

The Philosophy of Evidence-Based Principles and Practice in Nutrition

Bradley C. Johnston, PhD; John L. Seivenpiper, MD, PhD;
Robin W.M. Vernooij, PhD; Russell J. de Souza, RD, ScD;
David J.A. Jenkins, MD, PhD; Dena Zeraatkar, MSc; Dennis M. Bier, MD;
and Gordon H. Guyatt, MD

Abstract

The practice of evidence-based nutrition involves using the best available nutrition evidence, together with clinical experience, to conscientiously work with patients' values and preferences to help them prevent (sometimes), resolve (sometimes), or cope with (often) problems related to their physical, mental, and social health. This article outlines the 3 fundamental principles of evidence-based practice as applied to the field of clinical nutrition. First, optimal clinical decision making requires awareness of the best available evidence, which ideally will come from unbiased systematic summaries of that evidence. Second, evidence-based nutrition provides guidance on how to decide which evidence is more or less trustworthy—that is, how certain can we be of our patients' prognosis, diagnosis, or of our therapeutic options? Third, evidence alone is never sufficient to make a clinical decision. Decision makers must always trade off the benefits with the risks, burden, and costs associated with alternative management strategies, and, in so doing, consider their patients' unique predicament, including their values and preferences.

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NUTRITION AND CLINICAL PRACTICE

Nutrition is thought to play a fundamental role in the prevention, treatment, and prognosis of both acute and chronic diseases. The field of nutritional epidemiology, born from epidemiology and other fields of public health, has over the past few decades been the foundation to nutrition research and has had an important influence on the practice of dietitians and dietary advice globally.¹ Medicine, however, has often overlooked the role of nutrition in disease prevention and management for a multitude of reasons, including a dearth of adequate nutritional education, a lack of monetary compensation for nutritional advice, and because much of the current medical practice revolves around pharmaceutical and procedure-oriented care.^{2,3} Nutrition is not a major focus during medical training and is often disregarded in medical practice apart from fields such as diabetes and renal failure, where nutritional care is a mainstay of treatment.⁴

Additional barriers may include physicians' perceptions regarding the effectiveness of and adherence to nutritional advice.⁵

Although nutritional interventions may potentially offer safe and cost-effective alternatives to pharmaceutical and surgical interventions for the prevention and management of chronic health problems such as obesity and type 2 diabetes,⁶ clinicians may be misinformed about the best available evidence. For instance, unfiltered findings in nutritional science repeatedly make the news headlines; however, headlines seem to frequently contradict one another. A recent example includes a randomized clinical trial (RCT) of 148 participants published in the *Annals of Internal Medicine* that found that low-carbohydrate diets were superior to low-fat diets for weight loss.⁷ A second study, a network meta-analysis of 48 RCTs, totaling 7286 participants, was published just 1 day later in the *Journal of the American Medical Association* and demonstrated that current evidence shows very little

From the Department of Community Health and Epidemiology, Dalhousie University, Halifax, NS, Canada (B.C.J., R.W.M.V.); Department of Health Research Methods, Evidence, and Impact (B.C.J., D.Z., G.H.G.) and Department of Medicine (G.H.G.), McMaster University, Hamilton, ON, Canada; Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, ON, Canada (J.L.S., R.J.d.S., D.J.A.J.); Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre (J.L.S., R.J.d.S., D.J.A.J.), Li Ka Shing Knowledge Institute (J.L.S., D.J.A.J.), and Division of Endocrinology and Metabolism, Department of Medicine (D.J.A.J.),

Affiliations continued at the end of this article.

difference in weight loss with low-carbohydrate vs low-fat diets.⁸

Additional examples of dramatically differing study results come from the findings of several studies on dietary supplements for the prevention of major cardiovascular disease. Early observational studies suggested that vitamin E supplementation reduced cardiovascular death.⁹ Furthermore, a relatively large RCT of 2002 participants compared vitamin E with placebo and found a statistically significant 47% relative risk reduction in cardiovascular death and nonfatal myocardial infarction with vitamin E supplementation.¹⁰ However, a subsequent larger RCT of 9541 participants taking vitamin E vs placebo found no difference in myocardial infarction and death from cardiovascular causes,¹¹ and a meta-analysis and meta-regression, including 135,967 patients who participated in 19 RCTs, reported that vitamin E not only does not reduce mortality¹² but may also increase mortality when given in high doses.¹³ More recently, omega 3 supplementation has demonstrated discrepant results between observational studies and meta-analysis of RCTs among patients at high risk for major cardiovascular events,^{14,15} as has been the case with vitamin D for preventing cancer and cardiovascular disease.¹⁶⁻¹⁸

The practice of evidence-based nutrition (EBN) involves using the best available nutrition evidence, together with clinical experience, to help patients prevent (sometimes), resolve (sometimes), or cope with (often) problems related to their physical, mental, and social health, according to their values and preferences. The EBN approach necessitates seeking out and understanding clinical research evidence regarding the role of nutrition in health care problems. For those involved in making health care decisions, EBN encompasses creating implementation strategies, often among a team of multidisciplinary clinicians using a shared decision-making framework grounded in the patient's values.

At the core of EBN is a care and respect for patients, for whom it will be a disservice if clinicians provide advice that neglects or misinterprets research findings. Effective practitioners of EBN strive for a clear and comprehensive understanding of the evidence

underlying their clinical care, and work with each patient to ensure that chosen interventions are in the patient's best interest. Practicing EBN requires clinicians to understand how uncertainty about clinical research evidence intersects with an individual patient's predicament and preferences regarding the balance of nutrition and susceptibility to diseases related to nutrition. Herein, we outline how EBN proposes to achieve these goals and, in so doing, define the nature of EBN.

THE 3 FUNDAMENTAL PRINCIPLES OF EBN

Evidence-based nutrition involves 3 fundamental principles. First, optimal clinical decision-making requires awareness of the best available evidence that will ideally come from systematic summaries of the available evidence. Second, EBN provides guidance to decide whether evidence is more or less trustworthy—that is, how certain can we be of our patients' prognosis, of our therapeutic options, or of the properties of diagnostic tests? Third, evidence alone is never sufficient to make a clinical decision. Decision makers must always trade off the benefits with the risks, burden, and costs associated with alternative management strategies, as well as individuals' dietary habits and preferences, and, in so doing, consider their patients' unique predicament and values and preferences.¹⁹ Each of these principles assumes that best evidence is readily available to clinical decision makers.

BEST EVIDENCE SUMMARIES

Table 1 summarizes the recommendations from 5 major guidelines of experts regarding prophylactic use of probiotics for the prevention of *Clostridium difficile* infection in hospitalized and nonhospitalized patients, and Figure, using a forest plot, represents the evidence available at the time the recommendations were made.²⁰

Based on 20 trials and more than 3800 patients, the risk reduction of approximately 64% seems relatively secure by examination, but some doubt remains, for 2 reasons. First, the number of events in absolute terms, 148, is not large. Second, small studies tend to overestimate treatment effects, and most of the contributing studies are small. Authors concluded that their certainty in the estimate of effect was moderate; that is, the true effect

TABLE 1. Clinical Practice Guideline Recommendations Regarding Probiotics for the Prevention of *Clostridium difficile* Infection

Guideline	Year published	Recommendation	Strength	Evidence assessment by authors	Evidence assessment by reviewers ^a
American Journal of Gastroenterology	2013	Not recommended	Strong	Low quality	2
Association of Professionals in Infection Control and Epidemiology	2013	Not mentioned	Not assigned	Not assessed	Not applicable
European Society for Clinical Microbiology and Infectious Diseases	2014 ^b	Unclear	Not assigned	Not assessed	1, 2
Health Protection Agency/Department of Health	2008	Not recommended	Not assigned	Not assessed	1, 2
Society for Healthcare Epidemiology of America	2014	Unclear	Not assigned	Not assessed	1, 2

^aLevel 1 signifies a systematic review of randomized controlled trials, and level 2 signifies a single randomized controlled trial.

^bUpdated from the 2009 version without updating prevention strategies; however, a section on probiotics is updated. Evidence assessment is conducted using the Oxford levels of evidence-based medicine.²⁵

is likely to be close to the estimate of effect, but there is a possibility that it differs substantially. Authors suggested that another 2000 patients would need to be randomized before decision makers could be more secure in the pooled estimate of effect.²⁰ Soon thereafter, a large multicenter trial was published that randomized an additional 2941 participants, and found no benefit of taking probiotics.²¹ With 21 trials of 6759 participants and a large 61% relative risk reduction (95% CI, 46%-71%), and without concern regarding safety, a potential benefit of probiotic therapy remains possible.²² Two recently updated systematic reviews, including an individual patient data meta-analysis, identified 11 new RCTs suggesting consistent results with the previous reviews, particularly in participants taking 2 or more antibiotic drugs and in hospital settings where the risk of *C difficile* infection is 5% or greater.^{23,24}

Despite the promising 61% relative risk reduction, a systematic review of practice guidelines indicates that authoritative infectious disease organizations do not recommend administration of probiotics despite the fact that probiotics, particularly *Lactobacillus* GG and *Saccharomyces boulardii*, have the highest quality of evidence among available prophylactic strategies (eg, isolating patients with suspected infections, intensive use of disinfecting agents), and few hospitals and health authorities pay to have probiotics available.²⁵ Randomized trials, particularly small trials, continue in which half of the patients will

not receive the benefits of this prophylactic therapy. Is this necessary?

Until now, there has been considerable disagreement among experts, with many recommending against, or not mentioning, probiotic therapy. Why the expert disagreement, the lag behind the evidence, and the inconsistency between recommendations and evidence? Similar to other fields, to the detriment of patients who have not received probiotic therapy since 2013, it may take a decade for the experts to catch up with the evidence.²⁶ Some concerns with the safety of probiotics have been cited; however, this is a rare occurrence and tends to be among immunocompromised patients.^{27,28} Following EBN principles that limit reliance on biological rationale and place far more emphasis on empirical evidence, the experts should have started recommending probiotic therapy in 2013. Such a recommendation should be weak or conditional until an even larger definitive multinational trial is completed.

A similar but opposite example occurred with dietary guidelines for the general public, guidelines that for decades recommended reducing dietary fat to prevent cardiometabolic conditions and heart disease. These guideline recommendations were based primarily on observational studies, evidence considered to be low quality.²⁹⁻³² Starting in the 1970s, the US government began to promote a low-fat diet. The food industry as well as school, food assistance, and military

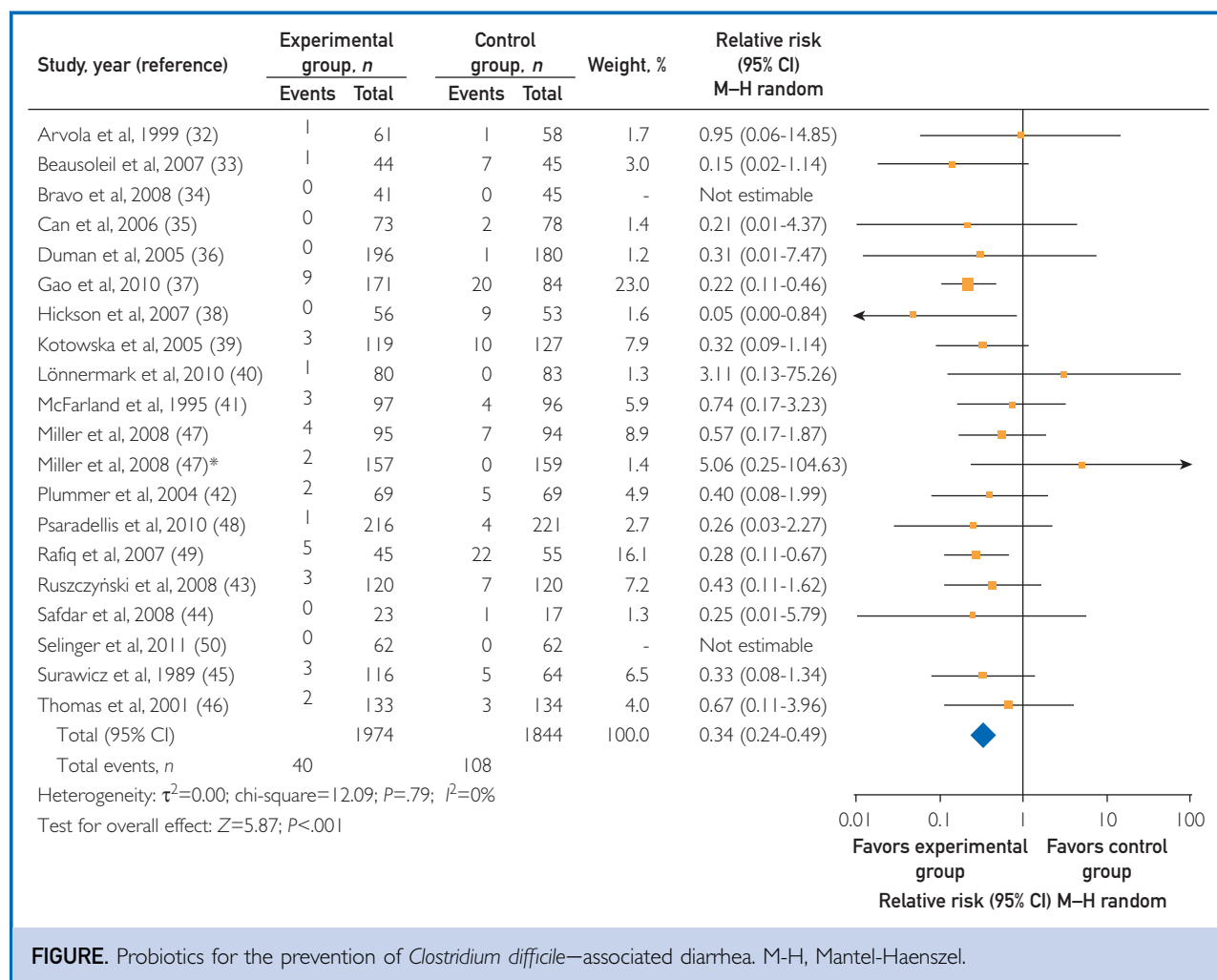


FIGURE. Probiotics for the prevention of *Clostridium difficile*—associated diarrhea. M-H, Mantel-Haenszel.

dietary programs, followed these recommendations, systematically replacing fat, particularly saturated fat from animal products, with sugar and starch. Evidence suggests that the proportion of fat in the US diet decreased by 25% while the prevalence of obesity and type 2 diabetes more than tripled.³³ Indeed, evidence from RCTs has now indicated that diets higher in fats (eg, exceeding 35%), and, in particular, replacing carbohydrates with healthy fats, reduces the risk of cardiometabolic disease.^{34,35} After almost 4 decades of low-fat recommendations, the 2015 US Dietary Guidelines have now placed no upper limit on total fat consumption.³⁶

Rational clinical decisions require systematic summaries of the best available evidence. Without such summaries, clinicians—expert or otherwise—will be unduly influenced by

their own preconceptions and by unrepresentative and often lower-quality evidence. This first principle of EBN immediately raises another question: “How does one recognize the best evidence?”

GUIDES TO CERTAINTY IN ESTIMATES

Summaries of the best evidence for diagnosis, prognosis, or therapeutic interventions present evidence on how to interpret test results, predict patients’ likely fate, or understand the impact of alternative management strategies, respectively. Sometimes, such evidence is trustworthy—we have high certainty in estimates of test properties, patients’ prognosis, or treatment effects. At other times, limitations in evidence leave us uncertain. Evidence-based principles provide guidance to distinguish

between these situations and the range of certainty between them.

Historically, the question “What is the best evidence?” was answered with hierarchies of evidence based on study design.³⁷ The most prominent is the hierarchy related to evidence that supports therapeutic interventions (Table 2). Issues of diagnosis or prognosis require different hierarchies. For studies of the accuracy of diagnostic tests, the top of the hierarchy includes studies that enroll patients about whom clinicians have diagnostic uncertainty and that undertake a blind comparison between the candidate test and a reference standard. For prognosis, prospective observational studies that accurately document exposures and objective outcomes, ideally with blind outcome assessment, and follow up all patients during relevant periods would sit atop the hierarchy. For example, hospitalists are often interested in predictors of prognosis, such as malnutrition on mortality in elderly patients after hospital discharge.³⁸

Noting the limitations of human intuition,³⁹ evidence-based principles place unsystematic observations based on a small number of case reports of individual clinicians lowest on the hierarchy (Table 2). Predictions based on physiologic experiments may be right but sometimes disastrously wrong; EBN places such experiments at the next step up in the hierarchy.^{40,41} Observational studies that measure the apparent effect on patient-important outcomes constitute the next step

up the hierarchy, and RCTs that measure this effect make up the next step on this hierarchy.

Although RCTs sit on top of the hierarchy of evidence for therapy and prevention questions, their limitations for evaluating nutrition questions have been raised by nutritional epidemiologists. First, trials often need to evaluate high vs low intake of a target nutrient; however, when decreasing one nutrient, such as fat, participants will substitute this nutrient with another, such as simple carbohydrates, which itself may have health consequences. Thus, it is difficult to isolate the effects of a single nutrient. This is a serious concern for studies of the major macronutrients (protein, carbohydrate, and fat) but can be more satisfactorily overcome in single-nutrient supplement studies (eg, vitamin E supplement vs placebo). A second important limitation of RCTs in human nutrition is the lack of adherence among trial participants and high dropout rates related to the often demanding nature of the intervention, the long period of follow-up, or both.^{42,43} Adherence issues, high dropout rates, and expense are particularly relevant to clinical trials of nutrition attempting to answer effectiveness questions for important outcomes such as cancer or cardiovascular mortality. To capture outcomes of this nature that have a long preclinical time course, clinical trials must follow participants for decades to adequately observe an effect. Comparatively, prospective observational studies are not faced with the same adherence, dropout, and expense limitations, allowing investigators to better capture and evaluate outcomes that often take decades to develop. Although observational studies have important advantages and roles in identifying issues for subsequent study and providing guidance before the conduct of definitive investigation, reliance on observational studies rather than RCTs may result in misleading inferences and recommendations.⁴⁴⁻⁴⁶ The shortcomings of RCTs to evaluate important nutrition questions are well recognized; however, these limitations should not be used to justify placing excessive trust in the results of typical observational studies given their higher risk of bias.^{15,47}

All of the sources of evidence mentioned thus far involve generalizations from groups

TABLE 2. Hierarchy of Evidence for Therapeutic Interventions

Quality of evidence	Study design
Interventional studies	N-of-1 trials Randomized controlled trials Nonrandomized controlled trials
Observational studies	Cohort studies Case-control studies Cross-sectional studies Case series Case reports
—	Background information, expert opinion, letter to the editor, animal research

of patients to an individual, and all are limited in this regard. There are also studies that involve single patients, and the same strategies that minimize bias in conventional therapeutic trials that involve multiple patients can guard against misleading results in these studies.^{48,49} In the most rigorous n-of-1 RCT, a patient and clinician are blinded to whether that patient is receiving active or placebo treatment. Take, for example, the potential use of probiotics for the treatment of a single patient with irritable bowel syndrome, where a patient alternates probiotics and placebo during several periods, and makes quantitative ratings of troublesome symptoms during each period. The n-of-1 RCT continues until both the patient and the clinician conclude that the patient is or is not obtaining benefit from the target intervention, based on statistical evidence. An n-of-1 RCT can provide definitive evidence of treatment effectiveness for an individual patient⁴⁸ and is, thus, at the top of the evidence hierarchy. Unfortunately, n-of-1 RCTs are restricted to chronic conditions with treatments that act quickly without carryover effects, or carryover effects that washout quickly, and are subject to considerable logistic challenges. We, therefore, must usually rely on studies of other patients to make inferences regarding our patient.

This evidence hierarchy is far from absolute, and a more sophisticated framework has emerged for judging certainty in estimates

of effect of the body of evidence rather than of individual studies. Table 3 summarizes that framework, formulated by the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) Working Group.^{50,51} The GRADE approach involves rating certainty in estimates of the effects of exposures or health care interventions (also referred to as quality of evidence) as high, moderate, low, or very low. Similar to the previous hierarchy (Table 2), in the GRADE guidance, systematic reviews of RCTs begin as high certainty, and reviews of observational studies are classified as low certainty. The body of evidence becomes less trustworthy, however, if the individual studies themselves have major problems in design and execution (risk of bias); results are imprecise (low event rates resulting in uncertainty in the effect estimates or CIs include both important benefit and harm), inconsistent (heterogeneity), or indirect (eg, the population of interest differs from the population studied); or we have a high suspicion of publication bias. When a body of RCT evidence has several of these limitations, the certainty in estimates may be low or even very low.

Similarly, if treatment effects are sufficiently large and consistent and there is a dose-response relationship between the exposure and the outcome of interest, the GRADE approach allows for moderate or even high

TABLE 3. GRADE Approach

1. Establish the initial level of certainty		2. Consider lowering or raising the level of certainty		3. Final level of certainty rating
Study design	Initial confidence in an estimate of effect	Lower if	Higher if	Certainty in an estimate of effect across those considerations
Randomized controlled trials	High	Risk of bias	Large effect	⊕⊕⊕⊕ High
Observational studies	Low	Inconsistency	Dose response	⊕⊕⊕○ Moderate
		Indirectness	All plausible confounding and bias would reduce a demonstrated effect or would suggest a spurious effect if no effect was observed	⊕⊕○○ Low
		Imprecision		⊕○○○ Very low
		Publication bias		

GRADE = Grading of Recommendation Assessment, Development, and Evaluation.

certainty ratings from carefully conducted observational studies. For example, observational studies have yielded moderate certainty in estimates for the association between body mass index and the risk of type 2 diabetes in women and men.^{52,53} Observational studies have produced high certainty in estimates of the association between vitamin and mineral intakes and deficiency diseases.⁵⁴⁻⁵⁶

Although there has been criticism from nutrition epidemiologists about evidence from observational studies starting at low certainty when using the GRADE approach,⁵⁷ as discussed previously herein, there are many examples in the medical and nutrition literature of dramatically different results from RCTs vs earlier observational findings, including the limited or adverse impact of antioxidants, omega-3 supplementation, and reduced dietary fat intake for cardiovascular disease.^{9,11,14,15,34,35,45,46} Some researchers in the nutrition field have argued that RCTs are not feasible for many diet-related questions and that a modified GRADE approach is needed.⁵⁸ However, as outlined previously herein, there are examples of moderate to high certainty evidence based on observational studies in the nutrition field where large treatment effects or a dose-response relationship has been demonstrated.^{52,53,56,59} Moreover, the limited number and commonly low quality of RCTs in some areas of nutrition is not a methodological shortcoming of the GRADE approach but a limitation of the evidence base.⁶⁰ The GRADE approach has been endorsed and adopted by more than 120 international organizations and societies worldwide, covering a variety of clinical and public health areas. In support of the original intent of the GRADE Working Group, we believe that it is important to maintain standards for assessing the certainty of evidence across health care fields.⁶⁰

The evidence-based approach implies defining a clear course of action for clinicians addressing patient problems. They should seek the highest-quality evidence available to guide their clinical decisions. The available evidence may warrant a very low certainty rating (ie, extensive uncertainty)—perhaps because the only evidence available is the unsystematic observation of a single clinician or physiologic studies that point to mechanisms of action that

are only indirectly related to a patient important outcome—but there is always at least some evidence.⁶¹ This consideration may be particularly relevant in human nutrition, where clinicians have to typically rely on observational studies (starting point of low quality) as the evidence base for dietary guidelines.^{62,63} The problem is complicated further by often implausible results from assessments of single nutrients or foods in isolation, such as saturated fat or red meat, assessments that fail to fully account for the complex interactions with the dietary and lifestyle patterns in which these nutrients are consumed.^{44,61,64,65} Now that we have the evidence, whatever it may be, we can progress to the third principle of EBN: clinical decision making.

EVIDENCE IS NEVER ENOUGH TO INFORM CLINICAL DECISION MAKING

Picture a woman with chronic pain from terminal and untreatable cancer. She has come to terms with her condition, resolved her affairs, said her goodbyes, and wishes to receive only palliative care. She develops impaired glucose tolerance and is at risk for type 2 diabetes. Evidence that a diet and lifestyle program reduces the risk of type 2 diabetes warrants moderate certainty.⁶⁶ This evidence does not, however, dictate that this patient should receive an interventional program. Her values—emerging from her comorbidities, social setting, and beliefs—are such that she would probably prefer to forgo such a restricted diet.

Now picture a second patient, an 85-year-old man with severe dementia who is mute and incontinent, has a small social circle, and spends his days in apparent discomfort. He is overweight and takes great pleasure in overconsuming sweets and desserts. This man develops severe glucose intolerance. Clinicians may well be divided in this situation on whether to administer a dietary program. Again, evidence of treatment effectiveness does not automatically imply that the restricted diet should be administered.

Finally, picture a third patient, a healthy 30-year-old mother of 2 children who is 2 months pregnant and develops gestational diabetes. No clinician would doubt the wisdom of recommending an exercise program and a diet high in fruits, vegetables, and whole

grains and low in refined high-glycemic index carbohydrates to this patient,⁶⁷ or alternatively a low carbohydrate diet.⁶⁸ This does not mean, however, that an underlying value judgment has been unnecessary. Rather, the values among the patient, family, and health care providers are concordant, and the benefits so overwhelm the risk and potential inconvenience of treatment that the underlying value judgment is unapparent.

By values and preferences, we are referring to the collection of goals, expectations, predispositions, beliefs, and abilities and resources to make the changes that individuals have for certain decisions that may influence their outcomes.⁶⁹ The explicit enumeration and balancing of benefits and risks that are central to EBN bring the underlying value judgments involved in making management decisions into focus and are typically quickly resolved using a shared decision-making model.

Acknowledging that values play a role in every important patient care decision highlights our limited understanding of how to ensure that decisions are consistent with an individual and, where appropriate, societal values. Developing efficient processes for helping patients, clinicians, and allied health professionals work together toward optimal decisions consistent with patient values and preferences (eg, decision aids) remains a frontier for evidence-based decision making.

CLINICAL SKILLS, HUMANISM, AND EBN

In summarizing the skills and attributes necessary for evidence-based practice, take, for example, a hypothetical scenario that illustrates the necessity of getting the diagnosis right before implementing EBN therapies, in which a clinician develops abdominal discomfort, bloating, and diarrhea. He self-diagnoses that he may have irritable bowel syndrome and finds promising evidence from systematic reviews of a variety of therapeutic options, including probiotics and soluble fiber.^{70,71} Soon after, realizing the dangers of self-diagnosis, he visits his family doctor, an experienced clinician, to discuss his remaining uncertainty. The subsequent investigation reveals celiac disease and highlights the uselessness of the evidence for soluble fiber or probiotics for a condition the patient did not have.

Additional clinical skills come in applying evidence, in this instance on the elimination of foods containing gluten or on potential therapies such as pancreatic enzyme supplementation for the treatment of celiac. For example, an assessment of the applicability of study findings occurs when doctors or dietitians seek the best available evidence and then rely on their clinical expertise to define features that affect the applicability of these results to the individual patient. The clinician must judge the extent to which differences in treatment (number of dosing regimens, inconvenience of taking the treatment, possibility of nonadherence to treatment or lifestyle modification) or patient characteristics (age, comorbidity, and the patient's cultural, religious, or personal circumstances) may affect estimates of benefit and risk that come from the published literature.

We note that some of these skills—the sensitivity to the patient's unique predicament and the communication skills necessary for shared decision making—are in many peoples' minds often not typically associated with evidence-based practice. We, however, believe that they are at its core. Understanding the patient's personal circumstances is of particular importance and requires advanced clinical skills, including listening skills and compassion. For some patients, incorporation of patient values for major decisions will mean a full enumeration of the possible benefits, risks, and inconveniences associated with alternative management strategies. For some patients and problems, this discussion should involve the patient's family and other caregivers.

ADDITIONAL CHALLENGES FOR EBN

Busy clinicians—particularly those early in their development of the skills needed for evidence-based practice—will often find time limitations as their biggest challenge. This challenge may arise from having inadequate access to various evidence-based resources. Fortunately, an array of sophisticated evidence-based information is now available for clinicians with online access (eg, PEN: Practice-based Evidence in Nutrition [<http://www.pennutrition.com>]), and the pace of innovation remains rapid.

Access to preprocessed information cannot, however, address other skills required

for efficient evidence-based practice. These skills include formulating focused clinical questions, matching prioritized questions to the most appropriate resources, assessing certainty in estimates, and understanding how to apply results to clinical decision making. Although these skills take time to learn, the reward in terms of efficient and effective practice can more than compensate.

This paper has dealt primarily with decision making at the level of the individual patient. Evidence-based approaches can also inform health care policy-making, day-to-day decisions in public health, and systems-level decisions, such as those facing hospital managers. In each of these areas, EBN can support the appropriate goal of gaining the greatest health benefit from limited resources.

Abbreviations and Acronyms: **EBN** = evidence-based nutrition; **GRADE** = Grading of Recommendation Assessment, Development, and Evaluation; **RCT** = randomized clinical trial

Affiliations (Continued from the first page of this article.): St Michael's Hospital, Toronto, ON, Canada; Department of Research, Netherlands Comprehensive Cancer Organisation, Utrecht (R.W.M.V.); Population Health Research Institute, Hamilton, ON, Canada (R.J.d.S.); Department of Medicine, Faculty of Medicine, University of Toronto, ON, Canada (D.J.A.J.); and Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX (D.M.B.).

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Correspondence: Address to Bradley C. Johnston, PhD, Department of Community Health and Epidemiology, Faculty of Medicine, Dalhousie University, Halifax, Canada (bradj49@gmail.com).

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