Dietary Supplements and Biomarkers: What Constitutes Evidence?

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What can’t you say about a dietary supplement? For one, you can’t say that it works, even if it works, until FDA says you can say it works.

At a recent annual conference of the American Heart Association, an attending physician stood in front of an exhibit staffed by representatives of a functional food company, challenging the validity of reduced LDL (low-density lipoprotein) oxidation capacity as a biomarker for heart health. When asked what she would accept as a valid biomarker, she replied, “Death. I want to see a change in the risk of death.”

That’s some biomarker. Depending on outcome to determine if a treatment is effective can require long and expensive clinical trials. Often, the intent is to reduce the risk of events that do not occur with high frequency, or that have a long interval between initiation and outcome. Debate becomes acrimonious when people cannot agree on whether the biomarker is truly predictive, or how to use it in a clinical context as compared to usefulness as a research tool. In this context, it is useful to remember what Robert Temple, MD, of FDA’s Center for Drug Evaluation and Research, defines as a clinical endpoint: “A direct measure of how a patient feels, functions, and survives.”

In May 2010, the Institute of Medicine (IOM) issued a report, “Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease.” Subsequently, the IOM conducted a two-day workshop in June 2010 to allow government and private-sector representatives an opportunity to discuss the report. This was published in January 2011 as “Perspectives on Biomarker and Surrogate Endpoint Evaluation.” Both reports are available at the IOM website in book form or pdf download, the first at a cost and the second for free. (1,2)

The reports outline a three-part framework for evaluation of a proposed biomarker:

• Analytical validation: Is the biomarker able to be accurately measured?
• Qualification: Is the biomarker associated with the clinical endpoint of concern?
• Utilization: What is the proper context for using the biomarker?

The reports also recommend that FDA convene expert panels to evaluate biomarkers and biomarker tests that have an impact on the regulation of food, drugs, or devices, and that the initial evaluation of a biomarker should be “conducted separately from a particular context of use.” They also suggested that the expert panels should subsequently reevaluate the analytical validation, qualification, and utilization of the biomarker on “a continual and a case-by-case basis.”

Douglas MacKay, ND, vice president of scientific and regulatory affairs for the Council for Responsible Nutrition (CRN), sees FDA’s involvement in validating more biomarkers as an absolute good, as researchers would have more guidance in designing relevant clinical trials.

Of the three-part framework, the ability to measure proposed biomarkers in a consistent manner is a given; whether or not the “biomarker” is really associated with the clinical endpoint takes up almost all the discussion; and how to actually use a confirmed biomarker is a neglected afterthought. The IOM reports, in the end, did recommend validation, qualification, and utilization, plus establishing a system of periodic reevaluation. The reports then pushed beyond their mandate to recommend that Congress strengthen FDA’s authority to insist that the same degree of scientific rigor applies to foods and supplements as to drugs. Furthermore, the reports recommended that Congress strengthen FDA’s management of postmarket surveillance, funding of research studies, and coordination with other federal agencies. Given that it was FDA in part that had requested IOM conduct this review, the reasoning felt a bit circular when IOM concluded that FDA needs more authority.

Perusing the IOM reports makes a few things clear. An intervention cannot be its own biomarker. We
are beyond the point of claiming that beta-carotene supplements are effective because serum beta-carotene is raised. However, there are still those who want to believe that raising plasma ORAC (oxygen radical absorbance capacity) is confirmation that feeding antioxidants is of benefit. Also, the proposed bioactive may not be the only bioactive. White willow bark is roughly 15% salicin—an aspirin-like compound. That means it is 85% something else. Even the researchers who believe willow bark is effective for relieving back pain and osteoarthritis hazard that other, as-yet unidentified compounds contribute to the benefit.

Table 1 (see attached graphic) shows diseases and biomarkers for which there is more consensus than most. Note the absence of HDL (high-density lipoprotein) cholesterol, triglycerides, homocysteine, or biomarkers for inflammation, arthritis, or most forms of cancer. Harry B. Rice, PhD, vice president of regulatory and scientific affairs for the Global Organization for EPA and DHA Omega-3s (GOED) and the United Natural Products Alliance (UNPA), is of the opinion that the evidence for triglycerides is as strong as for items listed in the table; others feel the same way about HDL cholesterol.

**Biomarker Bridging and Mushrooming**

In the second IOM report, committee member Thomas Fleming, PhD, identified “bridging” as a critical weakness. Functional food and dietary supplement use of biomarkers as substance for supporting health claims is suspect to a major problem—the assumption that changing the biomarker changes the endpoint, even though the mechanism is different from the treatment (usually a drug) that first connected biomarker to outcome. For example, statin drugs lower LDL cholesterol via interfering with cholesterol synthesis, and clearly reduce the risk of coronary disease, but some argue that it's inconclusive whether cholesterol absorption–blocking phytosterols have the same final effect. Likewise, five or six classes of drugs lower blood pressure, as do five or six different foods or supplements. We don't know conclusively if any of the non-drug interventions affect outcome. Compounding the problem is not knowing if the mechanism of action of these non-drugs are similar or distinct from those of the drug mechanisms.

“Mushrooming” is another weakness. For example, a body of evidence, typically epidemiological, suggests that a food may reduce the risk of a specific type of cancer. This leads to efforts to claim benefits for other types of cancer. Likewise, a tentative benefit for one type of dementia leads to claims for all types of dementia, or one type of arthritis to all types of arthritis. These marketing enthusiasms weaken the credibility of all functional foods and dietary supplements.

**Before the IOM Weighed In**

Stepping back for a moment from the three-year process that resulted in a FDA and IOM group hug, what we had was a core group of widely accepted biomarkers, some more flawed than others, and a larger group aspiring to enter the fold. LDL cholesterol is an example of the former; C-reactive protein, the latter. But of greater importance, the supplement and functional food industry had learned how to prosper without officially approved biomarkers.

First, the supplement and food industry borrowed biomarkers from the pharmaceutical industry. The “Big Three” of widely accepted biomarkers are blood lipids, blood sugar, and blood pressure. Many of the health claims officially approved by FDA since the advent of the system in 1993 pertain to these three biomarkers.

Second, the supplement and food industry invented putative biomarkers. What, exactly, is an “antioxidant superfruit,” and why should it matter that it has a high in vitro ORAC? How much folic acid is needed to lower plasma homocysteine, and it that a good thing? Steven Dentali, PhD, chief science officer of the American Herbal Products Association (AHPA), notes that everyone is looking to affirm new biomarkers as shortcuts to claiming clinical significance, and may be distracting themselves from efforts to find faster and less-expensive means of directly measuring clinical outcome.

So, what can’t you say about a dietary supplement? Well, for one, you can’t say that it works, even if it works, until FDA says you can say it works. And even when FDA says it works, only FDA’s wording is approved.

The net effect of FDA-approved health claims and qualified health claims is that applicants were damaged by their successes and doubly damaged by their failures. Success meant having to use the exact wording approved by FDA. Especially for qualified health claims, this could be faint praise indeed. Failure to garner any approved health claim, such as occurred for applications for vitamin E, glucosamine, lutein, and lycopene, hurt subsequent marketing, albeit not fatally.
So, third, the industry has learned to prosper quite nicely, thank you, with structure/function claim language standing in for FDA-approved health claims. Consumer acceptance of a structure/function statement along the lines of “Helps maintain a healthy heart” is surely stronger than the qualified health claim “Supportive but not conclusive research shows that eating 1.5 ounces per day of walnuts, as part of a low saturated fat and low cholesterol diet and not resulting in increased caloric intake, may reduce the risk of coronary heart disease.”

In this structure/function-driven world, there are plenty of examples of dietary supplement and functional food products that could possibly achieve a health claim, yet no application has ever been submitted. Examples include S-adenosylmethionine (SAMe), soy isoflavones, and dark chocolate.

A Two-Edged Sword

The drive to establish more biomarkers is clearly a two-edged sword, as likely to cut its users as it is its intended targets. If FDA moves to establish a process to identify and validate biomarkers, this will set the goals for drug and non-drug interventions. More goals to aim for, yes, but harder to reach. Functional foods and dietary supplements got the short end of the stick. The IOM clearly acknowledged that the non-drug industry is less inclined and less able to afford clinical trials of a scale and duration to prove clinical outcomes. The IOM also said, “Too bad, but you still have to meet the same degree of scientific rigor”—the point being, a food can still be sold as a food, but if the company wants more sales for a health claim, prove it. Guy Johnson, PhD, principal of the consulting firm Johnson Nutrition Solutions LLC, strongly disagrees with this position. In his opinion, “Foods and supplements are fundamentally different than drugs…it is virtually impossible to do randomized, fully blinded, placebo-controlled intervention studies with foods...Nevertheless, foods and supplements can have major public health benefits.”

The utilization criteria remains underaddressed. Clinical research measures changes in populations. For foods and supplements, the changes are often modest—say, a 10 to 15% decrease in relative risk of developing a chronic disease. While statistically significant, this provides little guidance to physicians, who treat individuals. Can physicians be comfortable telling patients to change their lifestyle for the rest of their life, on the chance that it will have an individual impact? Can the physician expect compliance when the patient will not feel or function differently for adding said functional food or dietary supplement to his or her daily regimen?

Looking forward, much will depend on whether FDA gets the funding and Congressional mandate to act on the IOM recommendations. If yes, expect a concerted industry effort to define new biomarkers. If not, then expect industry and the regulatory apparatus to continue to muddle along.

References


Sidebar: Medical Foods: Under the Radar

Traditionally, “medical foods” referred to meal-replacement products, usually in liquid form, that were fed to patients under a physician’s care. These could be orally consumed or enterally fed via a nasogastric tube and pump, but were always seen as providing most or all of the macronutrient requirements plus additional ingredients specifically relevant to the patient’s condition. This niche continues to be dominated by Ross Laboratories, with Nestlé Clinical Nutrition and various minor players rounding out the competition.

The niche for medical foods was clarified when, in passage of the Nutrition Labeling and Education Act of 1990, Congress exempted medical foods from health-claims limitations placed on conventional foods. Distinctions were that medical foods provided nutrients for specific clinical conditions, to replace or supplement the normal diet, and were used under medical supervision and ongoing medical care. Examples include semi-elemental products for patients with malabsorption problems,
or a specific protein and amino acid blend for those in renal failure. Recently, a number of companies have begun to market medical foods that are all but in name dietary supplements. The advantage is that medical foods do not require premarket approval from FDA, as long as use is under a physician’s supervision, the disease in question has distinctive nutritional requirements, and those requirements are based on recognized scientific principals with support in the form of clinical evidence.

At issue here is a deliberate sidestepping of FDA’s regulation of dietary supplements, plus potential for ethical conflict of interest. Physicians are prescribing capsules or tablets with strongly worded health claims for treatment of a specific disease, then selling those very products to their patients from their medical practices. Some of these products are even co-packaged with drugs intended for co-consumption. For several companies, this has become a multimillion-dollar business. CRN’s MacKay opines that FDA and the FTC are empowered to better control this growing niche, but perhaps the existing regulations are under-enforced. GOED/UNPA’s Rice concurs that there is a disconnect between the regulation of claims associated with medical foods versus non-medical foods.

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