Published in final edited form as:

Nat Rev Clin Oncol. ; 8(12): 735–741. doi:10.1038/nrclinonc.2011.151.

Personalized cancer medicine—advances and socio-economic challenges

David B. Jackson and

LIFE Biosystems GmbH, Belfortstraße 2, D 69115 Heidelberg, Germany

Anil K. Sood

Departments of Gynecologic Oncology and Cancer Biology, and Center for RNA Interference and Non-Coding RNA, University of Texas MD Anderson Cancer Center, 1155 Herman Pressler, Unit 1362, Houston, TX 77030, USA

Abstract

It was Hippocrates, the father of Western medicine, who first emphasized the patient as the most important determinant of therapeutic efficacy. Although the principle of adjusting treatment to specific patient characteristics has since been the strategy of physicians, this is undermined by a population-biased approach to drug development. Therefore, it is generally true to say that our current evidential approach to cancer treatment is driven more by drug-regulation requirements and market considerations than the specific needs of an individual patient. But, with cancer drug costs now spiraling out of control and the modest efficacy typically seen in patients, the community is again turning to Hippocrates' ancient paradigm—this time with emphasis on molecular considerations. Rapidly evolving technologies are empowering us to describe the molecular 'nature' of a patient and/or tumor and with this has come the beginning of truly personalized medicine, with maximized efficacy, cost effectiveness and hopefully improved survival for the patient.

Introduction

From the revolutionary success of imatinib,¹ to the follow-on promise of compounds such as crizotinib² and vemurafenib,³ a strong rationale exists for the principles of targeted therapy. Yet, even with the improved response rates demonstrated with such agents, it is clear that the therapeutic activity of a molecular-targeted drug is only achievable under certain biological conditions.⁴ The very modest benefit seen in the majority of patients administered targeted drugs, such as bevacizumab, is a stark reminder that the association between target activity and tumorigenic potential varies greatly across a patient population.⁵ Current clinical trial design compounds this problem, with large cohorts used to fulfill the needs of statistical significance rather than generating a deeper understanding of the biologically sensitive contexts within a trial population. What emerges is a system of evidentiary medicine that leaves patients more dependent on the rules of chance than those of biological fact. It is hardly surprising that with most therapies failing to improve outcomes in patients

© 2011 Macmillan Publishers Limited. All rights reserved

Correspondence to: A. K. Sood asood@mdanderson.org.

Competing interests

D. B. Jackson declares an association with the following company: LIFE Biosystems. See the article online for full details of the relationship. A. K. Sood declares no competing interests.

Author contributions

Both authors contributed to researching data, writing, editing and reviewing this article.

with metastatic disease, the war on cancer has contributed to a financially battered health-care system and a growing cancer patient population for whom traditional clinical practice often offers little but a lottery of hope.

The growing discordance between the enormous costs and marginal clinical benefit associated with many anticancer blockbusters has led to increasing concerns.^{6,7} Most stakeholders agree that urgent improvements in cost-to-benefit ratios are required; we strongly believe advances can only be realized through widespread adoption of truly targeted approaches to patient treatment. Thus, the definition of ‘personalized medicine’ that we have applied throughout this article is restricted to the process of identifying molecular subtypes of individuals or disease that are uniquely susceptible to a particular treatment. Using this truly personalized strategy, therapeutic interventions can be applied to those who will likely benefit, sparing expense and toxic side effects for those who will likely not benefit. Of course, the challenges of bringing molecularly targeted patient treatment to clinical reality are as diverse as the opportunities presented. Key stakeholders hold vested and often juxtaposed interests, making the challenge even greater. In this Perspectives article, we examine some of these issues and ask how financial and moral necessities are considered while achieving the widespread clinical implementation of targeted treatment to patients.

Targeted drugs versus therapies

Although the concept of targeted therapy has been embraced with considerable excitement, an unbiased appraisal of clinical response rates associated with drugs such as bevacizumab and cetuximab leads us to question the broad-scale validity of the term ‘targeted therapy’.⁸ Although targeted drugs act to specifically inhibit the activity of one or more oncoproteins, there is considerable uncertainty as to whether this inhibition will result in a therapeutic effect. This ambiguity derives in part from the heterogeneity of molecular drivers underlying a disease. Thus, to achieve targeted therapy, the molecular-targeted agent must be administered to patients where the intended target is a validated protagonist of disease progression in that tumor. For example, the BCR–ABL fusion protein is a ‘driver’ of disease in chronic myeloid leukemia, which explains why the tyrosine kinase (BCR–ABL) inhibitor imatinib is an effective treatment in patients with this disease.^{9,10} In an analogous manner, the activity of crizotinib is currently restricted to non-small-cell lung cancer (NSCLC) tumors possessing an *EML4–ALK* fusion¹¹ and the activity of vemurafenib is observed in melanomas possessing a V600E substituted BRAF protein.¹² However, early results suggest that the presence of the V600E BRAF substitution in colon cancer might be a poor predictor of vemurafenib response in this disease,¹³ emphasizing that targeted-drug activity is context specific. Moreover, examples exist where promising anticancer-drug targets act as tumor suppressor proteins in certain tumor subtypes. For example, Ephrin type-B receptor 4, which is a focus of current drug discovery and development efforts, has been shown to act as an oncogene in bladder cancer¹⁴ and as a tumor-suppressor gene in colorectal cancer.¹⁵ The use of targeted drugs without sufficient knowledge of the molecular context of the target in a particular patient might result in poor survival or severe adverse drug reactions, and for the health-care system it can lead to considerable financial waste and associated societal effects.

Drug cost versus benefit

Over the past decade, the poorly directed use of anticancer drugs has contributed to the emergence of many worrying trends. For example, spending on cancer medications has risen by 14% annually over the past few years.¹⁶ In 1995, the only widely used cancer drug that cost more than \$2,500 per month was paclitaxel.¹⁷ By contrast, many recently approved targeted drugs have entered the market priced at many times this cost, with more than 90%

of the anticancer agents approved by the FDA in the past 4 years costing more than \$20,000 for a 12-week course (Figure 1).¹⁸ With insurers bearing the brunt of these costs in the USA, their response has been to off load the expense onto patients; therefore, out-of-pocket spending has increased sharply, especially for low-income patients who are estimated to spend about 27% of their yearly income on medical costs,¹⁹ no doubt convincing many to avoid or discontinue treatment. It has been estimated that 62% of all personal bankruptcies in the USA are attributable to medical costs and, among those, cancer is often the illness that initiates the financial burden.²⁰ Moreover, given that evidence exists linking biobehavioral stress with tumor progression,²¹ it is clear that many patients may endure a vicious cycle of decaying wealth and health. With ASCO issuing a guidance statement affirming “the critical role of oncologists in addressing cost of care,”²² oncologists have become increasingly vociferous. However, their primary concern lies not with drug prices *per se*, but rather with what many perceive as a more-worrying pattern of diminishing therapeutic returns, where increases in price substantially outweigh the often modest benefit to the patient.^{6,7}

Antibody drugs provide particularly illustrative examples, for example, treatment with the antibody bevacizumab costs more than \$50,000 per year (note the median household income in the USA was \$52,029 in 2008),²³ with costs rising to about \$100,000 per year when drug administration and routine monitoring are also considered.⁵ Although early clinical studies showed enormous promise for this drug,²⁴ later-stage development produced a number of disappointing results (for example in patients with prostate cancer²⁵ and pancreatic cancer^{26,27}) along with modest successes in terms of overall survival in other cancers—typically measured in weeks (Table 1). Given the enormous unmet medical need, the FDA has approved bevacizumab for treatment of colorectal cancer,^{28,29} glioblastoma,³⁰ NSCLC,^{31,32,33} and renal-cell carcinoma.^{34,35} Approval for the treatment of relapsed or progressive glioblastoma was granted by the FDA on the basis of results from the phase II BRAIN study, and the large unmet medical need associated with this most-aggressive form of malignant brain cancer.³⁰ This approval came in the absence of large-scale phase III data and other data demonstrating whether or not the drug improves disease-related symptoms or survival in previously treated patients. It is noteworthy that the European Committee for Medicinal Products for Human Use (CHMP) issued a negative opinion regarding marketing approval based on the same data. Their main objection was the lack of a comparator arm without bevacizumab in the BRAIN study, and the fact that the CHMP tends to base its approval decisions on phase III studies only.³⁶ Most controversial of all, however, was the approval of bevacizumab for treatment of metastatic breast cancer in 2008;³⁷ this decision came counter to a recommendation by the Oncology Drugs Advisory Committee (ODAC), which expressed concern about the lack of overall survival benefit and significant risk of fatal adverse events.³⁸ Subsequent data from the AVADO³⁹ and RIBBON-1⁴⁰ trials have validated these concerns and a follow-up meeting in 2010 saw the ODAC vote 12 to one in favor of removing the metastatic breast cancer indication from the drug label of bevacizumab⁴¹—and the FDA is adhering to the advice.

It is astounding that the estimated costs for keeping a single patient with breast cancer alive for 1 year (or 1 quality-adjusted life year [QALY]) using bevacizumab is almost \$500,000.⁶ Similarly, Fojo *et al.*⁷ have estimated a cost of \$800,000 for keeping a patient with NSCLC alive for 1 QALY using cetuximab.⁷ Extrapolating their analysis to the 550,000 Americans who die from cancer each year, they estimated a financial implication of \$440 billion to extend the lives of these patients by a single year.⁷ Recent health economics modeling of bevacizumab use in ovarian cancer has also yielded stratospheric projections.⁴² Working with data from the GOG-0218 trial,⁴³ Cohn *et al.*⁴² examined the potential cost effectiveness of adding bevacizumab to first-line treatment of advanced-stage epithelial ovarian cancer. Their projections suggest a cost of \$1,305,000 per patient for maintenance bevacizumab added to the triple therapy combination of paclitaxel, carboplatin and bevacizumab and an

incremental cost-effectiveness ratio (compared with paclitaxel plus carboplatin) of \$401,088 per progression-free year of life saved.⁴² Costs such as these have encouraged considerable debate in the field, with Hensley,⁴⁴ asking what paying \$78.3 million for 3.8 months of progression-free survival (PFS) for 600 women means for other participants in the health-care system? Similar concerns were also raised by Munro and Niblock,⁴⁵ who were not only critical of the marginal overall survival benefit reported for treatment with the antibody trastuzumab in the ToGA study,⁴⁶ but they also questioned the societal implications of the estimated costs. After conservatively projecting that clinical use of trastuzumab in patients with HER2-positive advanced-stage gastric or gastro-esophageal junction cancer will cost about \$90,000 per life year gained, they examined the yearly health expenditure for citizens in 24 countries (range \$40–\$5,500) and asked, “what is the justification for introducing a treatment that might enable one individual to live a couple of months longer, but will consume, for each person treated, the total yearly health expenditure for scores of their fellow citizens?”⁴⁵ This question becomes all the more relevant given the clinical reality that most advanced-stage cancer patients will receive no survival benefit and on the contrary may have to contend with serious adverse drug reactions.⁴²

These facts raise important concerns about the poorly directed use of multiple targeted drugs in a single patient. With the appearance of every new targeted treatment option, has come the natural attempt to combine drugs with distinct targets and mechanisms. In the treatment of metastatic colorectal cancer (mCRC), for example, the cost of the 5-fluorouracil–leucovorin combination is less than \$100 for a 6-month course, but the addition of irinotecan or oxaliplatin costs an additional \$30,000, adding bevacizumab to the combination requires an additional \$24,000 and cetuximab a further \$50,000.⁴⁷ Therefore, the aggregate cost for treatment of patients with mCRC using this multiagent approach lies somewhere around \$150,000 to \$200,000 to achieve an additional year of survival compared with treatment with 5-fluorouracil–leucovorin alone.⁴⁷ So, although the growing adoption of multiagent therapeutic strategies is to be welcomed in scenarios of proven clinical benefit, the associated financial costs demand a greater emphasis on the development of combination therapy linked to predictive biomarkers in the hope that this will improve the cost–effectiveness ratio.

Factoring adverse events

A critical issue that is poorly factored into the aforementioned financial estimates is the cost incurred owing to adverse drug responses. Not only are adverse drug responses a crucial determinant of the outcome of patients with cancer, they also considerably compound the financial outlay required to treat the patient. In support of this view, two of the top five drug expenditures by clinics in the USA in 2010 (January to September) were for drugs that are used to treat the adverse effects induced by antineoplastic agents (Table 2).⁴⁸ In the case of the GOG-0218 trial, the 3.8 months of additional PFS was not only associated with enormous direct costs, but also with a 23% risk for developing grade 2 hypertension, a 10% risk for grade 3 or 4 hypertension, and a 2.3% risk for grade 3 or worse gastrointestinal perforation, fistula formation or hemorrhage.⁴³ The costs associated with hospitalization for these adverse events are presumably enormous. Interestingly, a recent meta-analysis of 10,217 patients with a variety of advanced-stage solid tumors from 16 randomized controlled trials showed that bevacizumab in combination with chemotherapy or biological therapy was associated with increased treatment-related mortality compared with chemotherapy alone.⁴⁹ The overall incidence of fatal adverse events with bevacizumab plus chemotherapy was 2.5%, and was some 1.5-fold more frequent among these patients than patients receiving chemotherapy alone. The most common of these events were hemorrhage (23.5%), neutropenia (12.2%), and gastrointestinal tract perforation (7.1%).⁴⁹ Such effects are a stark reminder of the importance of developing appropriate treatment biomarkers to

ensure that the optimal treatment is given to each patient, particularly in the context of highly expensive drugs that produce marginal survival benefits (Table 3).

Major ethics issue, minor benefit

The reason often put forth to explain the modest overall survival benefit derived from molecular-targeted therapies include the confounding effects of post-progression treatments, early follow up and/or insufficient statistical power. Investigators involved in the AVAiL trial suggested that “PFS benefit did not translate into a significant overall survival benefit, possibly due to the high use of efficacious second-line therapies”.³³ However, inspection of post-study therapies shows conclusively that they are essentially identical in both trial arms.⁶ A plausible explanation is that therapeutically positive effects on survival are being masked by patients whose disease becomes worse upon exposure to the treatment. For example, evidence from clinical studies suggests that the addition of cetuximab to chemotherapy in the 40% of patients whose tumors harbored mutant *KRAS*, may have led to worse survival and a significant increase in serious toxic effects.^{50,51} When one considers that tens of thousands of patients were treated with cetuximab who might never have responded in the first place, it is clear that before the advent of *KRAS* testing the drug posed considerable risk, worse quality of life and decreased survival for many of these patients. On the basis of this and similar evidence, one can only conclude that when a molecular-targeted drug is approved on the basis of minimal improvements in overall survival or PFS (typically in the absence of a predictive biomarker), we could be committing to shortening the lives of a considerable number of patients, in some cases almost as many patients as we are able to extend the lives of. Is this morally acceptable?

The marginal effects on overall survival must also be interpreted in the context of the tightly controlled randomized controlled trials from which these results derive. Trial patients are clinically more homogenous than patient populations in clinical practice, with their diverse comorbidities and other clinically mitigating factors. Although randomized controlled trials produce results that are statistically robust and easy to interpret, an important level of pragmatism and the ability to generalize is often lost. While comparative effectiveness research (Box 1) might provide important insights into the real-world value of such therapies,⁵² the future emphasis and associated investment must be biased towards the identification of clinically effective predictive biomarkers, starting at the point of clinical development. In cases such as cetuximab,⁵³ or bevacizumab,⁵⁴ where there is poor correlation between target status (for example, expression or mutation of the receptor) and response to the drug, a greater emphasis should be placed on identifying other gene predictors of tumor responsiveness and patient risk.

Moral imperative, clinical reality

The paucity of standard-treatment options for advanced-stage cancer patients emphasizes the urgent need for novel predictive biomarkers and associated therapies. Few would argue against the hypothesis that the earlier we can target a drug (or drugs) to the true molecular protagonists of a cancer, the greater the chance for improved patient outcomes. The inherent challenge is, however, highlighted by the diversity of aberrations in germline and tumor-based molecules that can impinge on the activity of a drug. With only 20 oncology drugs associated with FDA-approved predictive biomarkers⁵⁵—the result of years of research and investment—we are still far from the widespread adoption of personalized cancer medicine as a standard-of-care. Nevertheless, many important concepts (for example, oncogene addiction⁵⁶), technologies (such as next-generation sequencing⁵⁷) and projects⁵⁸ have been established during this time and we are currently witnessing a modestly rising trajectory of therapeutic return on investment.

We must aggressively realign our discovery efforts towards an enhanced assault on human disease systems, as opposed to model organism counterparts. For example, while there are enormous quantities of clinical data distributed throughout oncology practices, comprehensive cancer centers and pharmaceutical companies, such data are rarely accessible and are thus currently of limited benefit to the study of the disease. Yet, such data could provide us with an invaluable opportunity to study the relationship between a human phenotype and drug-induced protein perturbations within a patient system. Deciphering the molecular basis of clinical responses, through mapping of drug regimens to associated targets and pathways presents a unique opportunity to dissect disease systems in search of novel response biomarkers, drug targets and efficacious combination therapies. In addition, a significant proportion of such data also have associated tumor samples available, raising the exciting opportunity of aligning clinical profiles with matching molecular aberrations.

While efforts such as comparative effectiveness research might deliver important data that will assist immediate treatment and reimbursement needs, such investment still fails to deliver the fundamental determinants of drug response and risk. To achieve this, we must pursue a rebalancing of the funding ledger in favor of projects and technologies that encourage the widespread generation and integrative analysis of patient-specific clinical and molecular information for all cancer types. Efforts such as The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC)⁵⁸ represent positive, but tentative, steps in this direction. Moreover, while there is always a place for multiomics datasets in basic clinical research (such as gene and microRNA expression or gene methylation status), a more strategic use of funds would prioritize the generation of actionable clinical data. Three broad classes of such actionable predictive biomarkers, namely resistance biomarkers, response biomarkers and risk biomarkers—here captured under what we term the ‘3R principle’—can provide us with information about this actionable data (Figure 2). Resistance biomarkers help to define drugs for which the patient will most likely not respond, response biomarkers help identify patients for whom a drug may work, and risk biomarkers identify potential safety concerns such as suprapharmacological accumulation of an active drug species. Thus, while complete genome sequence information is much vaunted, a more-targeted appraisal of all genes and/or proteins that are associated with the pharmacokinetics and pharmacodynamics of a drug and its mode of action within a disease system might yield quicker, cheaper and more reliably interpretable results that can inform both trial design and clinical decision.

Genetic sequence data from clinical trial participants could be used prospectively to assess whether potential resistance mechanisms might exist or retrospectively to identify predictive biomarkers of response, resistance and risk—in our opinion, all these data points should be a compulsory part of future regulatory submissions. This change in the regulatory framework would allow us to build on both existing knowledge and the precedents set by innovative clinical studies such as the prospective and adaptively randomized BATTLE trial (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination) in heavily pretreated patients with NSCLC.⁵⁹ Combining both molecularly guided treatment with an adaptive Bayesian design, BATTLE provides an exciting paradigm for knowledge-driven drug and biomarker development. Beyond clinical trials, medical insurance companies in the USA could also contribute to the endeavor by encouraging coverage with evidence development (CED) for promising new biomarkers and/or therapies. CED provides coverage for medical technologies deemed ‘experimental’ or ‘investigational’ and is contingent on the member’s participation in a payer-organized clinical research program. Using this approach, coverage for FDG–PET as a diagnostic tool for various cancers was expanded by the Centers for Medicare and Medicaid Services (CMS) as a result of positive evidence from the National Oncologic PET Registry.⁶⁰ Armed with such diverse sources of clinical data, the community could drive the discovery of novel molecular-guided treatments

in an expedited fashion. Nevertheless, this still represents only one aspect of a potential solution.

As the catalog of candidate treatment biomarkers grows, so too does the challenge of prospectively validating them. And even when validated, further complex questions arise. Are the treatment implications of particular biomarkers extendible across indications? Does the medication history of a patient influence how we use such biomarker information? How do we address the influence of comorbidities and what influence might current medications have on biomarker fidelity and anticancer drug response? And, what is the best treatment option when numerous aberrations are encountered—can we design appropriate combinatorial treatments to offset the complex drug resistance effects? These are but a few of the complex questions that will face oncologists, and with the growing clinical application of next-generation molecular technologies, it seems clear that a molecular-data overload might quickly limit our ability to derive maximum clinical value from research investment. *In silico* technologies will, therefore, have a pivotal role in powering both knowledge-guided data generation and subsequent analytical processes. Efforts in system-specific data integration of text-based knowledge and omics-based data must remain a key focus in this endeavor,⁶¹ providing the framework for further integration and analysis of patient-specific clinical and molecular information. Once personalized in this manner, such models may provide the best foundation upon which to address the complex array of questions that face every treatment decision and clinical study.

Conclusions

We have reached a revolutionary turning point in the history of medicine. Technological advancements and conceptual foresight has advanced patient care, but at a considerable cost! Key to the long-term goal of cancer treatment is our understanding of the molecular compatibility between the mode of action of a drug and the driver mechanisms associated with tumor progression. Such knowledge provides the very foundation of factual clinical decision making and if those making the financial decisions regarding the availability of drugs could also integrate this into their evaluations, this could incentivize manufacturers to set prices commensurate with the actual health benefit delivered—as opposed to the level of patient need. The moral imperative for aggressively pursuing this path is enormous, as is the potential for new levels of patient survival and cure. As Hippocrates reminds us, physicians must have a leading role in guiding the diverse stakeholders along this revolutionary path: “Life is short, and the Art is long; the occasion fleeting; experience fallacious and judgment difficult. The physician must not only be prepared to do what is right himself, but also to make the patient, the attendants and externals cooperate”.⁶²

Acknowledgments

Portions of work presented here were supported by grants from the NIH (CA109298, CA110793, CA083639, CA098258 and U54 CA151668), Department of Defense (OC073399, OC093146 and BC085265), a Program Project Development Grant from the Ovarian Cancer Research Fund, the Marcus Foundation, the Gynecologic Cancer Foundation, the Blanton–Davis Ovarian Cancer Research Program, the RGK Foundation, the Laura and John Arnold Foundation, and the Betty Ann Asche Murray Distinguished Professorship.

References

1. La Rosée P, Deininger MW. Resistance to imatinib: mutations and beyond. *Semin. Hematol.* 2010; 47:335–343. [PubMed: 20875550]
2. Gerber DE, Minna JD. ALK inhibition for non-small cell lung cancer: from discovery to therapy in record time. *Cancer Cell.* 2010; 14:548–551. [PubMed: 21156280]

3. Smalley KS. PLX-4032, a small-molecule B-Raf inhibitor for the potential treatment of malignant melanoma. *Curr. Opin. Investig. Drugs*. 2010; 11:699–706.
4. Jackson DB. Molecular perspectives on the non-responder phenomenon. *Drug Discov. Today*. 2009; 14:373–379. [PubMed: 19200455]
5. Hayes DF. Bevacizumab treatment for solid tumors: boon or bust? *JAMA*. 2011; 305:506–508. [PubMed: 21285431]
6. Fojo T, Parkinson DR. Biologically targeted cancer therapy and marginal benefits: are we making too much of too little or are we achieving too little by giving too much? *Clin. Cancer Res*. 2010; 16:5972–5980. [PubMed: 21169250]
7. Fojo T, Grady C. How much is life worth: cetuximab, non-small cell lung cancer, and the \$440 billion question. *J. Natl Cancer Inst*. 2009; 101:1044–1048. [PubMed: 19564563]
8. Jackson DB. Clinical and economic impact of the nonresponder phenomenon—implications for systems based discovery. *Drug Discov. Today*. 2009; 14:380–385. [PubMed: 19200855]
9. Druker BJ, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N. Engl. J. Med*. 2001; 344:1038–1042. [PubMed: 11287973]
10. Druker BJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N. Engl. J. Med*. 2001; 44:1031–1037. [PubMed: 11287972]
11. Mok TS. Personalized medicine in lung cancer: what we need to know. *Nat. Rev. Clin. Oncol*.
12. Ribas A, Flaherty KT. BRAF targeted therapy changes the treatment paradigm in melanoma. *Nat. Rev. Clin. Oncol*. 2011; 8:426–433. [PubMed: 21606968]
13. Kopetz S, et al. PLX4032 in metastatic colorectal cancer patients with mutant BRAF tumors [abstract]. *J. Clin. Oncol*. 2010; 28(Suppl.):a3534.
14. Xia G, et al. EphB4 receptor tyrosine kinase is expressed in bladder cancer and provides signals for cell survival. *Oncogene*. 2006; 25:769–780. [PubMed: 16205642]
15. Davalos V, et al. EPHB4 and survival of colorectal cancer patients. *Cancer Res*. 2006; 66:8943–8948. [PubMed: 16982731]
16. Medco[®]. Drug Trend Report. 2010 [online], www.drugtrend.com/art/drug_trend/pdf/DT_Report_2010.pdf.
17. Chabner BA, Roberts TG Jr. Timeline: Chemotherapy and the war on cancer. *Nat. Rev. Cancer*. 2005; 5:65–72. [PubMed: 15630416]
18. Cohen, H. *Drug Topics Red Book*. 112th edn. New Jersey: Thomson Healthcare; 2008.
19. Kim P. Cost of cancer care: The patient perspective. *J. Clin. Oncol*. 2007; 25:228–232. [PubMed: 17210945]
20. Himmelstein DU, Thorne D, Warren E, Woolhandler S. Medical bankruptcy in the United States, 2007: results of a national study. *Am. J. Med*. 2009; 122:741–746. [PubMed: 19501347]
21. Antoni MH, et al. The influence of biobehavioural factors on tumour biology: pathways and mechanisms. *Nat. Rev. Cancer*. 2006; 6:240–248. [PubMed: 16498446]
22. Meropol NJ, et al. American Society of Clinical Oncology guidance statement: the cost of cancer care. *J. Clin. Oncol*. 2009; 27:3868–3874. [PubMed: 19581533]
23. US Census Bureau. USA QuickFacts from the US Census Bureau. 2011. [online], <http://quickfacts.census.gov/qfd/states/00000.html>
24. Bergsland E, Dickler MN. Maximizing the potential of bevacizumab in cancer treatment. *Oncologist*. 2004; 9(Suppl. 1):36–42. [PubMed: 15178814]
25. Kelly WK, et al. A randomized, double-blind, placebo-controlled phase III trial comparing docetaxel, prednisone, and placebo with docetaxel, prednisone, and bevacizumab in men with metastatic castration-resistant prostate cancer (mCRPC): Survival results of CALGB 90401 [abstract]. *J. Clin. Oncol*. 2010; 28(Suppl.) LBA4511.
26. Kindler HL, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J. Clin. Oncol*. 2010; 28:3617–3622. [PubMed: 20606091]

27. Van Cutsem E, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J. Clin. Oncol.* 2009; 27:2231–2237. [PubMed: 19307500]
28. Hurwitz H, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N. Engl. J. Med.* 2004; 350:2335–2342. [PubMed: 15175435]
29. Saltz LB, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J. Clin. Oncol.* 2008; 26:2013–2019. [PubMed: 18421054]
30. Friedman HS, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J. Clin. Oncol.* 2009; 27:4733–4740. [PubMed: 19720927]
31. Sandler A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N. Engl. J. Med.* 2006; 355:2542–2550. [PubMed: 17167137]
32. Reck M, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. *J. Clin. Oncol.* 2009; 27:1227–1234. [PubMed: 19188680]
33. Reck M, et al. Overall survival with cisplatin gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: Results from a randomised phase III trial (AVAiL). *Ann. Oncol.* 2010; 21:1804–1809. [PubMed: 20150572]
34. Rini BI, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J. Clin. Oncol.* 2010; 28:2137–2143. [PubMed: 20368558]
35. Rini BI, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J. Clin. Oncol.* 2008; 26:5422–5428. [PubMed: 18936475]
36. Roche. European medical advisory committee does not recommend approval of Avastin for deadly form of brain cancer. 2009 [online], http://www.roche.com/media/media_releases/med-cor-2009-11-20.htm.
37. Miller K, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N. Engl. J. Med.* 2007; 357:2666–2676. [PubMed: 18160686]
38. Burstein HJ. Avastin, ODAC, and the FDA: are we drafting the right players? *J. Natl Compr. Canc. Netw.* 2010; 8:833–834. [PubMed: 20870630]
39. Miles DW, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J. Clin. Oncol.* 2010; 28:3239–3247. [PubMed: 20498403]
40. Robert NJ, et al. RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC) [abstract 1005]. *J. Clin. Oncol.* 2009; 27(Suppl. 15): 42S.
41. Couzin-Frankel J, Ogale Y. FDA. Once on ‘fast track,’ avastin now derailed. *Science.* 2011; 333:143–144. [PubMed: 21737712]
42. Cohn DE, Kim KH, Resnick KE, O’Malley DM, Straughn JM Jr. At what cost does a potential survival advantage of bevacizumab make sense for the primary treatment of ovarian cancer? A cost-effectiveness analysis. *J. Clin. Oncol.* 2011; 29:1247–1251. [PubMed: 21383297]
43. Burger RA, et al. Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study [abstract]. *J. Clin. Oncol.* 2010; 28(Suppl. 18) LBA1.
44. Hensley ML. Big costs for little gain in ovarian cancer. *J. Clin. Oncol.* 2011; 29:1230–1232. [PubMed: 21383287]
45. Munro AJ, Niblock PG. Cancer research in the global village. 2010; 376:659–660.
46. Bang YJ, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet.* 2010; 376:687–697. [PubMed: 20728210]

47. Meropol NJ, Schulman KA. Cost of cancer care: issues and implications. *J. Clin. Oncol.* 2007; 25:180–186. [PubMed: 17210937]
48. Doloresco F, et al. Projecting future drug expenditures: 2011. *Am. J. Health Syst. Pharm.* 2011; 68:921–932. [PubMed: 21546644]
49. Ranpura V, Hapani S, Wu S. Treatment-related mortality with bevacizumab in cancer patients: a meta-analysis. *JAMA.* 2011; 305:487–494. [PubMed: 21285426]
50. Karapetis CS, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N. Engl. J. Med.* 2008; 359:1757–1765. [PubMed: 18946061]
51. Allegra CJ, et al. American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. *J. Clin. Oncol.* 2009; 27:2091–2096. [PubMed: 19188670]
52. Perlroth DJ, Goldman DP, Garber AM. The potential impact of comparative effectiveness research on U.S. health care expenditures. *Demography.* 2010; 47(Suppl.):S173–S190. [PubMed: 21302424]
53. Chung KY, et al. Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. *J. Clin. Oncol.* 2005; 23:1803–1810. [PubMed: 15677699]
54. Murukesh N, Dive C, Jayson GC. Biomarkers of angiogenesis and their role in the development of VEGF inhibitors. *Br. J. Cancer.* 2010; 102:8–18. [PubMed: 20010945]
55. US Department of Health and Human Services. Table of Pharmacogenomic Biomarkers in Drug Labels. 2011. [online], <http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>
56. Weinstein IB. Cancer. Addiction to oncogenes—the Achilles heel of cancer. *Science.* 2002; 297:63–64. [PubMed: 12098689]
57. Davey JW, et al. Genome-wide genetic marker discovery and genotyping using next-generation sequencing. *Nat. Rev. Genet.* 2011; 12:499–510. [PubMed: 21681211]
58. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. *Nature.* 2009; 458:719–724. [PubMed: 19360079]
59. Kim ES, et al. The BATTLE trial: personalizing therapy for lung cancer. *Cancer Discov.* 2011; 1:44–53. [PubMed: 22586319]
60. US Department of Health and Human Sciences. Centers for Medicare & Medicaid Services. 2009. [online], <https://www.cms.gov/transmittals/downloads/R108NCD.pdf>
61. Picker A, Jackson DB. Genetic determinants of anticancer drug activity: towards a global approach to personalized cancer medicine. *Expert Rev. Mol. Diagn.* 2011; 11:567–577. [PubMed: 21745011]
62. Adams, F. *The Genuine Works of Hippocrates.* Cox, London: Baillière, Tindall; 1939.
63. Kang Y, et al. AVAGAST: A randomized, double-blind, placebo-controlled, phase III study of first-line capecitabine and cisplatin plus bevacizumab or placebo in patients with advanced gastric cancer (AGC) [abstract]. *J. Clin. Oncol.* 2010; 28(Suppl. 18) LBA4007.
64. US Department of Health and Human Services. AHRQ Agency for Healthcare Research and Quality. 2011. [online], <http://www.effectivehealthcare.ahrq.gov/index.cfm/what-is-comparative-effectiveness-research1/>

Box 1 | Comparative effectiveness research

Comparative effectiveness research (CER) is aimed at providing evidence about the effectiveness, benefits, and risks of different treatment options. This is typically achieved through research reviews, which examine all available evidence about the benefits and risks of each treatment choice in a specific indication and/or through conduct of clinical studies that directly examine the effectiveness or comparative effectiveness of independent treatment options. Results of this research must then be disseminated in a form that is immediately actionable by patients, clinicians, policymakers and payers. The Agency for Healthcare Research and Quality (AHRQ) provides the following seven steps to the advancement of CER.⁶⁴

- Identify new and emerging clinical interventions
- Review and synthesize current medical research
- Identify gaps between existing medical research and the needs of clinical practice
- Promote and generate new scientific evidence and analytic tools
- Train and develop clinical researchers
- Translate and disseminate research findings to diverse stakeholders
- Reach out to stakeholders via a citizens forum

Figure 1.

The monthly costs of oncology drugs at the time of FDA approval (1965–2008). Prices have been adjusted to 2007 dollars and reflect the total price for the drug at the time of approval (including the amount of Medicare reimbursement and the amount paid by the patient or by a secondary payer). Permission obtained from Massachusetts Medical Society © Bach, P. B. *N. Engl. J. Med.* **360**, 626–633 (2009).

Figure 2.

Overview of the 3R principle. Predictive biomarkers are required to identify molecular determinants of resistance, response and risk associated with available cancer drugs. These principles will permit physicians to prioritize therapy on the basis of associated molecular information from patients and their tumors.

Table 1

Overview of phase III clinical trial results for the addition of bevacizumab

Tumor site	Study name	Primary end point	n	Design	Difference in PFS, months (P value)	Difference in OS, months (P value)
Prostate	CALGB 90401 ²⁵	OS	1,050	Docetaxel + prednisone ± bevacizumab	2.4 (0.0001)	1.1 (0.18)
Pancreas	CALGB 80303 ²⁶	OS	602	Gemcitabine ± bevacizumab	0.9 (0.07)	-0.1 (0.95)
Pancreas	Van Cutsem <i>et al.</i> (2009) ²⁷	OS	607	Gemcitabine + erlotinib ± bevacizumab	1 (0.0002)	1.1 (0.21)
Colorectal	Hurwitz <i>et al.</i> (2004) ²⁸	OS	813	Irinotecan + 5-fluorouracil + leucovorin ± bevacizumab	4.4 (<0.001)	4.7 (<0.001)
Colorectal	Saltz <i>et al.</i> (2008) ²⁹	PFS	1,401	FOLFOX4 or XELOX ± bevacizumab	1.4 (0.0023)	1.4 (0.0769)
Lung	ECOG E4599 ³¹	OS	878	Carboplatin + paclitaxel ± bevacizumab	1.7 (<0.001)	2 (0.003)
Lung	AVAiL ^{32,33}	OS → PFS *	1,043	Carboplatin + gemcitabine ± bevacizumab (7.5 mg/kg) Carboplatin + gemcitabine ± bevacizumab (15 mg/kg)	0.6 (0.0003) 0.4 (0.046)	0.5 (0.42) 0.3 (0.76)
Kidney	CALGB 90206 ^{34,35}	OS	732	Interferon-α ± bevacizumab	3.3 (<0.001)	0.9 (0.097)
Breast	ECOG E2100 ³⁷	PFS	722	Paclitaxel ± bevacizumab	5.9 (0.001)	1.5 (0.16)
Breast	AVADO ³⁹	PFS	736	Docetaxel ± bevacizumab (7.5 mg/kg) Docetaxel ± bevacizumab (15 mg/kg)	0.8 (0.116) 1.9 (0.006)	-1.1 (0.72) -1.7 (0.85)
Breast	RIBBON-1 ⁴⁰	PFS	1,237	Carboplatin ± bevacizumab	2.9 (0.0002)	7.8 (0.27)
Ovarian	GOG-0218 ⁴³	OS → PFS *	1,873	Carboplatin + paclitaxel vs carboplatin + paclitaxel + bevacizumab vs carboplatin + paclitaxel + bevacizumab + maintenance bevacizumab	0.9 (0.08) 3.8 (0.0001)	-0.6 (0.36) 0.4 (0.25)
Gastric	AVAGAST ⁶³	OS	774	Capecitabine or 5-fluorouracil + cisplatin ± bevacizumab	1.4 (0.0037)	2 (0.1)

* The primary end point was amended from OS to PFS.

Abbreviations: FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; OS, overall survival; PFS, progression-free survival; XELOX, capecitabine and oxaliplatin.

Table 2

Overview of the top five expenditures made by clinics in the USA for cancer drugs between January and September 2010⁴⁸

Drug	Drug type	Total expenditure (\$ in thousands)	Total drug expenditure (%)
Epoetin alfa	Erythropoiesis stimulant—treat chemotherapy-induced anemia	2,836,922	10.4
Bevacizumab	Prevention of angiogenesis—antineoplastic	1,884,105	6.9
Infliximab	Monoclonal antibody against TNF α —treatment of autoinflammatory disease	1,711,928	6.3
Pegfilgrastim	Stimulates neutrophils—prevent or treat infection in patients undergoing chemotherapy	1,611,027	5.9
Rituximab	Monoclonal antibody against CD20—antineoplastic	1,465,819	5.4

Table 3
Four targeted drugs are compared in terms of targets, costs, survival and serious adverse events

Drug	Target(s)	Total cost (\$)*	Increase in OS (months)*	Hypothetical cost for 1-year of increased survival (\$)*	Number of adverse events reported in FDA AERS [‡]	Most-frequent serious effects	Rate of event (%)
Cetuximab	EGFR	80,352	1.2	803,520	7,045	Dermatitis acneiform Pneumonia Neutropenia Death	3.90 3.48 3.11 3.64
Bevacizumab	VEGF-A	90,816	1.5	726,528	12,321	Pulmonary embolism Sepsis Pleural effusion	3.29 2.39 4.22
Erlotinib	EGFR and PDGFRB	15,752	0.3	630,080	3,984	Pneumonia Anemia Anorexia	3.89 3.79 5.11
Sorafenib	RAF1, VEGFR2 and VEGFR3	34,373	2.7	152,769	3,856	Death Thrombocytopenia	4.75 2.28

* Values derived from Fojo & Parkinson (2010).⁶
[‡] Adverse events information was derived from the FDA's AERS using a proprietary data mining tool called MASE (LIFE Biosystems, Heidelberg, Germany).
Abbreviations: AERS, adverse events reporting system; MASE, molecular analysis of side effect information; OS, overall survival.