CALIFORNIA
HEALTH BENEFITS REVIEW PROGRAM

Analysis of Assembly Bill 30: Health Coverage: Inborn Errors of Metabolism

A Report to the 2006-2007 California Legislature
August 24, 2007

CHBRP 07-08

The California Health Benefits Review Program (CHBRP) responds to requests from the State Legislature to provide independent analyses of the medical, financial, and public health impacts of proposed health insurance benefit mandates and proposed repeals of health insurance benefit mandates. CHBRP was established in 2002 to implement the provisions of Assembly Bill 1996 (California Health and Safety Code, Section 127660, et seq.), and was reauthorized by Senate Bill 1704 in 2006 (Chapter 684, Statutes of 2006). The statute defines a health insurance benefit mandate as a requirement that a health insurer or managed care health plan (1) permit covered individuals to obtain health care treatment or services from a particular type of health care provider; (2) offer or provide coverage for the screening, diagnosis, or treatment of a particular disease or condition; or (3) offer or provide coverage of a particular type of health care treatment or service, or of medical equipment, medical supplies, or drugs used in connection with a health care treatment or service.

A small analytic staff in the University of California's Office of the President supports a task force of faculty from several campuses of the University of California, as well as Loma Linda University, the University of Southern California, and Stanford University, to complete each analysis within a 60-day period, usually before the Legislature begins formal consideration of a mandate bill. A certified, independent actuary helps estimate the financial impacts, and a strict conflict-of-interest policy ensures that the analyses are undertaken without financial or other interests that could bias the results. A National Advisory Council, drawn from experts from outside the state of California and designed to provide balanced representation among groups with an interest in health insurance benefit mandates, reviews draft studies to ensure their quality before they are transmitted to the Legislature. Each report summarizes scientific evidence relevant to the proposed mandate, or proposed mandate repeal, but does not make recommendations, deferring policy decision making to the Legislature. The State funds this work through a small annual assessment on health plans and insurers in California. All CHBRP reports and information about current requests from the California Legislature are available at the CHBRP Web site, www.chbrp.org.

A Report to the 2007-2008 California State Legislature

Analysis of Assembly Bill 30:
Health Care Coverage: Inborn Errors of Metabolism

August 24, 2007

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PREFACE

This report provides an analysis of the medical, financial, and public health impacts of Assembly Bill 30, a bill to mandate the coverage of testing and treatment for inborn errors of metabolism. In response to a request from the California Assembly Committee on Health on June 26, 2007, the California Health Benefits Review Program (CHBRP) undertook this analysis pursuant to the provisions of Senate Bill 1704 (Chapter 684, Statutes of 2006) as chaptered in Section 127600, et seq. of the California Health and Safety Code.

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CHBRP gratefully acknowledges all of these contributions but assumes full responsibility for all of the report and its contents. Please direct any questions concerning this report to:

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TABLE OF CONTENTS

LIST OF TABLES

EXECUTIVE SUMMARY

California Health Benefits Review Program Analysis of Assembly Bill 30

The California Assembly Committee on Health requested on June 26, 2007, that the California Health Benefits Review Program (CHBRP) conduct an evidence-based assessment of the medical, financial, and public health impacts of Assembly Bill (AB) 30. In response to this request, CHBRP undertook this analysis pursuant to the provisions of Senate Bill 1704 (Chapter 684, Statutes of 2006) as codified in Section 127600, et seq. of the California Health and Safety Code.

AB 30 would require coverage for the testing and treatment of inborn errors of metabolism (IEM) by health care service plans regulated by the California Department of Managed Health Care (DMHC) and health insurance products regulated by the California Department of Insurance (CDI). AB 30 would add Section 1374.4 to the Health and Safety Code and Section 10123.90 to the Insurance Code.

Currently, health plans and insurers are required to provide coverage for the testing and treatment of phenylketonuria (PKU), one of the more common IEM disorders.[1]

Persons with IEM have genetic disorders that affect their ability to digest foods and metabolize nutrients. Left untreated, these disorders result in death, coma, seizures, and/or chronic, disabling conditions such as mental retardation, cardiovascular disease, encephalopathy, liver disorders, and renal failure. These disorders are rare, occurring on average in 1 birth in 5,000 in California. On average, about 105 newborns are identified each year with a non-PKU IEM disorder. In the insured population subject to this mandate, CHBRP estimates there are 687 persons with a non-PKU IEM disorder.

State Programs for Screening and Treatment

Currently, all newborns are tested for IEM disorders as part of the California Newborn Screening Program to promote early identification and treatment of over 75 hereditary and congenital disorders. The Newborn Screening Program can identify over 40 IEM disorders. Testing is a covered benefit for enrollees with private or publicly financed health insurance.

Treatment of IEM disorders is a covered benefit for residents who qualify for two public programs administered by the California Department of Health Care Services: the California Children's Services (CCS) program and the Genetically Handicapped Person's Program (GHPP). Beneficiaries of these programs include those insured by Medi-Cal and the Healthy Families Program. Few privately insured California residents meet the eligibility requirements for these programs unless their income is less than $40,000 per year. For residents eligible for coverage through GHPP, the application process poses a barrier to timely treatment of newborns. For example, privately insured residents must provide proof of denial by their insurance as part of the application process.

[1] Health and Safety Code Section 1374.56 and Insurance Code Section 10123.89

Current Law
Senate Bill (SB) 148, enacted in 1999, requires health plans and insurers to provide coverage for the testing and treatment of PKU. Under current law, treatment of PKU includes "those formulas and special food products that are part of a diet prescribed by a licensed physician and managed by a health care professional in consultation with a physician who specializes in the treatment of metabolic disease and who participates in or is authorized by the plan, provided that the diet is deemed medically necessary to avert the development of serious physical or mental disabilities or to promote normal development or function as a consequence of phenylketonuria (PKU)."

Requirements of AB 30
AB 30 would extend this treatment requirement to non-PKU IEM disorders. For the purpose of the bill, an IEM is defined as "an inheritable disorder of biochemistry detected through the California newborn screening program."

The definition of treatment in AB 30 does not specify the medical nutrition therapy used to treat these disorders. The definition sets a floor by requiring, at a minimum, enteral[2] formulas and special food products that are part of a diet prescribed by a physician. This definition, similar to the definition in current law for PKU, defines these treatments as the following:

- *Formula* means an enteral product or enteral products for use at home that are prescribed by a physician and surgeon or nurse practitioner, or ordered by a registered dietician upon referral by a health care provider authorized to prescribe dietary treatments, as medically necessary for the treatment of inborn errors of metabolism.
- *Special food product* means a food product that is both of the following:
    - Prescribed by a physician and surgeon or nurse practitioner for the treatment of inborn errors of metabolism and is consistent with the recommendations and best practices of qualified health professionals with expertise germane to, and experience in the treatment and care of, inborn errors of metabolism. It does not include a food that is naturally low in protein, but may include a food product that is specially formulated to have less than one gram of protein per serving.
    - Used in place of normal food products such as those sold at a grocery store for the general population.

Medical Effectiveness
Newborn screening facilitates prompt diagnosis and treatment of IEM disorders. In some cases, newborn screening can enable clinicians to identify infants with IEM disorders before they experience acute illness or chronic, disabling conditions. In other cases, results of screening tests can help clinicians diagnose and treat children who experience acute illness due to IEM disorders.

IEM disorders may be divided into three major categories:
- Protein disorders
- Fatty acid oxidation disorders
- Carbohydrate disorders

[2] "Enteral" commonly refers to a substance given via the digestive tract.

Although treatment varies across IEM disorders, it usually encompasses one or more of the following:

- Special formulas that do not contain the nutrients a person cannot metabolize
- Special food products (as described above)
- Vitamin supplements
- Amino acid and enzyme supplements
- Prescription drugs

- Protein disorders are treated by eating a combination of foods that are naturally low in protein and special food products that are formulated to have less protein than conventional foods. Special formulas that exclude nutrients that persons with these disorders cannot metabolize are also prescribed for many protein disorders. Vitamin supplements, amino acid supplements, carnitine (an enzyme cofactor that is not present in adequate quantities in persons with certain protein disorders), and/or prescription drugs may be prescribed as well, depending on the disorder.

- Treatment of fatty acid disorders involves avoiding fasting, eating foods that are naturally low in fat, and taking carnitine. A special formula and vegetable oil containing essential fatty acids may also be prescribed for persons with certain fatty acid disorders.

- Carbohydrate disorders are treated by restricting consumption of dairy products and other foods that contain lactose, galactose, and other carbohydrates.

This Medical Effectiveness analysis relies primarily on treatment guidelines based on consensus among experts. Information was primarily obtained from two review articles and three reference books that synthesized findings from the relatively sparse peer-reviewed literature on treatment of IEM disorders and the experience of experts on these conditions. In a few cases, supplemental information was obtained from articles published in peer-reviewed journals.

There are no published randomized controlled trials (RCTs) or nonrandomized studies with comparison groups that assess the effectiveness of special formulas or special food products for IEM disorders relative to no medical nutrition therapy. Most studies on treatment for these disorders are case studies of individual patients or small groups of patients, or present findings from surveys of clinicians. The lack of controlled studies is probably due to the rarity of these disorders and their potentially lethal consequences.

The lack of controlled studies is not as great a concern for IEM disorders as for many other conditions because IEM disorders are single-cause conditions for which the scientific basis and rationale for treatment are strong. Extensive research has been conducted on the roles of individual enzymes in metabolizing nutrients. Once a person has been diagnosed with an IEM, clinicians can draw upon evidence from case series of prior patients with the disorder to develop effective therapeutic regimens.

Utilization, Cost, and Coverage Impacts

Coverage

- Currently 100% of the privately and publically insured population have coverage for testing to detect IEM disorders. Testing is provided as part of the California Newborn Screening Program operated by the Department of Public Health.

- Currently about 39% of the insured population of California, an estimated 8,096,000, have coverage for the medical nutrition therapy of IEM disorders other than PKU—standard treatment includes formulas, special food products, and/or supplements. Coverage varies by market segment:
    - Coverage for medical nutrition therapy is available to 100% of individuals who qualify for the California Children's Services (CCS) program or the Genetically Handicapped Person's Program (GHPP). Medi-Cal and Healthy Families Program beneficiaries qualify for these programs.
    - Coverage for medical nutrition therapy is not available to enrollees in the California Public Employee's Retirement System (CalPERS).
    - In the privately insured market, coverage is available to about 25% of enrollees in health plans regulated by the DMHC and 58% of those insured by health insurance products regulated by the CDI.
- Among the insured population, approximately 687 are diagnosed with a non-PKU IEM disorder. About 301 currently have coverage for medical nutrition therapy and the remaining 386 would gain coverage for this benefit if AB 30 was enacted into law.

Utilization

- CHBRP has estimated the current utilization of prescribed medical nutritional therapy to be consistent with the medically necessary treatment. Despite the barriers to access to such treatment, clinical experts at the metabolic centers (where patients receive comprehensive treatment from multidisciplinary practioner teams) perceive that parents and providers obtain the necessary products regardless of insurance status to avert the devastating consquences of forgoing treatment. As a result, CHBRP estimated no increase in utilization for these products due to the mandate.

- AB 30 does not preclude carriers from charging copayment, coinsurance, deductible, or other cost-sharing for this benefit. The bill also does not preclude carriers from conducting utilization or medical necessity reviews.

Costs

- CHBRP has estimated an average annual cost of $6,000 per patient for the medical nutrition therapy necessary for treatment. This cost is based on the experience of metabolic centers approved by California Children's Services (CCS) throughout California that provide treatment for children and adults with IEM disorders.

- Total net annual expenditures are estimated to increase by $415,000 annually or 0.0006% mainly due to the administrative costs associated with providing coverage for persons who do not currently have it.

- Prior to the mandate, enrollees without coverage for medical nutrition therapy incurred an estimated $2,315,000 in out-of-pocket expenses annually. Postmandate, that $2,315,000 in out-of-pocket expenses would be shifted to health plans and insurers.However, enrollees would incur an additional $27,000 in co-payments for the newly covered benefits.

- The mandate is estimated to increase premiums by about $2.7 million. The distribution of the impact on premiums is as follows:
  - Total premiums for private employers are estimated to increase by $1,830,000, or 0.0042%.
  - Total employer premium expenditures for CalPERS are estimated to increase by $145,000, or 0.0055%.
  - Premiums paid by employees covered by group insurance (including CalPERS) would increase by an estimated $479,000 or 0.0042%.
  - Total premiums for those with individually purchased insurance are estimated to increase by $249,000, or 0.0045%.

Table 1. Summary of Coverage, Utilization, and Cost Impacts of AB 30

	Before Mandate	After Mandate	Increase/ Decrease	Change After Mandate
Coverage				
Number of individuals subject to the mandate	20,687,000	20,687,000	0	0%
Percentage of individuals with coverage for medical nutrition therapy	39.1%	100.0%	60.9%	156%
Number of individuals with coverage for medical nutrition therapy	8,096,100	20,687,000	12,590,900	156%
Utilization and Cost				
Total number using medical nutrition therapy	687	687	0	0%
Number of those using medical nutrition therapy who have coverage for the benefit	301	687	386	128%
Number of those using medical nutrition therapy who do not have coverage for the benefit	386	0	-386	-100%
Average per annum cost	$6,000	$6,000	0	0%
Expenditures				
Premium expenditures by private employers for group insurance	$43,944,936,000	$43,946,766,000	$1,830,000	0.0042%
Premium expenditures for individually purchased insurance	$5,515,939,000	$5,516,188,000	$249,000	0.0045%
CalPERS employer expenditures	$2,631,085,000	$2,631,230,000	$145,000	0.0055%
Medi-Cal state expenditures (a)	$4,015,964,000	$4,015,964,000	$0	0.0000%
Healthy Families state expenditures	$627,766,000	$627,766,000	$0	0.0000%
Premium expenditures by individuals with group insurance or CalPERS	$11,515,939,000	$11,516,418,000	$479,000	0.0042%
Individual out-of-pocket expenditures (deductibles, copayments, etc.)	$5,153,127,000	$5,153,154,000	$27,000	0.0005%
Expenditures for non-covered services (b)	$2,315,000	$0	-$2,315,000	-100%
Total annual expenditures	$73,407,071,000	$73,407,486,000	$415,000	0.0006%

Source: California Health Benefits Review Program, 2007.
Notes: The population includes individuals and dependents covered by employer sponsored insurance (including CalPERS), individually purchased insurance, or public health insurance provided by a health plan subject to the requirements of the Knox-Keene Health Care Service Plan Act of 1975. All population figures include enrollees aged 0 to 64 years and enrollees 65 years or older covered by employment sponsored insurance. Member contributions to premiums include employee contributions to employer sponsored health insurance and member contributions to public health insurance.
Key: CalPERS = California Public Employees' Retirement System
(a) Medi-Cal state expenditures for members under 65 years of age include expenditures for Major Risk Medical Insurance Program (MRMIP) and Access for Infants and Mothers (AIM) program.
(b) The expenditures for medical nutrition therapy for non-PKU IEM disorders paid by enrollees who currently do not have benefit for such treatments.

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Public Health Impacts

- Of the 834,373 California babies born between July 7, 2005, and December 31, 2006, a total of 158 newborns were identified with one of the non-PKU IEM disorders, where the primary treatment is the use of medical nutrition therapy, resulting in a prevalence of approximately 1 in 5,000 newborns.

- AB 30 will not result in an increase in utilization of medical nutrition therapy for the treatment of non-PKU IEM disorders and is therefore not expected to result in measurable improved health outcomes. AB 30 will, however, increase insurance coverage for this benefit to 386 individuals with a non-PKU IEM disorder and therefore will likely reduce the administrative burden and financial hardship associated with these disorders when health plans deny claims for medical nutrition therapy.

- No research was identified that found gender differences in the prevalence of non-PKU IEM disorders. Overall, the proportion of newborns identified with IEM disorders is comparable to the racial and ethnic distribution of births in California. Since there are no measurable gender or racial/ethic differences in the prevalence of IEM disorders and AB 30 is not anticipated to affect utilization of medical nutrition therapy, AB 30 is not expected to have a measurable impact on gender, racial, or ethnic disparities in health.

- For infants with non-PKU IEM disorders, the use of medical nutrition therapy is essential for the prevention of serious and costly health effects, including premature death. The costs of medical nutrition therapy for these disorders are minimal compared to the broader costs of screening programs and the medical costs associated with not getting proper and timely treatment. Since AB 30 is not expected to increase utilization of medical nutrition therapy, this mandate is not expected to have a measurable impact on premature death or the economic loss associated with non-PKU IEM disorders.

INTRODUCTION

Persons with inborn errors of metabolism (IEM) have genetic disorders that affect their ability to digest foods and metabolize nutrients. For each disorder, a unique enzyme that is involved in digesting food or metabolizing nutrients is deficient. Deficient enzymes result in malnourishment or a buildup of toxic substances that are harmful to the body. Left untreated, these disorders result in mental retardation, developmental delay, seizures, coma, and death.

Traditional therapies for metabolic diseases include medication, dietary management, and nutritional supplements. Dietary management can include protein restriction, avoidance of fasting, special formulas, and food products manufactured specifically for these conditions. Supplements can include amino acid compounds and B vitamins. Treatment varies by disorder and among individuals with a given disorder based on the severity of the deficiency. For some disorders, persons with severe deficiencies may need to take special formulas and supplements for their entire lives.

Assembly Bill (AB) 30 would require health care plans and insurers to provide coverage for testing and treatment of IEM disorders. The bill defines an IEM as "an inheritable disorder of biochemistry detected through the California newborn screening program." While all insured Californians have coverage for testing through the statewide screening program, not all insured have coverage for the prescribed dietary products necessary for treatment. Of the 550,000 babies born in California each year, the California Newborn Screening Program identifies about 1 in 5,000 with a metabolic disorder. On average, about 105 newborns are identified each year with an IEM disorder other than phenylketonuria (PKU). In the insured population subject to this mandate, CHBRP estimates there are 687 persons with a non-PKU IEM disorder.

Current Law

Newborn screening of infants for metabolic disorders began in California in 1966 with testing for PKU. All newborn screening begins with a health care provider collecting a blood sample from the newborn's heel. With the use of technology called "tandem mass spectrometry," the California Newborn Screening Program can now detect over 40 metabolic disorders using the one blood sample. Hospitals are assessed a fee of $101.75 per screening to cover the test. Health plans and insurers typically cover this fee as part of their coverage for maternity benefits. The state covers this expense for those who lack private insurance.

Newborns with a positive screening result are referred for a diagnostic evaluation to confirm the disorder. When a disorder is confirmed, the state recommends that newborns receive ongoing care at one of 16 metabolic centers approved by California Children's Services (CCS). Metabolic centers house a multidisciplinary team (physician, dietician, nurse, social worker, genetic counselor) to provide a comprehensive approach to assisting

the family. On average, the California Newborn Screening Program takes about 8 days from the time of birth to confirm a diagnosis.

In 1999, the California legislature enacted Senate Bill (SB) 148 requiring health plans and insurers to provide coverage for the testing and treatment of one metabolic disorder: PKU. The intent of the bill was to provide coverage for the formulas and special food products that are part of a prescribed diet deemed to be necessary for disease treatment (California Senate Committee Analysis for SB 148, 1999).

Requirements of AB 30

AB 30 requires all health plans and insurers to provide coverage for the treatment of all types of IEM disorders that are detectable through newborn screening, like PKU. This includes formulas and special food products ordered by a physician.

The AB 30 definition of treatment does not specify the medical nutrition therapy used to treat these disorders. The definition sets a floor by requiring, at a minimum, enteral formulas and special food products.[3] This definition, similar to the definition in current law for PKU, defines these treatments as the following:

- "Formula" means an enteral product or enteral products for use at home that are prescribed by a physician and surgeon or nurse practitioner, or ordered by a registered dietician upon referral by a health care provider authorized to prescribe dietary treatments, as medically necessary for the treatment of inborn errors of metabolism.
- "Special food product" means a food product that is both of the following:
    - Prescribed by a physician and surgeon or nurse practitioner for the treatment of inborn errors of metabolism and is consistent with the recommendations and best practices of qualified health professionals with expertise germane to, and experience in the treatment and care of, inborn errors of metabolism. It does not include a food that is naturally low in protein, but may include a food product that is specially formulated to have less than one gram of protein per serving.
    - Used in place of normal food products such those sold at a grocery store for the general population.

Coverage for Treatment

All health plans and insurers are required to provide coverage for testing and treatment for PKU IEM disorders. For IEM disorders other than PKU, about 39% of persons with private insurance have coverage for treatment, subject to medical review and medical necessity guidelines.

[3] "Enteral" commonly refers to a substance given via the digestive tract.

Two public programs administered by the California Department of Health Care Services provide coverage for treatment of metabolic diseases if applicants meet certain eligibility requirements. The California Children's Services (CCS) program provides coverage for children (birth up to 21 years of age). Families of children enrolled in Medi-Cal, Healthy Families Program, or whose household income is $40,000 or less would be eligible for coverage.

The Genetically Handicapped Person's Program (GHPP) provides coverage for children if they have been determined to be financially ineligible to receive services from the CCS. GHPP also provides coverage for adults with genetic diseases. For both children and adults, GHPP is the health care payor of last resort and will cover services only after it has been demonstrated that the family is not eligible for CCS and the health plan or insurer has denied coverage. In addition, the provider or client is required to exercise their appeal rights before GHPP will authorize and reimburse for these services.

Adults enrolled in state health insurance programs (e.g., Medi-Cal, Access for Infants and Children, Managed Risk Medical Insurance Program) would be eligible for coverage by GHPP. Clients are required to pay an annual enrollment fee. The amount of the fee is determined using a sliding scale based on income and family size.[4] According to the authorizing legislation, persons whose family income exceeds $40,000 per year and whose cost of care exceeds 20% of family income must pay the enrollment fee. Families with income in excess of $40,000 per year whose cost of care is 20% or less must pay either the enrollment fee or the cost of care, whichever is greater (SB 2265, 1975).

Typically, treatment costs for a person with an IEM disorder would average 11% of family income, rendering a family with an income in excess of $40,000 ineligible for GHPP coverage.[5]

The application process for coverage from state programs is a significant barrier to timely treatment for newborns. For patients with IEM disorders other than PKU, families can only apply for coverage with CCS if they have a letter of denial from their health plan or insurer. Families can only apply for coverage with GHPP if they are denied coverage by CSS and denied coverage by their health plan or insurance policy, including being denied on appeal. According to experts at the state-approved metabolic centers, the time from confirmed diagnosis to payment for formula can result in delays of up to 4 months.

[4] See www.dhs.ca.gov/pcfh/cms/onlinearchive/pdf/ccs/numberedletters/2007/ccsnl060307.pdf. www.dhs.ca.gov/pcfh/cms/onlinearchive/pdf/ccs/numberedletters/2007/ccsnl060307a1.pdf

[5] Based on data from the U.S. Census Bureau that has been adjusted for inflation, the median household income in California in 2005 was $53,815. Given the estimated average annual cost for treatment for IEM ($6,000), the average annual cost of medical treatment services would be about 11 percent of median household income.

Laws in Other States

For PKU, 45 state legislatures have established some form of coverage or reimbursement for medical nutrition therapy (National PKU News, 2007).

For other IEM disorders, 21 state legislatures have established some form of coverage or reimbursement for medical nutrition therapy. Statutes often require insurers to treat prescribed formulas and special food products similar to prescription drugs. A state may require coverage of low-protein foods, metabolic formula, or both. Some states also limit the amount of mandated coverage or reimbursement. An annual cap of $2,500 is the most common benefit limit (see Appendix F).

Legislation is pending in two states to provide coverage (Illinois, HB 1560) or tax credits (Oklahoma, SB6) for medically necessary foods.

Federal Activity

Federal activity includes:

- H.R. 2719 (Rep. Burton, IN) amends the Internal Revenue Code to treat amounts paid for foods for special dietary use, dietary supplements, and medical foods as medical expenses for purposes of the medical expense tax deduction.

- Medical foods (special food products) are excluded from any regulatory requirements with the exception of the good manufacturing practice regulations that govern all foods. In May 2007, the U.S. Food and Drug Administration issued a guidance document for the industry that represents the FDA's current thinking on medical foods. This guidance document does not establish legally enforceable responsibilities.[6]

- In 2004, the American College of Medical Genetics completed a report commissioned by the U.S. Department of Health and Human Services' Health Resources and Services Administration (HRSA) that recommended uniform screening of all infants born in the United States for a panel of 29 conditions. HRSA's Maternal and Child Health Bureau (MCHB) operates an Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children whose role is to make recommendations to improve screening and follow-up treatment by states. HRSA also funds a National Newborn Screening and Genetics Resource Center housed at the Department of Pediatrics at the University of Texas. The NNSGRC provides technical assistance to states' newborn screening programs.

[6] See www.cfsan.fda.gov/~dms/medfood.html.

MEDICAL EFFECTIVENESS

AB 30 would require health care plans and insurance carriers to provide coverage for testing and treatment of IEM disorders. These conditions are genetic disorders that affect a person's ability to use nutrients obtained from food and beverages. When nutrients enter the body, they are broken down and converted to energy through complex metabolic pathways. Waste products from this process are then excreted from the body. Deficiencies in any of the enzymes that are involved in the production of energy or elimination of waste can cause severe illness and can be fatal if not treated promptly. The California Newborn Screening Program currently screens for over 40 of these disorders.

This section of the report describes IEM disorders and recommended treatments for them. The review discusses conditions other than PKU, because health plans are already required to provide coverage for treatment of PKU under current California law. In addition, it focuses on conditions that can be detected through California's current newborn screening program, because AB 30 would provide coverage only for formula and special food products prescribed to persons with IEM disorders that can be detected through this program.[7]

Literature Review Methods

The literature on treatment of IEM disorders is relatively sparse. Most studies on this topic are case studies of individual patients, case series of small groups of patients, or surveys of clinicians regarding the treatments they prescribe. There are no published randomized controlled trials (RCTs) and no nonrandomized controlled studies on the effectiveness of special formulas, special food products, or supplements for IEM disorders relative to no dietary treatment.

The lack of controlled studies on the efficacy of medical nutrition therapy for IEM disorders is due to several factors, including the potentially fatal consequences of withholding treatment. Parents are unlikely to enroll their children in studies in which the control group receives no treatment because children who are not treated may die or contract chronic, disabling conditions. In addition, IEM disorders are very rare. Although data from the California Newborn Screening Program indicate an overall incidence rate for IEM disorders of 20.85 per 100,000 infants (approximately 1 in 5,000 infants), the incidence rates for many individual IEM disorders is less than 5 out of every 100,000 infants. The small number of persons with these disorders makes it very difficult for researchers to recruit sufficient numbers of subjects to carry out prospective, controlled

[7] Inborn errors of metabolism that cannot currently be detected through the California Newborn Screening Program include four carbohydrate disorders (glycogenosis Ia, glycogenosis Ib, glycogenosis III, hereditary fructose intolerance) and two urea cycle disorders (carbamyl phosphate synthase deficiency and ornithine transcarbamylase deficiency). Treatments for these disorders are similar to those prescribed for carbohydrate and urea cycle disorders that can be detected through newborn screening.

studies. The few RCTs that have been conducted have compared standard treatments for PKU to a different treatment that is hypothesized to be more effective.

The paucity of controlled studies of treatment for IEM disorders is not as great a concern as it would be for many other conditions, because IEM disorders are single-cause conditions for which the scientific basis for treatment are strong. Extensive research has been conducted on the roles of individual enzymes in metabolizing nutrients.[8] Once a person has been diagnosed with an IEM, clinicians can draw upon evidence from treatment of other patients with the disorder to develop effective therapeutic regimens.

This Medical Effectiveness analysis relies primarily on treatment guidelines based on consensus among experts. Information was primarily obtained from two review articles (Isaacs and Zand, 2007; Raghuveer et al., 2006) and three reference books (Fernandes et al., 2006; Nyhan et al., 2005; and Scriver et al., eds., 2001) that synthesized findings from the relatively sparse peer-reviewed literature on treatment of IEM disorders and the experience of experts in these conditions. In a few cases, supplemental information was obtained from additional articles published in peer-reviewed journals. A list of the articles and books that were reviewed, and brief descriptions thereof, appears in Appendix C.

Relationship Between Newborn Screening and Treatment of IEM Disorders

Newborn screening facilitates prompt diagnosis and treatment of IEM disorders. In some cases, newborn screening can enable clinicians to identify infants with IEM disorders before they experience acute illness or disability. In other cases, screening tests can help clinicians diagnose and treat children who experience acute illness due to an IEM. Although newborn screening tests are performed a few days following birth, test results usually are not available for approximately one week. Some infants who have an IEM may experience severe episodes of acute illness before the results are available. If an infant becomes acutely ill, clinicians treat his or her symptoms immediately and use the results of newborn screening tests to determine whether the symptoms may be due to an IEM. Regardless of whether a child is symptomatic or not, further diagnostic tests are conducted before a definitive diagnosis is made.

Consequences of Delay in Treatment of IEM Disorders

IEM disorders can be fatal if they are not diagnosed and treated promptly and appropriately. Many infants who have IEM disorders are born full-term and initially appear healthy. However, within a few days they begin to experience severe and persistent diarrhea, nausea, vomiting, dehydration, hyperammonemia, hypoglycemia, ketosis, lethargy, metabolic acidosis, and/or seizures (Fernandes et al., 2006; Nyhan et al., 2005; and Scriver et al., eds., 2001). Their conditions may worsen and progress to

[8] Scriver and colleagues' (2001) four-volume reference book contains a thorough synthesis of the literature on the causes and consequences of IEM disorders and other metabolic disorders.

coma and death unless they are diagnosed accurately and treated quickly. Those who survive may have chronic, disabling conditions such as blood disorders, cardiovascular disease, developmental delay, encephalopathy, failure to thrive, kidney disease, liver disease, neuromuscular disorders, pancreatitis, psychomotor retardation, respiratory failure, and vision problems (Fernandes et al., 2006; Nyhan et al., 2005; and Scriver et al., eds., 2001). Appropriate long-term treatment can extend life and greatly enhance quality of life for many persons with IEM disorders. However, even with treatment some persons experience repeated bouts of acute symptoms of their disorders when they contract other illnesses or experience severe mental or physical stress. For some disorders, treatment cannot prevent behavioral disorders, gonadal dysfunction, liver failure, neurological impairment, or renal failure (Chung, 1997; Isaacs and Zand, 2007; Ogier de Baulny et al., 2005).

Types of Inborn Errors of Metabolism and Treatments

IEM disorders may be divided into three major categories based on the type of nutrient affected:

- Protein disorders
- Fatty acid oxidation disorders
- Carbohydrate disorders

Long-term treatment for IEM disorders usually encompasses one or more of the following:

- Special formulas that do not contain the nutrients a person cannot metabolize
- Special food products
- Essential fatty acids
- Vitamin supplements
- Amino acid supplements
- Prescription drugs

Table 2 on the next page summarizes the recommended treatments for each major type of IEM. As the table illustrates, specific regimens vary across major categories of IEM disorders. They also vary to a lesser extent within major categories.

Although there are standard treatments for each type of IEM, specific treatment plans vary across persons with a given IEM. In some persons who have an IEM, the affected enzyme does not work at all. In others the enzyme functions, but not as well as in a person who has a normal metabolism. Persons who have some enzyme function can tolerate more carbohydrates, fats, or proteins than persons whose enzymes are completely defective. Treatment regimens may also change as a person matures. Some older children and adults can tolerate large amount of non-medical foods provided they continue to follow other aspects of their treatment regimens.

Table 2. Major Types of IEM Disorders and Recommended Treatments

Type of IEM	Recommended Treatments
Protein disorders	• Special formula that contains essential amino acids and/or does not contain amino acids that are not properly metabolized • Low-protein diet that includes special food products and natural foods • Amino acid supplements • Vitamin supplements • Carnitine (an enzyme cofactor) • Prescription drugs
Fatty acid oxidation disorders	• Avoid fasting • Low-fat diet composed of natural foods • Carnitine • Special formula • Essential fatty acids
Carbohydrate disorders	• Avoid dairy products • Diet low in carbohydrates, especially foods that contain lactose and galactose

Brief descriptions of each major type of IEM and recommended treatments are presented below. Additional information regarding the characteristics and consequences of individual disorders and recommended treatments is contained in Table 3, which appears at the end of the *Medical Effectiveness* section.

Protein Disorders

Inborn errors of protein metabolism can be divided into three major categories: amino acid disorders, organic acid disorders, and urea cycle disorders.

Amino acid disorders are caused by the malfunctioning of one or more enzymes that are involved in the process of metabolizing one or more of the amino acids contained in proteins (Isaacs and Zand, 2007). The most common type of amino acid disorder is PKU, the only IEM for which health plans are required to provide coverage under current California law. Persons who have PKU cannot properly metabolize the amino acid phenylalanine because the enzyme phenylalanine hydroxylase does not function properly in their bodies. As a consequence they accumulate toxic levels of phenylalanine, which can cause brain damage. The California Newborn Screening Program currently screens for four other types of amino acid disorders. Three of these disorders—biopterin deficiencies, homocystunuria, and tyrosinemia—prevent persons from breaking down individual amino acids. The fourth disorder, maple syrup urine disease, affects metabolism of three branched-chain amino acids.

Organic acid disorders occur when deficient enzyme function leads to the accumulation of intermediate metabolites that are not usually present in appreciable amounts in healthy people. Accumulation of these metabolites causes metabolic acidosis (i.e., excessive

acidity of the blood), which threatens the body's pH balance. Unlike amino acid metabolism disorders, the defective enzyme is several steps removed from the beginning of the protein metabolism pathway (Isaacs and Zand, 2007; Nyhan et al., 2005). California currently screens for 13 organic acid disorders.

Urea cycle disorders affect the removal of waste nitrogen from amino acids when they are converted to energy. In persons whose metabolisms are normal, the urea cycle produces nontoxic nitrogen in the form of urea that is removed from the body by urination (Leonard, 2001). In persons with urea cycle disorders, a deficient enzyme prevents the completion of the urea cycle. Inability to complete the urea cycle leads to the accumulation of a dangerously high concentration of ammonia in the body (Fernandes et al., 2006; Isaacs and Zand, 2007; Nyhan et al., 2005). The California Newborn Screening Program currently screens for five urea cycle disorders: argininemia, argininosucinic acid lyase deficiency, citrullinemia type I, citrullinema type II, and homocitrullinura-hperornithinemia-hyperammonemia.

All three types of protein disorders are treated by eating a diet composed of foods that are naturally low in protein and special food products that are formulated to have less protein than conventional foods. For many of these disorders, physicians also prescribe special formulas that exclude the amino acids that persons with the disorder cannot metabolize. Special formulas and special food products are needed because foods that are naturally low in protein do not provide adequate nutrition. In addition, most foods that are naturally high in protein contain multiple amino acids that cannot be easily separated from one another. Special formulas enable persons with these disorders to obtain a sufficient amount of protein without ingesting dangerous amounts of the amino acids they cannot metabolize. Vitamin supplements, amino acid supplements, enzyme cofactor supplements, and/or prescription drugs may be prescribed as well (Fernandes et al., 2006; Isaacs and Zand, 2007; Leonard, 2001; Nyhan et al., 2005; van der Meer et al., 1994; van der Meer et al., 1995).

Specific treatment regimens vary across protein disorders. For example, homocystinuria is treated with folic acid and vitamin B6 (pyridozine) supplements. Low-protein food products and special formulas that lack methionine, the amino acid that persons with homocystunria cannot metabolize, are also recommended. Other amino acid disorders and most urea cycle disorders are also treated with special formulas, special food products, and amino acid supplements. Persons with most organic acid disorders are prescribed special formulas and special food products, as well as carnitine, an enzyme cofactor derived from an amino acid. Carnitine supplements are needed because the bodies of persons with these disorders do not produce in adequate quantities of carnitine. For two organic acid disorders that cause multiple carboxylase deficiency, biotinidase deficiency and holocarboxylase synthase deficiency, biotin (vitamin B7) supplements are the only treatment necessary (Fernandes et al., 2006; Isaacs and Zand, 2007; Leonard, 2001; Nyhan et al., 2005; Ogier de Baulny et al., 2005; van der Meer et al., 1994; van der Meer et al., 1995; Yannicelli et al., 1994).

Fatty Acid Oxidation Disorders

Oxidation of fatty acids plays a major role in the production of energy needed for bodily functioning. Although most energy is obtained from conversion of carbohydrates into glucose (blood sugar), fatty acids provide energy during the late stages of fasting between meals (Fernandes et al., 2006). Persons with fatty acid oxidation disorders cannot properly use fatty acids to generate energy. Fatty acid disorders are difficult to diagnose and often appear later in infancy than other IEMs. Symptoms often do not occur until an infant experiences prolonged fasting when he or she begins sleeping for longer periods of time, or contracts a viral infection or other illness that decreases appetite and increases need for sleep (Fernandes et al., 2006).

The California Newborn Screening Program currently screens for 11 fatty acid oxidation disorders. These disorders can be divided into three groups based on the part of the fatty acid oxidation process in which the affected enzyme plays a role: carnitine cycle disorders (4 disorders), β-oxidation disorders (6 disorders), and electron transfer disorders (1 disorder).

Avoiding fasting is a critical element of long-term treatment for all fatty acid oxidation disorders. Ingesting carbohydrates during both day and night is necessary to ensure that persons have sufficient glucose in their bodies to generate energy so that they will not need to use fatty acids. Patients are often advised to consume a solution of cornstarch and water before going to sleep (Isaacs and Zand, 2007; Nyhan et al., 2005; Solis and Singh, 2002).

Treatment of fatty acid disorders also involves eating foods that are naturally low in fat and taking carnitine, an enzyme cofactor derived from an amino acid (Nyhan et al., 2005; Solis and Singh, 2002). Persons who have long-chain hydroxyacly-CoA dehydrogenase deficiency or very-long-chain acyl-CoA dehydrogenase deficiency are also prescribed essential fatty acids, usually in the form of vegetable oil or capsules thereof, and a special formula composed of medium-chain triglycerides to replace the long-chain and very-long-chain fats that they cannot metabolize (Fernandes et al., 2006; Gillingham et al., 1999; Nyhan et al., 2005; Scriver et al., eds., 2001; Solis and Singh, 2002). The recommended percentage of calories from fat varies across fatty acid oxidation disorders and is most restricted for persons with long-chain or very-long-chain disorders (Isaacs and Zand, 2007).

Carbohydrate Disorders

Carbohydrate disorders affect the body's ability to convert carbohydrates into energy. At present, classical galactosemia is the only carbohydrate disorder that can be detected through the California Newborn Screening Program. Persons with classical galactosemia cannot properly metabolize galactose, a monosaccharide that is produced when lactose is ingested, because the galactose-1-phosphate uridyltransferase enzyme is defective. This

defect thwarts completion of the carbohydrate metabolism cycle, which leads to accumulation of toxic levels of galactose and galactose-l-phosphate in the body.

Symptoms of classical galactosemia typically appear when a child begins ingesting breast milk or cow's milk–based formula, both of which contain large amounts of lactose. Large concentrations of galactose also occur naturally in some foods, such as persimmons (Gross and Acosta, 1991). In addition, some processed foods contain large amounts of casein, hydrolyzed whey, milk powder, milk solids, and other sources of galactose and lactose (Fernandes et al., 2006; Isaacs and Zand, 2007).

Classical galactosemia is treated by restricting consumption of foods that contain large amounts of lactose and galactose. Infants with classical galactosemia are typically fed a soy-based formula or other lactose-free formula. Older children and adults are prescribed a diet of foods that are naturally low in lactose and galactose and instructed to read labels carefully to avoid processed foods containing these carbohydrates (Chung, 1997; Isaacs and Zand, 2007; Raghuveer et al., 2006). Calcium supplements may also be prescribed (Fernandes et al., 2006).

Table 3. Disorders Detectable by California's Newborn Screening Program for Which Treatment Includes Medical Nutrition Therapy[9,10]

Disorder	Special Formulas	Foods	Vitamin and/or Amino Acid Supplements	Prescription Drugs	Enzyme Affected	Clinical Manifestations
Protein Metabolism Disorders – Amino Acid Disorders						
Biopterin deficiency	Special formula	Low protein special food products	5-hydroxy-tryptophan	Carbidopa, Tetrahydro-biopterin	Guanosine triphosphate cyclohydrolase 1, dihydropteridine reductase, Pterin-4ά-carbinolamine dehydratase deficiency, or 6-pyruvoyl-tetrahydropterin synthase deficiency	Cognitive impairment, difficulty swallowing, failure to thrive, hyper-phenylalaninemia, hypertonia, lethargy, low birth weight

Sources: Fernandes et al., 2006; Isaacs and Zand, 2007; Nyhan et al., 2005; Raghuveer et al., 2006; Scriver et al., 2001.

[9] For the purposes of CHBRP's analysis of AB 30, medical nutrition therapy encompasses formula prescribed or ordered by a health professional to treat inborn errors of metabolism, "special food products" prescribed by a health professional and used in place of food products consumed by the general population, and vitamin and amino acid supplements.

[10] Phenylketonuria (PKU) is not included in this table because health plans are required to cover medical nutrition therapy for PKU under current law. Medical nutrition therapy for PKU is similar to that used to treat other amino acid disorders.

Table 3. Disorders Detectable by California's Newborn Screening Program (Cont'd)

Disorder	Special Formulas	Foods	Vitamin and/or Amino Acid Supplements	Prescription Drugs	Enzyme Affected	Clinical Manifestations
Protein Metabolism Disorders – Amino Acid Disorders (Cont'd)						
Homocystinuria	Special formula lacking methionine	Low protein special food products	Folic acid, Vitamin B6	Betaine hydrochloride	Cystathionine beta-synthase	Developmental delay, ectopia lentis, osteoporosis and other skeletal abnormalities, psychiatric disorders, vascular disease
Maple syrup urine disease	Special formula lacking isoleucine, leucine, and valine	Low protein special food products	Isoleucine, Valine, Vitamin B1		Branched-chain alpha-keto acid dehydrogenase complex	Acute encephalopathy, developmental disabilities, dysmyelination, failure to thrive, hypertonia, metabolic acidosis, muscular weakness, osteoporosis
Tyrosinemia Type I		Low protein special food products		Nitisinione (NTBC)	Fumarylaceto-acetate hydrolase	Cardiomyopathy, coagulopathy, failure to thrive, hepato-splenomegaly, liver disease, rickets

Table 3. Disorders Detectable by California's Newborn Screening Program (Cont'd)

Disorder	Special Formulas	Foods	Vitamin and/or Amino Acid Supplements	Prescription Drugs	Enzyme Affected	Clinical Manifestations
Protein Metabolism Disorders – Organic Acid Disorders						
Beta-ketothiolase deficiency				Carnitine	Acetyl-CoA acetyltransferase	Repeated episodes of ketoacidosis
Biotinidase deficiency			Biotin		Biotinidase	Alopecia, apnoea, ataxia, difficulty breathing, hearing loss, hyper-ventilation, lethargy, muscular hypotonia, optic atrophy, psychomotor retardation, seizures, severe skin rash
Glutaric acidemia Type I	Special formula lacking lysine and tryptophan	Low protein special food products		Carnitine	Glutaryl-CoA dehydrogenase	Acute encephalopathy, cognitive impairment, frontotemporal atrophy, hypertonia, megalencephaly, striatal neurotoxicity
Holocarboxylase deficiency			Biotin		Biotinidase, Holocarboxylase synthetase	Alopecia, ataxia, coma, cutaneous lesions, hearing loss, hypothermia, hypotonia, ketosis, metabolic acidosis, seizures, vision loss

Table 3. Disorders Detectable by California's Newborn Screening Program (Cont'd)

Disorder	Special Formulas	Foods	Vitamin and/or Amino Acid Supplements	Prescription Drugs	Enzyme Affected	Clinical Manifestations
Protein Metabolism Disorders – Organic Acid Disorders (Cont'd)						
Isovaleric acidemia	Special formula lacking leucine	Low protein special food products	Calcium, glycine	Carnitine	Isovaleryl CoA dehydrogenase	Coma, hyperammonemia, hypotonia, ketosis, lethargy, leucopenia, metabolic acidosis, thrombocytopenia
Malonic acidemia		Diet high in natural carbohydrates; moderate restriction of fats and protein		Carnitine	Malonyl-CoA decarboxylase	Gastroenteritis, hepatomegaly, hypoglycemia, hypotonia, lethargy, seizures
Methylmalonic acidemia	Special formula lacking isoleucine, methionine, threonine, and valine	Low protein special food products	Vitamin B12	Carnitine	Methylmalonyl-CoA mutase	Acute encephalopathy, central nervous system disorders, coma, dehydration, developmental delay, failure to thrive, hepatomegaly, hyperammonemia, ketosis, lethargy, metabolic acidosis, moniliasis, neutropenia, pancreatitis

Table 3. Disorders Detectable by California's Newborn Screening Program (Cont'd)

Disorder	Special Formulas	Foods	Vitamin and/or Amino Acid Supplements	Prescription Drugs	Enzyme Affected	Clinical Manifestations
Protein Metabolism Disorders – Organic Acid Disorders (Cont'd)						
Methylmalonic acidemia/ Cobalamin C/D deficiency	Special formula lacking isoleucine, methionine, threonine, and valine	Low protein special food products	Vitamin B12	Betaine, Carnitine, Hydroxo-cobalamin	Cobalamin synthesis defects	Developmental delay, failure to thrive, megoloblastic anemia, microcephaly, nystagmus, visual impairment
Propionic acidemia	Low protein diet; Special formula lacking isoleucine, methionine, threonine, and valine	Low protein special food products		Carnitine	Propionyl-CoA-carboxylase	Cognitive impairment, coma, dehydration, hyperammonemia, hypotonia, ketosis, lethargy, metabolic acidosis, moniliasis, neutropenia, cardiomyopathy, thrombocytopenia
3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	Special formula lacking leucine	Diet low in protein and fat		Carnitine	3-Hydroxy-3-methylglutaryl-CoA lyase	Abnormal liver function, acidosis, hepatomegaly, hyperammonemia, hypoglycemia, hypotonia, pancreatitis, vomiting
3-methylcrotonyl-CoA carboxylase deficiency	Special formula lacking leucine	Low protein special food products	Biotin, glycine	Carnitine	3-methylcrotonyl-CoA carboxylase	Coma, hyperammonemia, hypoglycemia, hypotonia, ketosis, lethargy, metabolic acidosis

Table 3. Disorders Detectable by California's Newborn Screening Program (Cont'd)

Disorder	Special Formulas	Foods	Vitamin and/or Amino Acid Supplements	Prescription Drugs	Enzyme Affected	Clinical Manifestations
Protein Metabolism Disorders – Organic Acid Disorders (Cont'd)						
3-methylglutaconic aciduria, Type 1		Low protein special food products		Carnitine	3-methylglutaconyl-CoA hydratase deficiency	Athetoid movement disorder, developmental delay, encephalopathy, hypoglycemia, metabolic acidosis, psychomotor retardation
2-methyl-3-hydroxbutyryl-CoA dehydrogenase deficiency		Low protein special food products			2-methyl-3-hydroxbutyryl-CoA dehydrogenase	Dysarthria, dystonic posturing, rigidity, spastic diplegia and other severe symptoms of neurodegenerative disease
Protein Metabolism Disorders – Urea Cycle Disorders						
Argininemia	Essential amino acid mixture	Low protein special food products		Sodium benzoate, Sodium phenyl butyrate	Arginase	Behavioral problems, coma, developmental delay, gastrointestinal distress, heptomegaly, hyperammonemia, seizures, spasticdiplegia

Table 3. Disorders Detectable by California's Newborn Screening Program (Cont'd)

Disorder	Special Formulas	Foods	Vitamin and/or Amino Acid Supplements	Prescription Drugs	Enzyme Affected	Clinical Manifestations
Protein Metabolism Disorders – Urea Cycle Disorders (Cont'd)						
Argininosuccinic acid lyase deficiency/ Argininosuccinic acidemia	Essential amino acid mixture	Low protein special food products	Arginine, calcium	Sodium benzoate, Sodium phenyl butyrate	Arginosuccinic acid lyase	Behavioral problems, coma, developmental delay, gastrointestinal distress, hepatomegaly, hyperammonemia, seizures
Citrullinemia, Type I	Special formula	Low protein special food products	Arginine	Sodium benzoate, Sodium phenyl butyrate	Argininosuccinic acid synthetase	Behavioral problems, coma, developmental delay, gastrointestinal problems, hepatomegaly, hyperammonemia, seizures
Citrullinemia, Type II		Normal to high protein diet			Citrin	Behavioral problems, developmental delay, gastrointestinal distress, hepatomegaly, hyperammonemia, liver disease, neonatal jaundice
Gyrate atrophy of the choroid and retina	Special formula lacking arginine	Low protein special food products	Vitamin B6		Ornithine aminotransferase	Chorioretinal atrophy, constricted visual fields, myopia, night blindness
Homocitrullinuria, hyperornithinemia, hyperammonemia	Essential amino acid mixture	Low protein special food products	Citrulline	Sodium benzoate, Sodium phenyl butyrate	Ornithine transporter	Coma, developmental delay, hyper-ammonemia, lethargy, seizures, vomiting

Table 3. Disorders Detectable by California's Newborn Screening Program (Cont'd)

Disorder	Special Formulas	Foods	Vitamin and/or Amino Acid Supplements	Prescription Drugs	Enzyme Affected	Clinical Manifestations
Fatty Acid Oxidation Disorders						
Carnitine palmitoyl transferase deficiency, Type 1	Special formula high in medium-chain triglycerides	Foods that are naturally low in fat			Carnitine palmitoyl transferase	Hypoglycemia, coma, liver abnormalities, renal tubular acidosis
Carnitine palmitoyl transferase deficiency, Type 2	Special formula high in medium-chain triglycerides	Foods that are naturally low in fat		Carnitine	Carnitine palmitoyl transferase	Cardiomyopathy, cognitive impairment, coma, hypoglycemia, weakness
Carnitine translocase deficiency		Foods that are naturally low in fat		Carnitine	Carnitine-acylcarnitine translocase	Cardiopulmonary arrest, coma, hypoglycemia, ventricular arrhythmia
Carnitine transporter deficiency				Carnitine	Carnitine transporter	Cardiac failure, cardiomyopathy, coma, hyperammonemia, hypoglycemia, hypotonia, seizures, vomiting
Long-chain hydroxyacyl-CoA dehydrogenase deficiency	Special formula to replace long-chain triglycerides with medium-chain triglycerides	Foods that are naturally low in fat	Essential fatty acids	Carnitine	Long-chain hydroxyacyl-CoA dehydrogenase/ trifunctional enzyme	Acute encephalopathy, cardiomyopathy, rhabdomyolysis, cardio respiratory arrest, coma, lethargy, nonketotic hypoglycemia, seizures, vomiting, weakness

Table 3. Disorders Detectable by California's Newborn Screening Program (Cont'd)

Disorder	Special Formulas	Foods	Vitamin and/or Amino Acid Supplements	Prescription Drugs	Enzyme Affected	Clinical Manifestations
Fatty Acid Oxidation Disorders (Cont'd)						
Medium-chain acyl-CoA dehydrogenase deficiency		Foods that are naturally low in fat		Carnitine	Medium-chain acyl-CoA dehydrogenase	Acute encephalopathy, cardio respiratory arrest, chronic vomiting, coma, lethargy, liver disease, nonketotic hypoglycemia, seizures,
Medium-/short-chain L-3 hydroxy acyl-CoA dehydrogenase deficiency		Foods that are naturally low in fat		Carnitine	Medium-/short-chain L-3 hydroxy acyl-CoA dehydrogenase	Coma, hepatic lipid accumulation, hypoglycemia, myoglobinuria
Multiple acyl-CoA dehydrogenase deficiency/ glutaric acidemia, Type 2		Foods that are naturally low in fat	Vitamin B12	Carnitine	Electron-transferring-flavoprotein, Electron-transferring-flavoprotein dehydrogenase	Acidosis, cardiomyopathy, coma, hypoglycemia, hypotonia, midface hypoplasia, polycystic kidney
Short-chain acyl-CoA dehydrogenase deficiency		Foods that are naturally low in fat		Carnitine	Short-chain acyl-CoA dehydrogenase	Acidemia, developmental delay, failure to thrive

Table 3. Disorders Detectable by California's Newborn Screening Program (Cont'd)

Disorder	Special Formulas	Foods	Vitamin and/or Amino Acid Supplements	Prescription Drugs	Enzyme Affected	Clinical Manifestations
Fatty Acid Oxidation Disorders (Cont'd)						
Very-long-chain acyl-CoA dehydrogenase deficiency	Special formula to replace long-chain triglycerides with medium-chain triglycerides	Very low-fat diet	Essential fatty acids	Carnitine	Very-long-chain acyl-CoA dehydrogenase	Cardiomyopathy, coma, weakness
Carbohydrate Disorder						
Classical galactosemia	Lactose-free formula	Lactose-free diet; avoid foods that are naturally high in galactose	Calcium		Galactose 1-phosphate uridyltransferase	Cataracts, hepatocellular dysfunction, jaundice, vomiting

UTILIZATION, COST, AND COVERAGE IMPACTS

AB 30 would require health plans regulated by the DMHC and health insurance products regulated by the CDI to provide coverage for the testing and treatment of IEM disorders (other than PKU), for enrollees in group (large and small) and individual markets. AB 30 would also require CalPERS Knox-Keene[11] licensed plans to adhere to this mandate. (CalPERS self-funded plans would not be subject this mandate.) AB 30 does not preclude carriers from charging copayment, coinsurance, deductible, or other cost-sharing for this benefit. The bill also does not preclude carriers from conducting utilization or medical necessity reviews.

California residents with genetic disorders who are enrolled in publicly funded managed care plans, such as Medi-Cal and Healthy Families Program, qualify for Department of Health Care Services (DHCS) programs designed to treat persons with rare and complicated genetic disorders. Owing to coverage by DHCS programs, coverage would be excluded from managed care contracts and DHCS would be reimbursed from a variety of public funding sources.

This section will present first the current, or baseline, costs related to coverage of treatment for IEM disorders and then detail the estimated utilization, cost, and coverage impacts of AB 30. For further details on the underlying data sources and methods, please see Appendix D at the end of this document.

Present Baseline Cost and Coverage

Current Coverage of the Mandated Benefit

Approximately 20,687,000 individuals in California are enrolled in health plans or policies that would be affected by this legislation. About 39.1% of this population, or an estimated 8,096,100, currently have coverage for treatment for IEM disorders other than PKU (Table 1 and Table 4). All privately and publicly insured California residents have coverage for testing. Therefore, the discussion of coverage levels in this section will pertain to coverage for medical nutritional therapy of IEM disorders other than PKU. As discussed in the *Medical Effectiveness* section, standard treatment usually includes one or more of the following:

- Special formulas that do not contain the nutrients a person cannot metabolize
- Special food products (i.e., medical foods)
- Vitamin supplements
- Amino acid and enzyme co-factor supplements
- Prescription drugs

Because CHBRP assumes that prescription drugs deemed medically necessary for treatment would be covered under the insured's prescription drug coverage, this section

[11] Health maintenance organizations in California are licensed under the Knox-Keene Health Care Services Plan Act which is codified in the Health and Safety Code.

focuses on the formulas, special food products, and nutritional supplements deemed medically necessary for the management of the disorders.

Table 4. Current Coverage for Treatments for Non-PKU IEM Disorders

Insurance Plan Type	Percentage of Enrollees with Coverage
Privately insured market	
DMHC-regulated plans	
Large group	22%
Small group	30%
Individual	38%
All	25%
CDI-regulated policies	
Large group	50%
Small group	50%
Individual	70%
All	58%
Publicly insured market	
CalPERS	0%
Medi-Cal	100%
Healthy Families	100%
Total Enrollees with Coverage	39%

Source: California Health Benefits Review Program, 2007

Note: Beneficiaries of public health insurance programs are covered for treatment if they meet the income eligibility criteria for the CCS or GHPP program. All Medi-Cal and HFP beneficiaries, including babies born to women insured by the AIM program, are covered by CCS.

Based on data from the California Newborn Screening Program, CHBRP estimates a prevalence rate of 0.02% for newborns for non-PKU IEM disorders. Analysis of national claims data indicates prevalence rates decline with age in the insured population. CHBRP estimates prevalence rates for children aged 2 to 5 years at 0.0067%, for those aged 6 to 17 years at 0.0033% and for adults 18 and older at 0.002%. The weighted average of these prevalence rates is 0.0033% (approximately 1 in 30,000), yielding an estimate of 687 enrollees in California with one of the non-PKU IEM disorders requiring the use of special formulas, special food products, and/or supplements. Of these, 386 enrollees are currently without coverage for medical nutrition therapy and would gain coverage if AB 30 were to pass into law.

Coverage of the Commercially Insured Population Subject to the Mandate

CHBRP conducted a survey of the seven largest health plans and insurers in California to examine current coverage levels for medical nutrition therapy mandated under AB 30. All seven health plans and insurers responded to the survey, representing 84.5% of the

privately insured enrollees in the CDI-regulated market and 82.1% in the DMHC-regulated market.[12]

CHBRP's coverage survey of health plans indicated variations in coverage by market segment. For DMHC-regulated health plans, about 25% of enrollees have coverage: 22% of enrollees in the large group, 30% of enrollees in the small group, and 38% of enrollees who individually purchased insurance in DMHC-regulated health plans have coverage for the treatment of IEM disorders other than PKU. For CDI-regulated health insurance products, about 58% of enrollees have coverage: 50% of the group (large and small) market and 70% of insured who individually purchased insurance in CDI-regulated health products

Coverage of the CalPERS and Publicly Insured Population Subject to the Mandate

CalPERS does not provide coverage for medical nutrition therapy of non-PKU IEM disorders.

Children and adults with genetic disorders are eligible for coverage for IEM disorders through the California Children's Services (CCS) Program and the Genetically Handicapped Person's Program (GHPP) if they meet certain eligibility requirements. Services relating to CCS-eligible medical diagnosis are excluded from managed care contracts and reimbursed on a traditional fee-for-service basis from a variety of funding sources.

Current Utilization Levels and Costs of the Mandated Benefit

For many non-PKU IEM disorders, medical nutrition therapy is recommended regardless of age, as indicated in the *Medical Effectiveness* section. Medical nutrition therapy is primarily required for amino acid and organic acid disorders, which require foods that cannot be found in grocery stores and foods that are formulated to exclude the problematic amino or organic acids or include needed supplements. Treatment for persons with IEM disorders varies by type of disorder, as well as among patients with the same disorder. These variations require differential levels of utilization of formulas, special food products, and/or nutritional supplements. However, these variations are not specifically examined in this report due to the rarity of these disorders and subsequently small number of individuals affected by this mandate.

Estimating current utilization for persons with IEM disorders is problematic. Compliance with recommended dietary practice is hard to quantify and under-researched (MacDonald, 2000). The complexities of adhering to the prescribed diet, including the taste and palatability, the ease of finding and purchasing the special food products,

[12] DMHC-regulated plans represent about 91% of the privately insured market in California, while CDI-regulated plans represent 9%.

knowledge of how to prepare the foods, costs of the treatments without insurance coverage, and potential delays in reimbursement from insurance have the potential to reduce utilization of medical nutrition therapy to below medically recommended levels. However, clinicians at several metabolic centers in California indicated that families will obtain the dietary products for their children by any means possible, particularly because completely forgoing these products can have fatal consequences. Based on expert input, for the purposes of this analysis, CHBRP estimates that use of prescribed dietary products is consistent with medically recommended levels.

Unit price

As discussed in *Medical Effectiveness* section above, medical nutrition therapy for non-PKU IEM disorders usually includes use of specialized formulas, special food products, and/or nutritional supplements

CHBRP has estimated an average annual cost of $6,000 per patient for the special formulas, special food products, and nutritional supplements necessary for treatment. The estimate for the special formulas and food products is based on 2005 paid claims data for formulas and special food products authorized by the CCS and GHPP for persons with IEM disorders. The average annual per patient cost for formula was approximately $3,000. The average annual per patient cost for special food products was approximately $1,000. The average annual per patient cost for nutritional supplements was approximately $2,000 based on recommended daily dosages and pricing of amino acid and enzyme cofactor supplements for the proportion of those with IEM disorders for whom these supplements are part of the recommended treatment (See Table D-1). Data on recommended dosages was supplied to CHBRP by clinicians at the metabolic centers. CHBRP excluded costs associated with vitamin, mineral, and fatty acid supplements, since they were negligible.

AB 30 does not specifically address whether health plans and insurers would be required to cover nutritional supplements that are available through either a pharmacy or over the counter. The bill sponsor, the March of Dimes, argues the intent of the bill is to remedy denials of nutritional supplements from insurance companies. Clinicians at metabolic centers favor prescribing supplements from pharmacies to ensure the quality of the product for their patients. Depending on the health plan or insurer, supplements are sometimes covered as a prescription benefit. Depending on the legal analysis of AB 30 by the DMHC and CDI, health plans and insurers may be able to exclude nutritional supplements that are available over the counter from coverage and still be compliant with AB 30. The inclusion of nutritional supplements in the CHBRP model increases expenditures by $750,000 statewide.

The baseline costs associated with the mandate given current utilization and unit price are presented in Table 5.

The Extent to Which Costs Resulting from Lack of Coverage Are Shifted to Other Payers, Including Both Public and Private Entities

Based on discussions with clinicians at several metabolic centers, CHBRP has assumed that individuals with these disorders obtain the recommended treatment by any means possible and comply with the recommended treatment. It is likely that some individuals do not receive as much of these products as they are willing to use, but CHBRP estimates the potential increase in utilization due to the mandate to be minimal and offset by issues such as the poor taste and unpalatability of these products. Consequently, AB 30 would shift costs from out-of-pocket expenditures by insured individuals to costs covered and paid for by health plans and insurers. In other words, AB 30 requires certain coverage, the costs of which previously were paid on an out-of-pocket basis by insured individuals. No shifting of costs is estimated for those with publicly financed insurance, such as Medi-Cal and Healthy Families, since they are eligible for coverage through CCS and GHPP.

Public Demand for Coverage

Based on criteria specified under SB 1704 (2006), CHBRP is to report on the extent to which collective bargaining agents negotiate for and the extent to which self-insured plans currently have coverage for the benefits specified under the proposed mandate. Currently, the largest public self-insured plans are CalPERS' PERSCare and PERS Choice preferred provider organizations (PPO) plans. PERSCare and PERS Choice PPOs only cover testing and treatment for PKU. Medical nutrition therapy for non-PKU disorders is not covered. CalPERS' PPO self-insured plans have an exclusion for vitamins, minerals, and nutritional supplements, whether available over the counter or prescribed by a physician. The plans also exclude nutritional counseling or food supplements taken orally, except if they are covered under the diabetes self-management and education benefit or under the outpatient prescription drug benefit.

Based on conversations with the largest collective bargaining agents in California, there is no evidence that unions currently include such detailed provisions during the negotiations of their health insurance policies.[13] To determine whether any local unions engage in negotiations at such detail, they would need to be surveyed individually, an undertaking beyond the scope of CHBRP's 60-day analysis.

[13] Personal communication with the California Labor Federation and member organizations on January 29, 2007.

Impacts of Mandated Coverage

How Will Changes in Coverage Related to the Mandate Affect the Benefit of the Newly Covered Service and the Per-Unit Cost?

Impact on per-unit cost

Existing literature indicates a high level of medical effectiveness for formulas and special food products when medical necessity is indicated. CHBRP has assumed that individuals with IEM disorders currently use these products to their maximum levels of compliance/adherence. Given the rarity of these conditions, the relatively small numbers of individuals with these disorders, and the current utilization levels, CHBRP does not anticipate any changes to per-unit costs of these products.

Postmandate coverage

If AB 30 were to pass into law, approximately 12,590,900 additional insured individuals would gain coverage for medical nutritional therapy for non-PKU IEM disorders. Among the insured population approximately 687 are diagnosed with non-PKU IEM disorders. About 301 persons that need medical nutritional therapy currently have coverage and 386 would gain coverage.

Changes in coverage as a result of premium increases

As discussed in the section below, "Impact of the Mandate on Total Health Care Costs," CHBRP estimates premium increases of 0.0042% to 0.0055% across the privately insured market segments and CalPERS. Due to the very small size of the increase in premiums postmandate, CHBRP does not anticipate loss of insurance coverage, changes in availability of the benefit beyond those subject to the mandate, changes in offer rates of insurance, changes in employer contribution rates, changes in take-up of insurance by employees, or purchase of individual policies. This premium increase would not have a measurable impact on number of individuals who are uninsured.

How Will Utilization Change As a Result of the Mandate?

CHBRP estimates that utilization of medical nutritional therapy will remain unchanged under AB 30. As discussed in the "Current Utilization Levels" section above, expert input from clinicians at metabolic centers in California indicated that because of the devastating nature of these IEM disorders, families would find a way to overcome any potential cost barriers to obtain the dietary products for their children.

AB 30 would not address other compliance or utilization barriers including unpalatability, knowledge of how to prepare such foods, and the ease of finding and purchasing them. In the PKU population, for example, research has identified many barriers to adherence to diet, including time constraints and stress associated with food preparation and record-keeping, the restrictions imposed on social life, social support for the diet, and positive perceptions of treatment (Bilginsoy, 2005; Levy, 1994).

Subsequently, the potential increases in utilization levels are considered to be imperceptible.

To What Extent Does the Mandate Affect Administrative and Other Expenses?

All health care plans and insurers include a component for administration and profit in their premiums. The estimated impact of this mandate on premiums includes the assumption that plans and insurers will apply their existing administration and profit loads to the marginal increase in health care costs produced by the mandate. Given that utilization rates will remain the same after the mandate, the estimated increase of total expenditures is mainly due to the increase of the administrative costs as a proportion of the premium. Under AB 30, CHBRP estimates an increase of $415,000 in administrative costs for plans regulated by the DMHC and CDI.

Impact of the Mandate on Total Health Care Costs

Changes in total expenditures

Prior to the mandate, enrollees without coverage for medical nutritional therapy incurred an estimated $2,315,000 in out-of-pocket expenses annually. Postmandate, health plans and insurers would be required to cover the $2,315,000 that was paid on an out-of-pocket basis by insured individuals.

Postmandate, CHBRP estimates that total premiums would increase by $2,730,000, representing the $2,315,000 in costs incurred by enrollees out-of-pocket prior to the mandate and $415,000 in additional administrative costs. Total expenditures (including total premiums and out-of-pocket expenditures) would increase by $415,000 (0.0006%). This increase is attributable to the additional administrative costs associated with adding coverage for enrollees who did not have coverage for medical nutritional therapy for non-PKU IEM disorders prior to the mandate.

CHBRP estimates these postmandate expenditures would be distributed as follows:

- Individuals enrolled in CDI-regulated plans pay an additional $27,000 (0.0005%) in the form of copayments.
- Premiums paid by employers other than those in CalPERS would increase by $1,830,000 or 0.0042% in the large and small group markets, by $249,000 or 0.0045% in the individual market, and by $145,000 or 0.0055% among CalPERS employers.
- Premiums paid by employees covered by group insurance (including CalPERS) would increase by an estimated at $479,000 or 0.0042%.

Offsets and long-term cost impacts

CHBRP estimates no perceptible savings or offsets in other health care costs due to AB 30 since the bill would not change utilization rates. Similarly, AB 30 is not expected to have any noticeable long-term cost impacts. It is possible that delays in treatment may be averted with immediate coverage for medical nutritional therapy. However, the effects of this are unknown.

Costs or Savings for Each Category of Insurer Resulting from the Benefit Mandate

The total increase in expenditures reported above translates as follows:

- In the large group market, an estimated premium increase of 0.0045% ($0.0136 PMPM) in the DMHC-regulated market, and 0.0018% ($0.0072 PMPM) in the CDI-regulated market.
- In the small group market, an estimated premium increase of 0.0039% ($0.0134 PMPM) in the DMHC-regulated market, and 0.0023% ($0.0080 PMPM) in the CDI-regulated market.
- In the individual market, an estimated premium increase of 0.0048% ($0.0131 PMPM) in the DMHC-regulated market, and 0.0035% ($0.0052 PMPM) in the CDI-regulated individual market.
- In CalPERS, an estimated premium increase of 0.0055% ($0.018 PMPM).

A summary of the projected cost impacts as a result of AB 30 is summarized in Table 6. These estimates are projected for the mandate's effective date of January 1, 2008.

Impact on Access and Health Service Availability

As discussed in the "How Will Utilization Change As a Result of the Mandate" section above, expert input from clinicians at metabolic centers in California indicated that because of the devastating nature of these IEM disorders, families would find a way to overcome any potential cost barriers to obtain the dietary products for their children. AB 30 is also not expected to improve access by increasing the ease of finding and purchasing such products, nor is it expected to impact the availability of these products.

Consumer complaints

In response to consumer complaints after enactment of the PKU mandate, DMHC issued a memo in 2002 to California health maintenance organization (HMO) executives clarifying the HMOs' obligations with respect to the coverage of PKU. Problems reported by consumers included:

- HMO procedures requiring enrollees to first purchase medically necessary formulas and special food products and then request reimbursement from the plan;

- Inappropriate delays in reimbursing the costs of special foods and formulas;
- Lack of knowledge among plan personnel regarding coverage for PKU supplies; and
- Patterns of providing coverage only after enrollees dispute a denial of services.

Since 2001, DMHC has received 22 complaints relating to IEM disorders. Of these complaints, 14 related to coverage for PKU testing or treatment. The remaining 8 complaints involved non-PKU disorders. The majority of these complaints were coverage disputes as to whether the nutritional supplements were a covered benefit. Unless the individual had PKU, most plans did not cover nutritional supplements for IEM disorders. CHBRP also searched the DMHC's database on Independent Medical Review (IMR) that show which cases have been filed for review by a health plan enrollee to obtain coverage of a denied service. The search did not identify any IEM cases that had been reviewed as part of the IMR process.

Table 5. Baseline (Premandate) Per Member Per Month Premium and Expenditures by Insurance Plan Type, California, 2007

	Large Group		Small Group		Individual		CalPERS	Medi-Cal		Healthy Families	
	DMHC Regulated	CDI Regulated	DMHC Regulated	CDI Regulated	DMHC Regulated	CDI Regulated	HMO	Managed Care 65 and Over	Managed Care Under 65	Managed Care	Total Annual
Population Subject to the Mandate	10,354,000	363,000	3,086,000	679,000	1,268,000	794,000	791,000	165,000	2,513,000	681,000	20,694,000
Average Portion of Premium Paid by Employer	$249.51	$323.69	$249.52	$281.52	$0.00	$0.00	$277.19	$181.00	$120.43	$76.82	$51,194,004,000
Average Portion of Premium Paid by Employee	$53.66	$74.60	$94.73	$61.82	$269.42	$148.66	$48.92	$0.00	$0.85	$5.78	$17,057,625,000
Total Premium	$303.17	$398.28	$344.26	$343.34	$269.42	$148.66	$326.11	$181.00	$121.29	$82.60	$68,251,630,000
Member Expenses for Covered Benefits (Deductibles, copays, etc)	$16.35	$46.30	$25.58	$90.75	$45.45	$36.35	$16.82	$0.00	$0.56	$2.25	$5,153,127,000
Member Expenses for Benefits Not Covered	$0.01	$0.01	$0.01	$0.01	$0.01	$0.00	$0.02	$0.00	$0.00	$0.00	$2,315,000
Total Expenditures	$319.54	$444.59	$369.85	$434.09	$314.87	$185.02	$342.94	$181.00	$121.85	$84.85	$73,407,072,000

Source: California Health Benefits Review Program, 2007.
Note: The population includes individuals and dependents in California who have private insurance (group and individual) or public insurance (e.g., CalPERS, Medi-Cal, Healthy Families, AIM, MRMIP) under health plans or policies regulated by the DMHC or CDI. All population figures include enrollees aged 0 to 64 years and enrollees 65 years or older covered by employment-based coverage. Key: CalPERS = California Public Employees' Retirement System; HMO = health maintenance organization and point of service plans.

Table 6. Postmandate Impacts on Per Member Per Month and Total Expenditures by Insurance Plan Type, California, 2007

	Large Group		Small Group		Individual		CalPERS	MediCal		Healthy Families	
	DMHC Regulated	CDI Regulated	DMHC Regulated	CDI Regulated	DMHC Regulated	CDI Regulated	HMO	Managed Care 65 and Over	Managed Care Under 65	Managed Care	Total Annual
Population Subject to the Mandate	10,354,000	363,000	3,086,000	679,000	1,268,000	794,000	791,000	165,000	2,513,000	681,000	20,694,000
Average Portion of Premium Paid by Employer	$0.0112	$0.0059	$0.0097	$0.0066	$0.0000	$0.0000	$0.0153	$0.0000	$0.0000	$0.0000	$1,975,000
Average Portion of Premium Paid by Employee	$0.0024	$0.0014	$0.0037	$0.0015	$0.0131	$0.0052	$0.0027	$0.0000	$0.0000	$0.0000	$728,000
Total Premium	$0.0136	$0.0072	$0.0134	$0.0080	$0.0131	$0.0052	$0.0180	$0.0000	$0.0000	$0.0000	$2,703,000
Member Expenses for Covered Benefits (Deductibles, copays, etc)	$0.0000	$0.0015	$0.0000	$0.0015	$0.0000	$0.0009	$0.0000	$0.0000	$0.0000	$0.0000	$27,000
Member Expenses for Benefits Not Covered	-$0.0120	-$0.0077	-$0.0109	-$0.0077	-$0.0089	-$0.0044	-$0.0153	$0.0000	$0.0000	$0.0000	-$2,315,000
Total Expenditures	$0.0016	$0.0011	$0.0026	$0.0018	$0.0042	$0.0017	$0.0027	$0.0000	$0.0000	$0.0000	$415,000
Percentage Impact of Mandate											
Insured Premiums	0.0045%	0.0018%	0.0039%	0.0023%	0.0048%	0.0035%	0.0055%	0.0000%	0.0000%	0.0000%	0.0040%
Total Expenditures	0.0005%	0.0002%	0.0007%	0.0004%	0.0013%	0.0009%	0.0008%	0.0000%	0.0000%	0.0000%	0.0006%

Source: California Health Benefits Review Program, 2007.

Note: The population includes individuals and dependents in California who have private insurance (group and individual) or public insurance (e.g, CalPERS, Medi-Cal, Healthy Families, AIM, MRMIP) under health plans or policies regulated by the DMHC or CDI. All population figures include enrollees aged 0 to 64 years and enrollees 65 years or older covered by employment-based coverage. Key: CalPERS = California Public Employees' Retirement System; HMO = health maintenance organization and point of service plans.

PUBLIC HEALTH IMPACTS

As discussed in previous sections, IEM disorders are rare disorders that are often treated with a specific diet, typically a low-carbohydrate, low-protein, or low-fat diet where the main treatment is the use of formulas and special food products that replace everyday foods that are not properly metabolized due to the IEM disorder. Supplements such as carnitine are also used as principal treatment for some IEM disorders. Of the more than 40 IEM disorders identified through the California Newborn Screening Program, Table 7 details the prevalence of the disorders that are non-PKU IEM disorders where the primary treatment is the use of formulas, special foods and/or supplements for California babies born between July 7, 2005, and December 31, 2006. The prevalence of the disorders in Table 7 vary substantially and range from 0.12 per 100,000 for Argininemia and several other disorders to 4.79 per 100,000 for medium-chain acyl-CoA dehydrogenase deficiency (MCAD).

Table 7. California Newborn Screening Program, Prevalence of Non-PKU Disorders in Screened Population between 7/7/2005 and 12/31/2006 (n = 834,373)

Metabolic Disorder	Number of Cases[a]	Prevalence per 100,000 newborns
Carbohydrate Disorders		
Classical galactosemia	5	0.60
Protein Disorders (amino acid and organic acid disorders)		
Argininemia (ARG)	1	0.12
Arginnosuccinic acid lyase deficiency (ASAL)	2	0.24
Biopterin deficiencies (4 disorders - dihydropteridine reductase	0	[b]
Citrullinemia, Type I (CIT-1)	5	0.60
Citrullinemia, Type II (CIT-2)	1	0.12
Gyrate atrophy of the choroid and retina	0	[b]
Homocystinuria (HCY)	1	0.12
Homocitrullinuria, hyperornithinemia, hyperammonemia syndrome	0	[b]
Maple syrup urine disease (MSUD)	8	0.96
Tyroseinemia (TYR)	0	[b]
2-methyl-3-hydroxbutyryl-CoA dehydrogenase deficiency	0	[b]
3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMGCoA lyase deficiency)	0	[b]
3-methylglutaconic aciduria, Type I (3-methylglutaconyl-CoA hydratase deficiency)	0	[b]
3-methylcrotonyl-CoA carboxylase deficiency (3MCC)	22	2.64
Beta-ketohiolase deficiency (BKT)	0	[b]
Glutaric acidemia type-1 (GA-1)	6	0.72
Isovaleric academia (IVA)	7	0.84
Malonic acidemia	0	[b]
Methylmalonic academia (MMA)	9	1.08
Methylmalonic acidemia/Cobalmin C deficiency	12	1.44
Multiple carboxylase deficiency	2	0.24
Propionic academia (PA)	1	0.12
Fatty Acid Oxidation Disorders		
Carnitine palmitoyl transferase deficiency, Type 2 (CPT-2)	3	0.36
Carnitine transporter deficiency (CTD)	16	1.92
Carnitine translocase deficiency (CAT)	1	0.12
Long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)	1	0.12
Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	40	4.79
Medium-/short-chain L-3 hydroxy acyl-CoA dehydrogenase deficiency (M/SCHAD deficiency)	0	[b]
Multiple acyl-CoA dehydrogenase deficiency/ethylmalonic academia	2	0.24
Short-chain acyl-CoA dehydrogenase deficiency (SCAD)	17	2.04
Very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	12	1.44
Total	**174**	**20.85**

Source: California Newborn Screening Program, 7/7/2005 and 12/31/2006 (n = 834,373)

[a] Number includes cases of screened newborns identified via screening and also any cases not identified through the screening and later identified.
[b] No cases were identified in the specified time period and therefore no prevalence rate is reported.

A total of 174 newborns were identified with one of the disorders listed in Table 7 between July 7, 2005, and December 31, 2006, resulting in a prevalence of approximately 1 in 5,000 newborns.

While most of the newborns with the IEM disorders listed in Table 7 will require specialized infant formula, the nutritional needs for persons with IEM disorders vary substantially as infants age, based on the type and severity of their disorders. Some require formula, special food products, and supplements throughout their entire lives while others are able to transition to a restricted diet based primarily on conventionally available foods.

Looking beyond newborns to the broader insured population, according to CHBRP's analysis of national claims data for 2005, it is estimated that 687 individuals—or approximately 1 in 30,000 insured persons—have a diagnosis listed in Table 7.

Impact on Community Health

As detailed in the *Medical Effectiveness* section, there are multiple health outcomes associated with IEM disorders, with the most critical outcomes of coma, severe cognitive impairment, and death. Additionally, some of the other health outcomes related to IEM disorders include gastrointestinal distress, respiratory failure, developmental delay, and failure to thrive.

According to the *Cost* section, AB 30 will not result in an increase in utilization of medical nutrition therapy for the treatment of IEM disorders. AB 30 will, however, increase insurance coverage for this benefit to 386 individuals with a non-PKU IEM disorder. While these 386 are not expected to incur any improved health outcomes due to AB 30, this bill will likely reduce the administrative burden and financial hardship associated with these disorders when health plans deny claims for medical nutrition therapy (Winter and Buist, 1998).

Impact on Community Health Where Gender and Racial Disparities Exist

A literature review was conducted to determine if gender and racial/ethnic disparities exist with regard to the prevalence and treatment of the non-PKU IEM disorders. No research was identified that found gender differences in prevalence of the disorders listed in Table 7.

Racial and ethnic differences in prevalence vary by disorder and the population of analysis. For example, a North Carolina study found that compared to non-Hispanic whites, Hispanics had higher rates of 3-MCC deficiency disorder and lower rates of MCAD (Frazier et al., 2003). Since IEM disorders are typically genetic disorders, studies on racial and ethnic differences tend to focus on smaller ethnic communities where these rare conditions are more prevalent, such as MSUD among Mennonite groups (Puffenberger, 2003) and galactosemia among an Irish nomadic group (Murphy et al., 1999).

Data from the California Genetic Disease Branch and California birth records indicate that overall, the proportion of newborns identified with IEM disorders is comparable with the racial and ethnic distribution of births in California. Hispanics, however, have a somewhat lower

proportion of IEM disorders compared to their proportion of newborns (44% of IEMs compared to 50% of new births). (California Department of Health Care Services' Genetic Disease Branch, 2007; California Department of Health Care Services, 2007).

Since there are no measurable gender or racial/ethic differences in prevalence of IEM disorders and AB 30 is not anticipated to affect utilization of special formula, foods, and supplements, AB 30 is not expected to have a measurable impact on gender, racial, or ethnic disparities in health.

Reduction of Premature Death and Economic Loss Associated with Disease

For infants with disorders detailed in Table 7, the use of medical nutrition therapy is essential for the prevention of serious and costly health effects, including premature death. As stated previously, the necessity for these products varies for older children and adults according to the specific disorder and the severity of the condition.

Since IEM disorders are rare conditions where early diagnosis and treatment is crucial to preventing severe health outcomes, the focus of the economic literature is on the cost-effectiveness of statewide screening programs. The early identification and treatment of IEM disorders through screening programs have been found to be cost-effective according to accepted standards (Schoen et al., 2002; Carroll and Downs, 2006; Venditti et al., 2003). The costs of medical nutrition therapy for IEM disorders are minimal when compared to the broader costs of screening programs and the medical costs associated with not getting proper and timely treatment (Schoen et al., 2002; Carroll and Downs, 2006; Venditti et al., 2003; Filiano et al., 2002). Filiano et al. (2002) write that expanded newborn screening and treatment for IEM disorders is not only cost-effective, but can be one of the rare health interventions that is cost-saving by reducing morbidity and substantial medical costs through prompt treatment.

Although the early detection and treatments of IEM disorders is important in reducing associated premature death and economic costs, since AB 30 is not expected to increase utilization of medical nutrition therapy, this mandate is not expected to have a measurable impact on premature death or the economic loss associated with non-PKU IEM disorders.

APPENDICES

Appendix A: Text of Bill Analyzed

BILL NUMBER: AB 30 AMENDED BILL TEXT

AMENDED IN ASSEMBLY APRIL 10, 2007

INTRODUCED BY Assembly Member Evans

DECEMBER 4, 2006

An act *to add Section 1374.4 to the Health and Safety Code, and to add Section 10123.90 to the Insurance Code,* relating to health care coverage.

LEGISLATIVE COUNSEL'S DIGEST

AB 30, as amended, Evans. Health care ~~coverage.~~ *coverage: inborn errors of metabolism.*

Existing law, the Knox-Keene Health Care Service Plan Act of 1975 (the Knox-Keene Act), provides for the licensure and regulation of health care service plans by the Department of Managed Health Care and makes a willful violation of the act a crime. Existing law also provides for the regulation of health insurers by the Department of Insurance. Under existing law, a plan and a health insurer are required to provide coverage, as specified, for the testing and treatment of phenylketonuria.

This bill would extend this coverage requirement for health care service plans and insurers, as specified, to inborn errors of metabolism, as defined.

Because the bill would specify an additional requirement under the Knox-Keene Act, the willful violation of which would be a crime, it would impose a state-mandated local program.

The California Constitution requires the state to reimburse local agencies and school districts for certain costs mandated by the state. Statutory provisions establish procedures for making that reimbursement.

This bill would provide that no reimbursement is required by this act for a specified reason.

~~Existing law does not provide a system of health care coverage for all California residents and does not require employers to provide health care coverage for employees and their families, other than~~

~~coverage provided as part of the workers' compensation system for work-related employee injuries. Existing law provides for the creation of various programs to provide health care services to persons who have limited incomes and meet various eligibility requirements. These programs include the Healthy Families Program administered by the Managed Risk Medical Insurance Board, and the Medi-Cal program administered by the State Department of Health Care Services. Existing law provides for the regulation of health care service plans by the Department of Managed Health Care and health insurers by the Department of Insurance.~~

~~This bill would declare the intent of the Legislature to provide for reducing costs and improving quality of health care for working Californians and their families by minimizing administrative overhead, assuring that those working Californians and their families receive timely access to appropriate health care, and identifying and reducing health care that is both high cost and low quality.~~

Vote: majority. Appropriation: no. Fiscal committee: ~~no~~ *yes* . State-mandated local program: ~~no~~ *yes* .

THE PEOPLE OF THE STATE OF CALIFORNIA DO ENACT AS FOLLOWS:

SECTION 1. Section 1374.4 is added to the Health and Safety Code, to read:

1374.4. (a) Every health care service plan contract, except a specialized health care service plan contract, issued, amended, delivered, or renewed in this state on and after January 1, 2008, that provides coverage for hospital, medical, or surgical expenses shall provide coverage for the testing and treatment of inborn errors of metabolism under the terms and conditions of the plan contract.

(b) Coverage for treatment of inborn errors of metabolism shall include those formulas and special food products that are part of a diet prescribed by a licensed physician and surgeon and managed by a health care professional in consultation with a physician and surgeon who specializes in the treatment of metabolic disease and who participates in, or is authorized by, the plan, if the diet is deemed medically necessary to avert the development of serious physical or mental disabilities or to promote normal development or function as a consequence of inborn errors of metabolism.

(c) Coverage pursuant to this section is not required except to the extent that the cost of the necessary formulas and special food products exceeds the cost of a normal diet.

(d) For purposes of this section, the following definitions shall apply:

(1) "Formula" means an enteral product or enteral products for use at home that are prescribed by a physician and surgeon or nurse practitioner, or ordered by a registered dietician upon referral by a health care provider authorized to prescribe dietary treatments, as medically necessary for the treatment of inborn errors of metabolism.

(2) "Inborn errors of metabolism" means an inheritable disorder of biochemistry detected through the California newborn screening program.

(3) "Special food product" means a food product that is both of the following:

(A) Prescribed by a physician and surgeon or nurse practitioner for the treatment of inborn errors of metabolism and is consistent with the recommendations and best practices of qualified health professionals with expertise germane to, and experience in the treatment and care of, inborn errors of metabolism. It does not include a food that is naturally low in protein, but may include a food product that is specially formulated to have less than one gram of protein per serving.

(B) Used in place of normal food products, such as grocery store foods, used by the general population.

(e) A plan that provides the coverage required by this section shall be deemed to comply with Section 1374.56.

SEC. 2. Section 10123.90 is added to the Insurance Code , to read:

10123.90. (a) Every policy of health insurance issued, amended, delivered, or renewed in this state on and after January 1, 2008, that provides coverage for hospital, medical, or surgical expenses shall provide coverage for the testing and treatment of inborn errors of metabolism under the terms and conditions of the policy.

(b) Coverage for treatment of inborn errors of metabolism shall include those formulas and special food products that are part of a diet prescribed by a licensed physician and surgeon and managed by a health care professional in consultation with a physician and surgeon who specializes in the treatment of metabolic disease and who participates in, or is authorized by, the insurer, if the diet is deemed medically necessary to avert the development of serious physical or mental disabilities or to promote normal development or function as a consequence of inborn errors of metabolism.

(c) Coverage pursuant to this section is not required except to the extent that the cost of necessary formulas and special food products exceeds the cost of a normal diet.

(d) For purposes of this section, the following definitions shall apply:

(1) "Formula" means an enteral product or enteral products for use at home that are prescribed by a physician and surgeon or nurse

practitioner, or ordered by a registered dietician upon referral by a health care provider authorized to prescribe dietary treatments, as medically necessary for the treatment of inborn errors of metabolism.

(2) "Inborn errors of metabolism" means an inheritable disorder of biochemistry detected through the California newborn screening program.

(3) "Special food product" means a food product that is both of the following:

(A) Prescribed by a physician and surgeon or nurse practitioner for the treatment of inborn errors of metabolism and is consistent with the recommendations and best practices of qualified health professionals with expertise germane to, and experience in the treatment and care of, inborn errors of metabolism. It does not include a food that is naturally low in protein, but may include a food product that is specially formulated to have less than one gram of protein per serving.

(B) Used in place of normal food products, such as grocery store foods, used by the general population.

(e) A health insurer that provides the coverage required by this section shall be deemed to comply with Section 10123.89.

(f) This section shall not apply to vision-only, dental-only, accident-only, specified disease, hospital indemnity, Medicare supplement, long-term care, or disability income insurance, except that for accident only, specified disease, or hospital indemnity coverage, coverage for benefits under this section shall apply to the extent that the benefits are covered under the general terms and conditions that apply to all other benefits under the policy or contract. Nothing in this section shall be construed as imposing a new benefit mandate on accident only, specified disease, or hospital indemnity insurance.

SEC. 3. No reimbursement is required by this act pursuant to Section 6 of Article XIII B of the California Constitution because the only costs that may be incurred by a local agency or school district will be incurred because this act creates a new crime or infraction, eliminates a crime or infraction, or changes the penalty for a crime or infraction, within the meaning of Section 17556 of the Government Code, or changes the definition of a crime within the meaning of Section 6 of Article XIII B of the California Constitution.

~~SECTION 1. (a) The Legislature finds and declares that more than six million Californians lack health care coverage and that 80 percent of these Californians are members of working families. The Legislature further finds and declares that rising health care costs have limited health care access for both the insured, who must pay higher out-of-pocket costs, and the uninsured,~~

~~who are sicker, die younger, and face financial ruin due to the lack of health care coverage. Lack of health care coverage is also contributing to increasing health care costs by shifting costs to taxpayers and those employers who pay for health care benefits for employees and their families.~~

~~(b) It is the intent of the Legislature to provide for reducing costs and improving quality of health care for working Californians and their families by minimizing administrative overhead, assuring that working Californians and their families receive timely access to appropriate health care, and identifying and reducing health care that is both high cost and low quality.~~

Appendix B: Literature Review Methods

Appendix B describes methods used by the California Health Benefits Review Program (CHBRP) to review the literature on the medical effectiveness of the treatments for inborn errors of metabolism (IEM) addressed in AB 30.

CHBRP uses a hierarchy of evidence when conducting medical effectiveness reviews that is similar to hierarchies used by the U.S. Preventive Services Task Force and other organizations that assess the effectiveness of medical services. CHBRP's hierarchy of evidence consists of the following eight types of studies:

1. High-quality meta-analyses,[14] particularly those included in the Cochrane Library

2. Systematic reviews, particularly those performed by authoritative organization such as the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention, the Centers for Medicare & Medicaid Services, the National Institutes for Health, and the U.S. Preventive Services Task Force

3. Evidence-based guidelines

4. Well-designed randomized controlled trials (RCTs) and cluster RCTs[15]

5. RCTs and cluster RCTs with major weaknesses

6. Nonrandomized studies with comparison groups and time series analysis

7. Case series and case reports

8. Clinical practice guidelines based on consensus or opinion rather than on evidence

Although CHBRP has successfully applied this hierarchy to many reports, the literature on IEM disorders does not fit neatly into it. The peer-reviewed literature on dietary treatment for IEM disorders is relatively sparse. Most studies on this topic are case studies of individual patients or case series that track the health of small groups of patients over time. There are no RCTs and no

[14] "High-quality" meta-analyses are meta-analyses that have clear objectives and hypotheses, apply appropriate inclusion/exclusion criteria, assess meaningful outcomes, and use sound methods to find, select, and evaluate studies and to generate pooled estimates of an intervention's effects. *Cochrane Handbook for Systematic Reviews of Interventions 4.2.5*, Chichester, UK: John Wiley & Sons, 2005, p. 97-99. Egger M, Schneider M, Smith GD. Meta-analysis: Spurious precision? Meta-analysis of observational studies. *British Medical Journal* 1998;316:140-144. Egger M, Smith GD, Phillips AN. Meta-analysis: Principles and procedures. *British Medical Journal* 1997;315:1533-1537. Flather MD, Farkouh ME, Pogue JM, Yusuf S. Strengths and limitations of meta-analysis: Larger studies may be more reliable. *Controlled Clinical Trials*. 1997;18:568-579.

[15] "Cluster RCTs" are studies in which subjects are randomized in groups rather than as individuals. This research design is typically used in situations in which the intervention is administered to groups of subjects or in which it may be difficult to prevent persons in the intervention and control groups from exchanging information about the treatment with one another.

nonrandomized controlled studies on the effectiveness of special formulas, special food products, or supplements for IEM disorders relative to no medical nutrition therapy. The few RCTs that have been conducted have compared standard treatments for one IEM, phenylketonuria (PKU), to a different treatment that is hypothesized to be more effective.

The lack of controlled studies on the efficacy of medical nutrition therapy for IEM disorders is due to several factors. First, these disorders are potentially fatal. The consequences of withholding treatment are so severe that parents are unlikely to enroll their children in studies in which the control group receives no treatment. Second, IEM disorders are very rare. Most occur in less than 1 person per 100,000. The small number of persons with these disorders makes it very difficult for researchers to recruit sufficient numbers of subjects to carry out prospective, controlled studies. Third, the scientific basis for diagnosis and treatment of IEM disorders is strong. Extensive research has been conducted on the roles of individual enzymes in metabolizing nutrients[16] and diagnostic tests are available to determine whether enzymes are defective. If a person is diagnosed with an IEM, clinicians have a sound basis for identifying the nutrients he or she cannot metabolize and designing medical nutrition therapy that minimizes ingestion of those nutrients.

Due to the paucity of controlled studies of treatment for IEM disorders, CHBRP relied primarily on treatment guidelines based on consensus among experts. Information was primarily obtained from two review articles (Isaacs and Zand, 2007; Raghuveer et al., 2006) and three reference books (Fernandes et al., 2006; Nyhan et al., 2005; and Scriver et al., eds., 2001) that synthesized findings from the relatively sparse peer-reviewed literature on medical nutrition therapy for IEM disorders and the experience of experts in these conditions. In a few cases, supplemental information was obtained from additional articles published in peer-reviewed journals.

Unlike in most reports, CHBRP did not identify specific outcome measures or make "calls" on the strength of the evidence for individual outcomes. The outcomes of primary importance vary widely across IEM disorders because the health problems associated with them differ markedly. Mortality is a common outcome across all IEM disorders but attributing differences in mortality to differences in treatment is difficult, because the health of persons with IEM disorders is very fragile. Despite treatment, many persons with IEM disorders experience repeated episodes of metabolic decompensation, especially when they contract infections or other illnesses. In addition, articles on the effects of treatment tend to focus on the results of laboratory tests for specific disorders rather than on general measures of cognitive functioning, physical functioning, or quality of life.

PubMed was searched to retrieve articles on treatment of IEM disorders published in peer-reviewed journals. The search was limited to studies of human subjects aged 0 to 23 months that were published in English. Abstracts for 370 articles were reviewed. Seventeen articles were read in their entirety and eleven were ultimately included in the literature review along with the three reference books cited previously.

[16] Scriver and colleagues' (2001) four-volume reference book contains a thorough synthesis of the literature on the causes and consequences of IEM and other metabolic disorders.

The *Medical Subject Headings* (MeSH) terms used by the librarian in the PubMed search were:

Metabolism, Inborn Errors—All the MeSH terms for all diseases in this large category
AND
(Dietary Supplements OR Parenteral Nutrition OR Infant Food OR Infant Formula OR Food, Formulated OR Nutritional Supplements)

The same terms were used as keywords to identify recently published articles to which MeSH terms have yet to be assigned.

Appendix C: Sources of Information about the Impact of Medical Nutrition Therapy on IEM Disorders

Table C-1 lists the books and journal articles on treatment of inborn errors of metabolism cited in this report along with the disorders addressed and the type of publication. Full citations can be found in the list of references at the end of the report.

Table C-1. Sources of Information on Medical Nutrition Therapy for IEM Disorders

Citation	Disorder(s) Addressed	Type of Publication
Chung, 1997	Classical galactosemia	Review article
Fernandes et al., 2006	Multiple	Reference book
Gillingham et al., 1999	Long-chain 3-hydrozyacyl-coa-dehydrogenase deficiency	Case report and report of survey findings
Gross and Acosta, 1991	Classical galactosemia	Report on basic science research
Isaacs and Zand, 2007	Multiple	Review article
Leonard, 2001	Urea cycle disorders	Review article
Nyhan et al., 2005	Multiple	Reference book
Ogier de Baulny et al., 2005	Methylmalonic acidemia and propionic acidemia	Review article and case series
Raghuveer et al., 2006	Multiple	Review article
Scriver et al., 2001	Multiple	Multi-volume reference book
Solis and Singh, 2002	Fatty acid oxidation disorders	Report of survey findings
van der Meer et al., 1994	Methylmalonic acidemia	Case series
van der Meer et al., 1996	Propionic acidemia	Case series
Yannicelli et al., 1994	Glutaric acidemia type I	Review article

Appendix D: Cost Impact Analysis: Data Sources, Caveats, and Assumptions

This appendix describes data sources, general and mandate-specific caveats and assumptions used in conducting the cost impact analysis. For additional information on the cost model and underlying methodology, please refer to the CHBRP Web site, http://www.chbrp.org/analysis_methodology/cost_impact_analysis.php.

The cost analysis in this report was prepared by the Cost Team, which consists of CHBRP task force members and staff, specifically from the University of California, Los Angeles, and Milliman Inc. (Milliman). Milliman is an actuarial firm and provides data and analyses per the provisions of CHBRP authorizing legislation.

Data Sources

In preparing cost estimates, the Cost Team relies on a variety of data sources as described below.

Private Health Insurance

1. The latest (2005) California Health Interview Survey (CHIS), which is utilized to estimate insurance coverage for California's population and distribution by payer (i.e., employment-based, privately purchased, or publicly financed). The biannual CHIS is the largest state health survey conducted in the United States, collecting information from over 40,000 households. More information on CHIS is available at www.chis.ucla.edu.
2. The latest (2006) California Employer Health Benefits Survey is utilized to estimate:
   - size of firm,
   - percentage of firms that are purchased/underwritten (versus self-insured),
   - premiums for plans regulated by the Department of Managed Health Care (DMHC) (primarily health maintenance organizations [HMOs]),
   - premiums for policies regulated by the California Department of Insurance (CDI) (primarily preferred provider organizations [PPOs]), and
   - premiums for high deductible health plans (HDHP) for the California population covered under employment-based health insurance.

   This annual survey is released by the California Health Care Foundation/Center for Studying Health System Change (CHCF/HSC) and is similar to the national employer survey released annually by the Kaiser Family Foundation and the Center for Studying Health System Change. More information on the CHCF/HSC is available at www.chcf.org/topics/healthinsurance/index.cfm?itemID=127480.
3. Milliman data sources are relied on to estimate the premium impact of mandates. Milliman's projections derive from the Milliman Health Cost Guidelines (HCGs). The HCGs are a health care pricing tool used by many of the major health plans in the United States (see www.milliman.com/tools_products/healthcare/Health_Cost_Guidelines.php).

Most of the data sources underlying the HCGs are claims databases from commercial health insurance plans. The data are supplied by health insurance companies, Blues plans, HMOs, self-funded employers, and private data vendors. The data are mostly from loosely managed healthcare plans, generally those characterized as preferred provider plans or PPOs. The HCGs currently include claims drawn from plans covering 4.6 million members. In addition to the Milliman HCGs, CHBRP's utilization and cost estimates draw on other data, including the following:

- The MEDSTAT MarketScan Database, which includes demographic information and claim detail data for approximately 13 million members of self-insured and insured group health plans.
- An annual survey of HMO and PPO pricing and claim experience; the most recent survey (2006 Group Health Insurance Survey) contains data from six major California health plans regarding their 2005 experience.
- Ingenix MDR Charge Payment System, which includes information about professional fees paid for healthcare services, based upon approximately 800 million claims from commercial insurance companies HMOs and self-insured health plans.
- These data are reviewed for generalizability by an extended group of experts within Milliman, but are not audited externally.

4. An annual survey by CHBRP of the seven largest providers of health insurance in California (Aetna, Blue Cross of California, Blue Shield of California, CIGNA, Health Net, Kaiser Foundation Health Plan, and PacifiCare) to obtain estimates of baseline enrollment by purchaser (i.e., large and small group and individual) type of plan (i.e., DMHC- or CDI-regulated), cost-sharing arrangements with enrollees and average premiums. Enrollment in these seven firms represents 82% of enrollees in full service health plans regulated by the DMHC and 46% of lives covered by comprehensive health insurance products regulated by the CDI.

Public Health Insurance

5. Premiums and enrollment in DMHC- and CDI-regulated plans by self-insured status and firm size are obtained annually from CalPERS for active state and local government public employees and their family members who receive their benefits through CalPERS. Enrollment information is provided for fully funded, Knox-Keene–licensed health care service plans, which is about 75% of CalPERS total enrollment. CalPERS self-funded plans—approximately 25% of enrollment—are not subject to state mandates. In addition, CHBRP obtains information on current scope of benefits from health plans' evidence of coverage (EOC) publicly available at www.calpers.ca.gov.
6. Enrollment in Medi-Cal Managed Care (Knox-Keene–licensed plans regulated by the DMHC) is estimated based on CHIS and data maintained by the Department of Health Services (DHS). The DHS supplies CHBRP with the statewide average premiums negotiated for the Two-Plan Model, as well as generic contracts that summarize the current scope of benefits. CHBRP assesses enrollment information online at: www.dhs.ca.gov/admin/ffdmb/mcss/RequestedData/Beneficiary%20files.htm.

7. Enrollment data for other public programs: Healthy Families, Access for Infants and Mothers (AIM), and the Major Risk Medical Insurance Program (MRMIP) are estimated based on CHIS and data maintained by the Major Risk Medical Insurance Board (MRMIB). The basic minimum scope of benefits offered by participating plans under these programs must comply with all requirements of the Knox-Keene Act, and thus these plans are affected by changes in coverage for Knox-Keene licensed plans. CHBRP does not include enrollment in the Post-MRMIB Guaranteed-Issue Coverage Products as these individuals are already included in the enrollment for individual health insurance products offered by private carriers. Enrollment figures for AIM and MRMIP are included with enrollment for Medi-Cal in presentation of premium impacts. The enrollment information is obtained online at www.mrmib.ca.gov. Average statewide premium information is provided to CHBRP by MRMIB staff.

General Caveats and Assumptions

The projected cost estimates are estimates of the costs that would result if a certain set of assumptions were exactly realized. Actual costs will differ from these estimates for a wide variety of reasons, including:

- Prevalence of mandated benefits before and after the mandate may be different from CHBRP assumptions.
- Utilization of mandated services before and after the mandate may be different from CHBRP assumptions.
- Random fluctuations in the utilization and cost of health care services may occur.

Additional assumptions that underlie the cost estimates presented in this report are:

- Cost impacts are shown only for people with insurance.
- The projections do not include people covered under self-insured employer plans because those plans are not subject to state-mandated minimum benefit requirements.
- Employers and employees will share proportionately (on a percentage basis) in premium rate increases resulting from the mandate. In other words, the distribution of premium paid by the subscriber (or employee) and the employer will be unaffected by the mandate.
- For state-sponsored programs for the uninsured, the state share will continue to be equal to the absolute dollar amount of funds dedicated to the program.
- When cost savings are estimated, they reflect savings realized for one year. Potential long-term cost savings or impacts are estimated if existing data and literature sources are available and provide adequate detail for estimating long-term impacts. For more information on CHBRP's criteria for estimating long-term impacts please see http://www.chbrp.org/analysis_methodology/cost_impact_analysis.php.

There are other variables that may affect costs, but which CHBRP did not consider in the cost projections presented in this report. Such variables include, but are not limited to:

- Population shifts by type of health insurance coverage. If a mandate increases health insurance costs, then some employer groups or individuals may elect to drop their coverage. Employers may also switch to self-funding to avoid having to comply with the mandate.
- Changes in benefit plans. To help offset the premium increase resulting from a mandate, members or insured may elect to increase their overall plan deductibles or copayments. Such changes would have a direct impact on the distribution of costs between the health plan and the insured person, and may also result in utilization reductions (i.e., high levels of patient cost sharing result in lower utilization of health care services). CHBRP did not include the effects of such potential benefit changes in its analysis.
- Adverse Selection. Theoretically, individuals or employer groups who had previously foregone insurance may now elect to enroll in an insurance plan postmandate because they perceive that it is to their economic benefit to do so.
- Health plans may react to the mandate by tightening their medical management of the mandated benefit. This would tend to dampen the CHBRP cost estimates. The dampening would be more pronounced on the plan types that previously had the least effective medical management (i.e., PPO plans).
- Variation in existing utilization and costs, and in the impact of the mandate, by geographic area and delivery system models: Even within the plan types CHBRP modeled (HMO, including HMO and POS plans; and non-HMO, including PPO and FFS policies), there are likely variations in utilization and costs by these plan types. Utilization also differs within California due to differences in the health status of the local commercial population, provider practice patterns, and the level of managed care available in each community. The average cost per service would also vary due to different underlying cost levels experienced by providers throughout California and the market dynamic in negotiations between health plans and providers. Both the baseline costs prior to the mandate and the estimated cost impact of the mandate could vary within the state due to geographic and delivery system differences. For purposes of this analysis, however, CHBRP has estimated the impact on a statewide level.

<u>Bill Analysis: Specific Caveats and Assumptions</u>

- CHBRP analysis estimates the costs associated with types of inborn errors of metabolism (IEM) currently detected by the state's newborn screening (NBS) program. The cost analysis has excluded IEM disorders that are not currently detected by the NBS program or for which medical nutrition therapy is not the recommended treatment. The NBS program is always evaluating new diseases as testing techniques and treatments become available. Therefore, the types of disorders covered may expand in the future.
- CHBRP did not use claims data to estimate utilization rates because the conditions are rare, and such estimates would not be reliable. CHBRP assumed current utilization was

consistent with recommended practices because experts indicated that caretakers universally recognize the consequences of not adhering to the diet.

- CHBRP assumes that the prevalence of non-phenylketonuria (PKU) IEMs does not vary by type of insurance.
- CHBRP carrier survey found that 94.5% of enrollees in plans subject to the mandate have prescription drug coverage. For the purpose of this analysis, CHBRP assumed all insured with prescription drug coverage received medically necessary medications through this benefit.
- CHBRP estimated the cost of nutritional supplements by computing an average annual cost per patient for those supplements deemed medically necessary for treatment. Pricing of typical dosages was obtained from the UCI metabolic center. Fatty acid supplements (such as vegetable or fish oil), vitamins and minerals were excluded from this calculation because the cost was negligible.

Table D-1. Inborn Errors of Metabolism Disorders for Which Treatment Includes an Enzyme Cofactor, Amino Acid, Fatty Acid, Vitamin, or Mineral Supplement

Disorders for Which Treatment Includes an Enzyme Cofactor (e.g., carnitine)		
Disorder	**Enzyme Cofactor**	**Prevalence**
Beta-ketothiolase deficiency	Carnitine	*
Glutaric acidemia Type I	Carnitine	6
Isovaleric acidemia	Carnitine	7
Malonic acidemia	Carnitine	*
Methylmalonic acidemia	Carnitine	10
Methylmalonic acidemia/Cobalamin C/D deficiency	Carnitine	12
Propionic acidemia	Carnitine	1
3-hydroxy-3-methylglutaryl-CoA lyase deficiency	Carnitine	*
3-methylcrotonyl-CoA carboxylyase deficiency	Carnitine	22
3-methylglutaconic aciduria, Type I	Carnitine	*
Carnitine palmitoyl transferase deficiency, Type 2	Carnitine	3
Carintine translocase deficiency	Carnitine	1
Carintine transporter deficiency	Carnitine	16
Long chain hydroxyacyl-CoA dehydrogenase deficiency	Carnitine	1
Medium chain acyl-CoA dehydrogenase deficiency	Carnitine	40
Medium/short chain L-3 hydroxy acyl-CoA dehydrogenase deficiency	Carnitine	*
Multiple acyl-CoA dehydrogenase deficiency	Carnitine	2
Short-chain acyl-CoA dehydrogenase deficiency	Carnitine	17
Very long chain acyl-CoA dehydrogenase deficiency	Carnitine	12
Total number of disorders for which carnitine is recommended		**150**
Total number all inborn errors of metabolism except PKU		**232**
Percentage disorders requiring carnitine		**65%**

Source: CHBRP analysis of California Department of Public Health, Genetic Disease Branch prevalence data of genetic disorders detected in California from 7/7/2005 to 12/31/2006.

[1] The denominator of 232 cases is the same for all three estimates. It is equal to total number of cases of protein, fatty acid, and carbohydrate disorders (256) minus PKU cases (24).

* Indicates that no cases were detected in California between 7/7/2005 and 12/31/2006.

Table D-1. Inborn Errors of Metabolism Disorders for Which Treatment Includes an Enzyme Cofactor, Amino Acid, Fatty Acid, Vitamin, or Mineral Supplement (Cont'd)

Disorders for Which Treatment Includes an Amino Acid Supplement		
Disorder	**Amino Acid(s) or Fatty Acid(s)**	**Prevalence**
Arginiosuccinic acid lyase deficiency	Arginine	2
Citrullinemia, Type I	Arginine	5
Homocitrullinuria, hyperornithinemia, hyperammmonemia	Citrulline	*
Isovaleric acidemia	Glycine	7
3-methylcrotonyl-CoA carboxylase deficiency	Glycine	22
Maple Syrup Urine Disease	Isoleucine and valine	8
Biopterin deficiency	5-hydroxytryptophan	*
Total number of disorders for which an amino acid or fatty acid supplement is recommended		**44**
Total number all inborn errors of metabolism except PKU		**232**
Percentage of disorders requiring an amino acid or fatty acid supplement		**19%**
Disorders for Which Treatment Includes a Vitamin, Mineral or Fatty Acid Supplement		
Disorder	**Vitamin(s)**	**Prevalence**
Maple Syrup Urine Disease	B-1	8
Gyrate atrophy of the choroid and retina	B-6	*
Homocystinuria	B-6 and B-9 (folic acid)	1
Biotinidase deficiency	B-7 (biotin)	1
Multiple carboxylase deficiency	B-7 (biotin)	2
3-methylcrotonyl-CoA carboxylase deficiency	B-7 (biotin)	22
Methylmalonic acidemia	B-12	10
Methylmalonic acidemia/Cobalamin C/D deficiency	B-12	12
Multiply acyl-CoA dehydrogenase deficiency	B-12	2
Arginiosuccinic acid lyase deficiency	Calcium	2
Isovaleric acidemia	Calcium	7
Classical galactosemia	Calcium	5
Long chain hydroxyacyl-CoA dehydrogenase deficiency	Essential fatty acids	1
Very long chain acyl-CoA dehydrogenase deficiency	Essential fatty acids	12
Total number of disorders for which a vitamin, mineral, or fatty acid supplement is recommended		**85**
Total number of all inborn errors of metabolism except PKU		**232**
Percentage of disorders requiring a vitamin, mineral, or fatty acid supplement		**37%**

Appendix E: Information Submitted by Outside Parties

In accordance with CHBRP policy to analyze information submitted by outside parties during the first two weeks of the CHBRP review. No information was submitted directly by interested parties for this analysis.

For information on the processes for submitting information to CHBRP for review and consideration, please visit http://www.chbrp.org/recent_requests/index.php.

Appendix F: Laws in Other States as of August 2006

Table F-1. Laws in Other States as of August 2006

State	Citation	Summary
AK	§ 21.42.380	Shall provide coverage for formulas for treatment of PKU, with same copayment and deductible as for other illness.
AZ	§§ 20-2327; 20-826; 20-1057; 20-1342; 20-1402; 20-1404	Coverage that contains a prescription drug benefit shall provide coverage for medical foods to treat inherited metabolic disorders. Cover at least 50% of the cost of medical foods. Also cover amino acid-based formula that is ordered by a physician
AR	§§ 23-79-701 to 23-79-703 § 23-79-129	A tax credit up to $2,400 per year per child for medical food, low protein food for persons afflicted with PKU and other listed metabolic diseases is allowed against the Ark. income tax. All health plans shall provide coverage for PKU, galactosemia, organic acidemias and disorders of amino acid metabolism, subject to same copay and deductible as required by health plan, for amounts paid exceeding the tax credit. Every accident and health insurance policy or health care plan shall cover newborn children and shall include tests for PKU.
CA	Ins. § 10123.89; Health & Safety § 1374.56	Policies issued by a health care service plan or an insurer must cover testing and treatment of PKU, including special food products.
CO	§ 10-16-104	Coverage for inherited enzymatic disorders, including PKU, etc. Maximum age for PKU treatment is 21; no limit for other metabolic diseases. Cover medical foods used to treat metabolic disease. May impose coinsurance and deductibles.
CT	§§ 38a-492c; 38a-518c	Individual and group health insurance policies must cover low protein modified food products, amino acid modified preparations and specialized formulas intended for the dietary treatment if administered under the direction of a physician for children up to age 8. Covered same as prescriptions.
DC	§ 31-3802.01	All group and individual health policies providing maternity and newborn care shall include metabolic newborn screening.
FL	§ 627.42395	Any health insurance policy must offer prescription and nonprescription enteral formulas for treatment of inherited diseases as specified.
IN	§§ 27-8-24.1; 27-13-7-18	Must cover medical food intended for the dietary treatment of an inherited metabolic disease or condition. Same deductibles, coinsurance amounts as apply to other coverages.
HI	§§ 431:10A-120; 432:1-609	Must cover medical foods and low-protein modified food products for the treatment of an inborn error of metabolism.
KY	§ 304.17A-139	Provide coverage for amino acid modified preparations and low-protein modified food products for the treatment of inherited metabolic diseases. May be subject to a cap of $4,000 per year for low-protein foods and a separate cap of $25,000 for medical formulas.
LA	§§ 22:215.22; 22:2004.2; 22:3018.1	Must provide coverage for low protein foods for treatment of inherited metabolic disorders. Benefit limited to $200 a month.
ME	tit 24 § 2320-D; tit. 24-A §§ 2745-d; 2837-d; 4238	Must include coverage for metabolic formula and special modified low-protein foods for inborn error of metabolism. Benefit limited to $3,000 per year.

Table F-1. Laws in Other States as of August 2006 (Cont'd**)**

State	Citation	Summary
MD	Ins. § 15-807; 19-705.5 Ins. § 15-817	Group policy shall cover medical foods prescribed by doctor for therapeutic treatment of inherited metabolic disease. Child wellness services shall include a visit for the collection of adequate samples for hereditary and metabolic newborn screening.
MA	§ 175:47C §§176A:8B; 176B:4c; 175:47I; 176A:8L; 176B:4k; 176G:4D	Coverage of newborns shall include special medical formulas necessary for treatment of PKU. Shall provide coverage for nonprescription enteral formulas for home use. Coverage for inherited diseases of amino acids and organic acids shall include food products modified to be low protein. Benefit limit not to exceed $2,500 annually.
MN	§§ 62A.26; 62E.06	Must provide dietary treatment for PKU.
MO	§ 376.1219	Shall provide coverage for formula and low protein modified food products for PKU or any inherited disease of amino and organic acids. Insured must be less than six years of age.
MT	§§ 33-22-131; 33-31-102	Mandated coverage for dietary formulas for PKU sufferers. Covers treatment of inborn errors of metabolism. Coverage must include expenses of diagnosing, monitoring and controlling the disorder.
NV	§§ 689A.0423; 689B.0353; 695B.1923; 695C.1723	Mandated coverage for enteral formulas medically necessary for treatment of inherited metabolic diseases and up to at least $2500 per year for special food products prescribed by physician.
NH	§§ 415:6-c; 415:18-e; 420-A:17; 420-B:8-ff	Provide nonprescription enteral formula for treatment of impaired absorption of nutrients.
NJ	§§ 17:48-6s; 17:48A-7q; 17:48E-35.16; 17B:26-2.1*o;* 17B:27-46.1r; 17B:27A-7.4; 17B:27A-19.6; 26:2J-4.17 §§ 17:48-62; 17:48A-7y; 17:48E-35.24; 17B:27-46.1Z; 17B:26-2.1v; 17B:27A-7; 17B:27A-19; 26:2J-4.25	Cover expense of treatment of metabolic disease, including purchase of medical foods. Specialized non-standard infant formulas for babies with multiple food protein intolerance.
NM	§§ 59A-22-41.1; 59A-46-43.2; 59A-47-38	Every individual and group policy must provide coverage for genetic inborn errors of metabolism that involve amino acid, carbohydrate and fat metabolism and for which medically standard treatments exist.
NY	Ins. Law § 3216(i)(21); 3221; 4303; 4322	Every policy that provides coverage for prescription drugs, must include cost of enteral formulas when prescribed as medically necessary for disorders that will cause the individual to become malnourished. Includes modified solid food products that are medically necessary. Benefit limit is $2,500 per 12-month period.
ND	§ 26.1-36-09.7; 54-52.1-04.11	Cover medical foods and low protein modified food products for therapeutic treatment of inherited metabolic disease.
OR	§ 743.726 (Repealed effective 7/3/2009)	Must include coverage for inborn errors of metabolism. Coverage includes diagnosis, monitoring and controlling disorders, including medical foods.
PA	§ 40-39-342	Shall provide coverage for formulas for treatment of hereditary genetic metabolic disorders.
RI	§ 27-50-10	Standard health benefit plans shall include newborn metabolic screening.
SD	§§ 58-17-62; 58-18-41; 58-38-23; 58-40-21; 58-41-98	Mandated offer of coverage for testing and treatment, including dietary management and formulas.

Table F-1. Laws in Other States as of August 2006 (Cont'd**)**

State	Citation	Summary
TN	§ 56-7-2505	Mandated coverage for dietary formulas for treatment of PKU.
TX	I.C. Sec. 1359.003	Mandated coverage for formulas necessary for treatment of PKU, same as prescription drugs.
UT	§ 31A-22-623; R590-76-4; R590-194	Must include coverage for special dietary products for those suffering from hereditary metabolic disease.
VT	tit. 8 § 4089d	Must include coverage for medical foods prescribed for medically necessary treatment for an inherited metabolic disease. Coverage for low protein modified food products must be at least $2,500 per 12-month period.
WA	§§ 48.21.300; 48.46.510; 48.44.440; 48.20.520	Shall provide coverage for formulas for treatment of PKU.

Source: Maine Bureau of Insurance, 2007.

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A group of faculty and staff undertakes most of the analysis that informs reports by the California Health Benefits Review Program (CHBRP). The CHBRP **Faculty Task Force** comprises rotating representatives from six University of California (UC) campuses and three private universities in California. In addition to these representatives, there are other ongoing contributors to CHBRP from UC. This larger group provides advice to the CHBRP staff on the overall administration of the program and conducts much of the analysis. The CHBRP **staff** coordinates the efforts of the Faculty Task Force, works with Task Force members in preparing parts of the analysis, and coordinates all external communications, including those with the California Legislature. The level of involvement of members of the CHBRP Faculty Task Force and staff varies on each report, with individual participants more closely involved in the preparation of some reports and less involved in others.

As required by the CHBRP authorizing legislation, UC contracts with a certified actuary, Milliman Inc. (Milliman), to assist in assessing the financial impact of each benefit mandate bill. Milliman also helped with the initial development of CHBRP methods for assessing that impact.

The **National Advisory Council** provides expert reviews of draft analyses and offers general guidance on the program to CHBRP staff and the Faculty Task Force. CHBRP is grateful for the valuable assistance and thoughtful critiques provided by the members of the National Advisory Council. However, the Council does not necessarily approve or disapprove of or endorse this report. CHBRP assumes full responsibility for the report and the accuracy of its contents.

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