DRAFT STATEMENT
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NATIONAL INSTITUTES OF HEALTH
STATE-OF-THE-SCIENCE CONFERENCE STATEMENT
Multivitamin/Mineral Supplements and Chronic Disease Prevention
May 15–17, 2006

NIH consensus and state-of-the-science statements are prepared by independent panels of health professionals and public representatives on the basis of (1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ), (2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session, (3) questions and statements from conference attendees during open discussion periods that are part of the public session, and (4) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Introduction

At least half of American adults take a dietary supplement, the majority of which are multivitamin/multimineral (MVM) supplements. As more and more Americans seek strategies for maintaining good health and preventing disease, and as the marketplace offers an increasing number of products to fill that desire, it is important that consumers have the best possible information to make their choices. Assessing the available scientific evidence on the benefits of MVM supplement use for chronic disease prevention, identifying the gaps in the evidence, and recommending an appropriate research agenda to meet the shortfalls are subjects considered in this report.

The word "vitamine" was coined in 1912, as an abbreviated term meant to capture the notion of important factors in the diet, or "vital amines." This was preceded more than 150 years earlier by British navy physician James Lind's discovery—in the first recorded controlled trial—that citrus juice, a good source of what was found two centuries later to be vitamin C, could prevent scurvy in sailors. In 1913, the first vitamin was isolated: thiamine, the deficiency of which caused beriberi. Thirteen vitamins and 11 essential minerals have now been identified as important to human nutrition.

Large-scale fortification of diets began in the United States with the addition of iodine to table salt in 1924 to prevent goiter, followed by the addition of vitamin D to milk in 1933 to prevent rickets, and the addition of thiamin, riboflavin, niacin, and iron to flour in 1941. MVM

products providing more than vitamins A and D became available in pharmacies and grocery stores in the mid-1930s. In the early 1940s, the first MVM was introduced.

Although clinical deficiency of vitamins or minerals, other than iron, is now uncommon in the United States, growth in supplement use has accelerated rapidly with marketing spurred by claims—some based on scientific studies—that various chronic conditions could be prevented or treated by supplement use. Annual sales of supplements to Americans are now reported at about $23 billion, a substantial share of which is spent on vitamins and minerals.

With such widespread use of MVM, increasing public and medical confusion over apparently contradictory results from various studies, and reports of possible adverse effects from overuse in certain circumstances, the Office of Dietary Supplements (ODS) and the Office of Medical Applications of Research (OMAR) of the National Institutes of Health (NIH) convened a State-of-the-Science Conference on Multivitamin/Mineral Supplements and Chronic Disease Prevention, held on May 15–17, 2006, in Bethesda, MD. The goal of the conference was to assess the evidence available on MVM use and outcomes for chronic disease prevention in the generally healthy population of adults and to make recommendations for future research. The conference focused specifically on vitamins and minerals and did not engage issues related to botanicals, hormones, or other supplements. It also did not address the treatment of vitamin or mineral deficiencies. Except for considerations of safety, the conference also did not review issues of primary relevance to pregnant women or children.

Specifically, the conference explored the following key questions:

- What are the current patterns and prevalence of the public's use of MVM supplements?
- What is known about the dietary nutrient intake of MVM users versus nonusers?
- What is the efficacy of single vitamin/mineral supplement use in chronic disease prevention?
- What is the efficacy of MVM in chronic disease prevention in the general population of adults?
- What is known about the safety of MVM for the generally healthy population?
- What are the major knowledge gaps and research opportunities regarding MVM use?

An impartial, independent panel was charged with reviewing the available published literature in advance of the conference, including a systematic literature review commissioned through the Agency for Healthcare Research and Quality (AHRQ). The first day and a half of the conference consisted of presentations by expert researchers and practitioners as well as open public discussions. On May 17, the panel presented a statement of its collective assessment of the evidence to answer each of the questions above. The panel also held a press conference to address questions from the media. The draft statement was published online later that day, and the final version was released approximately 6 weeks after the conference,

For the purpose of this review, the term MVM refers to any supplement containing three or more vitamins and minerals; without herbs, hormones, or drugs; and with each component at a dose less than the tolerable upper level (UL) determined by the Food and Nutrition Board. (The UL is the maximum daily intake likely to pose no risk of adverse health effects.) Our review also included studies of the relationship of single-nutrient supplements and two-nutrient supplements with certain disease outcomes. The term primary prevention refers to preventing the development of disease in a person who does not have the disease in question. The chronic conditions assessed in the review included cancer; age-related sensory loss; and cardiovascular, endocrine, neurologic, musculoskeletal, gastroenterologic, renal, and pulmonary diseases.

A word is warranted about the nature of the evidence base reviewed by the panel. The range of vitamins and minerals of possible interest was so broad that the Conference Planning Committee chose to focus the formal literature review on those nutrients for which the potential for impact had been most strongly suggested. We also focused on those conditions for which supplements were thought to have the most potential influence.

The planning committee limited the focus of the literature review of interventions to randomized controlled trials (RCTs), which are generally considered the "gold standard" for evidence-based decisionmaking. They are studies in which participants are allocated by chance alone to receive one of two or more clinical interventions. For example, folate supplementation was initially shown to decrease the risk of neural tube defects in animal studies, as well as in some human trials that were criticized because they were not randomized. Not until these findings were confirmed by RCTs was public policy formulated, including fortification of cereal grains with folate.

In addition, an observational study is one in which the exposure or treatment of interest is not assigned to the subject by the investigator. Observational studies sometimes can be misleading. Such studies suggested that beta-carotene intake might protect against the development of some cancers. But RCTs of beta-carotene not only showed no benefit, they also revealed an increased risk of lung cancer in subjects who smoked cigarettes or who were exposed to asbestos. These examples illustrate the pitfalls of relying only on observational studies and the strengths of RCTs in identify both benefits and risks of vitamin supplementation.

Limiting the focus of our review to RCTs has some inherent limitations, however, given the potential of other types of studies to provide important insights. Observational studies, for example, are particularly useful for hypothesis generation, defining adverse effects, and documenting long-term treatment consequences. They are essential precursors to the well-conducted RCTs required for policy formulation.

Our principal recommendations focus on the important research activities that must be supported to better inform the decisions that millions of Americans are making each day to use or not to use MVM supplements to prevent chronic disease. At the same time, mindful of the constraints of the available evidence base, we have also taken care not to make premature recommendations about whether generally healthy Americans should or should not take MVM supplements. Because of the need for more reliable information on MVMs, we have made strong recommendations for research and increased U.S. Food and Drug Administration (FDA) oversight of the MVM industry.

1. What are the current patterns and prevalence of the public's use of MVM supplements?

More than half of American adults take MVM in the belief that they will feel better, have greater energy, improve health, and prevent and treat disease. There is consensus (based on national and regional studies) that the use of supplements has been steadily increasing and that growth is likely to continue. Currently, users spend more than $23 billion a year on supplements. Finally, among this supplement-using population, MVM is the major category of supplements. Despite these data, uncertainty remains in estimating prevalence of use because of (1) serious problems of definition in these products, (2) increasing complexity in the formulation of supplements including more non-MVM components and specialized formulas, and (3) frequency of use.

Use is higher among women (and children of women who use supplements); the elderly; those who have more education, higher income, healthier lifestyles and diets, and lower body mass index (BMI); and residents of the far western States. Those persons who have a chronic illness or are seeking to prevent recurrence of a serious disease (e.g., cancer) tend to be more frequent users. Many dietary supplement users perceive their health as better.

Conversely, MVM use is lower among smokers and certain ethnic and racial groups, such as African Americans, Hispanics, and American Indians, while certain Asian ethnic groups appear to use more. The irony is that those who are more likely to have nutritional inadequacy and who might benefit the most from MVM are the least likely to use such products.

2. What is known about the dietary nutrient intake of MVM users versus nonusers?

According to several studies, those taking an MVM supplement also have higher micronutrient intakes from their diet than those who do not (for adults, infants, toddlers [12–24 months], adolescents, and the elderly). Consequently, MVM users have an increased intake but are also at increased risk of exceeding the UL.

The national trend to "fortify" certain foods not required by law to be fortified with vitamins and minerals makes calculation of total intake more difficult. A recent industry report estimates that, in 2005, 65% of Americans used these fortified foods or beverages, worth $36 billion, and that these sales are increasing rapidly.

The measurement of dietary vitamin/mineral intake and intake from supplements is uncertain, and this undermines our ability to assess accurately the distribution of vitamin/mineral intake in the population. Uncertainties of measurement also greatly affect the ability of observational studies to detect effects of vitamin/mineral intake on chronic disease.

The origins of these uncertainties include individuals' difficulty in identifying correctly what supplements they are actually taking and the frequency of consumption (e.g., many products look alike but are very different in their composition). Moreover, the lack of databases of MVM composition limits the ability to translate supplement intake into amounts of various vitamins and minerals actually consumed. There are thousands of product labels, vast differences

in the amounts of vitamins/minerals delivered by various products, and major variability within even the same product over time and across batches.

These methodological difficulties should be resolved by two actions. The quality of self-report data of MVM use should be improved to enhance accuracy and specificity of reported MVM intake. New databases, that detail the exact composition of MVM supplements, need to be built and updated on a continuous basis.

3. What is the efficacy of single vitamin/mineral supplement use in chronic disease prevention?

Few high-quality clinical trials are designed to determine whether single use or paired vitamins/minerals prevent chronic diseases, and even fewer are generalizable to the U.S. population. A large, important Chinese study, for example, while well done and testing multiple relevant nutrients, was performed 20 years ago in a population (nutritionally deprived rural villagers) that is unlike today's U.S. population. Another concern is that much of the evidence in this area derives from post hoc analyses for outcomes not originally chosen as study endpoints.

Findings by Vitamin/Mineral

1. **Beta-carotene.** Two large trials designed to test lung cancer prevention with beta-carotene found a paradoxical *increase* in lung cancer incidence and deaths in smokers and male asbestos workers. There was no effect in preventing a number of other cancers, including gastric, pancreatic, breast, bladder, colorectal, and prostate cancer; as well as leukemia, mesothelioma, and lymphoma. The overall death rate was elevated in women treated with beta-carotene throughout the intervention and postintervention period. This effect was not observed in men. A third large trial, in healthy American men, found no effect of beta-carotene on cancers except an increased risk of thyroid and bladder cancers. Two other beta-carotene trials to prevent nonmelanoma skin cancers found no effect on subsequent skin cancer incidence. A large study of healthy American women also found no effect of beta-carotene on cancer incidence. Four of these beta-carotene trials also evaluated cardiovascular disease (CVD) and found no benefits. In healthy women, there was a suggestion of increased stroke risk in one study and an increased risk of CVD in women smokers.

2. **Vitamin A.** No trials were found for vitamin A alone. When vitamin A was paired with beta-carotene in one trial, lung cancer and CVD deaths were increased. When combined with zinc in another trial, there was no impact on esophageal or gastric cardia cancer, although noncardia stomach cancer decreased.

3. **Vitamin E.** Four trials tested vitamin E. One large study of healthy women recorded decreased cardiovascular deaths although there was no effect on incidence of CVD events. Another trial found a decreased risk of prostate cancer (and a suggestion of decreased colorectal cancer risk) in male smokers, as well as a decreased risk of angina and thrombotic stroke. No other effects were found on other cancers. There was a trend toward increased bleeding and subarachnoid hemorrhage and

hemorrhagic stroke in one study of male smokers, but in another study of women no such increase in hemorrhagic stroke was seen.

4. **Vitamin B2 and niacin.** One large Chinese trial of vitamin B2 and niacin found a decreased risk of development of nuclear cataracts. No effects were found on cortical cataracts, mortality, stroke, upper gastrointestinal dysplasia, or cancer.

5. **Vitamin B6.** Two small, short-duration studies of vitamin B6 to prevent cognitive decline in elderly men and women found no effects.

6. **Folic acid with or without vitamin B12.** Multiple studies have shown the effectiveness of folic acid use by women of childbearing age to prevent neural tube defects in offspring. Four small, short-duration studies of folic acid, with or without vitamin B12, to prevent cognitive decline found no effects.

7. **Selenium.** Three trials tested selenium supplementation to prevent cancer. In two Chinese trials, selenium decreased liver cancer incidence in patients at high risk because of either a family history of liver cancer or hepatitis B exposure status. The reports of these trials, however, lack many important details. The third selenium trial was conducted in men and women who had a history of skin cancer. It found no decrease in skin cancers but reported reductions in total cancer mortality and in the incidence of lung, prostate, and colorectal cancers (outcomes the study was not intended to investigate).

8. **Calcium and vitamin D.** Multiple studies demonstrate that calcium increases bone mineral density in postmenopausal women but by itself does not decrease fracture risk. Vitamin D alone does not increase bone mineral density or decrease fracture risk, but it does work in combination with calcium to decrease the risk of hip and nonvertebral fractures in postmenopausal women. Vitamin D and calcium may increase the risk of kidney stones. The single trial that tested the effect of calcium supplementation and vitamin D on colorectal cancer risk found no effect, but the doses may have been inappropriately low.

In summary, few trials of individual or paired vitamins and minerals for the prevention of chronic disease produced beneficial effects. We found no evidence to recommend beta-carotene supplements for the general population and strong evidence to recommend that smokers avoid beta-carotene supplementation. In combination, calcium and vitamin D have a beneficial effect on bone mineral density and fracture risk in postmenopausal women.

On the basis of single studies and analysis of secondary outcomes, there is a suggestion that selenium may reduce risk of prostate, lung, and colorectal cancers; vitamin E may decrease cardiovascular deaths in women and prostate cancer incidence in male smokers; vitamin A and zinc may decrease the risk of noncardia stomach cancer in rural China. Trials of niacin, folate, and vitamins B2, B6, and B12 produced no positive effects.

4. What is the efficacy of MVM in chronic disease prevention in the general population of adults?

Five RCTs conducted in the United States, the United Kingdom, China, and France were identified that studied the efficacy of MVM supplements in the primary prevention of cancer and CVD as well as in delay in the development or progression of cataract and age-related macular degeneration. The five studies used combinations of three to seven vitamins and/or minerals in one or more intervention arms.

We noted some limitations in these studies. In the study in China, while the body mass index (BMI) levels of study subjects were within the normal range, there were indications of inadequate intake of some micronutrients, limiting the generalizability of this study's findings to the U.S. population. Three studies addressed eye disease, and all were performed in subjects who had existing eye disease and were seen in ophthalmology clinics. One of these studies had only 71 subjects and included in the intervention several supplements other than vitamins and minerals. A binational study of cataracts had different entry criteria in each country.

Findings by Disease

1. **Cancer.** Both trials that examined cancer endpoints found a reduction in cancer incidence and/or mortality. In China, overall cancer incidence and mortality were significantly reduced, as were incidence and mortality for the two leading cancers, esophageal and gastric, in an arm of the study that included vitamin E, beta-carotene, and selenium. The decrease in esophageal cancer emerged as a statistically significant finding only after many years of followup. Another arm of the study, on zinc and vitamin A, was associated with a reduction in noncardia gastric cancer. In France, an intervention consisting of vitamin E, selenium, vitamin C, beta-carotene, and zinc was associated with a reduction in overall cancer incidence in men only, but no individual cancer was clearly reduced. Overall mortality in men was also lower in the intervention arm. No effect was seen in women. In China, younger subjects in the intervention arm had a lower incidence of esophageal cancer, but older subjects had a higher incidence. Among men in the French study with normal prostate-specific antigen (PSA) levels, the intervention was associated with a lower incidence of prostate cancer.

2. **Cardiovascular disease.** None of the reviewed studies showed any benefits or harm related to CVD resulting from MVM use in the studied populations.

3. **Cataract.** Mixed results emerged from studies in which cataract progression was the targeted outcome. Only modest and inconsistent effects were found in the two studies that reported any benefit.

4. **Age-related macular degeneration.** One study showed less progression of age-related macular degeneration in subjects receiving vitamins C and E, beta-carotene, and zinc.

The uncertainty resulting from the above trials suggests that multivitamin trials are unlikely to lead to generalizable knowledge. They cannot distinguish the effects of individual components; they are likely to be contaminated by MVM use in the placebo group; they have a weaker biologic basis than single vitamin or mineral studies; they would require very large sample sizes; and they will become outdated from a public health perspective because of the changing composition of commonly used MVMs.

There is evidence from one well-designed trial to consider use of antioxidants and zinc in adults with intermediate age-related macular degeneration. Some suggestive evidence points to possible benefit of selenium and/or vitamin E in cancer prevention, especially in men. However, studies have also shown subgroups of the population whose cancer risk might increase with such supplementation. Trials currently in progress (e.g., SELECT, Physicians Health Study II) should help determine the actual benefits and harms of such supplementation.

5. What is known about the safety of MVM for the generally healthy population?

Most people assume that the ingredients in MVM supplements are safe. There is evidence, however, that certain ingredients in MVM supplements can produce adverse effects, including reports from RCTs that noted excess lung cancers occurring in asbestos workers and smokers consuming beta-carotene. In addition, esophageal cancer excess was found with long-term follow up of older Chinese subjects treated with selenium, beta-carotene, and vitamin E supplements. There was also evidence for gender difference in patterns of lung cancer and CVD risk related to beta-carotene. In another study, one subset of subjects receiving an MVM intervention had higher incidence of prostate cancer. Finally, vitamin D and calcium may increase the risk of kidney stones. These data raise safety concerns both in general and in special populations. Although these studies are not definitive, they do provide evidence for possible safety concerns for primary components of multivitamins.

The RCTs and observational studies on vitamin and mineral supplements have provided little information on safety of single or MVM dietary supplements. Often, safety assessments were limited to adverse reports from subjects who dropped out of trials. The RCTs did not include assessment of well-known potential adverse endpoints. Issues that have not been adequately addressed include but are not limited to: (1) reproducibility of the MVM manufacturing process, (2) characterization of the vitamin mix, (3) demonstration of the absence of contaminants, (4) stability, and (5) interactions with other nutrients and/or drugs.

There is potential for adverse effects in individuals consuming dietary supplements that are above the UL. This can occur not only in individuals consuming high-potency single-nutrient supplements but also in individuals who consume a healthy diet rich in fortified foods and also consume an MVM supplement. Furthermore, by law, the listing of ingredient amounts on nutrient supplement labels is the minimum content; thus, higher intakes are probable. Data from the prospective studies have shown that individuals taking MVM dietary supplements improved their nutritional adequacy with respect to several nutrients but comparably increased the proportion of their intakes above the UL for several of the supplemented nutrients. With the strong trends for an increasing proportion of the population consuming MVM supplements, and the increasing fortification of the U.S. diet, we are concerned that a growing proportion of the

population may be consuming levels considerably above the UL and thus increasing the risk for adverse effects.

The FDA has insufficient resources and legislative authority to require specific safety data from dietary supplement manufacturers and/or distributors before or after their products are made available to the public. This lack of regulation exists despite the fact that many of the ingredients of MVMs would be subject to premarket approval if they were marketed as food additives, and in some cases the ingredients possess biological activities similar, if not identical, to those found in medications. The 1994 Dietary Supplement Health and Education Act (DSHEA) assumed that history of use of a given supplement was evidence for safety, thus grandfathering in all supplements on the market prior to the legislation. However, use of nutrients in foods and supplements in the United States is changing, and we are concerned that safety cannot be assumed. Adverse events from MVMs appear with some frequency in both the reports of the American Association of Poison Control Centers and the FDA's MedWatch system.

We found the primary recommendation of the 2005 Institute of Medicine committee report on dietary supplements compelling: "…the regulatory mechanisms for monitoring the safety of dietary supplements, as currently defined by DSHEA, [should] be revised. The constraints imposed on FDA with regard to ensuring the absence of unreasonable risk associated with the use of dietary supplements make it difficult for the health of the American public to be adequately protected." The FDA should have the authority to:

- Better inform consumers and health professionals regarding the existence of ULs as well as the possible risks of exceeding those levels
- Develop a formal, mandatory, adverse-event reporting system for dietary supplements
- Mandate provision of a MedWatch toll-free telephone number/Web site on product labels to facilitate reporting of adverse events

Further, we recommend that healthcare professionals, consumers, and manufacturers use the FDA MedWatch adverse-event reporting system to report adverse events associated with the use of dietary supplements. Finally, we recommend that Congress revise and update the law to reflect current knowledge.

6. <u>What are the major knowledge gaps and research opportunities regarding MVM use</u>?

This review of the State-of-the-Science has identified important gaps in knowledge on the relationship between MVM use and chronic disease prevention in generally healthy adults. These deficiencies are attributable to shortcomings in data quality and a paucity of rigorously designed and conducted observational studies, and especially RCTs. Hence, this report emphasizes the need and rationale for rigorous, state-of-the-art, methodologically and technologically forward-looking research to bridge these gaps. We therefore strongly recommend the following:

- Elicit more accurate information from individuals to improve the quality of self-report data on MVM use. Capitalize upon new electronic technologies, design and employ improved questionnaires, and develop new dietary and MVM recall methods—all to enhance accuracy and specificity of reported MVM intake.

- Build new MVM databases that detail the exact composition of supplements, update them on a continuous basis, and assure their constant availability to the research community. A national database, like that developed and maintained by the U.S. Department of Agriculture (USDA) for food composition, will be a major improvement for determining potential impact, benefits, and harms of MVM.

- Determine the most effective means to translate scientific information and improve communication on dietary supplements among consumers, healthcare providers, industry, scientists, and policy makers.

- Develop a strategy to support the study of possible interactions of MVMs with nutrients or prescribed and over-the-counter medications.

- Study populations that reflect the diversity of the United States ethnically, economically, and by age and sex. Focus on population segments previously underrepresented and also on individuals at increased risk of chronic disease.

- Study and develop techniques for assessing the basic biological mechanisms by which supplements may modify disease risks (for example, via nutritional genomics, molecular imaging, and systems biology network approaches). The resulting knowledge may identify important new biomarkers, early in the disease process, that may inform observational studies and RCTs.

- Design and conduct rigorous RCTs of the impact of individual supplements (or paired, when biologically plausible) to test their efficacy and safety in prevention of chronic disease, using well-validated measures. Select the vitamins and minerals to be studied based on their biologic plausibility and outcomes of appropriate observational and pilot studies. Include in trials the most modern and validated biomarkers of exposure, bioavailability intermediary metabolism, and early disease. When possible, incorporate relevant genetic polymorphisms into trial design. RCTs should employ cost-effective and innovative methods such as fractional factorial designs, which permit the simultaneous evolution of multiple single supplements and their low-order interactions. Assure sufficient trial duration of both observational studies and RCTs during intervention and follow up.

Conclusions

MVM use has grown rapidly over the past several decades, and dietary supplements are now used by more than half of the adult population in the United States. In general, MVMs are used by individuals who practice healthier lifestyles, thus making observational studies of the overall relationship between MVM use and general health outcomes difficult to interpret. Despite the widespread use of MVMs, we still have insufficient knowledge about the actual

amount of total nutrients that Americans consume from diet and supplements. This is at least in part due to the fortification of foods with these nutrients, which adds to the effects of MVMs and/or single vitamin or mineral supplements. Historically, fortification of foods has led to the remediation of vitamin and mineral deficits, but the cumulative effects of supplementation and fortification have also raised safety concerns about exceeding ULs. Thus, there is a national need to improve the methodology for obtaining accurate and current data on the public's total intake of these nutrients in foods and dietary supplements.

In systematically evaluating the effectiveness and safety of MVMs on chronic disease prevention, there are few rigorous studies upon which to base clear conclusions and recommendations. Most of these studies do not provide strong evidence for beneficial health-related effects of supplements singly, in pairs, or in combinations of three or more. Within some studies and/or subgroups of the populations, there is encouraging evidence of health benefits, e.g., increased bone mineral density and decreased fractures in postmenopausal women who use calcium and vitamin D supplements. However, several of these studies also provide disturbing evidence of risk, e.g., increased lung cancer risk with beta-carotene among smokers.

The current level of public assurance of the safety and quality of MVMs is inadequate, given the fact that manufacturers of these products are not required to report adverse events, and the FDA has no regulatory authority to require labeling changes or to help inform the public of these issues and concerns. It is important that the FDA's purview over these products be authorized and implemented.

Finally, the present evidence is insufficient to recommend either for or against the use of MVMs by the American public to prevent chronic disease. The resolution of this important issue will require advances in research and improved communication and collaboration among scientists, healthcare providers, patients, industry, consumers, and the public.

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