Preparing for Success With Comparative Effectiveness Research

THOMAS G. ROBERTS, JR.

Managing Member, Farallon Capital Management, L.L.C.

Disclosures of potential conflicts of interest may be found at the end of this article.

Thomas G. Roberts, Jr.

Decades of public and private investment in cancer biology research has led to an enhanced understanding of the fundamental genetic changes that lead to the formation and progression of cancer [1]. Clinical scientists have worked iteratively over this same period to develop nuanced chemotherapy regimens that have either extended survival expectations for most patients with common types of cancer, or in the cases of pediatric cancers, germ cell tumors, and some hematologic malignancies, effected cures. The last decade in particular has witnessed a period of intense productivity in the development of molecularly targeted therapies—many of these agents have produced impressive and sustained (though not yet curative) benefits in defined subgroups of patients, at least until resistance develops. Most recently, therapies rooted in knowledge of cancer immunology have shown promising results in subgroups that are not well served by existing cytotoxic and targeted therapies; these advances are highly likely to play a more meaningful role in the oncologist's future armamentarium [2]. In 2012 alone, the FDA approved 11 new molecular entities or biologic agents for the treatment of cancer, representing a third of FDA approvals across all therapeutic classes [3]. Over the last two years, the number of cancer approvals far exceeded those in all other fields. It is now possible for all but the most skeptical observers to envision an encouraging path forward.

One question that arises implicitly from this positive dynamic is whether the oncology community, particularly in the United States, has prepared for success. Have we developed systems to evaluate comprehensively new therapies in real world settings? Are we routinely generating the evidence that can help reduce practice variations and improve health outcomes in vulnerable groups? Are we applying the new therapies in the most appropriate settings, directing them primarily to patients most likely to receive a benefit? Have we refined methods that can estimate the value (both clinical and economic) of new therapies compared

to the clinical profiles and costs of reference standards? Complicating the matter further is the realization that oncology's very success, now and in the future—the direct result of one of the most productive public-private partnerships in American history—is threatened by fiscal budget constraints at the very same time that cancer care costs threaten the fiscal health of the United States. The National Cancer Institute estimates, using conservative assumptions, that the real costs of cancer care in the United States will increase at least 39% over the period from 2010 to 2020 and may exceed \$200 billion (constant currency) by the end of the decade [4]. These cancer care costs, which are growing faster than costs in other areas of medicine, will comprise a substantial portion of the Medicare and Medicaid budgets that have been cited by at least one major ratings agency as justification for the loss of America's AAA credit rating with further downgrades possible.

Comparative effectiveness research (CER), the latest name given to efforts that began in the 1970s to improve quality and maximize the value of health services, offers a systematic approach to addressing the conundrum brought upon by oncology's success. CER has been used in most developed countries to a greater or lesser extent to make evidence-based funding decisions and to formulate treatment guidelines [5, 6]. Indeed, the current environment should be yielding enthusiasm for the implementation of CER, yet the field has struggled to define its role within the American cancer community.

The challenges for CER have been manifold. First, the enormity of the task required to develop effective treatments has diverted attention understandably from some of the more contextual questions that CER seeks to address. Critical inquiry into the relative economic value of new treatments has not necessarily been encouraged as oncologists rightfully pushed for greater innovation. Second, until relatively recently, the cost of cancer care has been minor when compared to other

Correspondence: Thomas G. Roberts, Jr., M.D., Farallon Capital Management, L.L.C., One Maritime Plaza, Suite 2100, San Francisco, California 94111. E-Mail: troberts@faricap.com Received May 30, 2013; accepted for publication June 4, 2013. ©AlphaMed Press 1083-7159/2013/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2013-0213>.

areas of medicine and has largely escaped scrutiny in the United States. Before the development of paclitaxel in the 1990s, cancer care had a negligible impact on national budgets: few effective treatments existed once disease spread beyond primary sites, and patients who could not be cured were encouraged to seek supportive care at relatively modest costs. Third, Americans have shown neither a cultural affinity nor a political interest in CER, especially as it applies to issues of healthcare costs. The recently enacted Patient Protections and Affordable Care Act (ACA) in fact created and funded an entity to conduct CER, the Patient-Centered Outcomes Research Institute (PCORI), yet expressly prohibited it from performing cost-effectiveness research [7]. Finally, the research itself has suffered from important limitations as outcomes researchers have sought to generate timely, relevant, unbiased, and scientifically valid evidence that stakeholders could use to improve real world decisions. While oncologists have grown accustomed to high-quality efficacy studies with clear-cut outcomes, many of the CER studies, in contrast, have relied on observational data or required the incorporation of numerous assumptions based on incomplete data, and some model outputs have been criticized for false precision. All can agree on the appeal and commendable goals of CER, yet some of the publications in this area have devolved in highly technical methodological exercises that are poorly understood by the ultimate consumers of the research, thereby lessening their impact.

This backdrop provides a receptive context for two important papers published in this issue of *The Oncologist*, each led by prominent figures in the field, Gary Lyman and Scott Ramsey [8, 9]. Together, these articles advance a clear explanation of the goals, tools, and limitations of CER and call on oncologists to lead the discourse on the comparative value of cancer care options.

Gary Lyman makes three notable points. First, he defines succinctly what CER is and what it is not. Lyman describes CER as striving “to define the optimal strategies for delivering the most effective and safe interventions to appropriate populations in the most efficient way.” He expressly differentiates this goal from rationing, restrictions, and cost containment. Second, Lyman lists and discusses the toolkit of outcomes researchers, demonstrating the breadth of the CER field while discussing the promise, limitations, and future opportunities of each methodology. His table, which lists the work in progress for each of the methodologies, such as the CancerLinQ efforts of the American Society of Clinical Oncology (ASCO), will likely provide a roadmap for the field over the next 10 years. Finally, Dr. Lyman explains how CER may extend its reach to helping advance the promise of personalized and genomic medicine given the need for early and continuous statistical oversight and given the variable quality of research in this area, which in his view, is all too often lacking.

While Dr. Lyman produced a clear description of the field and a roadmap for its future, the group led by Scott Ramsey went further. Ramsey and colleagues provide one of the most reasonable and practical prescriptions to date for how the field of CER may move forward and realize its promise. The Ramsey paper first describes the opportunity for CER. Similar to Lyman, the authors note that the established phase 1-4 trial process in oncology provides an incomplete

picture of an agent’s promise. Questions such as how a drug will perform when given to broader patient populations, its longer-term safety and effectiveness profile, and its broader impact on patient care and outcomes (including economic outcomes) are usually left unanswered by trialists, even well after approval. Comparative effectiveness researchers have the opportunity to fill this broad evidence gap [9]. Ramsey and colleagues convened over fifteen stakeholders representing a broad array of perspectives over a two-day period to discuss five themes in the CER field. The group addressed directly the reasons why CER has found a limited audience in the United States and made specific recommendations for improvement.

Of the five areas on which the group focused, three were most illuminating: the need to consider cost in CER, separating well-conducted from poorly conducted CER, and better reporting to meet the needs of busy decision makers. It was interesting that all 15 stakeholders felt that cost is a vital issue for CER, despite the current political environment that discourages cost-effectiveness in government-funded CER. The group also presented suggestions for better reporting and identified five “kisses of death” when publishing CER, such as “extensive use of technical jargon ending with ambiguous conclusions” and “a comparison group that consists of outmoded treatments or incomparable patient populations.” This part of Ramsey et al.’s article should be required reading for any outcomes researcher planning to submit an article for publication in an oncology journal. Several of the stakeholders suggested the need to develop a checklist verifying the methodological issues that were addressed in the CER study (such as efforts to identify and reduce bias) and the establishment of a prospective CER registry that would require completion of such a checklist. This group should be commended for its open discussion about why CER has received relatively modest acceptance and for its clear and specific recommendations to move the field forward.

Looking back over the last 20 years or so, the system has worked. Innovation has happened; the pace of progress is accelerating. The combination of monopoly pricing for cancer drugs in the United States (during market exclusivity) and federal law that requires Medicare to cover any drug used in an anticancer regimen for a medically accepted indication has produced the potential for abnormally high returns for sponsors investing in cancer drug development. This return potential, including a so-called innovation premium, has created powerful incentives that could sustain the large and prolonged investment required to fund the risky business of cancer drug development. The rise in the cost of cancer care cost has been seen as the price of this innovation [10]. It is less clear today how much longer society is willing to support these costs, and it is an arithmetic certainty that the rate of growth in cancer costs is unsustainable. If the situation is left unchecked, and ultimately gets politicized, the outcome is likely to be unpredictable and suboptimal. The recent mandatory across-the-board 2013 budget cuts known as the sequester, in which the budget of the National Institutes of Health was slashed by \$1.7 billion and Medicare reimbursement cut by 2%, may provide an example of how blunt policy instruments could be applied to cancer funding in the future.

The articles by Lyman and Ramsey et al. provide optimism that the tools related to CER can help improve outcomes and avoid waste in a more intelligent way. There is also evidence elsewhere to suggest that physicians, and not politicians, are leading this debate as it relates to oncology. Steven Pearson and Peter Bach, for example, have articulated a straightforward and relatively simple idea of how Medicare could use CER in deciding on new coverage and reimbursement [11]. Elsewhere, more than 100 leading cancer specialists have joined together to protest high drug costs, as they have pointed out that more than 90% of the cancer drugs that received FDA approval last year cost in excess of \$100,000 per year [12]. The American Society of Clinical Oncology has recently identified five key opportunities to improve care and reduce costs [13] and is investing in a rapid learning system which may help oncologists, among many other things, incorporate more effectively these and other quality initiatives [14]. Other prominent oncologists have called for cost and comparative value of treatment to be considered in clinical practice guidelines.[15] Importantly, no physician has argued that it is appropriate for individual oncologists to make rationing decisions at the bedside. Finally, efforts by translational researchers to identify subsets of patients most likely to benefit from existing and future treatment will no doubt play an important role in improving the future value proposition of cancer treatments.

Longer term, CER will play a key role in efforts to optimize outcomes for cancer patients given society's finite willingness and ability to pay, but only when there is greater political and social acceptance of the field and hopefully when it has

a trusted administrative context in which organization and content decisions are made independently from its funding source [16]. The oncologist community has a distinguished history of leading research in comparative effectiveness dating back to the first randomized trials in acute leukemia in the 1950s. Oncologists have shown that they can come together for the benefit of patients in a way that elected representatives cannot. Now is the time for the oncology community to take more concrete steps to advance the vision that Lyman and Ramsey et al. have articulated. It is not too late to prepare for success, and for those clinical scientists interested in documenting their work in the important field of CER, *The Oncologist* is open for business.

ACKNOWLEDGMENTS

Dr. Roberts is a Managing Member of Farallon Capital Management, which in the normal course of business makes investments in public and private companies that may be developing products for the diagnosis or treatment of cancer. Dr. Roberts is also a board member of the Conquer Cancer Foundation (CCF) of the American Society of Clinical Oncology (ASCO). The views expressed herein are solely those of Dr. Roberts and not meant to represent positions of Farallon Capital, ASCO or the CCF.

DISCLOSURES

Thomas G. Roberts, Jr.: Farallon Capital Management (E).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

REFERENCES

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646-74.
2. Pardoll, DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252-64.
3. Food and Drug Administration. Hematology/Oncology (Cancer) Approvals & Safety Notifications. Available at: <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm>. Accessed May 28, 2013.
4. Yabroff KR, Lund J, Kepka D et al. Economic burden of cancer in the United States: estimates, projections, and future research. *Cancer Epidemiol Biomarkers Prev* 2011;20:2006-14.
5. Hoch JS, Hodgson DC, Earle CC. Role of comparative effectiveness research in cancer funding decisions in Ontario, Canada. *J Clin Oncol* 2012;30:4262-6.
6. Sorenson C., Drummond M., Chalkidou K. Comparative effectiveness research: the experience of the National Institute for Health and Clinical Excellence. *J Clin Oncol*. 2012;30:4267-74.
7. Neumann PJ, Chambers JD. Medicare's enduring struggle to define "reasonable and necessary" care. *N Engl J Med* 2012;367:1775-7.
8. Lyman, GH. Comparative Effectiveness Research in Oncology. *The Oncologist* 2013;18:752-759.
9. Ramsey, SD, Sullivan SD, Reed SD et al. Oncology Comparative Effectiveness Research: A Multi-stakeholder Perspective on Principles for Conduct and Reporting. *The Oncologist* 2013;18:760-767.
10. Schrag D. The price tag on progress--chemotherapy for colorectal cancer. *N Engl J Med* 2004;351:317-9.
11. Pearson SD, Bach PB. How Medicare could use comparative effectiveness research in deciding on new coverage and reimbursement. *Health Aff (Millwood)* 2010;29:1796-804.
12. Pollack A. "Doctors Denounce Cancer Drug Prices of \$100,000 a Year." April 25 2013. Available at: http://www.nytimes.com/2013/04/26/business/cancer-physicians-attack-high-drug-costs.html?pagewanted=all&_r=0. Accessed on May 28, 2013.
13. Schnipper LE, Smith TJ, Raghavan D et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. *J Clin Oncol* 2012;30:1715-24.
14. Lichter AS. Relentless progress: ASCO responds. *The Oncologist* 2012;17:160-1.
15. Basch E, Somerfield M, Partridge A et al. Commentary: should cost and comparative value of treatments be considered in clinical practice guidelines? *J Oncol Pract* 2011;7:398-401.
16. Pearson, SD. Cost, coverage, and comparative effectiveness research: the critical issues for oncology. *J Clin Oncol* 2012;30:4275-81.

EDITOR'S NOTE: Please see the accompanying articles on pages 752 and 760 of this issue.