Medical Foods for Inborn Errors of Metabolism: Issues in Patient Access

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Medical Foods . . . .

- Are the only recognized therapy for many IEM identified on newborn screen and clinically
- Reduce morbidity and mortality
- Have a half century history of use

So, why aren’t they accessible to all patients of all ages?
Focus of Discussion

• History of medical foods statutes in the U.S.
• Why and how they are used
• What a medical food is and what it is not
• Barriers to access and reimbursement
• Previous activities to rectify the problem
• Thoughts for a plan for moving forward

Disclaimer:
These are my views
I have no disclosures
History of Medical Food Statutes
1958 to 1972, commercial formulas for IEM were regulated as drugs

1972

Foods for Special Dietary Use

- Usefulness widely accepted
- Limited in number
- Less costly to develop

1973

Medical Foods
History, cont:

• 1988, Orphan Drug Amendments created the definition for medical foods 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.”

• Did not provide FDA with an evaluation mechanism to determine what fits and what does not
Inherent conflict! Foods cannot be used to “diagnose, cure, mitigate, or treat” disease
Medical Food for PAH Deficiency (PKU)—This Was Then
Medical Foods for IEM Today
Medical Food Categories

• Products with a full complement of nutrients EXCEPT the offending nutrient (e.g., for PAHD excludes phenylalanine)
  • Power to be reconstituted
  • Ready to drink
  • Bars

• Modular products
  • Amino acid mixtures
  • Ready to drink, low volume, low calorie
  • Tablets
  • “Sport drinks”

• Foods modified to be low in protein
  • Baked goods, pasta, rice
  • Meat and cheese substitutes
  • Snack foods
Medical Foods Are Management Modalities for Inborn Errors of Metabolism Identified on Newborn Screen

• 19 of the core conditions on the RUSP utilize medical foods and/or amino acids, vitamins, or cofactors

• These conditions wouldn’t be on the RUSP if it weren’t for these treatments

• Medical foods are required for other IEM diagnosed clinically (e.g., argininemia, OTC deficiency)
# Core RUSP Conditions

## Metabolic Disorders

<table>
<thead>
<tr>
<th>Organic Acidurias</th>
<th>Fatty Acid Oxidation</th>
<th>Amino Acids</th>
<th>Hematology</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propionic acidemia</td>
<td>Carnitine uptake defect/carnitine transport</td>
<td>Classic Phenylketonuria</td>
<td>Sickle cell anemia</td>
<td>Biotinidase deficiency</td>
</tr>
<tr>
<td>Methylmalonic academia (MUT)</td>
<td>Medium-chain acyl-CoA dehydrogenase</td>
<td>Maple syrup urine disease</td>
<td>S,β-thalassemia</td>
<td>Congenital adrenal hyperplasia</td>
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<tr>
<td>Methylmalonic academia (Cbl A,B)</td>
<td>Very long-chain acyl-CoA dehydrogenase</td>
<td>Homocystinuria</td>
<td>Sickle – C disease</td>
<td>Congenital hypothyroid</td>
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<tr>
<td>Isovaleric acidemia</td>
<td>Long-chain L-3-hydroxyacyl-CoA dehydrogenase</td>
<td>Tyrosinemia 1</td>
<td></td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>3-Hydroxy 3-methylglutaricaciduria</td>
<td>Trifunctional protein deficiency</td>
<td>Argininosuccinate aciduria</td>
<td></td>
<td>Classic</td>
</tr>
<tr>
<td>3-Methylcrotonyl-CoA carboxylase</td>
<td></td>
<td>Citrullinemia I</td>
<td></td>
<td>Galactosemia</td>
</tr>
<tr>
<td>Holocarboxylase synthase def</td>
<td></td>
<td></td>
<td></td>
<td>Pompe</td>
</tr>
<tr>
<td>β-Ketothiolase deficiency</td>
<td></td>
<td></td>
<td></td>
<td>Hearing loss</td>
</tr>
<tr>
<td>Glutaric acidemia 1</td>
<td></td>
<td></td>
<td></td>
<td>Severe combined immunodeficiency</td>
</tr>
</tbody>
</table>

Conditions in bold are treated with medical foods and/or single amino acids, amino acid mixtures, vitamins, or other cofactors
Failure to Treat--Examples

Depends on the condition

• Classic phenylketonuria (PKU)
  • Severe cognitive impairment, autistic-like features
  • Maternal PKU syndrome

• Homocystinuria
  • Cognitive impairment, ectopia lentis, osteoporosis, skeletal deformities

• MSUD
  • Cognitive impairment, growth failure, seizures, coma, cerebral edema, possibly death

• VLCADD
  • Hepatomegaly, cardiomyopathy, hypoketotic hypoglycemia, growth failure
Basic Principles of Dietary Management for IEM Using Phenylalanine Hydroxylase Deficiency (PKU) as an Example
Normal Phenylalanine Metabolism

Phenylalanine hydroxyalase

Food → Phenylalanine → tyrosine → DOPA, NE, EPI, Melanin

Catabolized tissue
Phenylalanine Hydroxylase Deficiency

Food

Phenylalanine

Catabolized tissue

\[ \text{Phenylalanine} \rightarrow \text{tyrosine} \]

\[ \text{tyrosine} \rightarrow \text{DOPA, NE, EPI, Melanin} \]
Phenylalanine Hydroxylase Deficiency

Phenylalanine

Food → Phenylalanine

Catabolized tissue → Phenylalanine

Phenylalanine → Phenylpyruvate

Phenylpyruvate → Phenylacetate, Phenyllactate

Phenylalanine → PHE, PHE, PHE, PHE, PHE

TRP → TRP

TYR → TYR

PHE → serotonin

tyrosine → DOPA, NE, EPI, Melanin
Phenylalanine Hydroxylase Deficiency

Solution:

- **Restrict the precursor**

  - **Phenylalanine**

  - **Food**
  - **Catabolized tissue**

  - **tyrosine**
  - **DOPA, NE, EPI, Melanin**

- **Supply the product and other essential nutrients**
That Is Done with Medical Foods

• Supply a source of protein for body growth and development
• Devoid of the offending nutrient
• Also contains essential nutrients, carbohydrate, and fat

• Along with the small amount of natural protein in a carefully planned diet
• Is the primary intervention
• Prevent or reduce adverse medical and developmental outcomes
• When used early at or near birth and continued throughout life can lead to normal or near-normal health outcomes
Medical Foods Work!
Sample daily intake for a 8 yr old with PAH deficiency
Phe tolerance of 350 mg (~ 6 g natural protein)

<table>
<thead>
<tr>
<th>Meal</th>
<th>Item</th>
<th>g pro</th>
<th>kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast:</td>
<td>1 slice low pro bread</td>
<td>0.2</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>8 oz medical formula</td>
<td>1.4</td>
<td>190</td>
</tr>
<tr>
<td>Lunch:</td>
<td>1 rice cake w 1 t marg</td>
<td>0.8</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>1/2 cup low pro soup</td>
<td>0.2</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>5 saltine crackers</td>
<td>1.4</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>8 oz medical formula</td>
<td>14</td>
<td>190</td>
</tr>
<tr>
<td>Snack:</td>
<td>2 c popcorn w 2 t marg</td>
<td>1.8</td>
<td>164</td>
</tr>
<tr>
<td>Dinner:</td>
<td>50 g low protein rice</td>
<td>0.3</td>
<td>176</td>
</tr>
<tr>
<td></td>
<td>3 T tomato sauce</td>
<td>0.6</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>8 oz medical formula</td>
<td>14</td>
<td>190</td>
</tr>
<tr>
<td>Snack:</td>
<td>3/4 oz potato chips</td>
<td>1.3</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>12 oz fruit drink</td>
<td>0</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>49 g</strong></td>
<td><strong>1400 kcal</strong></td>
</tr>
</tbody>
</table>

**Reality Check:**

- **1 oz cheese** = 355 mg Phe
- **1 oz chicken** = 345 mg Phe

6 g protein and 583 kcal from natural foods
43 g protein and 825 kcal from medical foods
Dinner: Represents 1/3 of the Phe allotment
Dinner: Add medical foods and you get a meal
The gear needed to feed a child with maple syrup urine disease
How do the statutes define medical foods?

- They are distinguished from the category of foods for special dietary use in that they
  - Are intended for the specific dietary management of a disease or condition (56 FR 60366 at 60377, November 27, 1991)
  - Meet distinctive nutritional requirements of a disease or condition
  - Used under medical supervision
- Specially formulated for the patient who is seriously ill or who requires the product as a major treatment modality
- Oral or tube feeding
- Does not pertain to all foods fed to sick patients
Medical Foods Labeling

• Labeled for the dietary management of a specific medical disorder, disease, or condition for which there are distinctive nutritional requirements

• Labeled for use under medical supervision
How are medical foods regulated?

• Federal Food, Drug and Cosmetic Act and the Fair Packaging and Labeling Act
  • Exempt from nutrition labeling, health claims, and nutrient content claims requirements
  • Ingredients must be approved food additives for their intended use or if not Generally Recognized as Safe (GRAS), have an exemption for investigational use

• Medical foods do not require premarket review or approval by FDA
  • Manufacturers must be registered with FDA, must comply with cGMP, and are inspected every 2 years

• FDA does not maintain a list of medical food products
What about infant formulas for IEM?

- Considered to be medical foods but regulated as infant formulas
- Categorized as “Exempt” infant formulas
- Must meet the same regulatory requirements as standard infant formulas, except
  - They are not required to contain the offending nutrient
- Have strict labeling requirements
- New products require a 90-day premarket notification to FDA
FDA Draft Guidance for Industry 2013

Further clarified FDA thinking on medical foods

• Definition of medical foods narrowly constrains the types of products that fit within this category
  • Specially formulated and processed--as opposed to naturally occurring
  • For partial or exclusive feeding orally or enteral feeding by tube
  • For a patient with limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foods or certain nutrients whereby dietary management cannot be achieved by modification of the normal diet alone
  • Used to manage unique nutrient needs resulting from a specific disease or condition determined by medical evaluation
  • Intended for a patient receiving active, ongoing medical supervision
• Final guidance has not yet been released
What Medical Foods Are Not

They are not prescription drugs
• No premarket review or approval
• They do not have NDC codes
• They do not require a prescription
  • But, the regulation states that they are to be used under medical supervision

They are not products developed for
• Pregnancy (unless the pregnant woman has PKU, for example), because pregnancy isn’t a disease
• Diabetes because people with diabetes can modify a normal diet

2013 FDA Draft Guidance
What Do Medical Foods Cost?

A lot!

But a whole lot less than Kuvan® at $200,000 per year for an adult with PAH deficiency
### Estimated Costs Per Year for Medical Foods for IEM, by Selected Age Group

<table>
<thead>
<tr>
<th>Age</th>
<th>Medical Foods with Protein Wholesale Cost (x 2.0 for markup) (A)</th>
<th>Foods Modified to be Low in Protein (B)</th>
<th>Total Cost for IEM Medical Foods (C=A+B)</th>
<th>Estimated Annual Expenditure for Foods (Non IEM) (D)</th>
<th>IEM-related MF Costs in Excess of Estimated Expenditure (C - D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant &lt; 1 yr</td>
<td>$1,817 ($3,634)</td>
<td>$0 — minimal</td>
<td>$3,634</td>
<td>$1,380*</td>
<td>$2,254</td>
</tr>
<tr>
<td>School-age (9-13)</td>
<td>$6,249 ($12,499)</td>
<td>$2,200 + $120 shipping</td>
<td>$14,819</td>
<td>$2,255*</td>
<td>$12,564</td>
</tr>
<tr>
<td>Late teen male</td>
<td>$9,551 ($19,102)</td>
<td>$5,000 + $120 shipping</td>
<td>$24,222</td>
<td>$2,525*</td>
<td>$21,700</td>
</tr>
<tr>
<td>Adult male or pregnant woman</td>
<td>$11,021 ($22,042)</td>
<td>$4,500 + $120 shipping</td>
<td>$26,662</td>
<td>Ave family of 4 spent $6,100** ($2,000 for adult)</td>
<td>$24,662</td>
</tr>
</tbody>
</table>

* Lino (2008). Estimates are based on the average of the highest and lowest income level.
**U.S. Census Bureau (2007).
What Medical Foods Cost to Families

• Costs per month paid out of pocket
  • 21% of parents paid >$100 for medical formula (some >$500)
  • 48% of parents paid >$100 for low protein foods

Berry 2013
How Patients Get Medical Foods

- Purchase out of pocket from pharmacies, hospitals, health departments, medical supply and medical food companies
  - Reimbursed by private insurance
  - Or not
- Programs administered by States
  - Medicaid/CHIP/WIC
- Military health benefits
- Newborn screening programs or metabolic clinics
- Many patients utilize multiple sources

Most medical food companies provide a small supply for newly diagnosed patients and cover some formula for pregnancies.

Berry 2013; Therrell 2014
Who Pays?

Depends on:

• Who you are (age, disorder)

• Where you live

• What type of health benefits you have
State Insurance Mandates

Prior to ACA, 38 states had passed mandates for State or private payer plan coverage
Since ACA?

• Don’t really know. No formal national survey of State practices has been undertaken

• ACA does not specifically address coverage of medical foods for IEM although newborn screening is a covered benefit without co-pay to families

• States with mandates may still have these mandates
  • Still may not apply to self-insured or Federal plans
  • Still have many inconsistencies and limited coverage
Here’s What Metabolic Dietitians Report

• Patient with PKU lives in NH (has a mandate) but has an IL insurance plan (no mandate). The patient’s IL plan rejected coverage for metabolic formula.

• Patient living in MD (has a mandate) has Federal BC/BS which does not cover medical food for patients over age 22 unless it is tube-fed or the sole source of nutrition so many adults are untreated.

• NJ has a comprehensive mandate, but Medicaid does not cover low protein foods.

• Patients in PA (has mandate for formula only) are not able to get low protein foods which affects their ability to fully comply with the diets.
How Outcomes Are Affected by State Policies

• NY is losing underinsured adults to care. It is hard to keep a patient motivated to seek care when they do not have a good paying job that has good insurance and the co-pays and co-insurances are prohibitive.

• This lack of access to medical foods and subsequent need to have multiple jobs to pay out-of-pocket leads to inconsistent metabolic control

• In VA state formula program became more restrictive after 2006 expanded NBS
Healthcare Common Procedure Coding System (HCPCS)

• Billing codes used by Medicare and monitored by CMS

• B4162—Enteral formula for IEM administered through an enteral feeding tube, 100 calories = 1 unit
  • CMS limits definition of “enteral” to tube feeding
  • Reimbursement units are based on calories
    • Calculations for diets for IEM are based on grams of protein
    • Products for older children and adults are high protein, low calorie so reimbursement falls way short of needs

• Private insurance companies may or may not adopt these codes
Efforts to Fix the Problem
Your Letters to the Secretary

May 19, 2009

- Committee reiterated 2007 recommendation to address gaps in coverage and reimbursement
  - More uniform approach and to amend Medicaid for uniform coverage by State programs
- Response on October 2, 2009
  - Enacting legislation is beyond the Department’s authority

June 14, 2010

- Committee recommended that health reform ensure access to medical foods and foods modified to be low in protein as essential health care services irrespective of the source of health coverage
- Interim Response on July 29, 2010
  - A response will be forthcoming
- Response on December 14, 2010
  - ”I cannot adopt the Committee’s recommendations at this time”; awaiting a DOL survey and IOM public workshop
Past Efforts--Legislative

- Medical Foods Equity Act (MFEA) of 2011 (S. 311; John Kerry)
  - Federal health programs and private insurance companies will cover
    - “medically necessary food” including formulas, pills, capsules, and bars;
    - Foods modified to be low in protein;
    - “pharmacological doses” of vitamins and amino acids as prescribed by a qualified medical provider.
  - Amends the Social Security Act definition of these products specifically for the treatment of conditions as recommended by the ACHDNC
- MFEA of 2013 (H.R. 3665; John Delaney)
  - Removed the requirement for private insurance companies to cover these products.
Past Efforts—Legislative

• American Health Security Act of 2011, 2013, 2015 (H.R. 1200 McDermott)
  • Provides coverage for medical foods and reiterated 1988 medical food definition
  • No committee action in any of the Congresses

• S.Res.324 – Designated December 3, 2015 as National Phenylketonuria Awareness Day
  • Multiple mentions of medical foods
Past Efforts—Advocacy Organizations

- NPKUA has advocated for coverage and reimbursement in a number of ways
  - Position statement on medical food coverage in the ACA
  - Educational information and resources on coverage under ACA for patients/families
  - Secured lead sponsors and led advocacy efforts for MFEA
- NORD hosted a conference on medical foods in Feb 2011
  - Address problems with HCPC codes
  - Revisit current definition of medical foods used by FDA
  - Support federal legislation
  - Investigate possibility of getting medical foods defined as essential health benefit in healthcare reform
Past Efforts—Literature and Professional Organizations

- Journal articles (e.g., Huntington 2009, Weaver 2010; Camp 2012; Berry 2013; Therrell 2014)
- SIMD & GMDI—Policy statements on Medical Foods 2007; SIMD updated in 2016; others, e.g. AAP
- ACMG—Management guidelines
  - PAH Deficiency—”Treatment for life mandates the need for medical insurance to provide coverage for medications and medical foods regardless of age.” (Vockley GIM 2014)
- GMDI—Management guidelines
  - PAH Deficiency—”Ensure access to medical and modified low-protein foods.” (Singh GIM 2014)
Consensus Statement on Phenylketonuria, 2000

- “Uniform policies need to be established to remove from the individual and the family financial barriers to the acquisition of medical foods and modified low-protein foods”
- Reimbursement should be covered by third-party providers. (Pediatrics 2001 108:972)

PKU Scientific Review Conference, 2012

- Full access across the lifespan to medical foods and foods modified to be low in protein provides the tools to succeed in managing PKU effectively on a daily basis. However, availability is inconsistent due to a patchwork of state laws and state programs that impact access (Camp and Parisi, et al. MGM 2014 112:87)
The Players

- Congress—legislation
- FDA—regulation
- CMS—Medicare, Medicaid, and CHIP; HCPCS
- HRSA—health services
- NIH—research
- USDA—funds states to administer WIC programs
- States—legislation; health services, WIC, etc.

- Patients/families/advocacy organizations
- Professional societies and organizations
- Clinicians and researchers
- Medical food and pharmaceutical companies
Congress—Legislation

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Thoughts on Where We are Now

- IEM are screened conditions because treatments are available--but not for everyone
- Patients and families continue to be saddled with high costs for medical foods
- Clinicians spend significant time dealing with coverage and reimbursement, leaving less for patient care and research
- Families spend significant time dealing with coverage and reimbursement, leaving less time to play with their kids
- > 50% of adults with PKU are not being followed (Berry 2013)
- Effect of the ACA on coverage and reimbursement nationally for medical foods is not known at this time
- Bills introduced but Congress has taken no action
The Future

• New treatments

• Patients want this!

Meanwhile, almost 500 babies are born each year with an IEM requiring medical foods as the primary management modality

• A small percentage of all children but it’s 100% to patients and their families
A Way Forward – Access for All

- Understand the current status of State mandates
- Efforts currently being undertaken

- Policy makers at the Federal and State level recognize the changes that need to be made
- Everyone gathers together to chip away at the barriers and challenges
- Other thoughts?

Regardless, it will take leadership, commitment, and persistence to navigate the complexities that lie ahead
Thank You

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