disease, published in Technical Supplement 23-ID-02. These definitions replace the symptomatic/asymptomatic classification with categories of cCMV infection, confirmed cCMV disease, and probable cCMV disease. The CDC is now using the CSTE definitions for its SET-NET project, which is designed to improve surveillance for cCMV.

Unfortunately, 80-90% of all children with cCMV are never diagnosed. Reasons why the diagnosis is missed include a lack of awareness of clinical risk factors and the need for testing within the first 21 days of life in order to distinguish congenital infection from postnatal infection, which can occur within the first three to four weeks of life.

(2) cCMV is amenable to treatment.

Screening for cCMV using the blood spot will identify newborns with cCMV whose diagnosis had been missed during routine clinical care. Every newborn diagnosed with cCMV will be evaluated for evidence of symptomatic infection and hearing loss, which will allow for appropriate treatment. Expert consensus statements from both the United States [20] and Europe[21] outline the recommended evaluation and treatment for any infant diagnosed with cCMV.

1. For all infants with cCMV, treatment may include:

- Laboratory testing to detect hematologic effects of cCMV;
- Laboratory testing to detect hepatic involvement;
- Brain imaging to detect central nervous system involvement. This will lead to closer monitoring of development, early intervention for developmental delays, and consultation with a pediatric neurologist;
- Ophthalmologic evaluation to detect retinitis and other ocular involvement; and
- Education for the family about the potential for future hearing loss and developmental delays.

2. For children with asymptomatic cCMV and no hearing loss detected at birth, treatment should include audiologic evaluation and repeated hearing testing during the first six years of life.

3. For children with asymptomatic cCMV with hearing loss, treatment should include:

- Audiologic evaluation and repeated hearing testing over the first six years of life;
- Consultation with a pediatric infectious disease specialist;
- Consultation with a pediatric otolaryngologist, assessment of the need for hearing assistive devices such as hearing aids or cochlear implants, and early provision of such devices, if chosen by the family;
- Treatment with speech therapy and/or training in non-verbal communication, such as American Sign Language (ASL);
- Close monitoring for developmental delays and treatment with developmental therapies such as physical and occupational therapy; and
- Close monitoring for vestibular and balance problems.

4. For newborns with symptomatic cCMV, treatment should include:

- All the care outlined in #3; and
- Consultation with a pediatric infectious disease specialist for discussion of the risks and benefits of treatment with valganciclovir, which has been shown to improve hearing and development in those with symptomatic cCMV [22]

(II) The incidence of the condition is sufficiently high to warrant screening.

cCMV affects about one in 200 newborns in developed countries like the United States. This equates to more than 18,000 children born with cCMV in the United States each year and more than 300 children born with cCMV in Colorado each year. The incidence of cCMV in Black/African-American infants in one U.S. study was about twice that in the general population.[23]

cCMV is the most common congenital viral infection worldwide and more common than any other condition screened during pregnancy or in newborns. Compare the incidence of cCMV, five in 1,000, to the most common conditions included on the newborn blood spot screening panel in Colorado: congenital hypothyroidism affects about one in 3,000 newborns, and sickle cell disease occurs in about one in 1,400 newborns, or one in 365 Black/African-American newborns. All of the other genetic and metabolic conditions screened using the newborn blood spot are rarer.

Using the estimation parameters adopted by Minnesota during their evaluation of cCMV for inclusion in newborn screening (0.45% incidence, screening test sensitivity 75%), we estimate 230 children with cCMV will be identified by newborn screening each year in Colorado. We estimate 23 of these newborns will have symptomatic cCMV (10%). Another 23-35 will have asymptomatic cCMV with hearing loss (10-15%), of whom about half will have hearing loss identified in the newborn period and half during the first six years of life. Of the 230 cases

detected each year, about 180 will have asymptomatic cCMV and probably never have clinical manifestations of the infection.

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

Recent improvements in techniques for extraction of CMV DNA have shown an average sensitivity of 75-85%, making population based screening using the blood spot more reasonable.[3]

Universal population based testing for cCMV using the newborn blood spot was implemented in both Minnesota and New York state in 2023. Connecticut plans to begin such testing in 2024 while another 15 states mandate testing for cCMV on a targeted basis. The province of Ontario, Canada, instituted universal population based testing for cCMV using the blood spot in 2019. In 2023, the provinces of Saskatchewan, Manitoba, and Alberta are beginning such testing.

A number of methods for testing have been established. Revvity currently provides a cCMV testing kit and reagent components for blood spot samples. CDC and other states have developed laboratory developed testing methods.

Every infant with CMV detected in the blood spot will also need to receive a urine PCR test to confirm the diagnosis of cCMV covered by CDPHE as part of the follow-up care.

(IV) The cost-benefit consequences of screening are acceptable within the context of the total newborn screening program.

There are four categories of costs described below, three of which are incurred by CDPHE. CDPHE will not be increasing its current provider NBS fee of $111 per newborn with the implementation of this testing.

Laboratory costs (CDPHE): The NBS cash fund and HRSA Propel grant will support laboratory costs for cCMV. This grant provides funding for initial costs for staffing and reagents through June 2028. The cost estimates below are for the Revvity NeoMDx™ cCMV real-time PCR assay. Additional cost savings would be realized with the development of a laboratory specific method using controls and reagents from approved vendors. The laboratory costs of adding cCMV screening are estimated below.

Item	Start-up or recurring	Cost
LIMS Modification*	Start-up	$30-60,000
Equipment modernization	Start-up	$0
Molecular testing platforms	Start-up	$0
Laboratory staff (FTE)	Start-up (.5 FTE)	$12,000

Laboratory staff (FTE)	Recurring (0.5 FTE)	$2,000/month
Reagents	Start-up	$1,000
Validation	Start-up	$20k
Daily screening*	Recurring	$6,670/month

* Based on 8,000 samples per year at $10 per sample.

Costs associated with the Department contracting with medical experts to provide follow-up services for cCMV (CDPHE): CONBSP expects to find 230 newborns a year when testing for cCMV, with an average follow-up cost of $46,000 based on $200 per newborn. Annual medical expert costs are expected to be approximately $46,000. Cost estimates include initial medical professional visit and diagnostic testing.

Cost estimates listed here are as per **Children's Hospital Colorado (CHCO) online cost estimator, for an uninsured patient at the Anschutz Campus (November 2023).**

1. Cost associated with confirmatory testing for cCMV (CDPHE):

   The cost of each urine CMV test is $58. If the State Lab runs 230 tests per year, the total yearly cost of cCMV confirmatory testing would be $13,340. CONBSP will contract to have this testing provided to families to cover the cost of confirmatory diagnostic testing.

2. Potential costs associated with initial evaluation of individuals diagnosed with cCMV (providers, insurance, families):

   In most cases, a primary care physician will be counseling the family and coordinating this initial evaluation. Some of the costs listed below are associated with hearing loss. These costs would not be covered by the CONBSP and would be the responsibility of the newborn's guardians.

Audiology lab	
CBC	$125
Hepatic function panel	$60
Creatinine	$5
Imaging	
US brain	$765
Consults	

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ENT/audiogram, new patient	$1,137
Ophthalmology, new patient	$148

3. Potential costs associated with ongoing care of individuals with symptomatic cCMV:

An estimated 46-58 patients will need such care; the services needed will vary. Not all diagnostic testing or treatments listed will be required for every newborn. Medical professionals will determine the appropriate procedures for each newborn. Insurance coverage and private pay costs will vary based on individual coverage.

Some of the costs listed below are associated with hearing loss and would be incurred based on an abnormal hearing screen.

ENT/ audiology, follow up per visit	$809
Speech therapy, per visit	$227
Hearing aid fitting, binaural	$2,673
Cochlear implant activation	$623
Infectious Disease follow up, per visit	$170
Valganciclovir treatment	$4,000

Specific Statutory Authority: Sections 25-4-1004(1)(c)(I-IV), C.R.S

Is this rulemaking due to a change in state statute?

____ Yes Rules are __ authorized __ required.

__X__ No

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

_____ Yes ___ URL __X____ No

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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

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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
Colorado's newborns	~63,400/yr	B
Parents/guardians/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[1]	S/B
Patient advocacy groups, e.g. March of Dimes, NORD	~6	S
Adult patients with rare diseases	~500,000[2]	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	~5	S

1. Colorado Physician Workforce Profile 2016 Association of American Medical Colleges.
2. 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 June 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, use this relationship categorization key:

C = Individuals/entities who implement or apply the rule.

S = Individuals/entities who do not implement or apply the rule but are interested in others applying the rule.

B = Individuals who 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.

More than one category may be appropriate for some stakeholders.

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.

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

Treatment costs are covered by insurance once the child is diagnosed and recommended by a medical professional. Early diagnosis allows for treatment to begin and limits the effects of the disorder on the child. Any delay of care can lead to increased costs, including both financial costs and medical trauma, impacting both infant and family long term.

Recommended treatments

GAMT:

- Creatine is supplemented daily, along with high or low-dose ornithine supplementation. Sodium benzoate may also be provided. In GAMT deficiency, creatine supplementation can restore brain creatine levels and improve neurological status.
    - Estimated costs:
        - The average annual cost of daily creatine, ornithine, and sodium benzoate supplementation is $350 - $1,250.

MPS II:

- Enzyme Replacement Therapy (ERT) is administered by intravenous solution (IV) weekly to replace or supplement the missing or low enzymes. ERT is not a cure. It slows progression and may improve growth, joint movement, sleep apnea, respiratory function, pain levels, vision, and liver/spleen enlargement.
    - Estimated costs attenuated MPS II:

        - For weekly ERT, the estimated annual cost is $300,000 - $400,000 plus infusion facility costs.
- Hematopoietic Stem Cell Transplantation (HSCT) - HSCT is the gold standard for the treatment of the severe form of MPS II in patients diagnosed and treated before 2-2.5 years old.
    - Estimated costs:
        - The cost of HSCT is currently approximately $500,000. ERT is often used while waiting for HSCT, then for up to six months following transplant (approximately one year in total).
- Physical therapy is a very important part of treating the signs and symptoms of MPS II. Consistent physical therapy early on can help preserve mobility and lessen pain and joint stiffness. Costs for physical therapy vary depending on patient-specific needs.
- Removal of the tonsils and adenoids, and insertion of ventilating (ear) tubes, can prevent some upper respiratory infections and may reduce hearing loss. Hearing aids may be recommended for some children. Those with mild to severe MPS II may develop a buildup of fluid in the brain (hydrocephalus); surgery to relieve the pressure inside the skull may be recommended. The various individual treatments would be determined necessary by a medical expert.
    - Estimated costs:
        - The cost of tonsil and adenoid removal is approximately $2,000.
        - The cost of ear tubes is approximately $1371.
        - The estimated cost for hearing aid fitting is approximately $2,673.
        - The estimated cost for hydrocephalus endoscopic third ventriculostomy (ETV) is approximately $94,797 or ventriculoperitoneal shunting (VPS) is approximately $130,839.

cCMV:

Potential costs associated with initial evaluation of individuals diagnosed with cCMV:

In most cases, a PCP will counsel the family and coordinate this initial evaluation. Some of the costs listed below are associated with hearing loss.

Audiology lab	
CBC	$125
Hepatic function panel	$60
Creatinine	$5
Imaging	

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U.S. brain	$765
Consults	
ENT/audiogram, new patient	$1,137
Ophthalmology, new patient	$148

Potential costs associated with ongoing care of individuals with symptomatic cCMV:

Once the child is diagnosed, costs for treatment recommended by a medical professional are covered by insurance or the patient's family. Some of the costs listed below are associated with hearing loss.

ENT/ audiology, follow up per visit	$809
Speech therapy, per visit	$227
Hearing aid fitting, binaural	$2,673
Cochlear implant activation	$623
Infectious Disease follow up, per visit	$170
Valganciclovir treatment	$4,000

Non-economic outcomes

Summarize the anticipated favorable and unfavorable 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 medical providers will benefit from timely detection and connection to medical experts when serving an infant with a GAMT, MPS II, and/or cCMV screen positive result.

Advocacy organizations, parents/guardians, and adult patients with rare genetic conditions might see the addition of GAMT, MPS II, and/or cCMV as a sign of the state's awareness about 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. Parents and guardians of newborns will benefit from a screening method that determines risk and can help prevent a diagnostic odyssey (an extended period of time between symptom onset and diagnosis). The Black/African-American population will benefit from improved health care outcomes for a disorder that is more prevalent in their population.

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

Anticipated CDPHE Revenues: N/A

Anticipated CDPHE Costs:

GAMT

Laboratory Costs: The CONBSP fee and HRSA Propel Grant will support laboratory costs for GAMT. This grant provides funding for initial costs for equipment, LIMS, modification, staff, and validation testing. GAMT can be multiplexed with the current CONBSP mass spectrometer testing kit and instrumentation.

Item	Start-up or recurring	Cost
LIMS modification*	Start-up	$10,000
Equipment modernization	Start-up	$0
MS/MS*	Start-up	$4,000
Laboratory staff (FTE)*	Start-up (.25 FTE)	$6,000
Laboratory staff (FTE)*	Recurring (0.0 FTE)	$0/month
Reagents	Start-up	$0
Validation*	Start-up	$4,000
Daily screening**	Recurring	$5,420/month

*Based on minimal additional time for multiplexed testing with established methods.
** Based on 65,000 samples per year at $1 per sample.

Costs associated with the Department contracting with medical experts to provide follow-up services for GAMT: CONBSP expects to find one newborn every four years when testing for GAMT, with an average follow-up cost of $1,000-$3,000 per newborn. The expected annual medical expert costs are approximately $500.

Costs associated with confirmatory testing and genetic tests to assess GAMT: Follow-up testing costs range from $200-$345 per sample.

MPS II

Laboratory costs: The NBS cash fund and HRSA Propel grant will support laboratory costs for MPS II. This grant provides funding for initial costs for staffing and reagents through June 2028. The laboratory cost estimates for adding the current MPS II screening method are below. Additional cost savings would be realized with the authorization of the multiplexed method.

Item	Start-up or recurring	Cost
LIMS modification*	Start-up	$15,000 - $30,000
Equipment modernization	Start-up	$0
Digital Fluidics Systems*	Start-up	$0
Laboratory staff (FTE)*	Start-up (.5 FTE)	$12,000
Laboratory staff (FTE)*	Recurring (0.0 FTE)	$0/month
Reagents	Start-up	$0
Validation	Startup	$8,000
Daily screening**	Recurring	$17,500/month

*Based on 65,000 samples per year at $3.23 per sample.

Costs associated with the Department contracting with medical experts to provide follow-up services for MPS II: CONBSP expects to find one to two newborns every three years when testing for MPS II, with an average follow-up cost of $1,000-$3,000 per newborn. Annual medical expert costs are expected to be $1,500.

Costs associated with confirmatory testing and genetic tests to assess MPS II: Genetic testing is provided by the vendor of the first tier testing method at no additional cost. Follow-up enzyme level testing cost ranges from $200-$350 per sample.

cCMV

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Laboratory costs: The NBS cash fund and HRSA Propel grant will support laboratory costs for cCMV. This grant provides funding for initial costs for staffing and reagents through June 2028. The laboratory cost estimates of adding cCMV screening, including the Revvity cCMV kit, are below. Additional cost savings would be realized with the development of a laboratory specific method using controls and reagents from approved vendors.

Item	Start-up or recurring	Cost
LIMS modification*	Start-up	$30,000 - $60,000
Equipment modernization	Start-up	$0
Molecular testing platforms	Start-up	$0
Laboratory staff (FTE)	Start-up (.5 FTE)	$12,000
Laboratory staff (FTE)	Recurring (0.5 FTE)	$2,000/month
Reagents	Start-up	$1,000
Validation	Start-up	$20,000
Daily screening*	Recurring	$6,670/month

* Based on 8,000 samples per year at $10 per sample.

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

S: Department of Health Care Policy and Financing (HCPF)

GAMT

Costs associated with confirmatory testing and genetic tests to assess GAMT: Follow-up testing costs range from $200-$345 per sample.

Costs associated with treatment of individuals diagnosed with GAMT, i.e. treatment of true positives: Once a child is diagnosed, costs for treatment recommended by a medical professional, may be covered by insurance or Medicaid. Supplement treatments though inexpensive and effective are not covered by every insurance provider. Early diagnosis and treatment results in improved clinical outcomes and prolonged survival of individuals with GAMT. Treatment costs are approximately $350 - $1,250 annually.

MPSII

Costs associated with confirmatory testing and genetic tests to assess MPS II: Genetic testing is provided by the vendor of the first tier testing method at no additional cost. Follow-up enzyme level testing cost ranges from $200-$350 per sample.

Costs associated with treatment of individuals diagnosed with MPSII, i.e. treatment of true positives: Once a child is diagnosed, costs for treatment recommended by a medical professional, may be covered by insurance or Medicaid. Early diagnosis and treatment results in improved clinical outcomes and prolonged survival of individuals with MPSII. Treatment costs average $500,000 annually.

cCMV

Costs associated with confirmatory testing and genetic tests to assess cCMV: A primary care physician will be counseling the family and coordinating initial evaluation and treatment. These initial costs can range from $2,200 - $8,500.

Costs associated with treatment of individuals diagnosed with cCMV, i.e. treatment of true positives: Once a child is diagnosed, costs for treatment recommended by a medical professional, may be covered by insurance or Medicaid. Early diagnosis and treatment results in improved clinical outcomes and prolonged survival of individuals with cCMV. Treatment costs average $11,000 annually.

Anticipated Revenues for another state agency: N/A

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

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

_X_ Comply with a statutory mandate to promulgate rules.

___ Comply with federal or state statutory mandates, federal or state regulations, and department funding obligations.

_X_ 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:

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Goal 1, Implement public health and environmental priorities
Goal 2, Increase Efficiency, Effectiveness and Elegance
Goal 3, Improve Employee Engagement
Goal 4, Promote health equity and environmental justice
Goal 5, Prepare and respond to emerging issues, and
Comply with statutory mandates and funding obligations

Strategies to support these goals:

___ Substance Abuse (Goal 1)

___ Mental Health (Goal 1, 2, 3 and 4)

___ Obesity (Goal 1)

___ Immunization (Goal 1)

___ Air Quality (Goal 1)

___ Water Quality (Goal 1)

_X_ Data collection and dissemination (Goal 1, 2, 3, 4, 5)

___ Implement quality improvement/a quality improvement project (Goal 1, 2, 3, 5)

___ Employee Engagement (Goal 1, 2, 3)

_X_ Decisions incorporate health equity and environmental justice (Goal 1, 3, 4)

___ Detect, prepare and respond to emerging issues (Goal 1, 2, 3, 4, 5)

___ Advance CDPHE Division-level strategic priorities.

cCMV is more prevalent within Colorado's Black/African-American population and the addition of this disorder to the CONBSP will improve health outcomes and the incidence rate. There are more than 240,000 Black/African-American Coloradans who are historically underserved by the health care community. Early testing for newborn screening focused on populations of Northern European descent and neglected disorders frequently found in minority populations. Equity in health care is a Department priority.

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. By implementing a multiplexed screening test, the CONBSP is selecting an efficient and cost-effective approach to newborn screening. For cCMV, testing targeted populations increases the per test cost, but limits the overall cost versus universal population based testing.

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

For the addition of GAMT, MPS II, and cCMV, the Department also considered keeping its newborn screening panel in its current form. This would mean newborns with these disorders who would benefit most from early diagnosis would not be identified through newborn screening. Families, who are aware of the risks posed by these disorders, could opt for prenatal screening or commercial newborn screening. However, this would be inconsistent with the Department's focus on health equity. Children identified with these disorders 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 health care 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 and reduce the child's reliance on medical interventions to maintain quality of life.

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.

References

[1] Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. C Clin Microbiol Rev 2013; 26: 86–102.

[2] Michael J. Cannon, Paul D. Griffiths, Van Aston, and William D. Rawlinson. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit? Rev Med Virol 2014 September 24 (5): 291-307.

[3] Dollard SC, Dreon M, Hernandez-Alvarado N, et al. Sensitivity of Dried Blood Spot Testing for Detection of Congenital Cytomegalovirus Infection. JAMA Pediatr. 2021;175(3):e205441.

[4] Dreher AM, Arora N, Fowler KB, et al. Spectrum of disease and outcome in children with symptomatic congenital cytomegalovirus infection. J Pediatr. 2014;164:855–859.

[5] Foulon I, Naessens A, Foulon W, Casteels A, Gordts F. A 10-year prospective study of sensorineural hearing loss in children with congenital cytomegalovirus infection. J Pediatr. 2008; 153:84–88.

[6] Goderis J, De Leenheer E, Smets K, Van Hoecke H, Keymeulen A, Dhooge I. Hearing loss and congenital CMV infection: a systematic review. Pediatrics 2014; 134: 972–82.

[7] Lanzieri TM, Chung W, Flores M, et al. Hearing Loss in Children With Asymptomatic Congenital Cytomegalovirus Infection. Pediatrics. 2017;139(3):e20162610.

[8] Foulon I, De Brucker Y, Buyl R, et al. Hearing Loss With Congenital Cytomegalovirus Infection. Pediatrics 2019;144(2):e20183095.

[9] Bernard, S., Wiener-Vacher, S., Van Den Abbeele, T., & Teissier, N. (2015). Vestibular Disorders in Children With Congenital Cytomegalovirus Infection. Pediatrics, 136(4), e887–e895.

[10] Shears A, Yan G, Mortimer H, et al. Vestibular and balance dysfunction in children with congenital CMV: a systematic review. Arch Dis Child Fetal Neonatal Ed Epub doi:10.1136/archdischild-2021-323380.

[11] Pinninti S, Christy J, Almutairi A, et al. Vestibular, Gaze, and Balance Disorders in Asymptomatic Congenital Cytomegalovirus Infection. Pediatrics. 2021;147(2):e20193945.

[12] Fowler KB, McCollister FP, Dahle AJ, et al. Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. J Pediatr. 1997; 130:624–630.

[13] Rosenthal LS, Fowler KB, Boppana SB, Britt WJ, Pass RF, Schmid SD, Stagno S, Cannon MJ. Cytomegalovirus shedding and delayed sensorineural hearing loss: results from longitudinal follow-up of children with congenital infection. Pediatr Infect Dis J. 2009 Jun;28(6):515-20.

[14] Morton C, Nance W. Newborn Hearing Screening — A Silent Revolution. N Engl J Med 2006;354:2151-64.

[15] World Health Organization (2021). World report on hearing. Geneva.

[16] Yoshinaga-Itano C, Sedey A, Coulter D, Mehl A. Language of early-and later-identified children with hearing loss. Pediatrics 1988; 102(5):1161-1171.

[17] Vohr B, Jodoin-Krauzyk J, Tucker R, Johnson MJ, Topol D, Ahlgren M, et al. Expressive language outcomes of children with hearing loss in the first 2 years of life: impact of early intervention. J Perinatol 2011; 31(4):274-80.

[18] Meinzen-Derr J, Wiley S, Grove W, et al. Kindergarten Readiness in Children Who Are Deaf or Hard of Hearing Who Received Early Intervention. Pediatrics. 2020;146(4):e20200557.

[19] Soren Gantt, MD, PhD, MPH; Francois Dionne, PhD; Fred K. Kozak. Cost-effectiveness of Universal and Targeted Newborn Screening for Congenital Cytomegalovirus Infection. JAMA Pediatr. 2016;170(12):1173-1180.

[20] Rawlinson, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis. 2017 Jun; 17(6): e177–e188.

[21] Luck S, Wieringa J, Blazquez-Gamero D et al. Congenital Cytomegalovirus, A European Expert Consensus Statement on Diagnosis and Management. The Pediatric Infectious Disease Journal Volume 36, Number 12, December 2017.

[22] D.W. Kimberlin, P.M. Jester, P.J. Sánchez et al. Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease. N Engl J Med 2015;372:933-43. DOI: 10.1056/NEJMoa1404599.

[23] Fowler KB, Ross SA, Shimamura M, et al. Racial and Ethnic Differences in the Prevalence of Congenital Cytomegalovirus Infection. J Pediatr. 2018 May 18. pii: S0022-3476(18)30597-3.

Additional Information:

Association of Public Health Laboratories Newborn Screening Technical assistance and Evaluation Program (NewSTEPs) [(accessed on 28 December 2023)]; Available online: http://www.newsteps.org

Association for Creatine Deficiencies. Newborn screening. Date unknown. Accessed December 28, 2023. https://creatineinfo.org/nbs/

Baby's First Test has information related to newborn screening. Use the links below to learn more about each of the New Disorders under consideration in Colorado.

Bilyeu, H., Washburn, J., Vermette, L., & Klug, T. (2020). Validation and implementation of a highly sensitive and efficient newborn screening assay for mucopolysaccharidosis type II.

International Journal of Neonatal Screening, *6*(4), 79. https://www.mdpi.com/2409-515X/6/4/79

Burton, B. K., Hickey, R., & Hitchins, L. (2020). Newborn screening for mucopolysaccharidosis type II in Illinois: an update. International journal of neonatal screening, 6(3), 73.

Colorado Revised Statutes 2023, Title 25, Public Health and Environment

CDC's CMV webpage

Colorado Chapter, American Academy of Pediatrics

EveryLife Foundation (2021). The National Economic Burden of Rare Disease Study. Available at: https://everylifefoundation.org/newborn-screening-take-action/state-rusp-alignment-map/

Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC)

Lahr, A., Henderson, N., Williams, L., Arnold, G., & Ortiz, D. (2023). Overview of Newborn Screening of Lysosomal Storage Diseases for Pediatric Care Providers. *OBM Genetics*, *7*(3), 1-12.https://www.lidsen.com/journals/genetics/genetics-07-03-194

Kemper, A. R., Lam, K. K., Letostak, T. B., Grosse, S. D., Ojodu, J., Prosser, L. A., ... & McCandless, S. Evidence-Based Review of Newborn Screening for Guanidinoacetate Methyltransferase (GAMT) Deficiency: Final Report (06/2/2022). https://pubmed.ncbi.nlm.nih.gov/37465909/

National Library of Medicine Mucopolysaccharidosis Type II

Kemper, A. R., Lam, K. K., Letostak, T., Grosse, S. D., Ojodu, J., Prosser, L. A., ... & McCandless, S. Evidence-Based Review of Newborn Screening for Mucopolysaccharidosis Type II: Final Report (02/20/2022). https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/meetings/mps-ii-final-report-3-28-2022.pdf

Mercimek-Mahmutoglu, S., Pop, A., Kanhai, W., Ojeda, M. F., Holwerda, U., Smith, D., ... & Salomons, G. S. (2016). A pilot study to estimate incidence of guanidinoacetate methyltransferase deficiency in newborns by direct sequencing of the GAMT gene. Gene, 575(1), 127-131.

Millington, D. S., & Ficicioglu, C. (2022). Addition of MPS-II to the Recommended Uniform Screening Panel in the United States. *International Journal of Neonatal Screening*, *8*(4), 55. https://www.mdpi.com/2409-515X/8/4/55/htm

National CMV Foundation

Ream, M. A., Lam, W. K., Grosse, S. D., Ojodu, J., Jones, E., Prosser, L. A., ... & Kemper, A. R. (2023). Evidence and Recommendation for Guanidinoacetate Methyltransferase Deficiency

Newborn Screening. Pediatrics, 152(2), e2023062100.
https://publications.aap.org/pediatrics/article-abstract/152/2/e2023062100/192800

Ream, M. A., Lam, W. K., Grosse, S. D., Ojodu, J., Jones, E., Prosser, L. A., ... & Kemper, A. R. (2023). Evidence and recommendation for mucopolysaccharidosis type II newborn screening in the United States. *Genetics in Medicine*, *25*(2), 100330.
https://www.sciencedirect.com/science/article/pii/S1098360022009984

Taylor, M., Khan, S., Stapleton, M., Wang, J., Chen, J., Wynn, R., ... & Tomatsu, S. (2019). Hematopoietic stem cell transplantation for mucopolysaccharidoses: past, present, and future. Biology of Blood and Marrow Transplantation, 25(7), e226-e246.

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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)
National Organization for Rare Disorders (NORD)/ Family member	Nick Kirchhof, Colorado Volunteer State Ambassador
Wyoming Department of Health (WYDOH)	Meg Callahan, Newborn Screening Coordinator
	Carleigh Soule, Women and Infant Health Program Manager
Rocky Mountain Pediatric Endocrinology (RMPE)	Dr. Aristides Maniatis
Children's Hospital Colorado (CHCO)/ University of Colorado	Dr. Cullen Dutmer, Immunology
	Dr. Scott Sagel, Cystic Fibrosis
	Dr. Stacey Martiniano, Cystic Fibrosis
	Erica Wright, Genetic Counselor
	Melissa Gibbons, Genetic Counselor
	Dr. Peter Baker, Inherited Metabolic Disease (IMD)

	Dr. Mark Abzug, Infectious Disease
	Dr. Brian Herrman, ENT
	Dr. Patricia Yoon, ENT
	Dr. Shawn McCandless, (IMD)
Rocky Mountain Hospital for Children	Dr. Ryan Mitchell, ENT
UCHealth University of Colorado Hospital	Dr. Mary Kohn
	Anne Behring, RN
UCHealth Fort Collins	Dr. Dan Satterwhite, neonatologist
University of Colorado / Sickle Center	Donna Holstein, Nurse
	Dr. Kathryn Hassell
Denver Health System	Dr. Tammy Wang, ENT
St. Francis Hospital	Dr. Bridget Buzzella, neonatologist
HealthOne system	Dr. Rachel Wright, pediatrician
Primary Care Partners Grand Junction	Dr. Patrice Whistler, Pediatrics
Center for Public Health Innovation (CPHI)	Marci Sontag, PhD
	Yvonne Kellar-Guenther, PhD
American Academy of Pediatrics (AAP)	Dr. Ted Maynard
Colorado Hands & Voices	Jami Fries, Director, cCMV parent Megan Nix, cCMV parent
Colorado Department of Public Health and Environment	Scott Bookman, Senior Division Director

(CDPHE)	Emily Travanty, PhD, Laboratory Director
	Gregory Bonn, Newborn Screening (NBS) Program Manager
	Kathy Inkhamfong, NBS Follow-Up and Education Supervisor
	Kendra Jones, NBS Scientist
	Leanne Glenn, Newborn Hearing Screening Program
	Karli Callaway, NBS Project Coordinator
Colorado Department of Human Services	Arlene Stredler-Brown, Early Hearing Detection and Intervention Program (EHDI)

The Department contacted a wide variety of stakeholders to solicit input on these proposed amendments. External stakeholders included advocacy groups, laboratory personnel, pediatricians, registered nurses (RNs), midwives, and other health care providers from pediatric offices and birthing centers. Due to consistent contract monitoring, external stakeholders also included contracted health care specialists and their input was assessed during quarterly stakeholder meetings. In addition to the stakeholder meetings, a bi-monthly newsletter was sent to stakeholders, which included a link to a survey to gather input about the addition of the three new disorders. Stakeholders can also access the survey via the program's webpage, and sharing it is encouraged.

The stakeholder meeting on March 21, 2023 included a presentation from Dr. Ted Maynard about the addition of cCMV testing. Prior stakeholder meetings in 2022 discussed different approaches to adding cCMV testing to blood spots. Stakeholders expressed their interest in adding cCMV initially as a test for newborns who failed their hearing test. This would be the initial first step prior to requesting population-based testing for cCMV.

On June 20, 2023, an agenda item of the stakeholder meeting was the addition of the remaining two conditions that are currently on the RUSP and not on the CONBSP panel. Experts in testing and treatment of these conditions provided detailed information to inform the stakeholder discussion. Stakeholders expressed their interest in adding these two conditions to the CONBSP panel.

On September 19, 2023, an agenda item of the stakeholder meeting was the addition of the remaining two disorders MPS II and GAMT, which are currently on the RUSP and not on the

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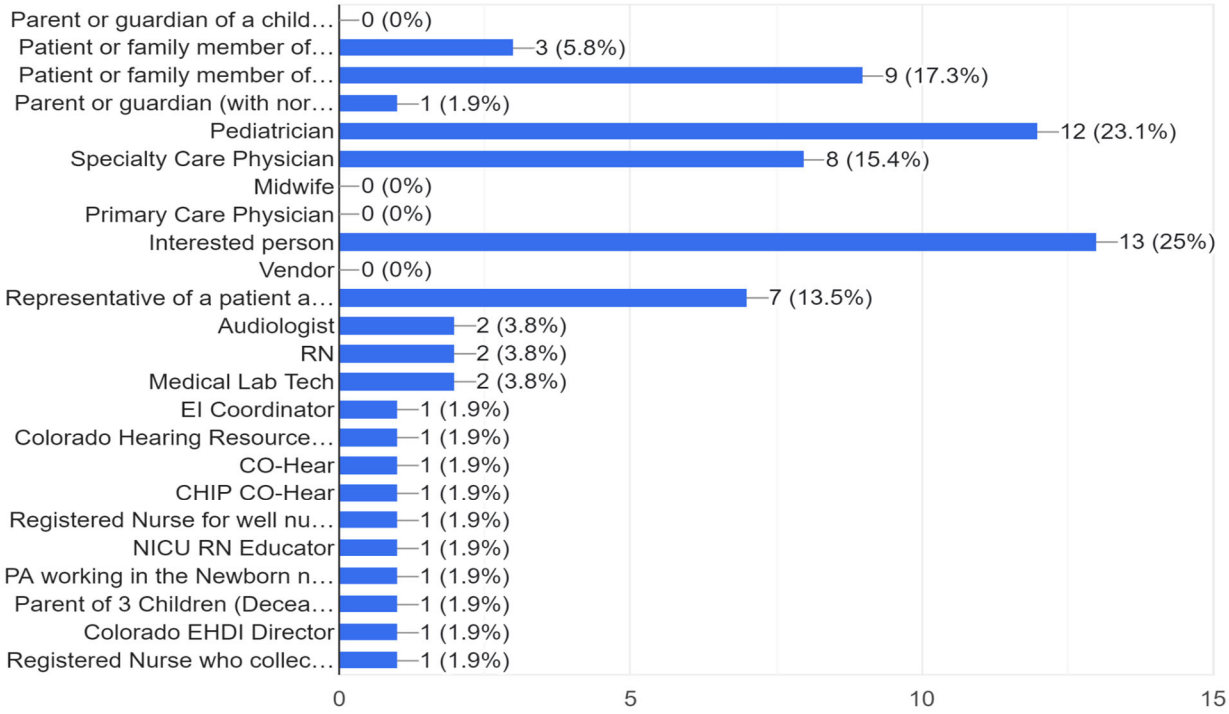
CONBSP panel. The stakeholders also discussed cCMV, and physicians expressed their interest in adding it to Colorado's panel. During the meeting, department staff also mentioned the survey to ensure stakeholders knew about and could share it. Stakeholder support for the addition of the conditions has remained consistent.

Connection to newborn screening community (52 responses)



Reference for above table in order from top to bottom: 1. Parent or guardian of a child with a false positive screen result. 2. Patient or family member of a child with a condition currently on the Colorado Newborn Screening panel. 3. Patient or family member of a child with a condition NOT currently on the Colorado Newborn Screening panel. 4. Parent or guardian (with normal test results or no experience with Newborn screening). 5. Pediatrician. 6. Specialty Care Physician. 7. Midwife. 8. Primary Care Physician. 9. Interested Person. 10. Vendor. 11. Representative of a patient advocacy group. 12. Audiologist. 13. RN. 14. Medical Lab Tech. 15. El Coordinator. 16. Colorado Hearing Resource Coordinator - CO-Hear. 17. CO-Hear. 18. CHIP CO-Hear. 19. Registered Nurse for well nursery. 20. NICU RN Educator. 21. PA working in the Newborn nursery at Denver Health. 22. Parent of 3 Children (Deceased) with MPS III B. 23. Colorado EHDI Director. 24. Registered Nurse who collects Newborn Screen samples and educates families.

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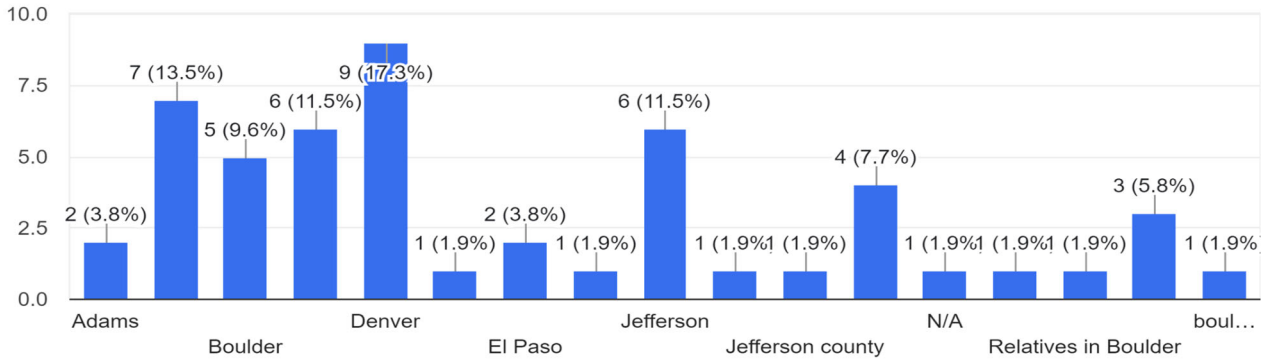
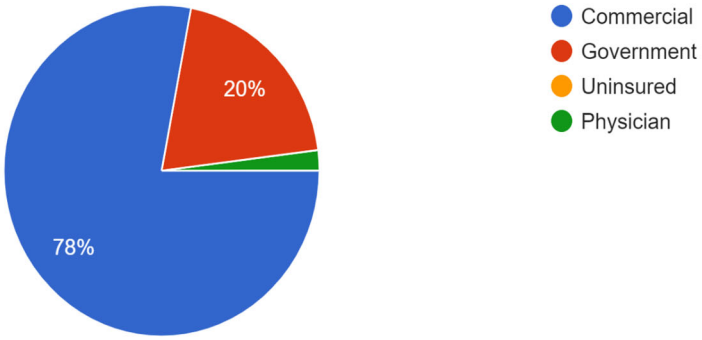
County of residence (52 responses)



Insurance status (50 responses)



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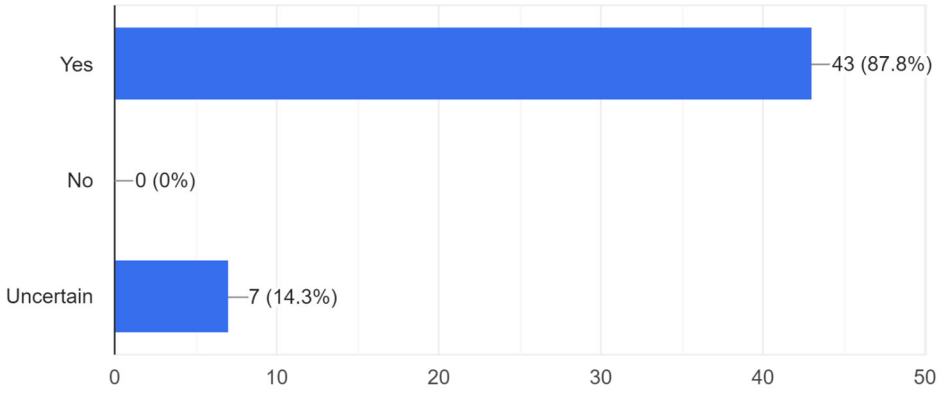
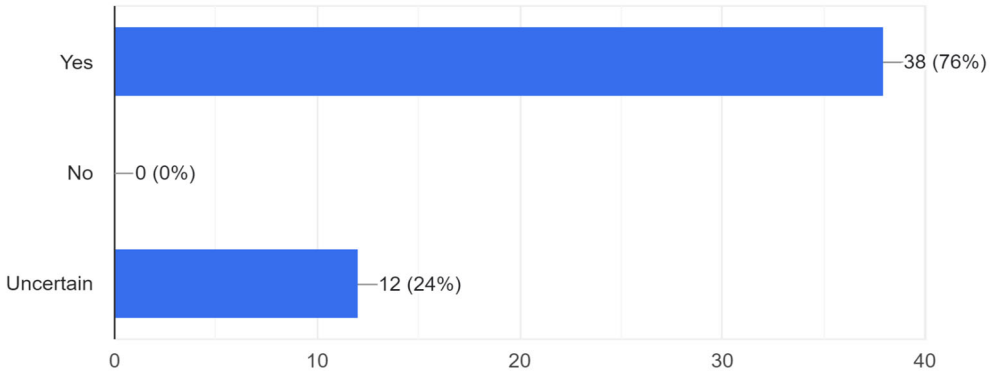
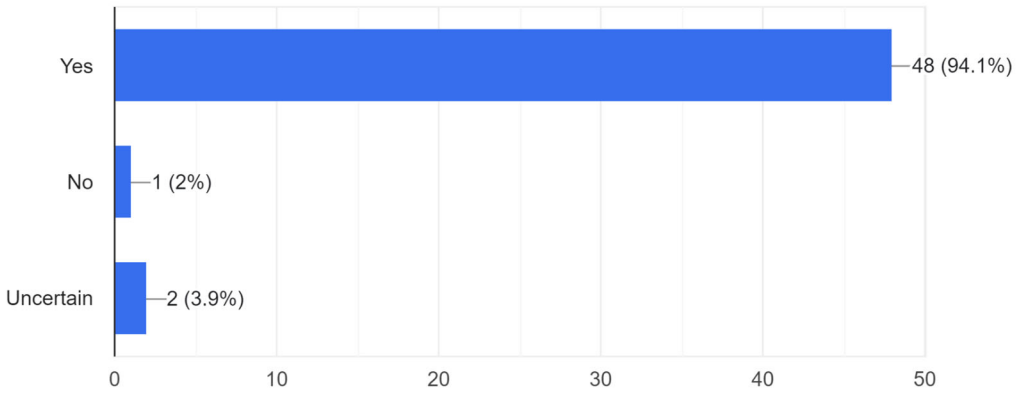
Responses for adding MPS-II to the Colorado Newborn Screening Panel (49 Responses)



Responses for adding GAMT to the Colorado Newborn Screening Panel (50 Responses)



Responses for adding cCMV to the Colorado Newborn Screening Panel (51 Responses)



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DEPARTMENT OF PUBLIC HEALTH AND ENVIRONMENT
Division of Disease Control and Public Health Response
NEWBORN SCREENING AND SECOND NEWBORN SCREENING

5 CCR 1005-4

Adopted by the Board of Health on March 17, 2021. Effective May 15, 2021.

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 Argininosuccinic Acidemia
2.4.17 Citrullinemia
2.4.18 Tyrosinemia
2.5.19 Hypermethioninemia
2.4.20 Maple Syrup Urine Disease
2.4.21 Homocystinuria

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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
2.4.37 Glycogen Storage Disease Type II (POMPE DISEASE)
2.4.38 Mucopolysaccharidosis Type 1 (MPS1)
2.4.39 X-Linked Adrenoleukodystrophy (X-ALD)
2.4.40 Mucopolysaccharidosis type 2 (MPS2)
2.4.41 Guanidinoacetate Methyltransferase Deficiency (GAMT)
2.4.42 Congenital Cytomegalovirus (cCMV) Screening of the following newborns:
2.4.42.1 All newborns who do not pass the initial hearing screen or who have not had a newborn hearing screen completed by day 10 of life, as determined by birth certificate or other testing facility records filed with the Department
2.4.42.2 All newborns for whom a medical provider has requested testing based on signs or symptoms related to hearing loss and/or cCMV
2.4.42.3 All newborns who meet the low birth weight standard as established by the Department.