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Minireview

Inborn errors of metabolism identified via newborn screening: Ten-year incidence data and costs of nutritional interventions for research agenda planning☆

Bradford L. Therrell Jr. [a,b,1,*], Michele A. Lloyd-Puryear [c,1], Kathryn M. Camp [c,1], Marie Y. Mann [d]

[a] Department of Pediatrics, University of Texas Health Science Center at San Antonio, San Antonio, TX 78220, USA
[b] National Newborn Screening and Global Resource Center, Austin, TX 78759, USA
[c] Office of Dietary Supplements, National Institutes of Health, Bethesda, MD 20892, USA
[d] Maternal and Child Health Bureau, Health Resources and Services Administration, Rockville, MD 20857, USA

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ABSTRACT

Inborn errors of metabolism (IEM) are genetic disorders in which specific enzyme defects interfere with the normal metabolism of exogenous (dietary) or endogenous protein, carbohydrate, or fat. In the U.S., many IEM are detected through state newborn screening (NBS) programs. To inform research on IEM and provide necessary resources for researchers, we are providing: tabulation of ten-year state NBS data for selected IEM detected through NBS; costs of medical foods used in the management of IEM; and an assessment of corporate policies regarding provision of nutritional interventions at no or reduced cost to individuals with IEM. The calculated IEM incidences are based on analyses of ten-year data (2001–2011) from the National Newborn Screening Information System (NNSIS). Costs to feed an average person with an IEM were approximated by determining costs to feed an individual with an IEM, minus the annual expenditure for food for an individual without an IEM. Both the incidence and costs of nutritional intervention data will be useful in future research concerning the impact of IEM disorders on families, individuals and society.

Contents

Abbreviations: CORN, Council of Regional Networks for Genetic Services; DSHEA, Dietary Supplement Health and Education Act; HRSA, Health Resources and Services Administration; IEM, inborn errors of metabolism; MS/MS, tandem mass spectrometry; NBS, newborn screening; NCHS, National Center for Health Statistics; NDSI-IEM, Nutrition and Dietary Interventions for Inborn Errors of Metabolism; NIH, National Institutes of Health; NNSGRC, National Newborn Screening and Genetics Resource Center; NNSIS, National Newborn Screening Information System; PKU, phenylketonuria; RUSP, Recommended Uniform Screening Panel; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

☆ The findings and conclusions in the paper are those of the authors and do not necessarily reflect the views of the University of Texas Health Science Center at San Antonio, NIH, HRSA or the Department of Health and Human Services.

* Corresponding author at: 3907 Galacia Drive, Austin, TX 78759, USA. Fax: +1 512 345 5685.
E-mail addresses: therrell@uthscsa.edu (B.L. Therrell), mpuryear@acmg.net (M.A. Lloyd-Puryear), campkm@od.nih.gov (K.M. Camp), mmann@hrsa.gov (M.Y. Mann).
[1] Consultant.

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1. Introduction

Inborn errors of metabolism (IEM) are genetic 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, toxic compounds may build up in the blood and brain, and other compounds may become deficient leading to adverse health outcomes. This definition is the theoretical basis for the use of nutritional interventions, which can bypass or overcome the metabolic consequences for some IEM. Early diagnosis and treatment at or near birth can often counter the adverse effects of some IEM, resulting in normal or near normal health outcomes. In many cases, nutritional interventions are the primary therapies used to manage these disorders and are required lifelong [1].

A National Institutes of Health (NIH) initiative, *Nutrition and Dietary Supplement Interventions for Inborn Errors of Metabolism* (NDSI-IEM), was launched in 2010 to identify gaps in knowledge concerning the safety, efficacy, and effectiveness of nutritional treatments, including dietary supplements, for IEM that would benefit from evidence-based research [1]. To inform research on IEM and provide necessary resources for researchers, we are providing previously unpublished tabulations of ten-year state incidence data for selected IEM detected through newborn screening (NBS). Additionally, we are providing approximated costs of medical foods used in the management of IEM and an assessment of corporate policies regarding provision of nutritional interventions to individuals with IEM at no or reduced cost. As the landscape of our health care system changes over the next few years, these data will be needed for assessing adequacy of states' reimbursement and coverage policies and practices for nutritional interventions for individuals with IEM.

2. Background

2.1. National newborn screening data collection

From 1989 to 2011, all U.S. NBS programs voluntarily contributed case finding and other performance evaluation information to the Council of Regional Networks for Genetic Services (CORN) and to the National Newborn Screening and Genetics Resource Center (now the National Newborn Screening and Global Resource Center—NNSGRC) through the National Newborn Screening Information System (NNSIS). These data were intended for both self- and inter-program evaluation. This dataset currently represents the only comprehensive national NBS data available.

Originally, the U.S. national NBS data were collected annually from each screening program using a multi-page questionnaire. The indicators for which data were collected addressed *system* quality assurance. They were developed through a consensus process that included a broad cross-section of laboratory and non-laboratory personnel working with (and in) public health NBS programs. The NBS program descriptors and indicators for which data were submitted by each program included:

- Conditions screened for which data were collected and available;
- Laboratories providing screening services in/for the NBS program;
- NBS program fees, collection mechanisms, and program elements covered by fees (including medical foods);
- Age of newborns at time of screening (i.e. number screened at 0–12 h, 13–24 h, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, over 7 days);
- Screening laboratory methodology for each screened condition;
- NBS programs' case definitions for:
  - Out-of-range reporting (by condition)
  - Level of follow-up action required (telephone or letter and serum or repeat filter card)
  - Diagnosed clinical cases;
- Specimens received per year:
  - Total of initial specimens and repeat specimens
  - Percentage of specimens unacceptable for analysis
  - Specimens reported with out-of-range results on initial and on repeat screening;
- Number of diagnosed individuals for each condition including race/ethnicity, sex, and time from birth until treatment was initiated; and,
- Number of individuals requiring follow-up who could not be located (i.e., "lost to follow-up").

The data elements collected and used for monitoring program quality assurance were reviewed and their validity reconfirmed on multiple occasions over the time period of their collection. Initially (1989–1999) this data repository was a function of CORN and later (1999–2011) it became a responsibility of the NNSGRC, both Health Resources and Services Administration (HRSA) funded initiatives. Beginning in 2000, these data were reported via the Internet (the NNSIS) and were available to the general public. The data tabulated and reported here were collected, summarized and revalidated by each NBS program prior to discontinuation of NNSGRC data collection activities in 2011. A more comprehensive review of the history and functioning of the national NBS data repository has been published previously [2].

2.2. Nutritional interventions for IEM

Nutritional interventions for IEM include medical foods and dietary supplements along with dietary modifications to exclude nutrients that cannot be metabolized due to the specific IEM. At least twenty-two IEM on the U.S. Secretary of Health and Human Services' Recommended Uniform Screening Panel (RUSP), which currently is composed of 31 conditions, require medical foods and/or dietary supplements to prevent death, intellectual disability or other adverse health outcomes [3].

A "medical food," is defined in the Orphan Drug Act (Act) (21 U.S.C. 360ee (b) (3)) [4]. In section 5(b) of the Act,[4] a medical food is "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." Additionally, under the Act, the use of medical foods is tied to the term rare disease or condition[2]: a medical food is for "… managing any disease or condition that occurs so infrequently in the United States that there is no reasonable expectation that a medical food for such disease or condition will be developed without assistance under subsection (a)[3] of this section."

Medical foods for IEM encompass two distinct product types. One type contains sufficient nutrients to meet the majority of nutritional

[2] Under the Orphan Disease Act, a rare disease or condition means in the case of a drug, "any disease or condition which (a) affects less than 200,000 persons in the United States, or (b) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug…".

[3] Subsection (a) defines the authority of the Secretary to defray costs of developing medical foods for rare diseases: The Secretary may make grants to and enter into contracts with public and private entities and individuals to assist in (1) defraying the costs of qualified testing expenses incurred in connection with the development of drugs for rare diseases and conditions, (2) defraying the costs of developing medical devices for rare diseases or conditions, and (3) defraying the costs of developing medical foods for rare diseases or conditions.

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