Food and Drug Administration, and pertussis experts should begin working on immediately.

In the interim, we need to use the vaccines we have (DTaP and Tdap [tetanus–diphtheria–acellular pertussis]) in the best ways possible. Of particular concern are the frightening rates of complications and death associated with pertussis in unimmunized young infants. The "cocooning" strategy — vaccinating people who have contact with infants — has been implemented but is often impeded by logistics. Immunizing pregnant women is fundamentally sound because it reduces the risk that the mother will acquire pertussis around the time of delivery, and it gives the infant some protection for perhaps 1 to 2 months. But women who have multiple pregnancies within a few years present a problem, since immunization with a vaccine containing tetanus toxoid (i.e., Tdap) could result in increased local reactions.

Although some U.S. states have noted an incidence similar to that in the 1940s and 1950s, today's national incidence is about one twenty-third of what it was during an epidemic year in the 1930s. Nevertheless, better vaccines are something that industry, the FDA, and pertussis experts should begin working on immediately.

Another approach would be to start DTaP immunization at a younger age, with shorter intervals between doses. This schedule could be started at birth, and the first three doses could be completed by 3 months of age. Notably, during the period of greatest reduction in pertussis incidence in the United States (1954–1974), the three-dose primary series was completed between 3 and 5 months of age.

In 2012, it is time to recognize the successes of the past and to implement new studies and direction for the control of pertussis in the future.

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1. Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to Bordetella pertussis and other Bordetella subspecies. Clin Microbiol Rev 2005;18:326-82.
2. Cherry JD. The present and future control of pertussis. Clin Infect Dis 2010;51:663-7.
3. Pertussis epidemic — Washington, 2012. MMWR Morb Mortal Wkly Rep 2012;61:517-22.
4. Cherry JD. Why do pertussis vaccines fail? Pediatrics 2012;129:968-70.
5. Winter K, Harriman K, Zipprich J, et al. California pertussis epidemic, 2010. J Pediatr 2012 July 20 (Epub ahead of print).

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Getting the Methods Right — The Foundation of Patient-Centered Outcomes Research

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Health care in the United States has changed dramatically over the past several decades. Today, patients have more options than ever. Making the right choices, whether for prevention, diagnosis, or treatment, requires a critical appraisal of the potential benefits and harms of the options, within the context of the patient's characteristics, conditions, and preferences.

Many of these choices are available thanks to advances in medical research. Yet most patients and many clinicians find research somewhat mysterious. They have difficulty sorting through the mountains of medical evidence to identify information that is reliable and actionable for their unique circumstances. Patient-centered outcomes research and comparative-effectiveness research promise to enhance decision makers' ability to fully understand and weigh alternatives. But just as health care interventions and delivery strategies have advanced markedly in recent decades, so have research methods (see table). Without systematic guidance for the appropriate and efficient use of these methods, their rapid growth and complexity will only add to the confusion.

Selected Milestones in Health Care Interventions and Delivery Strategies and in Research Methods.*

Decade	Milestones in Health Care Interventions and Delivery Strategies	Milestones in Research Methods
1940s	Antibiotic agents (penicillin and streptomycin), kidney dialysis, general anesthesia, radiotherapy, first heart-pump machine, influenza vaccine, Papanicolaou (Pap) smear to detect cervical cancer, cortisone, intraocular lens implants for cataracts	First large-scale, randomized, controlled trial
1950s	Cardiopulmonary resuscitation, kidney transplantation, vaccination against poliomyelitis, chlorpromazine for schizophrenia, Zeiss fluorescence microscope, antitubercular therapy, cardiac pacemaker, artificial heart valve, successful open-heart bypass surgery	Case–control methodology, Kaplan–Meier survival estimator
1960s	Charnley's hip replacement, coronary-artery bypass grafting surgery, heart transplantation, oral contraceptive pill, prenatal diagnosis of Down's syndrome	Explanatory versus pragmatic trial concept, data and safety monitoring, growth of observational research methods committees
1970s	Cure for some childhood cancers; neonatal intensive care; computed tomography; coronary angiography; quality measures in health care; ambulatory surgery; vaccinations against smallpox, measles, mumps, rubella, and pneumonia	Cox proportional-hazards model; meta-analysis; ascendancy of randomized, controlled trials; statistical stopping rules
1980s	Insulin therapies for diabetes mellitus, thrombolysis for heart attacks, antihypertensive drugs, magnetic resonance imaging, robotic surgery, permanent artificial-heart implant, deep-brain electrical stimulation system, first laser surgery on the human cornea, hepatitis B vaccine	Propensity score; large, simple trials; prognostic models (e.g., Framingham risk score), growth of decision and cost-effectiveness analyses
1990s	Coronary stents, triple therapy for the acquired immune deficiency syndrome, introduction of biologics, "physician extenders," facial transplantation, vaccine against hepatitis A, first rotavirus vaccines	Evidence-based medicine, cumulative meta-analysis, reporting guidelines (CONSORT statement), ascendancy of registries, electronic health records, Markov chain Monte Carlo sampling for Bayesian inference
2000s	Human Genome Project completed, drug-eluting coronary stents, FDA guidance on patient-reported outcomes, minimally invasive techniques for surgery, human papillomavirus vaccine to prevent cervical cancer	Trial registration (ClinicalTrials.gov), comparative-effectiveness research, implementation science, large-scale genomic research, reproducible research
2010s	Genomics, epigenomics, individualized medicine, health information technology, emergence of telehealth, meaningful-use initiatives, Affordable Care Act becomes law	Patient-centered outcomes research

* Information on health care interventions and delivery strategies are from Le Fanu.[1] CONSORT denotes Consolidated Standards of Reporting Trials, and FDA Food and Drug Administration.

On July 23, 2012, the Methodology Committee of the Patient-Centered Outcomes Research Institute (PCORI) released for public comment (http://www.pcori.org/survey/methodology-report) the draft of its first report recommending selected standards for the conduct of research leading to evidence-based, patient-centered health interventions.[2] These standards underscore the importance of employing the right methods for patient-centered outcomes research. Indeed, a basic understanding, on the part of all health care stakeholders, of the methods underlying medical research findings is essential for several reasons.

First, patients' health problems are increasingly complex. The aging of the U.S. population has been accompanied by increasing morbidity. The number of Americans who are 90 years of age or older has nearly tripled over the past three decades and is projected to more than quadruple over the next four. With increases in life expectancy at older ages, more people will have chronic health conditions. In 2010, a staggering 147 million Americans — approximately half of all adults — had at least one chronic illness.[3] Obesity is now a major health threat. More than one third of adults and almost 17% of young people in the United States were obese in 2009 and 2010.[4] Obesity increases the risks of many chronic conditions and complicates treatment, because obese patients are at higher risk for the toxic effects of therapies. With older patients who have more complex conditions, and with more complex therapies, the chances of differential responses to the same treatment increase markedly. Unless issues arising from compli-

cations and coexisting conditions are accounted for in study designs and methods, the results may not be relevant to many patients.

Second, the number and types of available treatment options for a given condition have increased. For example, in 1980, there were fewer than six disease-modifying treatments approved by the Food and Drug Administration for rheumatoid arthritis. In 2012, treatments include methotrexate, leflunomide, five tumor-necrosis-factor inhibitors, an interleukin-1 inhibitor, a T-cell costimulatory modulator, an anti-CD20 antibody, and an interleukin-6 inhibitor, with new small molecules on the horizon. Treatments for diabetes mellitus have also dramatically changed over the past 30 years. In the 1980s, first-generation sulfonylureas were the only oral agents available. Now, multiple classes of drugs with widely differing mechanisms are available, including third-generation sulfonylureas, metformin, thiazolidinediones, alpha-glucosidase inhibitors, bile acid sequestrants, glucagon-like peptide 1 analogues, and dipeptidyl peptidase IV inhibitors. In addition, multiple insulin analogues targeted toward achieving appropriate basal and postprandial insulin concentrations are now available. Consider the complexity of determining the optimal regimen for people with both conditions. Options for disease prevention have also increased rapidly: we now have numerous choices for primary and secondary screening as well as treatments to prevent diseases such as osteopenia and primary breast cancer. Sophisticated research methods are required to compare the benefits and harms of the many options.

Third, health care delivery systems are quickly changing in response to economic pressures and concerns about quality of care. The system of care is itself an important determinant of patient outcomes. Health care leaders are therefore increasingly relying on research findings in making business decisions and developing organizational policies to enhance the quality and efficiency of care. Elucidating the effects of the system of care on patient outcomes requires new methodologic approaches in order to identify what works in which setting and under what conditions.

For research to be meaningful, its methodologic foundation must be scientifically sound and patient-centered — and all stakeholders should be able to gauge the research's quality and usefulness for decision making.

Fourth, the promise of individualized medicine has launched a huge research enterprise to explore the ways in which genetic, epigenetic, and other personal characteristics influence responses to therapy. Personalized health research presents further methodologic challenges, since emphasis is placed on the individual response rather than on the population.

All these factors combine to create immense complexity, making it difficult yet imperative for patients and physicians to identify and understand the medical research information most relevant to their health decisions. An understanding of how a study is designed and conducted clarifies how useful the results will be to the health care decision at hand.

The PCORI was created to support research that can produce this information. Because it was recognized that, to be trusted, research must be generated with the use of rigorous, valid, patient-centered methods, the PCORI's founding legislation established a 17-member Methodology Committee, to be selected by the Government Accountability Office. The committee's charge is "to develop and improve the science and methods of comparative clinical effectiveness research" and to produce "methodological standards for research." The committee, on which we serve, aims to be the go-to scientific methodology resource for patient-centered outcomes research and the how-to group for the PCORI, addressing methodologic focus areas, advancing methodologic science, and enabling the PCORI to accomplish its agenda. The long-term vision involves wide adoption of PCORI methodologic standards that can catalyze the rapid development and implementation of evidence-based, patient-centered health interventions.

The draft of the first PCORI Methodology Report represents an important step in a process designed to address these challenges. It includes the first set of methodologic standards and ac-

tions recommended to promote wide use and effectiveness. It describes the rationale behind creating standards for patient centeredness, for prioritizing topics for research, for choosing a study design (including the first edition of the translation table for pairing research questions and appropriate methods), and for designing, conducting, and reporting patient-centered outcomes research. It also highlights gaps in the evidence to be addressed by the PCORI's program of methodologic research. The PCORI will incorporate these standards and recommendations into its funding process and encourage their adoption by the scientific community.

The report focuses on connecting research results to patients' health care needs and making the findings generally accessible. Its standards list is a milestone but not a destination. Transforming this foundational document into meaningful essential guidance for the broad health care community will require a systematic, iterative process of public commenting, public engagement, and revision. Over the coming years, input will be regularly solicited from the community. The Methodology Committee will systematically update and expand the scope of the standards to cover the full spectrum of patient-centered outcomes research questions and approaches and expand the translation tables to include more examples, methodologic issues, and approaches. The committee will work with the public to develop further reports, standards, and translation tables so as to produce better research methodology and better application of existing methods to aid all stakeholders — researchers planning investigations, policymakers weighing the value of health care interventions, and patients, clinicians, and caregivers facing health care decisions.

The legislative mandate to generate a methods report, methodologic standards, and a translation table as guidance for a national research initiative is visionary. It tells us that for research to be meaningful, its methodologic foundation must be scientifically sound and patient-centered — and that all stakeholders should be able to gauge the research's quality and usefulness for decision making. It tells us that if medical research is to realize the promise of improving health, the methods matter.

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1. Le Fanu JL. The rise and fall of modern medicine. 2nd ed. Boston: Little, Brown, 2011.
2. Patient-Centered Outcomes Research Institute. Preliminary draft methodology report. June 4, 2012 (http://www.pcori.org/assets/Preliminary-Draft-Methodology-Report.pdf).
3. Anderson G. Chronic care: making the case for ongoing care. Princeton, NJ: Robert Wood Johnson Foundation, 2010.
4. Ogden CL, Carroll ME, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009-2010. Atlanta: National Center for Health Statistics, 2012:1-8.

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Tackling Rising Health Care Costs in Massachusetts

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The federal system of the United States gives states substantial latitude and authority to regulate their economic affairs. With health care having grown from 13.8% of the national economy in 2000 to 17.9% in 2010, state governments have developed a major stake in ensuring that relentless growth in health care spending is controlled more effectively. In Massachusetts, for example, the costs of Medicaid for low-income residents and private health insurance for state employees account for approximately 40% of the state budget. Rising insurance premiums are also dampening wages in the private sector. A recently enacted Massachusetts law that seeks to control health care spending may therefore provide useful policy lessons for other states and the federal government.

Massachusetts is already a well-known venue for health care reform, with state leaders seeking to address two paramount challenges in the health care system.