Advisory Committee on Heritable Disorders in Newborns and Children

Committee Report

Medical Foods for Inborn Errors of Metabolism: The Critical Need to Improve Patient Access

Prepared by the Follow up and Treatment Workgroup

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Introduction

Successful intervention for inborn errors of metabolism (IEM) is a triumph of modern medicine. The prevention of severe intellectual disability, otherwise typical in untreated phenylketonuria (PKU), by treatment with a phenylalanine-restricted diet which includes a specially developed formula with a protein source extremely low in or devoid of phenylalanine, led to development of newborn bloodspot screening in the 1960s as states initiated public health programs to improve outcomes for affected infants [1]. For more than 50 years in the United States, early dietary intervention has resulted in near-normal or normal development of individuals with PKU. The success of treatment for PKU led to advances in similar dietary interventions for other IEM and the commercial production of medical foods for IEM treatment. For many of these conditions, medical foods are the cornerstone of therapy and the only effective interventions preventing disability or death.

Prior to 1972, metabolic formulas for IEM were classified by the Food and Drug Administration (FDA) as drugs. They were subsequently removed from the drug category. This change was made to reduce obstacles so that the formula industry would be better able to innovate, change, and make available these essential medical interventions[2]. In 1988, the term "medical food" was defined in section 5(b) of the Orphan Drug Act (ODA) (21 U.S.C. 360ee (b)(3)) as:

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

By establishing this definition, the ODA recognized the importance of these products for medical management and began the process of regulating this category. In 2016, the FDA published its most recent guidance for industry, which further specified the conditions and products that fit the

ODA definition. The guidance specifically indicated that medical foods are specially formulated and processed (as opposed to naturally occurring) and designed for partial or exclusive feeding orally or by tube. Most notably, they are designed for patients with limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foods or nutrients *whereby dietary management cannot be achieved by modification of the normal diet alone* (emphasis added). They are to be used to manage the unique nutrient needs of a specific disease or condition determined by medical evaluation and are intended for a patient receiving active, ongoing medical supervision[3]. The community of providers and families had long hoped that the classification of products to be used in management of IEM as a defined entity, medical foods, would facilitate access, in part by improving insurance coverage.

In the United States today, access to medical foods is not assured for many affected individuals despite their proven efficacy in the treatment of IEM, their universal use as the mainstay of IEM management, the endorsement of their use by professional medical organizations, and the obvious desire of families for effective care. Medical foods are not sufficiently covered by many health insurance plans in the U.S and, without insurance coverage, many families cannot afford their high cost.

PKU, as the first screened condition, serves as a paradigm disorder to illustrate this remarkable inconsistency in access to medical food. Without access to medical food, individuals with PKU are forced to suffer the consequences of toxic elevations in phenylalanine and its metabolites in the blood and brain. These abnormal levels have developmental, behavioral, and mental health consequences that include difficulties in school, work, and relationships. Moreover, some

affected individuals experience long-term neurologic damage related to failure to maintain dietary control[4] . For individuals with other IEM, lack of access to medical foods leads to growth failure and even to metabolic crisis with permanent neurologic damage and death[5] .

Despite the proven outcome of these effective interventions, children and adults with PKU and other IEM often struggle to obtain insurance coverage for their essential treatment[6] . Thus, access to medical foods is not assured. Lack of insurance coverage is an even greater problem for adults affected with IEM. This review will outline the history of medical foods, define their medical necessity, discuss the barriers to access and reimbursement resulting from the regulatory status of medical foods, summarize previous efforts to improve access and offer approaches for resolution of these issues.

Medical Foods Are Essential Management Modalities for IEM, Including Many That are Identified by Newborn Screening

National Mandate for Newborn Screening – relationship to medical foods:

Newborn screening is a successful, preventative public health program[7] , an essential health benefit[8] , and an established medical practice[9] and the use of medical foods is necessary to achieve the benefits of newborn screening. The success of PKU newborn screening and subsequent treatment with dietary intervention using medical foods, prompted screening for other conditions amenable to intervention. Increasing variation in conditions screened from state to state occurred as states expanded newborn screening panels. Some states added many new conditions to their NBS programs; other states did not. This, along with other factors such as the development of new screening methodologies, led to calls for an evidence-based Recommended Uniform Screening Panel (RUSP) to provide guidance to state newborn screening programs on

conditions for which screening should be done. In developing the RUSP, many of the conditions on the initial panel were included based on the utility of intervention with medical foods and/or amino acids, vitamins, or cofactors. An essential criteria for inclusion of a condition is the availability of an effective treatment [9]. As such, the use of medical foods is necessary to achieve the benefits of newborn screening. Sixteen of the core conditions recommended for screening employ medical foods as their primary intervention for successful treatment[5]. In addition to the conditions on the RUSP, there are other similar IEM for which no newborn screening test is currently available (for example, ornithine transcarbamylase deficiency) but where essential interventions require medical foods. For these conditions, treatment is initiated after clinical diagnosis.

What is an inborn error of metabolism? And why are some treated with medical foods?

Metabolism is the term used for the biochemical activity of cells, including the building and the recycling of molecules (called "metabolites") that are important for cell function. Metabolites include amino acids (the building blocks of protein), fats, and sugars that are ingested as well as those compounds made by the human body. IEM are genetic conditions and are present from the moment of conception; they are permanent. Each IEM is due to a genetic change that causes a decrease in the activity of one or more enzymes that control biochemical pathways. The function of an enzyme is to convert one molecule (called the "substrate") into a different molecule (called the "product"). Decrease in enzyme activity causes a slowing or a block in a biochemical pathway; as a result, the levels of the substrate become too high and the pathway does not make enough of the product. These abnormal levels then cause problems with health, growth and development, according to the function of each molecule.

In some conditions, elevated levels of the substrate act as a toxin or poison, and can cause a "metabolic crisis" that can be fatal, or can cause slowly developing chronic damage that can lead to permanent neurologic or other health damage or death. In other conditions, the critical problem is the lack of a product, either because it is important for energy, or as a building block for cells, or for some critical function like transmission of brain signals; this also can lead to acute collapse, chronic damage, or death.

Treatment for most IEM is aimed at either returning the altered metabolite levels to normal or ameliorating the adverse effects of those altered levels. When the IEM involves a metabolite that is found in the diet, then it may be possible to treat the IEM by medical management of the diet. The medical diet for IEM is altered either to limit the intake of the nutrient that cannot be tolerated, and/or to assure adequate supply of the nutrient that is needed. In some IEM, the treatment can be accomplished using combinations of regular foods. However, for other IEM, especially for those that involve metabolism of amino acids, it is not possible to create a life-sustaining diet with regular foods alone. This is because regular foods contain amounts of specific amino acids, depending on the condition, that while tolerated in people without an IEM, would not be tolerated by a person with an IEM. In those conditions, the only possible means to prevent damage from the IEM and sustain life is to use combinations of modified or artificial food. For example, for treatment of PKU, it is necessary to provide the majority of the protein in the diet from a medical food that has been modified so that it contains no phenylalanine but contains all of the other necessary amino acids. In addition to having medical foods specific for each condition, it is necessary to have manufactured medical foods made to be appropriate for

use in various stages of life, because newborns, infants, children, and adults have different needs for various nutrients.

How do medical foods differ from regular foods and why is a health care team necessary for their safe use?

Medical foods are not only designed to be specific for condition and age of the affected person, they are dangerous if used incorrectly. The nutrients that are not properly tolerated by the affected individual are nevertheless essential for survival. For example, although the individual with PKU does not metabolize phenylalanine properly, some phenylalanine is necessary in the diet of the affected individual[10]. This is because phenylalanine is an "essential amino acid", not made by the human body, and it is required for building proteins, making neurotransmitters, thyroid hormone, and skin pigment. Too much phenylalanine in the diet of an individual with PKU leads to developmental, behavioral, and mental health problems, but too little phenylalanine leads to skin rashes, growth failure, and death. The medical food that lacks the offending nutrient must therefore be used in combination with measured, limited amounts of foods that contain the essential nutrient. Each medical food is carefully designed to contain a balance of essential and non-essential nutrients and is provided in specific amounts to support the health (and in childhood, the growth and development) of the affected individual. Periodic blood testing is used to monitor whether intake of the offending nutrient, e.g., phenylalanine in PKU, is optimal. Using a combination of diet histories, physical evaluation and blood measurements, the dietitian working on the health care team with the physician determines the appropriate diet for the next period of time; the prescription includes specific amounts of the medical food and specific amounts of regular foods. These diets must be very carefully planned as either too

much or too little of the medical food and/or regular foods cause problems for the individual with IEM. In addition, use of medical foods by a person who does not have the IEM for which the medical food is designed to manage leads to nutritional deficiencies with consequences that can include death.

What are the consequences of failing to use medical foods in treatment of IEM?

Failure to initiate treatment with required medical foods results in significant morbidity and in some conditions, mortality. For example, individuals with untreated PKU suffer significant cognitive impairment, autistic-like features, and adult-onset psychosis [11]. Because high phenylalanine levels significantly impair fetal brain and heart development, pregnant women with untreated PKU will most likely bear children with maternal PKU syndrome, a condition that includes intellectual disability, small head size and heart defects. Maternal PKU syndrome is prevented if the fetus is not exposed to excessive phenylalanine during gestation [12]. Individuals with untreated homocystinuria suffer cognitive impairment, lens dislocation, skeletal deformities, and increased risk for stroke and heart attack [13]. Individuals with untreated very long chain acyl-CoA dehydrogenase deficiency may suffer hypoketotic hypoglycemia leading to death or severe impairment and may have cardiomyopathy or growth failure [14]. Each condition could be characterized similarly; they were included in the RUSP because of clear evidence that treatment, typically related to use of medical foods, improved outcomes.

Because all the screened conditions included on the RUSP amenable to intervention with medical foods are genetic disorders, they are permanent. While the likelihood for severe metabolic decompensation varies through the lifespan, and with each individual condition,

optimal outcome requires lifelong treatment. For example, The American College of Medical Genetics and Genomics (ACMG) recently published guidelines for PKU strongly endorsing lifelong treatment, citing later onset complications of treatment discontinuation [15]. Genetic Metabolic Dietitians International (GMDI) published evidence-based guidelines for nutritional management for PKU for affected persons of all ages reinforcing these concerns and defining how treatment should be performed [16] . Despite this knowledge and these recommendations, it is estimated that more than half of adults with PKU are not being followed and are likely untreated.

Poor outcomes for affected individuals can result from failure to use medical foods at all, but also result from insufficient treatment with medical foods, as is seen when a family can afford only part of the prescribed medical food. The costs (including but not limited to cost in dollars) to individual, family and society include:

- Cost of caring for an individual with IEM who has intellectual disability that could have been prevented by appropriate treatment[18]
- Birth defects and intellectual disability in the offspring of a woman with PKU who was not treated before pregnancy[12]
- Loss of life, either because of metabolic crisis or because of consequences of inadequately treated IEM
- Development of incapacitating problems in adults who were treated as children and lost access to medical food as adults. For example, this would include strokes in individuals with homocystinuria and neurologic and mental health problems in individuals with PKU, with increases in failures in school, work, and relationships for those who were previously successful.

How many persons are impacted by a need for medical foods?

All of the conditions included on the RUSP are rare, based on the definition provided in the 1983 Orphan Drug Act, meeting the criterion of occurring in less than 200,000 Americans. Therrell, *et al.* summarized data regarding positive cases identified by newborn screening from 10 years of reporting from the National Newborn Screening Information System (2001-2011). This information was provided voluntarily by states and represents a minimal estimate of the numbers of individuals affected. These data did not include individuals requiring medical food who were diagnosed by means other than the newborn screen. Considering only the sixteen core RUSP conditions requiring medical foods, this report indicates that 4,822 individuals affected with a core RUSP condition were identified over that 10-year period [5].

What are today's medical foods?

The nature of medical foods has evolved remarkably through the years. Beginning with a single product for the treatment of PKU, currently there are many types of products available for most IEM that respond to nutritional interventions. When dietary intervention was first developed a half century ago, diets for individuals with IEM were inherently monotonous, unappealing, and unlike anything approaching a normal diet. Over the years, companies that manufacturer medical foods have gone to great lengths to improve nutrient composition, taste, palatability, and appearance to maximize nutritional status and patient compliance to these difficult dietary regimens. Additional manufacturers have entered the marketplace and a variety of products for a much wider range of IEM is now available. These products come in multiple forms and are designed to provide age-appropriate options for patients, including condition-specific infant

formulas. Medical food products fall into three general categories: products in powder form or ready to drink that are devoid of the offending nutrient but are otherwise nutritionally complete; modular products that are not nutritionally complete but serve to provide a component of the diet devoid of the offending nutrient, such as amino acid mixtures, low volume products, and tablets; and foods modified to be low in protein, such as baked goods, pasta, and meat and cheese substitutes that provide needed calories and satiety.

History of Medical Food Statutes

The first commercial formula for management of an IEM was Lofenalac™, produced in 1958 for the treatment of PKU [19]. The availability of this product revolutionized management of the condition. After it was shown that early intervention prevented intellectual disability caused by PKU, and that a population-based test was feasible, newborn screening was initiated [20,21]. Initially, Lofenalac™ and other products that followed were regulated as drugs by the FDA. In 1972, these products were moved from categorization as drugs to the category of "foods for special dietary use" (FSDU). While this facilitated the expansion of types and availability of medical foods, allowing a less-expensive development process and thus improving access, an unintended consequence was that because medical foods were no longer regulated as drugs, a “loophole” emerged regarding coverage for payment, however well-intended the decision was.

In 1988, the Orphan Drug Amendments (U.S. Congress, Orphan Drug Amendments of 1988)[22] included a formal definition (see above) for medical foods. They were characterized as:

- a food which is formulated to be consumed or administered enterally
- under the supervision of a physician and
- which is intended for the specific dietary management of a disease or condition for

> which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.

While this definition served to identify aspects of "medical foods," ambiguity remained. Ultimately, this includes a potential for misunderstanding which conditions can be included under the rubric of "disease or condition for which distinctive nutritional requirements," opening the door for confusing the very specialized medical foods required for treatment of IEM with nutrition-based dietary treatments for conditions managed by modification of a normal diet or by the avoidance of specific components. Therefore, in 2016, the FDA clarified its thinking regarding the definition of medical foods in their Guidance for Industry[3] specifying their special formulation, emphasizing the requirement that they are to be used when dietary management cannot be achieved by modification of the normal diet alone, and that they are to be used to manage specific conditions under medical supervision. Clarification of the definition did not resolve all the issues with access to medical foods. Because medical foods are regulated under FDA statutes as foods, not drugs, there is an inherent conflict in their status. Foods are typically not used in the "diagnosis, cure, mitigation, treatment, or prevention of disease." These functions are the purview of *drugs* in our regulatory environment. However, while medical foods are administered with the purpose of providing nutrition and are not drugs, medical foods, like drugs, are specifically prepared products used under medical supervision for management of specific diseases.

How do the statutes currently define medical foods and how are they regulated?

Medical foods were distinguished from the category of foods for special dietary use in the regulations because they are intended for the specific dietary management of a disease or

condition to meet the critical and distinctive nutritional requirements for that condition (56 FR 60366 at 60377, November 27, 1991[23]). Additional clarification from the FDA came with Guidance for Industry released in 2016[3]. This guidance indicated that medical foods are specially formulated and processed for partial or exclusive feeding orally or by tube, designed for patients with limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foods or nutrients whereby dietary management cannot be achieved by modification of the normal diet alone, and are to be used to manage the unique nutrient needs of a specific disease or condition determined by medical evaluation. They are required to be used for a patient receiving active, ongoing medical supervision and must be specially formulated for a patient who is seriously ill or who requires the product as a major treatment modality. These features do not pertain to all foods fed to sick patients. Examples of conditions for which the regulatory category of medical food would not apply include pregnancy, which is not a disease, and chronic conditions such as diabetes and celiac disease, because these conditions can be managed with modification of a normal diet without the use of specially-prepared licensed commercial products.

The Federal, Drug, and Cosmetic Act and the Fair Packaging and Labeling Act exempted medical food products from nutrition labeling, health claims, and nutrient content claims requirements. Ingredients must be approved food additives for the intended use or, if not, are Generally Recognized as Safe (GRAS), or have an exemption for investigational use. Medical foods do not require premarket review or FDA approval but manufacturers must be registered with the FDA, must comply with certified good manufacturing processes (cGMP), and are inspected every two years. The FDA does not maintain a list of specific medical food products.

Medical foods intended for use by infants are regulated as infant formula. They are categorized as "exempt" but must meet the same regulatory requirements as standard infant formulas except that they are not required to contain the offending nutrient the absence of which creates the medical foods' effectiveness as a management modality for the respective IEM. These formulas have strict labeling requirements and new products require a 90-day premarket notification to FDA. Unlike medical foods developed for individuals over one year of age, manufacturers who make medical foods for infants are inspected annually.

The 2016 FDA Guidance also described what does not apply to medical foods. They are specifically not prescription drugs, they do not have NDC (National Drug Code) codes and they do not require a prescription. This clarification specifically identified IEM as conditions that a medical food could be used to manage. It was further specified that medical foods could not be marketed for diseases and conditions in which a normal diet could be modified to adequately manage the dietary needs.

How do patients access medical foods and who pays for them?

There is no uniform strategy for supplying medical foods to patients. Because medical foods are regulated as foods not drugs, they may be referred to as “over the counter”; however, in most cases, authorization is required by the pharmacy, company or organization dispensing the product to demonstrate supervision by a medical provider. In some cases, medical foods are dispensed in programs administered by states and are provided as part of their service infrastructure. This is undertaken either by a state directly or by metabolic clinics as part of

arrangements with the state. Families may receive their medical foods from pharmacies, hospitals, health departments, medical supply companies, or medical food companies. Payment for medical foods may occur through programs administered by states (Medicaid, the Children's Health Insurance Program, the Special Supplemental Nutrition Program for Women, Infants, and Children). Coverage of medical foods can also occur using military health benefits by dependents of active duty service members and retirees. Coverage by private insurance is variable. Most medical food companies provide a small supply for newly diagnosed patients and provide some formula for pregnancies in affected women but this practice must be viewed as a bridge until coverage from other sources can be obtained[4] . Many families purchase medical foods out-of-pocket[6]. The source of supply and coverage is thus highly variable and dependent on the age of the patient, gender, the IEM they have, where they live, and what health benefits they have.

As of 2016, 35 states had passed legislative mandates for state or private payer coverage of medical foods[24] . Such coverage, mandated on a state-by-state basis, does not apply to those who are self-insured or where state law was not applicable (e.g., Federal plans). In addition, there is wide variability in coverage from state to state. The IEM community hoped that the Affordable Care Act (ACA) might lead to improvement in access to medical foods, but the ACA did not specifically address medical foods; medical foods were not included as an essential health benefit although newborn screening itself is a covered benefit without co-pay for families.
In 2016, the Catalyst Center, a national center for health insurance and financing for children and youth with special health care needs, prepared an update summarizing state statutes and regulations on dietary treatment of disorders identified through newborn screening. In this

detailed assessment of current state-specific information, the Center found extensive state-to-state differences in diagnoses covered, types of medical foods provided, route of administration, age eligibility and benefit limits, and mandates for private insurance coverage resulting in major gaps for coverage and significant differences based on the state of residence [24] . Coverage was highly dependent on the state in which the individual resided. They found that six states have legislation specifically for medical foods required for children with PKU, six Medicaid programs only cover PKU and one Title V program covered only PKU. Title V refers to a federally funded program administered through a Maternal and Child Health Services Block Grant to support programs for children with special health needs (CSHCN) [25]. Thirty-five states had legislative mandates for coverage of medical foods for genetic IEM, 33 states provided coverage through their Title V/CSHCN or other programs and Medicaid programs in every state provided some level of coverage. Similarly, TRICARE, the health insurance program for military personnel and their families, covers medically necessary medical formula for children. In 2017, a revision to the National Defense Authorization Act extended coverage to adults and expanded coverage for foods modified to be low in protein [26]. The Catalyst Center report confirmed previously ascertained information regarding the highly variable nature of anticipated coverage and the state regulations governing this.

What is the cost to families?

While the vast majority of states have enacted laws requiring insurance companies to cover medical foods, self-insured plans are exempt from state laws regulating the business of insurance under the Employee Retirement Income Security Act (ERISA), and are not required to include medical foods as a covered benefit. Because about half of commercial health insurance plans are

ERISA plans, state insurance regulation has not provided a consistent or robust safety net to guarantee affordable access to medical food. The out-of-pocket costs of medical foods depend on the individual's age, the disorder and insurance coverage status. Therell, *et al.* estimated that annual costs for treating an IEM versus a person without an IEM ranges from $2,254 for an infant to almost $25,000 for an adult male or pregnant woman [5].

Again, using PKU care as an example, in 2012 Camp, *et al.* estimated that the annual wholesale cost to provide medical foods (medical formula only) for an infant was $1,248; for a child in elementary school, the annual cost was $2,643, and for an adult male, the cost was $8,522 [27]. It is important to note that patients and insurance companies typically pay as much as 200-300% of these wholesale costs. The products vary in cost dependent on the amount needed to feed an individual with products intended for use by children costing about twice as much as products for infants. Medical food costs also vary depending on the disorder intended for treatment. On one wholesale site, Phenex-2 (used in management of PKU) is listed at $313.39 per case of six 14.1 oz canisters, while Propimex-2, Hominex-2, and Valex-2 (for propionic/methylmalonic acidemia, homocystinuria, and disorders of leucine metabolism, respectively) are priced at $576.14 per case [28].

Medical food products are more expensive than standard formulas. For perspective, Phenex 1, an infant formula to treat PKU, costs $33 per can, $0.17 per kcal provided in the formula [29]. Similac powder, a comparable infant formula that is not a medical food, costs $16 per can, $0.088 per kcal [30]. The feedings prepared for an infant may contain both of these products. The daily recipe for a typical four-month-old would contain 85 g of Phenex 1 and 65 g of Similac

costing respectively $6.97 and $2.92 for a total cost per day of $9.89. If the baby did not require medical foods and was fed a similar amount with regard to caloric intake of Similac only, the cost would be $6.52 per day. Overall, the medical foods for infants with PKU, which are the lowest cost of an IEM medical food, are about twice what is standard. Moreover, formula costs rise considerably for rarer IEM.

In addition to medical foods, the inclusion of foods modified to be low in protein in daily meals not only provides needed calories, but also saves costs when these foods are used as an energy source versus medical foods alone. Huntington and Buist analyzed the cost comparison of a combination therapy of medical foods and foods modified to be low in protein versus medical foods' protein as a primary energy source for a 9-year old with PKU. If medical foods are the predominant energy source, the cost of treatment is 170% more than using a combination of medical foods and foods modified to be low in protein, which would realize a savings of $8,000 per year[31]. Though their use reduces the cost of dietary management overall, it should be noted that foods modified to be low in protein are two to eight times more expensive than their regular counterparts and typically must be specially ordered and shipped through a medical foods company. For example, Camp *et al.* estimated that the cost per 100 g of regular spaghetti is $0.37 while the low protein version is $2.20 per 100 g[27]. Despite their costs, foods modified to be low in protein are an integral part of dietary management for IEM where protein must be restricted. They allow the affected person to meet needed energy requirements, providing satiety and alternatives to standard foods that must be excluded or severely limited from the diet.

Berry, *et al.* examined insurance coverage for medical foods, dietary supplements, and supplies

for feeding in three Regional Genetics Collaboratives [6]. They found that although nearly all children with IEM had medical coverage, the cost to families "out-of-pocket" was notable for all types of products. For medical foods, 11% of families reported spending not covered by any insurance. For families needing to use foods modified to be low in protein, 59% reported out-of-pocket costs. The burden is not insubstantial: 21% of families using medical foods reported additional treatment-related expenses of $100 or more per month beyond the anticipated costs expected for feeding an unaffected child; a few families reported these costs exceeded $500 per month.

The New York-Mid Atlantic Regional Collaborative (NYMAC) conducted a survey of persons affected with PKU (Unpublished results – NYMAC, Beth Vogel, Project Manager). They found that although most individuals had used medical foods, many, particularly older patients, had difficulty getting their preferred type of product. Individuals receiving public insurance paid less out-of-pocket but the average out-of-pocket expenses for the group in the prior month were $337.50 (range zero to $2500). Forty-three percent of the respondents experienced gaps in coverage and 39% indicated that this gap occurred repeatedly. Although they found that the majority of their respondents did not have to pay out-of-pocket for medical foods specifically, 10% of individuals paid for at least half the cost out-of-pocket and 30% had no insurance coverage for their necessary medical foods. Like the observation in Berry*, et al.* [6], foods modified to be low in protein were much less frequently covered, and the majority of respondents had to pay for these products entirely out-of-pocket, receiving no coverage from insurance or other assistance. Respondents also reported experiencing requirements for a specific supplier, observation of "loopholes" for coverage, and problems arising if any insurance or provider

change occurred. The study group concluded that coverage was particularly a limitation for adults.

Healthcare Common Procedure Coding System (HCPCS) billing codes are used by Medicare and monitored by Centers for Medicare & Medicaid Services (CMS) [32]. Private insurance companies may or may not adopt these codes. This coding system causes problems for medical food reimbursement [31]. For example, the code B4155, covers enteral formula for IEM administered through an enteral feeding tube and specifies that one reimbursed unit equals 100 calories [32]. CMS defines "enteral" as feeding through a tube into the gastrointestinal tract, as opposed to consumption orally. Most individuals with IEM are oral eaters and do not require tube feeding. This can result in denial of reimbursement, or worse, performance of a surgical procedure to provide an "enteral" route. Furthermore, calculations for diets for IEM are based on grams of protein, not calories. Products for older children and adults are high in protein, and low in calories so reimbursement falls short of need as it is based on the wrong key element in the diet calculation.

Other costs in the current system:

Surveys of families and providers reveal that time is another important cost that needs to be considered. Families spend hours on the telephone and involved in paper work, communicating with providers and payers for pre-approvals and appeals. For some families, there is a cycle of insurers requiring re-application monthly or annually. When there is a change in insurance, the process begins again. Some families describe that the effort to access medical foods becomes "a full-time job." Working with families, health care providers also spend hours providing

documentation. Physicians, registered dietitians, and genetic counselors and their office staff spend hours filling out paper work for pre-approvals, requesting reconsideration of denials, and having telephone and even face-to-face meetings with insurers to protest denials. The work of the professional staff on these activities is not compensated.

It is more difficult to put a dollar value on the stress that families experience when they do not know whether or when access to the medically-necessary medical food will be granted. Health care providers also experience stress as they attempt to prioritize their limited time between medical management and the time required for pre-approvals and appeals when access is denied.

History of remediating efforts:

The Advisory Committee for Heritable Disorders in Newborns and Children (ACHDNC) has long recognized the inherent contradiction of requiring screening without ensuring treatment. Written communications specifically addressing medical foods from the ACHDNC to the Secretary of the Department of Health and Human Services in 2007, 2009, and 2010 recommended addressing gaps in coverage and reimbursement and urged a more uniform approach to coverage, specifically requesting that Medicaid regulations be amended to extend uniform coverage to all states. No actions directed at coverage for medical foods have resulted from these communications [33].

External to the ACHDNC and its subcommittees, several federal legislative initiatives have been undertaken. The Medical Foods Equity Act (MFEA) of 2011 (S. 311; John Kerry) included provisions that federal health programs and private insurance companies cover “medically

necessary food" and "pharmacologic doses" of vitamins and amino acid supplements as prescribed by qualified medical providers. It amended the Social Security Act definition of these products specifically for conditions as recommended by the ACHDNC. The MFEA of 2013 (H.R. 3665; John Delaney) used the same language and descriptors but removed the requirement for private insurance companies to cover these products. While these provisions would have improved access and management for persons with IEM, neither version of the legislation was enacted. A similar bill, the Medical Nutrition Equity Act (MNEA) of 2017 (H.R 2587; John Delaney) has recently been introduced. The American Health Security Acts of 2011, 2013, and 2015 (H.R. 1200 McDermott) proposed coverage for medical foods and reiterated the 1988 medical food definition, but no committee action occurred to enact this legislation. Of note, federal action for medical food coverage has taken place in one specific area, that of coverage by TRICARE, the health care program for uniformed service members and their families [26].

The 2017 revision to the National Defense Authorization Act defining TRICARE benefits notably improved coverage for families with a member affected with an IEM. Medical foods, medical equipment and supplies to administer, medically necessary vitamins, and modified low protein foods ordered by a medical provider were all specifically included benefits based on descriptions found in FDA guidance. The legislation exempts specific conditions (gluten sensitivity, diabetes, weight loss products) but specifies coverage for RUSP disorders as well as a list of IEMs not on the RUSP but treated similarly. Coverage is also mandated for medical foods used to treat a specified list of gastroenterological disorders [26]. This language is mirrored closely in H.R 2587, the 2017 MNEA.

Advocacy organizations (for example, National PKU Alliance and the National Organization for Rare Disorders) have strongly encouraged coverage through positions on medical food coverage in the ACA, urged appropriate education about coverage, sought appropriate coding for billing, and interacted directly with the FDA regarding the definition of medical foods. They led the way in advocacy for federal legislation and created position statements [34,35]. Despite concerted and thoughtful advocacy, little effect on regulation has occurred. Professional organizations (for example, the Society for Inherited Metabolic Disorders, Genetic Metabolic Dietitians International, the American College of Medical Genetics and Genomics, the American Medical Association, and the American Academy of Family Physicians) have also created policy statements, and more recently several professional guidelines, describing the essential character of these interventions and providing details about management that can be used to guide appropriate coverage [15,16]. The problem has been well described in the medical literature and at scientific consensus conferences (e.g., Camp *et al*.[36]) highlighting the necessity of establishment of uniform policies and strategies to remove financial barriers for appropriate treatment. The literature also describes a central barrier in attaining uniform access: laws and mandates regarding coverage are established on a state-by-state basis with varying state laws and programs.

Summary:

IEM are included on the Recommended Uniform Screening Panel because effective interventions are available, but financial barriers interfere with access to those interventions for a significant number of patients and their families. Patients and families continue to be saddled with high costs for medical foods, and metabolic care teams spend significant time dealing with

coverage and reimbursement requirements, leaving less for patient care and research. Families also spend significant time attempting to obtain coverage and reimbursement, leaving less time for normal life experiences and causing chronic anxiety about access to necessary treatments. Legislation has been introduced, advocates have spoken, professional organizations have provided expert opinion and recommendations, but the division of responsibilities between federal and state regulators as well as ambiguities about the regulation of medical foods have resulted in costly inaction. The recent inclusion of medical foods, the medical equipment and supplies to administer them, the medically necessary vitamins, and the modified low protein foods ordered by a medical provider as TRICARE benefits in the 2017 revision to the National Defense Authorization Act[26] is evidence that a uniform approach to access can be achieved.

It is time to provide stable and affordable access to the effective management required for optimal outcomes through the lifespan of patients after identification of an IEM either by newborn screening or clinical diagnosis.

The ACHDNC affirms the following principle:

- Medical foods as defined by the FDA should be covered as required medical benefits for persons of all ages who are diagnosed with an IEM (whether specified on the RUSP or identified in clinical practice), when the medical food requires authorization by a medical provider and the patient requires ongoing medical supervision and dietary intervention that cannot be achieved by modification of a normal diet alone.

Accomplishing this task will require planning and communication among all stakeholders. Recognizing the complexity of the actions required to accomplish comprehensive coverage for medical foods, the ACHDNC recommends a meeting of stakeholders to reach an agreement on how best to accomplish this goal expeditiously.

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