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# Medical Food for Treatment of Inborn Errors of Metabolism and State Legislative Mandates

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Newborn screening for inborn errors of metabolism (IEM) is a model of preventative medicine in public health. The primary treatment for about 30 IEM depends on medical foods as defined by federal legislation. Insurance reimbursement for medical foods in the United States is typically denied despite recognition of the therapeutic legitimacy of those foods. State legislation mandating medical food coverage represents a chaotic patchwork of laws limiting treatment of different disorders and medical food options. In addition, obstacles within the healthcare system also interfere with reimbursement. Families dealing with the same disorders in different states are faced with an inequitable financial burden. Federal standards for healthcare benefits should be established, recognizing the existence of rare diseases and the treatment requirements in relation to the developmental needs of children and adult metabolic homeostasis that will support uniform reimbursement. **Key words:** *children, healthcare, inborn errors of metabolism, medical food, reimbursement*

**N**EWBORN SCREENING (NBS) for inborn errors of metabolism (IEM) is a model of successful preventative medicine in public health.<sup>1</sup> Initiated more than 48 years ago in the United States, it affords the opportunity to reduce mortality, morbidity, and disabilities associated with treatable genetic metabolic conditions of the newborn. The best known is phenylketonuria (PKU) that occurs in approximately 1:13 600 births. In 2006, the American College of Medical Genetics called for the implementation of a uniform screening panel to establish a uniform standard of care

for screening across the country.<sup>2,3</sup> The technique of tandem mass spectrometry (MS/MS) now enables the diagnosis of more than 30 genetic metabolic diseases.<sup>4</sup> Using population estimates of births per year in the United States (4.2 million), the rate of detection of IEM by expanded NBS (1:2000), and the number of these patients requiring treatment with specialized medical foods (1:1,500), it is estimated that at least 2800 children born per year require the use of medical foods.

IEM disorders in the intermediary metabolism of protein, carbohydrate, or lipids cause serious problems in infants and are most amenable to treatment with medical nutritional therapy. In practice, this can mean total or significant exclusion of most normal foods. Such therapy is based on the principle that abnormal levels of metabolites in the blood cause serious or lethal complications that can be prevented only by normalizing the blood biochemistry through manipulation of specific nutrients in the diet. This is primarily achieved by means of special medical foods

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that are specifically designed and manufactured to manage the metabolic disease. Such highly artificial diets require close supervision and management by specialists trained in this field. Although evidence-based reports are few, such treatment is internationally accepted as essential for IEM.<sup>5-9</sup> Treatment allows children to grow and develop normally and for adult patients to maintain metabolic homeostasis and health.<sup>10</sup> For most of these conditions, medical nutritional therapy must be maintained for life to avoid late-onset complications such as declines in cognitive function or to injury to tissues such as the liver or heart.

Medical foods are therapeutic agents, comparable to any regular drug, and should be considered under the same rubric for prescribing and insurance purposes. However, insurance reimbursement in the United States for medical foods is frequently denied despite internationally agreed upon recognition of their therapeutic legitimacy. Therein lies one of the major weaknesses in the current provision of medical services for genetic metabolic conditions in the United States.<sup>11-15</sup> NBS is severely compromised without ensuring that the follow-up, definitive diagnosis, and particular treatment are included in the program design.<sup>3</sup> This situation confounds logic in that the development of successful dietary therapy for PKU provided the springboard for instituting universal NBS in the first place.<sup>16-19</sup> Consumer protection remedies legislated at the state level have attempted to address the inconsistency between a mandated public health program and treatment coverage. However, state mandates differ in coverage of the disorders themselves as well as in the types of medical food covered. This ultimately has led to inequitable delivery of health-care services for diseases identified through NBS.<sup>11</sup>

This review of treatment coverage specific to medical foods for IEM focuses on what constitutes a medical food, the rationale for medical necessity, the cost of medical food treatment, and comparison of treatment options, and how the current system of healthcare de-

livery interferes with access. Suggestions are included for clarifying and improving the reimbursement process for treatment of IEM.

## MEDICAL FOOD CATEGORIES

Based on Food and Drug Administration (FDA) definitions and state mandates, medical foods come in three basic formats.

### Infant medical formulas

For more than 50 years, infant medical formula products have used elemental forms of nutrients to make milk-like formula substitutes based on the composition of regular milk but lacking selected nutrient(s), generally specific amino acids, that must be restricted in the diet of persons with IEM. These formulas are designed as the main alternative to natural protein. Such products are ideal for use during infancy. These “milks” have been the main constituent in most metabolic diets. Some people consider them as the only legitimate form of medical food but the majority of state mandates have a broader definition of medical foods.

### Alternate medical protein products

When treatment of PKU started more than 50 years ago, the only products that were available were infant milk substitutes. However, a diet composed exclusively of a milk-type beverage is not ideal for older children or adults on an ongoing basis and presents therapeutic challenges for meeting the medical and nutritional needs of this subset of patients. As a result, different types of medical protein options have emerged to provide the same essential protein and partial energy needs for older patients as the formulas do for infants. These include products containing amino acids in a variety of forms: tablets, bars, gels, frozen sticks, and sauces. These products also exclude the specific amino acids that are associated with the primary diagnosis and are the most costly to manufacture.

### **Low-protein medical foods (LPMFs) as energy sources and alternate energy products**

As patients grow older, infant medical formulas alone are not a sustaining source of calories. Adequate energy intake is just as important to a balanced diet as the control of the primary underlying metabolic defect. Inadequate energy intake can cause metabolic decompensation that can result in neurological damage just as severe as if treatment had never been started. Low-protein products such as those that come in the form of baking mixes, pastas, rice, sauces, and premade items are designed to be as similar to their normal counterparts as possible but supply negligible protein. They are used to meet the energy requirements of the individual patient and are manufactured only for the exclusive purpose of treating disorders requiring protein restriction. Product nutrition labeling is required. A number of states that have passed medical food mandates specify that products considered to be LPMFs must supply less than 1 g of protein per serving and must be used under the direction of a physician. The FDA upholds a narrow definition of medical foods with the qualification that they are a necessary component for treatment of a specific medical disorder for which there are distinctive nutritional requirements. The question that arises is whether low-protein products have the limited application that fits the FDA requirement. In the example of pasta, regular pasta supplies 20 times the amount of protein than the low-protein alternative supplies per the same gram weight of product. The importance of calories for protein-restricted therapy precludes the use of normal pasta because of its calorie-to-protein ratio, thus making the low-protein option an important therapeutic application for treatment purposes. Protein restriction for IEM is extreme and thereby does not allow the substitution of one normal food for another such as bread made with rye instead of wheat.

LPMF substitutes also provide the opportunity for satiety and organoleptic satisfac-

tion. This markedly increases patient acceptance and adherence to treatment requirements. The notion that “formula only” should be the primary treatment strategy for patients other than infants is perplexing. Consider that a 9-year-old, who when properly treated, will have normal growth and development. How likely is this patient to forgo almost all of the normal foods of his or her peers? How much better is it to celebrate with a slice of low-protein birthday cake than with yet another glass of formula?

For other metabolic disorders, alternate energy sources are essential for preventing catabolism to avoid metabolic complications. For example, patients with fatty acid oxidation disorders cannot metabolize long-chain fatty acids and require an energy alternative that prevents life-threatening hypoglycemia and other health complications. The inclusion of medium-chain triglycerides in the form of oil or sachet powders is emphasized in diet therapy for these disorders.

### **INADEQUATE HEALTHCARE COVERAGE FOR IEM**

#### **Insurance industry denial strategies and healthcare priorities**

Over the years, a National Institute of Health consensus report on PKU and a number of scientific and medical professional organizations have issued position statements, recommending reimbursement for both medical formulas and low-protein foods for treatment of IEM.<sup>15,20-23</sup> Despite the number and consistency of these position statements, state mandates are the only measure that ensures that the medical needs of affected individuals are not left to the discretion and interpretation of medical necessity by health plan medical directors who have little understanding of IEM and/or who may be motivated to consider the profit margin in their decision making.

Additional barriers to proper insurance coverage include refusal by the companies to comply with state mandates and the

inability of parents to advocate for their children effectively. Lack of enforcement by state insurance commissioners contributes to a legal vacuum that ultimately erodes legislative intent. Even in the state where adequate legislation exists, the health insurance industry regularly denies coverage, creating an urgent need to engage in a demanding appeal process. In 2007, a national survey of metabolic nutritionists showed that 37/54 found that even with legislation the state mandates were not effective in resolving the reimbursement problems for their patients (Genetic Metabolic Dietitians International, unpublished data, 2007). Unfortunately families are called upon to argue medical necessity at a time when they have just had a newborn infant, when that infant is the most prone to biochemical damage, and when they are coping with grieving and the medical management of a complicated disease. Denials can follow for the same medical foods that were approved for previous dates of service. The appeal process can be daunting as it requires organizational skills, a sophisticated understanding of the disease to explain medical necessity, and a clear understanding of the reimbursement process. Perseverance is the ultimate requirement. Clinical staff members spend inordinate amounts of time advocating on behalf of patients with written testimony and telephone follow-ups that erode the time spent on actual patient care.

On the whole, private insurance products are designed typically to address adult healthcare needs and exclude coverage of chronic conditions.<sup>24,25</sup> These insurers often use medical management determinations that do not prioritize pediatric neurodevelopmental needs.<sup>26</sup> In response, the American Association of Pediatrics has recommended that the definition of medical necessity should be written in state insurance planning and managed care contracts. Interventions should be specific to the appropriate age and developmental status of children as well as support them in achieving, maintaining, or restoring health and functional capacity.<sup>27</sup> Access to healthcare is associated with positive health

outcomes in children; nonetheless, the health plan coverage of children with special needs does not guarantee reimbursement for critical services.<sup>28,29</sup> The Maternal and Child Health Bureau of Services for Children with Healthcare Needs created a definition of children with special healthcare needs to provide a platform for planning and developing systems of care for this unique population category:

Children with special health care needs are those who have or are at risk for a chronic physical, developmental, behavioral or emotional condition and who also require health and related services of a type or amount beyond those that are required by children generally.<sup>30(p138)</sup>

Children diagnosed with IEM are included in this classification. Kastner<sup>31</sup> argued that any healthcare system presuming to serve this population must support strategies that minimize the potential for developmental delay. Denials in healthcare coverage can interrupt the supply of medical food or cause inconsistent use, impacting on the control of metabolic disturbances associated with an IEM. This situation can irreversibly alter developmental outcomes and affect a child's neurological system.<sup>32,33</sup> Therefore, delays in treatment and underinsurance for this group of children undermines preventative healthcare and can result in reducing the potential for individuals and increasing costs to society.<sup>34</sup>

### **Problems with coding for diseases and reimbursement**

Insurance plans evaluate whether the services and products provided to a patient are covered by the patient's benefit plan through a system of coding. The *Current Procedural Terminology* coding system, the Health Care Common Procedural Coding System (HCPCS), and the *International Classification of Disease (ICD)* are used for this purpose. Reimbursement is determined on the codes related to a specific service and the monetary amount assigned to these codes. For many of the IEM, there is no clear diagnostic ICD code, and thus, there is no administrative evidence that the disorder even exists. In addition, there is confusion as to how medical

foods should be coded for billing purposes. In 2003, the Secretary of Health and Human Services delegated authority to the Centers for Medicare & Medicaid Services (CMS) to establish standards for coding and maintain the coding database.<sup>35</sup> Recommendations to establish, revise, or discontinue a code must follow a specific format provided by the CMS. Medical foods are referenced with a small assortment of codes from HCPCS II, a system that is used by both private and public health plans.<sup>35</sup> The codes most frequently used to bill for medical foods are shown in Table 1.

**B codes**

The current HCPCS codes create major problems for medical food reimbursement. Codes B4155, B4157, and B4162 all specify that the products be administered by tube. For most patients, the metabolic formulas and low-protein substitutes are consumed orally and are not administered by tube. The B4157 code covers only the use of “nutritionally complete” products and thus excludes the nutritionally incomplete formulas specifically manufactured for IEM. B4162 does not indicate whether the products can be nutritionally complete or not. B4155 comes closest to recognizing the nature of these medical foods but requires tube feeding. In some instances, health plan providers refuse to reimburse B4155 on the basis that they do not cover “supplements as in single amino acids.” For certain disorders, such treatment becomes essential because certain amino acids cannot be made synthesized in the body. It then becomes critical to differentiate between when a nutrient constitutes a “supplement” and when it is essential to life.

Clearly the B codes also do not recognize the current availability of the diverse number of products or in the ways that they can be used. The modifier, “BO” (meaning by mouth), is sometimes referenced with B4155, B4157, or B4162 codes designating that these treatments are taken orally, thus “legitimizing” their use. However, this creates a gray zone that enables reimbursement to be denied should health plan providers refuse to ac-

**Table 1.** HCPCS codes and description of products

HCPCS code	Description
B4155	Enteral formula, nutritionally incomplete/modular nutrients includes specific nutrients, carbohydrates (eg, glucose polymers), proteins/amino acids (eg, arginine and glutamine), fat (eg, medium chain triglycerides or combination), administered through an enteral feeding tube, 100 cal = 1 unit
B4157	Enteral formula, nutritionally complete for special metabolic needs for inherited disease of metabolism, includes proteins, fats, carbohydrates, vitamins, and minerals, may include fiber, administered through an enteral feeding tube, 100 cal = 1 unit
B4162	Enteral formula for pediatrics, special metabolic needs for inherited disease of metabolism, includes proteins, fats, carbohydrates, vitamins and minerals, may include fiber, administered through an enteral feeding tube, 100 cal = 1 unit
S9434	Modified solid food supplements for inborn errors of metabolism
S9435	Medical foods for inborn errors of metabolism

Abbreviation: HCPCS, Healthcare Common Procedural Coding System.

knowledge the modifier. The restricted list of formulas associated with these B-codes does not allow for other medical formula options such as bars and capsules. Nowhere do the B codes refer to the use of LPMFs.

Reimbursement for enteral solutions is based on 100 cal/unit. For example, a 240-mL can of Pediasure supplies 240 cal; the 2004 Medicare reimbursement rate for category 1 enteral formulas was \$0.61/unit.<sup>36</sup> Protein substitute medical food products do not

typically come in the form of enteral solutions such as in Pediasure or other category 1 products so reimbursement per 100 cal/unit does not reflect the typical medical protein product packaging format. Many of the medical formula powders supply greater than 1000 cal per can per unit. For example, a commonly used product for PKU supplies 1770 cal/can. This represents 18 units and at a reimbursement at \$0.61 unit covers \$10.98 of the cost of the can. That amounts to less than one-third of the current wholesale cost for this product. A variety of medical protein options are now available that supply only amino acids and/or restrict calories to balance the diet and to prevent iatrogenic obesity, specifically for the late adolescent and/or adult patients. The costs of these products are generally higher because of the higher protein content per unit with lower total calories. Therefore, when the B codes are used, reimbursement, using the definition "100 calories = 1 unit" strategy, does not reflect the nutritional purposes of the products nor does it capture a fair return even for the wholesale costs. For products listed with B4155, the cost of a powdered glucose polymer used to provide energy is not comparable with the cost for L-arginine, which is used for urea cycle disorders. Such discrepancies lead to efforts to circumvent the restriction that the HCPCS codes codify and this can result in the creation of medical diets that are nutritionally unsafe.

### **S codes**

The S codes have been used successfully in Oregon and in a small number of other states to reimburse for both medical formulas and low-protein foods. They were developed through collaboration between the Metabolic Clinic Program and Oregon Blue-Cross Blue Shield in 2001 after Oregon passed its first medical foods mandate in 1997. Other private and public health plans in the state then agreed to recognize these codes. The Oregon Metabolic Clinic has set up a distribution system of medical foods for patients with all conditions detected by NBS conditions that require medical nutritional

therapy. Any appropriate foods, labeled per FDA medical food guidelines for treatment of IEM, can be included in the inventory. These products are distributed under medical supervision and billed to insurance companies using code S9435. This system has offered patients considerable freedom to individualize their treatment and has allowed daily variation in the diets as well as a reduction in costs. In other states, code S9434, which refers to modified solid foods, has been used for low-protein substitute products. In general, however, S codes have limited utility as they are viewed to be temporary, although they can be used indefinitely. While S codes are usually recognized by private payers and, in some instances, by Medicaid, they are never processed for Medicare coverage and are used in a limited number of states. In summary, the current coding system lacks the appropriate descriptors, which reflect therapy applications currently in use for IEM.

### **Effect of ERISA, TRICARE, and Medicare regulations on state mandates**

The Employee Retirement Income Security Act (ERISA) is another example of opposing forces in the US healthcare system because it interferes with the states' ability to address shortcomings in healthcare coverage by preempting legislative mandates. When ERISA was enacted through federal legislation in 1974, it essentially abolished state regulation of employee benefit plans provided through self-insured employers.

One hundred thirty-four million Americans are insured through employer self-insured plans.<sup>37</sup> The purpose of ERISA was to protect enrollees' pension and benefit plans from abuse by those who invest and manage these plans. However, the law did not impose any requirements for healthcare benefits.<sup>38</sup> Standard health plans do not include benefits that expressly cover treatment requirements of rare conditions. *Rare diseases* are defined in the 1984 amendment to the Orphan Drug Act as "any disease or condition which affects less than 200,000 persons in the US."<sup>39</sup> The 1989 report by the National Commission on

Orphan Diseases highlighted the lack of adequate health insurance and coverage of medical expenses for these conditions.<sup>40,41</sup> Despite recognized standards for treatment of PKU with medical foods, denial of health-care coverage often occurs for self-insured plans. This creates a significant discrepancy between what is covered by group plans and self-insured options for disorders that are identified by state mandated NBS programs. Thus, ERISA upholds barriers that conflict with the states' ability to support healthcare priorities involving standard of care treatment that interfaces with public health programs implemented in all 50 states.

Inconsistent coverage by TRICARE and different federal health plans creates restrictions on portability and equal access to recognized standard of care. Medicare does not cover the cost of enteral solutions unless administered by tube feeding. The majority of patients with IEM requiring medical food for their treatment do not require tube feedings except in cases of severe neurological complications. Diet for life is a standard therapy recommendation. Medicare regulations are not sensitive to the treatment needs of this patient group with rare conditions who require specific therapy modalities that continue after childhood.

### **Variable state mandates and lack of federal guidelines regarding treatment**

The option for state-mandated health benefits was established through passage of the McCarran Ferguson Act in 1945, which allowed for state regulation of health insurance sold to small firms and individuals.<sup>42,43</sup> In general, mandated benefit laws require health plans to offer or provide coverage for particular services and/or types of providers or for the treatment of specific disease or conditions.<sup>42</sup>

In 1983, Wisconsin passed legislation that imposed no limits to age, type of medical formula, low-protein foods, or the number of disorders covered.<sup>44</sup> Twenty-four more states passed similar laws in the 1990s, which paralleled a national trend described as the managed care "backlash." During this time, there

was a large increase in mandated benefits.<sup>42</sup> In total, 38 states (76%), the most recent being Rhode Island (2008), have passed legislation that mandates a wide selection of approaches requiring coverage by either state funds or health plan providers. Table 2 outlines the different types of coverage by those states that have passed mandates. Some require treatment coverage for all disorders, and others cover only for PKU or a limited number of disorders. There are differences in what types of medical foods are covered. Some states impose caps and age limitations.<sup>44,45</sup>

The passage of Newborn Screening Saves Lives Act (SB1858) lends urgency to the situation in that there is federal pressure to detect these disorders but no universal federal or state program to ensure proper treatment. As of May 18, 2009, the National Newborn Screening and Genetics Resource Center Web site reported that 43 states require screening for 20 core metabolic disorders that are fully implemented by law or rule.<sup>49</sup> These include 5 disorders of fatty acid oxidation, 9 organic acidurias, and 6 aminoacidopathies. Two states require testing that is not yet implemented or indicate that certain disorders are likely to be detected and reported as a by-product of the MS/MS screening; 5 states do not include tyrosinemia. However, families confronted with the same disorder in various states face significantly different financial realities. The following disorders, which require treatment with medical food, are screened by all 50 states but the number that mandates treatment coverage falls short by a considerable margin: very long-chain acyl-CoA dehydrogenase deficiency and long-chain 3 hydroxyacyl CoA dehydrogenase—17 state mandates, homocystinuria—18; maple syrup urine disease—30; propionic—27; and citrullinemia—26. Given this discrepancy, moving from one state to another can have serious financial ramifications that can also impact on health outcomes.

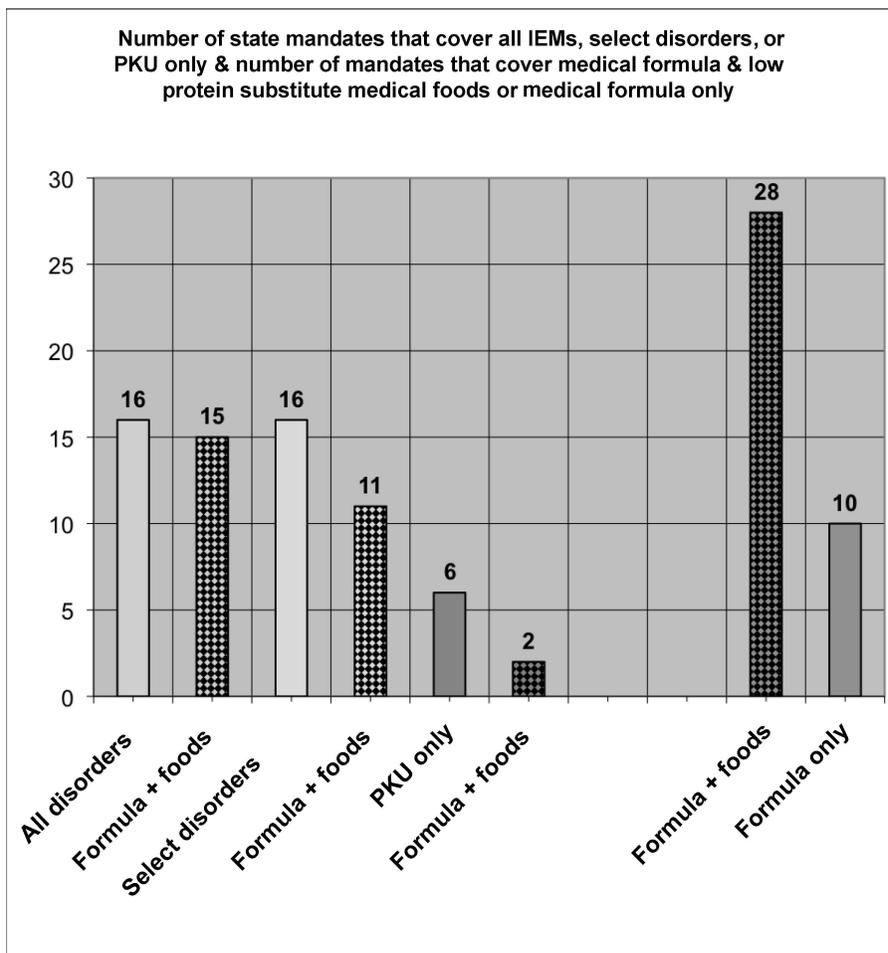
Of the 38 states with mandates, 28 (74%) include coverage of low-protein foods in addition to the medical formulas. It should be noted that states with mandates have

**Table 2.** States with medical food mandates, year of passage, disorders specified for coverage, type of medical food covered, and state or health insurance mandated coverage<sup>a</sup>

	Year of mandate	PKU only	Mandated coverage for selection of IEM other than PKU	All IEM	Formula only	Formula + low protein foods	State \$\$ support	Private payer support \$\$
Alaska	1991	x			x			x
Arizona	2000		x			x		x
Arkansas	1999		x			x		x
California	1999	x				x		x
Colorado	2001			x	x			x
Connecticut	1997			x		x		x
Delaware	2007			x		x		x
Florida	1995			x		x		x
Hawaii	1999			x		x		x
Indiana	2003		x		x			x
Kansas	1997		x		x		x	
Kentucky	2002			x		x		x
Louisiana	2001		x			x		x
Maine	1995			x		x		x
Maryland	1995			x		x		x
Massachusetts	1993		x			x		x
Minnesota	1985		x			x		x
Missouri	2002		x			x		x
Montana	1999			x		x		x
Nebraska	1998		x			x	x	
Nevada	1997			x		x		x
New Hampshire	1995		x			x		x
New Jersey	1997			x		x		x
New Mexico	2003			x		x		x
New York	1997			x		x		x
North Carolina	1997		x		x		x	
North Dakota	2001		x			x		x
Oregon	1997			x		x		x
Pennsylvania	1996		x		x			x
Rhode Island	2008		x			x		x
South Dakota	1992	x			x			x
Tennessee	1996	x			x			x
Texas	1999		x		x			x
Utah	1998		x			x		x
Vermont	1998			x		x		x
Virginia	2000	x				x	x	
Washington	1988	x			x			x
Wisconsin	1983			x		x	x	
Total	Out of a total of 38 states	6 PKU only	16 Mandated coverage for some disorders	16 All disorders	10 Formula only	28 Formula + low protein foods	5 State \$\$ support	33 Private payer support \$\$

Abbreviations: IEM, inborn errors of metabolism; PKU, phenylketonuria.

<sup>a</sup>From Schuett,<sup>44</sup> Nutricia Metabolic Partners,<sup>45</sup> Beth,<sup>46</sup> Barbara,<sup>47</sup> and National Conference of State Legislatures.<sup>48</sup>



**Figure 1.** Survey of states covering medical formulas and low-protein substitute medical foods with number of states covering PKU only, select disorders, or all disorders. IEM indicates inborn errors of metabolism; PKU, phenylketonuria.

overwhelmingly supported coverage for formula and low-protein foods by almost a 3:1 ratio (Fig 1). Since 2000, of 11/38 mandates that have been passed, all but 2 include coverage of low-protein foods.

In many states, the federal definition of medical foods is applied in the wording of their legislative mandate. The typical wording is

intended for the dietary treatment of an inherited metabolic disease for which nutritional requirements and restrictions have been established by medical research; and formulated to be consumed or administered enterally under the direction of a physician. (Editor’s note on source:

State of Delaware Insurance Code. Title 18, Chapter 33, Health Insurance Contracts. <http://delcode.delaware.gov/title18/c033/index.shtml>. Published 2009. Accessed September 22, 2009.)

Some other states mandate only medical protein treatment for protein disorders, a description that is highly restrictive and does not follow the federal definition. For example,

“Medical food” means an amino acid modified preparation that is intended to be used under the direction of a physician for the dietary treatment of an inherited metabolic disease. (Editor’s note on source: Vermont State Legislature, S.253, An Act Relating to Health Insurance Coverage for Nutritional § 4089d. Treatment of Inherited Metabolic

Diseases. <http://www.leg.state.vt.us/DOCS/1998/BILLS/SENATE/S-253.HTM>. Published October 1, 1998. Accessed September 22, 2009.)

Other states have chosen to clarify that more than just amino acid preparations should be considered medical foods. These states' laws define how low-protein-modified foods are distinguished as medical foods using the following text:

- <1 g of protein/serving,
- does not include natural food naturally low in protein,
- and/or prescribed by physician.

The states that have not passed mandates are listed in Table 3; funding supports services typically provided only for treatment of PKU through Medicaid or from other dedicated state funds. Four of the 12 states stipulate treatment for at least 1 other disorder than PKU. Not one of these states supports treatment for all disorders identified through expanded NBS; although 11 of these states have implemented expanded NBS for the 20 core metabolic disorders including tyrosinemia. None of these states include low-protein foods for coverage. It is less expensive to rely on a combination of medical protein sources in combination with low-protein substitute foods than to meet the majority of energy needs solely from a medical protein source. Ironically what may have been intended as a measure for cost savings turns out to be the most costly approach to treatment, in the long run.

### Cost of failure to treat

Based on 2003 dollars for persons born in 2000, the average lifetime economic impact of a single individual with mental retardation has been estimated to be \$1,014,000 including both direct (24% of total) and indirect costs (76%).<sup>50</sup> This estimate is in addition to the cost of living expenses incurred by the average individual not cognitively disabled. Direct medical costs involve physician visits, prescriptions, and inpatient hospital stays. Indirect nonmedical costs include home modifications and special education as well as the

estimated value of lost income due to limitations on work eligibility. The actual economic impact of mental retardation is even greater because other expenses including outpatient charges, emergency care, residential care, and familial out-of-pocket expenses are not factored into this analysis of fiscal impact.<sup>50</sup>

The US healthcare system places a priority on screening but not on follow-up. If a state NBS program is sued for missing a diagnosis in a baby, the resulting lawsuits have cost many millions of dollars.<sup>13</sup> We are not aware of similar lawsuits against an insurance carrier for failure to provide treatment but the potential for such action is obvious. Ironically, children with PKU who are placed under state guardianship for parental medical neglect are typically provided the whole gamut of medical foods while in foster care. Yet, if the child lives with their biological family, there are no concrete supports that make provisions for the same treatment modalities.

### Impact of medical food treatment on healthcare costs

Although expensive for individuals, the total cost of treatment for IEM has a small effect on overall healthcare costs. The Council for Affordable Health Insurance (CAHI), a US advocacy group supporting market-oriented solutions for the healthcare system, provides annual cost analysis on the impact of legislative health mandates.<sup>51</sup> In May 2009, the CAHI reported that the legislative mandates passed by more than 30 states for PKU formula contributes less than 1% of total healthcare costs.<sup>52</sup> In truth, it is more like 0.0001% of healthcare costs when you consider that in 2007 in the United States, total healthcare costs exceeded 2.2 trillion dollars.<sup>53</sup> The costs for treatment of IEM were 150 million dollars at the most. Under the CAHI's definition of mandated benefits, both formulas and low-protein products are included as follows:

Inherited metabolic diseases such as Phenylketonuria (PKU) which is a genetically determined abnormality caused by a missing enzyme called phenylalanine hydroxylase. Mandate provides for

**Table 3.** States that have not passed mandates, list of funding sources that provide assistance for treatment, disorders covered, and type of medical foods supported<sup>a</sup>

	State coverage			Medicaid coverage	Other state programs	Formula only	Formula + low protein foods
	No mandate only	Other disorders	PKU				
Alabama	x	No	x	Medicaid case by case	Children's Rehabilitation Services	x	No
Georgia	x	No	x	Enteral not oral	Emory University Children's Center	x	No
Idaho	x	No	x	Enteral not oral	Children's Special Health Program	x	No
Illinois	x	Yes	...	Yes	May be considered upon by request	x	No
Iowa	x	No	x	Yes	State Formulary Children's Special Health Care Services (CSHCS)	x	No
Michigan	x	No	x	Medicaid case by case	State Formulary; Children With Special Healthcare Needs	x	No
Mississippi	x	No	x	Medicaid case by case	Children's Medical Program; State Formulary	x	No
Ohio	x	HCU	...	Yes	State Formulary; OH Department of Health Metabolic Program; Bureau for Children With Medical Handicaps; Bureau of Early Intervention Program	x	No
Oklahoma	x	Individual consideration —case by case if not PKU	...	Yes	Children With Special Healthcare Needs	x	No
South Carolina	x	No	x	Enteral not oral	State Formulary; Children's Rehabilitation Services	x	No
West Virginia	x	Galactosemia	...	Referred to WV metabolic program	Department of Family Health—Metabolic Newborn Services Program	x	No
Wyoming	x	No	x	Yes	Genetic and Metabolic Clinic; SCHIP	x	No
Total	12	4	8			12	

Abbreviations: PKU, phenylketonuria; SCHIP, State Children's Health Insurance Program.  
<sup>a</sup>From Schuett,<sup>44</sup> Nutricia Metabolic Partners,<sup>45</sup> and National Conference of State Legislatures.

**Table 4.** Average cost per year of medical protein options for phenylketonuria for different age groups

Age group	Age-based protein requirement, g	Average monthly	Yearly average cost
Infancy, y	9.1–13.5	\$190	\$2 275
1–3	13	\$273	\$3 275
4–8	19	\$429	\$5 150
9–13	34	\$718	\$8 617
14–18 (F)	46	\$878	\$10 538
14–18 (M)	52	\$1040	\$12 483

evaluation, education, treatment and supplies like formula or special foods:<sup>51(p9)</sup>

#### Cost of medical food treatment and comparison of treatment options

From infancy through 18 years of age, the annual costs of medical protein formula for PKU range from \$2275 to \$1248, averaging \$7100 per year and \$220 000 from infancy through the age of 24 years (Table 4). These figures included a 160% markup over wholesale costs and were derived from review of the costs of different products available in the United States. (Note: pharmacy markup is typically 200%–300% of wholesale.) Calculations took into account age-based protein requirements and suggested recommendations for protein intake of L-amino acids.<sup>54,55</sup>

A comparison of costs of standard infant formula at retail with wholesale costs of infant formula medical foods for PKU and pro-

ponic aciduria demonstrates the significant financial burden for treatment. Medical formulas are typically dispensed through pharmacies via a physician “prescription,” although they are not considered the same as drugs. Whereas wholesale costs for PKU formula can exceed the retail cost of the regular infant formula by 30%, medical formula for propionic aciduria at wholesale can be 2<sup>1</sup>/<sub>2</sub> times the cost of retail. With a pharmacy markup of 200% to 300%, costs are prohibitive for most families. As a rule, the rarer the IEM, the more expensive the medical formula.

It is very costly to use the amino acid products as a primary source of calories since they are the most expensive products. Inclusion of the low-protein foods as an energy source results in significant annual cost savings over a treatment plan that is dependent on medical formula for both protein and the majority of calories. Table 5 provides 2 examples of

**Table 5.** Treatment cost comparison combination therapy versus medical protein as primary energy source for 9 year PKU age-based requirements: 34 g protein, 1950 cal protein restriction: 6 g, assume ~450 cal from natural foods

Medical food module	Medical protein per day, g	Calories supplied	Cost per day	Cost per month	Cost per year
Med Bev XX 266 g/d	80	1500	\$56.00	\$1 680	\$20 160
Med Bev XX 113 g/d	34	463	\$24	\$720	\$8 640
Low-protein modules	~2	1037	\$9	\$270	\$3 240
Total	36	1520	\$33	\$990.00	\$11 880

**Table 6.** Protein content and cost comparison of regular foods vs low-protein alternatives per 100 g weight of each type of product

Regular products	Retail cost/100 g	Grams of protein/100 g product		Wholesale costs/100 g product	
		10–33× higher than low protein versions	Low-protein versions	Wholesale 2–8× higher than retail for regular products	Grams of protein/100 g product
Spaghetti	\$0.37	13 g	Aproten low-protein pasta	\$2.20	0.6 g
Flour	\$0.17	10 g	Well-plan baking Mix	\$1.29	0.3 g
Bisquick	\$0.31	7.5 g	TC low-protein bake mix	\$0.58	0.3 g
Crackers	\$0.64	4 g	Loprofin crackers	\$1.95	0.4 g
Tortillas, 8 pack	\$0.40	10 g	Low-pro Tortillas, 6 pack	\$2.04	0.3 g
Peanut Butter	\$0.70	25 g	<i>Low-pro peanut spread</i>	\$1.94	0.4 g

different therapy approaches for a 9-year-old with PKU who tolerates about 6 g of normal protein per day. One plan utilizes medical formula as the primary source of energy and the other plan incorporates both medical formula and low-protein foods as energy sources. By emphasizing medical formula as the predominant energy source, the cost of therapy is 170% more than that of using a combination of low LPMFs and medical formula—a difference of more than \$8000 per year.

In Table 6, cost comparisons and protein content are listed to illustrate the differences between regular foods and low-protein substitute options. The protein content of normal foods can reach 33 times higher than the low-protein counterpart but the costs at wholesale for the latter can range from 2 to 8 times higher. Shipping adds to the cost and retail markups, depending on how the product is dispensed. These items are ordered through mail order or, in some rare situations, are provided through a grocery outlet that agrees to order the special products. The market for these manufactured low-protein foods is quite small with only about 20 000 patients requiring them in the United States; thus, the low-volume market results in significantly greater costs. The Oregon Metabolic Clinic program

provides a full service-dispensing program that supplies both medical formula and low-protein substitutes to patients diagnosed with genetic metabolic conditions associated with NBS. This arrangement allows an opportunity to review patient adherence to therapy recommendations and for medical supervision that the FDA stipulates in the definition for medical foods. Patient costs for low-protein substitute medical foods generally range, after infancy and the early toddler years, between \$1200 and \$3500 per year, depending on the age of the patient and the level of protein tolerance.<sup>56</sup>

**Other monetary considerations**

It has been suggested that the Supplemental Nutrition Assistance Program (SNAP) (formerly referred to as the Food Stamp Program) be used to fund medical foods specifically for the low-protein options.<sup>57</sup> The current maximum allotment for SNAP for a family of 4 is \$668 per month, which calculates out to \$167 per person.<sup>58</sup> However, from the financial constraints and the restrictions imposed by this program, it is evident that such a funding mechanism would not be appropriate. Given the higher costs of medical foods, the therapy needs of the affected individual

would be at odds with the food needs of the other family members who also depend on SNAP. Measured amounts of natural foods low in protein are integrated into the menu plans of a protein-restricted diet consisting primarily of fruits and vegetables, which are often the more expensive items in a food budget. While fruits and vegetables are inherently low in protein, they must still be used in measured quantities. This in turn limits the amount of calories that they supply.

**Case example**

In general, most patients with classic PKU can tolerate about 5 to 8 g of natural protein. Table 7 provides a breakdown of typical fresh fruits and vegetables that might be included as phenylalanine sources that give 6 g of protein per day. The estimated caloric contribution from this typical selection of natural foods is about 475 cal. The monthly cost for such items is about \$80, almost one half of the monthly allocation from SNAP for one individual. One daily serving of low-protein pasta supplies 0.2 g of protein and 213 cal at a cost of \$1.70, resulting in a cost of greater than \$50 per month. The energy requirement, for a 3-year-old, ranges between 1200 and 1400 cal/d. This amount of fruits and vegetables with the inclusion of one serving of low-protein pasta in the diet for a child of this age would not provide adequate energy intake. The gap between calorie needs and what is available in this circumstance is even greater for older children and adolescents. Protein tolerance does not increase for the older patient so natural foods are essential supplementary as far as this type of protein-restricted therapy is concerned. With this example, it is shown that SNAP is not a feasible alternative to health plan coverage for medical food treatment. In our example of a person with PKU, one half of the monthly individual allotment would be taken up by natural foods to meet the phenylalanine requirement, leaving inadequate funding for the provision of calories from low-protein foods to prevent catabolism.

**Table 7. Protein and caloric content of natural food examples supplying 6 g protein/d and monthly costs listed for food stamp comparison based local Portland, Oregon, supermarket<sup>a</sup>**

	2/3 Cup baked potato = 2 g protein (30 cal) 36-g weight		4 Tablespoon cooked broccoli = 1 g protein (13 cal) 450-g weight		1 1/2 Medium raw tomato = 1 g protein (39 cal) 186-g weight		One 8 3/4 in long banana = 1 g protein (105 cal) 114-g weight		3 Fresh Oregon pears, medium, 2 1/2 in diameter, peeled, sliced = 1-g protein (294 cal) 498-g weight
Fred Meyer's: \$0.59/lb Total cost/30 d—\$1.40	Fred Meyer's: \$1.49/lb Total cost/30 d—\$4.43	Fred Meyer's: \$1.99/lb Total cost/30 d—\$24.46	Fred Meyer's: \$0.59/lb Total cost/30 d—\$4.44	Fred Meyer's: \$1.49/lb Total cost/30 d \$49.00					

<sup>a</sup>Total protein: 6 g/d; total calories: 481/d—from these 5 regular foods in serving sizes listed. 481 cal: \$83.73. Total monthly allotment per individual for family of 4: \$167; balance remaining after fresh food deduction: \$83.27. The cost of one serving of low-protein pasta supplying about 200 cal: \$1.70. The monthly cost for just one daily serving of low protein pasta is more than \$50. Food stamps are not an appropriate monetary support for the medical treatment of phenylketonuria or other inborn errors of metabolism.

## FEDERAL DEFINITION OF FOODS FOR SPECIAL DIETARY USES, MEDICAL FOODS, AND NUTRITIONAL SUPPLEMENTS

The FDA regulated “foods for special dietary uses” as drugs until 1972 under the Federal Food, Drug and Cosmetic Act.<sup>59</sup> For promoting product development, the FDA removed the drug classification and changed the categorization of medical foods to “foods for special dietary use.”<sup>60</sup> Further clarification as to what constitutes a medical food was established through congressional action in the 1980s and FDA rules in the 1990s.<sup>59</sup>

The definition of what constitutes a medical food as opposed to a nutritional supplement is pivotal; the federal definition of a medical food is clearly laid out in the “Orphan Drug Amendments of 1988 of the Orphan Drug Act as follows”:

a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the condition for which distinctive nutritional requirements, based on recognized specific dietary management of a disease scientific principles, are established by medical evaluation.<sup>61,62</sup>

This definition clearly embraces almost all of the new products that are being marketed for treating IEM. It remains in sharp contrast to the federal definition of a nutritional supplement, which under the Dietary Supplement Health and Education Act (DSHEA) of 1994 is as follows:

A dietary supplement is a product taken by mouth that contains a “dietary ingredient” intended to supplement the diet.<sup>63</sup>

The DSHEA specifically restricts the labeling of nutritional supplements with claims that suggest that the use of the dietary supplement will diagnose, prevent, mitigate, treat, or cure a specific disease (unless approved under the new drug provisions of the amended Food, Drug and Cosmetic Act, 1994).<sup>64</sup> In comparison, in May 2007, the Center for Food Safety and Applied Nutrition, Office of Nutritional Products, Labeling and Dietary Supple-

ments, issued a guidance document for industry based on frequently asked questions about the definition of and regulations for medical foods.<sup>65</sup> In this document, the explanation specifically stated that medical foods:

1. Are distinguished from the broader category of foods for special dietary use and from foods that make health claims by the requirement that medical foods be intended to meet distinctive nutritional requirements of a disease or condition.
2. Are used under medical supervision and intended for the specific dietary management of a disease or condition.
3. Do not pertain to all foods fed to sick patients.
4. Are foods that are specially formulated and processed (as opposed to a naturally occurring foodstuff used in a natural state) for the patient who is seriously ill or who requires the product as a major treatment modality.
5. Must, at a minimum, meet the following criteria:
  - the product must be a food for oral or tube feeding;
  - the product must be labeled for the dietary management of a specific medical disorder, disease, or condition for which there are distinctive nutritional requirements; and
  - the product must be intended to be used under medical supervision.<sup>65</sup>

Other definitions in use include the following:

1. The USDA Center for Food Safety and Applied Nutrition (May 1997) specifies that medical foods are prescribed by a physician and cites as an example the treatment of PKU.
2. The FDA Office of Nutritional Products states (May 2007) that medical foods are “for patients with limited capacity to ingest, digest absorb, or metabolize certain nutrients.”
3. *Orphan medical foods* are defined as follows by the Orphan Drug Act [a] section 5 [b] [2] [3]: 1989: “to treat a disease or condition that occurs so rarely that there is no reasonable expectation

that a medical food for such disease will be developed without assistance.”

Creating additional complexity, foods for *special dietary uses* are defined by an international codex as “supplying particular dietary needs which exist by reason of a pathological or other condition including diseases, convalescence, pregnancy, infancy, or lactation . . . or supplementing or fortifying the usual diet with any vitamin or other dietary property” (Code of Federal Register, April 1999;21(2 pt 105)).

In the background information for the Medical Food and Food for Special Dietary Uses Act 2004, there is the following statement: “It should be noted that the very same product may qualify as a Medical Food [e.g. in an institution] and at other times, if purchased at retail, does not qualify as a Medical Food.”

Dietary supplements augment the intake of particular nutritional components but cannot claim that the purpose is to treat a disease nor are they intended to sustain the user. In contrast, medical foods are the primary source of nutrition for patients with IEM and are life sustaining, whereas regular foods are principally supplementary. Thus, medical foods and dietary supplements serve different purposes.

### Some possible solutions to the dilemma are recommended by the authors

1. Coverage of treatment for IEM should be set as a standard health benefit for all insurance plans, including those managed through ERISA, TRICARE, Medicaid, and Medicare and in any healthcare reform program established by Congress.
2. Attention must be given to any cost containment measures imposed as reimbursement standards that, if the ceiling is too low, it will reverse the intent of re-

lieving the financial burden of treatment for these rare conditions.

3. Given the structure of the healthcare system in the United States, it is essential to have an *ICD-9* and an HCPCS that recognize all forms of rare disease and describe the therapy modalities that are in actual use. An appropriate reimbursement schedule for the medical foods that are used for the treatment of IEM should be implemented.
4. Federal standards for healthcare benefits should recognize the existence of rare diseases, contemporary approaches to their treatment, and their relationships to the developmental needs of children.
5. Preexisting condition restrictions should be abandoned for NBS disorders so that continuity of care is not impeded.
6. Coverage should include pharmacological doses of amino acids and vitamins that are identified as essential for treatment and used under the supervision of a physician.
7. FDA-defined medical foods and low-protein foods labeled to be used for the treatment of protein disorders under the direction of a physician should be part of a standard health benefit program.

The underlying goal in resolving the incongruities of the current situation is to optimize an outcome through preventative measures involving medical food. It is reasonable to recognize that any new therapies that might present themselves as alternatives to current treatment modalities will change the cost of medical food treatment. Reimbursement costs for medical food are, in truth, a bargain. It is time to address what has endured far too long as a systemic incongruity in the American healthcare system.

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