

RESEARCH ON INTEGRATIVE HEALTHCARE: CONTEXT AND PRIORITIES

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It is important that integrative healthcare research be conducted to optimize the effectiveness, safety, costs, and social and economic impact of prospective, personalized, patient-centered, comprehensive, and holistic healthcare that focuses on well-being as well as disease management, and that the research itself be well understood. The scope of this research extends beyond evaluation of specific therapies, to include evaluations of multimodality whole system intervention, practitioner-patient relationships, patient goals and priorities, promoting self-care and resilience, personalized diagnostic and therapeutic measures, practitioner well-being, the comparative effectiveness of different educational and outreach strategies in improving health and

healthcare, and the environmental/social causes and consequence of health and healthcare. In this paper, we describe the state of the science of research on integrative healthcare, research needs, and opportunities offered by cutting-edge research tools. We propose a framework for setting priorities in integrative health research, list areas for discussion, and pose a few questions on a future research agenda.

Key words: Integrative health, integrative medicine, complementary and alternative medicine, holistic, whole system, research, research priorities

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INTRODUCTION

Integrative healthcare is defined here as prospective, relationship-based, patient-centered, comprehensive, and holistic healthcare that focuses on patients' priorities for well-being, as well as preventing, managing, rehabilitating, and palliating diseases and injuries. The scope of research for integrative healthcare as discussed in this paper is not only the evaluation of specific complementary and alternative medical (CAM) therapies for safety and effectiveness in treating specific medical problems (the Institute of Medicine published its report *Complementary and Alternative Medicine in the United States* in 2005¹), it also includes multidisciplinary whole system intervention, participant-centered evaluations of therapies and health practices, clinician-patient interaction, patient goals and priorities, health values and meaning, self-care, the comparative effectiveness of different educational and outreach strategies in promoting optimal health and healthcare, environmental factors and social policies affecting health, and system factors affecting availability of resources that promote health, health behaviors, or healthcare. Research must also address patient-centered care in the context of family, culture, and community. The research agenda for integrative medicine is by nature broad and comprehensive, rather than being focused solely on the effects and mechanism of selected therapies. In this paper, we describe the state of science of integrative

medicine research, research needs, and the opportunities offered by cutting-edge research tools. We propose a framework for setting priorities in integrative medicine research, list areas for discussion, and suggest a few questions for the research agenda.

CONTEXT: STATE OF THE SCIENCE, RESEARCH NEEDS, AND INTEGRATION WITH CUTTING-EDGE RESEARCH TOOLS

Research Methodology

Study design. Integrative health researchers embrace the randomized controlled trial (RCT) in evaluating many therapies. The RCT method helps reduce multiple sources of bias. Although RCTs are often viewed as the gold standard, it is not possible to conduct RCTs for every research question due to logistic, economic, or ethical concerns. Because many health practices and complementary therapies are widely available, patients can readily choose to use them whether or not they participate in a trial; this means that those with strong preferences for a particular therapy or practice may be unwilling to consent to randomization. Furthermore, although pharmacologic therapies are typically developed for one specific indication (eg, antihypertensive effects), many integrative therapies have multiple effects (eg, meditation may decrease blood pressure, anxiety, inattention, and insomnia), whose relative importance may vary even among patients within a single diagnostic group. Although the strongest conclusions and inferences can be reached when there is concordance between research using different methods (eg, RCT, quasi-experimental, and prospective cohort), such concordance is not always found (eg, the different conclusions reached by cohort vs RCT studies of hormone replacement therapy,^{2,3} antioxidant supplements to prevent cancer,⁴ or decreased risk of dementia/cancer in patients using statins⁵). Observational studies have provided important insights, such as the role of smoking, radiation, hormone levels, and high meat diets in the development

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of different kinds of cancer, lipids and coronary disease, hypertension and stroke, and sleeping position and sudden infant death syndrom.⁶ *Researchers need to recognize that different kinds of research serve complementary functions in developing balanced and mature evidence.*⁷

Integrative healthcare provides opportunities for innovative research designs. Patient-centered care implies active patient participation in prioritizing outcomes and selecting therapies. Similarly, community-based participatory research involves community members in identifying research priorities and developing methods. Likewise, research in integrative healthcare optimally involves its participants in identifying the most important outcomes and empowers them to choose whether to be randomized (or not) to a particular therapy. Research employing concurrent RCTs and quasi-experimental designs to evaluate therapies for low back pain has enriched our understanding of the impact of patient preferences and expectations on outcomes. *Research in integrative healthcare allows for innovative research paradigms such as participant-centered research; such designs not only empower participants, but may enhance study recruitment and retention, promote greater understanding of the impact of participants' experiences and expectations on outcomes, and improve study generalizability and translation to the clinic and community.*

Outcome assessment tools. Optimal health in integrative medicine refers to a state of well-being of the whole person: physical, mental, social, and spiritual.⁸⁻¹¹ Therefore, outcome measurements in integrative health research need to expand beyond reduction of a specific symptom or reversal of a specific disease process.^{12,13} For example, researchers can use outcome measures emphasizing functional performance and those taking into consideration the mental, emotional, spiritual, and social outcomes,¹⁴ such as instruments used in rheumatology,¹⁵ neurology,^{16,17} geriatrics,^{18,19} rehabilitation,^{20,21} pain, and palliative care.^{22,23} Research in integrative healthcare would also rely on broad functional measures such as those developed through the NIH PROMIS project,²⁴ as well as disease-specific measures. These measures form a broader, more comprehensive and meaningful foundation for building personalized yet global outcome measurement systems.

Another important aspect in outcome measurement is the role of the patient or study participant. In patient-centered care, what patients perceive is equally, or perhaps more, important than what physiological parameters tell us. Participant-centered integrative health research incorporates individual participant preferences in considering appropriate study outcomes.²⁵ The value of patient-reported outcome measures is recognized increasingly by the medical community.^{26,27} Integrative health researchers can incorporate previous knowledge into their own studies and develop new methods, as needed, tailored to their own practice models.²⁸⁻³⁰

Application of information technology. The impact of information technology on integrative medicine is enormous. Easy and instant access to a vast amount of health-related information on the Internet via search engines such as Google and Wikis plays a large role in patients' senses of empowerment. This decentralization of information makes practitioners not the sole source of information. Meanwhile, the information, not uncommonly inaccurate, false, or contradictory, overwhelms, confuses,

and frustrates patients. On the other hand, information technology provides researchers with numerous tools that have not been utilized adequately.

Information technology can be used to enhance research in its capacity as a communication tool in many ways.

1. E-mails and text messages improve communications between providers and patients.^{31,32} Do e-mail communications encourage patient's stake in self-care, facilitate timely management of emerging medical problems, or reduce unnecessary utilization of healthcare resources? Do e-mail/text message communications help monitor patient responses and adverse events, improve adherence, and refine patient-centered outcome evaluation in clinical studies?
2. Online support groups, bulletin boards, chat rooms, blogs, and social network sites are frequented by patients to exchange notes on their diseases and healthcare providers. These media can be used to learn patients' perspectives and evaluate, advise, monitor, and support them in optimizing health outcomes. They also serve as a venue to recruit a large number of patients to research studies.
3. The raw computing power available to researchers has made certain previously impossible research feasible now. This is most obvious in bioinformatics and personalized medicine. Information technology enables the processing of the astronomical amount of information generated from genomic studies and the establishing of links between genomic variations and clinical outcomes.
4. Image processing technologies can be used to standardize and quantify some of the diagnostic techniques in traditional medicine.³³⁻³⁵
5. Web 2.0 technology³⁶ provides a social, collective and collaborative platform that simplifies data creation, integration, sharing, and reuse.³⁷ When expanded beyond the research community, it also presents a platform in education to other healthcare providers and the public.^{38,39}
6. Finally, artificial intelligence has potentials in contributing to whole system research.^{40,41} Many traditional medical systems rely on pattern recognition for diagnosis. Application of artificial intelligence in the recognition of those patterns may represent empirical knowledge on clinical manifestations of some yet nondelineated pathophysiological links.⁴²

Epidemiological Studies

A large number of epidemiological studies have assessed the use of CAM therapies, which have been variously defined.⁴³⁻⁵² Continued collection of this data is essential to further understanding of the field.^{45,50-53} Research describing integrative medicine training and clinical programs (including how they were established, the services offered, and the training and research projects they are conducting) is emerging.⁵³⁻⁵⁵

It would be beneficial to the field if a standardized survey could be created to gather data about CAM and integrative medicine use, including benchmarks such as the use of conventional therapies or care. This may be the most efficient way to collect descriptive data about integrative medicine's utilization, cost effectiveness, and the characteristics and satisfaction of the individuals who use it. Continuation of the alternative medicine

supplement to the National Health Interview Survey⁵⁶ is a minimal requirement to maintain an understanding of the utilization of CAM in the United States. *Efforts should be made to review and update the supplemental questions to be sure that they reflect changes and trends in the field, such as including questions specifically about integrative medicine, CAM treatments, and conventional care recommended by licensed clinicians, lay providers, and family/community caregivers.*

Basic Science Research

Mechanistic studies of specific CAM modalities. Mechanistic studies have begun to elucidate biomedical mechanisms to explain clinical effects of CAM therapies. For biologically based therapies such as botanicals, the research generally identifies the (presumed) active constituents of the study agents and the physiological pathways through which those constituents affect physical systems.⁵⁷⁻⁵⁹ However, the complex composition of botanicals may contain multiple compounds that synergize for a greater total activity than individual constituents.⁶⁰⁻⁶³ Studying natural products with complex composition presents challenges, such as standardization and quality control, unknown active constituents, multiple potential biological targets, and complex interactions among the constituents.^{64,65} *Newer experimental paradigms are needed to assess the differential effects of complex mixtures versus simple compounds. Similar to conventional pharmacotherapy, this research needs to also take into account the effects of secondary metabolites of botanicals on biological materials.*

Mechanistic studies of energy medicine, manipulative practices, and mind-body therapies involve delineation of the physiological pathways modulated by them (eg, the interactions among behaviors, the conscious mind, the autonomic nervous system, hormones, and immune functions).^{66,67} Through such research, the relationships between stress and disease, especially stress and immune function, are being explored.⁶⁸⁻⁷² The neuroendocrine stress response and immune systems have a bidirectional relationship that can affect susceptibility to inflammatory diseases. Individual variability in neuroendocrine responsiveness may contribute toward the efficacy of mind-body therapies.⁷³

The brain plays a central role as a target of stress and stress therapy. Neuroplasticity, a dynamic process that constantly alters the neurochemical, structural, and functional components of the nervous system related to experience, would be a worthwhile target to study with mind-body interventions. Some of the examples of the effect of mind-body approaches on brain structure include the increase in prefrontal cortex volume following cognitive behavioral therapy in patients with chronic fatigue syndrome⁷⁴ and increase in prefrontal cortex and right insula volume with meditation.⁷⁵ The role of neurotrophins, particularly brain derived neurotrophic factor as a mediator for neuroplasticity, is beginning to emerge and needs to be further characterized with respect to mind-body intervention.⁷⁶ The brain is a malleable organ, and the lack of resilience may be a key aspect of anxiety and mood disorders as well as other systemic problems.

Like psychotherapy, many behavioral and mind-body interventions require active patient participation, which cannot be reproduced in animal studies. Advances in functional neuroimaging technology, such as functional magnetic resonance imaging or

positron emission tomography, can demonstrate changes in activity in regions of the brain in real time and enable us to study the complex neuronal matrix involved in real-world emotional and social experience.⁷⁷ The technology has been used to study mind-body therapies or energy-medicine modalities in recent years.⁷⁸⁻⁸³

The specific neurobiological changes that might mediate the placebo effect could offer innovative therapeutic insights.⁸⁴ The efficacy of placebo effect on enhancing frontal modulation of nociceptive sensory and/or affect processing and individual variability in placebo responsiveness as a predictor of efficacy of mind-body interventions is an interesting area for future exploration.^{85,86}

Because physiological pathways are increasingly understood to be nonlinear and multidimensional, traditional laboratory approaches tend to be too simplistic to capture the complexity of real clinical situations. Advanced mathematical and statistical modeling techniques will be important to advance research in the complex systems of integrative medicine. Sensitive and non-invasive methods that can measure multiple biomarkers are likely to help identify pathways that may be selectively affected by different interventions.^{87,88}

Application of genomic science to personalized healthcare. Some technologies developed in genomic sciences can be harnessed to enhance integrative medicine research, in particular toward personalized healthcare. Genomics refers to the study of all the genes of a cell, or tissue, at the DNA (*genome*), mRNA (*transcriptome*), or protein (*proteome*) levels. It is well known that individuals respond differently to risk exposure and interventions. More knowledge of the DNA sequence of the human genome and the function of individual genes and their variants makes it possible to identify individuals at risk for a particular medical condition or responsive to a particular intervention.

Variations at nearly 100 regions of the genome have been associated with an increased risk for diseases with a complex genetic background, such as diabetes, inflammatory bowel disease, cancer, and heart disease.⁸⁹ Genetic variants in nicotinic receptor genes were found to be linked to nicotine dependence and smoking behavior, which may explain why some patients are particularly resistant to smoking cessation measures.^{90,91}

Individuals respond differently to nutrients, and nutrients affect gene expression (*nutrigenomics*).⁹² Individuals with one genetic variant of an intestinal fatty acid-binding protein gene have significantly greater decreases in plasma total and low-density lipoprotein cholesterol and apolipoprotein B when consuming a diet rich in soluble fiber.⁹³ Better understanding of nutrigenomics would help us in understanding the “individuality” of one’s response to bioactive food components.⁹⁴ The Institute of Medicine has held a workshop to review the state of nutritional genomics research and to provide guidance for further development and translation of this knowledge into nutrition practice and policy.⁹⁵

The ever expanding database in *pharmacogenetics* helps us understand why individuals respond quite differently to the same biological intervention. Differences in response to drugs or dietary supplements may also come from varied metabolism from polymorphism in drug-metabolizing cytochrome P450 enzymes.⁹⁶ Depending on the allele combinations, a patient can be

a poor, intermediate, extensive, or ultrarapid metabolizer. Extensive metabolizers may have markedly increased risk of side effects, whereas poor metabolizers would experience poor efficacy of the drug.⁹⁷

Epigenetics refers to the study of heritable changes in gene function that occur without a change in DNA sequence.⁹⁸ Such changes can occur via mechanisms such as DNA methylation, chromatin structural modifications, and RNA interference.⁹⁹⁻¹⁰¹ Inspired by the Human Genome Project, researchers are working to provide high-resolution reference epigenome maps and speed progress in epigenetic research (the Alliance for the Human Epigenome and Disease).¹⁰² Epigenetics takes into consideration the effects of the environment on gene expression patterns that can be passed along to daughter cells, setting the stage for disease preventive interventions to have a lasting effect. These findings may lead to novel cancer prevention strategy that acts early in the cancer pathogenesis process,¹⁰³ including use of botanical agents or nutritional approaches.¹⁰⁴

Although these technologies are exciting and promising, they are expensive and require additional development before their results can be translated into effective clinical care. At this point, the science to make personalized treatment decisions is available at a level of confidence only for a handful of diseases. *Much work needs to be done to achieve the ideal of personalized integrative medicine based on genomic technologies.*

Clinical Research

Therapeutic clinical trials and meta-analysis. To date, the majority of CAM clinical trials have evaluated single components in treating a specific medical condition (eg, Saint-John's-wort for depression, a specific set of acupuncture points for headaches, a protocol of chiropractic adjustments for low back pain, or melatonin for insomnia). It is beyond the scope of this paper to provide a summary of all the clinical trials conducted in the field. In some cases, there have been enough studies on a particular treatment and condition to result in a systematic review or meta-analysis. *Cochrane Database Systematic Review* has published more than 600 articles related to complementary therapies as of November 2008. Readers are referred to those reviews for a summary of findings in clinical trials.¹⁰⁵⁻¹¹²

Two common limitations of nonpharmacologic interventions (including conventional therapies such as surgery and psychotherapy) are difficulty with blinding and providing a credible control intervention. Some of the approaches that used surgery and psychology that might be applicable include blinding participants to the study hypothesis, use of sham training approaches, sham procedures, similar attention-control interventions, and blinding of outcome assessors.¹¹³

Incorporating elements of the CONSORT statement for the nonpharmacologic treatments in designing trials may be helpful.¹¹⁴ *Taking a participant-centered approach and including outcomes that evaluate the basic mechanisms (such as modern imaging studies) as well as outcomes related to participant priorities, safety, and social/economic outcomes will increase the strength of the evidence even if the study can only be designed as a single-blind (investigator) trial.* Investigator neutrality may be particularly challenging for studies of nonpharmacologic interventions because part of the treatment effect may be related to the context and process of care, such as that

seen in Traditional Chinese Medicine.¹¹⁵ Concurrent use of different study designs (RCT, single-blind trials, quasi-experimental design, retrospective cohorts) can strengthen conclusions and enhance generalizability of results while providing rich information about the impact of patient and provider expectations and beliefs on outcomes.

Identification and inclusion of generalizable molecular markers that have been correlated with functional measures (such as inflammation and stress) and are responsive to treatment (such as telomerase activity and telomere maintenance capacity in human immune system cells improving with stress management) increase the credibility of study findings and provide objective surrogate outcome measures.^{116,117}

A challenging issue in studying biologically based therapies, such as dietary supplements, is securing a consistent study agent with multiple and sometimes unknown active constituents.¹¹⁸ Careful selection of the study population, endpoints, and sample sizes are also crucial for success. *Structured, well-thought-out approaches need to be developed so that limited resources are optimally used to test interventions with a high potential for efficacy,¹¹⁹ particularly in light of several recent expensive negative trials with dietary supplements.*¹²⁰⁻¹²⁴

Attention needs to be paid to the scope and overall design of the study with the intent to balance internal validity with external generalizability. *For dietary supplements, phase I/II trials are helpful for establishing optimal formulations, dosages, and safety before embarking on expensive phase III trials.^{125,126} For mind-body, energy-based, and manual interventions, initial focus on creating a structured and reproducible intervention consistent with how they are practiced in real life along with an appropriate control group would be worthwhile.*

Combining data for a meta-analysis can be particularly challenging in the field of integrative healthcare. For example, there are hundreds of forms of Qi gong, and each is used traditionally for different reasons; there are several traditions of acupuncture and many different needling techniques; herbal preparations can vary greatly depending on the growing conditions and extraction methods. The appropriateness of merging such a diverse group of therapies in meta-analysis and the resultant conclusions is subject to debate.

Whole system research and multimodality studies. A new trend in integrative health research is the push for *whole systems* research, which strives to examine the effect of a multimodality healthcare approach to provide individualized treatment, since this will more accurately evaluate the healthcare that is currently being provided to patients. There are several commentaries in the literature urging integrative medicine researchers to consider research methods beyond the RCT.¹²⁷⁻¹³⁰ For example, Ritenbaugh et al¹³¹ examined the effect of whole system Traditional Chinese Medicine versus naturopathic medicine versus usual care for treating temporomandibular disorders.

Several investigators have discussed the need to use more complex methods of analysis so that these systems of healthcare can be examined, rather than the efficacy of each part of the system.^{130,132,133} Some suggest using network and complex system analysis as methods for assessing whole systems research. However, it is critical for researchers interested in these methods

to work with skilled biostatisticians experienced with these more complex statistical methods.¹³² Verhoef et al¹³³ encourage researchers to add qualitative measures to studies because they can provide a source of data for unexpected outcomes and a way to measure the broader effects of a whole system, such as integrative medicine. *It is important for researchers in the field of integrative medicine to consider the range of effects the treatments may have for patients, and thus to measure a broad area of outcomes to detect these effects.*

Beyond Therapeutic Clinical Trials

Individual resilience and hardiness. Of the three variables in the triangle of disease causation (agent, host, and environment), host factors remain suboptimally addressed. Alternative medical systems consider strengthening the host as a primary focus. Resilience and hardiness refer to positive abilities and skills of an individual in response to stress and adversity.¹³⁴ Exposure to stress and traumatic events is common, but, not all of those exposed develop posttraumatic stress disorder or other negative health outcomes. Hardiness is correlated with positive health outcomes.¹³⁵⁻¹³⁷ Individual aspects of resilience are also associated with positive outcomes.^{138,139} For example, greater prevent internal locus of control prevents posttraumatic stress disorder in women giving birth¹⁴⁰ and maintains treatment gains for patients with posttraumatic stress disorder. Resilience is thus an important concept in the fields of physical, mental, and spiritual health. *Additional research is needed to enhance understanding of hardiness or resilience factors that protect an individual from developing physical and emotional illness in the face of stress, to identify optimal strategies in developing resilience within integrative medicine, and to identify social factors that can be modified to support hardiness to promote public health.*

Social factors and practitioner-patient relationship. Social support enhances resilience and improves many diverse health outcomes.¹⁴¹⁻¹⁴⁴ A strong network of friends was associated with improved survival in the elderly.^{145,146} The effect of social support on physical health and longevity may be mediated through improved depressive symptoms, perception of a better quality of life, better access to resources, improved use of resources, positive effects on the immune system, a sense of engagement, and a greater feeling of purpose.¹⁴⁷⁻¹⁵⁰ Practitioners can offer meaningful social support that enhances health outcomes.^{151,152} When individuals become a caregiver of a family member with a chronic disease, it is important to assess the strain and burden of this role and provide support and coping strategies to help maintain wellness of the caregiver.¹⁵³⁻¹⁵⁵

Integrative medicine emphasizes the importance of the *relationship* between practitioner and patient to achieve optimal health and healing through shared decision making.^{156,157} There has already been an enormous body of research in the area of the doctor-patient relationship and the process of care (eg, access, length, practice patterns, cost). There has also been substantial research in related areas such as social support,^{158,159} communication,^{160,161} patient-centered care,^{162,163} empathy,¹⁶⁴⁻¹⁶⁶ effective ways of promoting behavior change,¹⁶⁷⁻¹⁶⁹ different types of clinical encounters (eg, individual vs group; in person vs telephone or internet),¹⁷⁰⁻¹⁷² patient satisfaction,¹⁷³⁻¹⁷⁵ trust,^{176,177}

and team building and shared governance.^{178,179} *To date, little of this research on the processes of relationship-based care has been synthesized and integrated into the field of integrative medicine.* For example, research on acupuncture now often includes placebo needles, but has not examined closely the process of building the relationship between therapist and patient or compared the processes of care provided by acupuncturists with that provided by practitioners; nor have comparisons been made about the relationships among team members on traditional medical multidisciplinary teams (eg, clinician, nurse, social worker, physical therapist, occupational therapist) with integrative teams (eg, naturopathic practitioners, nutritionists, acupuncturists, massage therapists).

Self-care, behavior change, adherence. One of the most important issues in healthcare is how to best inspire, motivate, empower, and facilitate self-care. Self-care includes both processes and action capabilities.¹⁸⁰ The processes include life experience, learning processes, and ecological processes. Action capabilities include power and performance capabilities.

The primary aim of inspiring, motivating, and empowering patients is toward a single goal—improving health through positive behavior change. Several models have been developed to address behavior change. These include models based on attachment theory,¹⁸¹ the chronic care model,^{182,183} the extended parallel process model,¹⁸⁴ the health belief model,^{185,186} the problem-solving model,^{187,188} the self-management model,^{189,190} social cognitive theory,^{191,192} the transtheoretical model,^{193,194} and the theory of reasoned action.^{195,196} Ideally, clinical counseling incorporates several essential components for successful behavior change. Most of these models were developed to address a single specific medical condition. *Behavior change models need to be tested within the context of multiple, concurrent, common, complex medical conditions.*

Comprehensive, integrative treatment recommendations, even for patients with a single diagnosis, involve lifestyle modifications as well as medications, resulting in complex, multifaceted treatment plans.¹⁹⁷ Although most research on adherence has focused on medications, little is known about the impact of combining advice about medications with advice about other practices or therapies on adherence to the pharmaceutical regimen. Lifestyle counseling appears to increase patient satisfaction, but its overall impact on cost of care and adherence is largely unknown.^{198,199} Furthermore, adherence to specific recommendations may vary according to patients' *explanatory models*.²⁰⁰ For example, patients who believe their hypertension is related to stress may be more adherent to recommendations about stress management, whereas patients who believe their blood pressure is purely a genetic or biochemical problem may be more adherent to pharmaceutical regimens.²⁰¹ Different explanatory systems could have dramatically different impact on patients' willingness to embark on or adhere to different treatment regimens. *Research is needed on how to best match patients' explanatory models with treatment options and the impact of matching/mismatching on adherence, clinical outcomes, satisfaction with care, and cost of care.*

The global village—social determinants and consequences of health. Integrative healthcare looks beyond individual health behaviors to larger environmental, social and educational factors affecting health. Research has begun to establish the critical role of the environment on human health.²⁰²⁻²⁰⁵ Research will play an important role in determining the most effective, efficient, and equitable strategies for translating new knowledge about environment into integrative clinical practice. Providing conventional healthcare also impacts the environment (eg, pharmaceuticals contaminating drinking water supplies; biological and technical waste disposal; and incineration of mercury, polyvinyl chloride, and other products), which in turn affects human health.²⁰⁶⁻²¹¹ There is strong evidence that stress adversely affects health; yet little research has addressed ways in which healthcare institutions can effectively improve their environment, reducing stress for both clinicians and patients to achieve optimal healing environments. Social support mitigates the pernicious effects of many stressors, yet there has been little systematic research on the most cost-effective strategies to improve social support for patients, family members, clinicians, or staff within healthcare institutions, or the impact of such changes on health outcomes. *Research is needed to address ways in which integrative healthcare providers and institutions can reduce their adverse environmental impacts and promote positive healing environments while providing high-quality affordable, effective, comprehensive, patient-centered care.*

Advances in media, communication, commerce, and transportation technologies have resulted in well-documented changes in health behaviors (eg, decreases in fruit and vegetable intake, increases in sedentary behavior), access to health information and misinformation, and access to health services (eg, internet counseling, international travel for surgical procedures, telemedicine)²¹²⁻²¹⁸ and professional education. Integrative medicine has been a leader in providing online courses.²¹⁹⁻²²¹ *Research is needed to determine the most cost-effective and equitable strategies to provide integrative medicine and health education using modern telecommunications, including telephone, the Internet, webinars, and teleconferences for both individual and group models.*

Social policies also profoundly affect health. *Integrative health, as a holistic discipline, must include research to better understand the impact of public policies on overall health.* Little research has been conducted to evaluate the health consequences of variations in social policies about agriculture, transportation, education, or energy. Such studies might include regional comparisons in the United States, or comparisons of the effects of policy variations between countries and over time, on broad health outcomes.

Public policies that affect payments for certain kinds of healthcare (eg, certain providers: doctors of medicine, doctors of osteopathy, doctors of chiropractic) and a few kinds of therapy (prescription drugs and surgery) versus policies promoting payment for fitness club memberships, massage, nutritional supplements, and diverse health providers, may have very different impact on health outcomes. The current reimbursement schemes in the United States incentivize short, repeated visits in which patients do not improve much and continue to return frequently for medication refills. Certain kinds of care (eg, patient-centered, good communication skills, stress reduction coaching, lifestyle coaching,

etc) shown beneficial in research are unlikely to be sustainable in the absence of policies supporting their financial viability. *Thus, research is needed regarding the effective translation of knowledge about the environment and behavior into effective social policies and reimbursement schemes.*

SETTING PRIORITIES FOR THE INTEGRATIVE HEALTHCARE RESEARCH AGENDA

Framework to Set Priorities

Given the large number of research areas that need to be addressed, and limited resources, a systematic approach to prioritizing projects is needed. A model has been proposed that includes attention to high-priority conditions, populations, therapies, and a comprehensive view of important outcomes.²²²

Conditions. Priority should be given to conditions and diseases that satisfy the criteria in Table 1, those that impose a heavy burden of suffering for which current therapies are insufficient and for which integrative approaches offer a reasonable likelihood of being helpful and are already in use. Examples include anxiety; asthma; attention-deficit disorder; back pain; cancer; cardiovascular diseases and stroke; chronic and severe pain syndromes; depression; developmental disorders, including autism; insomnia; obesity/metabolic syndrome; recurrent respiratory infections; rheumatic and autoimmune disorders; and addictive disorders.

Therapies. Therapies requiring additional professional intervention are also priorities for research because of the substantial costs associated with professional care. Thus, research on the effectiveness, safety, and costs of chiropractic, acupuncture, elec-

Table 1. Criteria for Conditions, Diseases, and Risky Health Behaviors With High Priority for Integrative Health Research

Those that impose a heavy burden of suffering on individuals, families or the community either because of their	<ul style="list-style-type: none"> ● severity ● chronicity ● prevalence
And for which current mainstream therapies are unacceptable or insufficient because of	<ul style="list-style-type: none"> ● lack of proven efficacy ● substantial side effects ● cost ● lack of availability
And for which integrative health offers a reasonable likelihood of being helpful based on	<ul style="list-style-type: none"> ● proven safety in animal models ● lengthy historical use or compelling results from case reports, case series, epidemiologic studies, case-control trials or cohort studies, or clear scientific rationale
And for which widespread use by families and/or clinicians already occurs.	

troencephalographic biofeedback, hypnosis, or other mind-body techniques requiring licensed professional therapists should be high priorities.²²³⁻²²⁵ Research on interventions (eg, certain natural products) that have already been supported by a substantial amount of preliminary data and are on the verge of definitive evidence for widespread clinical application should also be prioritized, as such research is likely to be a high-yield investment.

Types of research: synthesis. Given the frequently conflicting data from medical research studies, overviews and data synthesizing analyses are critically important for translating research into practice. The Cochrane Collaboration and others have made important contributions to this field over the last 10 years, and additional analyses providing specific guidance to practicing clinicians, policy makers, and researchers is needed.²²⁶⁻²²⁹

Outcomes. Outcomes include not only traditional measures of morbidity, mortality, cost of care, and patient satisfaction, but also the impact of care on family cohesiveness, cultural identity, spiritual beliefs, resilience, coping, and self-efficacy, as well as clinician competence, burnout, quality of care, and impact on outcomes (Table 2). The impact on the environment, and social outcomes such as participation in work or school, also should be considered. *Additional outcome measures may need to be developed to address the concept of health as optimal functioning rather than as the absence of disease and to address patient priorities, particularly when there are multiple coexisting outcomes of interest.*

The following are specific areas of research for discussion in setting priorities.

Spectrum of Life Cycle

Integrative healthcare can be provided to patients across the demographic spectrum of age, gender, and race/ethnicity. There may be disparities in the availability and quality of services to different populations.²³⁰ Integrative care can also be provided for prevention, and acute and chronic illness, as well as rehabilitation and palliation. Among the most vulnerable populations that have been least studied are children and adolescents and patients suffering from genetic or congenital disorders. Other research populations that should be considered as high priorities include women across the life cycle, including those who are pregnant, breast-feeding, in different phases of the menstrual cycle, or at menarche and through menopause; the frail elderly; patients with complex conditions and multiple comorbidities; patients at the end of life; those with limited access to care; and patients from diverse cultural/ethnic backgrounds. It is also important to study how different therapies and practices differentially affect diverse individuals (age, gender, race/ethnicity, culture, socioeconomic status).

Epidemiological Studies

With the development of large integrative clinics across the United States, epidemiological methods can be used to generate novel data. A number of these institutions have begun collecting outcomes data on their patients to allow for prospective studies of integrative medicine for “The Outcomes Research

Table 2. Outcomes of Interest in Research on Integrative Health

Patient outcomes

- Mortality rates, years of life saved
- Morbidity: physical, mental, emotional, spiritual, and social symptoms; severity of illness
- Health behaviors: dietary, exercise patterns; smoking, drinking, drug use; unprotected sexual relations; sleep; stress management; positive communication and relationships
- Healthcare use and costs, including self-care, complementary and alternative medicine care, and conventional care
- Satisfaction with care
- Developmental milestones and behavior
- Activities of daily living
- Quality of life
- Costs associated with care
- Direct and indirect financial costs; opportunity costs of missed treatments; side effects: symptomatic and asymptomatic organ dysfunction, injuries, infection; adverse interactions with other therapies; x-ray and other toxic exposures

Social outcomes

- Days of work/school missed; delinquency, incarceration

Family outcomes

- Days of work missed, out-of-pocket costs, impact on insurability
- Psychosocial impact on families, emotional impact on sense of empowerment

Spiritual outcomes

- Coping, peace, serenity, harmony in relationships, a sense of meaning or purpose in life, self-efficacy, self-esteem

Social outcomes

- Divorce, employment, bankruptcy

Community outcomes

- Sense of cohesiveness, cultural identity; social capital
- Cost to society, rate of malpractice suits
- Environmental impact: cost of remedy to society, environment, (overharvesting of herbs leading to extinction; climate change; pollution)

Provider outcomes

- Provider satisfaction with role
- Burnout, sense of effectiveness and being part of healing community?

Project.”²³¹ In addition to outcomes data, it would be useful for these clinics to create patient registries to gather data on the specifics of the therapies and practices for each patient.

Comprehensive epidemiologic data are also important for clinical research studies because CAM therapies and lifestyle practices can confound findings of cohort and case-control studies. For example, individual vitamins can impact all causes of mortality.²³²⁻²³⁵ On the other hand, some dietary supplements can adversely interact with pharmaceuticals.²³⁶ Accounting for and minimizing possible confounding effects is not possible if the data are not collected.

Comparative effectiveness and health services research are also high priorities.^{237,238} Descriptive studies are needed to determine how providers practice, what patients seek care from integrative health clinics, the benefits they receive, and the cost effectiveness of integrative care.^{128,129,237,238} Before studying the efficacy of individual components of integrative care, pragmatic research should demonstrate the effectiveness of comprehensive integrative care in the real-world setting in which multiple complex interventions are used simultaneously. Better descriptions of the scope of this kind of care are urgently needed.²³⁷

Basic Science, Mechanistic Studies

Taking mechanistic research to the extreme may lose sight of the complex, interactive nature of human diseases and behaviors. Integrative researchers should guard against this. On the other hand, reductionist research is essential to understand the mechanisms of the effects of integrative care.

Among the areas that should be considered as priorities are the following:

1. Genomic/proteomic/pharmacogenetic studies investigating the individuality of patients, despite sharing the same diagnostic label. Such knowledge can be used to develop more personalized healthcare.
2. System biology studies to identify and characterize the interactions between multiple components of the biological processes and the interactions between mind and body. This research could improve appreciation of the interconnectedness of various components in human health and lead to therapeutic strategies that take advantage of such knowledge.
3. Research on how behavioral interventions can change biological processes at the molecular and cellular level. This would create more effective tools for further behavior modifications relevant to reversing human diseases.
4. Research on the brain's role in physiological adaptation and the effects of stress (eg, neuroimaging studies of adaptive plasticity).

Diagnostic Techniques

An area in need of further research is a critical assessment of the many novel laboratory assessments intended for evaluation of biomarkers indicative of disease risk, prognosis, or treatment options. Because of the novelty of these tests, little or no data exist about their sensitivity and specificity, making interpretation of results difficult. In some cases, the tests offered are not diagnostic but rather informative of the individual, with their clinical meaningfulness unknown. Until more research documents their validity and reliability, these tests will continue to be considered experimental and will not be reimbursed by conventional insurance, limiting their availability to certain economic groups.

Clinical Interventions

Study design. The paradigm of pragmatic (effectiveness) versus explanatory (efficacy) studies remains relevant for integrative healthcare.^{239,240} The pragmatic nature of a large RCT, even one with few restrictions for enrollment, is still limited because the

complex variables that go into individual decision making cannot be controlled in a clinical trials setting.²⁴¹ For research to be generalizable, it is important to define the real-world contexts in which the results are to be applied. Another important issue here is the selection of appropriate outcome measures. *Wherever possible, participants should help select meaningful outcome variables in pragmatic trials.*²⁴² The basic elements of study design and conduct need to be addressed adequately, as noted above.²⁴³ Even with a good study design, a single neglected issue could seriously impact the validity of the results.²⁴⁴ This highlights the relevance of concurrent studies with different designs to help minimize potential limitations from one type of trial (eg, limited enrollment in RCTs in which potential participants have ready access to the therapy or practice outside the trial and have strong preferences for one type of treatment). *Researchers should partner with practitioners and patients to develop and conduct community-based participatory research or participant-centered research with strong designs to minimize bias and maximize meaning and translation into improved practice and policy while being mindful of the appropriate stage of research (pragmatic vs explanatory).*

Personalized and holistic healthcare. In a holistic view, many health conditions are connected through underlying hub processes such as inflammation. This connection has been underappreciated in a reductionist research approach but is quite commonly reflected in the narratives of many traditional medical systems. Systems biology research has shown a network topology for disease comorbidity.²⁴⁵⁻²⁴⁷ Integrative health research can similarly use mathematical models to explore other such connections based on genetic and functional variables.^{132,133, 248}

To emphasize patient-centered care, future integrative health research should take advantage of technological advancements to individualize intervention and outcome assessment.²⁴⁹ Application of pharmacogenetics knowledge to herbal medicine trials may result in a better selection of the study population, reducing sample size while increasing the effect size, leading to more efficient use of research resources and minimizing the number of falsely negative trials.^{250,251} Computerized patient-centered outcomes assessment networks would produce efficacy endpoints. These endpoints should take into consideration patients' priorities, be clinically relevant, and be consistent with the goal of integrative health.²⁵²

Patients' expectations and beliefs about therapies are intricately linked to their explanatory models and sense of meaning.^{253,254} New methods and tools are being devised to assess patients' beliefs and attitudes, but these have not been widely implemented.²⁵⁵⁻²⁵⁷ Different practitioners' expectations, beliefs, values, and explanatory models are likely to affect the kinds of diagnostic evaluations, counseling, and treatments offered to patients.²⁵⁸⁻²⁶⁰ In addition, patients may have different values and priorities in addressing their symptoms, and attention to these priorities may affect satisfaction with care and adherence to recommendations.²⁶¹ *The complex issues inherent in providing patient-centered integrative care in the context of multiple conditions in patients with different priorities, values, expectations, and beliefs are poorly understood. It is possible that new research paradigms will be needed to address this lack of knowledge, not only for clinical outcomes,*

but for satisfaction with and cost of care for patients, as well as the impact on practitioners (eg, burnout and fatigue) and the public's health (eg, overall healthcare costs, impact on work/school, activities of daily living).

Promoting self-care and resilience. To encourage health-enhancing behavior and promote self-care, integrative healthcare relies on tools from psychological sciences, such as skills of motivational interviewing.²⁶² Resilience can be enhanced through use of mind-body modalities such as relaxation, hypnosis, visual imagery, meditation, yoga, Tai Chi, Qi gong, cognitive-behavioral therapies, group support, autogenic training, and spirituality. In addition, resilience can be reinforced through spiritual practices such as cultivating compassion, forgiveness, gratitude, and finding meaning and purpose to one's life.^{263,264} Optimal disease management and healthy lifestyles including nutrition, physical exercise, restorative sleep, and an optimal environment are also likely to foster resilience. Interventions primarily aimed to foster resilience are beginning to be tested in clinical trials.²⁶⁵⁻²⁶⁸ Early studies suggest that resilience might correlate with selective activation of the left prefrontal cortex.²⁶⁹ This needs to be further validated. *Effective strategies to promote optimal individual and social behaviors and policies need to be developed and tested to foster sustained health improvements. Research into (a) designing and testing resilience interventions incorporating the wisdom of traditional and indigenous healing systems and (b) further understanding of the neurobiology of resilience have the potential to transform healthcare; they are high priorities for research in integrative health.*

Practitioner-patient interaction and partnership. Integrative care entails incorporating biopsychosocial interdisciplinary content, emphasizing compassion, communication, mindfulness, respect, and social responsibility.²⁷⁰ A core aspect of such care is the relationship between practitioner and patient,^{157,271} (ie, relationship-centered care). The two key skills for practitioners to facilitate this relationship-centered care are to cultivate professionalism and humanism.²⁷² *The impact of training clinician healers is beginning to be investigated. A high priority for future research is comparative effectiveness of different educational and training strategies, including continuing education in integrative healthcare in achieving relationship-centered care.*

In a clinical trial, patients improve for multiple reasons. These include spontaneous remission, natural course, regression to the mean, biased reporting, nonspecific therapeutic effects, and specific therapeutic effects. The nonspecific therapeutic effect, which may account for improvement in up to 60% of patients for some of the conditions,²⁷³ has been considered more a nuisance than a useful therapeutic effect because of the need to control within the context of placebo-controlled trials for pharmacologic treatments. However the efficacy observed in the placebo arm may sometimes be significantly superior to no treatment or standard medical care.²⁷⁴⁻²⁷⁷ The skills of professionalism and humanism within an integrative encounter are likely to increase this nonspecific effect.

Instead of considering the placebo effect as of secondary importance, it might be more apt to consider the placebo effect as "contextual healing," or nonspecific psychoneuroimmunologic stimu-

lant, an aspect of healing that has been produced, activated, or enhanced by the context of the clinical encounter.²⁷⁸ Variables that maximize contextual healing include the environment of the clinical setting, cognitive and affective communication of practitioners, and the ritual of administering the treatment.²⁷⁹ Research designed to harness the nonspecific therapeutic effect rather than controlling for it is likely to offer expanded tools and additional insight into patient care. In situations where it is important to separate the specific effect from contextual healing, optimal effort needs to be placed toward validating a placebo control prior to pursuing large multicenter trials. *A high priority for future research is to better understand and promote the nonspecific psychoneuroimmunologic effects of placebo, relationship, and context within complex systems of integrative care.*

RECOMMENDATIONS FOR ACTION

The ultimate goal of integrative health research is to guide clinical practice and public policy to maximize health. When formulating guidelines, two factors are critical: strength of evidence and burden/risk to the patient. Because decisions must at times be made with limited information, burden and risk to the patient need to be taken into account. Although the highest level of evidence is desirable for every health intervention, it is simply not possible to achieve this goal. Limited research resources should be allocated according to priorities. Interventions or therapies with high risk or burden (economic, time, and effort) demand a high standard of evidence, often in the form of multiple RCTs, to be utilized in clinical practice. Those with low- or little risk/burden can be incorporated into practice even when the highest level of evidence is not available.²⁸⁰ Such an approach can be summarized in a simple 2 × 2 table (Table 3) about how to decide whether or not to use a particular therapy based on safety and effectiveness. Implicit in this model is the notion that the clinician and patient both understand and agree on the problem, the goal of therapy, the evidence regarding safety and effectiveness of the therapy being considered, the extent to which it is accessible, affordable, and that it is of high and consistent quality, as well as similar information about alternative treatments (or a combination of treatments) under consideration for this and possibly other problems or diagnoses.

In view of this relationship between research and clinical practice and the issues discussed in previous sections, we make the following recommendations for action regarding integrative medicine research; key stakeholders need to be identified to make it a collaborative, multidisciplinary effort for each item—including researchers, patients, and policy makers:

Table 3. Benefit and Risk Ratio and Selection of Therapies

	Effective	
	Yes	No
Safe		
Yes	Use	Tolerate
No	Monitor	Avoid

- prioritize pressing areas of research in integrative medicine and define the level of evidence required for their clinical applications
- establish a consortium of integrative medicine researchers to form consensus on how to implement the research priorities
- build an international information technology platform that standardizes and facilitates data acquisition, data banking, and communication between researchers to achieve synergy of productivity
- conduct comparative effectiveness and cost-effectiveness research to inform clinicians and policy-making bodies, especially in light of burgeoning healthcare cost to society, so that more resources can be allocated to integrative medicine research
- develop and evaluate new models of participant-centered research evaluating whole system interventions for patients with multiple, complex, chronic, common problems

We propose the following questions to be discussed:

1. What are the three most important research questions in integrative healthcare as a whole?
2. What should be the top three research priorities in integrative health in the setting of limited resources?
3. What progress would you like to see made in integrative health research in the next three to five years?

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