ENTERAL FORMULA FOR THE LIFE-LONG TREATMENT OF INBORN ERRORS OF METABOLISM

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BACKGROUND

Inborn errors of metabolism (IEM) are genetic disorders that impact the function of enzymes leading to the abnormal metabolism of protein, fat, or carbohydrate. Due to the lack of sufficient enzyme activity, one or more byproducts of the incomplete biochemical process accumulate to toxic levels within the individual, while other compounds may become deficient. Without early identification and medical intervention, these disorders can lead to developmental delay, irreversible cognitive dysfunction, and life-threatening metabolic crises. Treatment for many of these disorders consists of a diet low in protein, fat, or carbohydrate and daily supplementation of essential nutrients via enteral formula. Medical treatment guidelines over the last ten years reflect a consensus that this therapy must be maintained throughout the lifespan.[1-9] Table 1 summarizes the formula-component of the current treatment guidelines for the most prevalent IEM disorders and their rates of detection.

ISSUE

In Michigan, private insurance coverage of enteral formula – the mainstay of treatment for many IEM disorders – appears to be inadequate. Many health plans specifically exclude enteral formula when administered orally. These formulas are expensive – ranging from $1,125 to $15,000 annually depending upon age and dietary requirements, but averages about $8,550 per year.[11] Formula costs are in addition to typical food expenditures for these patients, placing a financial burden on the families dealing with these disorders that ultimately impacts treatment compliance. Exclusion of orally-administered enteral formulas for the treatment of IEM threatens the physical, cognitive, and emotional health of these beneficiaries. This issue brief provides an overview of enteral formula treatment for IEM and highlights insurance policy language that better reflects current standards of medical practice and reduces barriers to treatment compliance.

When proper documentation of medical necessity is submitted to the insurer, an enteral formula policy for the treatment of IEM should **INCLUDE**:

- coverage when administered **ORALLY**,
- board certified clinical or medical biochemical geneticist as an authorized ordering provider type,
- coverage for all “heritable diseases of metabolism” as denoted by ICD
- formula reimbursement rates comparable to current Michigan Medicaid policy.

An enteral formula policy for the treatment of IEM should **NOT INCLUDE**:

- age-, weight- or height- based restrictions,
- minimum caloric-intake threshold
- monthly or annual coverage maximums
- requirement of a recent albumin blood level

DISCUSSION

The Michigan Newborn Screening (NBS) Program, which screens for forty-two IEM, estimates that 315 patients are currently on a compound-replacement formula as part of their IEM treatment regimen, or about 3.18 patients per 100,000 Michigan residents. About 75% of these patients have phenylketonuria (PKU), with maple syrup urine disease, very long-chain acyl-CoA dehydrogenase deficiency, and argininosuccinic acidemia making up another 11% of IEM patients. These numbers do not incorporate non-compliant IEM patients, nor those with disorders not included on the NBS panel who nevertheless require formula, such as ornithine transcarbamylase deficiency and glycogen storage disease type 1.

Medical Necessity

Enteral formula is necessary for the treatment of IEM disorders when a compound-restricted diet leaves the patient deficient in other essential nutrients. For example, individuals with PKU are placed on a strict low-protein diet to restrict the intake of the offending amino acid, phenylalanine. Since protein also contains eight essential amino acids other than phenylalanine, the diet must be supplemented with at least these deficient nutrients via an amino acid-based enteral formula. Without the additional calories and other nutrients provided by this formula, the low-protein diet would leave these patients malnourished to the point of being incompatible with life.[11] Enteral formulas provide these missing essential nutrients for individuals with other IEM disorders in a manner similar to the PKU scenario.

For infants diagnosed with an IEM disorder, prompt nutritional treatment including replacement of essential nutrients via special enteral formula is vital. Untreated infants with these disorders will eventually suffer from any one, or a combination, of irreversible brain damage; poor physical development; progressive neurological disorders such as seizures and comas; metabolic crises; or death; among other complications.[12-14]

There is no evidence in the literature base suggesting that enteral formula may be discontinued after the age of two – or at any point during childhood. In fact, for the overwhelming majority of IEM patients, the medical necessity of enteral formula never diminishes with age. Adolescents and even adults must maintain their prescribed diet, including enteral formula, in order to maintain safe levels of otherwise toxic compounds in the blood. Females of reproductive age and pregnant women with IEM warrant special consideration, since the risk of developmental delay and congenital malformations of the offspring increases substantially without strict dietary control.[7]

Discontinuing dietary treatment altogether in adulthood has been shown to result in behavioral executive functioning deficits, phobias, depression, tremors, and gradual neurological deterioration.[7,11,15,16] Even temporarily suspending treatment puts an individual at risk for these complications, as returning to the strict treatment regimen is difficult due to the intense organization and planning that is required.[7,17,18] These complications are not only disabling, but can hamper an individual's educational attainment and socioeconomic status,[7] becoming costly to the patient's family, insurers, and society as a whole.

Oral Administration

The majority of IEM patients do not require gastric tube feeding nor intravenously-administered supplements. Only in rare circumstances do patients lose the ability to swallow or absorb nutrients in the gut. In Michigan, these disorders are managed clinically by a team consisting of a board-certified clinical biochemical geneticist and a metabolic dietitian, and not a gastroenterologist. Severe cases of some IEM disorders may necessitate tube feeding due to neurological involvement or prolonged non-compliance of the prescribed dietary treatment. For most individuals with IEM, orally-administered enteral formulas actually prevent the need for future tube or intravenous placement.

Medicaid Coverage

On February 1, 2015, Michigan Medicaid revised its policies to align with current medical practice for the treatment of IEM disorders (Medicaid Bulletin MSA 14-66).[19] These policies now include coverage for orally- administered enteral nutrition when the beneficiary is identified with an IEM disorder via the International Classification of Disease upon prior authorization.[20] In addition to lifting the oral route exclusion, this modification also removed the requirement for documentation of albumin blood level; and coverage restrictions based upon the patient's weight and height, age, and caloric intake.

This policy change also raised the Medicaid fee screen for products billed under Healthcare Common Procedure Coding System (HCPCS) codes B4157 and B4162. Through a manual pricing mechanism, MDHHS reimburses the durable medical equipment provider the cost of the formula product plus an additional 17%.[21-23] This fee screen reduces the likelihood of DME providers refusing to service IEM patients because of low reimbursement rates – an issue identified previously for some publicly- and privately-administered health plans.[24]

CONCLUSION

Through life-long dietary management under the supervision of a board-certified clinical biochemical geneticist and metabolic dietitian, IEM patients can lead healthy and productive lives. Private insurers can help ensure optimal health outcomes for these individuals by including coverage of orally-administered enteral formula products intended for IEM treatment as a DME benefit. Moreover, insurers would be better aligned with current standards of medical practice by lifting coverage restrictions for these products that are based upon the patient's age, weight, or caloric intake; documentation of albumin blood level; subspecialization of ordering physician; and annual monetary limitations.

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Table 1: Formula Treatment Guidelines for Michigan's Most Prevalent IEM Disorders

Disorder	Detection Rate*	Maintenance Treatment Guideline	Reference
Amino Acid Metabolism Disorders			
Argininosuccinic Acidemia (ASA)	1.25 per 100,000	Life-long, orally-administered essential amino acid formula; possibly enriched with leucine, valine, and isoleucine when indicated.	Häberle et al., 2012[1] Singh et al., 2005[2]
Citrullinemia	0.54 per 100,000	Life-long, orally-administered essential amino acid formula; possibly enriched with leucine, valine, and isoleucine when indicated.	Häberle et al., 2012[1] Singh et al., 2005[2]
Homocystinuria	0.36 per 100,000	Life-long, orally-administered methionine-free, cysteine-enriched amino acid formula.	Huemer et al., 2015[3] ACMG, 2012[4]
Maple Syrup Urine Disease (MSUD)	0.54 per 100,000	Life-long, orally-administered enteral leucine-, isoleucine-, and valine-free amino acid based formula.	Frazier et al., 2014[5]
Phenylketonuria (PKU)	4.64 per 100,000	Life-long, orally-administered enteral phenylalanine-free amino acid based formula.	Singh et al., 2014[6] Vockley et al., 2014[7]
Fatty Acid Oxidation Disorders			
Very Long-chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)	1.61 per 100,000	Life-long, orally-administered medium-chain triglyceride-enriched formula from infancy through adulthood.	GMDI, 2008[8]
Organic Acid Metabolism Disorders			
Glutaric Acidemia Type 1	0.54 per 100,000	Orally-administered enteral lysine-free, tryptophan-reduced amino acid formula until at least 6 years of age.	Kölker et al., 2011[10]
Methylmalonic Acidemia (MMA)	2.32 per 100,000	Continuous (long-term) oral administration of methionine-free, valine-free, threonine-reduced, and isoleucine-reduced amino acid mixture with other essential nutrients.	Knerr et al., 2011[9]
Propionic Acidemia (PROP)	0.18 per 100,000	Continuous (long-term) oral administration of methionine-free, valine-free, threonine-reduced, and isoleucine-reduced amino acid mixture with other essential nutrients.	Knerr et al., 2011[9]
Total	**11.96 per 100,000**		

*Detection rate calculated using Newborn Screening data from 2010 to 2014, with a total of 560,275 Michigan newborns screened.

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