A Study of the Health and Cost Effects of Five Dietary Supplements

Final Report

Prepared for:
Dietary Supplement Education Alliance

Prepared by:
The Lewin Group Inc.

March 29, 2005
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March 29, 2005
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I. EXECUTIVE SUMMARY

Surveys of dietary intake and physical and laboratory data reveal that the typical American diet does not always provide a sufficient level of nutrients to support optimal health. The report Nutrition and Your Health: Dietary Guidelines for Americans acknowledges that some Americans may need a vitamin and/or mineral or other supplement to meet specific nutrient needs.\(^1\)

Recent studies have also found health benefits associated with dietary supplements. For example, a Johns Hopkins study noted trauma patients who received vitamins E and C spent less time in Intensive Care Units and were “less likely to experience failure.”\(^2\) Progression of Alzheimer’s disease may be slowed by high doses of vitamins according to a Georgetown University pilot study\(^3\) with additional therapeutic trials underway. In a longitudinal study, high doses of vitamin supplements were beneficial to individuals with Age–related Macular Degeneration (AMD).\(^4\) A recent, limited Carolinas Medical Center study noted that adults with type–2 diabetes who take supplements reported fewer infections than those who did not take supplements.\(^5\)

The Lewin Group, Inc. was commissioned by the Dietary Supplement Education Alliance (DSEA) to conduct an evidence–based study of five dietary supplements that could potentially improve users’ health status. The purpose of this study was threefold: (1) to critically review the research literature for validity (closeness to the truth), impact (size of the effect), and applicability (usefulness in clinical practice), (2) to develop estimates of the potential health care expenditure savings that could result from daily use of two of the supplements, and (3) for supplements where there is emerging evidence, to suggest areas of future research that would fill existing knowledge gaps. Supplements covered in this study include (1) calcium (with Vitamin D), (2) folic acid, (3) omega–3 fatty acids, (4) glucosamine, and (5) saw palmetto.

Lewin was asked to develop estimates of the potential health care cost savings that could result from daily use of only those supplements for which the highest standard of evidence exists at this time. Cost estimates were developed for calcium (with Vitamin D) and folic acid, for which there is significant scientific agreement as to the improvement in health status and subsequent health expenditure reduction, and for which the Food and Drug Administration (FDA) has approved health claims.

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Conservative estimates of savings were developed for specific relevant outcomes: for calcium, estimates of savings for avoided hip fractures among over age-65 were developed. For folic acid, estimates of savings from avoided incidences of babies being born with neural tube defects (NTD) were developed, keeping in mind that not all NTDs are nutritionally related.

**Key Study Findings**

Supplements examined in this study are (1) calcium carbonate, (2) folic acid, (3) omega-3 fatty acids, (4) glucosamine sulfate, and (5) saw palmetto.

**Calcium:** Using a Congressional Budget Office (CBO-type) cost accounting methodology, the estimate of the five-year (2005–2009) net savings in hospital, nursing facility, and physician expenditures resulting from a reduction in the occurrence of hip fractures among the over age-65 population through daily intake of 1200 mgs of calcium with Vitamin D is $13.9 billion. Approximately 734,000 hip fractures could be avoided across the five years. Over one third of adults age-65 and over experience falls each year. Among injuries from falls, hip fractures cause the greatest number of deaths and lead to the most severe health problems. Hip fractures also tend to be the most costly because in addition to requiring an in-hospital surgical procedure to repair the hip nearly 50% of the operations result in a prolonged stay in a nursing home that can range from a few weeks to more than a hundred days or even longer. Up to 25% of community dwelling older adults who sustain hip fractures remain institutionalized for a whole year.

**Folic acid:** The total lifetime cost of a baby with the Neural Tube Defect (NTD) spina bifida in 2004 is roughly $532,000, including direct medical costs, therapies and equipment, and special education. Out of about 4 million live births annually, NTDs occur in one of every 1,000 pregnancies in the US. Of 64 million American women who are of childbearing age, if just 10.5 million additional women began taking 400 mcg of folic acid on a daily basis periconceptionally, approximately 600 babies would be born without NTDs, saving as much as $321,853,000 as a result. Over five years, taking into account the very low cost of the supplement, $1.3 billion in lifetime costs could potentially be saved. Longstanding and extensive research with supporting conclusions led the US Public Health Service, Institute of Medicine, and

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7 Office of Technology Assessment. (September, 1994). Hip Fracture Outcomes in People Age 50 and older.


Food and Drug Administration to establish recommendations and public health policies relating to folic acid intake and food fortification

- **Omega-3 fatty acids**: Recent studies have suggested that omega-3 fatty acids have beneficial effects on cardiovascular disease (CVD). CVD accounted for 38.5 percent of all deaths in the U.S. in 2001, including about 150,000 individuals who are under the age of 65. The cost of CVD in 2004 is estimated to be $368.4 billion. Although the research literature is not yet fully developed to the point that it supports the development of cost savings estimates, it contains many promising studies of varying quality concerning the health benefits of omega-3 fatty acids for a wide number of chronic conditions (e.g., depression, renal disease, rheumatoid arthritis, and asthma).

Our review found consistent evidence that omega-3 fatty acids help reduce deaths from CVD. In addition, there are studies demonstrating that omega-3 fatty acids may help lower blood pressure, may reduce the risk of re-blockage after an angioplasty, may increase exercise capacity in people with coronary atherosclerosis, and may reduce the risk associated with irregular heartbeats.

Most evidence for the health effects of omega-3 fatty acids in the general population (primary prevention studies) is from cohort studies conducted worldwide, whereas the bulk of the evidence for secondary prevention is from RCTs of limited duration. The data for secondary prevention mostly derives from one very large study; however, data on women are limited in this study. The specific effects on different CVD outcomes (especially MI and stroke) are uncertain.

In March 2004, the Agency for Healthcare Research and Quality (AHRQ) commissioned a systematic review of the literature to assess the benefits of omega-3 fatty acids on CVD outcomes. AHRQ found that studies of omega-3 fatty acids were heterogeneous in that they examined different forms of omega-3 fatty acids, including dietary and supplemental fish oil, and varying combinations of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (LNA) from plant sources. Also, studies tended to report on the different outcomes inconsistently. AHRQ concluded that focused and well–designed multicenter RCTs are now needed to validate earlier promising results and fill in any knowledge gaps. Our recommendation is to pursue these investigations in order to further advance the knowledge base concerning the health benefits of omega-3 fatty acids.

- **Glucosamine**: Glucosamine has been shown to have anti-inflammatory effects and is believed to repair and maintain cartilage. To date, however, clinical studies on

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glucosamine have not conclusively demonstrated reductions in health service utilization that result from these clinical benefits.

In order to further advance the science, the National Institutes of Health, National Center for Complimentary and Alternative Medicine (NCCAM) is now supporting two randomized double-blind studies of glucosamine. The first is the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), which is a placebo control, parallel assignment efficacy study designed to examine whether glucosamine can improve joint function and/or reduce symptoms of knee osteoarthritis. GAIT is in Phase III and is due to run another year. The other study is a pharmacokinetic study designed to examine the way glucosamine is absorbed and distributed throughout the body and is currently recruiting patients.

• **Saw Palmetto:** Preliminary findings from our review of randomized clinical trials of the effects of saw palmetto for alleviating the symptoms of benign prostatic hyperplasia (BPH) indicate that use of the herb yields slight to moderate improvement in symptoms for men with this chronic urinary syndrome. A recently released review of clinical trials of the herb also found that saw palmetto reduces the symptoms of BPH, increases urinary flow, improves the quality of life and is well tolerated, and may be considered a viable first-line therapy for treating lower urinary tract symptoms associated with BPH. Additionally, at this time there are no known safety hazards or contraindications to using saw palmetto with other medications. Currently the National Center for Complimentary and Alternative Medicine (NCCAM) is conducting a randomized, double-blind, placebo controlled clinical trial of the safety and efficacy of saw palmetto, with careful attention to the methodological deficiencies of prior studies (e.g., the influence of confounding variables on observed outcomes.)

**Conceptual Framework and Study Methods**

The Lewin Group used multiple sources of data in performing this study. An extensive English-language search of the scientific literature was conducted, using systematic review methods, on the use and clinical effects of each of the five supplements. Studies that were used for this analysis emphasize explicit and detailed documentation of methods, rationale, and assumptions. Examples of resources used include MedLine, PubMed, Institute of Medicine, and the NHS Economic Evaluation Database. Phone conversations with scientists at the Centers for Disease Control provided further background. Additionally, Web searches of relevant public agency and other organization sites (e.g., National Institutes of Health (NIH), Centers for Medicare & Medicaid Services (CMS), and Food and Drug Administration, among others) were conducted.

Structured protocols were used to locate materials and evaluate their quality, paying considerable attention to issues of both internal and external validity. We found that the research literature is variously developed for each of the supplements, ranging from a robust body of clinical trials, meta-analyses, and well controlled cohort studies.

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(as in the case of calcium and folic acid) to an emerging body of evidence of clinical trials of varying quality (as in the case of saw palmetto). In our assessment of the quality of the research and the strength of the existing evidence, the underlying criterion for use in developing a cost model was “the extent to which all aspects of the study’s design and conduct can be shown to protect against systematic bias, nonsystematic bias, and inferential error.”

We examined three types of studies: (1) studies that concerned the effect of the supplement on biological markers; (2) studies that concerned the clinical effect of either the supplement or the change in the biological markers; and (3) the potential reduction in health services utilization that might result from those clinical effects (e.g., avoided hospitalizations and/or nursing home stays, and avoided instances of birth defects). **Figure ES - 1** shows the conceptual framework for the study. In order to develop a cost estimate, sufficiently strong evidence from each type of study was needed.

![Conceptual Framework]

**Figure ES - 1
Conceptual Framework**


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**Supporting Cost Estimates**

The cost estimation methodology used for this project was initially developed by The Lewin Group Inc. for an Institute of Medicine preventive cost study performed for the
Centers for Medicare and Medicaid Services (CMS).\textsuperscript{14} We used Congressional Budget Office (CBO) “scoring” conventions as appropriate in developing cost estimates. The literature was sufficiently consistent to develop estimates of the costs and potential savings that could result from daily use of 1200 mgs of calcium among individuals over age 65 and 400 mcg of folic acid among women of childbearing age. Clinical effects for the models were (1) avoided hip fractures for calcium, and (2) avoided incidences of babies being born with NTD for folic acid.

**Calcium:** Using Congressional Budget Office (CBO) cost accounting conventions, gross and net costs to a payer were determined for a five-year period (2004 – 2008). Potential savings would be achieved through a reduction in hospitalizations and nursing facility stays for the reduced number of hip fractures (Table ES – 1).

### Table ES - 1
Costs and Potential Savings Resulting From Reduced Hip Fractures Among Adults Over Age 65

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gross Cost of Providing Daily Calcium for Adults over 65 (in millions)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cost of daily calcium for new users (adults over 65 not currently taking calcium) and current users paid for by payer over time</td>
<td>$331</td>
<td>$454</td>
<td>$564</td>
<td>$658</td>
<td>$785</td>
<td>$2791</td>
</tr>
<tr>
<td><strong>Potential Savings from Reduced Hip Fractures (in millions)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost offset due to avoided hospitalizations and SNF stays associated with reduced hip fractures for population most at risk</td>
<td>$2753</td>
<td>$2847</td>
<td>$2947</td>
<td>$3049</td>
<td>$3154</td>
<td>$14751</td>
</tr>
<tr>
<td><strong>Net Cost (Savings) of Providing Daily Calcium for Adults over 65, Before Premiums (in millions)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net cost (savings) of daily calcium for adults over 65</td>
<td>($2422)</td>
<td>($2393)</td>
<td>($2384)</td>
<td>($2391)</td>
<td>($2370)</td>
<td>($11960)</td>
</tr>
<tr>
<td><strong>Premium Offset (in millions)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premium offset (25% of additional program spending)</td>
<td>$83</td>
<td>$113</td>
<td>$141</td>
<td>$165</td>
<td>$196</td>
<td>$698</td>
</tr>
<tr>
<td><strong>Total Cost (Savings) to Payers, After Premiums (in millions)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total potential cost offset from avoided health care utilization associated with avoided hip fracture (savings)</td>
<td>($2505)</td>
<td>($2507)</td>
<td>($2525)</td>
<td>($2556)</td>
<td>($2567)</td>
<td>($12658)</td>
</tr>
</tbody>
</table>

Cost offsets result from the potential avoidance of approximately 138,000 hospitalizations for hip fractures, as well as avoided skilled nursing facility stays for some proportion of patients. The five-year estimated cost offset associated with avoided hospitalization for hip fracture is approximately $6.7 billion while the five-year estimated cost offset associated with avoided skilled nursing facility admissions associated with extended post-acute rehabilitation is approximately $8.1 billion, for a total of $14.8 billion. Thus, the total net cost or savings that would accrue to the payer would be $12.0 billion (the gross costs of $2.8 billion minus the cost offsets of $14.8

billion). Additionally, there would be a premium offset of approximately $700 million should this benefit be provided by the Medicare program, for a net effect of $12.7 billion.

**Folic acid:** Study results strongly indicate that the occurrence of neural tube defects (NTDs) is significantly reduced if women consume folic acid or a folic acid–containing supplement before they become pregnant, and continue to do so in the early stages of pregnancy. It is perhaps tragic given the strength of the scientific evidence that folic acid reduces the occurrence of birth defects (coupled with the low purchase price of the supplement) that not every woman of childbearing age is taking folic acid on a routine basis. As a public health intervention, daily intake of folic acid costs very little, and can result in very large cost savings to say nothing of emotional turmoil avoided as babies are born without NTD. Therefore, when policymakers prioritize the allocation of resources devoted to favorable health interventions; it seems that encouragement of folic acid use should be a primary public health priority (Table ES – 2).

**Table ES - 2**  
Costs and Potential Lifetime Savings Resulting From Fewer Cases of NTD

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annual Cost of Folic Acid Supplements for 10 Million New Users among Women of Childbearing Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Annual Per Person Cost of Daily Folic Acid Supplement for Women of Childbearing Age</strong></td>
<td>$6.90</td>
<td>$7.04</td>
<td>$7.22</td>
<td>$7.40</td>
<td>$7.58</td>
<td>$36.14</td>
</tr>
<tr>
<td><strong>Number of New Users of Folic Acid (in millions)</strong></td>
<td>10.5</td>
<td>10.8</td>
<td>11.0</td>
<td>11.0</td>
<td>10.9</td>
<td>54.2</td>
</tr>
<tr>
<td><strong>Gross Cost of Daily Folic Acid Supplement for New Users among Women of Childbearing Age (in millions)</strong></td>
<td>$72.3</td>
<td>$76.3</td>
<td>$79.4</td>
<td>$81.6</td>
<td>$82.6</td>
<td>$392.2</td>
</tr>
<tr>
<td><strong>Cost of NTDs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Lifetime Cost of NTD per Case (in thousands)</strong></td>
<td>$532</td>
<td>$543</td>
<td>$559</td>
<td>$573</td>
<td>$587</td>
<td></td>
</tr>
<tr>
<td><strong>Number of New Cases per Year</strong></td>
<td>4000</td>
<td>4100</td>
<td>4202</td>
<td>4308</td>
<td>4415</td>
<td>21025</td>
</tr>
<tr>
<td><strong>Annual Cost of New Cases of NTD (in billions)</strong></td>
<td>$2.13</td>
<td>$2.23</td>
<td>$2.35</td>
<td>$2.47</td>
<td>$2.59</td>
<td>$11.77</td>
</tr>
<tr>
<td><strong>Net Cost if 10 Million Women Began Taking Folic Acid (in millions)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Lifetime Savings associated with 600 Fewer NTD Cases (in millions)</strong></td>
<td>$319</td>
<td>$326</td>
<td>$335</td>
<td>$344</td>
<td>$352</td>
<td>$1677</td>
</tr>
<tr>
<td><strong>Net Cost of Providing 10 Million Women with Daily Folic Acid (savings) (in millions)</strong></td>
<td>-$247</td>
<td>-$250</td>
<td>-$256</td>
<td>-$262</td>
<td>-$270</td>
<td>-$1284</td>
</tr>
</tbody>
</table>

A 72 percent risk reduction on NTD recurrence due to periconceptional use of folic acid supplements was the outcome of a globe–spanning, multi–center–randomized trial conducted by the MRC Vitamin Study Research Group in 1991.17 One year later,

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another randomized clinical trial involving nearly 5,000 women conducted in Hungary affirmed that congenital malformations were significantly more prevalent in the group receiving the trace–element supplement than the group receiving vitamin supplements with folic acid. There were six cases in the trace supplement group compared to zero cases in the vitamin supplement group (P = 0.029). The MRC study was the catalyst for folic acid interventional trials and observational studies conducted in the United States, China, Chile, Canada, and Australia. Over the subsequent thirteen years, extensive research and similar supporting conclusions led the US Public Health Service, Institute of Medicine, and Food and Drug Administration to establish recommendations and public health policies relating to folic acid intake and food fortification. However, despite the overwhelming evidence demonstrating that NTDs could be reduced by 50 percent and national policies about the benefits of folic acid use education efforts “have not, in most cases resulted in increased supplement use.”

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II. BACKGROUND

Surveys of dietary intake reveal that the typical American diet does not always provide a sufficient level of vitamins and/or minerals. The report Nutrition and Your Health: Dietary Guidelines for Americans acknowledges that some Americans may need a vitamin and/or mineral supplement to meet specific nutrient needs.\(^{19}\)

Recent studies have also found health benefit to dietary supplements. For example, a Johns Hopkins study noted trauma patients who received vitamins E and C spent less time in Intensive Care Units and were “less likely to experience failure.”\(^{20}\) Progression of Alzheimer’s disease may be slowed by high doses of vitamins according to a Georgetown University pilot study\(^{21}\) with additional therapeutic trials underway. In a longitudinal study, high doses of vitamin supplements were beneficial to individuals with Age-related Macular Degeneration (AMD)\(^{22}\). A recent, limited Carolinas Medical Center study noted that adults with type-2 diabetes who take supplements reported fewer infections than those who did not take supplements.\(^{23}\)

As defined by Congress in the Dietary Supplement Health and Education Act (http://www.fda.gov/opacom/laws/dshea.html#sec3), which became law in 1994, a dietary supplement is a product (other than tobacco) that

- is intended to supplement the diet;
- contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents;
- is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and
- is labeled on the front panel as being a dietary supplement.

Scientists use several approaches to evaluate dietary supplements for their potential health benefits and safety risks, including their history of use and laboratory studies using cell or animal models. Studies involving people (individual case reports, observational studies, and clinical trials) can provide information that is relevant to how dietary supplements are used and demonstrate health outcomes.


\(^{22}\) Age-Related Eye Disease Study Research Group (October 2001). A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation with Vitamins C and E, Beta Carotene, and Zinc for Age-Related Macular Degeneration and Vision Loss by Age-Related Eye Disease. Archives of Ophthalmology, 119:1417–1436

III. PROJECT DESCRIPTION AND STUDY METHODS

In recent years, an important priority of the Federal Government and other health care payers and providers has been health promotion and disease prevention primarily through an evidence based approach. The Lewin Group Inc., was engaged by the Dietary Supplement Education Alliance™ to assess the potential public health impact and healthcare cost savings if selected dietary supplements were to be used by a broader proportion of the American public. The five dietary supplements considered in this report are: calcium carbonate, folic acid, omega-3 fatty acids, glucosamine sulfate, and saw palmetto.

A. Literature Review

This report provides a detailed analysis of the available research literature concerning the health effects of each of the five supplements studied. Analysts at The Lewin Group conducted extensive English-language searches on the internet and in print journals for relevant material on each supplement. Examples of resources used include MedLine, PubMed, Institute of Medicine, the Cochrane Library, the NHS Economic Evaluation Database, and National Institute of Health’s (NIH) Osteoporosis and Related Bone Disease’s National Resource Center. Telephone conversations were also conducted with researchers at NIH and with researchers at the Centers for Disease Control (CDC) in order to be sure that the latest research was identified and incorporated into the review.

Structured protocols were used to locate materials and evaluate their quality, paying considerable attention to issues of both internal and external validity. We found that the research literature is in various stages of development for each of the five supplements, ranging from a robust body of clinical trials, meta-analyses, and well controlled cohort studies (as in the case of calcium and folic acid) to an emerging body of evidence of clinical trials of varying quality (as in the case of saw palmetto). In our assessment of the quality of the research and the strength of the existing evidence, the underlying criterion for use in developing a cost model was “the extent to which all aspects of the study’s design and conduct can be shown to protect against systematic bias, nonsystematic bias, and inferential error.”

We examined three types of studies: (1) studies that concerned the effect of the supplement on biological markers; (2) studies that concerned the clinical effect of either the supplement or the change in the biological markers; and (3) the potential reduction in health services utilization that might result from those clinical effects (e.g., avoided hospitalizations and/or nursing home stays, and avoided instances of birth defects). Figure 1 shows the conceptual framework for the study. In order to develop a cost estimate, sufficiently strong evidence from each type of study was needed.

B. Cost Models:

For the supplements for which there is sufficient evidence supporting the relationship between the supplement and the biological markers, the clinical effects, and reduced healthcare utilization, we developed estimates of the costs and potential savings that could result from daily use of the supplement. Cost models were developed for calcium and for folic acid. Cost savings were derived from well documented clinical effects leading to reduced health care utilization. These were: (1) avoided hip fractures among individuals over age-65 for calcium, and (2) avoided incidences of babies being born with NTD for folic acid.

Our analytic process required estimations of both gross costs and net costs to a potential payer for the five-year period 2004 through 2008. Gross costs are the direct costs to the payer of the services, and net costs are the gross costs minus the potential cost offsets (including savings in health care expenditures and premium offsets) the payer might realize as a result of covering these services.

In the case of calcium, there is considerable evidence supporting its effect on reducing bone loss and/or osteoporosis, especially among post-menopausal women. There is also considerable evidence supporting the association of reduced bone loss and reduced fractures, with the best evidence supporting a reduction in hip fractures. Finally, there is considerable evidence supporting a reduction not only in the cost of the hospitalization to repair the hip, but also the post-acute stay for some proportion of patients in a skilled nursing facility. Our cost model is built upon the evidence found in the literature for each relationship shown in Figure 1 above.
In the case of folic acid, numerous peer-reviewed articles and research studies were found. Results of well-controlled studies provided the elements and parameters for developing a well supported cost model. The purpose of our work on folic acid was to estimate potential savings to the health care system resultant of an annual reduction in the number of neural tube defect (NTD) births, a reduction that would come from increased consumer awareness and understanding of the benefits of folic acid. Many investigators have found the strong negative relationship between folic acid and birth defects, specifically, study results indicate that the occurrence of NTDs is reduced if women consume folic acid or folic acid–containing supplement before they become pregnant, and continue to do so in the early stages of pregnancy. 25,26

Recent studies have suggested that omega–3 fatty acids have beneficial effects on cardiovascular disease (CVD).27 CVD accounted for 38.5 percent of all deaths in the U.S. in 2001, including about 150,000 individuals who are under the age of 65. The cost of CVD in 2004 is estimated to be $368.4 billion. Although the research literature is not yet fully developed to the point that it supports the development of cost savings estimates, it contains many promising studies of varying quality concerning the health benefits of omega–3 fatty acids for a wide number of chronic conditions (e.g., depression, renal disease, rheumatoid arthritis, and asthma).

Our review found consistent evidence that omega–3 fatty acids help reduce deaths from CVD. In addition, there are studies demonstrating that omega–3 fatty acids may help lower blood pressure, may reduce the risk of re–blockage after an angioplasty, may increase exercise capacity in people with coronary atherosclerosis, and may reduce the risk associated with irregular heartbeats.

Most evidence for the health effects of omega–3 fatty acids in the general population (primary prevention studies) is from cohort studies conducted worldwide, whereas the bulk of the evidence for secondary prevention is from RCTs of limited duration. The data for secondary prevention mostly derives from one very large study; however, data on women are limited in this study. The specific effects on different CVD outcomes (especially MI and stroke) are uncertain.

In March 2004, the Agency for Healthcare Research and Quality (AHRQ) commissioned a systematic review of the literature to assess the benefits of omega–3 fatty acids on CVD outcomes.28 AHRQ found that studies of omega–3 fatty acids were heterogeneous in that they examined different forms of omega–3 fatty acids, including dietary and supplemental fish oil, and varying combinations of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha–linolenic acid (LNA) from plant sources.


Also, studies tended to report on the different outcomes inconsistently. AHRQ concluded that focused and well-designed multicenter RCTs are now needed to validate earlier promising results and fill in any knowledge gaps. Our recommendation is to pursue these investigations in order to further advance the knowledge base concerning the health benefits of omega-3 fatty acids.

In the case of glucosamine sulfate and saw palmetto, the literature is not, in our view, sufficiently developed or consistent enough to estimate cost effects. In each case, there are studies that report on the relationship between the supplement and the biological marker, or the relationship between the supplement and the clinical effect (without supportive evidence of the change in the biological marker and the clinical effect) or the results of the available studies may be contradictory. Additionally, the evidence for a reduction in health care utilization is not developed. As these literatures continue to develop, we expect that these relationships will be explored more deeply.
IV. MAJOR COST FINDINGS

Conservative estimates of savings were developed for specific relevant outcomes: for calcium, estimates of savings for avoided hip fractures among over age–65 were developed. For folic acid, estimates of savings from avoided incidences of babies being born with neural tube defects (NTD) were developed, keeping in mind that not all NTDs are nutritionally related.

Calcium: Using Congressional Budget Office (CBO) cost accounting conventions, gross and net costs to a payer were determined for a five–year period (2004 – 2008). Potential savings would be achieved through a reduction in hospitalizations and nursing facility stays for the reduced number of hip fractures.

The potential five–year (2004–2008) estimated savings resulting from a reduction in the occurrence of hip fractures among the over age–65 population through daily intake of 1200 mgs of calcium is approximately $14.8 billion. The five–year estimated gross cost of providing older adults with daily calcium is approximately $2.8 billion (Table 1 and Attachment A). The gross cost is “incremental” in that coverage would initially provide additional, or “wrap around,” access to daily calcium for older adults who are not currently taking the supplement and paying for it themselves.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Costs and Potential Savings from Avoided Hip Fractures Among Older Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2004</td>
</tr>
<tr>
<td>Gross Cost of Providing Daily Calcium for Adults over 65 (in millions)</td>
<td></td>
</tr>
<tr>
<td>Total cost of daily calcium for new users (adults over 65 not currently taking calcium) and current users paid for by payer over time</td>
<td>$331</td>
</tr>
<tr>
<td>Potential Savings from Reduced Hip Fractures (in millions)</td>
<td></td>
</tr>
<tr>
<td>Cost offset due to avoided hospitalizations and SNF stays associated with reduced hip fractures for population most at risk</td>
<td>$2753</td>
</tr>
<tr>
<td>Net Cost (Savings) of Providing Daily Calcium for Adults over 65, Before Premiums (in millions)</td>
<td></td>
</tr>
<tr>
<td>Net cost (savings) of daily calcium for adults over 65</td>
<td>($2422)</td>
</tr>
<tr>
<td>Premium Offset (in millions)</td>
<td></td>
</tr>
<tr>
<td>Premium offset (25% of additional program spending)</td>
<td>$83</td>
</tr>
<tr>
<td>Total Cost (Savings) to Payers, After Premiums (in millions)</td>
<td></td>
</tr>
<tr>
<td>Total potential cost offset from avoided health care utilization associated with avoided hip fracture (savings)</td>
<td>($2505)</td>
</tr>
</tbody>
</table>

Cost offsets result from the potential avoidance of approximately 138,000 hospitalizations for hip fractures, as well as avoided skilled nursing facility stays for some proportion of patients. The five–year estimated cost offset associated with avoidable hospitalization for hip fracture is approximately $6.7 billion. The five–year estimated cost offset associated with avoidable skilled nursing facility admissions associated with extended post–acute rehabilitation is approximately $8.1 billion. Thus,
the net cost or savings that would accrue to the payer would be $12.0 billion (the gross costs of $2.8 billion minus the hospital and nursing facility cost offsets of 14.8 billion). Additionally, there would be a premium offset of approximately $700 million should this benefit be provided by the Medicare program to beneficiaries, for a net effect of $12.7 billion ($12.0B+ $.7B).

These estimates are conservative to the extent that we did not account for potential physician cost savings and savings resulting from other non-vertebral fractures, which are also discussed in the research literature. The evidence is best, however, for the effect of calcium on hip fractures.

**Folic Acid:** The total lifetime cost of a baby with Neural Tube Defect (NTD) is approximately $532,000, including direct medical costs, therapies and equipment, and special education (Table 2 and Attachment B).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Costs and Potential Savings Resulting From Fewer Cases of NTD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2004</td>
</tr>
<tr>
<td><strong>Annual Cost of Folic Acid Supplements for 10 Million New Users among Women of Childbearing Age</strong></td>
<td></td>
</tr>
<tr>
<td>Annual Per Person Cost of Daily Folic Acid Supplement for Women of Childbearing Age</td>
<td>$6.90</td>
</tr>
<tr>
<td>Number of New Users of Folic Acid (in millions)</td>
<td>10.5</td>
</tr>
<tr>
<td>Gross Cost of Daily Folic Acid Supplement for New Users among Women of Childbearing Age (in millions)</td>
<td>$72.3</td>
</tr>
<tr>
<td><strong>Cost of NTD</strong></td>
<td></td>
</tr>
<tr>
<td>Total Lifetime Cost of NTD per Case (in thousands)</td>
<td>$532</td>
</tr>
<tr>
<td>Number of New Cases per Year</td>
<td>4000</td>
</tr>
<tr>
<td>Annual Cost of New Cases of NTD (in billions)</td>
<td>$2.13</td>
</tr>
<tr>
<td><strong>Net Cost if 10 Million Women Began Taking Folic Acid</strong> (in millions)</td>
<td></td>
</tr>
<tr>
<td>Total Savings associated with 600 Fewer NTD Cases (in millions)</td>
<td>$319</td>
</tr>
<tr>
<td>Net Cost (Savings) of Providing 10 Million Women with Daily Folic Acid (in millions)</td>
<td>($247)</td>
</tr>
</tbody>
</table>

Each year about 4,000 children are born in the US with NTDs, in total there are roughly 4 million live births annually. Of the approximately 42 million American women who are of childbearing age and not taking folic acid, if just 10.5 million began taking 400 mcg of folic acid on a daily basis periconceptionally, 600 babies would be born without NTDs, saving as much as $319 million lifetime costs in the first year as a result. Over five years, taking into account the cost of the supplement, $1.3 billion could potentially be saved.

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V. SUMMARY FINDINGS FROM THE LITERATURE REVIEW

In this section, we present a review of the literature for each of the supplements. The evidence tables for each supplement are contained in the separate Appendices document.

C. Calcium

1. Summary Description of Calcium

Most people consume only 500 to 600 mg of calcium each day, less than half the recommended daily dose. Since the average American consumes less than 800 mg of calcium per day, calcium supplementation may be indicated for most adults. Adults require at least 1000 mg per day of calcium from age 19 to 50 and 1200 mg per day after the age of 50. Women who are menopausal and are not on hormone replacement therapy (HRT) require 1500 mg per day. The upper intake level is 2500 mg per day.\(^\text{31}\) (Dietary References Intakes, 1997).

2. Sources and Bioavailability

Calcium supplements are derivatives of natural products, and are often marketed as antacids. Calcium carbonate and phosphate preparations have the highest concentration of elemental calcium, about 40 percent. Calcium citrate contains 21 percent elemental calcium, with calcium lactate and gluconate containing 13 and 9 percent, respectively. A recent meta–analysis found that absorption of calcium citrate was 27 percent higher than that of calcium carbonate when taken on an empty stomach and 22 percent higher when taken with meals. It did not make a difference which preparation of calcium was taken or in which dosage.\(^\text{32}\)

Absorption of calcium at doses of 500 mg or less is increased when consumed with food. Calcium preparations must be dissolved before they can be absorbed; the absorption rate for calcium is about 20 to 30 percent. The absorption of calcium supplements differs by preparation. Foods such as spinach, rhubarb and wheat bran can decrease calcium absorption. Calcium can interfere with absorption of iron, zinc, bisphosphonates and tetracycline. Absorption also requires adequate doses of vitamin D. The recommended daily intake of vitamin D is 200 IU for adults younger than 50 years and 600 IU for those older than 70 years. Vitamin D supplementation is especially important in elderly persons because skin synthesis and absorption of vitamin D may be impaired.

In postmenopausal women with low dietary calcium intake, specially prepared 500-mg tablets of calcium citrate malate were more effective in preventing bone loss than 500-mg tablets of calcium carbonate, although the difference was not significant. In

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another study, 500 mg of calcium citrate taken with breakfast produced serum calcium levels significantly higher than those demonstrated after 500 mg of calcium carbonate.

3. **Adverse Effects**

The most common adverse effects of calcium supplements are constipation, intestinal bloating and excess gas. Adverse effects occur most frequently with calcium carbonate. Switching preparations or increasing fluid intake may relieve symptoms. Patients who form calcium–containing stones are generally advised not to take calcium supplements. However, a low intake of calcium can aggravate the risk of stone formation by increasing absorption and urinary excretion of oxalate. High calcium intakes can increase stone formation in patients with absorptive hypercalciuria. Those with renal hypercalciuria may experience increased bone loss if calcium intake is too low.

4. **Summary Literature Review: Osteoporosis**

Osteoporosis is a major public threat for more than 28 million Americans, 80 percent of whom are women. In the U.S. today, 10 million individuals already have the disease and 18 million more have low bone mass, placing them at increased risk for osteoporosis. Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures of the hip, spine and wrist.

5. **Definition of Osteoporosis**

Reviews of the literature show an almost uniform definition of osteoporosis. The accepted definition is the WHO standard of a Bone Mineral Density (BMD) of at least 2.5 standard deviations below the mean BMD for a person of the same sex between the ages of 20 and 29.

6. **Prevalence**

Because Osteoporosis is a “silent” disease – meaning that it has few if any symptoms until one suffers a fracture – it is difficult to ascertain with certainty its prevalence. The Osteoporosis and Related Bone Disease’s National Resource Center states that there are approximately 10 million Americans who currently have Osteoporosis, with 80% of the sufferers being women. The center also notes that an additional 34 million Americans have low bone mass putting them at risk of getting the disease.  

A 1998 Mayo Clinic study examined the prevalence of osteoporosis in both men and women and concluded that utilizing the WHO standard of Osteoporosis, the age-adjusted prevalence of Osteoporosis in women 50 years and older was 35% and the prevalence of Osteoporosis in men 50 years and older was 19%.

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7. **Consequences/Impact**

The National Center for Injury Prevention and Control states that one-third of adults aged 65 and over fall each year, with 20–30% suffering moderate to severe injuries, such as hip fractures.\(^{35}\) Although there is a wealth of research that examines the increased risk of fracture as a result of decreasing BMD, this literature review did not focus on the biological marker of increased BMD, because it is impossible to know the BMD of various segments of the Medicare population for the cost model. Instead, this analysis examines the prevalence of osteoporosis in an aged population, and then examines the prevalence and consequence of reduced hip fractures within this subset of the population.

8. **Costs**

Costs associated with osteoporosis are almost entirely related to fractures. Although researchers studying the disease have examined vertebral fractures as well as non-vertebral fractures, they most often focus on hip fractures because they are the most serious and lead to the greatest number of health problems and deaths. Hip fractures also tend to be the most costly because in addition to requiring an in-hospital surgical procedure to repair the hip nearly 50% of the operations result in a prolonged stay in a nursing home that can range from a few weeks to more than a hundred days or even longer.\(^{36}\) Up to 25% of community dwelling older adults who sustain hip fractures remain institutionalized for a whole year.\(^{37}\)

9. **Prevention**

Although a diet high in calcium is enough to create strong bones in children it does not appear to be sufficient to treat or reduce the risk of Osteoporosis in the later years of life. In a study by Feskanich\(^{38}\) in 1997 and another by Cummings\(^{39}\) in the same year the results showed that diets high in calcium were not sufficient to stem the risk of osteoporotic fracture. Supplements, taken at sufficient levels, however, have been shown to decrease the relative risk of osteoporotic fractures.

10. **Supplements**

The literature contains numerous recent studies examining the impact of calcium and vitamin D supplements. The majority of the studies look at the impact of both calcium

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\(^{36}\) Office of Technology Assessment. (September, 1994). Hip Fracture Outcomes in People Age 50 and older


and vitamin D supplements taken together, although there are some that examine the impact of each supplement separately.

Results from studies examining the impact of only vitamin D supplements on the fractures are mixed. While Trivedi\(^{40}\) showed in a 2003 study that large doses of vitamin D supplements given every four months for four or five years in fact reduced incidence of hip fracture in a British nursing home population, both Lips\(^{41}\) and Meyer\(^{42}\) in 1996 and 2002 show that vitamin D in varying doses over the course of two to three years does not have any impact on the incidence of hip fractures in nursing home populations. What the literature seems to be fairly certain of with regard to vitamin D is that the elderly are deficient. Previous research has shown independent elderly to be between 5 and 25 percent deficient, while those in facilities are between 48 and 80 percent deficient in vitamin D. It is widely held that vitamin D plays a critical role in the absorption of calcium.

There are numerous well-controlled studies that show that a sustained regimen of both calcium and vitamin D supplements does indeed reduce the relative risk of osteoporotic fracture.\(^{43}\) These studies date back to the 1980s\(^{44}\) and have been conducted throughout the United States and Europe.\(^{45}\) An 18 year prospective analysis by Feskanich, Willett, and Colditz\(^{46}\) found that an adequate consumption of vitamin D was associated with a reduced risk of osteoporotic hip fracture, while a high calcium diet was not associated with a reduction in hip fracture. The two most comprehensive and most often cited are those by Chapuy\(^{47}\) in France and Dawson–Hughes\(^{48}\) in the


United States. Both of these randomized controlled studies covered three years and showed both increases in bone density and decreased relative risk of fracture. Dosages of supplement however differed. While Chapuy used a regimen of 1200 mg of calcium and 800 IU of Vitamin D daily, Dawson–Hughes used 500 mg of calcium and 700 IU of Vitamin D daily. The Dawson Hughes study (using a 65+ population that mirrors Medicare beneficiaries) also noted that bone densities increased for the first year of the regimen and then remained constant for the next two years, implying that relative risk reduction was achieved in one year rather than three.

In a meta analysis and economic evaluation conducted by Bendich\textsuperscript{49} in 1999, both the Chapuy and Dawson–Hughes studies were pooled with a third study based in New Zealand to arrive at a pooled relative risk for hip fractures of the impact of calcium and vitamin D3 supplements over a 34 month period of 0.53.

In the case of calcium, there is considerable evidence supporting its effect on reducing bone loss and/or osteoporosis among post–menopausal women, especially when taken with vitamin D. There is also considerable evidence supporting the association of reduced bone loss and reduced fractures, with the best evidence supporting a reduction in hip fractures. Finally, there is considerable evidence supporting a reduction not only in the cost of the hospitalization to repair the hip, but also the post–acute stay for some proportion of patients in a skilled nursing facility. Our cost model is built upon the evidence found in the literature for each association.

D. Folic Acid

11. Summary Description of Folic Acid

Derived from the Latin word folium, meaning leaf, folate is a natural compound of the water-soluble vitamin B-complex group. Dark leafy greens, liver, dried beans, peanuts, and oranges all are rich in folate. Folic acid however, less commonly known as pteroylmonoglutamic acid, is a synthetic compound used to make dietary supplements and fortify cereal and grain products. According to the Institute of Medicine, the human body absorbs and metabolizes folic acid in supplement form and as fortified food products with greater bioavailability than naturally occurring folate. Although both folate and folic acid have the same biological function, only about 50 percent of the folate derived directly from food is absorbed as compared to 100 percent of the folic acid found in supplements.\textsuperscript{50}

A Policy Statement issued by the American Academy of Pediatrics states that the average diet in the United States contains only 200 mcg of folate. However, even as the grain products sold in this country are fortified with folate the rate of neural tube defect (NTD) occurrences has not decreased as dramatically as originally projected


most likely because dietary folate is not well absorbed.\(^{51}\)

When taken daily for at least one month before conception, research indicates that 400 mcg of a folic acid supplement or multivitamin taken daily is the most effective and reliable method to reducing the probability of NTDs. Fifty-one percent of the women in cross-sectional study conducted by Elkin & Higham in 2000 had complicated obstetrics histories and took folic acid supplements for the duration of the study. \(^{53}\) Results revealed that blood serum folate levels were lower when women relied on dietary intake for their daily folate in comparison to more elevated levels in the blood serum of women who took daily supplements of folic acid.

Not only was dietary alteration highly unlikely, but typically ineffective as well. \(^{52},^{53}\) Evidence suggests dietary folic acid supplements are a consistent and reliable way for a woman to reduce the chance her baby will be affected by an NTD. Periconceptual folic acid supplementation is especially important for women who are at higher risk, including those who have had one pregnancy affected by NTD, conditions of epilepsy, diabetes, and perhaps, obesity are at a greater risk for having a child born with a neural tube defect.

12. Summary Literature Review: Neural Tube Defects

Objective Sixteen of the Department of Health and Human Services (DHHS) Healthy People 2010 program is to “Reduce the occurrence of spina bifida and other neural tube defects (NTDs)” and “Increase the proportion of pregnancies begun with an optimum folic acid level.”\(^{54}\) More than 4,000 babies with neural tube defects, such as spina bifida and anencephaly, are born annually in the United States. An article published in the Centers for Disease Control Morbidity and Mortality Weekly Report identifies spina bifida as third on the list of birth defects with the highest total lifetime costs. \(^{55},^{56}\) Propitiously, there is strong research-based evidence to indicate that the


occurrence of NTDs is significantly decreased if periconceptional women consume folic acid, and continue to do so in the early stages of pregnancy.\textsuperscript{57, 58}

A mere 28 days after conception, when many women are not yet even aware that they are pregnant, a neural tube defect (NTD) may already have affected the fetus. It is imperative that females take precautions to protect their unborn children against potential birth defects before becoming pregnant. Researchers at the Institute of Medicine estimate the proportion of unplanned pregnancies in the United States may be as high as 60 percent, which lends credibility to the idea of defensive measures such as taking a dietary supplement or multivitamin infused with the B\textsuperscript{-}vitamin folic acid on a daily basis.\textsuperscript{59} It is unclear at this time just how folic acid's cell growth stimulating mechanism biologically prevents NTDs, but its benefit has been shown to be significant. Studies show evidence that folic acid is a necessary component to produce new DNA as cells multiply and aid in the growth of red blood cells. As a result of the 1998 Food and Drug Administration mandate that manufacturers fortify cereal, pasta, and grains with folic acid, the number of babies born with NTDs in the United States decreased by 26 percent.\textsuperscript{60}

\textbf{13. Definition of Neural Tube Defect}

Neural tube defects affect 4,000 babies born in the United States alone every year. Inadequate closure of the embryonic neural tube is a birth defect known as spina bifida. Anencephaly is a lethal malformation characterized by the absence of the cranial vault and cerebral hemispheres. The third NTD that occurs in the US is encephalocele, a defect in the skull that results in herniation of the meninges and brain tissue.\textsuperscript{61} When the neural tube, which later develops into the child’s brain, spine, and central nervous system, is defective, the result can be medically devastating.\textsuperscript{62} Portions of the brain and spinal cord may not be connected to designate nerves, and in most spina bifida occurrences, an Arnold–Chiari malformation (blockage of the normal


flow of cerebrospinal fluid) causes hydrocephalus. 63 Mid-level defects in the spinal cord will affect movement in the arms and legs and often result in paralysis. If the defect is situated further down the spinal cord, the bowel, bladder or sexual organs will be impacted. 64 It is estimated that while 41 percent of children born with spina bifida survive through adulthood, irreversible complications from the birth defect such as paralysis and incontinence will require varying intensities of care from infancy throughout their adult lives. Babies born with anencephaly (24 percent of all NTD babies), do not have a very good prognosis. Most of such babies are stillborn and the others will survive only a few days in the neonatal intensive care unit after birth. 65

14. Prevalence

On average, every day eleven pregnancies are affected, translating to about one out of every 1,000 newborns in the US. If one child is born with a NTD, a mother has a 2 to 3 percent risk of having another child or fetus with a NTD.62 Surprisingly however, 95 percent of neural tube defects occur in women with no family history of NTDs. 66

Racial and geographic data show that NTDs occur more often in the pregnancies of white women as compared to black women, and among Hispanic women more frequently than non–Hispanic females. The incidence of babies born with NTDs is higher in the eastern United States as compared to the western part of the country, perhaps due in part to hard-to-reach subpopulations in locations such as Appalachia.

The premise is further investigated in a 2002 Morbidity and Mortality Weekly Report article while data from a study of approximately 1,060 women who attended six family planning clinics in Georgia between 2000 and 2001 suggest that certain women are at higher risk for having inadequate folate intake. 67 According to the report, the at–risk population is comprised of women who are black, smokers, and Depo–Provera® users. Although these results cannot rigorously be applied to reflect at–risk groups, this study nonetheless illustrates that there are methods for identifying subgroups that would benefit from public awareness campaigns. Once the groups are discerned, educational material and programs can be “custom–tailored” for each distinct audience.

Outreach programs in West Virginia and South Carolina have taken advantage of their geographic location to focus on certain groups of residents. For example, the Appalachian Regional Commission works with state and local health officials on a


variety of initiatives to better serve one of the poorest counties in McDowell County, West Virginia. The folic acid education program has dispensed thousands of bottles of multivitamins with folic acid to women of childbearing age in the interest of decreasing the number of babies born with neural tube defects.  

Women’s diets have improved with respect to folic acid consumption through the fortification of bread and cereal. It also seems that women are increasingly aware of the association between inadequate folate status and NTD risk. In spite of public health educational strategies to develop widespread awareness of the importance of folate, increases in the use of dietary supplements have not kept pace. Statistics released by the Census Bureau for 2000 indicate that currently, approximately 63 million American women are in their reproductive years, or between the ages of fifteen and 45. A Gallup Poll sponsored by the March of Dimes in 2002 found the percentage of women who were aware of folic acid increased to 75 percent from 52 percent in 1995, but the proportion of women actually consuming folic acid only increased from 25 percent to 34 percent over those same five years.

**15. Consequences/Impact:**

The 20 to 30 percent decline in NTD rates attributable to the 1998 mandate of folic acid fortification of cereal and grains falls far short of the 1992 United States Public Health Service anticipated 50 to 70 percent decrease. If the HealthyPeople 2010 goal of 50 percent reduction in NTDs is to be achieved, specific intervention beyond what is being done currently must be initiated. Because no contraceptives on the market are 100 percent effective -- the Institute of Medicine’s researchers estimate that the proportion of unplanned pregnancies in the United States may be as high as 60 percent -- it is imperative that simple preventive measures against NTDs be undertaken by all women of childbearing age. Consumption of a 400 mcg of a dietary supplement or multivitamin infused with the B-vitamin folic acid on a daily basis, built up in a female’s body for at least a month before a planned or unplanned conception, may have life-saving benefits for the fetus. Projections indicate that the number of pregnancies affected by NTDs could decline by 50 to 70 percent if the mother has a sufficient concentration of blood folate in her blood periconceptionally.

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16. Costs:

The one and five year cost of intervention and the subsequent expected results are shown in Table 3. Annual net cost per person is the adjusted weighted average cost for a year’s supply of folic acid supplement, and lifetime expected cost per case represents direct medical costs, costs associated with therapies, and costs associated with special education. The cost of daily folic acid supplementation is considerably smaller than the cost of caring for a child with a neural tube defect.

Table 3
Annual Cost of Folic Acid Supplement vs. Lifetime Cost of Spina Bifida

<table>
<thead>
<tr>
<th>Annual Cost Per Person for Folic Acid Supplements (in dollars)</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual net cost of daily folic acid supplement for a woman of childbearing age</td>
<td>$6.90</td>
<td>$7.00</td>
<td>$7.20</td>
<td>$7.40</td>
<td>$7.60</td>
<td>$36.00</td>
</tr>
<tr>
<td>Lifetime Cost per Case of Spina Bifida (in thousands)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Lifetime Cost of Spina Bifida per Case</td>
<td>$532</td>
<td>$543</td>
<td>$559</td>
<td>$573</td>
<td>$587</td>
<td></td>
</tr>
</tbody>
</table>

17. Prevention

Consumption of folic acid regularly prior to, and for the first six weeks after conception has been demonstrated to protect against NTD incidences in newborns. This report and cost-benefit analysis suggests that the potential savings -- medical, physical, psychological, and emotional -- associated with increased folic acid consumption may be far greater than previously thought.

Targeted intervention by dissemination of information through public awareness campaigns, coupled with an increase in the number of women between the ages of fifteen and 45 taking a folic acid supplement could produce startling results; most directly a significant decrease in the number of babies born suffering from neural tube defects. Unpublished data from a 2002 Porter Novelli International survey reports that 88 percent of female participants indicated that they would take a folic acid supplement if their physician recommended it; only 37 percent of the women’s physicians actually recommended supplemental folic acid during their pregnancy.

18. Supplement Dose Levels

To date, there is insufficient long-term research to conclusively define the maximum safe dose of folic acid for the public. As a precaution, in 1992 the Centers for Disease Control set the maximum intake at 1,000 mcg (1 milligram) per day, unless under the supervision of a physician. Typically, folic acid has few, or no side effects when ingested as directed. Though rare, a reaction may occur in a few of the people taking the supplement. Signs would likely include fever, general discomfort, and shortness of breath or trouble breathing, reddened or itchy skin, wheezing, or a tight feeling in the chest. Though folic acid has no known toxicity, very high doses (more than 1,000

mcg daily) may mask symptoms of vitamin B\textsubscript{12} deficiency, also known as pernicious anemia, which in turn may delay proper diagnosis. Pernicious anemia most commonly afflicts women over the age of 50; the probability of the condition among women of childbearing age is rather low.\textsuperscript{52}

E. Omega-3 Fatty Acids

19. Summary Description of Omega-3 fatty acids

Omega-3 fatty acids are essential fatty acids, which are critical for proper physiological functioning, but cannot be synthesized by the body. There are three major types of omega-3 fatty acids: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). The major source of omega-3 fatty acids is dietary intake of fish (e.g., salmon, tuna, trout or sardines), fish oil and dietary supplements. While other sources of alpha-linolenic acid include non-hydrogenated canola oil, ground flaxseed and walnuts, these plant foods and vegetable oils lack EPA and DHA but do contain omega-6 fatty acids.

20. Health Benefits:

ALA from fish sources, fish oils and dietary supplements is converted to EPA and DHA by the body. DHA is highly concentrated in the brain and retina, which is important for cognitive and behavioral functioning. Enhancing synaptic functioning of the brain, DHA facilitates neuron communication by allowing signals to cross the gap between brain cells. EPA aids in the production of eicosanoids, which improve blood flow throughout the body. Moreover, EPA helps to thin the blood, preventing blood clotting, which in turn reduces inflammation.

Certain physiological functions have been linked to omega-3 fatty acids, including promoting fluidity of cell membranes for increased communication between cells, cell growth and membrane construction, diminished blood clotting, relaxation and contraction of muscles, and regulation and secretion of enzymes and hormones. Several studies have explored the role of omega-3 fatty acids in the prevention or treatment of particular health conditions, such as diabetes mellitus, renal disease, osteoporosis, gastrointestinal diseases, and asthma. Recent studies suggest that omega-3 fatty acids show favorable effects toward moderate improvement of some symptoms related to cardiovascular disease (CVD) and moderate improvement for psychiatric disorders such as depression. This report will focus on the clinical evidence that omega-3 fatty acids 1.) contribute to improved symptoms for patients with CVD and 2.) improve symptoms associated with major depressive disorder.

Omega-3 Fatty Acids and Cardiovascular Disease

21. Definition of Cardiovascular Disease

The term cardiovascular disease refers to diseases of the heart and/or blood vessels. Problems develop over time in the heart and blood vessels as they become clogged from a buildup of cells, fat and cholesterol. Blood clots cause heart attack and stroke. Preventing platelets from clotting can therefore prevent heart attacks and strokes. Heart disease and stroke are the principal components of CVD. Respectively, heart
disease and stroke are the first and third leading causes of death in the U.S. Other common types of CVD are hypertension (high blood pressure) and heart failure.

22. Prevalence of Cardiovascular Disease

The American Heart Association, using data from NHANES, estimates that about 64.4 million Americans, or 22.6 percent of the U.S. population, had some form of CVD in 2001. Almost 40 percent of these individuals are elderly (aged 65+ or older). Other notable statistics include:

• 50 million individuals have high blood pressure (defined as having systolic pressure above 140 mm and/or diastolic pressure above 90 mm or taking antihypertensive medication).

• 13.2 million individuals have coronary heart disease (including myocardial infarction and chest pain).

• 5 million individuals have had congestive heart failure.

• 4.8 million individuals have had a stroke.

• Cardiovascular disease affects as many women as men. About 1 in 5 men and women have some form CVD. In addition, CVD disproportionately affects the African-American population.

23. Consequences and Impact of Cardiovascular Disease

Cardiovascular disease accounted for 38.5 percent of all deaths in the U.S. About 150,000 individuals are under the age of 65 when they are killed by CVD. Declines in death rates due to CVD are responsible for the increase in the overall life expectancy in the U.S. Furthermore, if all major forms of CVD were eliminated, the life expectancy would rise by 7 years, from 77.2 years to 84.2 years.

24. Costs Associated with Cardiovascular Disease

The costs associated with CVD increase as the U.S. population ages. It is estimated that the cost of heart disease and stroke is $368.4 billion, with $226.7 billion for direct expenses in health care expenditures and $141.7 billion in indirect costs including lost productivity due to disability and mortality in 2004.

25. Treatment of Cardiovascular Disease

The conventional treatment for CVD has included pharmacological solutions to the underlying causes of the disease. Over-the-counter and prescription drugs have been used to treat CVD:


75 ibid.

76 ibid.
• **Aspirin.** Aspirin prevents blood clots. Preventing blood clots lowers the risk for heart attacks and recurrent strokes.

• **ACE (angiotensin converting enzyme) Inhibitors.** ACE inhibitors assist in neutralizing the production of a chemical that narrows the blood vessels. It is used to help control high blood pressure.

• **Beta blockers.** Beta blockers slow down the heart, preventing over-exertion of the heart. Beta blockers are used to control high blood pressure, chest pain, arrhythmias, and to prevent repeat heart attacks.

• **Calcium channel blockers.** Calcium channel blockers help to relax the blood vessels in an effort to alleviate high blood pressure and chest pain.

Surgical treatments may be recommended for severe cases of CVD. Treatments often include angioplasty, heart bypass surgery, valve replacement, pacemaker installation, and heart transplants.

Dietary and lifestyle changes are also recommended to decrease CVD. For example, high dietary intake of salt is linked with increased incidence of CVD incidence and death among overweight individuals. In addition, a diet rich in carotenoids and fruits and vegetables has been shown to be protective against heart disease. In term of lifestyle changes, eliminating smoking and reducing exposure to second-hand smoke decrease CVD risk. Moderate exercise also has cardio-protective effects.

### 26. Omega-3 Fatty Acids in the Treatment of Cardiovascular Disease

Currently, there is keen interest in the role of omega-3 fatty acids, particularly EPA and DHA in the prevention and management of CVD. Population-based studies have showed a relationship between the increased consumption of fish (which is rich in omega-3 fatty acids) and decreased mortality due to CVD events.

While there is on-going research, increased consumption of omega-3 fatty acids has been associated with decrease the risk of CVD by:

- Reducing arrhythmias which can lead to sudden cardiac death
- Decreasing risk of blood clots which can lead to heart attack or stroke
- Lowering serum triglyceride levels
- Slowing the growth of atherosclerotic plaque
- Improving the function of the vascular endothelial (the single cell layer that lines the inner surface of the blood vessels)
- Lowering of blood pressure
- Decreasing inflammation
The largest controlled trial of omega-3 fatty acid supplement with over 11,000 randomized patients was conducted by Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-Prevenzione. Patients with heart disease received omega-3 fatty acid supplements (850 mg per day of EPA and DHA) for 3.5 years. The study found that patients who took the omega-3 fatty acid supplement had a risk of sudden death that was 45 percent lower than those who did not consume supplemental omega-3 fatty acid. Furthermore, patients who took the supplement had a 20 percent lower risk of death from all-causes mortality.  

Results from a trial conducted by Singh showed that patients admitted to the hospital with an acute myocardial infarction were randomized to receive three different conditions: 1) capsules containing fish oil (1.8 g per day of EPA and DHA); 2) mustard oil (2.9 g per day of ALA); or 3) a placebo. After one year, total cardiac events (including non-fatal myocardial infarction) were significantly lower in the groups that received the fish oil or mustard oil compared to groups receiving the placebo.

A review of current studies conducted by Holub highlights the various biological markers of CVD that have been shown to be affected by the increased consumption of omega-3 fatty acids. Specifically, fatty acid analysis of serum and plasma phospholipids indicated that DHA levels are inversely related to coronary heart disease in men. Holub’s research focuses attention on the cardioprotective effects of EPA and DHA. He lists these cardioprotective mechanisms as:

- Reduction in malignant ventricular
- Increase in heart rate variability
- Antithrombotic effects and other effects on the hemostatic system
- Lipid lowering
- Improved endothelial relaxation
- Inhibitory effect on atherosclerosis and inflammation, and
- Suppressed production of inflammatory cytokines.

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81 Holub (2002), op. cit.
In March 2004, the Agency for Healthcare Research and Quality commissioned a systematic review of the literature to assess the benefits of omega-3 fatty acids on CVD outcomes.\(^{82}\) This review found that omega-3 fatty acids may help reduce deaths from heart disease. In addition, omega-3 fatty acids may help lower blood pressure slightly, may reduce the risk of re-blockage after an angioplasty, and may reduce the risk associated with irregular heartbeats. However, most studies to date have heterogeneous results and have not been long enough in duration to remark on sustained outcomes. The evidence table below (Table 4) delineates results found by AHRQ.

**27. Omega-3 Fatty Acids and Selected Health Conditions**

There have been numerous studies of varying quality of omega-3 fatty acids and various health conditions. The Table 5 illustrates the potential benefits of omega-3 fatty acids for selected health conditions and provides an assessment of the clinical evidence as to omega-3 fatty acids role in preventing and/or modulating these conditions.

While AHRQ’s systematic review of available literature found some evidence that increased consumption of omega-3 fatty acids may reduce some risk factors associated with cardiovascular disease, the evidence is not consistent across studies and thus does not lend itself to cost saving analysis at this time. AHRQ will continue to explore the evidence of the effects of omega-3 fatty acids on cardiovascular risk factors and other diseases factors that show promising results from omega-3 consumption. A cost savings analysis may be possible once AHRQ has released the results of their continued studies.

### Table 4
Omega-3 Fatty Acid Effects on CVD Risk Factors, a Meta-Analysis Summary

<table>
<thead>
<tr>
<th>CVD Risk Factor</th>
<th>Biological Marker</th>
<th>Studies Reviewed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Lipids</td>
<td>total cholesterol</td>
<td>23</td>
<td>Heterogeneous results with small, non-significant net increases in both HDL and LDL. No differences in effect by population except higher net increases in subjects on a higher fat diet than those on a lower fat diet.</td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>19</td>
<td>Heterogeneous results with small, non-significant net increases in both HDL and LDL. One study reported a steady increase in HDL levels over time (from 6 wks to 12 mos) with fish oil.</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study Count</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>15</td>
<td>Fairly uniformly found small net increases in LDL level. Strongest evidence across serum lipids. Net decrease of 10-33%, dose-dependent and consistent across subjects (healthy, with CVD, at risk of CVD, with dyslipidemia). Results were generally greater in those studies with higher mean baseline triglyceride levels. Duration of intervention is unclear and no data regarding sustained effect.</td>
</tr>
<tr>
<td>Tg</td>
<td>19</td>
<td>No consistent effect across 14 randomized studies of Lp(a) however one study reported a small but significant effect in subjects with elevated Lp(a). Of 27 randomized studies, no effect or a net decrease in level of apo AI with n-3 fatty acids. Of the 25 randomized studies with at least 20 subjects there was little consistency of effect through consumption of omega-3 fatty acid. Small net decreases resulted from consumption of omega-3 fatty acids.</td>
</tr>
<tr>
<td>LP(a)</td>
<td>23</td>
<td>Large, significant net increases were found. Small but significant reduction in systolic and diastolic blood pressure of about 2 mm Hg when fish oils were consumed. The effect was stronger in older and hypertensive subjects. Similar results were found in six randomized studies of diabetics. Overall there was no consistent effect of omega-3 fatty acids on glucose tolerance from 18 randomized trials of 10 or more subjects. A wide range of heterogeneous effects were noted regardless of the makeup of the study population, the range of effect was widest among the diabetic population.</td>
</tr>
<tr>
<td>apo AI</td>
<td>61</td>
<td>No consistent effect across 14 randomized studies of Lp(a) however one study reported a small but significant effect in subjects with elevated Lp(a). Of 27 randomized studies, no effect or a net decrease in level of apo AI with n-3 fatty acids. Of the 25 randomized studies with at least 20 subjects there was little consistency of effect through consumption of omega-3 fatty acid. Small net decreases resulted from consumption of omega-3 fatty acids.</td>
</tr>
<tr>
<td>apo B</td>
<td>52</td>
<td>No consistent effect across 14 randomized studies of Lp(a) however one study reported a small but significant effect in subjects with elevated Lp(a). Of 27 randomized studies, no effect or a net decrease in level of apo AI with n-3 fatty acids. Of the 25 randomized studies with at least 20 subjects there was little consistency of effect through consumption of omega-3 fatty acid. Small net decreases resulted from consumption of omega-3 fatty acids.</td>
</tr>
<tr>
<td>total apo B-100</td>
<td>4</td>
<td>No consistent effect across 14 randomized studies of Lp(a) however one study reported a small but significant effect in subjects with elevated Lp(a). Of 27 randomized studies, no effect or a net decrease in level of apo AI with n-3 fatty acids. Of the 25 randomized studies with at least 20 subjects there was little consistency of effect through consumption of omega-3 fatty acid. Small net decreases resulted from consumption of omega-3 fatty acids.</td>
</tr>
<tr>
<td>LDL apo B</td>
<td>6</td>
<td>No consistent effect across 14 randomized studies of Lp(a) however one study reported a small but significant effect in subjects with elevated Lp(a). Of 27 randomized studies, no effect or a net decrease in level of apo AI with n-3 fatty acids. Of the 25 randomized studies with at least 20 subjects there was little consistency of effect through consumption of omega-3 fatty acid. Small net decreases resulted from consumption of omega-3 fatty acids.</td>
</tr>
<tr>
<td>Systolic and</td>
<td>1</td>
<td>Small but significant reduction in systolic and diastolic blood pressure of about 2 mm Hg when fish oils were consumed. The effect was stronger in older and hypertensive subjects. Similar results were found in six randomized studies of diabetics. Overall there was no consistent effect of omega-3 fatty acids on glucose tolerance from 18 randomized trials of 10 or more subjects. A wide range of heterogeneous effects were noted regardless of the makeup of the study population, the range of effect was widest among the diabetic population.</td>
</tr>
<tr>
<td>diastolic blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose Tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes or insulin resistance</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Fasting blood sugar (FSB)</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>
Table 4 (continued)
Omega-3 Fatty Acid Effects on CVD Risk Factors, a Meta-Analysis Summary

<table>
<thead>
<tr>
<th>CVD Risk Factor</th>
<th>Biological Marker</th>
<th>Studies Reviewed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>Elevated levels of CRP</td>
<td>5</td>
<td>CRP is an acute phase reactant indicative of overall state of activation of the inflammatory system. No effect with fish oil supplementation was reported.</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Fibrinogen (liver protein)</td>
<td>59</td>
<td>Of 24 randomized studies of the assessment of clotting potential no consistent effect was found for trials of consumption of omega-3 fatty acids.</td>
</tr>
<tr>
<td>Factor VII</td>
<td></td>
<td>19</td>
<td>No consistent effect was found</td>
</tr>
<tr>
<td>Factor VIII</td>
<td></td>
<td>5</td>
<td>No consistent effect was found</td>
</tr>
<tr>
<td>vWF</td>
<td></td>
<td>9</td>
<td>Found a small, non-significant decrease in level of vWF with consumption of omega-3 fatty acids. Findings of 11 randomized trials with at least 15 subjects were heterogeneous depending on the aggregating agent, dose and measurement metric used. Most studies found no effect resulting from the intake of omega-3 fatty acids.</td>
</tr>
<tr>
<td>platelet aggregation</td>
<td></td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Coronary Artery Restenosis</td>
<td>Restenosis rates after coronary angioplasty</td>
<td>17</td>
<td>Findings of 12 randomized trials were heterogeneous across all studies with an overall trend toward net reduction in relative risk of 14% with fish oil intake. Findings were no different for males and females.</td>
</tr>
<tr>
<td>Carotid Artery Intima-Media Thickness</td>
<td>IMT</td>
<td>4</td>
<td>A random trial found no effect. Two cross-sectional studies found omega-3 to be correlated with thinner IMT. A cohort study of plant oil was inconclusive.</td>
</tr>
<tr>
<td>Exercise Tolerance Testing</td>
<td>Exercise capacity</td>
<td>6</td>
<td>Fish oil consumption may have a small benefit for exercise capacity for patients with coronary artery disease.</td>
</tr>
<tr>
<td>Heart Rate Variability</td>
<td>Heart rate variability</td>
<td>2</td>
<td>Consumption of omega-3 fatty acids may improve heart rate variability in patients who recently experienced MI but did not improve heart rate variability among the healthy population.</td>
</tr>
<tr>
<td>Tissue Levels</td>
<td>EPA and DHA</td>
<td>60</td>
<td>Meta-regression analysis of 30 randomized trials with at least 25 subjects revealed direct relationships between dose of consumed omega-3 fatty acids and changes in levels of EPA and DHA. A one gram supplementation correlates to a 1% increase in EPA+DHA levels.</td>
</tr>
</tbody>
</table>

Table 5
Omega-3 Fatty Acids and Selected Health Conditions

<table>
<thead>
<tr>
<th>Health Condition</th>
<th>Clinical Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Studies focusing on Type II diabetes indicate that omega-3 fatty acids significantly lower serum triglyceride levels relative to placebo in diabetic individuals. A meta-analysis found, however, that omega-3 fatty had no effect on total cholesterol, HDL or LDL cholesterol, fasting blood sugar or glycosylated hemoglobin.</td>
</tr>
</tbody>
</table>
Inflammatory Bowel Disease (Crohn's disease and Ulcerative Colitis)  
Randomized controlled trials of the effects of omega-3 fatty acids on patients with Crohn's disease reported variable effects. Two trials of fish oil supplementation of patients with Crohn's disease reported no benefit. However, in another trial, supplementation resulted in a reduction in the incidence of relapse. Three trials of omega-3 supplementation in ulcerative colitis patients reported improvement in at least one outcome measure (e.g., decreased corticosteroid use and production of inflammatory mediators, improvements in disease activity scores, histology scores, and weight gain). But, fish oil supplementation of ulcerative colitis patients in remission did not significantly alter the incidence of relapse over a two-year period.

Rheumatoid Arthritis  
A meta-analysis of 10 randomized controlled trials of patients with rheumatoid arthritis confirmed consistent findings that fish oil supplementation decreased the number of tender joints on physical examination and reduced morning stiffness in individuals. However, omega-3 fatty acids had no effects on self-reported pain, swollen joint count, and patient’s global assessment.

Asthma  
Some evidence suggests that omega-3 fatty acid supplementation can decrease the production of inflammatory mediators in asthmatics. However, evidence that fish oil supplementation decreases the clinical severity of asthma in randomized controlled trials has been inconsistent.

Renal Disease  
Results for a meta-analysis of five controlled studies show that the effect of fish oil supplementation on renal function was not statistically significant. There was conflicting evidence on the effect of fish oil supplementation on serum creatinine (which signals the decline of renal function) and creatinine clearance.

Osteoporosis  
Studies that focused on the effects of omega-3 fatty acids on bone density were variable. Furthermore, there were no studies that examined the effect of omega-3 fatty acids on fractures.

Omega-3 Fatty Acids and Depression

28. Definition of Depression

Depression is a common mental disorder that is characterized by a combination of symptoms including melancholy mood, low energy, change in appetite, weight gain or loss, difficulty sleeping or oversleeping, loss of interest or pleasure in activities that were once enjoyable, poor concentration, feelings of worthlessness or inappropriate guilt, or frequent thoughts of death or suicide. An individual is diagnosed with major depressive disorder if he/she has five or more of the symptoms described above and is impaired in normal functioning nearly every day during the same two-week period. Major depressive disorder may occur only once but more commonly occurs several times in one’s lifetime.

Another form of depression, which is less severe, is called dysthymic disorder. While dysthymia does not generally involve severe disability, the condition does involved long-term, chronic symptoms that keep an individual from functioning well. An individual is diagnosed with dysthymic disorder if he/she experiences depressed mood for at least two years and two other symptoms of depression. Individuals with dysthymic disorder may also develop major depressive disorder.

Individuals with bipolar disorder (or manic-depressive illness) also experience depression that cycle with mania. Mania is characterized by persistent elevated mood or irritability. Symptoms associated with mania include over-activity, talkativeness, racing thoughts, physical agitation, over-inflated self-esteem, and excessive risk-
taking. These mood swings from high (mania) to low (depression) generally occur gradually, but in some instance these changes may be rapid.

29. Prevalence of Depression

According to the National Institute for Mental Health (NIMH), depressive disorders affect about 18.8 million, or 9.5 percent of adult-aged individuals in the United States. Depression disproportionately affects women, with 12 percent of women compared to 6.6 percent of men are diagnosed with depression each year.

The following figures estimated the prevalence of major depressive disorder, dysthmic disorder and bipolar disorder.

• Major depressive order affects about 9.9 million American adults, or 5 percent of the population in a given year. This disorder affects nearly twice as many women as men each year (6.5 percent of women versus 3.3 percent of men).

• Dysthmic disorder affects about 10.9 million American adults, or 5.4 percent of the population during their lifetime. About 40 percent of individuals with dysthmic disorder also meet the criteria for major depressive disorder or bipolar disorder in a given year.

• Bipolar disorder affects about 2.3 million American adults, or 1.2 percent of the population in a given year. Men and women are equally likely to develop bipolar disorder.

30. Consequences and Impact of Depression

Major depression is the leading cause of disability in the U.S. and worldwide. In fact, four of the 10 leading causes of disability in the U.S. are mental disorders: major depression, bipolar disorder, schizophrenia, and obsessive-compulsive disorder. Left untreated or inadequately treated, depression may lead to suicidal behaviors. In 2000, almost 30,000 individuals died by committing suicide in the U.S.\(^{84}\) Moreover, more than 90 percent of these individuals have a diagnosable mental disorder.\(^{85}\)

Many individuals with symptoms of depressive disorders are often not adequately diagnosed or misdiagnosed. It has been estimated that between 40 to 80 percent of individuals with depression did not seek treatment. Individuals are discouraged from seeking treatment due to shame or stigma associated with depressive disorders.


\(^{84}\) ibid.

\(^{85}\) ibid.
31. Costs Associated with Depression

A study conducted by Croghan in 1998 estimated the cost impact of treatment of depressive disorder to be $2,279 for treatment of depressive illness alone and $8,037 for treatment of depressed individuals with comorbid conditions (e.g., other mental illnesses or neurological disorders).

Depressed individuals in the workplace often experience declines in reduced performance, increased accident rates, and increased disability claims. It has been estimated that depression accounts for $44 billion in lost workdays each year compared to $13 million in lost workdays of workers without depression.

Finally, it has been estimated that total lifetime earnings lost to the U.S. economy due to suicide was $7.5 billion in 1990.

32. Treatment of Depression

The most common treatment regimes for depression include psychotherapy and pharmacological options. There are many forms of psychotherapy used to help depressed individuals, including cognitive behavior therapy, behavior therapy, and psychodynamic therapy. These treatments focus help for individuals toward restructuring and overcoming negative thinking and behaviors associated with major depressive disorders.

Antidepressant medication aids individuals diagnosed with depression in restoring the chemical balance in the brain, thus relieving some of the symptoms associated with depression. There are a number of different types of antidepressant medication:

- **Selective serotonin reuptake inhibitors (SSRIs).** The brain of depressed individuals has low levels of a neurotransmitter called serotonin. SSRIs increase the amount of serotonin in the brain’s synapses by preventing the reuptake of serotonin. This allows the production of serotonin to continue and helps to relieve the symptoms of depression. SSRIs are generally well-tolerated and the side effects of these prescription drugs are mild.

- **Tricyclic antidepressants (TCAs).** Tricyclics have been used to treat depression for over 40 years. TCAs increase the amount of neurotransmitters, specifically norepinephrine and serotonin, in the brain. However, they also affect other neurotransmitters in the brain, resultant in a range of adverse side effects for the patient.

- **Monoamine oxidase inhibitors (MAOIs)** are also used to treat depressive disorders. Monoamine oxidase is an enzyme that breaks down neurotransmitters.

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88 Hall, R. The clinical and financial burden of mood disorders cost and outcome.
MAOIs slow the breakdown of norepinephrine and serotonin, allowing brain cells to more efficiently transmit messages.

Severe, chronic depression is treated with electroconvulsive therapy (ECT), but this is considered a treatment of “last resort”. During ECT, an electrical charge is sent to the brain that causes a brief and controlled seizure. There are varying opinions on how ECT impacts the memory.

**33. Omega-3 Fatty Acids for Treating Major Depressive Disorders**

Supplemental omega-3 fatty acids, in particular EPA and DHA, have received attention due to their possible effectiveness in alleviating symptoms associated with depression. Several epidemiological studies associated consumption of fish with reduced incidence of depression. For example, Hibbeln\(^9^9\) reported that there were cross-national differences in the prevalence of depression and that there was a correlation between higher national fish consumption and lower rates of depression. A study conducted of the general population in Finland found persons whose fish consumption was infrequent experienced a greater risk of symptoms associated with depression.\(^9^0\) Similarly, a study on bipolar depression found greater consumption of seafood lowered the prevalence of bipolar disorder.\(^9^1\) These studies and others suggest a possible inverse relationship between fish oil consumption and depressive disorders. The prevailing hypothesis is that because brain matter is rich in fatty acids, an imbalance of essential fatty acids (EPA and DHA) may affect behavior, mood and cognitive functioning. This imbalance may occur as a result of deficient levels of omega-3 fatty acids or an excess of omega-6 fatty acids, which are generally found in vegetable oils. These fatty acids work in conjunction to build cell membranes, and the imbalance in these fatty acids may hinder the ability of molecules to travel into and out of the cell.

We found several clinical studies that have explored the role of omega-3 fatty acids in the treatment of depression. Many of the clinical studies on major depression have been adjunctive therapies, where patients continued their current anti-depression therapy. Clinical studies examining the effects of EPA found significant improvements in symptoms of depression over the use of placebo.

Nemets\(^9^2\) found highly significant benefits of EPA (2 g per day) over placebo with 20 patients with major depressive order. Peet and Horrobin\(^9^3\) using differing doses of EPA

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(1, 2 or 4 g per day) and Su\textsuperscript{94} (using 9.6 g per day of omega-3 fatty acids) found similar results with 70 patients and 28 patients, respectively. However, in the first monotherapy study conducted by Marangell\textsuperscript{95}, omega-3 fatty acids, specifically DHA (2 g per day), failed to exhibit any significant effects toward improving symptoms of major depression. Another clinical study, recently conducted by Stoll\textsuperscript{96} examined the effects of omega-3 fatty acids in the treatment of bipolar disorder. This trial conducted with 30 patients found they were less likely to relapse when treated with omega-3 fatty acids (9.6 g per day, 6.2 g EPA and 3.4 g DHA) used as adjunctive treatment.

While the clinical evidence regarding the effect of omega-3 fatty acids on depression is promising, further clinical trials should emphasize studies of longer duration and those that encompass a greater number of patients. Furthermore, clinical studies should also examine the most effective dosage amounts of omega-3 fatty acids in treating major and mild depression and bipolar disorder.

F. Glucosamine and Chondroitin

34. Summary Description of Glucosamine and Chondroitin

Glucosamine sulfate and chondroitin sulfate are natural compounds found in the body and are believed to repair and maintain cartilage. Glucosamine is an amino sugar that promotes the production of compounds that are the building blocks of articular or joint cartilage. It inhibits inflammation and stimulates cartilage cell growth. Chondroitin is part of a protein molecule and gives cartilage their strength and elasticity.

There are no food sources for glucosamine. However, glucosamine can be derived from chitin found in crustaceans, such as crabs, lobsters, or shrimp. Chondroitin may be found in animal cartilage, such as tracheas or shark cartilage.

35. Health Benefits of Glucosamine and Chondroitin

The health benefits associated with glucosamine are associated with its repair and maintenance of cartilage. For cartilages to be healthy, an adequate source of glucosamine must be present. Glucosamine stimulates production of glycosaminoglycans, which are the main components of proteoglycans. Proteoglycans along with chondrocyte cells and collagen form the building blocks of cartilage. Glucosamine has been shown to have anti-inflammatory effects and potentially some protective effects on the cartilage.

Chondroitin is also found in cartilage. Similar to glucosamine, it seems to have anti-inflammatory effects and reduces pain. Some studies have suggested that chondroitin


may slow the breakdown of cartilage, since glycosaminoglycans found in bone consist of chondroitin sulfate.

**Glucosamine and Chondroitin in the Treatment of Osteoarthritis of the Knee**

### 36. Definition and Prevalence of Knee Osteoarthritis

Osteoarthritis (OA), a chronic degenerative joint disease, is one of the oldest and most common forms of arthritis. It affects the hands and joints, including the knees, hips, feet and back. As individuals age, the joint’s cartilage, which helps to cushion the ends of bones, begins to breakdown. Degeneration of the cartilage causes bones to rub against each other, causing pain, swelling, and limitation in movement. As the disorder initially develops, OA does not produce many symptoms. However, as it progresses, symptoms include morning stiffness, pain with activity, or mild swelling. In later stages, the disorder becomes more debilitating.

This disorder most commonly affects middle-aged and elderly individuals. In fact, Hungerford\(^97\) reports about 65 percent of people aged 65 years of age or older have OA in at least one joint. The prevalence of this disorder increases with age and will become more of a public health issue as the cohort of baby boomers continues to age. In addition, OA has gender-specific differences. The prevalence of OA in most joints is higher in men than in women before 50 years of age. However, after 50 years of age, women are most affected with OA in the hands, feet, and knee. Men are more affected with hip OA than women after 50 years of age. Knee OA occurs in approximately 6 percent of adults in the U.S. aged 30 years of age or older.\(^98\)

According to the American Academy of Orthopedic Surgeons (AAOS)\(^99\), in 1999, approximately 10 million adults reported being diagnosed with OA. Additionally, over 5 million adults reported having knee joint pain, swelling, and stiffness; about 25 percent of those with OA reported having all three knee joint symptoms. Consistent with other studies, two-thirds to three-fourths of adults with knee OA or OA are women.

### 37. Consequences and Impact of Knee Osteoarthritis

Osteoarthritis is a major cause of morbidity and disability.

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Knee osteoarthritis also has an impact on individual’s social life, socioeconomic status, and psychological well being. AAOS reported the following psychological impact of knee osteoarthritis\textsuperscript{100}:

• Those with knee osteoarthritis reported a higher degree of emotional distress compared with individuals without knee osteoarthritis or other health limitations.

• Individuals with knee osteoarthritis self–reported their health status as being worse that those without knee osteoarthritis: 40 percent with knee osteoarthritis rated their health as “fair” or poor, compared with 10 percent of individuals without knee osteoarthritis.

• Those with knee osteoarthritis had less sanguine expectations of their health. About 28 percent with knee osteoarthritis said that it is “definitely” or “mostly” true that their health will become worse, compared to 11 percent of individuals without knee osteoarthritis.

\textbf{38. Costs Associated with Knee Osteoarthritis}

Adults with knee OA reported losing an average of 13 days of work due to health reasons over the previous year, compared with adults without knee OA who lost fewer than 3 days of work. In addition, these adults spend an average of almost 18 days in bed because of health reasons, compared to adults without knee OA who had fewer than 2 days in bed due to health reasons.

The following presents some data from 1999 regarding the health care costs associated with knee osteoarthritis\textsuperscript{101}:

• Individuals with knee osteoarthritis made over 3.7 million visits to physician office and over 150,000 outpatient visits.

• About 30 percent of individuals with knee osteoarthritis went to the emergency room compared to 13 percent of adults without knee osteoarthritis.

• About 25 percent of individuals with knee osteoarthritis had some type of surgery compared to about 10 percent of adults without knee osteoarthritis.

• About 430,000 inpatient hospital stays for individuals with knee osteoarthritis were reported across all visits for all reasons.

• Across all stays for all reasons, individuals with knee osteoarthritis had an average length of stay of five days, with the average cost totaling about $18,000.


• The most frequent procedure performed for those with knee osteoarthritis is total knee replacement.

39. Treatment of Knee Osteoarthritis

Treatment for knee osteoarthritis can include both surgical and non-surgical options to reduce symptom of pain, stiffness, weakness, swelling, clicking, and decreased functional ability. A first line of defense for knee osteoarthritis is health and behavioral modifications, including: self-care programs, exercise, rest and joint care, weight loss, and use of braces and supports.

Pharmacological treatments include:

• Analgesics such as acetaminophen can be effective in reducing pain.

• Topical pain-relieving creams, rubs or sprays applied directly to the skin.

• Non-steroidal anti-inflammatory drugs (NSAID), such as ibuprofen or naproxen, also help to reduce pain. Generally, NSAIDs are used for patients would do not receive adequate symptom relief with analgesics.

• COX-2 inhibitor is a type of NSAID prescribed to those with moderate or severe knee pain. They also help to reduce inflammation.

Operative treatments for knee osteoarthritis include arthroscopic removal of degenerated cartilage or loose fragments. In addition, some individuals with isolated compartments of arthritis may have realignment surgery. Finally, total knee replacement surgery is used to treat severe forms of osteoarthritis.

40. Supplements

The use of glucosamine and chondroitin in treating osteoarthritis due to its reparative properties has been known for decades. These substances have been used in veterinary medicine for the relief of arthritis symptoms. During the late 1990s, the lay press touted the effectiveness of glucosamine and chondroitin in the treatment of arthritis, particularly after being featured in a book entitled, The Arthritis Cure, by Jason Theodasakis, MD. Increased consumer awareness of has resulted in glucosamine and chondroitin together being ranked as the third best-selling nutritional supplement.102

Glucosamine and chondroitin have been well studied since the 1960s. In 2000, the Journal of the American Medical Association published a meta-analysis of clinical studies conducted between 1966 and 1999 examining the efficacy glucosamine and chondroitin.103 McAlindon concluded that the supplements’ had beneficial effects; however the effects were exaggerated due to quality issues of the studies.


Two clinical studies, sponsored by Rotta Pharmaceuticals, examined the effect of glucosamine on the radiographic progress of knee osteoarthritis. Both studies recruited about 200 patients who received 1500 mg daily of glucosamine sulfate or placebo. Reginster et al.\(^{104}\) conducted a three-year, randomized; placebo-controlled study that found the joint-space loss was greater among the placebo group compared to the group on glucosamine. Critics of this study have noted that the radiographic technique used to assess joint space narrowing was subject to variation in interpretation. The other study sponsored by Rotta Pharmaceuticals and conducted by Pavelka et al.\(^{105}\) found that glucosamine retarded the progression of knee osteoarthritis.

Several independent investigations of glucosamine have demonstrated mixed results. Houpt et al.,\(^{106}\) using glucosamine hydrochloride (rather than sulfate), reported no significant differences in pain reduction between the glucosamine and placebo groups. A total of 118 patients with knee osteoarthritis were enrolled in an 8-week study and received 500 mg glucosamine hydrochloride three times daily or placebo. A randomized, placebo-controlled, double-blind clinical study conducted by Hughes and Carr\(^{107}\) concluded that glucosamine was no more effective than placebo in managing pain associated with knee osteoarthritis. Eighty patients were recruited for the study and received 1500 mg daily of glucosamine sulfate for six months or placebo. Another study conducted by Rindone\(^{108}\) on 114 male patients from the Veterans Affairs medical center examined the effectiveness of glucosamine in reducing pain from knee osteoarthritis. In a randomized, double-blind trial of glucosamine (500 mg three times daily) or placebo, the study found no statistical difference between the glucosamine group and placebo group. Thie et al.\(^{109}\) conducted a three-month clinical trial with 45 patients with temporomandibular joint (TMJ) osteoarthritis. They found glucosamine sulfate (500 mg, three times daily) to be superior to ibuprofen (400 mg, three times daily) in reducing pain levels. Glucosamine sulfate was also found to have a carry-over effect, with 70 percent of glucosamine sulfate users having at least a 39 percent reduction in pain.

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There have been a number of clinical trials on the efficacy of chondroitin sulfate on knee osteoarthritis. Bourgeois et al.\textsuperscript{110} conducted a three-month randomized trial of 127 patients with knee osteoarthritis and received chondroitin sulfate (1,200 mg per day) or placebo. These researchers found that those receiving chondroitin had less pain and had more mobility than those receiving placebo. Bucsi and Poor\textsuperscript{111} and Uebelhart\textsuperscript{112} found that chondroitin helped to diminish joint pain.

Clinical studies on glucosamine and chondroitin sulfate have not conclusively shown that they affect the symptoms of knee osteoarthritis. The National Center for Complementary and Alternative Medicine (NCCAM) at NIH is supporting a clinical trial to examine whether the two supplements individually or collectively improve joint function or reduce symptoms of knee osteoarthritis. This study tests both the short-term effectiveness of glucosamine and chondroitin as well as evaluating the impact of the supplements on the progression of knee osteoarthritis for an additional 18-month treatment regimen. About 1,600 patients were recruited for this study. As of July 2004, the study has been completed and the data currently are being analyzed.\textsuperscript{113}

\section*{G. Saw Palmetto}

\textbf{41. Summary Description of Saw Palmetto}

Saw palmetto (\textit{Serenoa repens}) is the bi-product of the berry fruit of the American dwarf palm tree indigenous to the southern and Atlantic regions of the United States and West Indies. Its use as an herbal remedy can be traced to the Mayans and the Seminole Native American peoples. Saw palmetto is very popular among European men for the treatment of symptoms of benign prostatic hyperplasia (BPH) but has yet to be considered the standard of care in the United States.\textsuperscript{114}

\begin{quote}
"Numerous human trials report that saw palmetto improves symptoms of benign prostatic hyperplasia (BPH) such as nighttime urination, urinary flow, and overall quality of life, although it may not greatly reduce the size of the prostate. The effectiveness may be similar to finasteride (Proscar) with fewer side effects."\textsuperscript{115}
\end{quote}

\begin{thebibliography}{99}
\bibitem{114} Complementary & Integrative Therapies @ CancerSource \textsuperscript{\texttrademark} \url{www.cit.cancersource.com}
\bibitem{115} ibid.
\end{thebibliography}
42. *Benign Prostatic Hyperplasia (BPH)*

The prostate is a walnut-sized gland that forms part of the male reproductive system. The gland is made of two lobes, or regions, enclosed by an outer layer of tissue. The prostate is located in front of the rectum and just below the bladder, where urine is stored. The prostate also surrounds the urethra, the canal through which urine passes out of the body.

The prostate gland continues to grow throughout a man’s life but does not usually cause problems until late in life. As a result of this continued growth the prostate gland may become enlarged to the point where it begins to constrict the urethra causing constant pulsing and an increased urge to urinate. Doctors call the condition benign prostatic hyperplasia (BPH), or benign prostatic hypertrophy.

43. *Prostatitis: Disorders of the Prostate*

Prostatitis affects young and middle-aged men as symptoms regarding the genital and urinary systems. The term prostatitis actually encompasses four disorders: acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis/chronic pelvic pain syndrome and asymptomatic inflammatory prostatitis.

Chronic prostatitis/chronic pelvic pain syndrome is the most common but least understood form of prostatitis. It is found in men of any age, its symptoms go away and then return without warning, and it may be inflammatory or non-inflammatory. In the inflammatory form, urine, semen, and other fluids from the prostate show no evidence of a known infecting organism but do contain the kinds of cells the body usually produces to fight infection. In the non–inflammatory form, no evidence of inflammation, including infection–fighting cells, is present.

44. *Prevalence and Cost*

The National Institutes of Health (NIH) estimates that 25 percent of all office visits by young and middle-aged men are for complaints involving the genital and urinary systems. In 2000 the National Center for Health Statistics (NCHS) reported 2.75 million visits to a physician’s office for benign prostatic hyperplasia (BPH). It is rare for BPH symptoms to manifest in males before the age of 40, however, it is estimated that more than half of men in their sixties and 90 percent of men in their eighties experience symptoms related to BPH.

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118 ibid.


119 CDC: NCHS – National Hospital Discharge Survey (NHDS), 2002.
"Prostate enlargement is as common a part of aging as gray hair. As life expectancy rises, so does the occurrence of BPH."\textsuperscript{120}

Because diseases of the prostate are more prevalent in the older population of males, they are among the most costly to the Medicare program. In 1996, the Agency for Healthcare Research and Quality (AHRQ) indicated that 105,514 transurethral resections of the prostate (TURP) surgeries were sought for surgical treatment for BPH with an average length of stay of 2.8 days and an average charge of $6,830.\textsuperscript{121} In the same year, 5,080 prostatectomies were sought by patients with BPH. The average length of stay was 6.2 days with an average charge of $14,343.\textsuperscript{122} Currently, the AHRQ (formerly AHCPR) recommends “watchful waiting” and better patient involvement for the management of mild BPH symptoms. Further recommending that prostate symptoms be measured subjectively, “to what degree a man is bothered by his symptoms”, rather than objectively through laboratory measures and urine flow rates.\textsuperscript{123} This recommendation will be demonstrated in the review of the literature based on studies of the affects of saw palmetto in alleviating mild BPH. Recent studies measure both quality of life (subjective) as well as urine flow and other laboratory measures (objective).

\section*{45. Health Care Utilization}

- In 2000, there were an estimated 2.75 million physician office visits where the principle diagnosis was hyperplasia of the prostate. Just over 2 million of these visits were conducted by an urologist, accounting for 15.3\% of all urologist visits.\textsuperscript{124}

- In 2002, there were 195,000 short–stay hospital discharges for prostatectomy. The incidence of prostatectomy increases with age. However, the number of procedures per 1,000 populations aged 75 and over has decreased from 16.1 per 1,000 populations in 1994 to an estimated 10.7 per 1,000 populations in 2001 (\textbf{Figure 2}).\textsuperscript{125}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Health Care Utilization}
\end{figure}

\textsuperscript{120} ibid.
\textsuperscript{121} “Patient Involvement Key to Better Prostate Care” found at www.ahrq.gov/news/press/pro2.htm
\textsuperscript{123} ibid.
Figure 2
Prostate Procedures per 1,000 Population
Source: CDC: NCHS National Hospital Discharge Survey, 1994 - 2001

- In 2002, there were 199,000 transurethral resections of the prostate (TURP) to alleviate symptoms of BPH.\(^{126}\)
- It is reported that greater than 50 percent of American adults use vitamins, minerals or supplements daily. In 2002, more than 2 million adults 18 years and over used saw palmetto for health reasons in the previous 12 month period.\(^{127}\)
- The average daily cost for the recommended dosage of saw palmetto and saw palmetto combination dietary supplements is $.50.\(^{128}\)

46. Safety\(^{129}\)

The preponderance of evidence from clinical trial research conducted on the effectiveness of the herbal remedy saw palmetto in alleviating symptoms of benign prostatic hyperplasia (BPH) indicates that this dietary supplement in its various standardized marketed forms is safe for consumption by the general population.

In one clinical study, 3 out of 70 people developed a mild allergic reaction to saw palmetto. The agent in this study was administered in a combination product (PC-SPES) which is no longer available commercially.

The most common complaints of side effects from use of saw palmetto related to the stomach and intestines: stomach pain, nausea, vomiting, bad breath, constipation or diarrhea. However, these side effects were reduced when the saw palmetto product was ingested with food.

There are also some findings in which saw palmetto may affect how the body reacts to the sex hormones estrogen and testosterone. Some men using saw palmetto reported difficulty with erections, testicular discomfort, breast enlargement or tenderness and diminished libido. It is thought that saw palmetto could artificially lower PSA (prostate specific antigen) scores which could lead to the delay in diagnosis of prostate cancer.

Direct side effects experienced in the clinical trial evidence for use of saw palmetto in the treatment of symptoms of the prostate are reflected in the Evidence Tables presented in the separate document that contains the appendices of this report.

47. Summary of Saw Palmetto Literature Review

The Natural Standard assigns a letter grade of “A” to saw palmetto which interprets as “strong scientific evidence for this use.” However, saw palmetto receives the letter


\(^{128}\) The Lewin Group analyst review of commercially available products at [www.GNC.com](http://www.gnc.com).

\(^{129}\) Complementary & Integrative Therapies @ CancerSource ™ [www.cit.cancersource.com](http://www.cit.cancersource.com)
grade of “D”, which is to say “fair scientific evidence against this use”, for the treatment of chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS). The scientific literature review of clinical trials supports this Natural Standard letter grade evaluation.\textsuperscript{130}

The literature reviewed includes reports of eight random clinical trials in which saw palmetto (or combination herbal product) was evaluated in blinded studies with either finasteride or placebo (Table 6). Studies were conducted between 1990 and 2004, with seven of the eight studies lasting 6 months or less. One study had more than one thousand participants; however seven of the studies had fewer than 200 subjects participating in the trial. Seven studies were designed to measure any improvement in the symptoms of mild– to moderate–BPH (benign prostatic hyperplasia) while one study was designed to measure improvement in chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS).

### Table 6

<table>
<thead>
<tr>
<th>Types and Frequency of Saw Palmetto Agent Administered in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saw Palmetto Extract (325mg)</td>
</tr>
<tr>
<td>1 clinical trial</td>
</tr>
</tbody>
</table>

Overall, subjects receiving saw palmetto (or combination herbal product) experienced some improvement (not statistically significant) in the symptoms of BPH. No significant adverse reactions or outcomes to the use of saw palmetto for treating BPH were reported in any of the clinical trials. In many of the studies reviewed subjects elected to continue use of the open label product they had taken during the blinded study. The most common criticism of these studies is that they were not long enough to indicate a durable and appreciable improvement in symptoms associated with BPH. Most studies concluded that more research was needed.

#### a. Finasteride vs. Saw Palmetto

Of the eight studies reviewed, two studies were blinded clinical trials of finasteride (5mg once daily) and saw palmetto (325mg daily) or plant extract (Permixon 320mg daily). In the one–year study of 64 men randomly assigned to either the “finasteride” group or the “saw palmetto” group, the study endpoint was the effect of the treatment on chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS). Subjects receiving finasteride experienced a statistically significant improvement in the mean score on the National Institutes of Health Chronic Prostatitis Symptom index (NIH–CPS) as well as improved quality of life and pain domains. The NIH–CPS index measures symptoms of pain or discomfort, urination frequency and emptying of bladder, impact of symptoms, and quality of life. Decreased libido was experienced by two subjects in the finasteride group. The saw palmetto subjects experienced no appreciable improvement in NIH–CPS index; three subjects experienced headache.

\textsuperscript{130} Natural Standard Patient Monograph © as quoted at \url{www.cit.cancersource.com}
In a six month randomized international study of 1,098 patients receiving either finasteride or Permixon, both groups experienced a decrease in their mean International Prostate Symptom Score (IPSS) and improved quality of life when treated for symptoms of BPH. In this study, the finasteride subjects experienced a marked decrease in prostate volume and serum PSA (prostate specific antigen) levels. Subjects receiving Permixon experienced little decreased prostate volume or reduced PSA levels. The finasteride subjects experienced decreased libido with some instances of impotence. This study concluded that both treatments relieve symptoms of BPH but Permixon has little effect on the androgen dependent measure – prostate specific antigen (PSA).

b. Saw Palmetto vs. Placebo

Review of the six studies where subjects were given either saw palmetto (or herbal combination) product or placebo for periods of up to six months reveals that overall, saw palmetto is an effective and tolerable agent for alleviating some symptoms of mild–to moderate–BPH. In studies where Permixon was used, subjects experienced a greater degree of statistically significant improvement in BPH symptoms. Repeated throughout these studies is the notion that the specific agent or mechanism by which saw palmetto is effective against symptoms of BPH is unknown.

In general, across studies of saw palmetto versus placebo, the mean symptom scores (IPSS and CPS) improved, quality of life improved, there was no diminishing of sexual function, and the frequency of both daytime and nighttime urination decreased. Saw palmetto seems to be a well–tolerated agent with no significant adverse side effects for the short term relief of symptoms associated with mild to moderate diagnosis of BPH.

48. Conclusions

The current evidence suggests that a campaign to increase the public’s awareness and use of saw palmetto for alleviating some symptoms associated with benign prostatic hyperplasia would be premature and of moderate benefit to the Dietary Supplement Education Alliance.

While there have been several studies resulting in safe and positive results from the use of saw palmetto, federal researchers have initiated studies of greater rigor and durability. In particular current federal efforts to improve clinical understanding of saw palmetto are underway at the National Institutes of Health Office of Dietary Supplement (ODS). The ODS five year strategic plan released winter 2004, includes as a research initiative:

“The IAG with the NIST has been expanded for an additional 5 years to develop reference materials for other botanicals, including St. John’s wort, ginko, and saw palmetto.”

Further, the NIH, in 2002, issued a grant to study “Alternative Therapies for Benign Prostate Symptoms – Clinical Trial” for a large trial consortium to conduct a simple

131 ODS, NIH, USDHHS. Promoting Quality Science in Dietary Supplement Research, Education and Communication: A Strategic Plan for the Office of Dietary Supplements 2004 – 2009,
controlled clinical trial of saw palmetto to placebo and a Pygeum to placebo and the
effects these herbal remedies have on symptoms of BPH. Thus we conclude that
while promising the use of saw palmetto for improving prostatic symptoms is not yet
proven to the point were cost saving calculations are warranted.

VI. DISCUSSION

In this study, we assessed the potential impact of five supplements on health care expenditures through an extensive review of the literature. The literature related to the health effects of each of the dietary supplements is at different stages of maturation in terms of its sophistication and statistical power. For each supplement, we attempted to determine if each of three casual links existed:

2. Does the supplement produce a physiological effect as shown by a change in biological markers? and if so;

3. Does this physiological effect create a change health status? and if so;

4. Is this change in health status associated with a decrease in health care expenditures?

For calcium and folic acid, the body of research is extensive, spanning over 30 years. The more recent studies address concerns raised in previous studies. In these two instances, the consensus is that findings from the studies reviewed reflect sufficient consistency, validity, and effect size to answer the above three questions affirmatively.

For the other three supplements, our findings are less conclusive. The studies have been conducted over a shorter period of time, and fewer exist. As such, the cumulative effect of checks and counter-checks which provides consistency and validity is yet to be achieved.

In the case of Omega-3 fatty acids, the literature is promising but not yet completely definitive. As indicated by AHRQ, well-designed multicenter RCTs are needed to confirm the observed effect of omega-3 fatty acids on CVD outcomes. Additionally, research should address questions about the effect of omega-3 fatty acids on CVD outcomes in specific subpopulations or individuals with chronic diseases (e.g., diabetes).

For Saw Palmetto and Glucosamine, the literature is more emergent in nature and much less consistent. Nevertheless, research findings continue to be promising. Large government-funded studies are now underway which should provide more definitive results and add to the body of scientific knowledge.

The overall conclusion of this study is that in certain instances, supplements are an inexpensive and safe way to improve health status and reduce health care expenditures. In these cases, the role of public policy to support their use is unambiguous. In other instances, although the available evidence is less definitive, it warrants attention from health care providers and their patients. As the research literature evolves and matures, more will be known about each of the supplements considered in this analysis, as well as supplements that will be studied in the future.
Attachment A:
Cost Estimation for Daily Calcium for Aged Medicare Beneficiaries
Table A - 1

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gross Cost Estimate of Daily Calcium for Aged Medicare Beneficiaries</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Projected number of aged Part A Medicare beneficiaries</td>
<td>34476000</td>
<td>34863000</td>
<td>35323000</td>
<td>35868000</td>
<td>36525000</td>
<td>186765000</td>
</tr>
<tr>
<td>2 Percent of aged Medicare beneficiaries estimated to take calcium currently and pay out of pocket</td>
<td>34%</td>
<td>39%</td>
<td>44%</td>
<td>49%</td>
<td>51%</td>
<td>75%</td>
</tr>
<tr>
<td>3 Number of aged Medicare beneficiaries estimated to take calcium currently and pay out of pocket</td>
<td>11721840</td>
<td>13596570</td>
<td>15542120</td>
<td>17575320</td>
<td>18627750</td>
<td>647847600</td>
</tr>
<tr>
<td>4 Percent of aged Medicare beneficiaries not taking calcium (potential new users) or taking and paying out of pocket (potential switchers)</td>
<td>66%</td>
<td>61%</td>
<td>56%</td>
<td>51%</td>
<td>49%</td>
<td>35%</td>
</tr>
<tr>
<td>5 Potentially Eligible Group - Number of aged Medicare beneficiaries not taking calcium (potential new users) or taking and paying out of pocket (potential switchers)</td>
<td>22754160</td>
<td>21266430</td>
<td>19780880</td>
<td>18292680</td>
<td>17897250</td>
<td>664206160</td>
</tr>
<tr>
<td>6 Take up rate - Proportion of new users among potentially eligible group Take-up rate includes new users and switchers.</td>
<td>30%</td>
<td>43%</td>
<td>56%</td>
<td>69%</td>
<td>82%</td>
<td>38%</td>
</tr>
<tr>
<td>7 Number of new users and switchers</td>
<td>6826246</td>
<td>9144565</td>
<td>11077293</td>
<td>12621949</td>
<td>14675745</td>
<td>497410000</td>
</tr>
<tr>
<td>8 Average Annual Cost of Daily Calcium (excluding beneficiary co-payment of 20%)</td>
<td>$48.43</td>
<td>$49.64</td>
<td>$50.88</td>
<td>$52.15</td>
<td>$53.46</td>
<td>$51.97</td>
</tr>
<tr>
<td>9 Gross cost for daily calcium for aged Medicare beneficiaries who are new users or switchers</td>
<td>$330595191</td>
<td>$453936202</td>
<td>$563612658</td>
<td>$658234651</td>
<td>$784565328</td>
<td>$2790944028</td>
</tr>
</tbody>
</table>

Current Cost of Hip Fracture in Aged Medicare Beneficiaries

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Proportion of female beneficiaries</td>
<td>58%</td>
<td>57%</td>
<td>57%</td>
<td>57%</td>
<td>57%</td>
<td>57%</td>
</tr>
<tr>
<td>11 Number of female beneficiaries</td>
<td>19858176</td>
<td>20023000</td>
<td>20223230</td>
<td>20425462</td>
<td>20629717</td>
<td>807730300</td>
</tr>
<tr>
<td>12 Proportion of male beneficiaries</td>
<td>43%</td>
<td>42%</td>
<td>43%</td>
<td>43%</td>
<td>43%</td>
<td>43%</td>
</tr>
<tr>
<td>13 Number of male beneficiaries</td>
<td>14686776</td>
<td>14781912</td>
<td>15047598</td>
<td>15319223</td>
<td>15669225</td>
<td>409650400</td>
</tr>
<tr>
<td>14 Prevalence of osteoporosis in females</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>15 Number of female beneficiaries with osteoporosis</td>
<td>6950362</td>
<td>7008050</td>
<td>7078131</td>
<td>7148912</td>
<td>7220401</td>
<td>28104300</td>
</tr>
<tr>
<td>16 Prevalence of osteoporosis in males</td>
<td>19%</td>
<td>19%</td>
<td>19%</td>
<td>19%</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>17 Number of male beneficiaries with osteoporosis</td>
<td>2790487</td>
<td>2808563</td>
<td>2859044</td>
<td>2910652</td>
<td>2977153</td>
<td>50590500</td>
</tr>
<tr>
<td>18 Total aged beneficiaries with osteoporosis</td>
<td>9740849</td>
<td>9816613</td>
<td>9937174</td>
<td>10059564</td>
<td>10197554</td>
<td>385054000</td>
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<tr>
<td>19 Take up rate</td>
<td>30%</td>
<td>30%</td>
<td>34%</td>
<td>38%</td>
<td>40%</td>
<td>36%</td>
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<tr>
<td>20 Number of osteoporotics who take calcium</td>
<td>2922255</td>
<td>2944984</td>
<td>3378639</td>
<td>3822634</td>
<td>4079021</td>
<td>117406000</td>
</tr>
<tr>
<td>21 Current number of hip fractures among aged beneficiaries</td>
<td>322000</td>
<td>328500</td>
<td>335000</td>
<td>341500</td>
<td>348000</td>
<td>1675000</td>
</tr>
<tr>
<td>22 Proportion of beneficiaries with hip fractures who require dependent care in nursing facility</td>
<td>68%</td>
<td>68%</td>
<td>68%</td>
<td>68%</td>
<td>68%</td>
<td>68%</td>
</tr>
<tr>
<td>23 Current number of beneficaries who require dependent care in facility</td>
<td>218960</td>
<td>223380</td>
<td>227800</td>
<td>232220</td>
<td>236640</td>
<td>699060</td>
</tr>
<tr>
<td>24 Average number of days for rehab</td>
<td>59</td>
<td>59</td>
<td>59</td>
<td>59</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>25 Average Rehab RUG per diem</td>
<td>$280</td>
<td>$280</td>
<td>$280</td>
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<td>$280</td>
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<tr>
<td>26 Total average SNF cost</td>
<td>$16520.00</td>
<td>$16520.00</td>
<td>$16520.00</td>
<td>$16520.00</td>
<td>$16520.00</td>
<td>$826000</td>
</tr>
<tr>
<td>27 Total cost for SNF care</td>
<td>$3617219200</td>
<td>$3690237600</td>
<td>$3763256000</td>
<td>$3836274400</td>
<td>$3909298000</td>
<td>$1881628000</td>
</tr>
<tr>
<td>28 Cost of hospitalization for hip fracture</td>
<td>$8647</td>
<td>$8923</td>
<td>$9227</td>
<td>$9532</td>
<td>$9846</td>
<td>$9846</td>
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<tr>
<td>29 Total direct hospitalization costs</td>
<td>$2784334000</td>
<td>$2931205500</td>
<td>$3091045000</td>
<td>$3255178000</td>
<td>$3426408000</td>
<td>$1548817050</td>
</tr>
<tr>
<td>30 Total current cost of hip fracture</td>
<td>$6401553200.00</td>
<td>$6621443100.00</td>
<td>$6854301000.00</td>
<td>$7091452400.00</td>
<td>$7335700800.00</td>
<td>$3430445050.00</td>
</tr>
</tbody>
</table>
### Potential Cost Offset Associated with Avoided Hip Fracture in Aged Medicare Beneficiaries who can Benefit from Daily Calcium

<table>
<thead>
<tr>
<th></th>
<th>Reduction in risk of hip fracture associated with taking calcium</th>
<th>Number of avoided hip fractures from taking calcium</th>
<th>Proportion of beneficiaries who require dependent care in nursing facility</th>
<th>Number of avoided episodes of dependent care from taking calcium</th>
<th>Cost offset (potential savings) from avoided SNF stays</th>
<th>Cost offset (potential savings) from avoided hospitalizations</th>
<th>Total cost offsets (potential savings) from avoided hip fractures due to calcium intake</th>
<th>Net cost of Medicare coverage of daily calcium for aged Medicare beneficiaries - expressed as savings</th>
<th>Total potential cost offset from avoided health care utilization associated with avoided hip fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>43% 43% 43% 43% 43%</td>
<td>138460 141255 144050 146845 149640</td>
<td>68% 68% 68% 68% 68%</td>
<td>94153 96053 97954 99855 101755</td>
<td>$1555404256 $1586802168 $1618200080 $1649697992 $1680995904</td>
<td>$1197263620 $1260418365 $1329149350 $1399726540 $1473355440</td>
<td>$2752667876 $2847220533 $2947349430 $3049324532 $3154351344</td>
<td>($330595191 $453936202 $563612658 $658234651 $784565328)</td>
<td>($2504721483 $2506768382 $2524639937 $2555648544 $2565927348)</td>
</tr>
<tr>
<td>32</td>
<td></td>
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</table>

#### Net Cost Estimate of Medicare Coverage of Daily Calcium

<table>
<thead>
<tr>
<th></th>
<th>Gross cost of daily Calcium for aged Medicare beneficiaries</th>
<th>Total cost offsets (potential savings) from avoided hip fractures due to calcium intake</th>
<th>Net cost of Medicare coverage of daily calcium for aged Medicare beneficiaries - expressed as savings</th>
<th>Premium Offset. Twenty-five percent of the gross cost of the intervention.</th>
<th>Total potential cost offset from avoided health care utilization associated with avoided hip fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>$330595191 $453936202 $563612658 $658234651 $784565328</td>
<td>$2752667876 $2847220533 $2947349430 $3049324532 $3154351344</td>
<td>$2422072685 $2393284331 $2383736772 $2391089881 $2369786016 (11959969687)</td>
<td>$82648798 $113484050 $140903164 $164556663 $196141332</td>
<td>($2504721483 $2506768382 $2524639937 $2555648544 $2565927348) ($12657705694)</td>
</tr>
<tr>
<td>39</td>
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<td>41</td>
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<tr>
<td>42</td>
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<tr>
<td>43</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Notes to Attachment A Supported by Summary of Evidence
Line numbers correspond to the numbered rows in Table A - 1

<table>
<thead>
<tr>
<th>Gross Cost Estimate of Daily Calcium for Aged Medicare Beneficiaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
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<td>6</td>
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<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current Cost of Hip Fracture in Aged Medicare Beneficiaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>13</td>
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<tr>
<td>15</td>
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<tr>
<td>27</td>
</tr>
<tr>
<td>29</td>
</tr>
<tr>
<td>30</td>
</tr>
</tbody>
</table>
Notes to Attachment A Supported by Summary of Evidence (continued)
Line numbers correspond to the numbered rows in Table A-1

<table>
<thead>
<tr>
<th>Line</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>Reduction in risk of hip fracture associated with taking calcium - Chapuy et al, 1992 (43%), Cumming et al, 1997 (20%-70%)</td>
</tr>
<tr>
<td>32</td>
<td>Number of avoided hip fractures from taking calcium - (Row 32 = Row 21 * Row 31)</td>
</tr>
<tr>
<td>33</td>
<td>Proportion of beneficiaries who require dependent care in nursing facility - same as Row 22</td>
</tr>
<tr>
<td>34</td>
<td>Number of avoided episodes of dependent care from taking calcium - (Row 34 = Row 32 * Row 33)</td>
</tr>
<tr>
<td>35</td>
<td>Cost offset (potential savings) from avoided SNF stays - (Row 35 = Row 26 * Row 34)</td>
</tr>
<tr>
<td>36</td>
<td>Cost offsets (potential savings) from avoided hospitalizations - (Row 36 = Row 32 * Row 28)</td>
</tr>
<tr>
<td>37</td>
<td>Total Cost offsets (potential savings) from avoided hip fractures due to calcium intake - (Row 37 = Row 35 + Row 36)</td>
</tr>
</tbody>
</table>

### Potential Cost Offsets Associated with Avoided Hip Fracture in Aged Medicare Beneficiaries who can Benefit from Daily Calcium

### Net Cost Estimate of Medicare Coverage of Daily Calcium

<table>
<thead>
<tr>
<th>Line</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>Gross cost of daily Calcium for aged Medicare beneficiaries: Row 9.</td>
</tr>
<tr>
<td>39</td>
<td>Total cost offsets (potential savings) from avoided hip fractures due to calcium intake: Row 37</td>
</tr>
<tr>
<td>40</td>
<td>Net cost of Medicare coverage of daily calcium for aged Medicare beneficiaries - (Row 40 = Row 38 - Row 39)</td>
</tr>
<tr>
<td>41</td>
<td>Premium Offset. Twenty-five percent of the gross cost of the intervention. Row 41 = Row 38 * 0.25.</td>
</tr>
<tr>
<td>42</td>
<td>Total potential cost offset from avoided hip fracture (Row 42 = Row 40 - Row 41)</td>
</tr>
</tbody>
</table>
Attachment B:
Details of Cost-Benefit Analysis of Strategies to Reduce the Rate of Neural Tube Defects
## Table B - 1
Cost-Benefit Analysis of Strategies to Reduce the Rate of Neural Tube Defects

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost Estimate of Daily Folic Acid Supply for Women of Child-Bearing Age for One Year (2005 - 2008)</td>
<td>$32598000</td>
<td>$249704997</td>
<td>$33535800</td>
<td>$34374000</td>
<td>$35233200</td>
<td>$1676610000</td>
</tr>
<tr>
<td>Projected number of women of child-bearing age (15 - 45 years old)</td>
<td>63767000</td>
<td>65767000</td>
<td>67767000</td>
<td>69767000</td>
<td>71767000</td>
<td>71767000</td>
</tr>
<tr>
<td>Percent of women of child-bearing age estimated to take folic acid currently</td>
<td>34%</td>
<td>39%</td>
<td>44%</td>
<td>49%</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>Number of women of child-bearing age estimated to take folic acid currently</td>
<td>21680780</td>
<td>25649130</td>
<td>29817480</td>
<td>34185830</td>
<td>38754180</td>
<td></td>
</tr>
<tr>
<td>Percent of women of child-bearing age not taking folic acid (potential new users)</td>
<td>66%</td>
<td>61%</td>
<td>56%</td>
<td>51%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>Potentially Eligible Group - Number of women of child-bearing age not taking folic acid (potential new users)</td>
<td>42086220</td>
<td>40117870</td>
<td>37949520</td>
<td>35851170</td>
<td>33012820</td>
<td></td>
</tr>
<tr>
<td>Take-up rate: Proportion of new users among potentially eligible group</td>
<td>25%</td>
<td>27%</td>
<td>29%</td>
<td>31%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Number of new users among potentially eligible group</td>
<td>10521555</td>
<td>10831825</td>
<td>11005361</td>
<td>11030163</td>
<td>10894231</td>
<td></td>
</tr>
<tr>
<td>Average annual cost of daily folic acid supplement per person</td>
<td>$6.87</td>
<td>$7.04</td>
<td>$7.22</td>
<td>$7.40</td>
<td>$7.56</td>
<td>$36.11</td>
</tr>
<tr>
<td>Total cost of daily folic acid for all women of child-bearing age who are new users</td>
<td>$72283083</td>
<td>$76275003</td>
<td>$79434424</td>
<td>$81603775</td>
<td>$82613070</td>
<td>$392209356</td>
</tr>
</tbody>
</table>

*Studies estimate the average female receives only 213 micrograms (±/+ 3 mcg) of dietary folate daily.


| 10 | Program Accounts Management | $42167 | $43221 | $44301 | $45409 | $46544 | $221641 |
| 11 | Campaign Message Development- Preliminary | $16768 | $17187 | $17617 | $18057 | $18605 | $88138 |
| 12 | Campaign Message Development- Research/Focus Groups | $17020 | $17448 | $17862 | $18292 | $18779 | $89463 |
| 13 | Campaign Message Development- Finalize | $9296  | $9528  | $9767  | $10011 | $10261 | $48663 |
| 14 | Program Process Measurement | $12606 | $12921 | $13244 | $13575 | $13915 | $66261 |
| 15 | Example: NY Campaign |
| 16 | NY Campaign Program Strategy | $23841 | $24437 | $25048 | $25674 | $26316 | $125316 |
| 17 | NY Campaign Materials | $86731 | $88899 | $91122 | $93400 | $95735 | $455887 |
| 18 | NY Campaign Presentation | $22390 | $22950 | $23523 | $24112 | $24714 | $117689 |
| 19 | NY Campaign Calendar News Releases | $12655 | $12971 | $13296 | $13628 | $13969 | $66519 |
| 20 | NY Campaign CBO/FBO Partnerships | $4692  | $4809  | $4930  | $5053  | $5179  | $24663 |
| 21 | Total NY Campaign | $150309 | $154067 | $157918 | $161866 | $165913 | $790073 |
| 22 | Total General Expenses Plus Cost Per State | $248166 | $254370 | $260729 | $267248 | $273929 | $1304442 |
| 23 | Total National Plan (All States) | $12408300 | $12718508 | $13036470 | $13362382 | $13696441 | $6522101 |

### Lifetime Cost of Care per Case of Spina Bifida (2004 - 2008)

| 24 | Total Lifetime Cost of Spina Bifida per Case | $5320000 | $5433000 | $5589300 | $5729000 | $5872200 |
| 25 | Total Saved by 600 Fewer NTD Babies | $319200000 | $32598000 | $33535800 | $34374000 | $35233200 | $167661000 |
| 26 | Net Savings after cost of supplement | $246916917 | $249704997 | $255923576 | $262136225 | $269718933 | $1284400644 |

**Notes to Attachment B**

- Numbers correspond to the numbered rows in Table B - 1.
- The estimated number of women of child-bearing age is derived from analysis of 2000 Census Bureau data collected on American females, the projected increases were calculated using the Census Bureau's 2010 Population Estimations.
- Studies estimate the average female receives only 213 micrograms (±/+ 3 mcg) of dietary folate daily.
- Numerical equivalent of 34 percent of current users.
- 100% less Row 2 (Current Users).
- Take-Up Rate is conservatively estimated at 25 percent as response to utilization of a national outreach campaign to increase awareness. Take-Up annually increases by 2 percent thereafter.
Cost is derived from an extensive internet search of folic acid vendors. The search start-point was commercial pharmacies: eckerd.com, walgreens.com, jys.com, riteaid.com and drugstore.com. Secondary use of vitamin search engines: findsupplements.com and bizrate.com to verify prices.

Sample size = 23 bottles (all 400 mcg), varying quantities with highest and lowest counts discarded. Weighted averages were constructed to find price per pill and account for wholesale discounts.

Row 10 (New Users) * Row 11 (Average Cost per Year)

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Source: Internal Lewin Group Data. Total cost plus fixed fee includes: 186 total hours billed by Sr. VP, VP and Managing Supervisor, administrative tasks, materials, commute time and indirect overhead costs.</td>
</tr>
<tr>
<td>11 101 billable hours, indirect overhead, materials, research, communications and fixed fee.</td>
</tr>
<tr>
<td>12 56 billable hours, indirect overhead, travel time, materials, and fixed fee.</td>
</tr>
<tr>
<td>13 44 billable hours, indirect overhead, communications and fixed fee.</td>
</tr>
<tr>
<td>14 42 billable hours, indirect overhead, communications and fixed fee.</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>16 50 billable hours, indirect overhead, communications and materials and fixed fee.</td>
</tr>
<tr>
<td>17 80 billable hours, indirect overhead, communications, design, printing, postage, translation and fixed fee.</td>
</tr>
<tr>
<td>18 103 billable hours, indirect overhead, communications, research and database searches, news releases, media kits, translation services and fixed fee.</td>
</tr>
<tr>
<td>19 6 billable hours, indirect overhead, communications, posters/banners/handouts, translation services, design and fixed fee.</td>
</tr>
<tr>
<td>20 70 billable hours, indirect overhead, communications and fixed fee.</td>
</tr>
<tr>
<td>21 Sum of figures in Rows 16 through 20</td>
</tr>
<tr>
<td>22 Sum of figures in Rows 10 through 14</td>
</tr>
<tr>
<td>23 Sum of figures in Rows 20 + 21 * 50 (states)</td>
</tr>
</tbody>
</table>

Cost of Care per Case of Spina Bifida for One Year (2004 - 2008)


Row 24 times 1000

Row 24 minus Row 9