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Expanding research to provide an evidence base for nutritional interventions for the management of inborn errors of metabolism ☆

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ABSTRACT

A trans-National Institutes of Health initiative, Nutrition and Dietary Supplement Interventions for Inborn Errors of Metabolism (NDSI-IEM), was launched in 2010 to identify gaps in knowledge regarding the safety and utility of nutritional interventions for the management of inborn errors of metabolism (IEM) that need to be filled with evidence-based research. IEM include inherited biochemical disorders in which specific enzyme defects interfere with the normal metabolism of exogenous (dietary) or endogenous protein, carbohydrate, or fat. For some of these IEM, effective management depends primarily on nutritional interventions. Further research is needed to demonstrate the impact of nutritional interventions on individual health outcomes and on the psychosocial issues identified by patients and their families. A series of meetings and discussions were convened to explore the current United States' funding and regulatory infrastructure and the challenges to the conduct of research for nutritional interventions for the management of IEM. Although the research and regulatory infrastructure are well-established, a collaborative pathway that includes the professional and advocacy rare disease community and federal regulatory and research agencies will be needed to overcome current barriers.

Abbreviations: IEM, inborn errors of metabolism; NIH, National Institutes of Health; ODS, Office of Dietary Supplements; ORDR, Office of Rare Diseases Research; HRSA, Health Resources and Services Administration; PKU, phenylketonuria; PAH, phenylalanine hydroxylase; PHE, phenylalanine; ODA, Orphan Drug Act; FDA, Food and Drug Administration; CTSA, Clinical and Translational Science Award; RDCRN, Rare Diseases Clinical Research Network; NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; NBSTRN, Newborn Screening Translational Research Network; CDER, Center for Drug Evaluation and Research; RDP, Rare Diseases Program; OOPD, Office of Orphan Product Development; FD&C Act, Federal Food, Drug and Cosmetic Act; DSHEA, Dietary Supplement Health and Education Act; PCMH, patient-centered medical home; ACA, Patient Protection and Affordable Care Act; LTFU, long-term follow-up; NCATS, National Center for Advancing Translational Sciences; HIE, health information exchange; CER, Comparative Effectiveness Research; PCORI, Patient-Centered Outcomes Research Institute; GRDR, Global Rare Disease Patient Registry and Data Repository; IRB, institutional review board; GPCI, Genetics in Primary Care Institute.

☆ The findings and conclusions of this report are those of the authors and do not necessarily represent the views of the NIH, the U.S. FDA, or the U.S. Department of Health and Human Services.

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1. Introduction

The purpose of this paper is to describe the need for research on nutritional interventions used in the management of individuals with inborn errors of metabolism (IEM) across their life span. To facilitate research in this arena, the trans-National Institutes of Health (NIH) initiative, Nutrition and Dietary Supplement Interventions for Inborn Errors of Metabolism (NDSI-IEM), was launched in 2010 and an NIH-sponsored NDSI-IEM workshop was held in December 2011 to initiate discussions with the IEM community. The findings from the NDSI-IEM workshop, input from additional rare disease and metabolic disorders experts, and a review of the literature were used in the development of this paper. A description of IEM, the research and regulatory infrastructure in the United States that governs the discovery and approval of pharmaceutical drug treatments and nutritional interventions for rare disorders and IEM, the challenges and barriers to conducting research and developing new treatments and interventions and proposed solutions to these challenges, and tools and resources useful for researchers are provided.

1.1. NDSI-IEM: an initiative to build a research framework for IEM

NDSI-IEM was established within NIH's Office of Dietary Supplements (ODS) and Office of Rare Diseases Research (ORDR). The mission of NDSI-IEM is to: identify gaps in research on the safety and utility of nutritional interventions for IEM. Through collaboration with multiple interested parties, challenges and barriers that limit evidence-based research and solutions to improve the evidence base for the nutritional interventions used in IEM will be identified.

The NDSI-IEM workshop that was convened in late 2011 included representatives from advocacy and patient organizations; professional associations; companies that make prescription drugs, medical foods, and other nutritional products used in IEM; the Health Resources and Services Administration's (HRSA) Genetic and Newborn Screening Services Regional Collaboratives; agencies, institutes, and centers within the Department of Health and Human Services; and the metabolic clinical, research, and academic community. In addition to identifying knowledge gaps and the challenges and barriers to the conduct of evidence-based research for nutritional interventions for IEM, activities were proposed that would support the metabolic research community. These activities have been organized into short-, mid-, and long-range projects and in addition to the development of this paper, other NIH-sponsored and professional association activities are underway.

1.2. IEM: the need for a research agenda

IEM include inherited biochemical disorders in which specific enzyme defects interfere with the normal metabolism of exogenous (dietary) or endogenous protein, carbohydrate, or fat [1]. As a result of reduced or absent enzyme activity, there is an accumulation of a precursor to the controlled reaction and a subsequent deficiency of a product which can lead to morbidity and mortality. This definition is the intellectual basis for understanding the use of dietary manipulation to manage these disorders. Nutritional interventions can bypass or overcome the metabolic consequences of the genetic mutations for some IEM, but are required lifelong [1]. Nutritional products used in the dietary management of IEM include: medical foods that provide the majority of nutrient needs, specialized for individual disorders; and dietary supplements that are used to enhance diminished catalytic function, replace conditionally essential nutrients, or provide essential nutrients that may be missing due to dietary restrictions. The regulation of these products is described in Sections 2.1 and 2.3.

Phenylketonuria (PKU), the "poster child" for much of our understanding of IEM, exemplifies successful management by dietary manipulation and its impact on the patient, family, and society. PKU is due to a defect in the functioning of phenylalanine hydroxylase (PAH) or secondarily to defects in synthesis or recycling of tetrahydrobiopterin, a cofactor for PAH. PAH is an enzyme that converts the amino acid phenylalanine (PHE) into its sister amino acid, tyrosine. Left untreated, PKU causes PHE to accumulate in the blood and brain and can lead to severe cognitive impairment in virtually all individuals affected. A series of studies in affected patients and their newborn siblings demonstrated that restricting PHE in the diet by lowering protein intake and supplementing the other 19 amino acids in a special formula prevented progression of the condition. The success of dietary intervention led to the development of newborn screening for PKU in all countries of the developed world and the potential to eliminate severe cognitive impairment due to this condition. While costly, the diet proved to be an excellent investment for society showing a favorable benefit-to-cost ratio [2,3]. The development and use of multiplex technologies such as tandem mass spectrometry has expanded the number of disorders screened and most State newborn screening programs are now screening newborns for more than 30 conditions [4,5]. Newborn screening also has improved our understanding of the clinical variability and heterogeneity of IEM and has identified patients whose biochemical changes may have otherwise gone unnoticed in the absence of the screening process.

The dramatic success of nutritional interventions for PKU and some other IEM comes at a price to the patient who faces foregoing a normal diet, and the emotional and financial cost to the patient and family who must commit to this difficult dietary regimen for life. An increasing market for nutritional products for the management of IEM detected through expanded newborn screening, and vastly improved medical foods and development of foods modified to be low in protein have helped to alleviate the severity and monotony of the dietary restrictions endured by patients with these disorders. However, the improved nutritional composition and palatability of new products have not totally mitigated the difficulties in coping with current dietary regimens. In addition, as many patients eventually relax their dietary vigilance, a new set of medical and psychological problems develops [6,7].

While nutritional interventions are the standard-of-care for many IEM, the extent to which all patients identified through newborn screening or in a clinical setting will benefit from or even require such interventions, is unknown. In addition, patients and their families and health care professionals may need to rely on nutritional interventions that often have not been studied in clinical trials. Participants of the 2011 NDSI-IEM workshop indicated that further research is needed regarding the impact of nutritional interventions on health outcomes and on the psychosocial issues identified by patients and their families. To understand the complexities involved in conducting research on nutritional interventions for IEM, we provide an overview of the entities that fund research and regulate medical products below.

2. Current federal research infrastructure for rare disorders and IEM

2.1. The Orphan Drug Act and IEM

The Orphan Drug Act (ODA) [8,9], was approved by the 98th U.S. Congress in 1983, and subsequently amended in 1984, 1985, and 1988. ODA facilitates the development and availability of drugs to treat rare diseases and provides the legislative basis for most of the research for rare disorders, including IEM. Because of ODA, both NIH and the Food and Drug Administration (FDA) now have specific programs that focus on research and development of treatments for IEM, as outlined below. While the legislation connects the research activities of NIH with the regulatory processes of FDA for drug development for rare disorders, including IEM, there is no similar connection between the research and regulatory processes for nutritional interventions for IEM.

The 1988 amendment defined a rare disease as a disease or condition with prevalence of less than 200,000 individuals in the U.S. population