

# Vitamin, Mineral, and Multivitamin Supplements for the Primary Prevention of Cardiovascular Disease and Cancer: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force\*

**Description:** Update of the 2003 U.S. Preventive Services Task Force (USPSTF) recommendation on vitamin supplementation to prevent cardiovascular disease and cancer.

**Methods:** The USPSTF reviewed the evidence on the efficacy of multivitamin or mineral supplements in the general adult population for the prevention of cardiovascular disease and cancer.

**Population:** This recommendation applies to healthy adults without special nutritional needs (typically aged 50 years or older). It does not apply to children, women who are pregnant or may become pregnant, or persons who are chronically ill or hospitalized or have a known nutritional deficiency.

**Recommendation:** The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of

multivitamins for the prevention of cardiovascular disease or cancer. (I statement)

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of single- or paired-nutrient supplements (except  $\beta$ -carotene and vitamin E) for the prevention of cardiovascular disease or cancer. (I statement)

The USPSTF recommends against  $\beta$ -carotene or vitamin E supplements for the prevention of cardiovascular disease or cancer. (D recommendation)

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For author affiliation, see end of text.

\* For a list of the members of the USPSTF, see the **Appendix** (available at [www.annals.org](http://www.annals.org)).

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**T**he U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

## SUMMARY OF RECOMMENDATIONS AND EVIDENCE

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of

multivitamins for the prevention of cardiovascular disease or cancer. (I statement)

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of single- or paired-nutrient supplements (except  $\beta$ -carotene and vitamin E) for the prevention of cardiovascular disease or cancer. (I statement)

The USPSTF recommends against  $\beta$ -carotene or vitamin E supplements for the prevention of cardiovascular disease or cancer. (D recommendation)

See the Clinical Considerations section for suggestions for practice regarding the I statements.

See the **Figure** for a summary of the recommendation and suggestions for clinical practice.

**Appendix Table 1** describes the USPSTF grades, and **Appendix Table 2** describes the USPSTF classification of levels of certainty about net benefit (both tables are available at [www.annals.org](http://www.annals.org)).

See also:

**Print**

Summary for Patients. . . . . I-24

**Web-Only**

CME quiz

Consumer Fact Sheet

## RATIONALE

### Importance

Use of dietary supplements is common in the U.S. adult population. Forty-nine percent of adults used at least 1 dietary supplement between 2007 and 2010, and 32% reported using a multivitamin–multimineral supplement

*Figure.* Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: clinical summary of U.S. Preventive Services Task Force recommendation.

## Annals of Internal Medicine



### VITAMIN, MINERAL, AND MULTIVITAMIN SUPPLEMENTS FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE AND CANCER CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

|  |  |  |   |
|--|--|--|---|
| <b>Population</b>                            | Healthy adults without special nutritional needs.<br>This recommendation does not apply to children, women who are pregnant or may become pregnant, or persons who are chronically ill or hospitalized or have a known nutritional deficiency.   |  |   |
| <b>Recommendation</b>                        | <b>Multivitamins:</b><br>No recommendation.<br>Grade: I statement  | <b>Single- or paired-nutrient supplements:</b><br>No recommendation.<br>Grade: I statement   | <b>β-Carotene or vitamin E:</b><br>Do not recommend.<br>Grade: D  |
| <b>Preventive Medications</b>                | Evidence on supplementation with multivitamins to reduce the risk for cardiovascular disease or cancer is inadequate, as is the evidence on supplementation with individual vitamins, minerals, or functional pairs.<br>Supplementation with β-carotene or vitamin E does not reduce the risk for cardiovascular disease or cancer.  |  |   |
| <b>Balance of Benefits and Harms</b>         | The evidence is insufficient to determine the balance of benefits and harms of supplementation with multivitamins for the prevention of cardiovascular disease or cancer.  | The evidence is insufficient to determine the balance of benefits and harms of supplementation with single or paired nutrients for the prevention of cardiovascular disease or cancer. | There is no net benefit of supplementation with vitamin E or β-carotene for the prevention of cardiovascular disease or cancer. |
| <b>Other Relevant USPSTF Recommendations</b> | The USPSTF has made several recommendations on the prevention of cardiovascular disease and cancer, including recommendations for smoking cessation; screening for lipid disorders, hypertension, diabetes, and cancer; obesity screening and counseling; and aspirin use. These recommendations are available at <a href="http://www.uspreventiveservicestaskforce.org">www.uspreventiveservicestaskforce.org</a> . |  |   |

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to [www.uspreventiveservicestaskforce.org](http://www.uspreventiveservicestaskforce.org).

(1). Supplement use is more common in women and older adults than in men and younger adults (2). Most dietary supplements are used to improve or maintain overall health (1). The substantial effect of cardiovascular disease and cancer on health status and mortality in the United States has been well-described (3), and many supplements are promoted to prevent these conditions (4).

#### Benefits of Vitamin Supplementation

The USPSTF found inadequate evidence on the benefits of supplementation with multivitamins to reduce the risk for cardiovascular disease or cancer. The USPSTF found inadequate evidence on the benefits of supplementation with individual vitamins or minerals or functional pairs in healthy populations without known nutritional deficiencies to reduce the risk for cardiovascular disease or cancer. The USPSTF found adequate evidence that supplementation with β-carotene or vitamin E in healthy populations without known nutritional deficiencies does not reduce the risk for cardiovascular disease or cancer.

#### Harms of Vitamin Supplementation

The USPSTF found inadequate evidence on the harms of supplementation with multivitamins and most single vitamins or minerals or functional pairs. The USPSTF found adequate evidence that supplementation with β-carotene increases the risk for lung cancer in persons who are at increased risk for this condition. The USPSTF found adequate evidence that supplementation with vitamin E has few or no substantial harms.

#### USPSTF Assessment

The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of supplementation with multivitamins for the prevention of cardiovascular disease or cancer. The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of supplementation with single or paired nutrients (except β-carotene or vitamin E) for the prevention of cardiovascular disease or cancer. The USPSTF concludes with moderate certainty that there is no net benefit of supplementation with vitamin E or β-

carotene for the prevention of cardiovascular disease or cancer.

## CLINICAL CONSIDERATIONS

### Patient Population Under Consideration

The focus of this recommendation is healthy adults without special nutritional needs. Populations studied were typically aged 50 years or older. This recommendation does not apply to children, women who are pregnant or may become pregnant, or persons who are chronically ill or hospitalized or have a known nutritional deficiency.

### Suggestions for Practice Regarding the I Statements

#### Potential Preventable Burden

Evidence from *in vitro* and animal research and population-based epidemiologic studies supports the hypothesis that oxidative stress may play a fundamental role in the initiation and progression of cancer and common cardiovascular diseases (3). If this hypothesis is correct, then some combination of specific supplements, a specific dose, a vulnerable host, and specific timing may be found to be useful.

#### Potential Harms

Important harms have been shown with  $\beta$ -carotene in persons who smoke tobacco or have an occupational exposure to asbestos. There are several known adverse effects caused by excessive doses of vitamins; for example, moderate doses of vitamin A supplements may reduce bone mineral density, but high doses may be hepatotoxic or teratogenic. Otherwise, the vitamins reviewed by the USPSTF had few known risks. Because many of these vitamins are fat-soluble, the lifetime effect of high doses should be taken into consideration.

The USPSTF did not address doses higher than the tolerable upper intake level, as determined by the U.S. Food and Nutrition Board. Vitamins A and D have known harms at doses exceeding the tolerable upper intake levels (5), and the potential for harm from other supplements at high doses should be carefully considered.

The U.S. Pharmacopeia has developed reference standards to aid in quality control of dietary supplement production; however, the content and concentration of ingredients in commercially available formulations probably vary considerably. This variability in the composition of dietary supplements makes extrapolating results obtained from controlled clinical trials challenging.

#### Costs

Although dietary supplements themselves are not particularly costly, the cumulative effect of this class of agent on spending is substantial. In 2010, \$28.1 billion was spent on dietary supplements in the United States (6).

### Current Practice

Surveys conducted by the dietary supplement industry suggest that many physicians and nurses have recommended dietary supplements to their patients for health and wellness (7).

### Additional Approaches to Prevention

Appropriate intake of vitamin and mineral nutrients is essential to overall health (5). Despite the uncertain benefit of vitamin supplementation, the 2010 Dietary Guidelines for Americans (8) suggest that nutrients come primarily from foods and provide guidance on how to consume a nutrient-rich diet. Adequate nutrition by eating a diet rich in fruits, vegetables, whole grains, fat-free and low-fat dairy products, and seafood has been associated with a reduced risk for cardiovascular disease and cancer (9, 10).

Specific groups of patients with well-defined conditions may benefit from specific nutrients. For example, women who are planning to or may become pregnant should receive a daily supplement containing folic acid to help prevent neural tube defects. The USPSTF also recommends vitamin D supplements for older persons at risk for falling.

### Useful Resources

The USPSTF has a large portfolio of recommendations for prevention of cardiovascular disease and cancer, including recommendations for smoking cessation; screening for lipid disorders, hypertension, diabetes, and cancer; obesity screening and counseling; and aspirin use (available at [www.uspreventiveservicestaskforce.org](http://www.uspreventiveservicestaskforce.org)).

## OTHER CONSIDERATIONS

### Research Needs and Gaps

A critical gap in the evidence is the lack of studies of multivitamin combinations in groups generalizable to the U.S. population. Two randomized, controlled trials (RCTs) of multivitamin supplements suggest a potential cancer prevention benefit in men but not women. Future trials should be more representative of the general population, including women and minority groups, and should have enough power to show whether there are true subgroup differences. Targeting research toward persons who can be identified as high-risk for nutrient deficiency rather than the general population may be more productive.

There are substantial challenges to studying nutrient supplementation by using methods similar to those used in studying pharmaceutical interventions. New and innovative research methods for examining effects of nutrients that account for the unique complexities of nutritional research but maintain rigorous designs should be explored.

The paucity of studies and general lack of effect of any single nutrient or nutrient pair makes it difficult to draw meaningful conclusions on the balance of benefits and harms without a coordinated research effort and focus. A general lack of standardized methods to determine relevant

serum nutrient levels, agreement on thresholds for sufficiency and insufficiency, or predictive validity of current mechanistic models further hinders progress in understanding potential benefits of dietary supplements.

## DISCUSSION

### Burden of Disease

Cardiovascular disease and cancer are the largest contributors to the burden of chronic disease in the developed world. In 2011, these diseases accounted for 23.7% and 22.8% of all deaths in the United States, respectively (11).

### Scope of Review

In order to update its 2003 recommendation, the USPSTF reviewed evidence of the efficacy of multivitamin or mineral supplements in the general adult population for the prevention of cardiovascular disease and cancer (3, 12). The value of vitamins that naturally occur in food and the use of vitamin supplements for the prevention of other conditions (for example, neural tube defects) and for the secondary prevention of complications in patients with existing disease are outside the scope of this review.

### Effectiveness of Preventive Medication

#### *Multivitamin and Antioxidant Combinations*

The USPSTF reviewed 4 RCTs and 1 cohort study assessing health outcomes of a multivitamin supplement (3). The studies varied in the nutrients and doses used. No effect on all-cause mortality was found in the 3 trials that assessed this outcome. Two trials assessed cardiovascular disease outcomes. Overall, there was no effect on incidence of cardiovascular disease events. One trial reported a borderline significant decrease in fatal myocardial infarctions.

Two large trials, the Physicians' Health Study II (13) and the SU.VI.MAX (Supplementation in Vitamins and Mineral Antioxidants) study (14), showed a decrease in overall cancer incidence in men (pooled unadjusted relative risk, 0.93 [95% CI, 0.87 to 0.99]) (3). The Physicians' Health Study II included 14 641 male U.S. physicians at an average age of 64.3 years. The intervention used a commercially available multivitamin that contained 30 ingredients. The unadjusted relative risk for total cancer incidence was 0.94 (CI, 0.87 to 1.00) after 11.2 years of follow-up. The homogeneity of this study population (primarily older white male physicians) limits its generalizability.

The SU.VI.MAX study was conducted in 13 017 men and women at an average age of 49 years in France. The intervention supplement included nutritional doses of vitamins C and E plus  $\beta$ -carotene, selenium, and zinc. Outcomes were reported for the end of the intervention phase at 7.5 years and again at 12.5 years after randomization. During the supplementation period, overall cancer incidence was not affected in women but decreased by 31% in men (adjusted relative risk, 0.69 [CI, 0.53 to 0.91]). The lack of effect in women and the use of different supple-

ment formulations in the 2 trials make extrapolating these findings to the general population difficult.

### *Single and Paired Vitamins and Minerals*

The USPSTF reviewed 24 studies of individual vitamins or minerals or functional nutrient pairs (3). Across all of the supplements studied, there was no evidence of beneficial effect on cardiovascular disease, cancer, or all-cause mortality. However, the limited number of studies for most individual nutrients and differences in study designs make pooling effects across supplements difficult. Therefore, the USPSTF is not able to conclude with certainty that there is no effect. The evidence for each individual nutrient is discussed here.

*Vitamin A.* The USPSTF reviewed 3 RCTs and 2 cohort studies of vitamin A (3). None of the studies reported cardiovascular disease incidence. One good-quality trial showed an increased risk for lung cancer and related death. The baseline population (smokers and workers who had been exposed to asbestos) was at high risk for lung cancer, so the increased mortality may be attributable to the  $\beta$ -carotene component. Two trials reported all-cause mortality, but no significant difference was observed between intervention and control groups at the longest follow-up. Increased risk for hip fractures was observed in 1 large prospective cohort study of postmenopausal women.

*Vitamin C.* Two RCTs studied the effects of vitamin C, either alone or in combination with other supplements, and found no statistically significant effect on cardiovascular disease, cancer, or all-cause mortality (3).

*Vitamin D With or Without Calcium.* Three trials studied the effects of vitamin D on cardiovascular disease and cancer (3). Two trials found no effect on cardiovascular disease incidence or mortality. One trial reported cancer incidence and death and found no difference between intervention and control groups. Two trials reporting all-cause mortality found no statistically significant difference.

Two trials studied vitamin D and calcium combined. One small, fair-quality study found a statistically significant decreased risk for cancer with supplement use (15). The WHI (Women's Health Initiative) trial, a larger, good-quality trial using lower doses of vitamin D and calcium supplements, found no effect on cancer incidence or mortality (16). A post hoc subgroup analysis of women who were not receiving supplements at baseline showed an association between vitamin D and calcium supplements and lower total cancer and breast cancer incidence (17).

Only the WHI trial reported cardiovascular disease incidence and mortality and all-cause mortality, and it found no effect after 7 years of follow-up. Four trials of calcium supplementation found no effect on overall cardiovascular disease, cancer, or all-cause mortality (3).

*Vitamin E.* Six RCTs assessed vitamin E supplementation (3). Three trials reported cardiovascular disease in-

cidence and mortality. One trial in women reported a lower cardiovascular disease mortality in the intervention group, but mortality rates for myocardial infarction and stroke did not differ statistically. One trial found an increased risk for hemorrhagic stroke in the intervention group.

Four RCTs reported cancer incidence. Overall, there was no significant effect on incidence of all types of cancer or on cancer mortality rates. No effect on all-cause mortality was observed in the 5 trials reporting this outcome.

Vitamin E was not found to have any effect on site-specific cancer incidence, although the results for prostate cancer were mixed. The ATBC (Alpha-Tocopherol, Beta Carotene Cancer Prevention) study (18) reported a decreased incidence of prostate cancer, but the effect did not persist with longer follow-up. Conversely, SELECT (Selenium and Vitamin E Cancer Prevention Trial) (19) reported an increased risk for prostate cancer after extended follow-up.

***β-Carotene.*** A consistent body of evidence from 6 clinical trials suggests that  $\beta$ -carotene supplementation does not decrease the risk for cardiovascular disease events, overall cancer incidence, or cancer mortality (3). Two trials, the ATBC study (18) and CARET (Carotene and Retinol Efficacy Trial) (20), showed an increased risk for lung cancer incidence and mortality and all-cause mortality in participants with a high baseline risk for lung cancer. A meta-analysis of  $\beta$ -carotene trials reported an increased risk for lung cancer (pooled odds ratio, 1.24 [CI, 1.10 to 1.39]) in current smokers (21).

***Selenium.*** Two trials studied selenium alone or in combination with other nutrients and found no effect on cardiovascular disease or all-cause mortality (3). The effect on cancer was mixed. One trial found a decrease in risk for cancer incidence and mortality; the other found no significant difference. Additional analyses showed a decrease in cancer incidence only in men with the lowest levels of selenium, suggesting a potential effect resulting from treatment of selenium deficiency. No differences in all-cause mortality were found in either trial.

***Folic Acid.*** Only 1 trial studied folic acid (3). It found no effect on cardiovascular disease incidence or all-cause mortality. There was an increased incidence of cancer, attributed to an excess number of deaths from prostate cancer in the intervention group.

### Potential Harms of Preventive Medication

Overall, few significant harms were reported from these interventions except for  $\beta$ -carotene. As described previously, 2 trials reported increased risk for lung cancer and lung cancer mortality in smokers, especially heavy smokers. No trials observed an increased risk for cancer in nonsmokers.

The literature contains reports of less serious harms, such as hypercarotenemia or yellowing of the skin (multivitamins and  $\beta$ -carotene), rashes (multivitamins), minor

bleeding events (multivitamins), and gastrointestinal symptoms (calcium and selenium). Rare but more serious harms were associated with some nutrient trials, including hip fractures (vitamin A), prostate cancer (folic acid), and kidney stones (vitamin D and calcium).

### Estimate of Magnitude of Net Benefit

The USPSTF found inadequate evidence on the effectiveness of multivitamin supplements to prevent cardiovascular disease or cancer. Therefore, the USPSTF concludes that the evidence is lacking and the balance of benefits and harms cannot be determined. The USPSTF also found inadequate evidence on the effectiveness of supplementation with most single or paired vitamins or minerals and is therefore unable to determine the balance of benefits and harms of their use to prevent cardiovascular disease or cancer.

Only 2 vitamin supplements have sufficient data to estimate net benefit.  $\beta$ -Carotene has been associated with a statistically significant increased risk for lung cancer in smokers. The USPSTF concludes with moderate certainty that the net benefit of  $\beta$ -carotene supplementation is negative (that is, there is a net harm).

A large and consistent body of evidence has shown that vitamin E supplementation has no effect on cardiovascular disease, cancer, or all-cause mortality. The USPSTF concludes with moderate certainty that the net benefit of vitamin E supplementation is zero.

### How Does Evidence Fit With Biological Understanding?

The risk factors for cardiovascular disease are well-established. Risk factors for cancer are considerably more complex because of the heterogeneous nature of different types of cancer and environmental and genetic influences. Inflammation, oxidative stress, and methionine metabolism have been theorized as common pathologic mechanisms for cardiovascular disease and cancer.

The potential antioxidant and anti-inflammatory effects of many nutrient supplements are the basis for their proposed use to prevent cardiovascular disease and cancer (3). The oxidative properties of antioxidants are not fully understood; however, research has suggested that these properties may vary in relation to other factors, such as the concentration of the nutrient and presence of other oxidants or antioxidants. The harmful association between  $\beta$ -carotene and lung cancer suggests that other variables may influence whether  $\beta$ -carotene acts as an antioxidant versus a pro-oxidant.

### Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 12 November to 9 December 2013. In response to these comments, the USPSTF added language emphasizing that the harms of  $\beta$ -carotene were found in persons at increased risk for lung cancer. The discussion of vitamin E was revised to clarify the consistency of evidence showing a lack of benefit. Additional language was added to the Research

Needs and Gaps section to highlight other challenges in nutrient research. The Recommendations of Others section was enhanced with recommendations from additional organizations.

### UPDATE OF PREVIOUS USPSTF RECOMMENDATION

This recommendation updates the 2003 USPSTF recommendation on vitamin supplementation to prevent cardiovascular disease or cancer. At that time, the USPSTF concluded that the evidence was insufficient to recommend for or against supplements of vitamins A, C, or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cardiovascular disease or cancer (I statement). The USPSTF also recommended against  $\beta$ -carotene supplements, either alone or in combination with other supplements, for the prevention of cardiovascular disease or cancer (D recommendation).

In the current recommendation, the USPSTF considered evidence on additional nutrient supplements, including vitamin D, calcium, selenium, and folic acid, for the primary prevention of cardiovascular disease and cancer. New evidence on vitamin E increased the USPSTF's certainty about its lack of effectiveness in preventing these conditions.

### RECOMMENDATIONS OF OTHERS

An independent consensus panel sponsored by the National Institutes of Health concluded that the present evidence is insufficient to recommend for or against multivitamins to prevent chronic disease (22). The Academy of Nutrition and Dietetics (formerly the American Dietetic Association) noted in a 2009 position statement that, although multivitamin supplements may be useful in meeting the recommended levels of some nutrients, there is no evidence that they are effective in preventing chronic disease (23).

The American Cancer Society found that current evidence does not support the use of dietary supplements for the prevention of cancer (10). The American Institute for Cancer Research determined in 2007 that dietary supplements are not recommended for cancer prevention and recommended a balanced diet with a variety of foods rather than supplements (24).

The American Heart Association recommends that healthy persons receive adequate nutrients by eating a variety of foods rather than supplementation (25). The American Academy of Family Physicians' clinical recommendations are consistent with the USPSTF recommendations (26).

From the U.S. Preventive Services Task Force, Rockville, Maryland.

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## APPENDIX: U.S. PREVENTIVE SERVICES TASK FORCE

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Virginia A. Moyer, MD, MPH, *Chair* (American Board of Pediatrics, Chapel Hill, North Carolina); Michael L. LeFevre, MD, MSPH, *Co-Vice Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Linda Ciofu Baumann, PhD, RN (University of Wisconsin, Madison, Wisconsin); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Francisco A.R. García, MD, MPH

(Pima County Department of Health, Tucson, Arizona); Jessica Herzstein, MD, MPH (Air Products, Allentown, Pennsylvania); Douglas K. Owens, MD, MS (Veterans Affairs Palo Alto Health Care System, Palo Alto, and Stanford University, Stanford, California); William R. Phillips, MD, MPH (University of Washington, Seattle, Washington); and Michael P. Pignone, MD, MPH (University of North Carolina, Chapel Hill, North Carolina). Previous Task Force member Wanda K. Nicholson, MD, MPH, MBA, also made significant contributions to this recommendation.

† For a list of current Task Force members, go to [www.uspreventiveservicestaskforce.org/members.htm](http://www.uspreventiveservicestaskforce.org/members.htm).

**Appendix Table 1. What the USPSTF Grades Mean and Suggestions for Practice**

| Grade       | Definition   | Suggestions for Practice  |
|-------------|--|---|
| A           | The USPSTF recommends the service. There is high certainty that the net benefit is substantial.  | Offer/provide this service.   |
| B           | The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.  | Offer/provide this service.   |
| C           | The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.                      | Offer/provide this service for selected patients depending on individual circumstances.   |
| D           | The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.  | Discourage the use of this service.   |
| I statement | The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. | Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms. |

**Appendix Table 2. USPSTF Levels of Certainty Regarding Net Benefit**

| Level of Certainty* | Description  |
|---------------------|--|
| High                | The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.   |
| Moderate            | The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as:<br>the number, size, or quality of individual studies;<br>inconsistency of findings across individual studies;<br>limited generalizability of findings to routine primary care practice; and<br>lack of coherence in the chain of evidence.<br>As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion. |
| Low                 | The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of:<br>the limited number or size of studies;<br>important flaws in study design or methods;<br>inconsistency of findings across individual studies;<br>gaps in the chain of evidence;<br>findings that are not generalizable to routine primary care practice; and<br>a lack of information on important health outcomes.<br>More information may allow an estimation of effects on health outcomes.  |

\* The USPSTF defines *certainty* as “likelihood that the USPSTF assessment of the net benefit of a preventive service is correct.” The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.