University of North Carolina at Chapel Hill

The University of North Carolina at Chapel Hill Department of
Biostatistics Technical Report Series

Year 2012

Paper 25

Research Methods for Clinical Trials in Personalized Medicine: A Systematic Review

Zheng Ren* Marie Davidian[†] Stephen L. George[‡]
Richard M. Goldberg** Fred A. Wright^{††}
Anastasios A. Tsiatis^{‡‡} Michael R. Kosorok[§]

*University of North Carolina at Chapel Hill, renzheng@email.unc.edu

[†]North Carolina State University, davidian@ncsu.edu

[‡]Duke University, georg001@mc.duke.edu

**Ohio State University, Richard.Goldberg@osumc.edu

^{††}University of North Carolina at Chapel Hill, fred_wright@unc.edu

^{‡‡}North Carolina State University, tsiatis@stat.ncsu.edu

[§]University of North Carolina at Chapel Hill, kosorok@unc.edu

This working paper is hosted by The Berkeley Electronic Press (bepress) and may not be commercially reproduced without the permission of the copyright holder.

<http://biostats.bepress.com/uncbiostat/art25>

Copyright ©2012 by the authors.

Research Methods for Clinical Trials in Personalized Medicine: A Systematic Review

Zheng Ren, Marie Davidian, Stephen L. George, Richard M. Goldberg, Fred A. Wright, Anastasios A. Tsiatis, and Michael R. Kosorok

Abstract

Background: Personalized medicine, the notion that an individual's genetic and other characteristics can be used to individualize the diagnosis, treatment and prevention of disease, is an active and exciting area of research, with tremendous potential to improve the health of society.

Methods: Seventy-six studies using personalized medicine analysis techniques published from 2006 to 2010 in six high-impact journals - Journal of the American Medical Association, Journal of the National Cancer Institute, Lancet, Nature, Nature Medicine, and the New England Journal of Medicine - were reviewed. Selected articles were manually selected based on reporting of the use of genetic information to stratify subjects and on analyses of the association between biomarkers and patient clinical outcomes.

Results: We found considerable variability and limited consensus in approaches. Approaches could largely be classified as data-driven, seeking discovery through statistical analysis of data, or knowledge-driven, relying heavily on prior biological information. Some studies took a hybrid approach. Eliminating two articles that were retracted after publication, 56 of the remaining 74 (76%) were cancer-related.

Conclusions: Much work is needed to standardize and improve statistical methods for finding biomarkers, validating results, and efficiently optimizing better individual treatment strategies. Several promising new analytic approaches are available and should be considered in future studies of personalized medicine.

Research Methods for Clinical Trials in Personalized Medicine: A Systematic Review

Zheng Ren, Marie Davidian, Stephen L. George, Richard M. Goldberg, Fred A.
Wright, Anastasios A. Tsiatis, Michael R. Kosorok

Affiliations of authors: Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC (ZR, FAW, MRK); Department of Statistics, North Carolina State University, Raleigh, NC (MD, AAT); Cancer Center Biostatistics, Duke University Medical Center, Durham, NC (SLG); Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, NC (SLG, MD, AAT); Comprehensive Cancer Center, The Ohio State University Medical Center, Columbus, OH (RMG); Department of Statistics and Operations Research, University of North Carolina at Chapel Hill, Chapel Hill, NC (MRK).

Correspondence to: Micheal R. Kosorok, PhD, Department of Biostatistics and Department of Statistics and Operations Research, University of North Carolina-Chapel Hill, 3101 McGavran-Greenberg Hall, CB 7420, Chapel Hill, NC 27599-7420 (e-mail : kosorok@unc.edu).

Abstract

Background: Personalized medicine, the notion that an individual's genetic and other characteristics can be used to individualize the diagnosis, treatment and prevention of disease, is an active and exciting area of research, with tremendous potential to improve the health of society.

Methods: Seventy-six studies using personalized medicine analysis techniques published from 2006 to 2010 in six high-impact journals - Journal of the American Medical Association, Journal of the National Cancer Institute, Lancet, Nature, Nature Medicine, and the New England Journal of Medicine - were reviewed. Selected articles were manually selected based on reporting of the use of genetic information to stratify subjects and on analyses of the association between biomarkers and patient clinical outcomes.

Results: We found considerable variability and limited consensus in approaches. Approaches could largely be classified as data-driven, seeking discovery through statistical analysis of data, or knowledge-driven, relying heavily on prior biological information. Some studies took a hybrid approach. Eliminating two articles that were retracted after publication, 56 of the remaining 74 (76%) were cancer-related.

Conclusions: Much work is needed to standardize and improve statistical methods for finding biomarkers, validating results, and efficiently optimizing better individual treatment strategies. Several promising new analytic approaches are available and should be considered in future studies of personalized medicine.

The emerging field of personalized medicine has been the focus of vigorous research in recent years. Since the initiation of the Human Genome Project twenty years ago (1), researchers have successfully identified tens of thousands of genes and studied their protein products and functions. More recently, genetic typing and sequencing techniques have revolutionized our understanding of individual genetic variation (2,3), spurring research on new therapeutic agents that can target genetic differences across individuals. Differences in therapeutic response among individuals may arise from a number of other sources, such as cumulative environmental exposures, which may be difficult to assess. The genetic revolution has thus provided a measurable basis for personalized medicine, and has placed the field in the national spotlight. The goal of the Genomics and Personalized Medicine Act of 2010 (GPMA), introduced in the United States House of Representatives in May 2010, is to encourage genomics research and the application of personalized medicine (4); a similar act was introduced previously in the United States Senate by then-Senator Barack Obama. As public awareness and interest in genetic testing continues to heighten, research on the use of genomic and other patient information to improve the prevention, diagnosis and treatment of disease is likely to accelerate.

The ultimate goal of personalized medicine is to make the optimal treatment decision based on all of the information from a patient, including not only genetic information but also age, gender, other clinical factors, current disease status and other information. Methods for exploiting very large quantities of data, integrated with biological knowledge, and innovative study designs are critical to this goal. In this article, we review approaches that have been applied in published studies to use patient genomic

information as the basis for improving the efficacy of treatments and reducing toxicity. Issues and challenges in the design and analysis of personalized medicine studies are also discussed, and new approaches are proposed.

Definition of Personalized Medicine

There is no single definition of “personalized medicine,” and differing terminology has been used in the literature by various stakeholders to describe the concept, including personalized medicine (5-8), personalized therapy (9,10), personalized drugs (11) and tailored therapy (12,13). The National Institutes of Health (NIH), for example, defines personalized medicine as “an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease. Knowledge of a patient's genetic profile can help doctors select the proper medication or therapy and administer it using the proper dose or regimen.” For the U.S. Food and Drug Administration (FDA), the goal of personalized medicine is “to get the best medical outcomes by choosing treatments that work well with a person's genomic profile or with certain characteristics in the person's blood proteins or cell surface proteins” (14). In the GPMA, personalized medicine is defined as “any clinical practice model that emphasizes the systematic use of preventive, diagnostic, and therapeutic interventions that use genome and family history information to improve health outcomes.” Recently, Margaret A. Hamburg, Commissioner of the FDA, and Francis S. Collins, Director of NIH, shared their joint opinion about the concept (15), proposing that the goal of personalized medicine is to identify the best treatment strategy to achieve the optimal clinical outcome based on a patient's individual profile. Note that the definitions encompass variation in constitutional genetic profile, which is stable for

an individual, as well as more variable genomic or other biomarkers that may be specific to a disease state, tumor, or tissue.

The Promise of Personalized Medicine

Personalized medicine has demonstrated the potential to lead to enhanced treatment effect in clinical studies of already-approved therapies within gene-profile stratified subgroups (16), to avoid unnecessary toxicity associated with treatments (17) and to minimize the rate of adverse events (18). In many settings, it is likely that some subgroups of patients will have a better response to a new treatment and others will have a worse response. If the population is considered as a whole, the overall difference would be attenuated by those with poorer responses, and no significant improvement would be detected for the population (Figure. 1). Therefore, personalized medicine has the potential to improve the performance of therapy for individual patients through recognizing and capitalizing on patient heterogeneity. Note that the very concept of personalized medicine represents a profound shift in the interpretation of treatment data, especially in the context of controlled clinical trials, for which subgroup analysis has often been viewed with suspicion as a potential source of spurious findings.

A striking example of meaningful subgroup analysis occurred in a randomized prospective phase III clinical trial in patients with advanced non-small cell lung cancer that confirmed the benefit of first-line gefitinib, an epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor, to chemotherapy. In subjects with *EGFR* mutation-positive tumors, PFS was significantly improved for gefitinib versus chemotherapy (median PFS, 9.5 months vs. 6.3 months), suggesting that the presence of *EGFR* positive

mutation should be used as a criterion for determining first-line therapy for the patients with advanced non-small-cell lung cancer (19).

Methods

Literature Search

In this review, we summarize studies related to personalized medicine that were published in six high-impact journals - Journal of the American Medical Association, Journal of the National Cancer Institute, Lancet, Nature, Nature Medicine, and the New England Journal of Medicine - from 2006 to 2010. All papers were manually selected and reviewed. The inclusion criteria were: 1) papers published between January 1, 2006 and December 31, 2010; 2) papers reporting the results of original clinical studies using genetic information obtained from DNA, RNA, protein or tumor mutations to stratify the study population; and 3) papers reporting the association between biomarkers and patient clinical outcomes. Exclusion criteria were: 1) papers focused mainly on the association between genetic profile and incident disease; 2) papers focused on identifying biomarkers for disease diagnosis; and 3) papers reporting systematic reviews and meta-analysis. Seventy-six articles (12 papers published in Journal of the American Medical Association, 17 papers published in Journal of the National Cancer Institute, 9 papers published in Lancet, 6 papers published in Nature, 7 papers published in Nature Medicine, and 25 papers published in the New England Journal of Medicine) were selected meeting the above criteria (16,20-94). As discussed shortly, two of these (74,87) have since been retracted and are not included in the summaries in Table 1 or elsewhere in this article. The predominance of cancer studies reflects the fact that cancer inherently involves genetic dysregulation, increasing the likelihood that suitable biomarkers and

targeted therapies may be identified. The genomic data in most of the reviewed studies consisted of transcriptional expression, profiled by microarray or polymerase chain reaction (PCR).

Results

Approaches to Finding Biomarkers for Personalized Medicine

A complete process leading to effective personalized medicine will typically include the following five key elements: obtaining patient genetic/genomic data using array and other high throughput technology (95); identifying one or more biomarkers (as discussed shortly) (96); developing new or selecting available therapies (97); measuring the relationship between biomarkers and clinical outcomes, including the prognosis and response to therapy; and verifying the relationship in a prospective randomized clinical trial (98).

A biomarker is an indicator that can potentially stratify patients into subgroups with common features. Biomarkers can consist of DNA, RNA, proteins and types of tumors. Because of the so-called “curse of dimensionality” (99), where there are vast numbers of genes relative to patient samples, identifying a potential biomarker from patient genomic profiles is a tremendous challenge for geneticists and statisticians. Many techniques for the development and validation of biomarkers are available (100,101). In the studies reviewed, two main approaches were taken: a data-driven approach (102) and a knowledge-driven approach (103) (Figure. 2).

In the data-driven approach, extensive genetic information is collected on each participant, and an analysis is conducted to select those genes or sets of genes that are most strongly associated with the targeted clinical outcome. The strength of this approach

is that it is unbiased in the sense that all genes are considered and their relationship to clinical outcome is tested. During the selection process, new genes or gene functions can potentially be identified as involved in disease. For example, in one simple data-driven approach, information on response to a therapy and gene expression data is collected on each patient. Each gene's expression is compared between the response and non-response groups, and p-values are calculated using t-tests; then the p-value for each gene is adjusted upward to account for multiple comparisons via the Bonferroni method and based on the number of genes used in the tests (104). Genes with significant adjusted p-values are considered to be potential biomarkers for the response to the therapy, which can be verified in follow-up trials (35).

A typical data-driven approach attempts to identify a potential biomarker profile constructed from one or more genes from among tens of thousands, a process complicated by the correlation structure and multiplicity of high dimensional data. Many statistical methods have been used to identify promising genetic patterns from numerous genes, including the correlation coefficient (12), t-tests (82), hierarchical clustering (105), Significance Analysis of Microarrays (SAM) (106), Prediction Analysis for Microarrays (PAM) (107), and principal component analysis (PCA) (108). Once the number of candidate genes is narrowed down to several hundred, other statistical techniques can be applied, such as the proportional hazards model (109) or a Receiver Operator Characteristic (ROC) (110) analysis. In one microarray study, the expression of 25,000 genes was measured in 78 lymph-node-negative breast cancers, and 5,000 genes expressed in more than 3 of 78 tumors were selected. The correlation coefficient of the expression for each gene with disease outcome was calculated and the 5,000 genes were

further narrowed to 231 (correlation coefficient <-0.3 or >0.3). This group of 231 genes was rank-ordered on the basis of the magnitude of the correlation coefficient. A subset of 5 genes was subsequently added to the prognosis classifier until the accuracy was maximized. Seventy genes were identified to constitute a signature based on correlation coefficients for predicting clinical outcome of breast cancer (12). The signature was validated in a follow up study, and it outperformed the current standard method in predicting all endpoints (37).

Data quality is a key issue for the data-driven approach and, indeed, for any approach. Several studies with similar experimental designs generated different gene signatures from similar populations based on this approach, possibly owing to varying data quality (103,111,112). Moreover, gene signatures identified by this approach are difficult to interpret because the genes may not be causal but may result instead from correlation with some underlying causal mechanism. In addition, large sets of genes are highly correlated, and additional follow-up studies are usually required to refine the gene signature. New statistical methods and software continue to be proposed to identify gene signatures in a more efficient and precise way. Several articles have systematically reviewed such statistical methods (103,113,114), but there is no clear consensus in the statistics and data mining community about which methods should be used for data-driven gene signature identification.

The knowledge-driven approach is based on existing knowledge of the biological functions of certain genes or proteins that may arise, for example, through a pathway analysis to establish a mechanism for growth inhibition in tumor cells (8). A targeted inhibitor that may benefit patients with a specific gene mutation can be designed using

this approach, as with cetuximab and panitumumab, approved by the FDA and targeting the epidermal growth factor receptor in multiple cancers (115). The knowledge-driven approach can also help limit the number of candidate genes investigated. For example, only pre-determined single nucleotide polymorphisms (SNPs) or proteins might be considered as biomarkers. This was illustrated in a recent metastatic colorectal cancer study, where 15 candidate genes were investigated as predictors of adverse events and response to chemotherapy. Finally, four genes showed significant association with adverse events (116). This method avoids the issues associated with interpreting high-dimensional data that arise in the data-driven approach and improves the accuracy of the analysis; however, the drawback is that the results are only as good as the existing state of knowledge: genes that are not already known to be involved in a process are not considered.

Some studies in our sample combined the two approaches to develop a gene signature. The data-driven approach is employed first to reduce the number of available genes from tens of thousands to several hundred, and then the knowledge-driven approach employs a pathway analysis. Only the genes that appear on both lists are included in the final gene signature. Grouping genes according to different biological pathways is another way to combine the two approaches and reduce the dimension of available information efficiently.

Overall, 56 of 74 studies in our sample explored new biomarkers and eighteen studies validated the biomarkers discovered in previous studies. Among fifty-six exploratory studies, sixteen of them used primarily a data-driven approach, thirty-six studies used a knowledge-driven approach, and four studies used a combined approach. Across the 74

studies, 62 used a gene signature comprising fewer than ten genes, mutations or SNPs as the biomarker to stratify the study population, perhaps because biomarkers with fewer genes are easier to analyze and interpret.

Prognostic and Predictive Biomarkers

In the studies reviewed, two types of relationships between biomarkers and clinical outcomes were investigated, association between biomarkers and patient prognosis and association between biomarkers and response to treatment. In common parlance, the first type of analysis refers to “prognostic” biomarkers and the second to “predictive” biomarkers. In the study of potential prognostic biomarkers, patient information is pooled and a prognostic indicator is generated based on patient clinical outcomes without considering the different treatments or perhaps restricting to some standard treatment. The prognostic indicator is expected to predict patient survival without regard to the treatments the patients received. A good example would be the 70-gene signature for breast cancers mentioned above. This kind of investigation can be conducted by pooling available data sets from several similar studies. The results can help clinicians predict patient performance but cannot be used to assign the proper treatment to patients based on their genetic profiles and clinical factors. In the study of potential predictive biomarkers, responses to different treatments are compared within biomarker strata and between patients with different biomarkers. These studies require well-designed clinical trials to verify the hypotheses and to show efficacy in and between biomarker groups. In the study conducted by Amado et al., the effectiveness of panitumumab was compared between patients with wild type and mutations of KRAS in colorectal cancers in a phase

III clinical trial. Panitumumab was shown to significantly improve the survival of patients with wild type KRAS as compared to best supportive care alone, but there was no significant improvement for mutation carriers. KRAS mutations showed resistance to panitumumab treatment, and this finding was confirmed in several follow-up studies (116). Results obtained from both types of investigations are important for clinical practice, but knowledge that a specific treatment elicits different outcomes across subgroups is more valuable for personalized medicine, because it can guide an optimal treatment plan based on biomarker information. For example, it has been shown that patients with Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer have a worse prognosis than other subgroups, but have a better response to trastuzumab, which is designed to interfere with the HER2 receptor (117). According to these results, a patient with HER2-positive breast cancer would be given trastuzumab to maximize treatment benefit.

In the reviewed literature, nineteen studies compared the efficacy of different treatments for one group of patients; thirty-three investigated the effect of the same therapy among different subgroup populations; and sixteen studies made both types of comparisons.

Discussion

Reliability and Reproducibility of Personalized Medicine

A continuing controversy of personalized medicine focuses on its reliability and reproducibility. Some personalized medicine studies have been reported as non-replicable, and the related clinical trials have been suspended and scrutinized (118,119); indeed, two of the papers reviewed were retracted on this basis (74,87). The complexity

of the data and statistical analyses involved in personalized medicine make study of reproducibility of results essential. Hence the associated datasets must be made publicly available for verification of results. The obtained biomarkers need to be validated in a different group of patients to avoid potential selection bias from the study population. Because extensive, high-dimensional data are involved in many personalized medicine studies, data management is another important issue. Some recommendations for improved data management in genetics research and personalized medicine have been made (2,120-122).

Future Clinical Trial Designs for Personalized Medicine

The identification and verification of new biomarkers requires significant resources of time, money and patients. Developing efficient and effective methods for the discovery and verification of new biomarkers is a fundamental challenge. There are two general statistical approaches for assessing personalized treatment regimens in current work.

One general approach relies on standard regression models of clinical outcomes given treatment and other covariates. Interactions between treatment and covariates are included in such regression models, and the optimal decision rules are obtained by identifying the treatment leading to the largest mean clinical outcome based on the model for any combination of covariate values. Some new clinical trial designs for personalized medicine have been developed using this approach, such as the biomarker-adaptive threshold design (123-125) and Bayesian designs (126), including the currently active Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And moLecular analysis (I-SPY 2) trial, which involves an adaptive design to investigate biomarkers for women with breast cancer (Figure. 3) (127). These designs allow

comparison of several different biomarkers with different treatments in the same clinical trial. Bayesian designs have also been implemented in ongoing phase III clinical trials to find the best treatment for patients with different biomarkers (126).

The second general approach uses machine learning techniques to determine the relationship between clinical outcomes and treatment plus characteristics such as age, gender and biomarkers (128). These methods, used extensively in artificial intelligence, lead to models for these relationships that are more flexible than those in standard regression analysis and thus can more easily describe complex relationships. Designs based on these techniques have been developed and implemented for chronic diseases such as cancer and have shown the capability of discovering the best treatment for each individual based on a reasonable sample size (129,130); however, they have not yet been implemented in practice. The machine learning technique is expected to discover new relationships between biomarkers and patient response to treatments without any prior knowledge about the true relationship, similar to what the data-driven approach does for identifying biomarkers.

It is important to recognize, especially in the case of chronic diseases and conditions, that “treatment” is often an ongoing process involving a series of decisions made over time. For example, the treatment of cancer may involve selection of a first line of chemotherapy and observation of the patient’s response, followed by selection of a second line therapy in the event of no response or of a maintenance or intensification treatment if a positive response is elicited. At each decision point, issues of selection of therapy among available options, choice of dosage and timing of therapy, and so on must be addressed. Identifying the overall strategy for making the entire sequence of decisions

to optimize clinical outcome, taking into account the evolving status of the patient at each point, would be a major advance for personalized medicine. It is possible that the treatment that appears “best” with respect to clinical outcome for a single decision point may not be the best choice when viewed in the context of an entire series of decisions. For example, a treatment given early may cause bone marrow toxicity that compromises the dose intensity of future cytotoxic regimens, thus rendering subsequent treatments less effective.

Methods for determining optimal decision-making strategies for personalized medicine using existing databases have been developed (131) but are limited by the quality of the data, as all information relevant to each decision point may not have been recorded. A promising alternative approach is to conduct a prospective clinical trial focused on this goal using the so-called Sequential Multiple Assignment Randomized Trial (SMART) design (132). SMARTs have been conducted for this purpose in the study of substance abuse and depression, and a similar design suitable for trials involving life-threatening diseases has been developed (129). In a typical SMART design, participants are initially randomized to treatment options based on their profile; at the end of the first treatment segment, patient response to the first treatment and status are reviewed and the second treatment decision is made based on response and status; randomization of treatment may also be employed at this step and later steps; and the steps are repeated until the end of study. The best decision strategy for each individual can be generated from such designs using artificial intelligence techniques such as reinforcement learning (122,123), as has been demonstrated for lung cancer. For example, this dynamic decision method can discover the best personalized therapy in a

complex clinical trial setting involving multiple treatments, multiple biomarkers and several decision points.

Conclusions

Personalized medicine has demonstrated considerable promise, although many additional challenges need to be addressed and interpreted in future studies. Even though biomarker and related clinical studies have shown potential application in clinical practice, there is no strong evidence that shows that gene-based biomarkers can completely replace traditional clinical characteristics (133); using the biomarkers in clinical trials can cause unbalanced randomization, which can produce biased assessment of treatment (134). In addition, gene-gene and gene-environment interactions potentially should also be included and modeled using high dimensional data analysis methods. Addressing all these challenges will require the development of new statistical tools for finding biomarkers, validating results and discovering better decision making processes for selecting the optimal treatment strategy in an efficient way. This endeavor will not be easy, but the potential gains in human health are enormous.

References

1. Adams MD, Kelley JM, Gocayne JD, Dubnick M, Polymeropoulos MH, Xiao H, et al. Complementary DNA sequencing: expressed sequence tags and human genome project. *Science*. 1991;252(5013):1651-1656.

2. Leek JT, Scharpf RB, Bravo HC, Simcha D, Langmead B, Johnson WE, et al. Tackling the widespread and critical impact of batch effects in high-throughput data. *Nat Rev Genet.* 2010;11(10):733-739.
3. Weir BA, Woo MS, Getz G, Perner S, Ding L, Beroukheim R, et al. Characterizing the cancer genome in lung adenocarcinoma. *Nature.* 2007;450(7171):893-U822.
4. Lee SS, Mudaliar A. Medicine. racing forward: the genomics and personalized medicine act. *Science.* 2009;323(5912):342.
5. Haselden JN, Nicholls AW. Personalized medicine progresses. *Nat Med.* 2006;12(5):510-511.
6. Davis JC, Furstenthal L, Desai AA, Norris T, Sutaria S, Fleming E, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. *Nat Rev Drug Discov.* 2009;8(4):279-286.
7. Ng PC, Venter JC, Murray SS, Levy S. An agenda for personalized medicine. *Nature.* 2009;461(7265):724-726.
8. Schilsky RL. Personalized medicine in oncology: the future is now. *Nat Rev Drug Discov.* 2010;9(5):363-366.
9. Hayden EC. Personalized cancer therapy gets closer. *Nature.* 2009;458(7235):131-132.
10. Harris T. Gene and drug matrix for personalized cancer therapy. *Nat Rev Drug Discov.* 2010;9(8):660.
11. Clayton TA, Lindon JC, Cloarec O, Antti H, Charuel C, Hanton G, et al. Pharmaco-metabonomic phenotyping and personalized drug treatment. *Nature.* 2006;440(7087):1073-1077.

12. van't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, et al. Gene expression profiling predicts clinical outcome of breast cancer. *Nature*. 2002;415(6871):530-536.
13. Schwartz PJ. The congenital long QT syndromes from genotype to phenotype: clinical implications. *J Intern Med*. 2006;259(1):39-47.
14. Meadows M. Genomics and personalized medicine. *FDA Consum*. 2005;39(6):12-17.
15. Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med*. 2010;363(4):301-304.
16. Hayes DF, Thor AD, Dressler LG, Weaver D, Edgerton S, Cowan D, et al. HER2 and response to paclitaxel in node-positive breast cancer. *N Engl J Med*. 2007;357(15):1496-1506.
17. Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS, McLeod HL, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med*. 2005;352(22):2285-2293.
18. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol *Proc Natl Acad Sci U S A*. 2005;102(17):6237-6237.
19. Fukuoka M, Wu Y-L, Thongprasert S, Sunpaweravong P, Leong S-S, Sriuranpong V, et al. Biomarker Analyses and Final Overall Survival Results From a Phase III, Randomized, Open-Label, First-Line Study of Gefitinib Versus Carboplatin/Paclitaxel in Clinically Selected Patients With Advanced Non-Small-Cell Lung Cancer in Asia (IPASS). *J Clin Oncol*. 2011;29(21):2866-2874.

20. Acharya CR, Hsu DS, Anders CK, Anguiano A, Salter KH, Walters KS, et al. Gene expression signatures, clinicopathological features, and individualized therapy in breast cancer. *JAMA*. 2008;299(13):1574-1587.
21. De Roock W, Jonker DJ, Di Nicolantonio F, Sartore-Bianchi A, Tu DS, Siena S, et al. Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. *JAMA*. 2010;304(16):1812-1820.
22. Gentles AJ, Plevritis SK, Majeti R, Alizadeh AA. Association of a leukemic stem cell gene expression signature with clinical outcomes in acute myeloid leukemia. *JAMA*. 2010;304(24):2706-2715.
23. Lynch AI, Boerwinkle E, Davis BR, Ford CE, Eckfeldt JH, Leiendecker-Foster C, et al. Pharmacogenetic association of the NPPA T2238C genetic variant with cardiovascular disease outcomes in patients with hypertension. *JAMA*. 2008;299(3):296-307.
24. Maron BJ, Roberts WC, Arad M, Haas TS, Spirito P, Wright GB, et al. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. *JAMA*. 2009;301(12):1253-1259.
25. Moore J, McKnight AJ, Simmonds MJ, Courtney AE, Hanvesakul R, Brand OJ, et al. Association of Caveolin-1 gene polymorphism with kidney transplant fibrosis and allograft failure. *JAMA*. 2010;303(13):1282-1287.
26. Mostertz W, Stevenson M, Acharya C, Chan I, Walters K, Lamlertthon W, et al. Age- and sex-specific genomic profiles in non-small cell lung cancer. *JAMA*. 2010;303(6):535-543.

27. Schetter AJ, Leung SY, Sohn JJ, Zanetti KA, Bowman ED, Yanaihara N, et al. MicroRNA expression profiles associated with prognosis and therapeutic outcome in colon adenocarcinoma. *JAMA*. 2008;299(4):425-436.
28. Schroth W, Goetz MP, Hamann U, Fasching PA, Schmidt M, Winter S, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated With tamoxifen. *JAMA*. 2009;302(13):1429-1436.
29. Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, et al. Association of Cytochrome P450 2C19 Genotype With the Antiplatelet Effect and Clinical Efficacy of Clopidogrel Therapy. *JAMA*. 2009;302(8):849-858.
30. Waldman SA, Hyslop T, Schulz S, Barkun A, Nielsen K, Haaf J, et al. Association of GUCY2C expression in lymph nodes with time to recurrence and disease-free survival in pN0 colorectal cancer. *JAMA*. 2009;301(7):745-752.
31. Yang JJ, Cheng C, Yang WJ, Pei DQ, Cao XY, Fan YP, et al. Genome-wide interrogation of germline genetic variation associated with treatment response in childhood acute lymphoblastic leukemia. *JAMA*. 2009;301(4):393-403.
32. Abramson N, Costantino JP, Garber JE, Berliner N, Wickerham DL, Wolmark N. Effect of factor V leiden and prothrombin G20210→A mutations on thromboembolic risk in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention trial. *J Natl Cancer Inst*. 2006;98(13):904-910.
33. Ansems M, Hontelez S, Looman MWG, Karthaus N, Bult P, Bonenkamp JJ, et al. DC-SCRIPT: Nuclear receptor modulation and prognostic significance in primary breast cancer. *J Natl Cancer Inst*. 2010;102(1):54-68.

34. Asgharzadeh S, Pique-Regi R, Sposto R, Wang H, Yang Y, Shimada H, et al. Prognostic significance of gene expression profiles of metastatic neuroblastomas lacking MYCN gene amplification. *J Natl Cancer Inst.* 2006;98(17):1193-1203.
35. Azzato EM, Tyrer J, Fasching PA, Beckmann MW, Ekici AB, Schulz-Wendtland R, et al. Association between a germline OCA2 polymorphism at chromosome 15q13.1 and estrogen receptor-negative breast cancer survival. *J Natl Cancer Inst.* 2010;102(9):650-662.
36. Barry EL, Baron JA, Bhat S, Grau MV, Burke CA, Sandler RS, et al. Ornithine decarboxylase polymorphism modification of response to aspirin treatment for colorectal adenoma prevention. *J Natl Cancer Inst.* 2006;98(20):1494-1500.
37. Buyse M, Loi S, van't Veer L, Viale G, Delorenzi M, Glas AM, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *J Natl Cancer Inst.* 2006;98(17):1183-1192.
38. Cheang MCU, Chia SK, Voduc D, Gao DX, Leung S, Snider J, et al. Ki67 Index, HER2 status, and prognosis of patients with luminal B breast cancer. *J Natl Cancer Inst.* 2009;101(10):736-750.
39. Ellis MJ, Tao Y, Luo J, A'Hern R, Evans DB, Bhatnagar AS, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst.* 2008;100(19):1380-1388.
40. Gordon GJ, Dong LS, Yeap BY, Richards WG, Glickman JN, Edenfield H, et al. Four-gene expression ratio test for survival in patients undergoing surgery for mesothelioma. *J Natl Cancer Inst.* 2009;101(9):678-686.

41. Holm C, Rayala S, Jirström K, Stål O, Kumar R, Landberg G. Association between Pak1 expression and subcellular localization and tamoxifen resistance in breast cancer patients. *J Natl Cancer Inst.* 2006;98(10):671-680.
42. Nielsen M, van Steenbergen LN, Jones N, Vogt S, Vasen HFA, Morreau H, et al. Survival of MUTYH-associated polyposis patients with colorectal cancer and matched control colorectal cancer patients. *J Natl Cancer Inst.* 2010;102(22):1724-1730.
43. O'Malley FP, Chia S, Tu D, Shepherd LE, Levine MN, Bramwell VH, et al. Topoisomerase II alpha and responsiveness of breast cancer to adjuvant chemotherapy. *J Natl Cancer Inst.* 2009;101(9):644-650.
44. Pine SR, Mechanic LE, Ambs S, Bowman ED, Chanock SJ, Loffredo C, et al. Lung cancer survival and functional polymorphisms in MBL2, an innate-immunity gene. *J Natl Cancer Inst.* 2007;99(18):1401-1409.
45. Porter PL, Barlow WE, Yeh IT, Lin MG, Yuan XP, Donato E, et al. p27Kip1 and cyclin E expression and breast cancer survival after treatment with adjuvant chemotherapy. *J Natl Cancer Inst.* 2006;98(23):1723-1731.
46. Pottier N, Yang W, Assem M, Panetta JC, Pei D, Paugh SW, et al. The SWI/SNF chromatin-remodeling complex and glucocorticoid resistance in acute lymphoblastic leukemia. *J Natl Cancer Inst.* 2008;100(24):1792-1803.
47. Tryggvadottir L, Vidarsdottir L, Thorgeirsson T, Jonasson JG, Olafsdottir EJ, Olafsdottir GH, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. *J Natl Cancer Inst.* 2007;99(12):929-935.

48. Winnepenninckx V, Lazar V, Michiels S, Dessen P, Stas M, Alonso SR, et al. Gene expression profiling of primary cutaneous melanoma and clinical outcome. *J Natl Cancer Inst.* 2006;98(7):472-482.
49. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, 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(9742):687-697.
50. Bleecker ER, Postma DS, Lawrance RM, Meyers DA, Ambrose HJ, Goldman M. Effect of ADRB2 polymorphisms on response to longacting β 2-agonist therapy: a pharmacogenetic analysis of two randomised studies. *Lancet.* 2007;370(9605):2118-2125.
51. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet.* 2009;373(9660):309-317.
52. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet.* 2010;375(9712):377-384.
53. Nanto-Salonen K, Kupila A, Simell S, Siljander H, Salonsaari T, Hekkala A, et al. Nasal insulin to prevent type 1 diabetes in children with HLA genotypes and

- autoantibodies conferring increased risk of disease: a double-blind, randomised controlled trial. *Lancet*. 2008;372(9651):1746-1755.
54. Smith I, Procter M, D Gelber R, Guillaume S, Feyereislova A, Dowsett M, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*. 2007;369(9555):29-36.
55. Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet*. 2010;376(9737):235-244.
56. Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet*. 2010;376(9749):1320-1328.
57. Wechsler ME, Kunselmon SJ, Chinchilli VM, Bleecker E, Boushey HA, Calhoun WJ, et al. Effect of β 2-adrenergic receptor polymorphism on response to longacting β 2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial. *Lancet*. 2009;374(9703):1754-1764.
58. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med*. 2009;361(10):958-967.

59. Barnetson RA, Tenesa A, Farrington SM, Nicholl ID, Cetnarskyj R, Porteous ME, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. *N Engl J Med*. 2006;354(26):2751-2763.
60. Brock MV, Hooker CM, Ota-Machida E, Han Y, Guo MZ, Ames S, et al. DNA methylation markers and early recurrence in stage I lung cancer. *N Engl J Med*. 2008;358(11):1118-1128.
61. Chen HY, Yu SL, Chen CH, Chang GC, Chen CY, Yuan A, et al. A five-gene signature and clinical outcome in non-small-cell lung cancer. *N Engl J Med*. 2007;356(1):11-20.
62. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med*. 2006;355(26):2733-2743.
63. Ji J, Shi J, Budhu A, Yu Z, Forgues M, Roessler S, et al. MicroRNA expression, survival, and response to interferon in liver cancer. *N Engl J Med*. 2009;361(15):1437-1447.
64. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med*. 2008;359(17):1757-1765.
65. Ley TJ, Ding L, Walter MJ, McLellan MD, Lamprecht T, Larson DE, et al. DNMT3A mutations in acute myeloid leukemia. *N Engl J Med*. 2010;363(25):2424-2433.

66. Liu R, Wang XH, Chen GY, Dalerba P, Gurney A, Hoey T, et al. The prognostic role of a gene signature from tumorigenic breast-cancer cells. *N Engl J Med*. 2007;356(3):217-226.
67. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362(25):2380-2388.
68. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579.
69. Marcucci G, Radmacher MD, Maharry K, Mrozek K, Ruppert AS, Paschka P, et al. MicroRNA expression in cytogenetically normal acute myeloid leukemia. *N Engl J Med*. 2008;358(18):1919-1928.
70. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361(10):947-957.
71. Mullighan CG, Su XP, Zhang JH, Radtke I, Phillips LAA, Miller CB, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. *N Engl J Med*. 2009;360(5):470-480.
72. Pare G, Mehta SR, Yusuf S, Anand SS, Connolly SJ, Hirsh J, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *N Engl J Med*. 2010;363(18):1704-1714.

73. Poeta ML, Manola J, Goldwasser MA, Forastiere A, Benoit N, Califano JA, et al. TP53 mutations and survival in squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2007;357(25):2552-2561.
74. Potti A, Mukherjee S, Petersen R, Dressman HK, Bild A, Koontz J, et al. A genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. *N Engl J Med*. 2006;355(6):570-580. Retraction, *N Engl J Med*. 2011;364(12):1176.
75. Pritchard KI, Shepherd LE, O'Malley FP, Andrulis IL, Tu DS, Bramwell VH, et al. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. *N Engl J Med*. 2006;354(20):2103-2111.
76. Rennert G, Bisland-Naggan S, Barnett-Griness O, Bar-Joseph N, Zhang SY, Rennert HS, et al. Clinical outcomes of breast cancer in carriers of BRCA1 and BRCA2 mutations. *N Engl J Med*. 2007;357(2):115-123.
77. Schlenk RF, Dohner K, Krauter J, Frohling S, Corbacioglu A, Bullinger L, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *N Engl J Med*. 2008;358(18):1909-1918.
78. Schwarz UI, Ritchie MD, Bradford Y, Li C, Dudek SM, Frye-Anderson A, et al. Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med*. 2008;358(10):999-1008.
79. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Meneveau N, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*. 2009;360(4):363-375.

80. Zethelius B, Berglund L, Sundstrom J, Ingelsson E, Basu S, Larsson A, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med.* 2008;358(20):2107-2116.
81. Zheng Z, Chen TG, Li XL, Haura E, Sharma A, Bepler G. DNA synthesis and repair genes RRM1 and ERCC1 in lung cancer. *N Engl J Med.* 2007;356(8):800-808.
82. Chibon F, Lagarde P, Salas S, Perot G, Brouste V, Tirode F, et al. Validated prediction of clinical outcome in sarcomas and multiple types of cancer on the basis of a gene expression signature related to genome complexity. *Nat Med.* 2010;16(7):781-788.
83. Farmer P, Bonnefoi H, Anderle P, Cameron D, Wirapati P, Becette V, et al. A stroma-related gene signature predicts resistance to neoadjuvant chemotherapy in breast cancer. *Nat Med.* 2009;15(1):68-74.
84. Finak G, Bertos N, Pepin F, Sadekova S, Souleimanova M, Zhao H, et al. Stromal gene expression predicts clinical outcome in breast cancer. *Nat Med.* 2008;14(5):518-527.
85. Li Y, Zou LH, Li QY, Haibe-Kains B, Tian RY, Li Y, et al. Amplification of LAPTM4B and YWHAZ contributes to chemotherapy resistance and recurrence of breast cancer. *Nat Med.* 2010;16(2):214-U121.
86. McKinney EF, Lyons PA, Carr EJ, Hollis JL, Jayne DRW, Willcocks LC, et al. A CD8(+) T cell transcription signature predicts prognosis in autoimmune disease. *Nat Med.* 2010;16(5):586-591.

- 87.** Potti A, Dressman HK, Bild A, Riedel RF, Chan G, Sayer R, et al. Genomic signatures to guide the use of chemotherapeutics. *Nat Med.* 2006;12(11):1294-1300. Retraction, *Nat Med.* 2011;17(1): 135.
- 88.** Shedden K, Taylor JMG, Enkemann SA, Tsao MS, Yeatman TJ, Gerald WL, et al. Gene expression-based survival prediction in lung adenocarcinoma: a multi-site, blinded validation study. *Nat Med.* 2008;14(8):822-827.
- 89.** Fellay J, Thompson AJ, Ge DL, Gumbs CE, Urban TJ, Shianna KV, et al. ITPA gene variants protect against anaemia in patients treated for chronic hepatitis C. *Nature.* 2010;464(7287):405-408.
- 90.** Ge DL, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature.* 2009;461(7262):399-401.
- 91.** Hurtado A, Holmes KA, Geistlinger TR, Hutcheson IR, Nicholson RI, Brown M, et al. Regulation of ERBB2 by oestrogen receptor-PAX2 determines response to tamoxifen. *Nature.* 2008;456(7222):663-U693.
- 92.** Sakai W, Swisher EM, Karlan BY, Agarwal MK, Higgins J, Friedman C, et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. *Nature.* 2008;451(7182):1116-U1119.
- 93.** Schwickart M, Huang XD, Lill JR, Liu JF, Ferrando R, French DM, et al. Deubiquitinase USP9X stabilizes MCL1 and promotes tumour cell survival. *Nature.* 2010;463(7277):103-U114.

94. Tsai WW, Wang ZX, Yiu TT, Akdemir KC, Xia WY, Winter S, et al. TRIM24 links a non-canonical histone signature to breast cancer. *Nature*. 2010;468(7326):927-U320.
95. Yaes RJ. Human genome sequence. *Nature*. 1988;331(6151):10.
96. Dhanasekaran SM, Barrette TR, Ghosh D, Shah R, Varambally S, Kurachi K, et al. Delineation of prognostic biomarkers in prostate cancer. *Nature*. 2001;412(6849):822-826.
97. Capdeville R, Buchdunger E, Zimmermann J, Matter A. Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. *Nat Rev Drug Discov*. 2002;1(7):493-502.
98. George SL, Wang X. Targeted clinical trials. In: Harrington D, ed. *Designs for clinical trials: Perspectives on current issues (Applied bioinformatics and biostatistics in cancer research)* New York: Springer; 2011.
99. Catchpoole DR, Kennedy P, Skillicorn DB, Simoff S. The curse of dimensionality: A blessing to personalized medicine. *J Clin Oncol*. 2010;28(34):723-724.
100. George SL. Statistical issues in translational cancer research. *Clin Cancer Res*. 2008;14(19):5954-5958.
101. Simon R. Clinical trials for predictive medicine: new challenges and paradigms. *Clin Trials*. 2010;7(5):516-524.
102. Yeung KY, Haynor DR, Ruzzo WL. Validating clustering for gene expression data. *Bioinformatics*. 2001;17(4):309-318.

- 103.** van't Veer LJ, Bernards R. Enabling personalized cancer medicine through analysis of gene-expression patterns. *Nature*. 2008;452(7187):564-570.
- 104.** Hochberg Y. A Sharper Bonferroni Procedure for Multiple Tests of Significance. *Biometrika*. 1988;75(4):800-802.
- 105.** Eisen MB, Spellman PT, Brown PO, Botstein D. Cluster analysis and display of genome-wide expression patterns. *Proc Natl Acad Sci U S A* 1998;95(25):14863-14868.
- 106.** Tusher VG, Tibshirani R, Chu G. Significance analysis of microarrays applied to the ionizing radiation response. *Proc Natl Acad Sci U S A*. 2001;98(9):5116-5121.
- 107.** Tibshirani R, Hastie T, Narasimhan B, Chu G. Diagnosis of multiple cancer types by shrunken centroids of gene expression. *Proc Natl Acad Sci U S A*. 2002;99(10):6567-6572.
- 108.** Yeung KY, Ruzzo WL. Principal component analysis for clustering gene expression data. *Bioinformatics*. 2001;17(9):763-774.
- 109.** Raponi M, Zhang Y, Yu J, Chen G, Lee G, Taylor JM, et al. Gene expression signatures for predicting prognosis of squamous cell and adenocarcinomas of the lung. *Cancer Res*. 2006;66(15):7466-7472.
- 110.** Wang Y, Klijn JG, Zhang Y, Sieuwerts AM, Look MP, Yang F, et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. *Lancet*. 2005;365(9460):671-679.
- 111.** Haibe-Kains B, Desmedt C, Piette F, Buyse M, Cardoso F, van't Veer L, et al. Comparison of prognostic gene expression signatures for breast cancer. *Bmc Genomics*. 2008;9:394.

112. van't Veer LJ, Dai HY, van de Vijver MJ, He YDD, Hart AAM, Mao M, et al. Gene expression profiling predicts clinical outcome of breast cancer. *Nature*. 2002;415(6871):530-536.
113. Ioannidis JPA, Allison DB, Ball CA, Coulibaly I, Cui XQ, Culhane AC, et al. Repeatability of published microarray gene expression analyses. *Nat Genet*. 2009;41(2):149-155.
114. Allison DB, Cui X, Page GP, Sabripour M. Microarray data analysis: from disarray to consolidation and consensus. *Nat Rev Genet*. 2006;7(1):55-65.
115. Overington JP, Al-Lazikani B, Hopkins AL. How many drug targets are there? *Nat Rev Drug Discov*. 2006;5(12):993-996.
116. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26(10):1626-1634.
117. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2002;20(3):719-726.
118. Goldberg P. JCO retracts key Duke genomics paper: Duke shuts down three phase II trials. *The CANCER LETTER*. 2010;36(42):3.
119. Keith A, Baggerly KRC. Deriving chemosensitivity from cell lines: Forensic bioinformatics and reproducible research in high-throughput biology. *Ann Appl Stat*. 2009;3(4):1309-1334.

- 120.** Dupuy A, Simon RM. Critical review of published microarray studies for cancer outcome and guidelines on statistical analysis and reporting. *J Natl Cancer Inst.* 2007;99(2):147-157.
- 121.** Quackenbush J. Computational analysis of microarray data. *Nat Rev Genet.* 2001;2(6):418-427.
- 122.** Owzar K, Barry WT, Jung SH, Sohn I, George SL. Statistical challenges in preprocessing in microarray experiments in cancer. *Clin Cancer Res.* 2008;14(19):5959-5966.
- 123.** Jiang W, Freidlin B, Simon R. Biomarker-adaptive threshold design: a procedure for evaluating treatment with possible biomarker-defined subset effect. *J Natl Cancer Inst.* 2007;99(13):1036-1043.
- 124.** Dawson R, Lavori PW. Sample size calculations for evaluating treatment policies in multi-stage designs. *Clin Trials.* 2010;7(6):643-652.
- 125.** Lavori PW, Dawson R. Adaptive treatment strategies in chronic disease. *Annu Rev Med.* 2008;59:443-453.
- 126.** Zhou X, Liu S, Kim ES, Herbst RS, Lee JJ. Bayesian adaptive design for targeted therapy development in lung cancer - a step toward personalized medicine. *Clin Trials.* 2008;5(3):181-193.
- 127.** Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy. *Clin Pharmacol Ther.* 2009;86(1):97-100.

128. Shipp MA, Ross KN, Tamayo P, Weng AP, Kutok JL, Aguiar RCT, et al. Diffuse large B-cell lymphoma outcome prediction by gene-expression profiling and supervised machine learning. *Nat Med.* 2002;8(1):68-74.
129. Zhao Y, Kosorok MR, Zeng D. Reinforcement learning design for cancer clinical trials. *Stat Med.* 2009;28(26):3294-3315.
130. Zhao Y, Zeng, D., Socinsky, M. and Kosorok, M. R. Reinforcement learning strategies for clinical trials in non-small cell lung cancer. *Biometrics.* 2011; In press.
131. Murphy SA. Optimal dynamic treatment regimes. *J R Stat Soc B.* 2003;65(2):331-366.
132. Murphy SA. An experimental design for the development of adaptive treatment strategies. *Stat Med.* 2005;24(10):1455-1481.
133. Boulesteix AL, Sauerbrei W. Added predictive value of high-throughput molecular data to clinical data and its validation. *Brief Bioinform.* 2011;12(3):215-229.
134. Elsaleh H, Joseph D, Grieu F, Zeps N, Spry N, Iacopetta B. Association of tumour site and sex with survival benefit from adjuvant chemotherapy in colorectal cancer. *Lancet.* 2000;355(9217):1745-1750.

Table 1. Summary of personalized medicine studies published between 2006 and 2010 in six journals

The number of genes or proteins in each biomarker	Greater than 100 genes	4 (5%)
	Between 10 and 100 genes	8 (11%)
	Between 2 and 10 genes	10 (14%)
	Only 1 gene	52 (70%)
Sample size	Larger than 1000 patients	17 (24%)
	between 500 and 1000 patients	12 (16%)
	between 100 and 500 patients	35 (47%)
	Less than 100	10 (14%)
Cancer	Breast cancer (16,20,28,33, 35,37,38,41,43,45,52, 54,55,62,66,75,76,83-85,91,94)	22 (30%)
	Lung cancer (26,44,58,60,61,67,70,81,88)	9 (12%)
	Leukemia (22,31,39,46,65,69,71,80)	8 (11%)
	Colorectal cancer and adenomas (21,27,30,36,42,59,64)	7 (9%)
	Gastric cancer (49)	1 (1%)
	Liver Cancer (63)	1 (1%)
	Lymphomas (93)	1 (1%)
	Melanoma (48)	1 (1%)
	Mesothelioma (40)	1 (1%)
	Neuroblastomas (34)	1 (1%)
	Ovarian carcinomas (92)	1 (1%)
	Prostate cancer (47)	1 (1%)
	Sarcomas (82)	1 (1%)
	Skin cancer (75)	1 (1%)
Non-Cancer	Cardiovascular (23,24,29,51,56,72,79,80)	8 (11%)
	Asthma (50,57)	2 (3%)
	Hepatitis C virus (89,90)	2 (3%)
	Thrombosis and anti-coagulation (32,78)	2 (3%)
	Autoimmune disease (86)	1 (1%)
	Diabetes (53)	1 (1%)
	HIV (68)	1 (1%)
	Kidney Transplant (25)	1 (1%)

Figure Legends

Figure 1:

The comparisons among subgroups.

Figure 2:

Two approaches for identifying genetic biomarkers for personalized medicine.

Figure 3:

The overall trial design for I-SPY 2: MRI and blood sample draw is used to determine biomarker signature and eligibility; patients are randomized to seven treatment groups including two control groups and five new treatment groups. After 3 weeks of the assigned treatment, patients receive a repeat MRI and core biopsy and finish treatment over 9 additional weeks. A third MRI and core biopsy are performed before initiating standard chemotherapy with doxorubicin and cyclophosphamide. Another blood sample draw and a fourth MRI are given prior to surgery. Tumor tissue is collected at surgery to assess whether the patient has pathologic complete response, which is used to recalculate the randomization probability of each treatment group for new patients.

Figure 1. Comparisons among subgroups.

Figure 2. Two approaches for identifying genetic biomarkers for personalized medicine.

Figure 3. The overall trial design for I-SPY 2: MRI and blood sample draw is used to determine biomarker signature and eligibility; patients are randomized to seven treatment groups including two control groups and five new treatment groups. After 3 weeks of the assigned treatment, patients receive a repeat MRI and core biopsy and finish treatment over 9 additional weeks. A third MRI and core biopsy are performed before initiating standard chemotherapy with doxorubicin and cyclophosphamide. Another blood sample draw and a fourth MRI are given prior to surgery. Tumor tissue is collected at surgery to assess whether the patient has pathologic complete response, which is used to recalculate the randomization probability of each treatment group for new patients.