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

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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.

☆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.

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Keywords

newborn screening; inborn errors of metabolism; medical foods; incidence; costs; nutrition

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 1989–2011, 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 hr, 13–24 hr, 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 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 comprised 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[1]: 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)[2] of this section."

Medical foods for IEM encompass two distinct product types. One type contains sufficient nutrients to meet the majority of nutritional requirements, is disorder specific, and excludes the nutrient(s) that cannot be metabolized. For example, for phenylketonuria (PKU; now more accurately referred to as phenylalanine hydroxylase deficiency [5]), phenylalanine is excluded; whereas, for fatty acid oxidation disorders, certain fatty acids are limited. Depending on the disorder, this product type includes drinks made by reconstituting powders, ready to drink products, customized modular products, and bars. The other type of medical food includes products that are modified to be low in protein. These are designed for use in natural protein-restricted diets and provide required energy, satiety, and variety in the diet (e.g. specially modified flour, cereals, and baked goods, meat and cheese substitutes, pasta, and rice).

Dietary supplements provide for other unmet nutritional needs due to dietary restriction (e.g. essential amino acids, vitamins, or minerals) or are used in large doses to enhance enzyme activity (e.g. vitamins) or assist in the removal of toxic metabolites (e.g. carnitine). The U.S. Congress defined the term "dietary supplement" in the Dietary Supplement Health and Education Act (DSHEA) of 1994 [6] as a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. The "dietary ingredients" in these products may include such items as vitamins, minerals, herbs or other botanicals, or amino acids. Dietary supplements can also be extracts or concentrates, and may be found as tablets, capsules, softgels, gelcaps, liquids, and powders, or in other forms, such as bars. Information on the product label must not represent the product as a conventional food or a sole item of a meal or diet. DSHEA places dietary supplements in a special category under the general umbrella of "foods," not drugs, and requires that every supplement be labeled as a dietary supplement.

[1]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…"

[2]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.

For some IEM, dietary supplements are used as treatment modalities, often in large doses, and thus do not conform strictly to the definition of a dietary supplement. Additionally, they only rarely undergo the Food and Drug Administration approval process required for drugs.

2.3. Financing nutritional interventions for IEM

Since its inclusion in NBS, tandem mass spectrometry (MS/MS) screening has been shown to be a cost effective method for IEM detection. Many reports exist assessing the economics of screening for multiple conditions simultaneously [7–10] or for individual conditions as part of a multi-analyte panel [11–14]. Cost effectiveness modeling is complex and beyond the scope of our discussion here. It suffices to say that societal cost savings are positive, but the amount saved varies by condition, complexities of the screening infrastructure, and modeling assumptions.

Access to nutritional interventions for screened disorders throughout the life span of individuals with IEM is essential for optimal outcomes. The amounts and costs of medical foods and/or dietary supplements needed to prevent adverse health outcomes are variable and depend on the IEM, the nutritional products required, and the treated individual's age. Payment for medical foods for children identified with IEM is achieved through: (1) partial use of NBS fees by the state program and/or funds from other state or federal programs; (2) third-party health care payers; or (3) families' or individuals' “out-of-pocket” purchases. At least 46 NBS programs charge a fee (usually to the birthing center) to pay for the cost of supporting their newborn screening system [15, 16]. In the review by Therrell, et al [16], 37% of these programs reported that fee monies supported various non-laboratory program activities, including the provision of medical foods.

In both public and private insurance programs, coverage may vary depending on factors that include the diagnosis, nutritional content of the medical food, age of the individual, and the method of administration (orally or by a feeding tube into the gastrointestinal tract). A 2010 analysis by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children [17] and others in 2010 and 2013 [18, 19], showed that insurance coverage of medical foods and foods modified to be low in protein vary depending on the state of residence for the individual/family or type of their insurance plan. Thirty-two states were found to mandate some form of private insurance coverage if certain disorders were identified through NBS.

A recent survey among families of children less than 18 years of age with IEM evaluated usage of nutritional interventions among, and the associated cost burden to, their families. The study revealed that 80% of children utilized at least two different types of nutritional products and almost half used three or more (e.g., a protein-containing medical food, plus foods modified to be low in protein, plus a dietary supplement) [19]. At the time of the survey, the costs of protein-containing medical foods were covered for most children through payment sources such as Medicaid, private insurance, and the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), while payment for foods modified to be low in protein were covered for only 40% of children. These studies documented that the full costs of medical foods and dietary supplements used to treat IEM are not covered completely by health care payers. As a result, families and individuals must bear a significant financial burden in order to provide recommended medical interventions across the lifespan for both children and adults [19].

None of the previous studies examined coverage of NBS treatments under newer state health care payer systems. Furthermore, Federal Medicaid regulations are silent on coverage of nutritional interventions for IEM, although currently nutritional interventions are covered for children who qualify for Medicaid. Many state policies will undoubtedly change over time as individual states define their essential health benefits package. Analysis of the state policies addressing nutritional interventions for IEM that have emerged since enactment of new Federal laws and regulations is beyond the scope of this paper. Nonetheless, the way in which these policy changes affect access to essential medical therapies for treating IEM is one of the more critical research issues now and for the future.

3. Methods

3.1. IEM incidence data

To estimate the number of newborns with a screened IEM who are detected and diagnosed annually in the U.S., NBS data were obtained from the NNSIS for the period of 2001–2010. In order to confirm the accuracy of the recorded data, programs were provided with tables of cases reported for each disorder annually for the ten years for revalidation and correction (if necessary). Because many U.S. NBS programs expanded their screening panels for IEM during this time period, we also confirmed the screening start dates for disorders begun during the 10-year study period. Data from a limited number of U.S. NBS programs (four programs) could not be revalidated either because the data were no longer available to the state program or because of other program constraints (primarily personnel time and effort). In order to provide as complete a dataset as possible, and because the likelihood was high that the data initially input into the NNSIS were correctly entered, these data elements were included in our tables and tabulations (identified as such through footnotes).

Since IEM disease case-definitions are not standardized nationally, the definitions of confirmed cases were left to the discretion of NBS programs and their medical advisors throughout the period of data collection. Listings of the case definitions used were available as part of the online data system for comparison between programs. Where variations in case definitions existed, the specific differences often appeared to be subtle and rarely appeared to affect the nutritional treatment. For purposes of this report, we have assumed that physician sub-specialists confirmed all IEM cases reported by NBS programs using generally agreed upon case-definitions.

The majority of U.S. NBS programs do not link birth records with NBS data [20] and therefore, most programs are not able to provide a valid non-duplicated tally of babies screened. For consistency, we obtained data on numbers of births by place of occurrence from the NNSIS, which had been obtained by request from the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS), and we assumed complete birth coverage by the screening programs. In cases where data recording for a specific disorder began within the 10-year study period, we approximated the number of babies screened by assuming an even distribution of births monthly over the year. We then calculated the number of babies screened by multiplying the monthly average by the number of months for which data existed. In most instances data reporting began on the first day of the month, but when data reporting began on a date other than the first of the month, calculations were made to the nearest 1/2-month.

3.2. Estimate of average costs per year for medical foods for IEM

To estimate the costs associated with the use of nutritional intervention products, the appropriate literature and publically available national data were reviewed and relevant cost data were extracted to the extent possible. The costs of medical foods depend on the disorder, the individual's age, and the mechanisms through which individuals obtain these products. Thus, it is difficult to ascertain total societal costs for providing these products for all individuals at any one time. We created a table of conditions and their nutritional interventions and combined this with the 2001–2010 national incidence data as a way of summarizing the information to be considered. We then estimated the costs of medical foods containing protein plus the costs of foods modified to be low in protein for selected age groups. In order to determine the costs of medical foods in excess of what it costs to feed the average person within the selected life stage, we subtracted the estimated annual expenditure for food for an individual without an IEM. These costs were summarized in tabular form for inclusion in our report. Note that we have not attempted to estimate the costs of dietary supplements, whether used in addition to a medical food (e.g., homocystinuria) or used as a sole treatment modality (e.g., biotinidase deficiency) because costs vary too widely depending on where and from which company the product is obtained.

3.3. Corporate policies

To better understand the overall impact of commercial practices associated with providing IEM nutritional products to individuals with IEM and families at no or reduced cost, we identified 11 U.S. companies that manufacture and/or distribute medical food products specifically for the nutritional management of IEM. Of these, three (27%) make exempt infant formulas.[3] These three companies and five others also make medical foods with protein for children over age 1 (73% of total companies). Eight of the 11 companies make or distribute foods modified to be low in protein (73%), and three (27%) exclusively make products modified to be low in protein. To understand the overall contribution of these industry practices to product availability for individuals, in the fall of 2012, one of us (KC) sent a short questionnaire to the eight companies in the United States that manufacture and/or distribute medical foods with protein for infants and individuals over 1 year of age. Replies were received from six of the eight companies (75%).

[3]Exempt infant formulas do not include the offending nutrient(s); e.g. infant formulas for PKU do not contain phenylalanine. They must, however, meet the regulatory requirements of standard infant formulas, with the exception that they are exempt from applicable good manufacturing processes, nutrient content, and labeling requirements.

4. Results

4.1. National NBS data

Tabulations of the national NBS data on births by place of occurrence and confirmed cases are given in Tables 1–7 organized by the regional NBS and genetics collaboratives defined by the Maternal and Child Health Bureau, HRSA [21][Note: Nevada was originally in Region 7 and was transferred to Region 6 in 2006 where it now resides.]. National summary incidence data and their treatment modalities are included in Table 8. Summary data similarly collected and tabulated have been published for the previous 10-year period allowing comparisons for those IEM that were included on state NBS panels during that time period (available at: http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/resources/genetics/10yeardatareport.pdf; accessed March 19, 2014). A published summary of the 1991–2000 data also exists [2]. It is important to note that birth data used in NBS studies must be based on place of birth occurrence rather than residence. While current birth data by place of occurrence are available from the NCHS on request, this is not the usual format for their published birth data. (http://www.cdc.gov/nchs/.

4.2. Costs of nutritional interventions

Along with the national summary incidence data in Table 8, summary information on the nutritional interventions employed with the IEM studied are included. These summary data provide a basis for estimating costs relative to treatment expenses for the IEM listed. Based on these data, nutritional costs for managing a typical IEM over and above costs for persons without an IEM are estimated for four age groups (see Table 9). Annual costs range from $2,254 for an infant to almost $25,000 for an adult male or pregnant woman.

4.3. Corporate policies regarding nutritional products for IEM

A limited number of manufacturers and distributors of medical foods for IEM currently serve the U.S. Of the six companies who responded to the request for information about policies regarding the provision of medical foods to individuals, all stated that they provide products to individuals at no or reduced cost in specific or limited situations. Most often, the amount and types of products provided and length of provision depended on individual circumstances. At least two companies provide products throughout a pregnancy, and one has no limit on the length of time that they will provide a product for a specific individual. Most of the companies also noted a willingness to help individuals and families obtain coverage from health care payers or other sources. Based on the responses, the overall contribution of nutritional products at no or reduced cost to individuals must be viewed only as a bridging mechanism until coverage from other sources can be obtained.

5. Discussion

In order to accurately address issues related to cost and treatment for IEM detected through NBS, it is essential to know the number of confirmed cases detected nationally. We obtained the most comprehensive case data available and have tabulated it here as an aid in future research. The NBS incidence data are presented in regional format in order to provide for comparisons with previous data similarly tabulated (available at: http://genesrus.uthscsa.edu/sites/genes-r-us/files/resources/genetics/10yeardatareport.pdf; accessed March 19, 2014). This regional format should facilitate future discussions concerned with coordinating regional activities focused on access to care.

Screening for the majority of IEM currently on the RUSP was initiated during the decade from 2001–2010; summary incidence data for the ten-year period of 1991–2000 are limited to only a few IEM. We elected to revalidate and use the 2001–2010 data since these data covered a time period in which a more sensitive screening technique, tandem mass spectrometry (MS/MS), was used in the NBS laboratories and when screening results for IEM on the RUSP were more widely available. We used the combined reported incidences for PKU and clinically significant hyperphenylalaninemia in our calculations for these reasons: programs reported both conditions; the case definitions appeared to vary and overlap; and both conditions require nutritional interventions.

The only previously published comprehensive national incidence data for the U.S. addressed the 10-year period immediately preceding our study period, and these data were collected and validated in the same way as the data in our study [2]. Only a few IEM were included in the earlier study since most programs had not yet implemented MS/MS screening. Abbreviated comparisons of the two decades of data follow. Reported national incidences for 1991–2000 were: biotinidase (1:61,319; n~12.8 million), GALT (1:53,261; n~35.9 million), PKU (1:19,079; n~40.0 million), clinically significant hyperphenylalaninemia (1:51,850; n~40.0 million), MSUD (1:230,028; n~13.8 million); HCY (1:343,650; n~12.0 million). Calculated national incidences for 2001–1010 were: biotinidase (1:67,766; n~28.6 million); GALT (1:53,554; n~41.2 million), phenylketonuria (1:23,080; n~41.3 million); clinically significant hyperphenylalaninemia (1:58,272; n~40.3 million); MSUD (1:197,714; n~31.2 million); HCY (1:456,726; n~29.2 million). The combined apparent incidence of PKU + clinically significant hyperphenylalaninemia was 1:13,947 in the previous decade versus (1:16,500) for 2001–2010.

Difficulties with analyzing national incidence data are encountered because of the lack of national standards governing NBS data, such as uniform case definitions. Early attempts by CORN to apply case definitions to data submitted by NBS programs resulted in a poor response rate, since consensus case-definitions did not exist. Therefore, beginning in 1991, NBS programs were asked to submit data to the national NBS data repository using their own case definitions. The definitions used by each program were then tabulated and reported separately with the hope that by sharing case definitions, consensus would be generated thus improving the national data [2]. Between 1991 and 2011, all U.S. NBS programs except New York contributed data to the national database. New York data were maintained on a state-supported website and were periodically copied into the NNSIS to form a comprehensive national dataset.

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6. Conclusion

Despite challenges and their need for future resolution, we still were able to tabulate credible national incidence data in order to inform our discussion. Nevertheless, future research depends on access to a robust data system. As illustrated by our efforts to obtain national

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incidence data for the various conditions detected through NBS, the lack of national consensus on case definitions restricts the degree of accuracy of national incidence numbers essential to any research and evaluation. Similarly, a voluntary national data system that depends on unfunded cooperation and collaboration among the 51 national partnering programs (50 states and the District of Columbia) results in tenuous data collection that is often reported slowly and may be prone to inaccuracies. The inability of most U.S. NBS programs to compare births to screens in real time, so that screening all babies can be assured and reliable screening data can be obtained for calculating accurate disease incidences, remains a challenge. Linking birth records with NBS results would alleviate that inaccuracy and would allow the calculation of the number of babies screened. While we assumed 100% screening coverage and used births reported by vital records managers and not the NBS program, more precise coverage data are needed for more accurate incidence calculations.

Left untreated, infants and children with IEM experience serious adverse health outcomes including intellectual disability, behavioral dysfunction, inadequate growth, abnormal development, nutrient deficiencies, and sequelae that require complex hospital care. Furthermore, with the success of NBS and appropriate nutritional interventions, there are adults living with IEM. The nutritional cost data presented serve to highlight the challenges facing individuals and families seeking access to affordable medical foods as part of their continuing lifelong treatment.

Part of future translational research must include ways to assess affordable access to medical foods. As one example, investigation and development of a thorough understanding of impediments and challenges to making nutritional interventions available to individuals with IEM and their families might be initiated. Research would include partnering with public health and health care professionals and payers and families and individuals though disease advocacy organizations to identify and provide the information needed by policymakers to take actions to eliminate identified barriers. Areas to be investigated could include private health insurance plans/mandates, state and federal supplemental programs, and the impact of federal laws and regulations on state policies concerning provision of medical foods and dietary supplements. Not only would such research help provide the foundation needed to remove barriers to treatments developed through medical research, but removing these barriers to treatments would facilitate research on the clinical spectrum of the disease as well as a better understanding of the effect of nutritional interventions on the long-term health outcomes of individuals with IEM.

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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

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Highlights

- From 1989-2011, all U.S. NBS programs contributed case data to a national database.
- At least 22 IEM on the national RUSP for NBS require nutritional interventions.
- IEM screening cost-savings vary by condition, NBS complexities and model assumptions.
- Costs for nutritional interventions for IEM add significantly to family expenses.
- U.S. NBS incidence and nutritional cost data will be useful for future IEM research.

Table 1

Region 1 newborn screening incidence data for selected metabolic conditions from January 1, 2001 – December 31, 2010

Condition	Newborn Screening Programs in Region 1											
	Connecticut[a]		Maine[b]		Massachusetts		New Hampshire[c]		Rhode Island[d]		Vermont[e]	
	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births
3-MCC	3	252,625	3	135,961	16	785,953	0	47,020	2	56,665	1	48,316
ASA	1	252,625	1	135,961	4	785,953	1	47,020	1	56,665	0	48,316
BIO	8	417,425	2	135,961	8	785,953	1	63,368	7	131,019	2	60,572
Partial BIO	23	417,425	10	135,961	23	785,953	6	63,368	3	131,019	1	60,572
BKT	0	252,624	0	135,961	2	785,953	0	47,020	0	56,665	0	48,316
CBL A,B	0	252,625	0	135,961	3	785,953	0	47,020	0	56,665	0	29,832
CIT	3	252,625	1	135,961	3	785,953	1	47,020	1	56,665	0	48,316
CUD	0	256,170	3	135,961	7	785,953	1	47,020	1	56,665	0	35,764
GA-1	2	256,170	1	135,961	1	785,953	0	47,020	0	56,665	0	48,316
GALT	11	417,425	3	135,961	12	785,953	5	138,094	4	131,019	0	60,572
HCY	1	417,425	1	135,961	1	785,953	0	47,020	0	131,019	0	60,572
HMG	0	252,625	0	135,961	0	785,953	0	47,020	0	56,665	0	48,316
IVA	4	252,625	6	135,961	1	785,953	0	47,020	0	56,665	0	48,316
LCHADD	0	273,897	0	135,961	4	785,953	1	47,020	1	56,665	0	48,316
MCADD	15	288,079	11	135,961	44	785,953	1	63,368	4	117,700	3	48,316
MCD	0	252,625	0	135,961	0	785,953	0	47,020	0	56,665	0	29,832
MSUD	2	417,425	0	135,961	4	785,953	0	47,020	0	131,019	0	60,572
MUT	3	252,625	0	135,961	4	785,953	0	47,020	1	56,665	0	48,316
PKU	13	417,425	10	135,961	42	785,953	9	138,094	0	131,019	3	60,572
PKU Variant	32	417,425	11	135,961	10	785,953	0	138,094	2	131,019	1	60,572
PROP	1	252,625	0	135,961	2	785,953	0	47,020	0	56,665	0	48,316
TFP	0	288,079	0	32,918	1	785,953	0	47,020	0	56,665	0	29,832
TYR-I	0	273,897	0	135,961	2	785,953	0	27,230	1	56,665	0	48,316
VLCADD	6	256,170	4	135,961	22	785,953	4	47,020	1	56,665	2	48,316

Abbreviations: 3-MCC, 3-Methylcrotonyl-CoA carboxylase deficiency; ASA, Argininosuccinic aciduria; BIO, biotinidase; BKT, Beta-ketothiolase deficiency; CBL A,B, methylmalonic acidemia (cobalamin A and B); CIT, Citrullinemia; CUD, Carnitine uptake defect; GA-1, Glutaric acidemia type I; GALT, Galactosemia transferase deficiency (classical galactosemia); HCY, Homocystinuria; HMG, 3-Hydroxy 3-methyl glutaric aciduria; IVA, Isovaleric acidemia; LCHADD, Long-chain L-3- hydroxyacyl-CoA dehydrogenase deficiency; MCADD, Medium-chain acyl-CoA dehydrogenase

deficiency; MCD, Multiple carboxylase deficiency; MSUD, Maple syrup (urine) disease; MUT, Methylmalonic academia (methylmalonyl-CoA mutase deficiency); PKU, Phenylketonuria; PROP, Propionic acidemia; TFP, Trifunctional protein deficiency; TYR-I, Tyrosinemia type I; VLCADD, Very long-chain acyl-CoA dehydrogenase deficiency

[a]Data began: Jan 1, 2004 for MCADD; May 1, 2004 for LCHADD, TYR; Oct 1, 2004 for CUD, GA1, VLCADD; Jan 1, 2005 for CIT; Nov 1, 2004 for 3-MCC, BKT, CBL A,B, HMG, IVA, MCD, MUT, PROP

[b]Data began: Jul 1. 2008 for TFP

[c]Data began: May 1, 2006 for BIO, MCADD; Jul 1, 2007 for All except BIO, GALT, MCADD, and PKU

[d]Data began: Jan 1, 2002 for MCADD; Jul 1, 2006 for All except BIO, GALT, HCY, MCADD, MSUD, PKU

[e]Data began: Jan 1, 2003 for 3-MCC, ASA, BKT, CIT, GA-1, HMG, IVA, LCHADD, MCADD, MUT, PROP, TYR-I, VLCADD; Jan 1, 2005 for CUD; Jan 1, 2006 for CBL A,B, MCD, TFP

Table 2

Region 2 newborn screening incidence data for selected metabolic conditions from January 1, 2001 – December 31, 2010

Condition	Newborn Screening Programs in Region 2															
	Delaware[a]		District of Columbia[b]		Maryland[c]		New Jersey[d]		New York[e]		Pennsylvania[f]		Virginia[g]		West Virginia[h]	
	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births
3-MCC	0	97,626	5	29,416	11	509,796	18	797,029	159	1,755,287	4	215,616	7	504,761	0	40,279
ASA	0	97,626	0	29,416	0	509,796	3	938,324	4	1,755,287	2	215,616	0	504,757	0	40,279
BIO	7	61,161	1	71,904	6	718,032	17	1,041,163	48	2,517,602	6	215,616	25	1,019,793	1	74,454
Partial BIO	4	61,161	1	71,904	14	718,032	91	1,041,163	NA	–	37	215,616	66	1,019,793	16	74,454
BKT	0	97,626	0	29,416	0	509,796	0	656,334	2	1,755,287	0	215,616	0	504,757	0	40,279
CBL A,B	0	48,743	0	29,416	0	509,796	2	656,334	12	1,755,287	0	215,616	0	504,757	0	40,279
CIT	0	97,626	0	29,416	3	509,796	4	938,324	9	1,755,287	3	215,616	2	504,757	1	40,279
CUD	2	48,743	0	29,416	0	367,966	9	656,334	32	1,755,287	0	215,616	17	504,757	3	40,279
GA-1	1	97,626	0	29,416	6	509,796	6	797,029	81	1,755,287	5	215,616	1	504,757	1	40,279
GALT	0	120,710	NA	–	22	718,032	28	1,106,869	56	2,517,602	30	1,457,789	39	1,019,793	6	212,612
HCY	0	97,626	0	103,183	1	718,032	3	656,334	7	2,517,602	0	215,616	3	1,019,793	0	212,612
HMG	0	97,626	0	29,416	0	509,796	4	797,029	2	1,755,287	1	215,616	0	504,761	0	40,279
IVA	0	97,626	0	29,416	4	509,796	4	797,029	8	1,755,287	1	215,616	5	504,761	0	40,279
LCHADD	0	97,626	1	29,416	1	509,796	2	656,334	3	1,755,287	1	215,616	0	504,757	0	40,279
MCADD	6	97,626	2	29,416	26	509,796	46	938,324	85	2,262,573	11	215,616	48	726,877	5	40,279
MCD	0	97,626	0	29,416	0	509,796	NA	–	0	1,755,287	0	215,616	0	504,757	0	40,279
MSUD	0	97,626	0	103,183	10	718,032	10	1,041,163	14	2,517,602	27	1,457,789	10	1,019,793	0	212,612
MUT	1	97,626	0	29,416	4	509,796	5	938,324	19	1,755,287	1	215,616	1	504,757	0	40,279
PKU	9	120,710	0	103,183	18	718,032	53	1,106,869	98	2,517,602	104	1,457,789	11	1,019,793	14	212,612
PKU Variant	4	120,710	1	103,183	10	718,032	24	1,106,869	12	2,517,602	43	1,457,789	13	1,019,793	0	212,612
PROP	0	97,626	1	43,205	7	509,796	5	938,324	5	1,755,287	3	215,616	5	504,757	0	40,279
TFP	0	48,743	0	29,416	0	509,796	1	656,334	0	1,755,287	0	215,616	0	504,757	0	40,279
TYR-I	0	97,626	1	29,416	2	718,032	2	656,334	3	1,755,287	1	215,616	0	504,757	0	40,279
VLCADD	1	97,626	1	29,416	7	509,7961	12	938,324	14	1,755,287	2	215,616	12	504,757	1	40,279

Abbreviations: 3-MCC, 3-Methylcrotonyl-CoA carboxylase deficiency; ASA, Argininosuccinic aciduria; BIO, biotinidase; BKT, Beta-ketothiolase deficiency; CBL A,B, methylmalonic acidemia (cobalamin A and B); CIT, Citrullinemia; CUD, Carnitine uptake defect; GA-1, Glutaric acidemia type I; GALT, Galactosemia transferase deficiency (classical galactosemia); HCY, Homocystinuria; HMG, 3-Hydroxy 3-methyl glutaric aciduria; IVA, Isovaleric acidemia; LCHADD, Long-chain L-3- hydroxyacyl-CoA dehydrogenase deficiency; MCADD, Medium-chain acyl-CoA dehydrogenase

deficiency; MCD, Multiple carboxylase deficiency; MSUD, Maple syrup (urine) disease; MUT, Methylmalonic academia (methylmalonyl-CoA mutase deficiency); PKU, Phenylketonuria; PROP, Propionic acidemia; TFP, Trifunctional protein deficiency; TYR-I, Tyrosinemia type I; VLCADD, Very long-chain acyl-CoA dehydrogenase deficiency

[a]Data began: Jan 1, 2003 for all except BIO, CBL A,B, CUD, GALT, PKU, TFP; Jan 1, 2006 for BIO; Jan 1, 2007 for CBL A,B, CUD, TFP

[b]Data began: Jan 1, 2006 for BIO; Jan 1, 2006 for all except BIO, GALT, HCY, MSUD, PKU, PROP, No data available from program for 2008–2010 for any condition; No data available for GALT; All other data displayed are those reported to the National Newborn Screening Information System by District of Columbia program staff and have not been validated by the program.

[c]Data began: Jan 1, 2004 for all except BIO, CUD, GALT, HCY, MSUD, PKU, TYR-1

[d]Data began: Jul 31, 2001 for BIO, MSUD; Jul 1, 2002 for ASA, CIT, MCADD, MUT, PROP, VLCADD; Oct 3, 2003 for 3-MCC, GA-1, HMG, IVA,; Jan 1, 2005 for BKT, CBL A,B, CUD, HCY, LCHADD, TFP, TYR-I; no data available for MCD

[e]Data began: Jan 1, 2002 for MCADD; Jan 1, 2004 for all except BIO, GALT, HCY, MCADD, MSUD, PKU; no data available for partial BIO

[f]Data began: Jul 1, 2009 for all except GALT, MSUD, PKU

[g]Data began: Jan 1, 2004 for MCADD; Mar 1, 2006 for all except BIO, GALT, HCY, MCADD, MSUD, PKU

[h]Data began: Jul 1, 2007 for BIO ; Feb 1, 2009 for all except BIO, GALT, HCY, MSUD, PKU; Data displayed are those reported to the National Newborn Screening Information System by West Virginia program staff and have not been validated by the program.

Table 3

Region 3 newborn screening incidence data for selected metabolic conditions from January 1, 2001 – December 31, 2010

Condition	Newborn Screening Programs in Region 3															
	Alabama[a]		Florida[b]		Georgia[c]		Louisiana[d]		Mississippi[e]		North Carolina[f]		South Carolina[g]		Tennessee[h]	
	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births
3-MCC	1	210,215	21	1,145,134	36	577,945	6	322,531	3	322,489	42	1,245,716	7	358,022	25	615,964
ASA	0	378,676	3	1,145,134	2	577,945	1	322,531	1	322,489	1	1,245,716	2	358,022	3	615,964
BIO	3	409,733	13	1,201,738	21	1,097,254	20	644,606	5	322,489	5	768,812	2	358,022	9	782,587
Partial BIO	0	409,733	24	1,201,738	15	1,097,254	18	644,606	30	322,489	3	768,812	4	358,022	6	782,587
BKT	0	210,215	1	1,145,134	0	577,945	0	322,531	0	322,489	0	1,245,716	0	358,022	0	615,964
CBL A,B	0	378,676	0	1,145,134	5	577,945	0	322,531	0	322,489	8	1,245,716	0	358,022	0	615,964
CIT	2	378,676	4	1,145,134	1	577,945	3	322,531	0	322,489	7	1,245,716	7	358,022	6	615,964
CUD	2	378,676	2	1,145,134	0	577,945	1	322,531	0	322,489	NA	–	0	358,022	0	531,109
GA-1	0	263,070	7	1,145,134	6	577,945	3	322,531	3	322,489	11	1,245,716	2	358,022	3	615,964
GALT	11	603,370	39	2,213,751	27	1,417,732	15	578,986	17	421,378	16	1,245,716	7	562,008	11	866,108
HCY	1	378,676	5	1,145,134	3	1,417,732	0	448,564	1	322,489	3	1,245,716	0	358,022	2	615,964
HMG	0	210,215	0	1,145,134	2	577,945	0	322,531	1	322,489	0	1,245,716	0	358,022	1	615,964
IVA	0	263,070	4	1,145,134	1	577,945	2	322,531	3	322,489	6	1,245,716	1	358,022	4	615,964
LCHADD	0	228,879	3	1,145,134	3	577,945	1	322,531	0	322,489	3	1,245,716	3	358,022	2	615,964
MCADD	24	378,676	39	1,145,134	45	871,341	26	448,564	22	322,489	88	1,245,716	30	562,008	33	615,964
MCD	0	210,215	0	1,145,134	0	577,945	0	322,631	0	322,489	1	1,245,716	0	358,022	0	615,964
MSUD	0	378,676	5	1,145,134	4	1,417,732	0	448,564	1	322,489	5	1,245,716	2	358,022	3	615,964
MUT	1	378,676	1	1,145,134	0	577,945	4	322,531	0	322,489	6	1,245,716	1	358,022	0	615,964
PKU	31	603,370	87	2,213,751	41	1,417,732	26	644,606	8	421,378	50	1,245,716	22	562,008	36	866,108
PKU Variant	22	603,370	39	2,213,751	15	696,311	5	644,606	0	421,378	25	1,245,716	2	562,008	7	517,903
PROP	1	378,676	5	1,145,134	1	577,945	2	322,531	3	322,489	5	1,245,716	1	358,022	0	615,964
TFP	1	228,879	1	1,145,134	3	577,945	0	322,531	0	322,489	2	1,245,716	0	358,022	0	615,964
TYR-I	1	378,676	1	233,429	1	1,417,732	1	322,531	2	322,489	1	1,245,716	0	358,022	2	615,964
VLCADD	0	228,879	6	1,145,134	7.	577,945	9	322,531	3	322,489	20	1,245,716	3	358,022	5	615,964

Abbreviations: 3-MCC, 3-Methylcrotonyl-CoA carboxylase deficiency; ASA, Argininosuccinic aciduria; BIO, biotinidase; BKT, Beta-ketothiolase deficiency; CBL A,B, methylmalonic acidemia (cobalamin A and B); CIT, Citrullinemia; CUD, Carnitine uptake defect; GA-1, Glutaric acidemia type I; GALT, Galactosemia transferase deficiency (classical galactosemia); HCY, Homocystinuria; HMG, 3-Hydroxy 3-methyl glutaric aciduria; IVA, Isovaleric acidemia; LCHADD, Long-chain L-3- hydroxyacyl-CoA dehydrogenase deficiency; MCADD, Medium-chain acyl-CoA dehydrogenase

deficiency; MCD, Multiple carboxylase deficiency; MSUD, Maple syrup (urine) disease; MUT, Methylmalonic academia (methylmalonyl-CoA mutase deficiency); PKU, Phenylketonuria; PROP, Propionic acidemia; TFP, Trifunctional protein deficiency; TYR-I, Tyrosinemia type I; VLCADD, Very long-chain acyl-CoA dehydrogenase deficiency

[a]Data began: Apr 1, 2004 for BIO: Oct 25, 2004 for ASA, CBL A,B, CIT, CUD, HCY, MCADD, MSUD, MUT, PROP, TYR-I; Oct 2, 2006 for GA-1, IVA; Apr 16, 2007 for LCHADD, TFP; VLCAD; Aug 6, 2007 for 3-MCC, BKT, HMG, MCD,

[b]Data began: Oct 1, 2005 for BIO; Jan 1, 2006 for all except BIO, GALT, PKU, TYR-1; Dec 17, 2009 for TYR-I

[c]Data began: May 13, 2003 for BIO; Jan 1, 2005 for MCADD; Jan 1, 2007 for all except BIO, GALT, HCY, MCADD, MSUD, PKU, TYR-I; No Data for PKU variants for 2007–2010.

[d]Data began: Jan 1, 2002 for GALT; Jan 1, 2004 for HCY, MCADD, MSUD; Jan 1, 2006 for all except BIO, HCY, GALT, MCADD, MSUD, PKU

[e]Data began: Jun 1, 2003 for all except PKU, GALT

[f]Data began: Jan 1, 2005 for BIO

[g]Data began: Nov 1, 2004 for all except MCADD, PKU, GALT

[h]Data began: Jan 1, 2002 for BIO; Jan 1, 2004 for all except BIO, CUD, GALT, PKU; Jan 1, 2006 for CUD; No Data for PKU variants for 2005–2006 and 2009–2010

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Table 4

Region 4 newborn screening incidence data for selected metabolic conditions from January 1, 2001 – December 31, 2010

Condition	Newborn Screening Programs in Region 4													
	Illinois[a]		Indiana[b]		Kentucky[c]		Michigan[d]		Minnesota[e]		Ohio[f]		Wisconsin[g]	
	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births
3-MCC	26	1,567,305	19	704,310	7	273,250	10	690,037	9	637,598	10	1,035,764	18	695,148
ASA	5	1,567,305	3	704,310	2	273,250	3	690,037	4	637,598	4	1,334,848	2	695,148
BIO	13	1,748,391	12	876,526	3	277,799	15	1,246,254	9	499,535	20	948,567	4	695,148
Partial BIO	1	1,748,391	18	876,526	97	277,799	134	1,246,254	39	499,535	9	948,567	0	695,148
BKT	1	1,567,305	0	704,310	0	273,250	0	690,037	0	637,598	0	1,035,764	2	695,148
CBL A,B	2	1,567,305	2	704,310	4	273,250	0	690,037	1	428,917	0	1,035,764	0	381,129
CIT	5	1,567,305	5	704,310	0	273,250	2	690,037	8	637,598	7	1,334,848	2	548,252
CUD	2	672,886	8	704,310	4	273,250	3	690,037	1	428,917	3	636,513	1	381,129
GA-1	13	1,567,305	4	704,310	1	273,250	6	690,037	4	637,598	3	1,035,764	8	695,148
GALT	30	1,748,391	21	876,526	21	541,304	24	1,246,254	15	705,026	39	1,486,881	12	695,148
HCY	4	1,567,305	2	876,526	0	273,250	1	769,794	2	705,026	1	1,486,881	1	548,252
HMG	1	1,567,305	0	704,310	0	273,250	0	690,037	0	637,598	1	1,035,764	0	695,148
IVA	23	1,567,305	4	704,310	3	273,250	1	690,037	6	637,598	11	1,035,764	6	695,148
LCHADD	3	1,567,305	0	704,310	0	273,250	1	690,037	4	705,026	2	1,035,764	0	695,148
MCADD	81	1,567,305	42	725,687	46	273,250	62	942,110	62	705,026	112	1,486,881	30	695,148
MCD	2	1,567,305	0	704,310	0	273,250	0	690,037	0	637,598	1	1,035,764	0	381,129
MSUD	7	1,478,516	2	876,526	1	273,250	4	1,246,254	1	705,026	4	1,486,881	2	548,252
MUT	9	1,567,305	0	704,310	0	273,250	6	690,037	3	637,598	6	1,334,848	13	695,148
PKU	84	1,748,391	78	876,526	33	541,304	65	1,246,254	54	705,026	98	1,486,881	45	695,148
PKU Variant	17	1,748,391	27	876,526	1	541,304	2	1,246,254	25	705,026	23	1,486,881	5	695,148
PROP	4	1,567,305	4	704,310	0	273,250	3	690,037	1	637,598	19	1,334,848	3	695,148
TFP	0	1,567,305	0	704,310	0	273,250	0	690,037	1	637,598	0	1,035,764	1	381,129
TYR-I	1	1,567,305	0	704,310	1	273,250	0	690,037	0	705,026	0	948,567	1	548,252
VLCADD	17	1,567,305	6	704,310	19	273,250	7	690,037	6	637,598	26	1,035,764	7	695,148

Abbreviations: 3-MCC, 3-Methylcrotonyl-CoA carboxylase deficiency; ASA, Argininosuccinic aciduria; BIO, biotinidase; BKT, Beta-ketothiolase deficiency; CBLA.B, methylmalonic acidemia (cobalamin A and B); CIT, Citrullinemia; CUD, Carnitine uptake defect; GA-1, Glutaric acidemia type I; GALT, Galactosemia transferase deficiency (classical galactosemia); HCY, Homocystinuria; HMG, 3-Hydroxy 3-methyl glutaric aciduria; IVA, Isovaleric acidemia; LCHADD, Long-chain L-3- hydroxyacyl-CoA dehydrogenase deficiency; MCADD, Medium-chain acyl-CoAdehydrogenase

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deficiency; MCD, Multiple carboxylase deficiency; MSUD, Maple syrup (urine) disease; MUT, Methylmalonic academia (methylmalonyl-CoA mutase deficiency); PKU, Phenylketonuria; PROP, Propionic acidemia; TFP, Trifunctional protein deficiency; TYR-I, Tyrosinemia type I; VLCADD, Very long-chain acyl-CoA dehydrogenase deficiency

[a] Data began: Jan 1, 2002 for all except BIO, CUD, GALT, MSUD, PKU ; Jul 1, 2002 for MSUD; Jan 18, 2007

[b] Data began: Oct 1, 2002 for MCADD; Jan 1, 2003 for all except BIO, GALT, HCY, MCADD, MSUD, PKU

[c] Data began: Dec 1, 2005 for BIO; Jan 1, 2006 for all except BIO, GALT, PKU

[d] Data began: Apr 1, 2003 for MCADD; Sep 1, 2004 for HCY; April 18, 2005 for all except BIO, GALT, HCY, LCHADD, MCADD, MSUD, PKU;

[e] Data began: Jan 1, 2002 for 3-MCC, ASA, BKT, CIT, GA-1, HMG, IVA, MCD, MUT, PROP, TFP, VLCADD; Jan 1, 2004 for BIO; Jan 1, 2005 for CBL A,B, CUD

[f] Data began: Jan 1, 2002 for ASA, CIT, MUT, PROP; Jan 1, 2004 for 3-MCC, CIT, LCHADD, MCD, TFP, VLCADD; Aug 1, 2004 for BIO, TYR-I ;Aug 31, 2006 for CUD

[g] Data began: Mar 1, 2003 for CIT, HCY, MSUD, TYR-I; Aug 1, 2005 for CUD, CBL A,B, MCD, TFP

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Table 5

Region 5 newborn screening incidence data for selected metabolic conditions from January 1, 2001 – December 31, 2010

Condition	Newborn Screening Programs in Region 5															
	Arkanasas[a]		Iowa[b]		Kansas[c]		Missouri[d]		Nebraska[e]		North Dakota[f]		Oklahoma[g]		South Dakota[h]	
	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births
3-MCC	1	96,056	7	316,368	1	105,394	6	483,977	7	200,373	2	64,625	1	119,427	1	97,956
ASA	0	96,056	1	316,368	1	105,394	0	483,977	1	200,373	0	64,625	1	119,427	1	97,956
BIO	6	96,056	12	354,187	2	105,394	3	607,997	5	264,034	10	79,304	0	52,347	0	69,668
Partial BIO	0	96,056	21	354,187	0	105,394	34	607,997	34	264,034	2	79,304	0	52,347	6	69,668
BKT	0	96,056	0	316,368	0	105,394	0	483,977	0	200,373	0	64,625	0	119,427	0	97,956
CBL A,B	0	96,056	1	316,368	0	105,394	5	483,977	2	200,373	0	64,625	0	119,427	0	97,956
CIT	3	96,056	0	316,368	1	105,394	1	483,977	0	200,373	0	64,625	2	119,427	0	97,956
CUD	0	96,056	2	316,368	4	105,394	7	404,454	0	200,373	1	64,625	0	119,037	0	69,668
GA-1	0	96,056	1	316,368	0	105,394	4	483,977	2	200,373	0	64,625	1	119,427	0	97,956
GALT	8	382,133	10	391,943	8	411,781	12	793,504	1	264,034	25	97,020	8	515,776	3	86,453
HCY	0	96,056	0	391,943	0	105,394	1	483,977	1	200,373	0	79,304	0	137,334	0	97,956
HMG	0	96,056	0	316,368	0	105,394	0	483,977	0	200,373	0	64,625	0	119,427	0	97,956
IVA	1	96,056	5	316,368	0	105,394	5	483,977	0	200,373	1	64,625	0	119,427	0	97,956
LCHADD	0	96,056	0	316,368	0	105,394	4	483,977	1	200,373	1	64,625	0	119,427	0	97,956
MCADD	5	96,056	30	316,368	9	105,394	31	562,568	16	226,170	6	77,007	24	244,811	6	97,956
MCD	0	96,056	0	316,368	0	105,394	0	483,977	0	200,373	0	64,625	0	119,427	1	97,956
MSUD	0	96,056	0	391,943	0	105,394	0	483,977	0	200,373	0	97,020	0	119,427	0	97,956
MUT	0	96,056	0	316,368	1	105,394	1	483,977	1	200,373	0	64,625	1	119,427	0	97,956
PKU	15	382,133	21	391,943	21	411,781	47	793,504	11	264,034	8	97,020	24	515,776	10	119,755
PKU Variant	0	382,133	8	391,943	2	411,781	6	793,504	12	264,034	0	97,020	8	515,776	6	119,755
PROP	0	96,056	1	316,368	0	105,394	4	483,977	0	200,373	0	64,625	0	119,427	1	97,956
TFP	0	96,056	0	316,368	0	105,394	0	483,977	0	200,373	0	64,625	0	119,427	0	97,956
TYR-I	0	96,056	0	391,943	0	105,394	0	483,977	0	200,373	0	64,625	0	119,427	0	97,956
VLCADD	1	96,056	6	316,368	1	105,394	6	483,977	3	200,373	4	64,625	2	119,427	5	97,956

Abbreviations: 3-MCC, 3-Methylcrotonyl-CoA carboxylase deficiency; ASA, Argininosuccinic aciduria; BIO, biotinidase; BKT, Beta-ketothiolase deficiency; CBL A,B, methylmalonic acidemia (cobalamin A and B); CIT, Citrullinemia; CUD, Carnitine uptake defect; GA-1, Glutaric acidemia type I; GALT, Galactosemia transferase deficiency (classical galactosemia); HCY, Homocystinuria; HMG, 3-Hydroxy 3-methyl glutaric aciduria; IVA, Isovaleric acidemia; LCHADD, Long-chain L-3- hydroxyacyl-CoA dehydrogenase deficiency; MCADD, Medium-chain acyl-CoA dehydrogenase

deficiency; MCD, Multiple carboxylase deficiency; MSUD, Maple syrup (urine) disease; MUT, Methylmalonic academia (methylmalonyl-CoAmutase deficiency); PKU, Phenylketonuria; PROP, Propionic acidemia; TFP, Trifunctional protein deficiency; TYR-I, Tyrosinemia type I; VLCADD, Very long-chain acyl-CoA dehydrogenase deficiency

[a] Data began: July 1, 2008 for all except GALT, PKU

[b] Data began: Jan 1, 2002 for BIO; Jan 1, 2003 for all except BIO, GALT, HCY, MSUD, PKU, TYR-I; Data displayed are those reported to the National Newborn Screening Information System by Iowa program staff and are not available at the program for further validation.

[c] Data began: Jul 1, 2008 for all except PKU, GALT

[d] Data began: Jun 1, 2003 for BIO; Jan 1, 2004 for MCADD; Jan 1, 2005 for all except BIO, GALT, MCADD, PKU, CUD; Jan 1, 2006 – CUD

[e] Data began: Jul 1, 2002 for MCADD; Jul 1, 2003 for all except BIO, GALT, MCADD, PKU

[f] Data began: Jan 1, 2003 for BIO, HCY; Apr 1, 2003 for MCADD; Aug 1, 2004 for all except BIO, GALT, HCY, MCADD, MSUD, PKU

[g] Data began: Jun 1, 2006 for MCADD; May 27, 2008 for HCY; Oct 1, 2008 for all except BIO, GALT, HCY, MCADD, PKU; Jan 1, 2010 – BIO

[h] Data began: Jan 1, 2003 for all except BIO, CUD, GALT, PKU; Jun 1, 2005 for BIO, CUD; No data available for 2001–3 for GALT

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Table 6

Region 6 newborn screening incidence data for selected metabolic conditions from January 1, 2001 - December 31, 2010

Condition	Newborn Screening Programs in Region 6															
	Arizona[a]		Colorado[b]		Montana[c]		Nevada[d]		New Mexico[e]		Texas[f]		Utah[g]		Wyoming[h]	
	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births
3-MCC	7	419,677	9	313,189	1	59,836	3	297,539	1	114,820	35	1,661,279	10	328,729	1	32,458
ASA	0	419,677	1	313,189	0	59,836	4	297,539	0	114,820	5	1,661,279	0	276,174	0	32,458
BIO	12	942,747	3	691,931	0	48,310	4	360,734	3	281,724	23	1,627,456	6	267,086	4	67,179
Partial BIO	6	942,747	30	691,931	0	48,310	16	360,734	8	281,724	107	1,627,456	7	267,086	1	67,179
BKT	1	419,677	0	313,189	0	59,836	0	297,539	0	114,820	0	1,661,279	0	276,174	0	32,458
CBL A,B	0	419,677	1	313,189	0	59,836	0	297,539	0	114,820	2	1,661,279	2	276,174	0	32,458
CIT	4	462,653	4	313,189	0	59,836	0	297,539	0	114,820	10	1,661,279	0	276,174	0	32,458
CUD	2	419,677	3	313,189	0	59,836	0	229,554	0	114,820	12	1,661,279	1	276,174	0	32,458
GA-1	2	419,677	5	313,189	0	59,836	4	297,539	0	114,820	25	1,661,279	6	276,174	0	32,458
GALT	7	942,747	13	691,931	2	93,206	0	360,734	3	281,724	49	3,939,957	9	530,983	3	67,179
HCY	4	942,747	0	313,189	0	59,836	3	360,734	2	114,820	6	1,661,279	0	431,628	0	32,458
HMG	1	419,677	0	313,189	0	59,836	0	297,539	0	114,820	1	1,661,279	0	328,729	0	32,458
IVA	1	419,677	1	313,189	0	59,836	0	297,539	0	114,820	7	1,661,279	0	328,729	0	32,458
LCHADD	2	419,677	1	313,189	0	59,836	0	297,539	0	114,820	7	1,661,279	1	276,174	0	32,458
MCADD	13	419,677	15	313,189	0	59,836	11	297,539	2	114,820	94	1,661,279	36	276,174	3	32,458
MCD	0	419,677	1	313,189	0	59,836	0	297,539	0	114,820	2	1,661,279	0	276,174	0	32,458
MSUD	3	942,747	0	313,189	0	59,836	3	360,734	0	114,820	5	1,661,279	0	276,174	0	32,458
MUT	0	419,677	2	313,189	0	59,836	2	297,539	2	114,820	6	1,661,279	0	276,174	0	32,458
PKU	28	942,747	29	691,931	3	93,206	17	360,734	5	281,724	91	3,939,957	42	530,983	11	67,179
PKU Variant	38	942,747	1	691,931	3	93,206	0	360,734	7	281,724	32	3,939,957	11	530,983	1	67,179
PROP	4	419,677	0	313,189	0	59,836	1	297,539	0	114,820	4	1,661,279	0	276,174	0	32,458
TFP	0	419,677	0	313,189	0	59,836	0	297,539	0	114,820	0	1,661,279	0	276,174	0	32,458
TYR-I	0	462,653	0	313,189	0	59,836	0	297,539	0	114,820	0	1,661,279	1	276,174	0	32,458
VLCADD	2	419,677	5	313,189	0	59,836	5	297,539	3	114,820	45	1,661,279	10	276,174	1	32,458

Abbreviations: 3-MCC, 3-Methylcrotonyl-CoA carboxylase deficiency; ASA, Argininosuccinic aciduria; BIO, biotinidase; BKT, Beta-ketothiolase deficiency; CBL A,B, methylmalonic acidemia (cobalamin A and B); CIT, Citrullinemia; CUD, Carnitine uptake defect; GA-1, Glutaric acidemia type I; GALT, Galactosemia transferase deficiency (classical galactosemia); HCY, Homocystinuria; HMG, 3-Hydroxy 3-methyl glutaric aciduria; IVA, Isovaleric acidemia; LCHADD, Long-chain L-3- hydroxyacyl-CoA dehydrogenase deficiency; MCADD, Medium-chain acyl-CoA dehydrogenase

deficiency; MCD, Multiple carboxylase deficiency; MSUD, Maple syrup (urine) disease; MUT, Methylmalonic academia (methylmalonyl-CoA mutase deficiency); PKU, Phenylketonuria; PROP, Propionic acidemia; TFP, Trifunctional protein deficiency; TYR-I, Tyrosinemia type I; VLCADD, Very long-chain acyl-CoA dehydrogenase deficiency

[a]Data began: Apr 5, 2006 for CIT, TYR-I; Aug 31, 2006 for all except BIO, CIT, GALT, HCY, MSUD, PKU, TYR-1

[b]Data began: Jul 1, 2006 for all except BIO, GALT, PKU

[c]Data began: Jan 1, 2004 for all except BIO, GALT, PKU; Jan 1, 2005 for BIO; No data reported for 2007–8; Data displayed are those reported to the National Newborn Screening Information System by Montana program staff and have not been validated by the program.

[d]Data began: Jan 1, 2003 for all except BIO, GALT, HCY, MSUD, PKU; Data prior to 2003 are not available at the program for validation. All other data have been validated.

[e]Data began: Jan 1, 2007 for all except BIO, GALT, PKU; Data prior to 2007 are not available at the program for validation. All other data have been validated.

[f]Data began: Dec 6, 2006 for all except BIO, GALT, PKU; Jan 1, 2007 for BIO

[g]Data began: Jan 1, 2006 for all except BIO, PKU, GALT

[h]Data began: Jul 1, 2006 for all except BIO, PKU, GALT

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Table 7

Region 7 newborn screening incidence data for selected metabolic conditions from January 1, 2001 – December 31, 2010

Condition	Newborn Screening Programs in Region 7											
	Alaska[a]		California[b]		Hawaii[c]		Idaho[d]		Oregon[e]		Washington[f]	
	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births	Cases	Births
3-MCC	1	86,374	58	2,997,046	3	149,783	1	184,644	8	428,110	0	220,866
ASA	0	86,374	7	2,997,046	1	149,783	1	184,644	5	428,110	0	220,866
BIO	1	106,126	25	1,875,211	1	184,422	1	244,254	4	474,310	4	605,494
Partial BIO	3	106,126	33	1,875,211	5	184,422	8	244,254	15	474,310	16	605,494
BKT	0	86,374	2	2,997,046	0	149,783	0	184,644	0	288,758	1	220,866
CBL A,B	0	44,851	6	2,997,046	0	149,783	0	184,644	0	428,110	0	220,866
CUD	0	86,374	41	2,997,046	0	149,783	2	184,644	2	428,110	0	220,866
CIT	0	86,374	10	2,997,046	0	149,783	2	184,644	1	428,110	0	220,866
GA-1	3	86,374	24	2,997,046	1	149,783	3	184,644	2	428,110	3	220,866
GALT	11	106,126	59	5,417,932	2	184,422	4	225,254	5	474,310	7	843,161
HCY	0	86,374	2	2,997,046	0	167,295	0	205,093	1	382,057	1	605,494
HMG	0	86,374	1	2,997,046	0	149,783	0	184,644	0	428,110	0	220,866
IVA	0	86,374	21	2,997,046	2	149,783	1	184,644	1	428,110	0	220,866
LCHADD	0	86,374	6	2,997,046	0	149,783	1	184,644	4	428,110	0	220,866
MCADD	9	86,374	115	2,997,046	4	149,783	16	184,644	28	428,110	32	605,494
MCD	0	86,374	3	2,997,046	1	149,783	0	184,644	0	288,758	0	220,866
MSUD	2	106,126	21	2,997,046	2	184,422	2	225,254	0	474,310	2	605,494
MUT	0	86,374	44	2,997,046	0	149,783	3	184,644	5	428,110	1	427,302
PKU	7	106,126	171	5,417,932	1	184,422	15	225,254	20	474,310	52	843,161
PKU Variant	0	106,126	139	5,417,932	1	184,422	1	225,254	6	474,310	31	843,161
PROP	2	86,374	6	2,997,046	0	149,783	1	184,644	0	428,110	0	220,866
TFP	0	86,374	2	2,997,046	0	149,783	0	184,644	0	288,758	0	220,866
TYR-I	1	86,374	10	2,997,046	0	149,783	0	184,644	0	428,110	0	220,866
VLCADD	3	86,374	37	2,997,046	7	149,783	3	184,644	3	428,110	5	220,866

Abbreviations: 3-MCC, 3-Methylcrotonyl-CoA carboxylase deficiency; ASA, Argininosuccinic aciduria; BIO, biotinidase; BKT, Beta-ketothiolase deficiency; CBL A,B, methylmalonic acidemia (cobalamin A and B); CIT, Citrullinemia; CUD, Carnitine uptake defect; GA-1, Glutaric acidemia type I; GALT, Galactosemia transferase deficiency (classical galactosemia); HCY, Homocystinuria; HMG, 3-Hydroxy 3-methyl glutaric aciduria; IVA, Isovaleric acidemia; LCHADD, Long-chain L-3- hydroxyacyl-CoA dehydrogenase deficiency; MCADD, Medium-chain acyl-CoA dehydrogenase

deficiency; MCD, Multiple carboxylase deficiency; MSUD, Maple syrup (urine) disease; MUT, Methylmalonic academia (methylmalonyl-CoA mutase deficiency); PKU, Phenylketonuria; PROP, Propionic acidemia; TFP, Trifunctional protein deficiency; TYR-I, Tyrosinemia type I; VLCADD, Very long-chain acyl-CoA dehydrogenase deficiency

[a] Data began: Jan 1, 2003 for all except BIO, CBL A,B, GALT, MSUD, PKU; Jan 1, 2007 for CBL A,B

[b] Data began: Jul 11, 2005 for all except BIO, GALT, PKU; Jul 16, 2007 for BIO

[c] Data began: Jan 1, 2002 for HCY; Jan 1, 2003 for all except BIO, GALT, HCY, MSUD, PKU

[d] Data began: Jan 1, 2002 for HCY; Jan 1, 2003 for all except BIO, GALT, HCY, MSUD, PKU

[e] Data began: Jan 1, 2002 for all except BIO, BKT, GALT, HCY, MCD, MSUD, PKU, TFP; Jan 1, 2003 for HCY; Jan 1, 2005 for BKT, MCD, TFP

[f] Data began: Jan 1, 2004 for BIO, HCY, MCADD, MSUD; Jul 1, 2008 for all except BIO, GALT, HCY, MCADD, MSUD, PKU

Table 8

Summary of 2001–2010 incidence data and nutritional intervention(s)

Condition[1]	Total Cases	Total Screens	Incidence 1:X	Medical Foods Used[2,3]	Dietary Supplements[2]	Untreated Medical and Neurocognitive Outcomes[4,5]	Treatment Modality,(level of evidence)/Treatment Effect*)[6]
3-MCC	633	24,456,304	38,636	I-Valex-1 & 2; LMD; XLeu Analog, Maxamaid, & Maxamum	Glycine	Asymptomatic in newborns.	Dietary protein restriction; L-carnitine, glycine, biotin supplements; avoid fasting (expert opinion)
					L-Carnitine	Untreated: Episodic hypoglycemia, lethargy, hypotonia, mild dev delay	Standard of care (C)
ASA	82	25,012,585	305,032	Cyclinex-1 & 2; WND 1 & 2; UCD Anamix Jr; Essential Amino Acid Mix; Essential Amino Acid Supplement; Pro-Phree; PDF Toddler & 2	L-Arginine	May present in newborn with hyperammonemia, seizures, failure to thrive, lethargy, coma.	Dietary protein restriction, arginine supplementation, sodium benzoate, phenylbutyrate (Individual cohort study)
						Untreated: Cognitive impairment, seizures, spastic diplegia.	Standard of care (B,C,D,E,F,G)
BIO [Partial BIO]	422 [1,045]	28,597,455 [26,079,853]	67,766 [24,957]	None	Biotin	Untreated: Developmental delay, seizures, alopecia, and hearing deficits.	Biotin supplements (outcomes research) Standard of care (A, E, G)
BKT	12	24,123,697	2,010,308	None	L-Carnitine	Presents in 1st year of life with lethargy, vomiting, fever, ketonuria, hypoglycemia, coma.	Avoid fasting, sick day management, protein restriction (expert opinion)
						Untreated: Cognitive impairment, poor growth, dystonia	Standard of care (C)
CBL A,B	58	23,799,921	410,343	Propimex-1 & 2; OA 1 & 2; Milupa OS 2; XMTVI Analog, Maxamaid, & Maxamum; MMA/PA Gel, Express, & Cooler; Pro-Phree; PDF Toddler & 2	Betaine Folate L-Isoleucine L-Carnitine L-Valine Pyridoxine Vitamin B12	Variable outcomes; can include ketoacidosis, vomiting, lethargy, death; developmental delay, poor growth, spastic quadriparesis, dystonia, seizures, osteoporosis.	Hydroxycobalamin, protein restriction (individual case controlled study or case report) Standard of care (C,G)
CIT	160	24,908,665	155,679	Cyclinex-1 & 2; WND 1 & 2; UCD Anamix Jr; Essential Amino Acid Mix; Essential Amino	L-Arginine	May present in newborn with hyperammonemia, seizures, failure to thrive, lethargy, coma.	Dietary protein restriction, arginine supplementation, sodium benzoate,

Condition[1]	Total Cases	Total Screens	Incidence 1:X	Medical Foods Used[2,3]	Dietary Supplements[2]	Untreated Medical and Neurocognitive Outcomes[4,5]	Treatment Modality,(level of evidence)/Treatment Effect*)[6]
				Acid Supplement; Pro-Phree; PDF Toddler & 2 Acid Supplement; Pro-Phree; PDF Toddler & 2			phenylbutyrate (Individual cohort study)
							Standard of care (B,C,D,E,F,G)
CUD	147	20,908,664	142,236	ProViMin; Protifar	L-Carnitine	Variable expression & age of onset; rarely presents in neonates.	Not given
						Untreated: Lethargy, hypotonia, hepatomegaly, cardiac decompensation due to cardiomyopathy. Hypoglycemia in acute episodes	
GA-1	265	24,460,145	92,302	Glutarex-1 & 2; Xlys, XTrp Analog Maxamaid, & Maxamum; GA; GA Gel & Express; GlutarAde Essential GA-1, Amino Acid Blend & Jr GA1; Pro-Phree PDF Toddler & 2	CoQ10	Macrocephaly in newborn.	Lysine restriction, L-carnitine supplements (outcomes research)
					Glutamine	Untreated: metabolic ketoacidosis, FTT, onset of dystonia & athetosis; irreversible striatal damage.	Standard of care (C,D,E,G)
					L-Carnitine	Treatment prevents neurological disease in 60–70% of individuals.	
					Lipoic Acid powder		
					Riboflavin		
GALT	770	41,236,503	53,554	None	Calcium	Presents in first few days of life with poor feeding, vomiting, jaundice, *E. coli* sepsis can occur and is often fatal	Dietary galactose restriction
					Vitamin D (To suppl diet due to restriction of dairy)		
HCY	64	29,230,466	456,726	Milupa HOM 2; Methionaid; XMet, Analog, Maxamaid, & Maxamum; HCU Cooler, Express & Gel; Hominex 1 & 2; HCY 1 & 2; Pro-Phree; PDF Toddler & 2	Vitamin B6	Asymptomatic in neonate	Methionine restriction, +/− B6, +/− betaine (outcomes research)
					Vitamin B12	Untreated: Cognitive impairment, ectopia lentis, osteoporosis, other skeletal deformities, thromboembolism.	Standard of care (C,D,G)
					Betaine		
					Cystine		
					FolicAcid		
					Vitamin C		
HMG	16	24,456,304	1,528,519	None	L-Carnitine	Asymptomatic in newborn.	Protein restriction, avoid fasting, sick day

Condition[1]	Total Cases	Total Screens	Incidence 1:X	Medical Foods Used[2,3]	Dietary Supplements[2]	Untreated Medical and Neurocognitive Outcomes[4,5]	Treatment Modality,(level of evidence)/Treatment Effect*)[6]
							management (expert opinion) management (expert opinion)
						Hypertrophic cardiomyopathy, pancreatitis, hearing & vision loss, cognitive impairment.	Standard of care (C)
IVA	154	24,509,159	159,150	l-Valex-1 & 2; OA 1 & 2; XLeu Analog, Maxamaid, & Maxamum; Pro-Phree; PDF Toddler & 2	L-Carnitine	Presents in newborn with metabolic ketoacidosis, “sweaty feet” odor, dehydration	Dietary protein restriction; L-carnitine supplements, avoid fasting, sick day management (outcomes research)
					L-Glycine	Untreated: Hyperammonemia, ketonuria, vomiting, hypoglycemia, failure to thrive, cognitive impairment.	Standard of care (C,G)
LCHADD	67	24,370,414	363,738	Portagen; Tolerex; Monogen; Lipistart; MCT Pro-Cal; EnfaPort	L-Carnitine	Acute presentation associated with high mortality.	Not given
					MCT Oil	Untreated: Hepatomegaly, cardiomyopathy, lethargy, hypoketotic hypoglycemia, FTT, rhabdomyolysis.	
MCADD	1,554	27,597,936	17,759	None	L-Carnitine	Usually asymptomatic in newborn; can present with hypoglycemia, metabolic acidosis, hyperammonemia, hepatomegaly.	Not given
						Untreated: Associated with high mortality, vomiting, lethargy, and hypoketotic hypoglycemia	
MCD	12	23,134,961	1,927,913	None	Biotin	May present in newborn period. Hypotonia, metabolic crisis, hypoglycemia, metabolic acidosis, hyperammonemia, ketonuria, seizures.	Biotin supplements (individual case controlled study or case report)
						Untreated: long term spasticity, poor growth, seizures, hearing and vision loss.	Standard of Care (A,E,G)
MSUD	158	31,238,787	197,714	Ketonex 1 & 2; Complex Essent MSD; Complex	L-Isoleucine	Presents in newborn with feeding intolerance, failure	Dietary branched chain amino acid restriction, avoid

Condition[1]	Total Cases	Total Screens	Incidence 1:X	Medical Foods Used[2,3]	Dietary Supplements[2]	Untreated Medical and Neurocognitive Outcomes[4,5]	Treatment Modality,(level of evidence)/Treatment Effect*)[6]
				MSD AA Blend & Bar; Complex Jr MSD; BCAD 1 & 2; Milupa MSUD 2; MSUD Analog, Maxamaid, & Maxamum; Acerflex; MSUD Ai MSD AA Blend & Bar; Complex Jr MSD; BCAD 1 & 2; Milupa MSUD 2; MSUD Analog, Maxamaid, & Maxamum; Acerflex; MSUD Ai MSD AA Blend & Bar; Complex Jr MSD; BCAD 1 & 2; Milupa MSUD 2; MSUD Analog, Maxamaid, & Maxamum; Acerflex; MSUD Ai MSD AA Blend & Bar; Complex Jr MSD; BCAD 1 & 2; Milupa MSUD 2; MSUD Analog, Maxamaid, & Maxamum; Acerflex; MSUD Ai MSD AA Blend & Bar; Complex Jr MSD; BCAD 1 & 2; Milupa MSUD 2; MSUD Analog, Maxamaid, & Maxamum; Acerflex; MSUD Ai MSD AA Blend & Bar; Complex Jr MSD; BCAD 1 & 2; Milupa MSUD 2; MSUD Analog, Maxamaid, & Maxamum; Acerflex; MSUD Ai MSD AA Blend & Bar; Complex Jr MSD; BCAD 1 & 2; Milupa MSUD 2; MSUD Analog, Maxamaid, & Maxamum; Acerflex; MSUD Ai MSD AA Blend & Bar; Complex Jr MSD; BCAD 1 & 2; Milupa MSUD 2; MSUD Analog, Maxamaid, & Maxamum; Acerflex; MSUD Ai MSD AA Blend & Bar; Complex Jr MSD; BCAD 1 & 2; Milupa MSUD 2; MSUD Analog, Maxamaid, & Maxamum; Acerflex; MSUD Ai MSD AA Blend & Bar; Complex Jr MSD; BCAD 1 & 2; Milupa MSUD 2; MSUD Analog, Maxamaid, & Maxamum; Acerflex; MSUD Ai		to thrive, vomiting, lethargy, and maple syrup odor to urine and ear wax.	fasting (individual case control and cohort study or case reports)
					Thiamin	Untreated: Progresses to irreversible cognitive impairment, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death.	Standard of care (B, C, D)
					L-Valine		
MUT	158	25,219,021	159,614	Propimex-1 & 2; OA 1 & 2; Milupa OS 2; XMTVI Analog, Maxamaid, & Maxamum; MMA/PA Gel, Express, & Cooler; Pro-Phree; PDF Toddler & 2	Betaine	Presents in the newborn period with metabolic ketoacidosis, dehydration, hyperammonemia, ketonuria, vomiting, hypoglycemia, and failure to thrive.	Dietary protein restriction, L-carnitine supplements, avoid fasting, sick day management (outcomes research)
					Folate		Standard of care (C,G)
					L-Isoleucine		
					L-Carnitine		
					L-Valine		
					Pyridoxine		
					Vitamin B12		
PKU	1,791	41,335,425	23,080	Phenex 1 & 2; PhenylAde	Tyrosine	Asymptomatic in newborn.	Dietary phenylalanine restriction (systematic review of cohort studies).
						Untreated: Irreversible cognitive impairment, hyperactivity, autistic-like features, seizures	Standard of care (B, D, E)
PKU Variant	691	40,265,799	58,272	Essential, 40, 60, AA Blend, AABar, RTD PKU 10 & PheBloc LNAA Powder; Phenyl-Free 1, 2 & 2HP;			
Combination of PKU + PKU Variant	2,482	~41,000,000	~16,500	Milupa PKU-2, 3; XPhe Maxamaid, Maxamum; Periflex Infant, Jr, & Advance; Lanaflex; Phlexy-10 Drink Mix, Add-Ins, & Tablets; Lophlex Powder & Liquid; Camino Pro PKU; Glytactin Bettermilk, Restore,			Dietary treatment prevents mental retardation in most individuals[7,8]

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Condition[1]	Total Cases	Total Screens	Incidence 1:X	Medical Foods Used[2,3]	Dietary Supplements[2]	Untreated Medical and Neurocognitive Outcomes[4,5]	Treatment Modality,(level of evidence)/Treatment Effect*)[6]
				RTD, & Swirl; PKU Cooler, Express, & Gel RTD, & Swirl; PKU Cooler, Express, & Gel			
PROP	105	25,026,374	238,346	Propimex-1 & 2; OA 1 & 2; Milupa OS 2; XMTVI Analog, Maxamaid, & Maxamum; MMA/PA Cooler, Express, & Gel; Pro-Phree; PDF Toddler & 2	Biotin L-Carnitine L-Isoleucine L-Valine	Present in the newborn period with metabolic ketoacidosis, dehydration hyperammonemia, ketonuria, vomiting, hypoglycemia, and failure to thrive.	Dietary protein restriction; L-carnitine supplements, avoid fasting, sick day management, (outcomes research) Standard of care (C,G)
TFP	13	23,693,387	1,822,568	Portagen; Tolerex; Monogen; Lipistart; MCT Pro-Cal; EnfaPort	L-Carnitine	Acute presentation associated with high mortality.	Not given
					MCT Oil	Untreated: Hepatomegaly, cardiomyopathy, lethargy, hypoketotic hypoglycemia, failure to thrive, rhabdomyolysis	
TYR-I	36	24,521,197	781,144	Tyrex 1 & 2; TYROS 1 & 2; XPhe, XTyr Analog & Maxamaid; Tyr Cooler, Express, & Gel	Tyrosine	Usually asymptomatic in newborn Untreated: Liver disease and cirrhosis early in infancy	Not given
VLCADD	387	24,567,249	63,481	Portagen; Tolerex; Monogen; Lipistart; MCT Pro-Cal; EnfaPort	L-Carnitine	May present acutely in newborn with high mortality.	Not given
					MCT Oil	Untreated: Hepatomegaly, cardiomyopathy, heart arrhythmias, lethargy, hypoketotic hypoglycemia, and failure to thrive.	

Note: There are inherited metabolic disorders not captured on this table (because they are either included on the secondary panel or are not screened in the newborn period) that require medical foods and/or dietary supplements. Additionally, there are other products that may be used in dietary treatment of these IEM that are not considered medical foods such as Polycose (an easily absorbed form of carbohydrate used as a calorie source).

Table Citations:

A=improves psychomotor/cognitive development; B=improves behavioral/psychiatric disturbances; C=prevents acute metabolic decompensation; D=prevents, halts, or slows clinical deterioration; E=improves neurological manifestations (incl neuro-imaging); F=improves seizure/epilepsy control; G=improves systemic manifestations

Abbreviations: 3-MCC, 3-Methylcrotonyl-CoA carboxylase deficiency; ASA, Argininosuccinic aciduria; BIO, biotinidase; BKT, Beta-ketothiolase deficiency; CBL A,B, methylmalonic acidemia (cobalamin A and B); CIT, Citrullinemia; CUD, Carnitine uptake defect; GA-1, Glutaric acidemia type I; GALT, Galactosemia transferase deficiency (classical galactosemia); HCY, Homocystinuria; HMG, 3-Hydroxy 3-methyl glutaric aciduria; IVA, Isovaleric acidemia; LCHADD, Long-chain L-3- hydroxyacyl-CoA dehydrogenase deficiency; MCADD, Medium-chain acyl-CoA dehydrogenase deficiency; MCD, Multiple carboxylase deficiency; MSUD, Maple syrup (urine) disease; MUT, Methylmalonic academia (methylmalonyl-CoA mutase deficiency)); PKU, Phenylketonuria; PROP, Propionic acidemia; TFP, Trifunctional protein deficiency; TYR-I, Tyrosinemia type I; VLCADD, Very long-chain acyl-CoA dehydrogenase deficiency

[1] Primary panel newborn screened inborn errors of metabolism that utilize medical foods and/or dietary supplements [22]

[2] Secretary's Advisory Committee on Heritable Disorders in Newborns and Children [23]

[3] Obtained from medical food companies' websites. Accessed April 2014

[4] American College of Medical Genetics [24]

[5] Star-G Screening, Technology, and Research in Genetics [25]

[6] van Karnebeek, CDM and Stockler, S. [26]

[7] Blau, N, MacDonald A, van Spronsen F. [27]

[8] Burgard, P, Rey F, Rupp A, Abadle V, Rey J. [28]

* The following represent areas of treatment effect cited in the last column of the table above.

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Table 9

Estimated annual costs associated with medical foods for IEM detected by NBS by age

Age	Medical Foods with Protein: Wholesale Cost (x 2.0 for markup) (A)	Cost for Foods Modified to be Low in Protein (B)	Total Cost for IEM Foods (C = A + B)	Estimated Annual Expenditure for Non IEM Foods (D)	IEM-related Costs Exceeding Estimated Expenditure (C–D)
Infant < 1 year	$1,817 ($3,634)	$0 — minimal	$3,634	$1,380[a]	$2,254
School-age (9–13)	$6,249 ($12,499)	$2,200+ $120 shipping	$14,819	$2,255[a]	$12,564
Late teen male	$9,551 ($19,102)	$5,000+ $120 shipping	$24,222	$2,525[a]	$21,700
Adult male or pregnant woman	$11,021 ($22,042)	$4,500+ $120 shipping	$26,662	Average family of 4 spent $6,100[b] (assume $2,000 for adult)	$24,662

[a]From Lino (2008)[29]. Estimates are based on an average of the highest and lowest income levels.

[b]From U.S. Census Bureau (2007) and Kelley (n.d.) [30]. Calculations assume that an estimated 580 infants are born each year with an IEM requiring medical foods.