Clinical research provides health care providers with information on the natural history of disease, clinical presentations of disease, and diagnostic and treatment options. Consumers, patients, and caregivers also require this information to decide how to evaluate and treat their conditions. All too often, the information necessary to inform these medical decisions is incomplete or unavailable, resulting in more than half of the treatments delivered today without clear evidence of effectiveness. This uncertainty contributes to great variability in managing clinical problems, with costs and outcomes differing markedly across the country.

Comparative effectiveness research (CER) is a way to identify what works for which patients under what circumstances. Congress, in the American Recovery and Reinvestment Act (ARRA) of 2009, appropriated $1.1 billion to jump-start the nation’s efforts to accelerate CER. In ARRA, the Institute of Medicine (IOM) was asked to recommend national priorities for research questions to be addressed by CER and supported by ARRA funds. The IOM committee identified three report objectives: 1) establish a working definition of CER, 2) develop a priority list of research topics to be undertaken with ARRA funding using broad stakeholder input, and 3) identify the necessary requirements to support a robust and sustainable CER enterprise.

WHAT IS COMPARATIVE EFFECTIVENESS RESEARCH?

As the committee developed its priority list of research topics, it repeatedly referred to its definition of CER:

CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.

The key elements of this definition are the direct comparison of effective interventions, the study of patients in typical day-to-day clinical care, and the aim of tailoring decisions to the needs of individual patients.

CER can take many forms. Systematic reviews of the literature are the starting point for practice guidelines. They summarize a body of evidence, identify information gaps, and generate new ideas for research questions. Large established databases, including electronic health records, provide a window into current health care practices and their outcomes. These databases, however, seldom specify the rationale for medi-
cal decisions. Prospective registries and cohort studies are undertaken to understand the natural progression of disease and the factors that influence clinical outcomes. These observational research methods have many advantages but cannot escape a key limitation: characteristics of the patient drive real-life clinical decisions, leading to uncertainty about whether they, or the intervention itself, cause the observed outcomes. Therefore, researchers often turn to randomized controlled trials (RCTs), in which patients are randomly assigned to different interventions eliminating much of the uncertainty that plagues the interpretation of observational research. Over time, differences in response to these interventions reveal which work best and identify factors that might predict the benefits or harms of an intervention. Although RCTs are considered the gold standard of evidence, they have shortcomings. Researchers must choose among these methodologies and must inform the public about their methodological advantages and shortcomings.

**STAKEHOLDER INPUT AND THE DEVELOPMENT OF A PORTFOLIO OF RESEARCH PRIORITIES**

The specific charge to the IOM was to develop a list of high priority research questions for CER to address. The first step was to consult stakeholders. The committee made more than 20,000 solicitations and received input from direct mail, a public session, and a web-based questionnaire. At the public session, 54 individuals representing consumers, patient advocacy groups, provider groups, insurers, manufacturers, and academia spoke directly to the committee and responded to follow-up questions. The web-based questionnaire requested nominations, was open for 3 weeks, and received 1,758 submissions of more than 2,600 topics.

The committee developed criteria for assessing the importance of these recommended topics and a process for prioritization. Criteria included condition-level criteria (for example, burden of disease, cost, and variability) and priority topic-level criteria (for example, appropriateness for CER, gaps in existing knowledge, and the likelihood that the results would improve health). Through three rounds of voting, the committee narrowed the list to 100 highest-priority research topics (see accompanying list of priorities by quartile ranking).

The committee recommends a balanced portfolio of research topics that, collectively, address broad societal needs. To evaluate a topic’s importance, the committee formulated criteria that would identify not only those diseases and conditions with the greatest aggregate effect on the health of the U.S. population, but also less common conditions that severely affect individuals in vulnerable subgroups of the population. Among the high priority topics were interventions such as disease prevention, systems of care, drug therapies, devices, surgery, and monitoring of disease.

The priority list includes 29 research areas (see Figure 1), affecting a broad range of age and ethnicity. Twenty-four of the 100 topics affect special populations. Nominees felt that RCTs were the most appropriate methodology for 49 of the topics, but also recognized the value of prospective observational studies, database reviews, and systematic literature reviews for studying many research topics.

**RECOMMENDATIONS FOR A ROBUST CER ENTERPRISE**

The committee concludes that the nation’s investment in CER should continue beyond the conclusion of research on the current priority list of topics. The filling of gaps
in knowledge, the emergence of new disease threats, and the advance of medicine will require a continuous evaluation of research topic priorities. Regular reporting of the activities, recommendations, and findings of CER should lead to periodic re-evaluation of the nation’s CER portfolio.

A sustainable national program of CER will require coordination of private and public strategies. The program must be accountable to the American people through periodic progress reports. Moreover, consumers, patients, and caregivers as well as their health care providers must be involved in all aspects of CER to ensure its relevance to everyday health care delivery. A large public-private CER enterprise will require a supporting infrastructure to efficiently move the science forward. In addition to the capacity to support high-efficiency, pragmatic randomized trials, the program will require large-scale clinical and administrative data networks that enable observational studies of patient care while protecting patient privacy and data security. New methods for linking patient-level data from multiple health care organizations will promote inclusion of populations frequently omitted from clinical trials. The expansion of CER mandated in ARRA will stress the limited capacity of the current CER workforce, increasing the need for trained experts in biostatistics, epidemiology, systematic reviews, observational and clinical trials, and more refined research methods for CER. The goal of CER is better decision making by patients and providers. To achieve this, the nation will need effective strategies for disseminating CER findings and promoting their adoption into clinical practice.

**FIGURE 1: DISTRIBUTION OF THE RECOMMENDED RESEARCH PRIORITIES BY PRIMARY AND SECONDARY RESEARCH AREAS**

The goal of CER is better decision making by patients and providers. To achieve this, the nation will need effective strategies for disseminating CER findings and promoting their adoption into clinical practice.
LIST OF PRIORITY TOPICS BY QUARTILE RATINGS
(DISPLAY WITHIN QUARTILE DOES NOT INDICATE PRIORITY RANK).

FIRST QUARTILE

Compare the effectiveness of treatment strategies for atrial fibrillation including surgery, catheter ablation, and pharmacologic treatment.

Compare the effectiveness of the different treatments (e.g., assistive listening devices, cochlear implants, electric-acoustic devices, habilitation and rehabilitation methods [auditory/oral, sign language, and total communication]) for hearing loss in children and adults, especially individuals with diverse cultural, language, medical, and developmental backgrounds.

Compare the effectiveness of primary prevention methods, such as exercise and balance training, versus clinical treatments in preventing falls in older adults at varying degrees of risk.

Compare the effectiveness of upper endoscopy utilization and frequency for patients with gastroesophageal reflux disease on morbidity, quality of life, and diagnosis of esophageal adenocarcinoma.

Compare the effectiveness of dissemination and translation techniques to facilitate the use of CER by patients, clinicians, payers, and others.

Compare the effectiveness of comprehensive care coordination programs, such as the medical home, and usual care in managing children and adults with severe chronic disease, especially in populations with known health disparities.

Compare the effectiveness of different strategies of introducing biologics into the treatment algorithm for inflammatory diseases, including Crohn’s disease, ulcerative colitis, rheumatoid arthritis, and psoriatic arthritis.

Compare the effectiveness of various screening, prophylaxis, and treatment interventions in eradicating methicillin resistant Staphylococcus aureus (MRSA) in communities, institutions, and hospitals.

Compare the effectiveness of strategies (e.g., bio-patches, reducing central line entry, chlorhexidine for all line entries, antibiotic impregnated catheters, treating all line entries via a sterile field) for reducing health care associated infections (HAI), including catheter-associated bloodstream infection, ventilator associated pneumonia, and surgical site infections, in children and adults.

Compare the effectiveness of management strategies for localized prostate cancer (e.g., active surveillance, radical prostatectomy [conventional, robotic, and laparoscopic], radiotherapy [conformal, brachytherapy, proton-beam, and intensity-modulated radiotherapy]) on survival, recurrence, side effects, quality of life, and costs.

Establish a prospective registry to compare the effectiveness of treatment strategies for low back pain without neurological deficit or spinal deformity.

Compare the effectiveness and costs of alternative detection and management strategies (e.g., pharmacologic treatment, social/family support, combined pharmacologic and social/family support) for dementia in community-dwelling individuals and their caregivers.
Compare the effectiveness of pharmacologic and non-pharmacologic treatments in managing behavioral disorders in people with Alzheimer’s disease and other dementias in home and institutional settings.

Compare the effectiveness of school-based interventions involving meal programs, vending machines, and physical education, at different levels of intensity, in preventing and treating overweight and obesity in children and adolescents.

Compare the effectiveness of various strategies (e.g., clinical interventions, selected social interventions [such as improving the built environment in communities and making healthy foods more available], combined clinical and social interventions) to prevent obesity, hypertension, diabetes, and heart disease in at-risk populations such as the urban poor and American Indians.

Compare the effectiveness of management strategies for ductal carcinoma in situ (DCIS).

Compare the effectiveness of imaging technologies in diagnosing, staging, and monitoring patients with cancer including positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT).

Compare the effectiveness of genetic and biomarker testing and usual care in preventing and treating breast, colorectal, prostate, lung, and ovarian cancer, and possibly other clinical conditions for which promising biomarkers exist.

Compare the effectiveness of the various delivery models (e.g., primary care, dental offices, schools, mobile vans) in preventing dental caries in children.

Compare the effectiveness of various primary care treatment strategies (e.g., symptom management, cognitive behavior therapy, biofeedback, social skills, educator/teacher training, parent training, pharmacologic treatment) for attention deficit hyperactivity disorder (ADHD) in children.

Compare the effectiveness of wraparound home and community-based services and residential treatment in managing serious emotional disorders in children and adults.

Compare the effectiveness of interventions (e.g., community-based multi-level interventions, simple health education, usual care) to reduce health disparities in cardiovascular disease, diabetes, cancer, musculoskeletal diseases, and birth outcomes.

Compare the effectiveness of literacy-sensitive disease management programs and usual care in reducing disparities in children and adults with low literacy and chronic disease (e.g., heart disease).

Compare the effectiveness of clinical interventions (e.g., prenatal care, nutritional counseling, smoking cessation, substance abuse treatment, combinations of these interventions) to reduce incidences of infant mortality, pre-term births, and low birth weights, especially among African American women.

Compare the effectiveness of innovative strategies for preventing unintended pregnancies (e.g., over-the-counter access to oral contraceptives or other hormonal methods, expanding access to long-acting methods for young women, providing free contraceptive methods at public clinics, pharmacies, or other locations).
<table>
<thead>
<tr>
<th>SECOND QUARTILE</th>
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<tbody>
<tr>
<td>Compare the effectiveness of therapeutic strategies (e.g., behavioral or pharmacological interventions, the combination of the two) for different autism spectrum disorders (ASD) at different levels of severity and stages of intervention.</td>
</tr>
<tr>
<td>Compare the effectiveness of the co-location model (psychological and primary care practitioners practicing together) and usual care (identification by primary care practitioner and referral to community-based mental health services) in identifying and treating social-emotional and developmental disorders in children ages 0-3.</td>
</tr>
<tr>
<td>Compare the effectiveness of diverse models of comprehensive support services for infants and their families following discharge from a neonatal intensive care unit.</td>
</tr>
<tr>
<td>Compare the effectiveness of treatment strategies for vascular claudication (e.g., medical optimization, smoking cessation, exercise, catheter-based treatment, open surgical bypass).</td>
</tr>
<tr>
<td>Compare the effectiveness of mindfulness-based interventions (e.g., yoga, meditation, deep breathing training) and usual care in treating anxiety and depression, pain, cardiovascular risk factors, and chronic diseases.</td>
</tr>
<tr>
<td>Compare the long-term effectiveness of weight-bearing exercise and bisphosphonates in preventing hip and vertebral fractures in older women with osteopenia and/or osteoporosis.</td>
</tr>
<tr>
<td>Compare the effectiveness of shared decision making and usual care on decision outcomes (treatment choice, knowledge, treatment-preference concordance, and decisional conflict) in children and adults with chronic disease, such as stable angina and asthma.</td>
</tr>
<tr>
<td>Compare the effectiveness of strategies for enhancing patients' adherence to medication regimens.</td>
</tr>
<tr>
<td>Compare the effectiveness of patient decision support tools on informing diagnostic and treatment decisions (e.g., treatment choice, knowledge acquisition, treatment-preference concordance, decisional conflict) for elective surgical and nonsurgical procedures—especially in patients with limited English-language proficiency, limited education, hearing or visual impairments, or mental health problems.</td>
</tr>
<tr>
<td>Compare the effectiveness of robotic assistance surgery and conventional surgery for common operations, such as prostatectomies.</td>
</tr>
<tr>
<td>Compare the effectiveness (including resource utilization, workforce needs, net health care expenditures, and requirements for large-scale deployment) of new remote patient monitoring and management technologies (e.g., telemedicine, Internet, remote sensing) and usual care in managing chronic disease, especially in rural settings.</td>
</tr>
<tr>
<td>Compare the effectiveness of diverse models of transition support services for adults with complex health care needs (e.g., the elderly, homeless, mentally challenged) after hospital discharge.</td>
</tr>
<tr>
<td>Compare the effectiveness of accountable care systems and usual care on costs, processes of care, and outcomes for geographically defined populations of patients with one or more chronic diseases.</td>
</tr>
</tbody>
</table>
Compare the effectiveness of different residential settings (e.g., home care, nursing home, group home) in caring for elderly patients with functional impairments.

Compare the effectiveness (including survival, hospitalization, quality of life, and costs) of renal replacement therapies (e.g., daily home hemodialysis, intermittent home hemodialysis, conventional in-center dialysis, continuous ambulatory peritoneal dialysis, renal transplantation) for patients of different ages, races, and ethnicities.

Compare the effectiveness of treatment strategies (e.g., artificial cervical discs, spinal fusion, pharmacologic treatment with physical therapy) for cervical disc and neck pain.

Compare the effectiveness of film-screen or digital mammography alone and mammography plus magnetic resonance imaging (MRI) in community practice-based screening for breast cancer in high-risk women of different ages, risk factors, and race or ethnicity.

Compare the effectiveness of new screening technologies (such as fecal immunochemical tests and computed tomography [CT] colonography) and usual care (fecal occult blood tests and colonoscopy) in preventing colorectal cancer.

Compare the effectiveness of coordinated care (supported by reimbursement innovations) and usual care in long-term and end-of-life care of the elderly.

Compare the effectiveness of pharmacologic treatment and behavioral interventions in managing major depressive disorders in adolescents and adults in diverse treatment settings.

Compare the effectiveness of an integrated approach (combining counseling, environmental mitigation, chronic disease management, and legal assistance) with a non-integrated episodic care model in managing asthma in children.

Compare the effectiveness (including effects on quality of life) of treatment strategies (e.g., topical steroids, ultraviolet light, methotrexate, biologic response modifiers) for psoriasis.

Compare the effectiveness of treatment strategies (e.g., cognitive behavioral individual therapy, generic individual therapy, comprehensive and intensive treatment) for Post-traumatic Stress Disorder stemming from diverse sources of trauma.

Compare the effectiveness and outcomes of care with obstetric ultrasound studies and care without the use of ultrasound in normal pregnancies.

Compare the effectiveness of birthing care in freestanding birth centers and usual care of childbearing women at low and moderate risk.

THIRD QUARTILE

Compare the effectiveness of different opioid and non-opioid pain relievers, in different doses and durations, in avoiding unintentional overdose and substance dependence among subjects with acute and non-cancer chronic pain.

Compare the effectiveness of aggressive medical management and percutaneous coronary interventions in treating stable coronary disease for patients of different ages and with different comorbidities.
Compare the effectiveness of innovative treatment strategies (e.g., cardiac resynchronization, remote physiologic monitoring, pharmacologic treatment, novel agents such as CRF-2 receptors) for congestive heart failure.

Compare the effectiveness of traditional risk stratification for coronary heart disease (CHD) and noninvasive imaging (using coronary artery calcium, carotid intima media thickness, and other approaches) on CHD outcomes.

Compare the effectiveness of different treatment strategies (e.g., modifying target levels for glucose, lipid, or blood pressure) in reducing cardiovascular complications in newly diagnosed adolescents and adults with type 2 diabetes.

Compare the effectiveness of acupuncture for various indications using a cluster randomized trial.

Compare the effectiveness of dietary supplements (nutriceuticals) and usual care in the treatment of selected high-prevalence conditions.

Compare the effectiveness of different treatment options (e.g., laser therapy, intravitreal steroids, anti-vascular endothelial growth factor [anti-VEGF]) for diabetic retinopathy, macular degeneration, and retinal vein occlusion.

Compare the effectiveness of treatment strategies for primary open-angle glaucoma (e.g., initial laser surgery, new surgical techniques, new medical treatments) particularly in minority populations to assess clinical and patient-reported outcomes.

Compare the effectiveness and cost-effectiveness of conventional medical management of type 2 diabetes in adolescents and adults, versus conventional therapy plus intensive educational programs or programs incorporating support groups and educational resources.

Compare the effectiveness of alternative redesign strategies—using decision support capabilities, electronic health records, and personal health records—for increasing health professionals’ compliance with evidence-based guidelines and patients’ adherence to guideline-based regimens for chronic disease care.

Compare the effectiveness of adding information about new biomarkers (including genetic information) with standard care in motivating behavior change and improving clinical outcomes.

Compare the effectiveness of different quality improvement strategies in disease prevention, acute care, chronic disease care, and rehabilitation services for diverse populations of children and adults.

Compare the effectiveness of formulary management practices and usual practices in controlling hospital expenditures for products other than drugs including medical devices (surgical hemostatic products, radiocontrast, interventional cardiology devices, and others).

Compare the effectiveness of different benefit design, utilization management, and cost-sharing strategies in improving health care access and quality in patients with chronic diseases (e.g., cancer, diabetes, heart disease).

Compare the effectiveness of HIV screening strategies based on recent Centers for Disease Control and Prevention recommendations and traditional screening in primary care settings with significant prevention counseling.
Establish a prospective registry to compare the effectiveness of surgical and nonsurgical strategies for treating cervical spondylotic myelopathy (CSM) in patients with different characteristics to delineate predictors of improved outcomes.

Compare the effectiveness of traditional and newer imaging modalities (e.g., routine imaging, magnetic resonance imaging [MRI], computed tomography [CT], and positron emission tomography [PET]) when ordered for neurological and orthopedic indications by primary care practitioners, emergency department physicians, and specialists.

Compare the effectiveness of comprehensive, coordinated care and usual care on objective measures of clinical status, patient-reported outcomes, and costs of care for people with multiple sclerosis.

Compare the effectiveness of treatment strategies for obesity (e.g., bariatric surgery, behavioral interventions, pharmacologic treatment) on the resolution of obesity-related outcomes such as diabetes, hypertension, and musculoskeletal disorders.

Compare the clinical and cost-effectiveness of surgical care and a medical model of prevention and care in managing periodontal disease to increase tooth longevity and reduce systemic secondary effects in other organ systems.

Compare the effectiveness of atypical antipsychotic drug therapy and conventional pharmacologic treatment for Food and Drug Administration-approved indications and compendia-referenced off-label indications using large datasets.

Compare the effectiveness of management strategies (e.g., inpatient psychiatric hospitalization, extended observation, partial hospitalization, intensive outpatient care) for adolescents and adults following a suicide attempt.

Compare the effectiveness of different strategies to engage and retain patients in care and to delineate barriers to care, especially for members of populations that experience health disparities.

Compare the effectiveness of topical treatments (e.g., antibiotics platelet-derived growth factor) and systemic therapies (e.g., negative pressure wound therapy, hyperbaric oxygen) in managing chronic lower extremity wounds.

**FOURTH QUARTILE**

Compare the effectiveness of smoking cessation strategies (e.g., medication, individual or quitline counseling, combinations of these) in smokers from understudied populations such as minorities, individuals with mental illness, and adolescents.

Compare the effectiveness of computed tomography (CT) angiography and conventional angiography in assessing coronary stenosis in patients at moderate pretest risk of coronary artery disease.

Compare the effectiveness of anticoagulant therapies (e.g., low-intensity warfarin, aspirin, injectable anticoagulants) for patients undergoing hip or knee arthroplasty surgery.

Compare the effectiveness of focused intense periodic therapy and usual weekly therapy in managing cerebral palsy in children.
Compare the effectiveness of different disease management strategies in improving the adherence to and value of pharmacologic treatments for the elderly.

Compare the effectiveness of care coordination with and without clinical decision supports (e.g., electronic health records) in producing good health outcomes in chronically ill patients, including children with special health care needs.

Compare the effectiveness of coordinated, physician-led, interdisciplinary care provided in the patient’s residence and usual care in managing advanced chronic disease in community-dwelling patients with significant functional impairments.

Compare the effectiveness of minimally invasive abdominal surgery and open surgical procedures on post-operative infections, pain management, and recuperative requirements.

Compare the effectiveness of traditional behavioral interventions versus economic incentives in motivating behavior changes (e.g., weight loss, smoking cessation, avoiding alcohol and substance abuse) in children and adults.

Compare the effectiveness of diagnostic imaging performed by non-radiologists and radiologists.

Compare the effectiveness of different techniques (e.g., audio, visual, written) for informing patients about proposed treatments during the process of informed consent.

Compare the effectiveness of different disease management strategies for activating patients with chronic disease.

Compare the effectiveness of different delivery models (e.g., home blood pressure monitors, utilization of pharmacists or other allied health providers) for controlling hypertension, especially in racial minorities.

Compare the effectiveness of alternative clinical management strategies for hepatitis C, including alternative duration of therapy for patients based on viral genomic profile and patient risk factors (e.g., behavior-related risk factors).

Compare the effectiveness of different treatment strategies in the prevention of progression and disability from osteoarthritis.

Compare the effectiveness (e.g., pain relief, functional outcomes) of different surgical strategies for symptomatic cervical disc herniation in patients for whom appropriate nonsurgical care has failed.

Compare the effectiveness of different treatment strategies on the frequency and lost productivity in people with chronic, frequent migraine headaches.

Compare the effectiveness of monotherapy and polytherapy (i.e., use of two or more drugs) on seizure frequency, adverse events, quality of life, and cost in patients with intractable epilepsy.

Compare the effectiveness of surgical resection, observation, or ablative techniques on disease-free and overall survival, tumor recurrence, quality of life, and toxicity in patients with liver metastases.

Compare the effectiveness of hospital-based palliative care and usual care on patient-reported outcomes and cost.
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Compare the effectiveness of different treatment approaches (e.g., integrating mental health care and primary care, improving consumer self-care, combination of integration and self-care) in avoiding early mortality and comorbidity among people with serious and persistent mental illness.

Compare the effectiveness of traditional training of primary care physicians in primary care mental health and colocation systems of primary care and mental health care on outcomes including depression, anxiety, physical symptoms, physical disability, prescription substance use, mental and physical function, satisfaction with the provider, and cost.

Compare the effectiveness of different treatment strategies (e.g., psychotherapy, antidepressants, combination treatment with case management) for depression after myocardial infarction on medication adherence, cardiovascular events, hospitalization, and death.

Compare the effectiveness of different long-term treatments for acne.

Compare the effectiveness of different strategies for promoting breastfeeding among low-income African American women.
FOR MORE INFORMATION . . .

Copies of Initial National Priorities for Comparative Effectiveness Research are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, www.nap.edu. The full text of this report is available at www.nap.edu.

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