COLORADO
Department of Public Health & Environment

Dedicated to protecting and improving the health and environment of the people of Colorado

To: Members of the State Board of Health

From: Dan Wright, Newborn Screening Program Manager, Laboratory Services Division

Through: Laura Gillim-Ross, Division Director, Laboratory Services Division *LGR*

Date: July 1, 2015

Subject: **Request for Rulemaking Hearing**
Proposed Amendments to 5 CCR 1005-4, Newborn Screening and Second Newborn Screening, with a request for the rulemaking hearing to occur in September, 2015.

We are requesting that the Board of Health amend 5 CCR 1005-4 to include Pompe Disease as the 36th disorder on the Colorado Newborn Screening (NBS) Panel. This proposal is in response to the recommendation made by the Colorado NBS Advisory Committee, in January, 2015, to add Pompe to the panel. The Colorado NBS advisory committee made this recommendation following action by the federal Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC). SACHDNC voted to add Pompe disease to the Recommended Uniform Screening Panel (RUSP) in May 2013 following an **objective evidence review and public health impact assessment.** The Secretary of Health and Human Services (Sylvia Mathews Burwell) approved Pompe disease for addition to the RUSP in March 2015.[1]

Pompe Disease is an inborn error of metabolism in which the deficiency of the enzyme acid alpha-glucosidase (GAA) results in accumulation of excess glycogen. This accumulation of glycogen leads to progressive weakness/damage of muscles and cardiomyopathy. Those with the infantile-onset disease begin to show symptoms within the first days of life with cardiac, musculoskeletal, respiratory, and gastrointestinal involvement. Aside from massive cardiomyopathy and muscle weakness, patients with infantile-onset Pompe disease will have respiratory insufficiency and recurrent infections, poor feeding, and poor growth. If untreated, patients with infantile-onset Pompe disease will often die within the first year of life from cardiac failure or secondary respiratory disease.[2] Patients with late-onset Pompe disease have symptoms after one year of age with progressive skeletal muscle symptoms and respiratory involvement but with slower progression. They may or may not have cardiac involvement. Lifespan is also shortened.[3]

Pompe disease is treated with enzyme replacement therapy (ERT) administered once every two weeks by intravenous (IV) infusion. ERT is an effective treatment, but not curative. Data shows improved survival if treatment is initiated within the first 6 months of life with normalization of cardiac size.[4] **However, ERT does not reverse skeletal muscle damage**.[5] Therefore, initiation of treatment within the first weeks of life results in the best outcomes.[6] Recent published literature reported on 10 patients with infantile-onset Pompe diagnosed by newborn screening that began receiving treatment between 6-34 days of life. After a median

treatment time of 63 months (28-90 months), all could walk independently and none required mechanical ventilation (breathing machine). All 10 patients were able to participate in daily activity but did show some muscle weakness, speech issues, and eye muscle weakness.[7]

Based on anonymous screening of newborn dried blood spots, the incidence of Pompe disease was found to be 1 in 28,000.[8] Approximately 30% of patients have infantile onset.[2] Therefore in Colorado, there should be about 1 patient diagnosed clinically with infantile onset every 1-2 years. However, per the specialists in Colorado, there have only been two patients diagnosed clinically during the last 12 years since enzyme replacement therapy has been a viable option for treatment.

There has been limited controversy regarding newborn screening for Pompe disease. Following SACHDNC's recommendation to add Pompe disease to the RUSP, some states voiced concern regarding their readiness to add another disorder to the panel due to both financial and programmatic constraints. In Colorado, it has been more than 3 years since the last disorder was added to the NBS blood spot panel. Hence, the CDPHE Newborn Screening Program is prepared to add an additional disorder to the panel. Another concern is the identification of patients with pseudo-deficiency via newborn screening. These patients are found to have lower than average enzyme activity but do not have disease and therefore require no management or treatment.[9] Identification of pseudo-deficiencies by newborn screening causes unnecessary parental anxiety and stress. The newborn screening laboratory plans to conduct screening utilizing tandem mass spectrometry to limit false positives caused by pseudo-deficiency.

To conclude, the justification for the addition of Pompe disease to Colorado's newborn screening panel is as followed:

- Proven technology allowing for population based screening of Pompe disease via newborn screening on dried blood spots.
- Proven treatment with outcome showing significant reduction of morbidity and mortality especially in most patients with infantile-onset Pompe Disease.
- Currently, patients with infantile-onset Pompe disease are either missed or treated late after significant muscle damage has occurred.
- Although cost of ERT is high, there would likely be a net savings since early diagnosis provides opportunity for appropriate disease-specific intervention. Accurate and timely diagnosis is proven to avoid medical complications thereby eliminating unrelated testing and significantly reducing the number and average length of hospital stays, emergency and costly intensive care services.
- Colorado now screens for 31 out of 32 of the core disorders on the RUSP.[10] With the addition of Pompe Disease, Colorado will have one of the most comprehensive newborn screening panels in the country.

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:
Under Section §25-4-803 and §25-4-1004(1) (b), C.R.S., the Board of Health has the authority to add conditions to the newborn screening panel.

Prior to this amendment, the newborn screening regulations provided that babies born in Colorado would be screened for a total of thirty-five disorders. In May, 2013, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children voted to recommend adding Pompe disease to the core panel of the Recommended Uniform Screening Panel (RUSP) following an objective evidence review and public health impact assessment.[11] The Secretary of Health and Human Services approved Pompe disease for addition to the RUSP in March 2015.[1] Additionally, the Colorado Newborn Screening Advisory Committee has concluded that Pompe disorder warrants inclusion in the Colorado panel of disorders.

The Colorado Newborn Screening and Genetic Counseling and Education Act, §25-4-1001 to 1006 C.R.S., specifies the criteria for the inclusion of disorders for newborn screening. These criteria are:

1. "Condition for which the test is designed presents a significant danger to the health of the infant or his family." Pompe disease is an inborn errors of metabolism in which the deficiency of the enzyme acid alpha-glucosidase (GAA) results in accumulation of excess glycogen. This accumulation of glycogen leads to progressive weakness/damage of muscles and cardiomyopathy. There is a broad clinical spectrum of the disease. Patients presenting with symptoms within the first year of life are classified as infantile-onset Pompe disease. Infantile-onset Pompe disease accounts for approximately 30% of patients. Patients presenting after the first year of life are classified as late-onset. Those with infantile-onset Pompe disease begin to show symptoms within the first days of life with cardiac, musculoskeletal, respiratory, and gastrointestinal involvement. These symptoms include massive cardiomegaly and cardiomyopathy, progressive muscle weakness with muscle wasting, secondary respiratory insufficiency and recurrent infections, poor feeding, and poor growth. Patients with infantile-onset are cognitively normal. If untreated, patients with infantile-onset Pompe disease will often die within the first year of life from cardiac failure or secondary respiratory disease.[2] Patients with late-onset Pompe disease may or may not have cardiac involvement. They have progressive skeletal muscle symptoms and respiratory involvement but with slower progression. Often the muscle weakness can go unrecognized in childhood. Many seek care in adulthood but diagnosis is often delayed by 8-10 years. If unrecognized and untreated, lifespan is shortened.[3]

   "Condition is amenable to treatment." Patients with Pompe disease are treated with enzyme replacement therapy (ERT) administered once every two weeks by intravenous infusion. ERT is an effective treatment, but not curative. Data shows improved survival if treatment is initiated within first 6 months of life with normalization of cardiac size.[4] However, ERT does not reverse skeletal muscle damage.[5] Therefore, initiation of treatment within first weeks of life would result in best outcome.[6]

Outcome of treatment is also influenced by CRIM status (cross reacting immunologic material). CRIM+ patients (75%) have some residual enzyme activity. Therefore, CRIM+ patients do not typically produce significant antibodies to ERT and hence, have a generally better response to ERT. CRIM- patients (25%) have no residual enzyme activity and historically have a poor response to ERT with minimal functional gains. However, new research shows that immune-modulation prior to or simultaneous to ERT can decrease antibody titer and improve response to therapy.[12]

Recent published literature reported on 10 patients (all CRIM+) with infantile-onset Pompe diagnosed by newborn screening that began receiving treatment between 6-34 days of life. After a median treatment time of 63 months (28-90 months), all could walk independently and none required mechanical ventilation (breathing machine). All 10 patients were able to participate in daily activity but did show some muscle weakness, speech issues, and eye findings.[7] Data from the Genzyme Pompe registry showed improved survival and mechanical ventilation free status for patients with infantile-onset Pompe disease that were treated prior to 3 months of age (includes both CRIM+ and CRIM-).[11]

Initiation of ERT in clinically diagnosed late-onset Pompe patients has been proven to improve outcome.[13] However, there is no data evaluating presymptomatic treatment in this population. Since ERT cannot reverse muscle damage, experts in the field predict that presymptomatic treatment in late-onset patients will have benefit while others recommend close monitoring for subclinical muscle findings.[11,14]

2. "Incidence of the condition is sufficiently high to warrant screening." The incidence of Pompe disease was historically reported as 1 in 40,000. However, recent anonymous screening of dried blood spots followed by confirmatory DNA studies in Washington state found an incidence of 1 in 28,000.[8] Approximately 30% of clinically diagnosed patients have infantile-onset Pompe disease.[2]

3. "The test to detect the condition meets commonly accepted standards of reliability." There are three techniques to perform newborn screening for Pompe: enzymatic, digital microfluidics, and tandem mass spectrometry (MS/MS). Recent data suggests that the MS/MS technique limits the number of patients with pseudodeficiencies that screen positive. Patients with pseudodeficiency have a lower enzyme activity than the general population, but do not have disease. Specifically, New York state reports that after screening 257,546 patients since October 2014 using MS/MS, only one patient was incidentally found to have a pseudodeficiency.[15] The CDPHE lab has been testing for other disorder using MS/MS technology and is very familiar and comfortable with this technology.

4. "Cost-benefit consequences of screening are acceptable." Cost per test is estimated to be $7.00 per newborn including follow-up. This cost benefit is comparable to the other disorders currently screened for in Colorado. Although cost of treatment with enzyme replacement therapy is high at $100,000-300,000 per year, there would likely be a net savings since early diagnosis provides opportunity for appropriate disease-specific intervention. Accurate and timely diagnosis is proven to avoid medical complications such as recurrent respiratory illnesses, mechanical ventilation, cardiac failure, and loss of ambulation, thereby eliminating unrelated testing and significantly reducing the number and average length of hospital stays, emergency room care and costly intensive care services.[4, 6, 7, 11]

Specific Statutory Authority: These rules are promulgated pursuant to the following statutes:
Sections 25-4-801 through 25-4-804 and 25-4-1004, C.R.S

SUPPLEMENTAL QUESTIONS

Is this rulemaking due to a change in state statute?

_____ Yes, the bill number is _____; rules are ___ authorized ___ required.
__X___ No

Is this rulemaking due to a federal statutory or regulatory change?

_____ Yes
__X___ No

Does this rule incorporate materials by reference?

_____ Yes
___X__ No

Does this rule create or modify fines or fees?

_____ Yes
__X _ No

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

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

The costs for implementation of screening for Pompe will be borne by the CDPHE laboratory using NBS fund balance.

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.

Quantitative: An estimated three newborns with a significant treatable defect will be discovered every two years allowing for the initiation of appropriate treatment procedures.[8] One out of these three infants identified will have infantile onset Pompe disease. Untreated infants with infantile onset Pompe disease typically die within the first year of life.[2] Late treated infants with infantile onset Pompe disease will be at high risk for death, mechanical ventilation, and significant irreversible muscle damage.[11] Patients on mechanical ventilation have recurrent respiratory infections requiring frequent hospitalizations including admissions to intensive care units. Patients that have severe muscle weakness will require wheelchairs and other expensive adaptive equipment. Patients with poor outcome will also require additional nursing care due to the complexity of their healthcare needs.

Qualitative: Parents of these newborns affected with the infantile form of the disorder will be spared the suffering of their children through severe health issues and the death of their baby within the first year of life. The family will be relieved of the protracted diagnostic and treatment burden associated with difficult to diagnose disorder. Treatment becomes more efficacious with early diagnosis and the child benefits from better outcome. The Colorado Newborn Screening program will be recognized as meeting current standard of care for newborn screening nationally.

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.

The CDPHE NBS fund balance will be used to cover the initial cost of implementation.

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

It is estimated that it will cost $471,000 annually to implement this rule change. The CDPHE NBS fund balance will be used to cover the initial cost of implementation. To take no action will result in death or significant disability of approximately one Colorado newborn per every one to two years in undiagnosed or late treated patients with infantile-onset Pompe disease. Outcome measures typically reported on for Pompe disease are survival and mechanical ventilation status. Recent published studies from Taiwan show that in the cohort of 10 patients with infantile onset Pompe disease diagnosed by newborn screening and thus began ERT within the first weeks of life (6-34 days) maintained mechanical ventilation free throughout the course of the

reporting period (median treatment time of 63 months with range of 28-90 month). All ten patients were alive and independently walking at the time of reporting.[7] Unpublished data provided by the Genzyme registry showed that in patients with infant onset Pompe disease with treatment initiated greater than 3 months of age, the survival rate at 36 months of age in the cohort of 96 patients was 61.3%. Of the 65 patients alive at 36 months, only 55.3% remained mechanical ventilation free.[11]

Health care costs for patients on mechanical ventilation are exceedingly high due to frequent respiratory infections and hospital admissions. Although costs of treatment with ERT are high, there would likely be a net savings since early diagnosis provides opportunity for appropriate disease-specific intervention. Accurate and timely diagnosis is proven to avoid medical complications thereby eliminating unrelated testing and significantly reducing the number and average length of hospital stays, emergency and costly intensive care services.

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

No alternative is available.

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

No alternative to screening is available. The cost of supplemental screening through the private sector far exceeds the cost for CDPHE to perform screening in-house. Currently, parents could elect to have additional newborn screening performed on their child through a supplemental panel that includes Pompe disease. The only commercial panel available is through PerkinElmer Genetics and costs $199.00 for the additional screening.[16] Also, the screening through the commercial laboratory does not include the confirmatory testing costs if the newborn has abnormal results.

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.

Data was analyzed from the two largest cohorts of patients with infantile onset Pompe disease on treatment with a focus on outcome and age of initiation of ERT.

Data from the Taiwan Newborn Screening Program:[7]

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Long-Term Prognosis of Patients with Infantile-Onset Pompe Disease Diagnosed by Newborn Screening and Treated since Birth

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Objective To determine the benefit of newborn screening for the long-term prognosis of patients with classic infantile-onset Pompe disease (IOPD).

Study design A cohort of patients with classic IOPD were diagnosed by newborn screening, treated with recom- binant human acid a-glucosidase (rhGAA), and followed prospectively. Outcome measurements included survival, left ventricular mass, serum creatinine kinase, motor function, mental development, and systemic manifestations.

Results Ten patients who presented with left ventricular hypertrophy at diagnosis received rhGAA infusions starting at a median age of 16 days (6-34 days). All patients were cross-reactive immunologic material-positive. After a median treatment time of 63 months (range 28-90 months), all could walk independently, and none required me- chanical ventilation. All patients had motor capability sufficient for participating in daily activities, but muscle weak- ness over the pelvic girdle appeared gradually after 2 years of age. Ptosis was present in one-half of the patients, and speech disorders were common. Anti-rhGAA antibody titers were low (median maximal titer value 1:1600, range: undetectable rv 1:12 800).

Conclusion By studying patients treated since birth who have no significant anti-rhGAA antibody interference, this prospective study demonstrates that the efficacy of rhGAA therapy is high and consistent for the treatment of classic IOPD. This study also exposes limitations of rhGAA treatment. The etiology of the manifestations in these early-treated patients will require further study. (J Pediatr 2015;166:985-91).

Data from the Pompe Disease Registry (unpublished date previously provided to the external Condition Review Workgroup as part of SACHDNC process, obtained permission from Genzyme to reproduce for purpose of rule change):[11]

Findings from the Pompe Disease Registry

We requested that Genzyme query the Pompe disease registry to compare survival and ventilator-free survival comparing those who began ERT before 3 months of age to those who began ERT at three months of age and older for those with classic infantile-onset Pompe disease. The results of this request as directly reported appear in the box below. Genzyme provided two analyses. The first includes all subjects in the database, and the second excludes those managed in Taiwan, many of whom would have been detected by newborn screening and have higher rates of ventilator-free survival. The second table in this analysis describes the expected outcomes for clinically detected cases.

Survival Outcomes for Infantile-Onset Pompe Disease by Age at First ERT:

Findings from the Pompe Disease Registry

Summary

Patients from the Pompe Registry with symptom onset ≤12 months of age with evidence of cardiomyopathy who received their first treatment with ERT prior to 3 months of age report better survival and invasive ventilator-free survival at 12 months, 24 months, and 36 months of age than patients who received their first treatment with ERT at 3 months of age or older.

Results

Table 3.4. All Patients with Symptom Onset ≤12 months of age with Evidence of Cardiomyopathy

	Age of First Treatment	
	ERT <3 months	ERT ≥3 months
Survival	(Percent Surviving (95% CI))	
	n=36	n=104
12 months	94.1% (78.5, 98.5)	91.3% (84.0, 95.4)
24 months	84.6% (66.8, 93.3)	73.3% (63.3, 81.0)
36 months	80.9% (62.2, 91.0)	63.5% (52.7, 72.5)
Mechanical Ventilation-Free Survival		
	n=24	n=69
12 months	91.3% (69.5, 97.8)	89.8% (79.8, 95.0)
24 months	81.7% (58.2, 92.7)	66.4% (53.1, 76.8)
36 months	76.2% (51.7, 89.4)	56.5% (42.6, 68.2)

Table 3.5. Patients with Symptom Onset ≤12 months of age with Evidence of Cardiomyopathy, Excluding Patients from Taiwan

	Age of First Treatment	
	ERT <3 months	ERT ≥3 months
Survival	(Percent Surviving (95% CI))	
	n=30	n=96
12 months	92.9% (74.3, 98.2)	90.6% (82.7, 95.0)
24 months	81.0% (60.2, 91.7)	72.1% (61.5, 80.3)
36 months	76.5% (54.8, 88.8)	61.3% (49.9, 70.9)
Mechanical Ventilation-Free Survival		
	n=20	n=65
12 months	89.5% (64.1, 97.3)	89.2% (78.6, 94.6)
24 months	77.5% (50.5, 91.0)	65.9% (52.1, 76.7)
36 months	71.1% (43.6, 86.9)	55.3% (40.9, 67.5)

Discussion

The analysis is descriptive in nature; no adjustments have been made for severity of disease or any potential confounding factors that may influence the time of diagnosis, the time of treatment, length of survival or ventilator-free survival, or variables that may influence censoring (i.e. loss to follow-up in the Registry).

The Pompe Registry does not collect information on newborn screening. Because patients from Taiwan may have been identified by newborn screening (and not clinically diagnosed), all patients from Taiwan were excluded from the analysis presented in Table 4.2.

Data are not presented for patients with symptom onset ≤12 months without evidence of cardiomyopathy. No deaths from this population meeting the study criteria were reported to the Registry.

Methods

All treated patients in the Pompe Registry with symptom onset ≤12 months with a record of treatment with ERT were eligible for analyses. Patients were stratified into those with and without evidence of cardiomyopathy; and data for patients with cardiomyopathy were included.

Kaplan-Meier curves were fitted, stratified by those patients with a record of first infusion <3 months of age or ≥3 months of age, for the population with symptom onset ≤12 months and evidence of cardiomyopathy. Events were defined as (1) death, and (2) use of invasive ventilation therapy or death. The time to the event was derived as time from birth. Only patients at risk for the event were included in the Kaplan-Meier analyses.

The 95% confidence intervals (CIs) of event-free survival are reported from the Kaplan-Meier estimation. The CIs are calculated using a transformation of the log (-logS(t)) function; the limits are then transformed back to the survival function.

Patients with a reporting physician from Taiwan were excluded from the second analysis.

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

The following individuals and/or entities were included in the development of these proposed rules:

Colorado Newborn Screening Advisory Committee

- Committee composed of community health care providers (pediatrician, family practice physician, obstetrician, nurse, midwife), pediatric specialists (endocrinologists, geneticist, pulmonologist, immunologist, neonatologist, hematologist, genetic counselor), consumers, and representatives from entities with vested interest in newborn screening (March of Dimes, AAP, Colorado Hospital Association)

Inherited Metabolic Diseases Clinic at Children's Hospital Colorado/University of Colorado Denver
States currently screening for Pompe disease

The following individuals and/or entities were notified that this rule-making was proposed for consideration by the Board of Health:

Colorado Hospital Association
Hospitals and midwives contacts were notified via CDPHE newborn screening distribution list. List includes hospital laboratory supervisors and managers and labor and delivery nurses, and other pertinent personnel involved in the newborn screening process.
Hospitals and birthing facilities were notified through the CDPHE Health Facilities Portal

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 opposition was encountered during the stakeholder meetings. The only comments provided by the stakeholders were positive. Feedback consisted of questions surrounding logistics for the hospitals and midwives as well as outcome of Pompe disease with early diagnosis. For example:

- Will extra blood need to be collected?
  - Answer: no
- Will hospitals have enough lead time to add this disease to their respective computer systems?
  - Answer: Hospitals should have almost a year after the rule hearing.
- Will the price of the screening increase and if so, how much?
  - Answer: No, there will be no fee increase at this time.
- Is outcome improved in patients diagnosed with Pompe disease via newborn screening?
  - Yes, we reviewed data regarding age of initiation of treatment and outcome.
- Is there dietary modification that will improve outcome?
  - No, the only proven treatment is enzyme replacement therapy.
- Will there be long-term monitoring of labs by community hospitals?
  - The vast majority of treatment and monitoring labs will be obtained at Children's Hospital Colorado.

It was also mentioned that further comments or questions could be forwarded through the original invitation email of to the NBS Program Manager whose email address was given during the meeting.

Please identify health equity and environmental justice (HEEJ) impacts. Does this proposal impact Coloradoans equally or equitably? Does this proposal provide an opportunity to advance HEEJ? Are there other factors that influenced these rules?

Mandated newborn screening for Pompe disease reduces health care disparities by ensuring that newborns receive equal access to timely diagnosis and treatment regardless of race, ethnicity, socioeconomic status, and geography.

Department of Public Health and Environment

~~**Laboratory Services Division**~~

NEWBORN SCREENING AND SECOND NEWBORN SCREENING

5 CCR 1005-4

Effective Date: July 1, 2016

NEWBORN SCREENING REGULATIONS

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1.6 List of Conditions for Newborn Screening

1.6.1 The Laboratory shall conduct screening tests for the following conditions:

1.6.1.1	Phenylketonuria
1.6.1.2	Congenital Hypothyroidism
1.6.1.3	Hemoglobinopathies
1.6.1.4	Galactosemia
1.6.1.5	Cystic Fibrosis
1.6.1.6	Biotinidase Deficiency
1.6.1.7	Congenital Adrenal Hyperplasia
1.6.1.8	Medium Chain Acyl-CoA dehydrogenase deficiency
1.6.1.9	Very Long Chain Acyl-CoA dehydrogenase deficiency
1.6.1.10	Long-Chain L-3-Hydroxy Acyl-CoA dehydrogenase deficiency
1.6.1.11	Trifunctional protein deficiency
1.6.1.12	Carnitine Acyl-carnitine translocase deficiency
1.6.1.13	Short Chain Acyl-CoA dehydrogenase deficiency
1.6.1.14	Carnitine palmitoyltransferase II deficiency
1.6.1.15	Glutaric acidemia Type 2
1.6.1.16	Arginosuccinic acidemia
1.6.1.17	Citrullinemia
1.6.1.18	Tyrosinemia

23		1.6.1.19	Hypermethionemia
24		1.6.1.20	Maple Syrup urine disease
25		1.6.1.21	Homocystinuria
26		1.6.1.22	Isovaleric acidemia
27		1.6.1.23	Glutaric acidemia Type 1
28		1.6.1.24	3-hydroxy-3-methylglutaryl-CoA Lyase deficiency
29		1.6.1.25	Multiple Carboxylase deficiency
30		1.6.1.26	3-methylcrotonyl-CoA carboxylase deficiency
31		1.6.1.27	3-methylglutaconic aciduria
32		1.6.1.28	Methylmalonic acidemias
33		1.6.1.29	Propionic acidemia
34		1.6.1.30	beta-Ketothiolase deficiency
35		1.6.1.31	Carnitine uptake defect
36		1.6.1.32	Arginase deficiency
37		1.6.1.33	Malonic acidemia
38		1.6.1.34	Carnitine palmitoyltransferase deficiency 1A
39		1.6.1.35	Severe Combined Immunodeficiency
40		1.6.1.36	POMPE DISEASE
41			
42	*****		