Improving Medical Decisions Through Comparative Effectiveness Research: Cancer as a Case Study

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AUTHORS

Co-Chairs:

Al Benson III, MD, FACP, Associate Director for Clinical Investigations, Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Kim Lyerly, MD, Director, Duke Comprehensive Cancer Center

Committee Members:

Amy Abernathy, MD, Associate Professor of Medicine, Division of Medical Oncology; Director, Duke Cancer Care Research Program, Duke University School of Medicine

David Alberts, MD, PhD, Director, Cancer Control and Prevention, Arizona Cancer Center

Carolyn "Bo" Aldige, President & Founder, Prevent Cancer Foundation

Jeff Allen, PhD, Executive Director, Friends of Cancer Research

Robert Bast, MD, Vice President for Translational Research, M.D. Anderson Cancer Center

Donald Berry, PhD, Chairman, Department of Biostatistics; Frank T. McGraw Memorial Chair of Cancer Research, M.D. Anderson Cancer Center

Michael Caligiuri, MD, Director, Ohio State Comprehensive Cancer Center; CEO, James Cancer Hospital & Solove Research Center, The Ohio State University

Bruce Chabner, MD, Clinical Director, Massachusetts General Hospital Cancer Center

Adam Clark, PhD, Director of Health Policy, Lance Armstrong Foundation

William Dalton, MD, PhD, CEO & Director, H. Lee Moffitt Cancer Center & Research Institute

Nancy Davenport-Ennis, CEO & President, National Patient Advocate Foundation

Craig Earle, MD, MSc, FRCP(C), Director, Health Services Research Program, Cancer Care Ontario and the Ontario Institute for Cancer Research

Bart Kamen, MD, PhD, Chief Medical Officer, Leukemia and Lymphoma Society

Jennifer Malin, MD, PhD, Associate Professor, Jonsson Comprehensive Cancer Center, UCLA

William McGivney, PhD, CEO, National Comprehensive Cancer Network

William Nelson, MD, Director, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University

Gilbert Omenn, MD, PhD, Professor of Internal Medicine, Human Genetics and Public Health, Center for Computational Medicine and Biology, University of Michigan

Daniel Sargent, PhD, Professor of Biostatistics, Professor of Oncology, Mayo Clinic

Deborah Schrag, MD, Associate Professor, Dana Farber Cancer Institute

Ellen Sigal, PhD, Chair and Founder, Friends of Cancer Research

Daniel Sullivan, MD, Director, Imaging Program, Duke Comprehensive Cancer Center

Eric Winer, MD, Director, Breast Oncology Center; Chief, Division of Women's Cancers, Dana Farber Cancer Institute; Professor of Medicine, Harvard Medical School

Jerome Yates, MD, National Vice President for Research (ret.), American Cancer Society

EXECUTIVE SUMMARY

In recent years, the Institute of Medicine and other entities have called for a large expansion of comparative effectiveness research (CER) in the United States. CER involves a comparison of the effectiveness of two or more different health care interventions when administered to a diverse population of patients in the real world. The hope is that generating and using additional information on comparative effectiveness will lead to improved decisions about health care by U.S. patients, physicians, health care purchasers, and others, thereby improving the effectiveness of care and potentially restraining the growth in U.S. health care costs.

Much of the evidence on comparative effectiveness of health care interventions now available comes from systematic reviews and meta-analyses of published scientific literature. Unfortunately, synthesis of scientific literature has several limitations. One is that such syntheses do not provide up-to-date information based on the latest scientific research. In many cases, the quality and amount of evidence available to be synthesized (e.g., randomized clinical trials, cohort studies, case-control studies, cross-sectional studies, and case series) may not be sufficient to reach definitive conclusions about an intervention's effectiveness or comparative effectiveness. In particular, the evidence available for more recently approved interventions is in general limited and from highly selected patient populations. Finally, the quality and objectivity of systematic reviews is highly variable, and that often makes them less trustworthy in the view of experts.

The committee that authored this report—a group of leading academic scientists, clinicians, and advocates in the field of cancer—believes a new paradigm for conducting CER in the United States is needed. While this report describes the experiences of the oncology community as a case study, many of the recommendations can be applied to other diseases as well as system-wide improvements. A comprehensive CER program should prioritize the linking of data from public and private entities to build upon existing data collection and research capabilities. Such an initiative would allow researchers and clinicians to analyze data in ways that have never before been possible. It will be important not to overgeneralize these results, but observations that emerge from analyzing such data could readily identify gaps in evidence and generate hypotheses about the reasons for differing responses between groups of patients (based on factors such as race, ethnicity, age, sex, etc.), which then could be used to design appropriate clinical trials. This approach would support the development of "personalized" or stratified medicine.

To ensure that evidence-based information on the effectiveness and comparative effectiveness of medical care keeps pace with the newest diagnostic and therapeutic interventions, the nation's approach to the performance of CER must be structured to ensure continuous learning and the rapid translation of the best available evidence into clinical practice. Ultimately, we need to move closer to the development of a sustainable, "learning" U.S. health care system that develops research insights as a natural byproduct of the care process and gets the right care to people when they need it and then captures the results for improvement.

Recommendations for the Expansion of Comparative Effectiveness Research (CER)

Recommendation #1: A comprehensive CER program should be developed to better identify the most effective health care options.

a. An agenda for CER should be developed by the broad health care community to address clinically important questions where clear options exist.

b. CER studies should examine the totality of health care options for a given condition.

c. CER studies should examine racial, ethnic and geographic variations in care that affect health outcomes, as well as socioeconomic factors that may limit access to or affect the type of medical care provided.

d. CER studies should be designed to evaluate clinical outcomes across a variety of settings and patient populations in order to provide usable information to patients, providers, and payers.

Recommendation #2: A comprehensive CER program should link data from public and private entities to build upon existing data collection and research capabilities.

a. The expansion of CER activities should prioritize public-private coordination and linking of data from clinical research networks and health care databases to generate hypotheses.

b. Research through an expanded data network should be used to assist systematic reviews, generate data from real-world clinical practice, and develop new methods of outcome analyses and modeling.

c. Although observational real-world studies have limitations, secondary analyses of existing data should be used as an initial step to identify information gaps, provide transparency to research priorities, and generate hypotheses for which further clinical trials and research may be necessary.

Recommendation #3: CER studies should support the development of "personalized" or stratified medicine.

a. Emphasis should be placed not only on the "average" patient, but also on the minority who experience prolonged survival or improved quality of life and who can be identified with biomarkers or other clinical characteristics.

b. Analyses of data from an integrated data network should be performed to identify factors that contribute to disease susceptibilities and differences in clinical outcomes.

c. Prospective clinical studies (including randomized trials) should be designed to further explore real-world effectiveness, characterize subpopulations for which a therapy is effective, and emphasize the collection of biospecimens to measure predictive markers.

d. CER studies should have the ability to utilize all types of research methods and explore the use of more efficient research techniques.

Recommendation #4: Processes should be developed to ensure that information gained through CER is incorporated into clinical practice and better informs decisions made among patients, their health care providers, and payers.

a. Processes should be determined to ensure that information generated through CER studies is evaluated and reported in conjunction with current clinical guidelines to efficiently incorporate emerging scientific evidence.

b. A comprehensive CER initiative should support the design of studies that provide a rational and scientific basis for reimbursement decisions and strategies of public and private health care payers.

c. Physicians should receive feedback on the outcomes of their choices, as well as the costs to patients and their payers.

d. Hospital and clinical pharmacy committees should seek and utilize robust CER findings when providing information to health care providers about treatment options.

1. INTRODUCTION

Unsustainable costs and system-wide inefficiencies have led experts to call for a fundamental overhaul of the entire U.S. health care system.[1] The United States spends more per citizen on health than any other country in the world. In 2007, total U.S. health expenditures reached $2.2 trillion ($7,421 per person), which translates to 16.2 percent of the nation's gross domestic product (GDP).[2] At current growth rates, total health expenditures in the United States will account for 25 percent of GDP by 2014.

The cost of treating cancer is particularly staggering. U.S. spending on cancer care has remained virtually constant as a portion of total health expenditures for the past three decades, but between 1995 and 2004, the overall costs of treating patients with various cancers increased by 75 percent. In 2004, the direct economic costs of cancer treatment in the United States, including inpatient and outpatient care, drugs, and medical devices, were estimated by the National Cancer Institute (NCI) to be $72.1 billion—representing just under 5 percent of U.S. spending for all medical treatment.[3]

> The nation's approach to the performance of CER must be structured to ensure continuous learning and the rapid translation of the best available evidence into clinical practice.

It is generally recognized that the current growth in U.S. health care costs is not sustainable. Rising health care costs are damaging the competitiveness of U.S. businesses that provide health insurance to employees, and making health care increasingly unaffordable for Americans. In 2007, 45.7 million people age 18-65 in the United States—or 15.3 percent of the total U.S. population—lacked health insurance.[4] And despite the escalating costs of health care in this country, the U.S. health care system consistently underperforms other advanced nations on important measures, including infant mortality and healthy life expectancy.

In recent years, the Institute of Medicine, the Blue Cross and Blue Shield Association, the Medicare Payment Advisory Commission, the Health Industry Forum, President Obama's health plan, several congressional proposals,[5] and others, have called for a large expansion of comparative effectiveness research (CER). CER involves a comparison of the effectiveness of two or more different health care interventions—for example, two different treatments for the same condition—within a defined set of individuals in real-world clinical settings.[6]
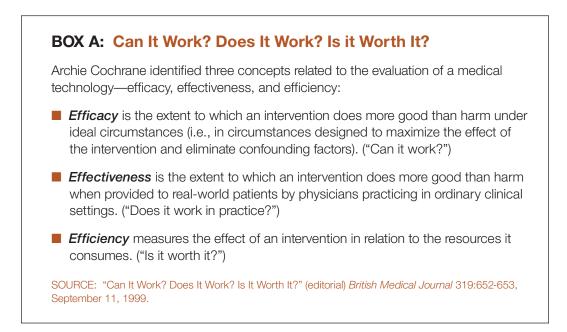
The hope is that generating and using additional information on comparative effectiveness will lead to wiser decisions about health care by U.S. patients, providers, health care purchasers, and others, thereby improving the effectiveness of care and potentially restraining the growth in health care costs.[7, 8] Some authorities believe that less than half of all medical care in the United States is based on or supported by adequate evidence about its effectiveness.[9]

The authoring committee of this report believes that a new paradigm for conducting CER in the United States is needed. While this report describes the experiences of the oncology community as a case study, many of the recommendations can be applied to other diseases as well as system-wide improvements. To ensure that evidence-based information on the effectiveness and comparative effectiveness of medical care keeps pace with the newest diagnostic and therapeutic interventions, the nation's approach to the performance of CER must be structured to ensure continuous learning and the rapid translation of the best available evidence into clinical practice.[10] Ultimately, we need to move closer to the development of a sustainable, "learning" U.S. health care system that develops research insights as a natural byproduct of the care process and results in a system that gets the right care to the right people at the right time and then captures the data needed for research and quality improvement.[11]

2. FINDING OUT WHAT WORKS IN HEALTH CARE

The terms *efficacy* and *effectiveness* have different meanings when applied to health care interventions, although they are often used incorrectly. *Efficacy* is the extent to which a health care intervention is beneficial when administered under optimal circumstances (e.g., in a clinical trial designed to evaluate whether the intervention can work when administered to a small group of carefully selected, highly-compliant patients in a research protocol). *Effectiveness* is the extent to which a health care intervention does more good than harm when provided to a wide assortment of real-world patients with different baseline health risks by physicians or other care providers practicing in diverse clinical settings across the country.

The founder of the Cochrane Collaboration, an international organization that evaluates health care interventions, described another way of thinking about the distinctions between efficacy, effectiveness, and efficiency (or cost effectiveness) (Box A).

BOX A: Can It Work? Does It Work? Is it Worth It?

Archie Cochrane identified three concepts related to the evaluation of a medical technology—efficacy, effectiveness, and efficiency:

■ *Efficacy* is the extent to which an intervention does more good than harm under ideal circumstances (i.e., in circumstances designed to maximize the effect of the intervention and eliminate confounding factors). ("Can it work?")

■ *Effectiveness* is the extent to which an intervention does more good than harm when provided to real-world patients by physicians practicing in ordinary clinical settings. ("Does it work in practice?")

■ *Efficiency* measures the effect of an intervention in relation to the resources it consumes. ("Is it worth it?")

SOURCE: "Can It Work? Does It Work? Is It Worth It?" (editorial) *British Medical Journal* 319:652-653, September 11, 1999.

A. Randomized Clinical Trials: The Gold Standard for Evaluating Efficacy

The "gold standard" for determining a health care intervention's efficacy is the randomized clinical trial (RCT).[12] An RCT is an experimental study with a research protocol in which investigators randomly assign patients who meet criteria to different groups to develop evidence about whether a particular health care intervention can work under *optimal* circumstances. Data collected by RCTs are considered to be the highest level or Category I of medical evidence (Box B).

BOX B: Levels of Evidence

Category I: Evidence from at least one properly conducted randomized controlled trial.

Category II-1: Evidence from well-designed controlled trials without randomization.

Category II-2: Evidence from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Category II-3: Evidence from multiple times series with or without intervention or dramatic results in uncontrolled experiments, such as the results of the introduction of penicillin treatment in the 1940s.

Category III: Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

SOURCE: Russell P. Harris, et al., "Current Methods of the U.S. Preventive Services Task Force: A Review of the Process," *American Journal of Preventive Medicine*. April 20 (3 Supplement): 21-35, 2001. http://www.ahrq.gov/clinic/ajpmsuppl/harris1.htm (accessed March 15, 2009).

The manufacturers of new drugs are typically required to submit evidence of their products' safety and efficacy from at least two pivotal RCTs in order to gain the U.S. Food and Drug Administration's (FDA) approval for marketing in the United States. FDA's standards for the regulation of new medical devices are different; surprisingly, only some classes of devices are required to have clinical data showing safety and efficacy prior to approval. In addition, many diagnostic tests and surgical procedures go through no FDA oversight and no required testing at all. The RCTs required by FDA for market approval of new drugs do not provide all the information that patients, providers, health care purchasers, or others need to make wise decisions when selecting interventions.[13]

Unfortunately, RCTs conducted in small, relatively homogenous populations to demonstrate efficacy do not necessarily meet the needs of health care decision-makers about which interventions work best in diverse real-world patients:

■ RCTs may not provide evidence of a health care intervention's effectiveness among highly diverse patient populations administered by clinicians of varying capabilities and experience in the real world.

■ RCTs that compare a health intervention to a placebo do not answer the question of how that intervention compares with available alternatives.

■ Many RCTs use intermediate measures of efficacy (e.g., progression-free survival) and do not yield information on other important health outcomes of interest (e.g., death rates, quality of life).

■ Exclusion criteria in RCTs generally eliminate patients with co-existing diseases that may markedly increase the risks of adverse effects, depending on the disease and the actions of the drug.

In addition, the indications for a drug or other health intervention's use may change after the initial RCTs are conducted to gain FDA marketing approval. RCTs designed to demonstrate the efficacy of a

new cancer drug, for example, are often conducted in cancer patients whose cancer has spread to other organs (metastasized). In cancer patients with advanced disease, responses to new drugs are generally low and side effects high. After a drug is first approved by FDA, new research may show that the drug also works in patients who have the same cancer in earlier stages (or in patients with other cancers). Therefore, in many cases, continued rigorous research, including RCTs, should be encouraged to further characterize the potential benefits and risks associated with the use of a medical intervention in additional settings other than those studied to gain initial FDA approval. The failure to conduct such research could lead to the failure to use some of our most promising new drugs in patients most likely to have higher benefit.

Rituxan® (rituximab) is an example of a drug for which additional research after the initial FDA approval showed that it also provides benefits for patients who were not included in the original RCTs. Rituxan® selectively targets CD20+ B-cells and gained initial FDA approval as a single agent in 1997 based on durable response rate (50 percent) in relapsed indolent lymphoma. It was later shown, in combination with chemotherapy, to significantly prolong survival in patients with aggressive lymphoma, indolent lymphoma and chronic lymphoid leukemia. It has also been approved for use, in combination with methotrexate, in patients with rheumatoid arthritis following tumor necrosis factor antagonist treatment. This case demonstrates the incremental progress of science and the need for CER studies, which include additional clinical trials, and the conclusions drawn from them to recognize the potential use of medical interventions in alternative settings.

B. Methodological Approaches to Evaluating Effectiveness and Comparative Effectiveness[14]

A number of methodological approaches can be used to evaluate the effectiveness, safety, and comparative effectiveness of health care interventions.[15] Different types of study designs have strengths and limitations that should govern decisions about their use. Designs vary in terms of their validity, generalizability, cost, and other factors.[16]

When designing a comprehensive comparative effectiveness program, it is important to bear in mind the following hierarchy of evidence:

- Clinical trials (head to head, cluster, randomized, adaptive design, or practical/pragmatic trials) and meta-analyses of clinical trials

- Observational studies based on large data sets (natural experiments, prospective registries, retrospective database studies)

- Systematic reviews of the scientific literature

1. Clinical Trials

A clinical trial is an experimental study design in which investigators actively intervene to answer a clinical question. It is used to compare the effects of two or more health care interventions. Clinical trials, which include RCTs and other types of trials, can take place in various locations, among them hospitals, universities, community clinics, and doctors' offices.[17] The most rigorous clinical trial design is a randomized, controlled, double-blind study. Additionally, by synthesizing the findings of multiple randomized clinical trials, well-executed meta-analyses of RCTs provide very high quality evidence of the relative effectiveness of treatment options.

Currently, RCTs and other types of clinical trials in the United States are sponsored or funded by a variety of organizations or individuals (such as physicians, medical institutions, foundations, voluntary groups, and biotechnology and pharmaceutical companies), in addition to federal agencies such as

the National Institutes of Health (NIH), the Department of Defense, and the Department of Veterans Affairs. Large RCTs, called "pivotal" by the FDA, are nearly always funded by the pharmaceutical manufacturer.

Well-designed RCTs or other clinical trials comparing two health care interventions head to head have the potential to yield the most robust evidence about efficacy and comparative efficacy. The use of meta-analyses of multiple RCTs provides valuable information about completed clinical trials with similar regimens. Meta-analyses have the ability to expand the available information by linking individual patient data, including different therapy options. Ultimately, creating pooled data sets from individual patients that could be routinely built upon would create a better opportunity to understand efficacy in different subpopulations. Unfortunately, however, clinical trials are very expensive and take many years to conduct and analyze. As a result, they may not be conducted or funded long enough to determine long-term effects.[18] Therefore, it is also important to explore other research methods that may be able to supplement RCT-generated data.

2. Observational Studies

In observational studies—also called nonexperimental studies—investigators observe the natural course of events without intervention and ascertain whether there is an association between one factor and changes or differences in another characteristic(s) (e.g., whether or not a treatment patients received was associated with a difference in survival).[19]

Retrospective observational studies of cancer patients often rely on existing administrative data such as insurance claims and cancer registry data. Such data provide a grainy snapshot of the use of cancer services such as surgery, radiation therapy, and chemotherapy and allow for general comparisons of outcomes across different cohorts of patients.[20] However, there are several methodological limitations with using claims data for observational studies in oncology, including lack of detailed clinical information such as tumor characteristics (e.g., grade, stage, histology), exact treatment setting (e.g., knowing whether treatment line is adjuvant, first, or a subsequent line of therapy; knowing history of prior treatment and surgical procedures, etc.), and limited information on comorbid/concurrent conditions patients may have and how this affects treatment choice. Moreover, because claims data collection is designed for billing and not research purposes, data quality is often limited. Nonetheless, it may be useful for exploratory, hypothesis-generating research that can be followed up with more rigorous study designs.

Observational studies play an important role in evaluating the effectiveness and comparative effectiveness of health care interventions—particularly, in identifying research questions and generating hypotheses that can be followed up with clinical research and trials. Because there can be many sources of bias in observational studies, it is imperative to conduct them with utmost rigor to minimize this bias. Examples of how to minimize bias include careful matching of patients based on clinical and socio-demographic criteria, stratification of patients into subgroups based upon such criteria, careful measurement of potential confounding variables, and using appropriate techniques in statistical analyses of data. If they are conducted with such rigor, observational studies can generate evidence that can be extremely informative, provide supplemental data, and aid hypotheses generation for future clinical trials.

3. Systematic Reviews of the Literature

Systematic reviews of the existing scientific literature on the effectiveness of health interventions includes structured analyses of available evidence from a comprehensive search of the published studies, and it can also include meta-analysis, a formal analytical approach to summarizing the findings.[21] Of note, well-executed meta-analyses of randomized controlled trials are considered to provide the highest level of evidence of effectiveness.

Much of the evidence on comparative effectiveness currently available from international organizations such as the Cochrane Collaboration or from public and private entities in the United States, including the Agency for Healthcare Research and Quality (AHRQ) and the Blue Cross and Blue Shield Technology Evaluation Center, is based on systematic reviews of the existing literature. In the cancer field, for example, AHRQ's Effective Health Care Program has performed systematic reviews of the evidence on the effectiveness and safety of radiotherapy treatments for head and neck cancers, of new diagnostic technologies for breast cancer screening, of therapies for localized prostate cancer, of red blood cell-stimulating agents for managing anemia in cancer, and of chemotherapy agents in the prevention of primary breast cancer in high-risk women.[22] Health care providers and the developers of clinical guidelines or recommendations interpret the findings of such reviews to decide to which patients the findings should apply.

Syntheses of the published scientific literature have many limitations. For instance, due to publication lag, such syntheses may not provide up-to-date information based on the latest scientific research. In addition, because there can be a bias against publishing negative results, researchers sometimes hesitate to submit and editors hesitate to publish studies with negative findings. Thus, the pool of available published studies may be disproportionately—and inaccurately— positive. In some cases, the quality and amount of evidence available to be synthesized (RCTs, cohort studies, case-control studies, cross-sectional studies, and case series) may not be sufficient to reach

> Comparisons of two or more treatment alternatives are particularly challenging in genetically diverse diseases like cancers that afflict heterogeneous patients.

definitive conclusions about an intervention's effectiveness or comparative effectiveness.[23] Moreover, the quality and objectivity of systematic reviews is highly variable, as are the studies reviewed, and that variability often causes reviews not to be trusted by the health care community. For example, the outcomes of large RCTs may not be predicted accurately by systematic review of previously published literature on the same topics.[24]

C. Understanding How Subpopulations Respond to Medical Interventions

Subpopulations can be defined by any number of common, distinguishing factors. In medicine, different subpopulations often respond differently to a particular medical intervention. Therefore, a subpopulation could even be defined by a specific response to therapy without understanding the biological factors that contribute to that response.

Recent scientific advancements, such as the sequencing of the human genome and research on gene regulatory pathways, have revealed a wealth of information about the genetic, biological, dietary, behavioral, and environmental and other origins of diseases as well as factors that modify response to treatments. This has allowed scientists and clinicians to begin to develop more effective tools for prevention, screening and diagnosis, treatment, and follow-up that is tailored to the unique genetic makeup or other features of individual patients or subpopulation of patients—thereby improving health outcomes.[25, 26]

Comparisons of two or more treatment alternatives are particularly challenging in genetically diverse diseases like cancers that afflict heterogeneous patients. It is important to note that absence of finding statistically significant differences among cancer treatments in a randomized clinical trial (RCT) does not mean that the outcomes of the compared treatments are the same. A finding of no differences may be due to the misclassification of cancer "type" among patients participating in an RCT of the efficacy of a cancer drug or other intervention, a trial that examined an insensitive endpoint, or a trial that was too small to detect a clinically meaningful difference in outcomes overall or particularly within a sub-population. No net difference could also be the result of offsetting efficacious and adverse effects.

In the past, cancers have been categorized by their organ of origin and by how they appear "under the microscope,"—that is, by their pathologic appearance. But in recent years, research in genomics and bioinformatics has demonstrated clearly that some cancers previously regarded as one disease are actually a group of different disease "types." This finding has major implications for cancer clinical trials.

The importance of targeting cancer treatment only to the subset of patients who will benefit is illustrated by the biologic products Erbitux® (cetuximab) and Vectibix® (panitumumab), which improve survival in patients with metastatic colorectal cancer only in those who have the normal KRAS gene but not those with the mutant activated form of the KRAS gene.

BOX C: **The Importance of Identifying Subsets of Patients for Whom Cancer Drugs Are Effective**

Until the mid-1990s, the only treatment for patients with metastatic colorectal cancer was 5-fluorouracil plus leucovorin (FU/LV), and the median survival time for patients who received this treatment was about 12 months. Recently, the development of the cytotoxic agents irinotecan, oxaliplatin, and capecitabine, and of the monoclonal antibodies Erbitux® (cetuximab) and Vectibix® (panitumumab), has increased therapeutic options for these patients.

Retrospective analyses of data from several large clinical studies showed that patients with metastatic colorectal cancer who had the normal KRAS gene had improved survival outcomes when treated with Erbitux® or Vectibix® rather than with standard chemotherapy alone, but that patients with a mutant, activating form of the KRAS gene did not benefit.

This means that ascertaining whether colorectal cancer patients have a normal or mutant form of the KRAS gene is essential, so that treatment can be targeted to the subset of patients who have the normal form of the KRAS gene. It is estimated that using cetuximab to treat only patients with metastatic colorectal cancer who have the normal KRAS gene—and not to treat patients with the mutant KRAS gene—would also save the United States more than $600 million annually.

SOURCES: Eric Van Cutsem, "Metastatic Colorectal Cancer Leads to Many Challenges," *Journal of Clinical Oncology* 24(21) 2006:3325-3327. http://jco.ascopubs.org/cgi/content/full/24/21/3325 (accessed February 5, 2009); an d Carmen Phillips, "Study Forecasts Savings for Marker-Based Colorectal Cancer," NCI Cancer Bulletin, Vol. 6, No. 2, January 27, 2009. http://www.cancer.gov/ncicancerbulletin/012709/page2 (accessed February 5, 2009).

Suppose a new cancer treatment under consideration only affects the outcomes of individuals with one cancer disease "type," but cancer disease type has not been taken into account in the selection and randomization of patients. The ability of the RCT to demonstrate benefit is weakened because the impact of the new treatment is watered down by including individuals with nonresponsive cancer types in the treatment group. As a result, the effectiveness of a potentially useful cancer treatment will be *underestimated* for individuals with the appropriate cancer disease type and *overestimated* for other individuals. If by chance only a few of the responsive cancer types are in the treatment group in the RCT, it is very likely that investigators will erroneously conclude that the drug or other treatment

is not effective. We have seen this happen in the past. Consider, for example, HER-2/neu-positive ("HER-2+") breast cancer patients treated with Herceptin® (trastuzumab); BCR-ABL positive chronic myelogenous leukemia patients treated with Gleevec® (imatinib); and natural KRAS (without a mutation) colon cancer patients treated with Vectibix® (panitumumab) or Erbitux® (cetuximab). Through identification of the particular subpopulations mentioned and rigorous clinical testing, these agents were shown to be far more effective for the subgroups than they appeared in the overall population.

New cancer clinical trials should utilize appropriate biomarkers in selecting individuals in those situations where there is an expectation that the treatment will only be effective in those having this biomarker. Regardless of the presence of a biomarker at the initiation of a trial, prospective tissue collection is vital to allow the subsequent identification of a predictive biomarker (such as was the case with KRAS mutations in colon cancer).

Cancer disease type also can play a significant role in clinical trials that attempt to demonstrate the bioequivalence of a new drug. Assume that a new drug is not bioequivalent to the standard drug for some cancer disease types but bioequivalent for others—hence, in general, we would like to conclude that the two drugs are not bioequivalent. If the test is performed on the aggregated, non-typed cancer patients, one might conclude the new drug is bioequivalent to the standard drug. In this case, the results of the trial would be in error due to a misclassification problem, and many cancer patients could lose the services of a potentially superior drug. Biomarkers themselves need to be subjected to comparative effectiveness studies. There are many potential specimen or imaging biomarkers that could be used to distinguish among subtypes of patients, and these biomarkers need to be tested against each other.

It is important to note that since host genetics are determined at birth and since tumor genetics can be determined retrospectively, the ability to generate data on whether currently available therapies vary by host or tumor genetic profiles are particularly well suited to observational studies. To this end, carefully annotated clinical biorepositories can provide valuable evidence in this regard.

Additionally, many more Americans are living beyond cancer, resulting in a new area of research called cancer survivorship. As discussed earlier, treatment options differentially impact populations of patients based on a number of factors, including their particular genotype. Implications from these treatments include acute toxicities during the treatment course to a host of late effects that occur years beyond the treatment, and these can affect quality of life and the risk of cancer recurrence. Cancer survivorship should play a role in appropriately measuring the impact of various treatment options on the patient.

D. Generating Comparative Effectiveness Research in the United States and Other Countries

The United States has a decentralized health care system and, perhaps not surprisingly, also has a highly decentralized approach to developing evidence on the comparative effectiveness of health interventions. A variety of public and private entities conduct CER (defined in different ways) for their own purposes—clinical decision-making, purchasing, coverage and formulary decisions, and cost containment[27]—and there is no coordination of this effort at the national level. This situation is expected to change now that the Congress in February 2009 appropriated $1.1 billion for comparative effectiveness research (in approximately thirds to AHRQ, NIH, and the Office of the Secretary of Health and Human Services) in the American Reinvestment and Recovery Act as a "down payment toward health care reform".

Comparative effectiveness evidence in the United States is used in a number of ways. The Medicare Evidence Development and Coverage Advisory Committee for example, reviews and evaluates the

medical literature and technology assessments and advises the Centers for Medicare and Medicaid Services (CMS) on national coverage decisions.[28] NIH convenes independent panels of researchers, health professionals, and public representatives who produce consensus development statements on specific topics. Medical professional societies, patient advocacy groups, and others have processes for analyzing systematic reviews and other evidence of effectiveness to develop clinical guidelines.

Several industrialized countries, including the United Kingdom, Canada, Germany, and Australia, have centralized processes for generating comparative effectiveness information. These countries use comparative effectiveness information in different ways, including coverage, pricing, cost containment, and/or clinical decision-making.[29] In some countries with national health systems, including the United Kingdom, assessments of comparative effectiveness are important or required elements in coverage or reimbursement decisions.[30]

CER should not be viewed as a panacea for constraining the growth in U.S. health care costs. In fact, experts have difficulty predicting the amount of savings that could result from a large CER program.[31] The National Institute for Health and Clinical Excellence (NICE), a part of the National Health Service (NHS) in the United Kingdom, routinely conducts cost assessments and recommends which new treatments should be paid for by the government. The role of NICE is to provide unbiased and transparent technology appraisals as well as to develop guidelines regarding the use of new medical interventions. While the information generated by the assessments provides rigorous information about comparative clinical and cost effectiveness of different treatment options, the use of the information generated by these assessments has at times created controversy. The National Health Service has established parameters that when a new treatment exceeds a pre-determined threshold (currently £20-30,000 per quality-adjusted life-year in most cases), the treatment may not be covered by the government.[32] This has resulted in treatments that are available in the United States not being covered by the UK's NHS. For example, NICE recently recommended that three kidney cancer drugs not be covered by the NHS because they deemed the treatment cost too high for the benefits to patients treated with the new drugs compared with existing therapies. Because of public concerns that patients were being denied access to potentially beneficial treatments, NICE has since reconsidered this decision and in January 2009 allowed for an adjusted cost-effective threshold when appraising life-extending, end of life treatments.[33] In other cases, manufacturers have reduced prices or entered cost-sharing agreements in order to overcome negative cost-effectiveness reviews from NICE.[34] Although the cost of medical care should be a factor when considering health care options, the use of CER information in the United States should take into consideration other factors including the value of treatment to patients and their families confronted with the disease, equity issues, and supporting continued innovation. Initially, many countries with centralized processes for CER tended to focus their comparative effectiveness analyses on drugs and medical devices. Because drug expenditures account for only about 10 cents of each health care dollar, however, many countries are broadening their focus to include medical procedures.[35]

3. RECOMMENDATIONS

Expanding comparative effectiveness research in the United States is essential to provide reliable data on the risks and benefits of health interventions, so that this information can be used by patients and physicians, professional medical societies developing practice guidelines or clinical recommendations, public and private health care purchasers, and other health care decision-makers.[36] In order to comprehensively address this need for comparative medical evidence, particularly for challenging diseases like cancers, the authoring committee of this paper presents the following four recommendations.

Recommendation #1:
A comprehensive CER program should be developed to better identify the most effective health care options.

a. An agenda for CER should be developed by the broad heath care community to address clinically important questions where clear options exist.

To maximize transparency and accountability, policymakers planning the expansion of CER in the United States should develop a national agenda for CER on high-priority, clinically important medical questions, in conjunction with a diverse and broad range of stakeholders in health care, including; the National Institutes of Health, the Food and Drug Administration, Agency for Healthcare Research and Quality, professional societies, the health care industries, advocates, and patients.

CER should focus primarily on generating evidence about the effectiveness of health care options and clinical outcomes that result from different medical interventions for the same condition. Such outcomes could include survival, harm, response rates to therapy, quality of life, and/or impact on the health system (e.g., amount of required follow-up care). Prior to embarking on a large-scale CER study, high-priority, clinically important medical questions should be identified so that the cost of the study, study duration, and trial design can be appropriately evaluated.

It is important that the agenda be coordinated across government agencies and, to the extent possible, with international officials, so that research conducted in the United States and other countries is not unnecessarily duplicated. However, it is also important to note that international efforts should recognize that health practice may be different from country to country, so any actions taken based on results should be localized for the health system.

b. CER studies should examine the totality of health care options for a given condition.

CER studies should be designed to examine the totality of health care options for a given condition to best inform decisions by patients, providers, health care purchasers, and other health care decision-makers. CER could include research about various preventive interventions, screening tests, diagnostic tests, treatments, follow-up strategies, and end-of-life care, as well as of community-based interventions (e.g., programs to encourage smoking cessation). For any particular question, however, it is unlikely that prevention, diagnosis, and treatment will all play a role.

> It is important for CER studies to generate information about a wide array of medical interventions and processes.

Although generating evidence about the wide range of strategies that influence long-term health outcomes for a given condition is important, doing this can be difficult. Diagnostic tests, either imaging or laboratory-based, provide information that can help medical decision-making. Assessing how the use of that information by clinicians affects health outcomes and subsequent treatment choices is extremely challenging because of the difficulty of controlling all the intervening variables.

Drug-versus-drug studies of comparative effectiveness are sometimes considered more feasible. For many conditions, a larger body of evidence is already available. It is important to bear in mind, though, that prescription drugs account for only about 10 percent of total U.S. health care spending.[37] It is also important to consider that for many conditions, the use of a drug therapy may be only one of several options. For example, most cancer patients are rarely treated with just one drug. Instead a complete treatment regimen may include several drugs, radiation, or surgical procedures in varying sequence. Therefore, it is important for CER studies to generate information about a wide array of medical interventions and processes.

c. CER studies should examine racial, ethnic and geographic variations in care that affect health outcomes, as well as socioeconomic factors that may limit access to or affect the type of medical care provided.

Evidence suggests that there is tremendous variation in the use of a wide range of health interventions from one region of the United States to another (among even the best American institutions) for specific conditions, including hip fracture, colorectal cancer, acute myocardial infarction, and end-of-life care. For more than 20 years, the Dartmouth Atlas Project has documented how medical resources are distributed and used in the United States. Patients in high-cost regions have access to the same technology as those in low-cost regions, and those in low-cost regions are not deprived of needed care. In fact, care is often *better* in low-cost areas. The differences appear to be due to discretionary decisions by physicians that are influenced by the local availability of hospital beds, specialty physicians, imaging centers and other resources—and a payment system that greatly rewards growth and higher utilization.[38]

> Studies should aim to reduce health disparities and close the gap between the care that we already know works well and the care patients actually receive.

CER studies should examine variations in community-accepted treatment practices to generate information about different treatment approaches to disease management that may improve or negatively impact outcomes. In some cases, the variation may stem from insufficient evidence about what is most effective. For localized prostate cancer, for example, there is significant geographic variability in medical practice (e.g., in the use of radiation, surgical intervention, and watchful waiting).[39] This variation is due in part to the fact that evidence to suggest the superiority of one treatment option over another is lacking, and in part to the strong preferences of different physicians.

CER studies should also consider sex, race and ethnicity (and other socioeconomic factors) in recognizing and accounting for the variation in outcomes of medical treatments. These studies should aim to reduce health disparities and close the gap between the care that we already know works well and the care patients actually receive. These studies should also seek to bolster and expand information and knowledge about quality without restricting access to care.

Similarly, CER studies should also examine socioeconomic factors that may affect treatment decisions. More than 45 million Americans lack health insurance, and a similar number have poor coverage or lack insurance altogether part of the year. Underinsured and uninsured adults and children are far more likely to go without needed care because of costs than their counterparts with adequate health insurance.[40] While the impact of insurance status is relatively well understood, the effect of other socioeconomic factors on treatment decisions and health outcomes is not as well known. In order to better understand the impact, the Robert Wood Johnson Foundation has started an initiative called "Aligning Forces for Quality." This is the largest effort of its kind by a U.S. philanthropic organization and will focus on identifying disparities and implementing high quality care in 14 different communities across the country.[41]

d. CER studies should be designed to evaluate clinical outcomes across a variety of settings and patient populations in order to provide usable information to patients, providers, and payers.

CER should be expanded in the United States to help evaluate clinical outcomes across a variety of settings and patient populations in order to provide usable information to patients, physicians, and payers. This will allow for better decisions regarding the use of specific health care interventions that take individual circumstances into account. Improving medical decision-making will help eliminate the use of treatments that are not appropriate for particular patients and increase the selection of appropriate treatments.

CER should incorporate patient-reported outcome (PRO) measurements—including quality of life (QoL) data—as an additional component for evaluation. In some circumstances, treatment-related changes in PROs can influence the clinical decision-making process based on the needs and goals of the patient. For example, there are a variety of treatment options for prostate cancer including surgery (radical prostatectomy), internal radiation (brachytherapy), external beam radiation therapy, and hormone therapy. Additionally, since prostate cancer is a very slow growing tumor, expectant management, (also called active surveillance, where the patient is not treated immediately and the tumor is monitored), is another option. Each of these options comes with a different set of risks and benefits including incontinence, or impaired bowel function, and reduced sexual activity that affect the QoL of both the patient and his partner or caregiver. Incorporating PRO measurement into longitudinal, prospective CER studies will provide a more detailed platform to evaluate options.

Recommendation #2:
A comprehensive CER program should link data from public and private entities to build upon existing data collection efforts and research capabilities.

a. The expansion of CER activities should prioritize public-private coordination and linking of data from clinical research networks and health care databases to generate hypotheses.

Insufficient funding for any public or private entity responsible for aligning and maintaining a robust data network has resulted in piecemeal and potentially misleading clinical outcomes research. A coordinated effort to link currently isolated public and private databases has the potential to generate an unprecedented amount of information for a variety of research activities. Given the variety of available data sources and differing uses of data, minimum standards of acceptable data quality will be essential to ensure validity of data collection efforts.[42] The difficulty of this enterprise should not be underestimated. Agreement on common definitions for both diagnosis and treatment interventions coupled with a method of collecting longitudinal data without compromising privacy, would make the effort much more feasible. Federal leadership and support will be needed to advance this project.

Much of the CER that is now done by international entities such as the Cochrane Collaboration and by U.S. entities such as AHRQ and the Blue Cross Blue Shield Technology Evaluation Center is based on literature reviews and meta-analyses of individual trials. These are important CER studies that help to synthesize existing information for clinical practice, but they cannot generate new knowledge beyond that included in the original studies. Such studies may have their own limitations. They may be dated in design and comparative therapies, and generally do not provide insights into the effectiveness of health care interventions outside of clinical trials in real-world settings, as the majority of the data for such reviews is generated by clinical trials designed to assess efficacy, not effectiveness.

In order to truly improve understanding of the outcomes of different treatment options and health services and to incorporate rapidly evolving information as it is developed, a new model and system for performing CER is needed. The databases routinely established, maintained, and audited for clinical research (and in some cases, preclinical research) contain detailed information about individual patients and their health outcomes. These data sets offer a potentially valuable source of information for CER. Yet clinical data sets from randomized clinical trials often include a relatively homogeneous patient population and take a long period of time to establish. Frequently, such datasets are not configured to be readily combined with other data sets, or are proprietary to manufacturers.

To begin to address the challenges to linking and sharing information from clinical databases, biospecimen repositories, and clinical researchers in the field of oncology, the National Cancer Institute (NCI) has developed a biomedical informatics infrastructure to enable cancer researchers, physicians, and patients to share data and knowledge. The cancer Biomedical Informatics Grid™(caBIG™) was established by NCI and its Cancer Centers as a pilot project in 2003 with a 3-year budget of $60 million.[43] In 2007, caBIG™ advanced into an enterprise phase with the goal of connecting the entire cancer community, including NCI-designated Cancer Centers, other NCI programs, other NIH institutes and interested federal health agencies, industry groups, and the broader biomedical research community.[44]

> A coordinated effort to link currently isolated public and private databases has the potential to generate an unprecedented amount of information for a variety of research activities.

caBIG™ participants have developed readily disseminated standards, tools, and information systems for the management of clinical and research activities in oncology. Using tools in areas including clinical trials management, tissue banks and pathology, imaging, and integrative cancer research, researchers and clinicians are able to analyze massive amounts of diverse types of data in ways that have never before been possible. caBIG™ is a nationwide, interoperable, interconnected information technology platform that enables information sharing and the capability to enable large science initiatives at NCI such as the development of The Cancer Genome Atlas.[45]

caBIG™ is based on the principles of open access, open development, open source, and federation,[46] and the caBIG™ infrastructure and tools are widely applicable beyond the cancer community. In fact, they are already being modified for use as a resource for similar efforts in cardiovascular and other diseases.[47] caBIG™ is also being integrated into the architecture of the HHS-sponsored National Health Information Network to provide secure, national access to health information.

caBIG™ provides an overarching informatics infrastructure with tremendous potential for performing CER for health care interventions with data from across the country. By providing a unifying biomedical informatics platform, the caBIG™ infrastructure and tools have the potential to enable researchers and clinicians to answer questions about interventions for cancer and other conditions more rapidly and efficiently, thereby accelerating progress in research and the translation of research into clinical practice.

Several medical communities have begun developing large-scale prospective databases that allow for collection and analysis of clinical and disease biomarker data that will ultimately be used for clinical trial-matching and potentially as a clinical decision-making tool. The Total Cancer Care™ (TCC) Program launched by the Moffitt Cancer Center in Tampa, Florida, for example, is an innovative project that is clinically following more than 28,000 patients in 16 different communities throughout their lifetimes, storing tumor specimens from these patients for molecular analysis, and collecting patients' clinical data for use not only in treatment but also in research.[48]

Administrative databases such as insurance claims databases, though not as detailed and not as expensive to generate as clinical databases, are another potentially valuable source of information on health outcomes and associated factors. Private insurers such as UnitedHealth Group and others routinely collect a wide array of data on individual patients' characteristics, medical care received, and the outcomes experienced for their covered populations. Such databases enable private insurers to better understand the services that they are paying for and to gain valuable information on health outcomes associated with the use of those services. For example, Blue Health Intelligence™, developed by the Blue Cross Blue Shield Association, is beginning to bring together the claims

experience of 80 million plan members nationwide.[49] This collection of de-identified data serves as a research tool to help understand health care trends and other factors related to care delivery and outcomes. The ability to collect longitudinal data might be greatly enhanced if a system for patient identification that would be voluntary and not be used for punitive purposes could be structured to capture the large population of patients who shift to multiple different payer systems over the course of their medical history. Comparable information can be gained by examining government-operated Medicare and Medicaid claims databases or data from the Veterans Affairs hospital systems. The move to electronic health records (EHRs) for all Americans may further enrich public and private insurers' databases with data from patients' EHRs, though all or most shared data will be de-identified at an early stage.

A critical element of this expanded data-network model is an established set of policies and procedures to promote data sharing among patients, investigators, health systems, third-party payers, and others. The current competitive climate may hinder sharing, rather than promote it. Data governance arrangements, supporting "use cases", or a goal-oriented set of interactions between external users and the data network that demonstrate the synergistic value of sharing, and ongoing efforts including research in ethics and policy are key. This will require commitment and collaboration between multiple sectors and stakeholders.

b. **Research through an expanded data network should be used to assist systematic reviews, generate data from real-world clinical practice, and develop new methods of outcome analyses and modeling.**

With the aid of new national health policies and a public-private partnership, the building blocks of a robust and diverse national database previously described could be assembled for the mining and analysis of data on health outcomes and associated factors. The public-private effort must ensure that individuals' privacy is maintained, establish data standards, and facilitate queries and other types of data mining to identify factors that may be contributing to the effectiveness of a particular medical intervention or to compare outcomes associated with the use of different health care interventions.

The information on health outcomes gained by mining and analyzing data from existing clinical and other databases must not supplant more scientifically rigorous data. As previously noted, Randomized Clinical Trials (RTCs) generate the highest level of clinical evidence. Information produced through data mining represents a lower level of evidence and should be treated as such and not result in clinical decisions in the absence of corroborating evidence. In areas where a higher level of evidence is not available, however, mining and analyzing data will generate information associated with the use of health interventions among real-world patients in real-world clinical practice settings and provide a foundation for designing hypotheses for further clinical research.

The oncology community is investing in several efforts that will create useful information on health outcomes that can be used to supplement data from RCTs. At a cost of more than $34 million, the NCI-funded Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) is enrolling population-based cohorts of patients newly diagnosed with lung and colorectal cancer from multiple regions and health care systems, including approximately 11,000 patients to date.[50] Data are being collected by CanCORS investigators from patients, caregivers, physicians, as well as patient medical records. Findings from these large population-based cohort studies supplement data from RCTs, help to fill gaps where no RCT data exist, and generate additional research questions for further study in clinical trials.

c. Although observational real-world studies have limitations, secondary analyses of existing data should be used as an initial step to identify information gaps, provide transparency to research priorities, and generate hypotheses for which further clinical trials and research may be necessary.

Information produced through robust secondary data analyses represents a lower level of evidence than information produced via randomized clinical trials, but standard RCTs can be expensive and time-consuming. Given limited resources, the impossibility of designing RCTs to answer every question, and the rapid evolution of scientific data, the mining and analysis of data on large numbers of patients from public and private databases could be a useful tool. Researchers could use information from secondary data analyses to identify gaps in the research, to provide transparency to research priorities, and to generate hypotheses for which further clinical research may be necessary.[51] They could also use such information to inform application of research results outside of clinical trials scenarios, providing better assessment of effectiveness in real-world populations.

Linking established data networks can be a significant challenge, but the FDA Sentinel Network illustrates the potential. The FDA Sentinel Network aligns established data sets to allow probing for questions regarding adverse events experienced with the use of a drug therapy. If a safety signal is detected through this network, specific clinical trials may be required to fully establish a causal relationship between the treatment and the clinical outcome identified through secondary data analyses.

Effectiveness studies require accurate and very detailed clinical information. It will undoubtedly be more difficult to create a national data system that links large clinical and other databases for research to compare the effectiveness of health interventions, than to create a national data system to detect safety signals such as the FDA Sentinel Network. The collaboration of public and private entities will be required to create such a network, facilitate interoperability, take necessary steps to ensure privacy, and establish standards for the conduct, analytic methods, and reporting of all CER studies, including registration of studies (e.g., The NIH maintains www.clinicaltrials.gov).

In the realm of CER, analyzing data from existing clinical research and other databases could be a tool that helps identify specific subpopulations that respond differently to a particular treatment or other health care intervention. As an example, data from a high-quality database could be analyzed to examine whether one of three particular interventions resulted in reduced hospitalization times. The full analysis might initially reveal that the use of drug X cuts down on duration of hospitalization. Hypothetically, a subset analysis based on patient characteristics from such a robust data set could then reveal that for Hispanic females, or another subpopulation, the results from that drug are quite different. It would be important not to overgeneralize from these results, especially subgroup analyses of dubious statistical reliability, but observations that emerge from analyzing data could be used to generate hypotheses about the reasons for the findings, which then could be used to design appropriate clinical trials.

Recommendation #3:
CER studies should support the development of "personalized" or stratified medicine.

a. Emphasis should be placed not only on the "average" patient, but also on the minority who experience prolonged survival or improved quality of life and who can be identified with biomarkers or other clinical characteristics.

Approval of new drugs by the FDA and formulation of the standard of care for particular types of cancer has often depended on RCTs that demonstrate prolonged survival or improved quality of life

after different kinds of treatment. In conducting these trials, patients are sorted according to known characteristics (e.g., age, sex, previous treatment, performance status, etc.) that might influence outcome and then randomized to different treatment groups, making each group of patients as similar as possible. Thus, the improvement in outcome established by these trials applies to the "average" patient with cancer from a particular organ. Improvements in overall survival are generally measured at the 50th percentile and can ignore a significant minority of patients who experience a dramatic prolongation of time to progressive cancer growth or improvement in symptoms. Epidermal growth factor receptor (EGFR) inhibitors such as Tarceva® (erlotinib) have only a modest effect on overall survival of the "average" lung cancer patient, but dramatically benefit 10 percent of those treated. Recent insights in cancer biology indicate that no two cancers are alike and each has a unique combination of genetic changes. Only a fraction of lung cancers contain critical mutations in the EGFR and most of the dramatic responses are observed in this group, which is also enriched for non-smoking women of Asian descent who have adenocarcinomas rather than squamous cell histotypes. For decades the presence of estrogen receptor and progesterone receptor in breast cancers has identified women who are more likely to benefit from hormonal treatment. If hormonal therapy were given arbitrarily to all women with breast cancer regardless of receptor status, the impact on response rate and survival would be diminished. Consequently, in studies of CER it is critical that recognizable "minorities" as well as the "average" patient be considered.

b. **Analyses of data from an integrated data network should be performed to identify factors that contribute to disease susceptibilities and differences in clinical outcomes.**

Personalized medicine involves the tailoring of prediction, diagnostics, and therapeutics, to the individual, based on that person's particular biologic makeup.[52] A growing number of examples of personalized medicine are already in practice today,[53, 54] particularly in the cancer field, which for numerous reasons has been at the forefront of personalized approaches.

Specific instances of the value of molecular subgrouping of patient populations are emerging. For example, genotyping patients for a particular gene called CYP2D6 may help indicate differences in drug metabolism rates. However, the genotyping test itself and understanding how to specifically tailor treatment decisions based on expression levels will require further study. The aggregation of large numbers of clinical outcomes as a data "input" for prospective studies, combined with the genotyping of all cancer patients, would provide the advantage of a new generation of "molecularly informed" CER that would have the multiple benefits of learning how best to target drugs to the appropriate patient subgroups; how to avoid unnecessary adverse events; and how to optimize cost effectiveness by treating only those patients who will respond to a given therapy.

The addition of patient-reported data, including the patient-reported phenotype, patient-reported quality-of-life, and other patient-reported outcome information, will enhance the development of personalized care. Future development of a nationwide (if not global) electronic health record of all patients will facilitate such molecularly informed, patient-centered, comparative effectiveness, making it easier to execute the seamless continuum known as the "learning" health care system.[55]

Part of the challenge to achieving personalized medicine is the chronic problem in biomedicine of institutional silos. Data sharing is often not done within one institution, and it rarely occurs between and among different institutions or biomedical sectors.

In 2008, to provide a model for collaboration among all the sectors of biomedicine—including diagnostic and therapeutic product developers, academics, payers, patients, consumers, laboratories, and others—NCI launched an initiative called the BIG Health Consortium™.[56] This consortium conducts projects that link clinical care, clinical research and scientific discovery, using the tools, infrastructure and standards of caBIG™.

To support the growth of personalized medicine in the meantime, the analysis and mining of data from integrated data networks can be used to begin to identify factors that contribute to disease susceptibilities. Examples of such factors include differences in race and ethnicity, sex, comorbidities, drug-drug interactions, nutritional status, smoking, living conditions (city-country, smog, increased ozone), drinking behavior, and other behavioral factors. Understanding the biological basis for any difference identified through data mining and analysis will require additional research, but the initial data analysis will help identify gaps in the evidence and generate new hypotheses for clinical studies based upon subpopulation characteristics which, in turn, will help to further advance "personalized" medicine. Moreover, the use of harmonized data networks will help increase transparency to research priorities and create an expansive collection of outcomes data for which comparisons of different treatment options can be performed.

In order to better understand how technology platforms can catalyze the development of personalized medicine, a series of proof-of-concept demonstration projects should be designed to highlight opportunities and feasible methods and to illuminate next steps needed for discovery and implementation of learning health systems. Example projects include: a Patient-Reported Outcome (PRO) based system that can be used as a platform for a learning health environment and bridge to personalized care;[57] decision support software that provides real-time calculation of risk at point-of-care using a wide range of molecular and clinical inputs and evidence-based, iteratively refined risk models; and clinical practice guidelines implemented at point-of-care that "learn" as new evidence is generated.

c. **Prospective clinical studies (including randomized trials) should be designed to further explore real-world effectiveness, characterize subpopulations for which a therapy is effective, and emphasize the collection of biospecimens to measure predictive markers.**

To build upon information generated through data mining research, prospective clinical studies should be designed to help validate subpopulations for which a therapy is effective. Such studies will require large populations followed over time. Well-founded biologically based hypotheses for such variation will help stratify study populations.

One type of prospective clinical study that could be used to develop high-quality scientific evidence about effectiveness that would be useful in health care decision-making is a "pragmatic" (or "practical") clinical trial.[58] This is a clinical trial for which the hypothesis and study design are developed specifically to answer questions faced by decision-makers. A pragmatic clinical trial selects clinically relevant alternative interventions to compare; includes a large, diverse population of study participants; recruits participants from heterogeneous practice settings; and collects data on a broad range of health outcomes (although data collection is still greatly minimized compared to standard FDA-style registration trials). Analyses of data on subpopulations in pragmatic clinical trials can be used to explore the extent to which the average benefits observed within a trial differ greatly from those that might be expected for a given individual or group.

Pragmatic clinical trials are conducted in other countries, but the major funders of clinical research in the United States—the National Institutes of Health (NIH) and the medical products industry—do not focus on supporting these trials, so supply of pragmatic clinical trial data is limited. Such trials can be time consuming and expensive, and their design would be aided by the hypotheses generated through database analysis as described above. The growth of practice-based research networks and electronic health records will make it increasingly feasible to conduct large research studies in community-based practice settings.[59]

A second option that maintains the substantial benefit of generating evidence based on randomized data while substantially reducing the burden of clinical trials at the individual patient level is use of cluster randomized trials.[60] In these trials, randomization is performed not at the individual patient level, but rather in "clusters" (which may be treating physicians, treating locations, group practices, cities, or states, for example) which are randomized to treat all patients within the cluster the same way. Outcomes are then compared between the randomized groups at the cluster level. This approach is particularly well-suited for trials of educational or prevention initiatives that occur at a community level or for specialized interventions that require a large investment in new technology that once in place within a "cluster", usage restrictions such as demanded by individual patient randomized trials may be problematic.

As previously described, research to provide a higher level of evidence, such as an RCT, should be conducted to validate lower levels of evidence generated through database analysis for CER. When appropriate, clinical studies should seek to identify biological markers that either modify prognosis of the underlying disease (prognostic factors) or predict the likelihood that particular treatments will be beneficial and/or unsafe (predictive factors). CER studies should be explicit in identifying strategies that permit the delivery of "personalized" treatments that may provide substantial benefit for particular segments of the population. The identification of these prognostic and predictive biomarkers will only be possible through prospective biospecimen collection on these trials, to allow both the prospective and retrospective analyses to associate biomarker levels with clinical outcomes.

d. CER studies should have the ability to utilize all types of research methods and explore the use of more efficient research techniques.

The difficulties associated with performing high-quality, high-impact CER are great. Although the RCT remains the gold standard of generating evidence about the causal relationship between a medical intervention and outcome, the cost and time required to conduct RCTs preclude their use as the only option for CER. For that reason, CER studies must include a wide range of research methods and explore the use of innovative, more efficient research methods, including novel statistical analyses, computer modeling, bayesian analysis, and adaptive trial techniques.

The use of computer models to simulate the effects of health interventions is an approach that has been suggested as an alternative or supplement to clinical trials. There are many well-designed models, including Archimedes, a full-scale simulation model of human physiology, diseases, behaviors, interventions, and health care systems.[61, 62] Archimedes is intended for problems that cannot be practically studied empirically with formal trials or other evaluation designs. The NCI has a similar effort underway, known as the Cancer Intervention and Surveillance Modeling Network (CISNET) that is using biostastistical modeling to help guide clinical and policy decisions on cancer control.[63] Well-designed models provide a way of exploring important questions at a fraction of the cost and time of empirical methods.

Recommendation #4:
Processes should be developed to ensure that information gained through CER is incorporated into clinical practice and better informs decisions made among patients, their health care providers, and payers.

a. Processes should be determined to ensure that information generated through CER studies is evaluated and reported in conjunction with current clinical guidelines to efficiently incorporate emerging scientific evidence.

Evidence from CER must be communicated rapidly to physicians and translated into everyday

practice or it will not be of much value. For that reason, processes should be established to ensure that information generated through CER studies is evaluated and reported in conjunction with current clinical guidelines to efficiently incorporate emerging scientific evidence. It is important to ensure that guidelines are continuously updated to reflect new research; otherwise, guidelines may hinder, not foster, improved quality of care.[64, 65] In addition, research is needed to identify the best way to ensure these guidelines and findings are incorporated into practice.

In the field of oncology, professional societies and not-for-profit organizations including the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) have existing processes to develop and update professional practice guidelines for physicians and patients. In addition, the American College of Surgeons (ACS) has the ability evaluate hospital-based management through its tumor registry database. These processes include routine input from practicing oncologists, which allows for the rapid incorporation of emerging scientific information. Other professional societies outside of cancer follow similar procedures. For that reason, it is important to establish processes for the way evidence generated by an expanded government-sponsored CER program will be incorporated into existing clinical guidelines.

b. A comprehensive CER initiative should support the design of studies that provide a rational and scientific basis for reimbursement decisions and strategies of public and private health care payers.

The national CER initiative should support the design of studies that provide a rational and scientific basis for reimbursement decisions and strategies of public and private health care payers, including the federal Centers for Medicare and Medicaid Services (CMS). This is an ultimate goal and the correct infrastructure needs to be in place, rigorous methodologies enforced, and systematic approaches utilized in order for CER to be routinely used in reimbursement decision-making.

Recently, however, CMS, which administers Medicare, Medicaid, and the Children's Health Insurance Program, began instituting a policy for Medicare called "coverage with evidence development" for promising drugs, biologics, devices, diagnostics, and procedures that would otherwise not meet Medicare's evidentiary standards of being "reasonable and necessary."[66] Under this policy, Medicare covers the cost of treatments or tests with promising but uncertain medical benefits for patients who agree to participate in either a practical clinical trial (a real-world effectiveness trial) or some kind of registry to develop evidence about the treatment.[67] Medicare used a similar approach in designating one center for reimbursement of cardiac transplantation decades ago when that procedure was experimental and of unknown efficacy.[68] Other major procedures have been introduced similarly.

Coverage with evidence development is an approach to providing access to innovative technologies while also documenting risks and benefits to patients. CMS has applied the Medicare "coverage with evidence development" policy to off-label uses of new biologics for colorectal cancer. Thus, Medicare coverage was provided for the use of these products for patients in selected NCI-sponsored clinical trials with the understanding that clinical data on these patients' treatments and health outcomes would be collected in the trials.

CMS is also developing a set of pay-for-performance (P4P) initiatives to support quality improvement in the care of Medicare beneficiaries by giving financial incentives to health care providers for high quality care. In this approach, reimbursement rates vary, and are dependent on reaching certain quality measures (e.g., treatment response, treatment outcome). CER studies should be designed to support pay-for-performance initiatives. That is, these studies should examine the value of P4P approaches as compared to traditional payment approaches. These studies should develop and use quality measures based on patient outcomes versus clinician processes.

c. **Physicians should receive feedback on the outcomes of their choices, as well as the costs to patients and their payers.**

Communicating the results of an expanded CER program will be critical to improve medical practice and decision-making. In order to demonstrate the utility of such information, data regarding the outcomes of medical decision will help physicians better measure the results of care provided. In order to do so, infrastructure and processes should be developed so that physicians receive feedback on the outcomes of their treatment choices, including patient adherence, adverse events and treatment outcomes, as well as the charges to patients and their payers. In addition, health care organizations should routinely monitor the quality of care patients receive to ensure that existing clinical practices are consistent with evidence-based guidelines. Information showing that processes of care deviate markedly from recommendations should trigger quality improvement efforts. Along these lines, research is needed that identifies the most effective strategies for promoting the dissemination and implementation of changes in clinical practice when new evidence emerges.

d. **Hospital and clinical pharmacy committees should seek and utilize robust CER findings when providing information to health care providers about treatment options.**

Finally, hospital and clinical pharmacy committees composed of physicians, pharmacists, and other health care professionals consider essentially all the matters related to the use of drugs in a particular setting, evaluation of drugs and dosage forms and safe use of investigational drugs, and cost. Their role is to help develop policies and procedures related to the therapeutic use of drugs and to monitor issues relating to drug safety throughout the hospital or clinic. Pharmacy committees also prepare drug formularies, which provide information on various drugs to be used in the hospital or other setting. These committees should seek and utilize national CER findings, rather than institutional analyses alone, when providing information to care providers about treatment options as well as in the routine updates and development of institutional guidelines for product use.

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For more information please contact Friends of Cancer Research at:
info@focr.org or 703.302.1503