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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.

## Keywords

Inborn errors of metabolism; Newborn screening; Genetic; Rare diseases; Dietary supplements; Medical foods

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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 and for which there is little realistic chance of generating industry interest in drug development because the cost of development would far outweigh any revenue generated by sales. Rare diseases, representing an estimated 7000 discrete disorders [10], collectively affect six percent of the U.S. population or between 25

and 30 million people [11]. The term “orphan product” was defined by the ODA to describe drugs, biologics, and medical devices developed to treat rare diseases, including IEM.

The 1988 amendment to ODA also created a definition of medical foods [12], 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.” Medical foods include infant formulas developed specifically for IEM and those products developed and marketed to persons over 1 year of age that meet the definition of a medical food. Regulatory infrastructure for approval for the use of drugs for rare disorders, including IEM, is quite different from the regulatory infrastructure that governs the marketing, distribution, and third-party reimbursement for dietary supplements and medical foods. As a result, a dichotomy exists between the federal regulatory, research, and payer agencies and the pharmaceutical industry and research communities regarding the use of drug treatments versus dietary supplements and medical foods in the management of IEM.

## 2.2. National Institutes of Health

**2.2.1. Research programs and initiatives**—NIH is the largest funder of biomedical research in the world. Research at NIH is conducted through its intramural programs at its main campus and through extramural research programs based at academic institutions throughout the U.S. The NIH Clinical Center, which opened in 1953, together with academic health centers, including those with a Clinical and Translational Science Award (CTSA) [13], remains the principal venues for rare disease research in the United States. Over the past two decades, provisions in ODA and the launching of several other new offices, programs, and intra- and extramural initiatives at NIH have stimulated research to discover the causes and develop treatments for rare diseases, including IEM. NIH tools and resources useful for researchers are listed in Table 1.

ORDR was created in 1993 within the Office of the Director of NIH to address the need for rare disease research. Subsequently, Public Law 107–280, the Rare Diseases Act of 2002 [14], established ORDR by statute. In 2003, ORDR, in collaboration with six NIH Institutes and Centers created and funded the Rare Diseases Clinical Research Network (RDCRN) to facilitate multisite collaborative clinical research in rare disorders, including IEM, and to train young physician-researchers. RDCRN currently consists of 17 consortia, each of which is focused on a minimum of three related rare disorders and partners with patient advocacy groups [15]. The goals of each consortium are to identify biomarkers for disease risk, severity, and progression; develop clinical outcome measures; and encourage the development of new approaches to diagnosis, prevention, and treatment. Three RDCRN consortia are relevant to IEM: the Urea Cycle Disorders Consortium; the North American Mitochondrial Disease Consortium; and the Sterol and Isoprenoid Research Consortium [15].

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development’s (NICHD) Newborn Screening Translational Research Network (NBSTRN) [16] also supports IEM research. The NBSTRN’s purpose is to provide infrastructure support to

investigators to advance diagnostics and treatment of disorders detected through newborn screening programs and conditions that may be amenable to newborn screening in the future. Resources developed include: a virtual repository of de-identified residual dried bloodspots for use by investigators; laboratory testing algorithms and decision matrices; and a longitudinal pediatric data repository to allow long-term clinical follow-up and research of infants detected with IEM or other congenital abnormalities.

### 2.3. Food and Drug Administration

The mission of FDA is to promote and protect the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biologics, medical devices, the nation's food supply, cosmetics, and products that emit radiation. FDA recognizes that streamlining the process for drug and biological product development is critical for development of products used to treat IEM and other rare and common disorders [17].

FDA has several programs that coordinate and oversee products for rare diseases, including IEM. Within the Center for Drug Evaluation and Research (CDER), the Rare Diseases Program (RDP) was created in 2010 to facilitate and support the research, development, regulation, and approval of drugs and biological products for the treatment of rare disorders. RDP serves as the focal point of CDER to the rare disease drug development community. RDP coordinates the development of CDER policy, procedures, and training for the review and approval of treatments for rare diseases. Additionally, RDP actively collaborates with external and internal rare disease stakeholders to support the development of treatments for rare disorders. For example, RDP meets regularly with NIH's ORDR and Therapeutics for Rare and Neglected Diseases Program.

FDA's Office of Orphan Product Development (OOPD) is also involved in advancing development of products (drugs, biologics, devices, and medical foods) that demonstrate promise for the diagnosis, management, and/or treatment of rare diseases or conditions. OOPD administers the Orphan Drug Designation, the Humanitarian Use Device, and the Orphan Products Grants programs.

Recently, FDA created the Rare Diseases Council with representatives from across several FDA Centers including the Office of the Commissioner, the Center for Biologics Evaluation and Research, CDER, the Center for Devices and Radiological Health, and the Center for Food Safety and Nutrition. The goal of this Council is to coordinate development of products for rare disorders across FDA. Under the Food and Drug Safety and Innovation Act passed by Congress in 2012 [18], there are provisions that allow sponsors to request that their drug be designated as a "breakthrough therapy" and outlines procedures for an expedited FDA review and approval process.

**2.3.1. Development, regulations, and definitions for drugs, dietary supplements, and medical foods used in IEM**—Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA has defined a drug as a substance recognized by an official pharmacopoeia or formulary that is intended for the diagnosis, cure, mitigation, treatment, or prevention of disease. In order for drugs and biological products to be approved in the U.S., there must be substantial evidence of effectiveness. Evidence generally consists of adequate



and well-controlled investigations so that the effect of the drug can be distinguished from the effect of other influences such as spontaneous change in the course of the disease, placebo effect, or biased observation. This evidentiary standard must be met for products used to treat rare diseases as well [19]. However, FDA has regulatory flexibility in interpreting the requirements for demonstration of substantial evidence of effectiveness for rare disease products. For example, carglumic acid for the treatment of *N*-acetylglutamate synthase, or NAGS, deficiency was approved by FDA in 2010 based on a case series derived from fewer than 20 patients and comparison to a historical control group.

A dietary supplement is defined as a product taken by mouth that contains a “dietary ingredient” (e.g., a vitamin, mineral, botanical, and amino acid) intended to supplement the diet [20]. Dietary supplements must meet the requirements of the Dietary Supplement Health and Education Act (DSHEA) [20], which is governed under the FD&C Act [21]. In general, the FDA regulations for dietary supplements are different from those for prescription or over-the-counter drugs. Unlike drugs, dietary supplements do not require premarket review or approval by the FDA. While the dietary supplement manufacturer is responsible for having evidence that their products are safe and the label claims are truthful and not misleading, they do not have to provide that evidence to FDA before the product is marketed [22]. However, dietary supplements may not be promoted as a treatment, prevention, or cure for a specific disease or condition. If a dietary supplement were used to treat, prevent, or cure disease, it would be considered a drug. As such, the dietary supplement would be regulated under drug statutes and require well-controlled trials to establish evidence of safety and effectiveness to support the intended claim.

With regard to medical foods, there are no requirements for FDA approval of medical foods prior to marketing and medical foods do not need to be registered with FDA. However, the manufacturers of medical foods must be registered with and are inspected by FDA, as is the case for all food manufacturers in the U.S. and they must meet the requirements of good manufacturing practices. Medical foods for persons over 1 year of age are exempt from the nutrition labeling, health claims, and nutrient content claim requirements of the Nutrition Labeling and Education Act of 1990 [23]. All manufacturers of infant formulas must notify FDA at least 90 days prior to marketing a new infant formula or an infant formula with a major change. An infant formula that is represented and labeled for use by an infant who has an IEM is exempted from certain requirements. However, if a manufacturer wants to market this type of infant formula, a submission must be made that includes a detailed description of the medical condition for which the infant formula is represented and includes justification for any deviations from any of the nutrient requirements (see: 21 CFR 107.50c [21]).

**2.3.2. The status of drug development for rare disorders and IEM—**Total spending on all health-related research has tripled since the ODA and successive legislation were enacted [24,25]. Despite a historical dearth of therapeutics for rare diseases, product development for these disorders appears to be increasing. Since the passage of the ODA in 1983, more than 400 drugs and biological products have been approved to treat rare diseases [26] compared to the 10 products approved to treat rare diseases between 1973 and 1983. In a recent review of rare disease product approvals in the U.S. between 2006 and 2010, new

molecular entities and new biologics for rare diseases comprised 30% of all marketing applications reviewed and approved by FDA during the study period. Notably, more than half of the 26 new biologic applications submitted to CDER were for rare disease indications. Furthermore, approval rates for marketing applications for rare and common disease indications were similar (77% approval rate for rare disease products and 71% approval for non-rare disease products) [27–29]. For IEM, there were six products approved during this same time period (2006–2010). Two of these products, Kuvan® (sapropterin dihydrochloride) for PKU, and Carbaglu® (carglumic acid) for NAGS deficiency, are used in IEM that prior to the development of the drugs, relied primarily on nutritional interventions. The other four products were developed for Pompe disease, Hunter syndrome, and Gaucher, in which nutritional interventions are not used as part of their standard management.

Kuvan® was the first FDA-approved drug therapy for PKU. Kuvan® is used in conjunction with a low-PHE diet, reducing blood PHE levels in some patients. The introduction of Kuvan® as an adjunct therapy required specific dietary protocols to be developed by genetic metabolic dietitians in partnership with medical geneticists and the drug manufacturer.

Pharmacologic agents for PKU and other IEM are currently being developed. For example, for PKU, pegylated phenylalanine ammonia lyase (PEG-PAL), will enter Phase 3 clinical trials in 2013 [30]. PEG-PAL is administered by injection and appears to be effective in lowering blood PHE levels, even in patients on a completely unrestricted diet. Clinical trials have focused on use in adolescent and adult patients with poorly controlled blood PHE levels.

### 3. IEM research partners

#### 3.1. Pharmaceutical and medical food industry

Members of the pharmaceutical, dietary supplement, and medical food industry are in an important position to increase availability of the products that support the nutritional management of IEM. Before these products can come to market, research and development require time, money, and for some products, successful approval through FDA regulatory processes mandated by Congress. The industry has engaged genetic metabolic professionals to assess the needs of the IEM community and has provided unrestricted research and educational grants to allow research and other projects to move forward. The industry also has been able to facilitate and support the development of multicenter clinical trials and patient registries.

#### 3.2. Genetic professionals

Health care professionals, inclusive of medical biochemical geneticists, genetic metabolic dietitians, and genetic counselors, who manage the treatment of individuals with IEM, are often located in large academic centers and engage in clinical, translational, and basic science research. These health care professionals focus on the diagnosis, treatment, and long-term follow-up of patients with IEM. Medical biochemical geneticists have specific subspecialty training in the care of patients with IEM. They are responsible for the overall coordination of patient care and directly manage medical issues related to IEM in both the



outpatient and inpatient setting. In institutions where a medical biochemical geneticist is not available, a medical geneticist often assumes these responsibilities. A metabolic genetic counselor assists in the assessment of an IEM, acts as an advocate for the patient through the process of the metabolic genetics evaluation, and helps him/her understand what a diagnosis of an IEM means for each family member. Genetic metabolic dietitians design and implement nutritional interventions aimed at mitigating the biochemical abnormality presented by the IEM and ensure that the individual maintains an appropriate nutritional status. Standards of professional practice for genetic metabolic dietitians were published in 2008 [31] and their role as advanced practitioners in genetics has been characterized [32]. Together these health care professionals provide complex care to patients with IEM and are central to the development of a research infrastructure as they have direct access to patients and know the research questions that need to be addressed.

### **3.3. Primary care and public health professionals**

Primary care professionals, including pediatricians, internists, family physicians, obstetricians, and nurse practitioners, have a role in the care of individuals with IEM. These roles span evaluation and referral, co-management with the public health newborn screening system and genetic health care professionals. The patient-centered medical home (PCMH) model of primary care, which emphasizes continuous, comprehensive, and coordinated care, provides a mechanism to gather patient data over the life span of a patient and a system of co-management with other health care professionals. While about half of the states are implementing PCMH for their Medicaid populations [33], the Patient Protection and Affordable Care Act (ACA) of 2010 will encourage expansion of PCMH through incentives and resources [34]. Natural history studies and the development of treatments require a system of long-term follow-up (LTFU) for those affected by IEM. Since many individuals with IEM are first identified within newborn screening programs, public health professionals play an essential role in maintaining the system of LTFU for these children. Together, through systems of PCMH and LTFU, primary care and public health professionals will be critical to successful research endeavors for IEM.

### **3.4. Patients, families, and disease-specific advocacy groups**

Patients with IEM, their families, and patient support and advocacy groups are essential partners in any research endeavor. Their concerns include the cost and palatability of products used in disease management, the variation in treatment protocols from clinic to clinic, and the variable access to product coverage mechanisms from state to state. Patients and their families, and advocacy groups are often able to educate Congress about needed legislation and research through their own personalized stories.

### **3.5. International metabolic community**

Collaboration with the international metabolic community will strengthen research endeavors in IEM by providing investigator expertise and increasing the number of patients available for research. The NDSI-IEM workshop included metabolic specialists from Australia, France, Switzerland, and United Kingdom. Workshop participants voiced a need to support international collaboration to define diseases, develop standards of care, and compare definitions of medical foods globally. Several international initiatives in rare

diseases and IEM specifically serve as examples of these collaborations and include the Global Rare Diseases Patient Registry and Data Repository (GRDR) in ORDR and the International Rare Diseases Research Consortium [35].

#### 4. Establishing a coordinated infrastructure for collaboration

For institutional transformation to occur and collaboration to be established, partnering entities need to work together by sharing resources, information, materials, and personnel. Collaborators then bring work, money, knowledge and/or experience to the task of developing partnerships and infrastructure to develop treatments for rare disorders. The identified tasks then are “outsourced” to the defined group of collaborators. The gaps in the translational pathway are bridged through these partnerships to distribute the risks and benefits involved in research and development for rare disorders [36].

Collaborative approaches to the therapeutics development are becoming more important for rare diseases and IEM, especially when no approved therapy is available. The work done in eosinophilic esophagitis [37] and the RDCRN'S Urea Cycle Disorders Consortium serve as examples of the benefits of collaboration across multiple sectors and with multiple partners. In particular, the Urea Cycle Disorders Consortium enabled the development of a treatment, Raviciti (glycerol phenylbutyrate), for the chronic management of some urea cycle disorders in patients ages 2 years and older. It is intended for patients whose urea cycle disorder cannot be managed by a protein-restricted diet or amino acid supplements alone. Along with the consortium, NIH's National Center for Advancing Translational Sciences (NCATS) and NICHD and the National Urea Cycle Disorders Foundation were collaborators in this study.

NDSI-IEM workshop participants emphasized the need to utilize the existing RDCRN and NBSTRN infrastructure and to build upon them for future research. Through NBSTRN and RDCRN, collaborations have been formed for research, to provide clinical care, and to gather a significant number of individuals and families with rare disorders to conduct research. While these collaborations offer access to large-scale resources such as biobanks or data warehouses, they also increase the complexity of coordination, accountability, management, and communication between the researcher and participant. An additional challenge in multicenter approaches is providing clinical services for patients from out of state. A State's Medicaid program generally does not contract with health care professionals practicing in a second State to provide care for another State's population unless that health care professional is also licensed in that first state. These challenges are beginning to be mitigated through several efforts, as exemplified by the HRSA-funded Regional Genetics and Newborn Screening Collaboratives [38] These Collaboratives have developed several regional models to deliver subspecialty care across state borders while allowing families to remain primarily with their local provider for their clinical care. The NBSTRN was able to utilize the Region IV Regional Genetics and Newborn Screening Collaborative's multi-site service infrastructure to support a collaborative research effort, while preserving the patient's medical home.

Improved means of capturing patients eligible for research and clinical trials in a distributed way with a common protocol can also be seen as a health information exchange (HIE) issue

rather than a logistics issue of sending patients to distant centers. Information that captures the key elements of each individual patient and links them to a larger set of data provides the necessary foundation for assessing the optimal health outcome of individuals with IEM. Since research funds generally do not pay for the care of patients locally, an informatics approach, combined with telemedicine would allow for broad multi-state collaboration, balancing the need for local care and payer access with national research. The partnership between some of the HRSA-funded Regional Genetics and Newborn Screening Collaboratives [38] and the NIH-funded NBSTRN described above is an example of using HIE.

## 5. Conducting research in IEM

In rare disease research, randomized controlled trials that are adequately powered to demonstrate effectiveness often are considered difficult. Reasons include small sample size, heterogeneity and geographic diversity in phenotype, and affected individuals' exposure to many prior treatments or interventions. Additionally, meaningful health outcomes over the clinical course of a disorder may not be measurable for many years. Constructing a well-designed clinical evaluation is possible, however, and challenges can be overcome through the use of specialized study designs and biostatistical techniques that maximize data from small numbers of subjects [39].

### 5.1. Research study designs

**5.1.1. Natural history studies**—The foundation of successful pharmaceutical drug treatment or dietary management of IEM rests upon an understanding of the disease pathophysiology, the mechanism of action of the candidate therapeutic, the expected effect of the intervention on the disease, and how the effect will be measured. Data collected from a well-designed natural history study may provide important information to enable appropriate design of clinical trials or alternative designs (e.g., appropriate patient population, length of study, and selection of clinically meaningful end-points). Several of the current NBSTRN projects are examples of natural history studies for IEM, for example the Longitudinal Pediatric Data Resource [16].

**5.1.2. Comparative Effectiveness Research (CER) and patient-centered outcomes**—To receive full approval for commercial marketing in the US, all FDA-approved drugs must demonstrate substantial evidence of clinical effectiveness and safety, and must be shown to have a favorable benefit-to-risk assessment in the treatment of the disease [40]. CER allows stakeholders, including affected individuals, policymakers, and health care providers, to compare explicitly the potential benefits and harms of different treatment approaches.

Most CER on rare diseases, including IEM, requires collaboration across multiple sites to obtain a sufficient patient population for a study. The NBSTRN and RDCRN are two programs that provide the collaborative infrastructure necessary to conduct CER for IEM, while addressing the need for a patient-centered approach.

The critical need to include patient perspectives on therapeutic effectiveness of treatments is underscored by the creation of the non-governmental Patient-Centered Outcomes Research Institute (PCORI) by the ACA Patient-centered outcomes research is designed to help people, together with their families, researchers, and health care providers, better assess treatment options. A patient-centered approach not only captures what is essential to patients and families, it potentially engages lay advocacy groups in the design of studies, facilitating compliance with treatments and wider participation in the studies.

**5.1.3. Alternate designs**—Alternate approaches to study designs include [39,41]: case-control studies, crossover studies, quasi-experimental design studies, and “before-and-after studies” designs (a form of time-series design, commonly used retrospectively but can also be done prospectively). Griggs et al. [39] describe multiple approaches for study designs that could be used for rare disorders.

Many of the existing databases and registries established by the NBSTRN and RDCRN (see Section 5.4) offer the opportunity to construct a “simulated” or faux randomized control trial. The existing collaborative multi-centered infrastructure provided by the NBSTRN and the RDCRN capture the majority of the patients affected by various disorders into registries or centralized databases. Utilization of common data elements in these programs also allows researchers to begin to recognize patterns of clinical effects that may support decisions concerning clinical validity and utility of various therapeutic approaches. Although the research activities undertaken by the NBSTRN or the RDCRN have been focused largely on natural history studies, this work is essential and provides the platform for the development and assessment of both pharmaceutical drug treatments and nutritional interventions for IEM.

## 5.2. Identifying endpoints and biomarkers for rare disease research

Identification of potential clinical outcome measures that will be used as endpoints should be considered as early as possible and prior to initiating clinical trials. An appropriate clinical endpoint must be based on a clearly defined disease process and detailed understanding of how the endpoint is expected to change over time in a specific disease. While the identification of a well-defined endpoint may be difficult to establish in rare diseases, careful collection of natural history data for a disease should include information that will aid in the identification of potential clinical endpoints for study.

Surrogate endpoints are measurements or a physical sign used as a substitute for a clinically meaningful endpoint that would measure directly how a patient feels, functions, or survives. FDA’s Accelerated Approval Regulations for reliance on a “surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to *predict clinical benefit*” [42] have been in place for many years. For example, everolimus was approved in 2010 for the treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis which requires therapeutic intervention but is not a candidate for curative surgical resection. The approval was based on an analysis of change in SEGA volume. Since 2009, FDA has issued 21 approvals under accelerated approval regulations. A detailed description of these regulations may be found elsewhere [43].

Biomarkers are also potentially useful in clinical development programs for drugs and can be used during all phases of drug development. Biomarkers can identify an appropriate target population, establish or refine dosing of the product, and assess the effect of clinical intervention on a disease (i.e., clinical endpoint). Careful consideration of potential biomarkers and their role in clinical trials should be performed early and discussed with FDA.

### 5.3. Recruitment and retention of research subjects

Beyond the basic problems common to all clinical trials, recruitment and retention of the few geographically dispersed and often quite ill patients with rare disorders are major challenges for IEM investigators. Patients and families may not have the resources to travel to academic research centers and conversely, not all academic health centers will have the required expertise for all rare disorders. Thus, creative mechanisms must be developed and implemented to maximize recruitment and retention of research subjects.

### 5.4. Patient registries, databases, and common data elements for rare disorders

Patient registries and collective databases provide mechanisms to overcome geographic dispersion while furnishing a collective infrastructure to assemble sufficient numbers of patients and a means for tracking and retaining patients enrolled in specific protocols for robust research. Through utilization of these data collection tools, regular, lifelong contact with patients can be maintained. These tools and ongoing contact with the patient and family also provide mechanisms for locating patients who are lost-to-follow-up. Patients and families may report health status to the participating research and clinical centers and protocol-specific outcome data may be collected. The registries additionally provide a mechanism to collect cumulative therapeutic exposure data (via therapeutic summaries completed online by treating institutions) on patients completing active therapy.

Many current registries and databases were built on different platforms using different terminology and vocabulary, thus making it extremely difficult to share data or information among them. Because the rarity of the disorders necessitates a multi-centered approach, it is critical that data definitions and study protocols be standardized to ensure data compatibility among those participating. To address some of these issues, two projects within NIH have been launched: the Global Rare Disease Patient Registry and Data Repository (GRDR) project in ORDR and the NBSTRN natural history study project in NICHD. Both initiatives have worked together with the NIH National Library of Medicine and the HRSA funded Regional Genetics and Newborn Screening Collaboratives to develop common data elements to facilitate data sharing and data aggregation. The GRDR utilizes rare disease patient registries to create a registry with aggregated and de-identified patient information. The NBSTRN utilizes a network of databases to support the capture and storage of longitudinal clinical data from individuals following newborn screening. The registries and databases allow analyses within a disease or across many diseases.

### 5.5. Institutional review boards: a multicenter approach

Although a system of networks may address limited specialty resources and bring geographically disparate patients together, differing consent and institutional review board

(IRB) procedures required by individual centers may impede multicenter trials. There have been numerous efforts to reform the IRB review process for multicenter studies [44–47]. Marsolo [48] reviews two approaches—centralized and federated IRBs. Centralized IRBs are not tied to an institution, may be disease or geographical location specific, and may be established commercially or by networks of researchers [48]. Concerns related to research integrity and lack of local context in centralized IRBs led to the development of federated IRBs. Federated IRBs allow institutions to select the degree of control they wish to retain in the IRB process, ranging from using their own IRB to selecting the IRB of record. For example, about half of NICHD-funded National Children’s Study sites use the IRB of the NICHD as the IRB of record [49]. A toolkit with materials and information about establishing a Federated IRB model for multi-site collaborations is available upon request from the National Children’s Study at: [ContactNCS@mail.nih.gov](mailto:ContactNCS@mail.nih.gov).

## 5.6. The genetic workforce

The current medical genetic service workforce is not expected to meet patient care needs in the next 5–15 years, widening the gap between the expansion of knowledge, service needs, and workforce size [50]. Young physicians are not entering the fields of either genetics/genomics in general or IEM, specifically [51]. Many states and geographic areas have an inadequate supply of medical geneticists while the need has increased due to the ongoing expansion of newborn screening for congenital disorders.

Few analyses exist that set the baseline for how many such providers are needed. Assessments by the Royal College of Physicians in 2004 indicate that the health care system requires one clinical geneticist and associated service team per 250,000 people [52]. The medical genetics workforce in the U.S. numbers about 1132 or 1 per 616,200 persons [53], suggesting that there are insufficient medical geneticists to meet the growing need for genetic services.

Genetic counselors and genetic metabolic dietitians (who are registered dietitians with specialized expertise in the nutritional management of IEM) work with patients with complex genetic disorders, including inborn errors of metabolism. To date, there have been no published surveys to evaluate the number of genetic counselors or registered dietitians with specific expertise in IEM.

**5.6.1. The need for increased training and research opportunities**—Health care professionals have many demands on their time, even beyond patient care, which limits their ability to devote significant time to research. Most are academically based and spend about 45% of their time in direct patient care with the balance applied to teaching, research, and administration. While serving a prominent role in patient care, only four percent of registered dietitians overall hold doctoral degrees [54] limiting their ability to serve independently as principal investigators.

Strategies to increase the genetic metabolic professional workforce and their research expertise will be critical to effective development of a research infrastructure. There are a number of initiatives in progress by the American Society of Human Genetics, the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors



to expand the entire genetic services workforce, including activities that target high school, college, medical school, and residency training. Additionally, a recommendation from the NDSI-IEM workshop focused on providing research training opportunities for the genetic metabolic workforce. To this end, a series of webinars and educational sessions at professional meetings are planned.

There are also specific initiatives that focus on the need for increased genetics education and training of primary care professionals. The Genetics in Primary Care Institute (GPCI) was established as a cooperative agreement between HRSA's Maternal & Child Health Bureau and the American Academy of Pediatrics to address this need [55]. In the context of a medical home, the GPCI will foster genetic literacy and the integration of genetic medicine into health information technology. As the capacity to engage in multi-directional HIE and genetic literacy improves and increases, the role of primary care providers as research partners should increase.

## 6. Need for novel approaches for IEM product development

### 6.1. Strategy for product development

The research plan for product development is linked to study design and therefore should begin well before clinical trials are contemplated. The overall strategy requires collaboration across multiple sites to achieve a sufficient patient population to study and benefits from careful advanced planning and interaction with FDA. All interested parties and should be identified to participate in the planning process and potential sources of support also identified. Important considerations during the planning process include: definition of the disease, the populations to be studied, the overall goals of the intervention, and the sequential steps that will need to be taken to achieve the overall goals. Additional critical elements include review of the currently available knowledge about the intervention and the disease; how effects of the intervention will be measured; and whether currently existing measurement tools are adequate for assessment of these effects.

Currently, a non-iterative process prevails in the development of pharmaceutical drug treatments, medical foods, and dietary supplements for IEM. Study designs often do not provide a coordinated approach that couples development of an intervention and criteria for regulatory approval for use in a clinical setting with an ongoing accumulation and examination of knowledge to refine the intervention. Research strategies should provide for an iterative collection of data to periodically inform researchers, clinicians, and relevant federal agencies about the clinical validity or utility of the intervention, allowing for adjustments or refinements as needed.

It was noted at the NDSI-IEM workshop by some product developers that reimbursement cannot be sought for clinical interventions under development. Further, it was also noted that lack of insurance coverage may keep patients who might want to be in a clinical trial from participating. One suggested solution by NDSI-IEM workshop participants is to allow for reimbursement for a clinical intervention, while linking with the research and development process through a coordinated effort among federal research funders, health care payers, and regulatory agencies. What is unique to this approach is allowing for reimbursement for the

intervention during the clinical trial period. It should be noted that as of January 1, 2014, regulations under the ACA will require health insurance coverage for the routine medical costs of people taking part in clinical trials. Insurers will not be allowed to drop or limit coverage because a person chooses to participate in a clinical trial. This regulation will apply to all clinical trials involving life-threatening diseases and would be applicable to many IEM.

## 6.2. Regulatory science

Regulatory science is another very important but challenging area of research that impacts the development and availability of treatments and interventions for diseases. Regulatory science is a systemized body of knowledge (practiced by FDA and similar regulatory agencies world-wide) concerning drug and other product regulations, regulatory standards, law, and procedures across many disciplines with an aim to improve assessment of experimental drug therapies, nutritional interventions, and diagnostics. It includes public protection-oriented medical product regulations and scientific methods utilized in the evaluation and approval of all the products that FDA regulates [56].

FDA has advanced a strategic plan for regulatory science [56] with the aim of delivering efficacious medical products to patients by increasing efforts to reduce the uncertainties in the FDA development and approval process. As previously outlined, under the current regulatory and research infrastructure, there are significant differences between the regulatory agencies and the pharmaceutical and research communities in the development and approval of pharmaceutical drug treatments versus that of medical foods and dietary supplements, in general and for IEM. Without FDA approval—and in the current regulatory infrastructure medical foods and dietary supplements for management of IEM are not approved by the FDA—there are potentially problematic shortfalls in knowledge about the safety and utility of nutritional interventions, and in the ability of individuals with IEM to obtain and receive coverage for these interventions. If the current regulatory infrastructure is deemed to be restrictive in facilitating goals of approving new therapies, policies may be needed to facilitate translational science and build models of approval for new drug therapies and nutritional interventions that combine the assessment process with interim approval and use of these therapies or interventions. In order to follow such a pathway, developers of medical foods and dietary supplements for IEM may need to follow a developmental and regulatory pathway similar to that required for pharmaceuticals used in the management of IEM.

## 6.3. Federal coordination to enhance research

The December 2011 NDSI-IEM workshop participants pointed to a need for improved coordination among the federal agencies, a sentiment also articulated by Health and Human Services Secretary, Kathleen Sebelius in *Health Affairs* [57]. The participants highlighted two primary areas for coordination: within the agencies' solicitation processes and during the process of product development.

NDSI-IEM workshop participants proposed that NIH and FDA proactively provide researchers with guidance in the conduct of research and navigating the intricacies of the

research and development pathway for treatments and interventions for IEM. For example, receipt, review, and funding schedules for federal agencies vary considerably, presenting applicants with a challenging planning task. NIH has standard due dates for most competing applications which are fairly uniform across NIH Institutes and Centers [58]. However, targeted solicitations such as a Request for Applications have their own special due dates and separate funding schedules. Furthermore, other agencies (Centers for Disease Control and Prevention, and HRSA) have separate review and funding schedules for their competitions. Regulatory submissions processes (for agencies like the FDA) also have distinct schedules and timelines. Applicants considering submissions to multiple agencies within a short time frame, or with linked projects requiring coordinated planning, may need to contact staff at multiple agencies for guidance on scheduling and other submission requirements.

#### 6.4. Applying new technologies

There is clear interest in applying new genomics concepts and technologies to newborn screening and other aspects of child health. New technologies such as genomics and related “omics” have the potential to identify new drug targets to pursue or to refine current treatments, for example, by stratifying populations based on genetic-based biomarkers. Genomic data would reveal how individuals might respond to, be resistant to, or have adverse effects from a drug or nutritional interventions such as medical foods or dietary supplements. NDSI-IEM workshop participants suggested that a centralized DNA-sequencing facility to analyze newborn screening samples could study different IEM-associated mutations, genotyping every infant who has a positive newborn screen. A similar suggestion was proposed by participants in a workshop entitled ‘Newborn Screening in the Genomic Era: Setting a Research Agenda’ sponsored by NICHD, the National Human Genome Research Institute and ORDR that took place in December 2010 [59].

NDSI-IEM workshop participants pointed to the need to better understand the phenotype/genotype relationships of the various IEM to improve drug treatments and nutritional interventions through faster, cheaper molecular characterization. Our earliest understanding of IEM as an “all or nothing condition” was quickly modified by the observation of inter- and intra-familial variation in phenotypes, as the clinical course of IEM is variable. These clinical variations are due not only to genetic or genomic variants but also to differences in the patient’s natural environment and physiological responses to the biochemical disruption.

Many questions including those of predicting disease course or understanding outcomes over time in patients with later onset conditions will require longitudinal data collection from a patient rather than a point-in-time assessment. With large-scale data collection, more bioinformatics capacity and capability will be necessary. To allow for assessment of individual phenotypic data, they need to be stored in an accessible location at either remote or distributed sites including within a patient’s own electronic medical record. Standard descriptive terms will be necessary so that data entry and interpretation will be as uniform as possible. Thus current efforts to develop common data elements will be critical moving forward.

The Mitochondria Phenome Knowledgebase (MitoPhenome) represents an early example of a tool designed to aid clinicians and researchers in understanding how genetic variation among individuals contributes to clinical disease phenotypes and traits [60]. Detailed information on distinct clinical disease phenotypes of known mitochondrial gene defects were catalogued into a searchable database after classification of each clinical or biochemical feature using National Library of Medicine Medical Subject Headings (MeSH) terms. As genomic and bio computational technologies continue to advance, our level of understanding of phenotype/genotype relationships will rise significantly, which will have a positive effect on treating IEM [59].

## 7. Conclusions: addressing the problem and achieving the goal

The lay and professional rare disease communities and federal research, funding, regulatory, and payer agencies will need to collaborate to develop an improved roadmap to overcome current barriers and address the challenges that impede conducting evidence-based research for nutritional interventions for IEM. Below we propose action steps that, if implemented broadly, could transform biomedical research and how federal support for and approval of new nutritional interventions are obtained.

### 7.1. What is needed

1. Improve coordination among the regulatory agencies, industry and research communities, through collaborations among federal agencies (those responsible for regulation, research and health care payments), industry and nongovernmental organizations.
2. Develop models of collaboration and co-management that facilitate necessary partnerships between subspecialty and specialty providers.
3. Develop coordinated regional and federal infrastructures to:
  - Utilize HIE to integrate the service delivery system with researchers.
  - Enhance opportunities for collaboration while distributing cost sharing and sharing of resources.
  - Utilize a centralized or federated IRB approach.
4. Establish CER and patient-centered research models to:
  - facilitate participation in research projects,
  - facilitate participatory and shared decision-making processes, and
  - increase understanding by advocacy groups of the importance of research.
5. Design research studies to:
  - identify appropriate populations for study
  - identify clinically meaningful endpoints and biomarkers/surrogate endpoints in rare disorders
  - establish patient-centered, rigorous approaches to study designs.

6. Develop strategies to increase training opportunities for both specialty and subspecialty providers in the area of metabolic and genetic/genomic disorders.

Individuals with IEM and their families face challenges daily. Thus, seizing the opportunity for collaboration to mitigate these challenges and improve outcomes is critical. The concerned entities involved in drug, biologics, medical food, and dietary supplement development, including academia, industry, and federal funders and regulators must continue to work collaboratively and proactively for the benefit of public health. Proactive collaboration ultimately would entail the use of appropriately structured clinical trials for not only the development of pharmaceuticals for the treatment of IEM but also medical foods and dietary supplements used in the management of IEM. The goal of development and facilitation of optimal management strategies for those individuals affected with rare and orphan diseases is mutually important for all involved entities.

## Abbreviations

<b>IEM</b>	inborn errors of metabolism
<b>NIH</b>	National Institutes of Health
<b>ODS</b>	Office of Dietary Supplements
<b>ORDR</b>	Office of Rare Diseases Research
<b>HRSA</b>	Health Resources and Services Administration
<b>PKU</b>	phenylketonuria
<b>PAH</b>	phenylalanine hydroxylase
<b>PHE</b>	phenylalanine
<b>ODA</b>	Orphan Drug Act
<b>FDA</b>	Food and Drug Administration
<b>CTSA</b>	Clinical and Translational Science Award
<b>RDCRN</b>	Rare Diseases Clinical Research Network
<b>NICHD</b>	<i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development
<b>NBSTRN</b>	Newborn Screening Translational Research Network
<b>CDER</b>	Center for Drug Evaluation and Research
<b>RDP</b>	Rare Diseases Program
<b>OOPD</b>	Office of Orphan Product Development
<b>FD&amp;C Act</b>	Federal Food, Drug and Cosmetic Act
<b>DSHEA</b>	Dietary Supplement Health and Education Act
<b>PCMH</b>	patient-centered medical home
<b>ACA</b>	Patient Protection and Affordable Care Act

<b>LTFU</b>	long-term follow-up
<b>NCATS</b>	National Center for Advancing Translational Sciences
<b>HIE</b>	health information exchange
<b>CER</b>	Comparative Effectiveness Research
<b>PCORI</b>	Patient-Centered Outcomes Research Institute
<b>GRDR</b>	Global Rare Disease Patient Registry and Data Repository
<b>IRB</b>	institutional review board
<b>GPCI</b>	Genetics in Primary Care Institute.

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**Table 1**

## Examples of NIH tools and resources for researchers.

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The NIH Guide for Grants and Contracts (<http://grants.nih.gov/grants/guide>) lists NIH funding opportunities.

The NIH Research Portfolio Online Reporting Tools (RePORTER) database (<http://projectreporter.nih.gov/reporter.cfm>) provides information on projects that NIH currently funds or has funded in the past. RePORTER is helpful for establishing a research network and identifying research that NIH is already funding.

Information about U.S. and international clinical trials is available from [clinicaltrials.gov](http://clinicaltrials.gov) website, though nutritional interventions not subject to FDA oversight, and therefore may not be listed.

The NIH Clinical Center's website (<http://clinicalcenter.nih.gov>) provides details on ongoing NIH clinical trials. At this time, use of the Clinical Center is restricted to intramural investigators and their collaborators. However NIH may open the Clinical Center to extramural investigators in the future.

Common Fund Regulatory Science Program fosters development, availability and evaluation of new or improved ways to understand and improve evaluation of product safety, quality, effectiveness, and manufacturing throughout the life-cycle of a product (<http://commonfund.nih.gov>).

Common Fund Undiagnosed Diseases Program was initiated to promote use of genomic data in disease diagnosis and engage basic researchers to elucidate the mechanisms underlying the diseases so that treatments may be identified (<http://commonfund.nih.gov/diseases/>).

Therapeutics for Rare and Neglected Diseases program (<http://www.ncats.nih.gov/research/rare-diseases/trnd/trnd.html>) build collaborations with NIH, FDA and academic scientists, nonprofit organizations, and pharmaceutical and biotechnology companies to speed development of new therapies.

Cures Acceleration Network (<http://www.ncats.nih.gov/funding-and-notice/can/can.html>) was established to stimulate the development of high need cures for debilitating and life threatening diseases by reducing the number of barriers that investigators face between the time of basic research discoveries and initiation of clinical trials.

The Bridging Interventional Development Gaps program (<http://www.ncats.nih.gov/research/rare-diseases/bridgs/bridgs.html>) provides successful applicants developing therapeutic agents with access to critical resources in support of pre-clinical studies.

*Discovering New Therapeutic Uses for Existing Molecules* (<http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html>)

is a collaborative pilot program of NCATS designed to develop partnerships between pharmaceutical companies and the biomedical research community to advance therapeutic development.

*Tissue Chip for Drug Screening* initiative represents an interagency collaboration with Defense Advanced Research Projects Agency (DARPA) and NCATS (<http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html>).

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