CHAPTER 2

Conceiving the Research Question and Developing the Study Plan

Steven R. Cummings, Warren S. Browner, and Stephen B. Hulley

The **research question** is the uncertainty that the investigator wants to resolve by performing her study. There is no shortage of good research questions, and even as we succeed in answering some questions, we remain surrounded by others. Clinical trials, for example, established that treatments that block the synthesis of estradiol (aromatase inhibitors) reduce the risk of breast cancer in women who have had early stage cancer (1). But this led to new questions: How long should treatment be continued; does this treatment prevent breast cancer in patients with BRCA 1 and BRCA 2 mutations; and what is the best way to prevent the osteoporosis that is an adverse effect of these drugs? Beyond that are primary prevention questions: Are these treatments effective and safe for preventing breast cancer in healthy women?

The challenge in finding a research question is defining an important one that can be transformed into a feasible and valid **study plan**. This chapter presents strategies for accomplishing this (Figure 2.1).

ORIGINS OF A RESEARCH QUESTION

For an established investigator the best research questions usually emerge from the findings and problems she has observed in her own **prior studies** and in those of other workers in the field. A new investigator has not yet developed this base of experience. Although a fresh perspective is sometimes useful by allowing a creative person to conceive new approaches to old problems, lack of experience is largely an impediment.

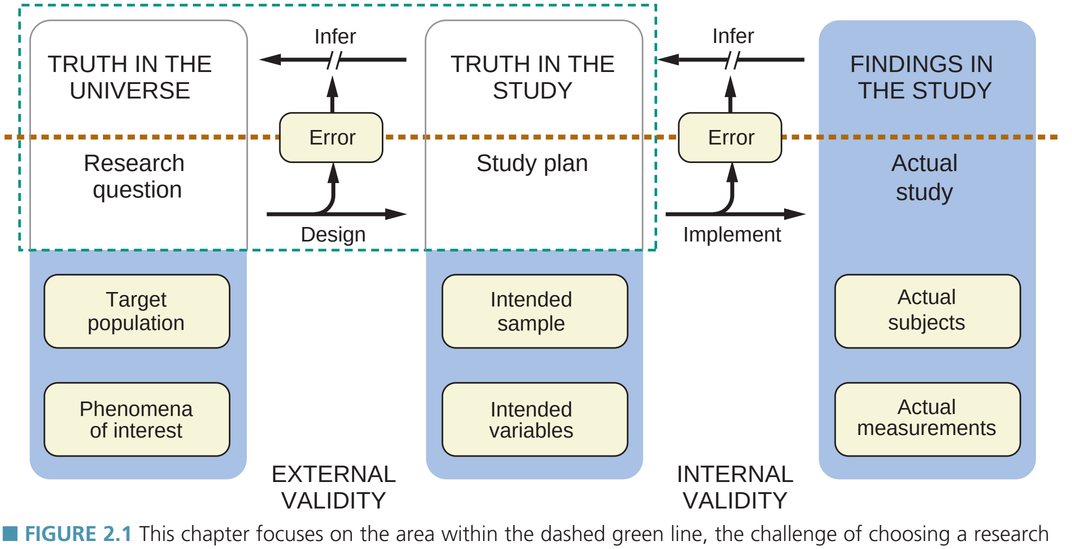


FIGURE 2.1 This chapter focuses on the area within the dashed green line, the challenge of choosing a research question that is of interest and can be tackled with a feasible study plan.

A good way to begin is to clarify the difference between a **research question** and a **research interest**. Consider this research question:

- Does participation in group counseling sessions reduce the likelihood of domestic violence among women who have recently immigrated from Central America?

This might be asked by someone whose research interest involves the efficacy of group counseling, or the prevention of domestic violence, or improving health in recent immigrants. The distinction between research questions and research interests matters because it may turn out that the specific research question cannot be transformed into a viable study plan, but the investigator can still address her research interest by asking a different question.

Of course, it's impossible to formulate a research question if you are not even sure about your research interest (beyond knowing that you're supposed to have one). If you find yourself in this boat, you're not alone: Many new investigators have not yet discovered a topic that interests them and is susceptible to a study plan they can design. You can begin by considering what sorts of research studies have piqued your interest when you've seen them in a journal. Or perhaps you were bothered by a specific patient whose treatment seemed inadequate or inappropriate: What could have been done differently that might have improved her outcome? Or one of your attending physicians told you that hypokalemia always caused profound thirst, and another said the opposite, just as dogmatically.

Mastering the Literature

It is important to master the published literature in an area of study: **Scholarship** is a necessary precursor to good research. A new investigator should conduct a thorough search of published literature in the areas pertinent to the research question and critically read important original papers. Carrying out a **systematic review** is a great next step for developing and establishing expertise in a research area, and the underlying literature review can serve as background for grant proposals and research reports. Recent advances may be known to active investigators in a particular field long before they are published. Thus, mastery of a subject entails participating in meetings and building relationships with **experts** in the field.

Being Alert to New Ideas and Techniques

In addition to the medical literature as a source of ideas for research questions, it is helpful to attend **conferences** in which new work is presented. At least as important as the formal presentations are the opportunities for informal conversations with other scientists at posters and during the breaks. A new investigator who overcomes her shyness and engages a speaker at the coffee break may find the experience richly rewarding, and occasionally she will have a new senior colleague. Even better, for a speaker known in advance to be especially relevant, it may be worthwhile to look up her recent publications and contact her in advance to arrange a meeting during the conference.

A **skeptical attitude** about prevailing beliefs can stimulate good research questions. For example, it was widely believed that lacerations which extend through the dermis required sutures to assure rapid healing and a satisfactory cosmetic outcome. However, Quinn et al. noted personal experience and case series evidence that wounds of moderate size repair themselves regardless of whether wound edges are approximated (2). They carried out a randomized trial in which all patients with hand lacerations less than 2 cm in length received tap water irrigation and a 48-hour antibiotic dressing. One group was randomly assigned to have their wounds sutured, and the other group did not receive sutures. The suture group had a more painful and time-consuming treatment in the emergency room, but blinded assessment revealed similar time to healing and similar cosmetic results. This has now become a standard approach used in clinical practice.

The application of **new technologies** often generates new insights and questions about familiar clinical problems, which in turn can generate new paradigms (3). Advances in imaging and in molecular and genetic technologies, for example, have spawned translational research studies that have led to new treatments and tests that have changed clinical medicine. Similarly, taking a new concept, technology, or finding from one field and applying it to a problem in a different field can lead to good research questions. Low bone density, for example, is a risk factor for fractures. Investigators applied this technology to other outcomes and found that women with low bone density have higher rates of cognitive decline (4), stimulating research for factors, such as low endogenous levels of estrogen, that could lead to loss of both bone and memory.

Keeping the Imagination Roaming

Careful **observation** of patients has led to many descriptive studies and is a fruitful source of research questions. **Teaching** is also an excellent source of inspiration; ideas for studies often occur while preparing presentations or during discussions with inquisitive students. Because there is usually not enough time to develop these ideas on the spot, it is useful to keep them in a **computer file** or notebook for future reference.

There is a major role for **creativity** in the process of conceiving research questions, imagining new methods to address old questions, and playing with ideas. Some creative ideas come to mind during informal conversations with colleagues over lunch; others arise from discussing recent research or your own ideas in small groups. Many inspirations are solo affairs that strike while preparing a lecture, showering, perusing the Internet, or just sitting and thinking. Fear of criticism or seeming unusual can prematurely quash new ideas. The trick is to put an unresolved problem clearly in view and allow the mind to run freely around it. There is also a need for **tenacity**, returning to a troublesome problem repeatedly until a resolution is reached.

Choosing and Working with a Mentor

Nothing substitutes for experience in guiding the many judgments involved in conceiving a research question and fleshing out a study plan. Therefore an essential strategy for a new investigator is to apprentice herself to an experienced **mentor** who has the time and interest to work with her regularly.

A good mentor will be available for regular meetings and informal discussions, encourage creative ideas, provide wisdom that comes from experience, help ensure protected time for research, open doors to networking and funding opportunities, encourage the development of independent work, and put the new investigator's name first on grants and publications whenever appropriate. Sometimes it is desirable to have more than one mentor, representing different disciplines. Good relationships of this sort can also lead to tangible resources that are needed—office space, access to clinical populations, data sets and specimen banks, specialized laboratories, financial resources, and a research team.

A bad mentor, on the other hand, can be a barrier. A mentor can harm the career of the new investigator, for example, by taking credit for findings that arise from the new investigator's work, or assuming the lead role on publishing or presenting it. More commonly, many mentors are simply too busy or distracted to pay attention to the new investigator's needs. In either case, once discussions with the mentor have proved fruitless, we recommend finding a way to move on to a more appropriate advisor, perhaps by involving a neutral senior colleague to help in the negotiations. **Changing mentors** can be hazardous, emphasizing the importance of choosing a good mentor in the first place; it is perhaps the *single most important decision* a new investigator makes.

Your mentor may give you a database and ask you to come up with a research question. In that situation, it's important to identify (1) the overlap between what's in the database and your own research interests, and (2) the quality of the database. If there isn't enough overlap or the data are irrevocably flawed, find a way to move on to another project.

CHARACTERISTICS OF A GOOD RESEARCH QUESTION

The characteristics of a research question that lead to a good study plan are that it be Feasible, Interesting, Novel, Ethical, and Relevant (which form the mnemonic **FINER**; Table 2.1).

Feasible

It is best to know the practical limits and problems of studying a question early on, before wasting much time and effort along unworkable lines.

- **Number of subjects.** Many studies do not achieve their intended purposes because they cannot enroll enough subjects. A preliminary calculation of the sample size requirements of the study early on can be quite helpful (Chapter 6), together with an estimate of the number of subjects likely to be available for the study, the number who would be excluded or refuse to participate, and the number who would be lost to follow-up. Even careful planning often produces estimates that are overly optimistic, and the investigator should assure that there are enough eligible and willing subjects. It is sometimes necessary to carry out a pilot survey or chart review to be sure. If the number of subjects appears insufficient, the investigator can consider several strategies: expanding the inclusion criteria, eliminating unnecessary exclusion criteria, lengthening the time frame for enrolling subjects, acquiring additional sources of subjects, developing more precise measurement approaches, inviting colleagues to join in a multicenter study, and using a different study design.
- **Technical expertise.** The investigators must have the skills, equipment, and experience needed for designing the study, recruiting the subjects, measuring the variables, and managing and analyzing the data. Consultants can help to shore up technical aspects that are unfamiliar to the investigators, but for major areas of the study it is better to have an experienced colleague steadily involved as a coinvestigator; for example, it is wise to include a statistician as a member of the research team from the beginning of the planning process. It is best to use familiar and established approaches, because the process of developing new

TABLE 2.1 FINER CRITERIA FOR A GOOD RESEARCH QUESTION AND STUDY PLAN

Feasible

Adequate number of subjects
Adequate technical expertise
Affordable in time and money
Manageable in scope
Fundable

Interesting

Getting the answer intrigues the investigator and her colleagues

Novel

Provides new findings
Confirms, refutes, or extends previous findings
May lead to innovations in concepts of health and disease, medical practice, or methodologies for research

Ethical

A study that the institutional review board will approve

Relevant

Likely to have significant impacts on scientific knowledge, clinical practice, or health policy
May influence directions of future research

methods and skills is time-consuming and uncertain. When a new approach is needed, such as measurement of a new biomarker, expertise in how to accomplish the innovation should be sought.

- **Cost in time and money.** It is important to estimate the costs of each component of the project, bearing in mind that the time and money needed will generally exceed the amounts projected at the outset. If the projected costs exceed the available funds, the only options are to consider a less expensive design or to develop additional sources of funding. Early recognition of a study that is too expensive or time-consuming can lead to modification or abandonment of the plan before expending a great deal of effort.
- **Scope.** Problems often arise when an investigator attempts to accomplish too much, making many measurements at repeated contacts with a large group of subjects in an effort to answer too many research questions. The solution is to narrow the scope of the study and focus only on the most important goals. Many scientists find it difficult to give up the opportunity to answer interesting side questions, but the reward may be a better answer to the main question at hand.
- **Fundability.** Few investigators have the personal or institutional resources to fund their own research projects, particularly if subjects need to be enrolled and followed, or expensive measurements must be made. The most elegantly designed research proposal will not be feasible if no one will pay for it. Finding sources of funding is discussed in Chapter 19.

Interesting

An investigator may have many motivations for pursuing a particular research question: because it will provide financial support, because it is a logical or important next step in building a career, or because getting at the truth of the matter is interesting. We like this last reason; it is one that grows as it is exercised and that provides the intensity of effort needed for overcoming the many hurdles and frustrations of the research process. However, it is wise to confirm that you are not the only one who finds a question interesting. Speak with mentors, outside experts, and representatives of potential funders such as NIH project officers before devoting substantial energy to develop a research plan or grant proposal that peers and funding agencies may consider dull.

Novel

Good clinical research contributes new information. A study that merely reiterates what is already established is not worth the effort and cost and is unlikely to receive funding. The novelty of a proposed study can be determined by thoroughly reviewing the literature, consulting with experts who are familiar with unpublished ongoing research, and searching for abstracts of projects in your area of interest that have been funded using the NIH Research Portfolio Online Reporting Tools (**RePORT**) website (http://report.nih.gov/categorical_spending.aspx.) Reviews of studies submitted to NIH give considerable weight to whether a proposed study is **innovative** (5) such that a successful result could shift paradigms of research or clinical practice through the use of new concepts, methods, or interventions (Chapter 19). Although novelty is an important criterion, a research question need not be totally original—it can be worthwhile to ask whether a previous observation can be replicated, whether the findings in one population also apply to others, or whether a new measurement method can clarify the relationship between known risk factors and a disease. A confirmatory study is particularly useful if it avoids the weaknesses of previous studies or if the result to be confirmed was unexpected.

Ethical

A good research question must be ethical. If the study poses unacceptable physical risks or invasion of privacy (Chapter 14), the investigator must seek other ways to answer the question.

If there is uncertainty about whether the study is ethical, it is helpful to discuss it at an early stage with a representative of the institutional review board (IRB).

Relevant

A good way to decide about relevance is to imagine the various outcomes that are likely to occur and consider how each possibility might advance scientific knowledge, influence practice guidelines and health policy, or guide further research. NIH reviewers emphasize the **significance** of a proposed study: the importance of the problem, how the project will improve scientific knowledge, and how the result will change concepts, methods, or clinical services.

■ DEVELOPING THE RESEARCH QUESTION AND STUDY PLAN

It helps a great deal to write down the research question and a brief (one-page) outline of the **study plan** at an early stage (Appendix 1). This requires some self-discipline, but it forces the investigator to clarify her ideas about the plan and to discover specific problems that need attention. The outline also provides a basis for specific suggestions from colleagues.

Problems and Approaches

Two complementary approaches to the problems involved in developing a research question deserve special emphasis.

The first is the importance of getting good **advice**. We recommend a research team that includes representatives of each of the major disciplines involved in the study, and that includes at least one senior scientist. In addition, it is a good idea to consult with specialists who can guide the discovery of previous research on the topic and the choice and design of measurement techniques. Sometimes a local **expert** will do, but it is often useful to contact individuals in other institutions who have published pertinent work on the subject. A new investigator may be intimidated by the prospect of writing or calling someone she knows only as an author in the *Journal of the American Medical Association,* but most scientists respond favorably to such requests for advice.

The second approach is to allow the study plan to gradually emerge from an **iterative process** of making incremental changes in the study's design, estimating the sample size, reviewing with colleagues, pretesting key features, and revising. Once the one-page study outline is specified, formal review by colleagues will usually result in important improvements. As the protocol takes shape pilot studies of the availability and willingness of sufficient numbers of subjects may lead to changes in the recruitment plan. The preferred imaging test may turn out to be prohibitively costly and a less expensive alternative sought.

Primary and Secondary Questions

Many studies have more than one research question. Experiments often address the effect of the intervention on more than one outcome; for example, the Women's Health Initiative was designed to determine whether reducing dietary fat intake would reduce the risk of breast cancer, but an important secondary hypothesis was to examine the effect on coronary events (5). Almost all cohort and case–control studies look at several risk factors for each outcome. The advantage of designing a study with several research questions is the efficiency that can result, with several answers emerging from a single study. The disadvantages are the increased complexity of designing and implementing the study and of drawing statistical inferences when there are multiple hypotheses (Chapter 5). A sensible strategy is to establish a **single primary research question** around which to focus the study plan and sample size estimate, adding **secondary research questions** about other predictors or outcomes that may also produce valuable conclusions.

■ TRANSLATIONAL RESEARCH

Translational research refers to studies of how to translate findings from the ivory tower into the "real world," how to assure that scientific creativity has a favorable impact on public health. Translational research (6) comes in two main flavors (Figure 2.2):

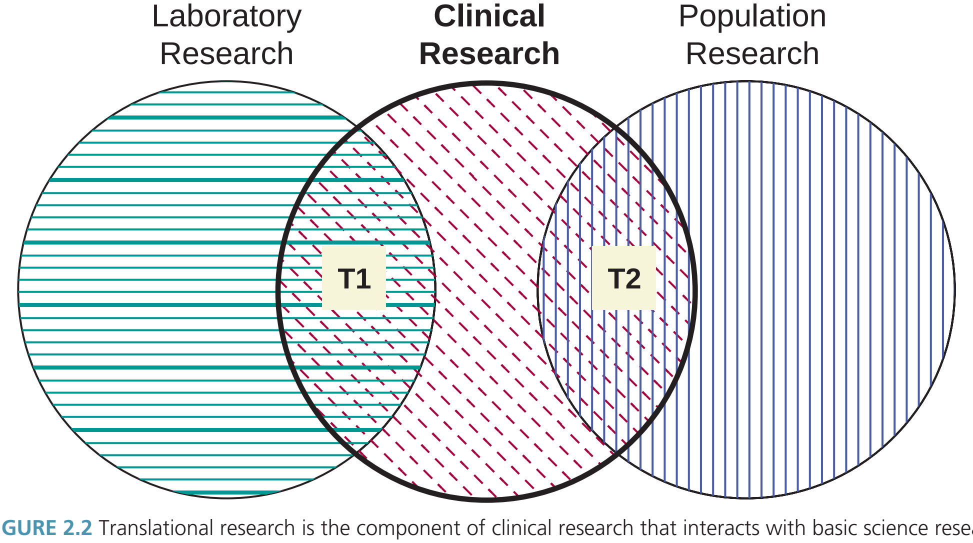
- Applying basic science findings from laboratory research in clinical studies of patients (sometimes abbreviated as **T1** research), and
- Applying the findings of these clinical studies to alter health practices in the community (sometimes abbreviated as **T2** research).

Both forms of translational research require identifying a "translation" opportunity. Just as a literary translator first needs to find a novel or poem that merits translating, a translational research investigator must first target a scientific finding or new technology that could have an important impact on clinical research, practice, or public health. Among the strategies for making this challenging choice, it may be helpful to pay attention to colleagues when they talk about their latest findings, to presentations at national meetings about novel methods, and to speculation about mechanisms in published reports.

Translating from Laboratory to Clinical Research (T1)

A host of **tools** have become available for clinical investigations, including DNA sequencing, gene expression arrays, molecular imaging, and proteomics. From the viewpoint of a clinical investigator, there is nothing epidemiologically different about these novel measurements, technologies, or test results. The chapter on measurements will be useful in planning studies involving these types of measurements (Chapter 4), as will the advice about study design (Chapters 7–12), population samples (Chapter 3), and sample size (Chapter 6). Especially relevant to genomics and other "omics" will be the concern with multiple hypothesis testing (Chapter 5).

Compared with ordinary clinical research, being a successful T1 translational investigator often requires having an additional skill set or working with a collaborator with those skills. **Bench-to-bedside** research necessitates a thorough understanding of the underlying basic science. Although many clinical researchers believe that they can master this knowledge—just like many laboratory-based researchers believe doing clinical research requires no special training—in reality, the skills hardly overlap. For example, suppose a basic scientist has identified a gene that



■ **FIGURE 2.2** Translational research is the component of clinical research that interacts with basic science research (hatched area T1) or with population research (hatched area T2).

affects circadian rhythm in mice. A **clinical investigator** whose expertise is in sleep has access to a cohort study with data on sleep cycles and a bank of stored DNA, and wants to study whether there is an association between variants in the human homolog of that gene and sleep. In order to propose a T1 study of that association she needs collaborators who are familiar with that gene, as well as the advantages and limitations of the various methods of genotyping.

Similarly, imagine that a **laboratory-based investigator** has discovered a unique pattern of gene expression in tissue biopsy samples from patients with breast cancer. She should not propose a study of its use as a test for predicting the risk of recurrence of breast cancer without collaborating with someone who understands the importance of clinical research issues, such as test-retest reliability, sampling and blinding, and the effects of prior probability of disease on the applicability of her discovery. Good translational research requires expertise in more than one area. Thus a research team interested in testing a new drug may need scientists familiar with molecular biology, pharmacokinetics, pharmacodynamics, phase I and II clinical trials, and practice patterns in the relevant field of medicine.

Translating from Clinical to Population Research (T2)

Studies that attempt to apply findings from clinical trials to larger and more **diverse populations** often require expertise in identifying high-risk or underserved groups, understanding the difference between screening and diagnosis, and knowing how to implement changes in health care delivery systems. On a practical level, this kind of research usually needs access to large groups of patients (or clinicians), such as those enrolled in health plans or large clinics. Support and advice from the department chair, the chief of the medical staff at an affiliated hospital, the leader of a managed care organization, or a representative from a community organization may be helpful when planning these studies.

Some investigators take a short cut when doing this type of translational research, expanding a study in their own clinic by studying patients in their colleagues' practices (e.g., a house staff-run clinic in an academic medical center) rather than involving practitioners in the community. This is a bit like translating Aristophanes into modern Greek—it will still not be very useful for English-speaking readers. Chapter 18 emphasizes the importance of getting as far into the community as possible.

Testing research findings in larger populations often requires adapting methods to fit organizations. For example, in a study of whether a new office-based diet and exercise program will be effective in the community, it may not be possible to randomly assign individual patients. One solution would be to randomly assign physician practices instead. This may require collaborating with an expert on cluster sampling and clustered analyses. Many T2 research projects aimed to improve medical care use proxy "process" variables as their outcomes. For example, if clinical trials have established that a new treatment reduces mortality from sepsis, a translational research study comparing two programs for implementing and promoting use of the new treatment might not need to have mortality as the outcome. Rather, it might just compare the percentages of patients with sepsis who received the new treatment. Moving research from settings designed for research into organizations designed for medical care or other purposes requires flexibility and creativity in applying principles that assure as much rigor and validity of the study results as possible.

■ SUMMARY

1. All studies should start with a **research question** that addresses what the investigator would like to know. The goal is to find one that can be developed into a good **study plan**.
2. **Scholarship** is essential to developing research questions that are worth pursuing. A **systematic review** of research pertinent to an area of research interest is a good place to start. Attending **conferences** and staying alert to new results extends the investigator's expertise beyond what is already published.

3. The single most important decision a new investigator makes is her choice of one or two senior scientists to serve as her **mentor(s)**: experienced investigators who will take time to **meet**, provide **resources** and **connections**, encourage **creativity**, and promote the **independence** and visibility of their junior scientists.
4. Good research questions arise from finding new collaborators at **conferences**, from critical thinking about clinical practices and problems, from applying **new methods** to old issues, and from considering ideas that emerge from **teaching**, **daydreaming**, and **tenacious pursuit** of solutions to vexing problems.
5. Before committing much time and effort to writing a proposal or carrying out a study, the investigator should consider whether the research question and study plan are "FINER": **feasible**, **interesting**, **novel**, **ethical**, and **relevant**. Those who fund research give priority to proposals that may have innovative and **significant impacts** on science and health.
6. Early on, the research question should be developed into a one-page written **study outline** that specifically describes how many subjects will be needed, how the subjects will be selected, and what measurements will be made.
7. Developing the research question and study plan is an **iterative process** that includes consultations with advisors and friends, a growing familiarity with the literature, and **pilot studies** of the recruitment and measurement approaches.
8. Most studies have more than one question, and it is useful to focus on a **single primary question** in designing and implementing the study.
9. **Translational research** is a type of clinical research that studies the application of basic science findings in clinical studies of patients (**T1**) and how to apply these findings to improve health practices in the community (**T2**); it requires collaborations between **laboratory** and **population-based investigators**, using the **clinical research methods** presented in this book.

REFERENCES

1. The ATAC Trialists Group. Anastrazole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomized trials. *Lancet* 2002;359:2131–2139.
2. Quinn J, Cummings S, Callaham M, et al. Suturing versus conservative management of lacerations of the hand: randomized controlled trial. *BMJ* 2002;325:299–301.
3. Kuhn TS. *The structure of scientific revolutions*. Chicago, IL: University of Chicago Press, 1962.
4. Yaffe K, Browner W, Cauley J, et al. Association between bone mineral density and cognitive decline in older women. *J Am Geriatr Soc* 1999;47:1176–1182.
5. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer. *JAMA* 2006;295:629–642.
6. Zerhouni EA. US biomedical research: basic, translational and clinical sciences. *JAMA* 2005;294:1352–1358.