SMGroup

Understanding of Personalised Medicine Pathway in Breast Cancer

Farzad Heidari*

Genetic Research Group, Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia

***Corresponding author:** Farzad Heidari, Genetic Research Group, Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor 43400, Malaysia, Email: farzad720@gmail.com

Published Date: December 29, 2015

ABSTRACT

The advanced development of "- omics" innovations announced another time of customised prescription. Personalised medicine as the capacity to measure heterogeneous subjects of patients who reaction to helpful mediation inside of every sub group is homogeneous. This new worldview in human services started to influence both examination and clinical practice. The way to be productive is to reveal the sub-atomic solution that drives the unique assortment of remarkable biomarkers in clinical results or medication reactions. In this review starts with an overview of personalised medicine in breast cancer, showing the very utilised factual methodologies as a part of the late writing custom-made to for revealing gene signatures.

Keywords: Biomarker discovery; Breast neoplasms; Individualised medicine; Predictive biomarker; Prognostic biomarker.

INTRODUCTION

Not all patients react similarly to cancer therapeutic compounds. Late advances in high-throughput genomic, transcriptomic, furthermore, proteomic technologies with the always expanding understanding of the sub-atomic systems of growths grant revealing qualities that harbour individual varieties in clinical results or medication reactions. Customised prescription has reformed the social insurance worldview by incorporating individual genomic data, enhancing the medication treatment practicality, moving the act of drug, and making opportunities to present new business and medicinal services financial models.

The conventional standard "one-dose-fits-all" approach to deal with medication advancement and clinical treatment has been insufficient, as it causes all dangers of consequent medication toxicities and treatment familiars [1]. The rate of patients for whom a major drug is effective is presented in (Figure 1) [1]. With the considerable variability across disease, 38% to 75% of patients fail to respond to a treatment. The normal reaction rate of a tumor medication is the most minimal at 25%. Adverse drug reactions as an outcome of treatment are more of a problem. Among medications approved in the U.S., 16% have demonstrated poor medication responses [1]. A frequently cite meta-analysis revealed that 6.7% of all hospitalised patients are connected with poor medication responses in the U.S also, that the quantity of passing surpasses 100,000 cases every year [2]. A study directed in a major hospital identified 2,227cases of adverse drug reaction impacts among hospitalised patients and reported that half of these cases are liable to be identified with genetic factors [3]. Customised prescription is the capacity to portion heterogeneous subsets of patients whose reaction to a helpful intercession inside of every subset is homogeneous [4]. Under this new medical services worldview, physicians can make ideal decisions to augment the probability of compelling treatment and all the while maintain a critical distance from the dangers of drug adverse reactions; researchers can enhance the medication disclosure procedure and pharmaceutical company can manufacture devices to forecast patients prognosis, encouraging prime sickness location. A specific objective of personalised medicine is to outfit the appropriate treatment to the perfect individual at the opportune time [5]. The potential effect of personalised care is dependent upon an adequate disclosure of a novel biomarker from genome-wide candidates that record for varieties crosswise over people. This audit starts with a review of customised medication and shows the most experienced specific methodologies for revealing biomarkers used in the late writing.

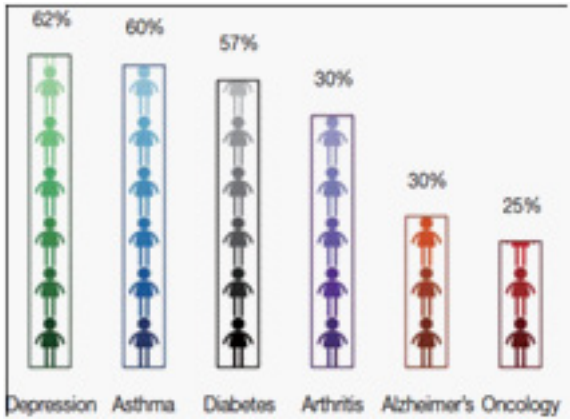

Figure 1: Inefficacy of the one-dose-fits-all approach. This figure depicts the percentage of patients for whom a major drug is effective on average. With the high variability across diseases, 38% to 75% of patients fail to respond to a treatment. The average response rate of a cancer drug is the lowest at 25%, suggesting that 75% of patients with cancer are over-dosed and will potentially suffer from an adverse drug reaction. From Spear BB, et al. [1].

DEFINITION OF PERSONALIZED MEDICINE: INDIVIDUALIZED TREATMENT *VS.* TREATMENT FOR A SUB-PATIENT GROUP

Customised drug has been characterised from various perspectives.

According to the U.S. National Institutes of Health (NIH), customised drug is "a developing routine of medication that uses an individual's genetic profile to guide choices made on the anticipation, conclusion, and treatment of illness" [6]. The U.S. Food And Drug Administration (FDA) defended customised prescription as "the best restorative results by picking medications that function admirably with a person genomic profile or with particular qualities in the individual's blood proteins or cell surface proteins" [7]. The President's Council of Advisors on Science and Technology (PCAST) described customised medication as "customising of medicinal treatment to the individual qualities of every patient" [4]. It is imperative to perceive that customised drug does not mean uniqueness. The thought of customised prescription has regularly been misrepresented, as proposed in a feature in Newsweek (June 10, 2005)"Medicine Tailored Just for you." In fact, another treatment regimen is evaluated on a group of carefully select patients however not individuals [5]. As such, PCAST reports that personalised medicine is the ability to classify individuals in to subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment" [4]. If another treatment works viable on a sub-patient group, a preventive mediation can then be outfitted to the individuals who will advantage, staying away from wrong medication impacts and saving cost for the individuals who won't.

BIOMARKERS: PROGNOSTIC *VS.* PREDICTIVE

A biomarker is a reliable and exact measurement that shows a typical natural process, a pathogenic procedure, or a pharmacological reaction to a helpful intercession [8]. With this expansive and general definition, biomarkers incorporate physiological estimations, for example, lung capacity, blood pressure or electroencephalography, molecular (DNA, protein, metabolite) or cell measures from bio fluids (blood, plasma, serum and pee), molecular, cell or histopathological measures from independent tissue samples, and estimations from attractive reverberation imaging or figured tomography images [9]. In this review, we will focus on "prognostic" and "proactive" biomarkers that estimate big results. A prognostic a biomarker is connected with a patients clinical result and can be utilised to choose patients for adjuvant systemic treatment independent of the patient reaction to treatment, in contrast a predictive biomarker is identified with the patients reaction to a special intercession. As indicated by a U.S. NIH Consensus Conference, "a clinical helpful prognostic biomarker must be a demonstrated autonomous, a significant component that is anything but difficult to decide and translate and that has restorative results" [10]. A prognostic biomarker provides information about the patients overall cancer outcome irrespective of the therapeutic response [11]. In this way, a prognostic biomarker can be misused to choose patients for adjuvant systemic treatment, but does not conjecture the treatment reaction [6]. Decision making about adjuvant systemic treatment for the breast cancer is normally based on nodal status [12-14], tumour size [15,16], tumour type/grade [17-20], lymphatic and vascular attack [21,22], tumour hormone receptor and human epidermal development variable receptor 2 (HER2)/neu status [23-26], age [27,28], and ethnicity [29-31]. Prognostic biomarkers that give better data on backsliding danger could anticipate numerous patients from chemotherapy danger without bargaining survival [32]. Predictive characteristic of a biomarker needs to be exhibited in randomised clinical trials. Interestingly, a predictive biomarker gives data about the impact of a helpful mediation [32]. In other words, a predictive biomarker empowers screening of a subset of patients that are receptive to a particular treatment where the reaction is characterised by any of the clinical endpoints commonly measured in clinical trials [33]. As a predictive biomarker shows heterogeneous advantages dependent upon sub-quiet In contrast, a predictive biomarker provide information about the impact of a therapeutic intervention [32]. In other words, a predictive biomarker empowers screening of a subset of patients that are receptive to a particular treatment where reaction is characterised by any of the clinical endpoints generally measured in clinical trials [33]. As a predictive biomarker shows heterogeneous advantages dependent upon sub-patient risk group categorised by the status of the biomarker, a significant interaction communication between treatment impacts and patient categories should be statistically validated, in a randomised clinical trial [34].

Prescient biomarkers can assist doctors in forecasting the impacts of a particular treatment. Various proteins and qualities exist that are mainly connected with breast cancer development, proliferation, and metastasis. The more profound comprehension of their parts on the reactions

of different treatments might empower physicians to decide ideal medicines for patients with breast cancer [35]. Some biomarkers are both prognostic and predictive (Table 1) [36,37]. For instance, patients with Estrogen Receptor (ER) what's more, or Progesterone Receptor (PR)-positive tumors have longer survival than those with hormone receptor-negative tumors [15,38]. Furthermore, a late randomised trial reported that high cell ER and PR expression predicts the advantage from adjuvant tamoxifen [39]. As another example, HER2/neu gene amplification, which leads to over expression of its receptor on the cell membrane in around 30% of human breast tumors, is related to a worse prognosis in patients with node-positive breast cancer. Because of expanded proliferation and angiogenesis and inhibition of apoptosis [23-26]. HER2/neu is likewise the objective for the monoclonal neutraliser trastuzumab from which patients with HER2/neu over expressing tumors advantage in a metastatic and adjuvant setting [40-42].

Biomarker	Drug		Compound	Indication
BRCA1/2				Guides surveillance and preventive treatment based on susceptibility risk for breast and ovarian cancer
Estrogen receptor (Hormone receptor)	Selective estrogen receptor modulators	Nolvadex®	Tamoxifen	Tamoxifen is currently used for the treatment of estrogen receptor positive breast cancer in pre- and post-menopausal women. Additionally, it is the most common hormone treatment for male breast cancer. It is also approved by the FDA for the prevention of breast cancer in women at high risk of developing the disease
		Fareston®	Toremifen	Toremifen is an estrogen agonist/antagonist indicated for the treatment of breast cancer in postmenopausal women with estrogen-receptor positive tumors
	Aromatase inhibitors	Femara®	Letrozole	Letrozole is indicated for the treatment of postmenopausal women with hormone receptor positive breast cancer
		Arimidex®	Anastrozole	Anastrozole is indicated for the treatment of postmenopausal women with hormone receptor-positive breast cancer
		Aromasin®	Exemestane	Exemestane is indicated for the treatment of postmenopausal women with hormone
	Estrogen receptor Antagonist	Faslodex®	Fulvestrant	Fulvestrant is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy
	mTOR inhibitor	AFINITOR®	Everolimus	Everolimus is a mTOR inhibitor indicated for the treatment of postmenopausal women with advanced or metastatic hormone receptor-positive, HER2-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole
HER2/*neu* over expression	Monoclonal antibody	Herceptin®	Trastuzumab	Trastuzumab is indicated for use in combination with cytotoxic chemotherapy for the treatment of breast cancer in women with HER2-positive tumor
(HER2-positive)		Perjeta®	Pertuzumab	Pertuzumab is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease
	Tyrosine kinase Inhibitor	Tykerb®	Lapatinib	Lapatinib is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab

National Cancer Institute. Drug information: drugs approved for breast cancer. http://www.cancer.gov/cancertopics/druginfo/breastcancer [37].

WHY PERSONALIZED MEDICINE?

The wide-ranging impacts and myriad opportunities provided by personalised medicine can be summarised in reference to its four primary attributes [5].

Personalized

Personalised medicine incorporates personal genetic or protein profiles to strengthen healthcare at a more individualised level, particularly with the aid of recently emerging "-omic" technologies such as nutritional genomics, pharmacogenomics, Proteomics, and Metabolomics [43]. Personalised medicine targets what positively affect a persisting disease and after that develops safe and efficient treatments for that particular disease [5]. In fact, genetic biomarker that may be mainly related to an infection state is the foundation of personalised medicine. Knowledge of a patient's genetic profile leads to the proper medication or therapy so that physicians can manage a patient's disease or predisposition towards it using the proper dose or treatment regimen [6].

Protection

Personalised medicine seeks after not response but response. With the capacity to estimate disease risks or vicinity some time recently clinical symptoms show up, personalised medicine offers the opportunity to advanced stages of a disease through ahead of schedule intercession. Intervention can be life saving in many cases. For instance, females with genetic mutation in the BRCA1 or BRCA2 genes have a higher possibility of breast cancer compared to women in public [44,45]. An accurate test of these breast cancer susceptibility genes can guide surveillance and preventive treatment based on objective risk measurements such as increased frequency of mammography, prophylactic surgery, and chemoprevention (Table 2) [46].

Treatment	Diagnostic device	Indication
Chemotherapy	Mammostrat®	An immunohistochemicalmultigene test to predict the risk of early recurrence for estrogen receptor positive postmenopausal patients who will receive endocrine therapy and are considering adjuvant chemotherapy, node negative, estrogen receptor
	MammaPrint®	A microarray based in vitro test based on a 70-gene expression profile to assess a patient's risk for distant metastasis
	Oncotype DX®21-gene signature	A diagnostic test based on a 16-gene signature (plus five reference genes) to assess the risk of recurrence for estrogen receptor positive patients High-risk patients may require additional chemotherapy whereas hormone therapy may be sufficient for low-risk patients
	Compan DX® 31-gene signature	A diagnostic test based on a 31 gene panel to predict time to metastasis following initial surgery and biopsy

*Data from U.S. Food and Drug Administration. Drugs@FDA: FDA approved drug products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda [46].

Personalised medicine has capability of leading physicians to choose and optimal treatment method to avoid ADR. Moreover molecular diagnostic devices are design as a predictive biomarker, which provides practical information concerning protein structures that would benefit from specific therapy. For example, Oncotype DX® (Genomic Health, Redwood City, USA) uses a 16-genesignature to determine whether women with certain types of breast cancer are likely to benefit from chemotherapy [47-49]. MammaPrint® (Agendia, Amsterdam, the Netherlands) uses a 70-gene expression profile to assess the risk of distant metastasis in patients with early-stage breast cancer [50].

These complex diagnostic tests can be used to classify patients in to subgroups to inform physicians whether patients would be treated successfully with hormone therapy alone or may require more aggressive chemotherapy treatment. Applying these diagnostic tests should be established as patient's classifier therefore physicians forecast whether patients would be treated successfully with hormone therapy alone or may require more aggressive chemotherapy treatment.

Participatory

Personalised medicine science would be a promising cutting edge science to treat patients [51]. Patients are more likely to fulfill treatments if they are convinced having less ADV, expenses and failure.

STATISTICAL STRATEGIES FOR UNCOVERING GENE SIGNATURES THAT PREDICT CLINICAL OUTCOMES AND DRUG RESPONSES

Uncovering gene signatures are the critical key that drives individual's variability in clinical outcomes or drug response in personalised medicine. Quit number of molecular approaches have been used to identify genes of interest among cancer's screening programs. This review focuses on the most practical methods for biomarker discovery; data-driven and knowledge-driven-approaches.

In the data-driven approach, biomarkers associated with tumor traits are objectively searched in genome-wide analysis using data-mining tools. Unbiased biomarker discovery is the merit of this approach. However, in the downside, data-driven approach is found difficult to interpret due to limited knowledge about the proteomics functions.

In contrast, the knowledge-driven approach attempts to select candidate genes using prior knowledge or surveying the literature for evidence of linkage to either cancer pathological processes or pathways important in drug responses. As such, genes that are unknown to be involved in a progress can't be included.

Gene signature development has become so rapid by using combination of the data-driven and knowledge-driven approach [48]. Biomarker discovery in genome-wide analysis is subject to the curse of dimensionality, i.e., the situation in which there are far more genomic variables than the number of samples [52].

On way to manage this issue is to apply the knowledge-driven methodology to decrease those total of candidate genes distinguished by an unbiased genome-wide search.

As a outlining of the information driven methodology, recently proposed methodical data-driven methodologies based on *in vitro*-generated extrapolative profiles utilising cell-line models involve five key specialised steps 1) data collection, 2) quality control, 3)identification of candidate gene biomarkers, 4) construction of a multivariate prediction model, and 5) independent validation of the prediction model [53-57]. Biomarker revelation starts by molecular data collection in drug response experiment. A lot of genomic or genetic characteristics on cell-lines are uncertainly decided using high-throughput technology. The drug's designs of achievement in cells are measured on a persistent (percent of cell survival or death) or discrete scale (responsive or resistant). The direct procedure ensuing achievement of a large amount of molecular data is quality control or pre-processing.

Due to the nature of high-throughput technologies that introduce unavoidable non-biologic noises and biases during data collection, appropriate normalisation according to specific array technologies is performed before further analysis. It is important to notify, mostly downstream data analysis method manipulated by quality control procedure.

The following step after reassuring an acceptable level of normalisation is to identify the subsection of genes that are candidate interpreters highly associated with drug activities. This step reduces the parameter space of gene variables in a very high dimension [41]. In the former studies, various practical approaches have been used, including classical two-sample tests, variant t-tests [58-61], experiential Bayes methods [62-64], a linear mixed effect model [65], and the generalised likelihood ratio test [66] and the local-pooled-error test [67]. Note that these statistical approaches rely on underlying assumptions such as distributional specifications, exchangeability for arandom-effect distribution, constant coefficients of variation, a mean-variance relationship, and others.

Upon narrowing down candidate genes to a few hundred, a statistical classification modeling technique is then used to construct a multivariate prediction model. Single biomarkersare less likely to furnish sufficient sensitivity and specificity for most applications [35]. Several classification methods have been utilised, including a variant of linear discriminant analysis [68], support vector machines [69-71], Bayesian regression [72], partial least squares [73], principal component regression [74], and between-group analysis [75]. The performance of a statistical prediction model should be tested and assessed by various statistical measures such as classification error rate and area under the receiver operating characteristic curve, the product of posterior classification probabilities [76-78], and an index so-called the misclassification-penalized posterior [79]. The leave-one-out approach, random splitting, and bootstrapping are often employed for an internal cross endorsement. Additionally, multicentre endorsement is also performed for an external cross validation. It has been implied from previous studies that no one dominating classy outperforms all other methods.

Finally, the ultimate evidence of the usefulness of a prediction model in a clinical setting is randomised, prospective validation in a clinical trial [80]. After improvement and endorsement in independent associates, the covariates in the prediction model can be used to develop assays that precisely predict prediction and responses to chemotherapeutic agents, contributing to the development of "personalised medicine" for patients with cancer.

CONCLUSION

Personalised medicine is receiving a large amount of growing responsiveness for its remarkable potential with untold new opportunities. The ultimate promise of personalised medicine relates on the discovery of the personal genetic causes of disease such as breast cancer. The remarkable advent of current cutting-edge technologies in combination with improved knowledge of the molecular basis of malignancy provides a solid base for identifying novel molecular targets. This revolutionised paradigm in healthcare is already beginning to affect both research and clinical practice. The use of high-throughput technologies is likely to greatly increase in the next few years as the cost of technologies will continue to drop (Figure 2) [81]. Genomic sequencing and its interpretation will have to be further developed and standardised for routine clinical practice to develop efficient and effective methods for discovering and verifying new biomarkers and enabling personalised medicine technologies. In particular, efforts to standardise present technologies will lead to more reproducible and robust identification of biomarkers.

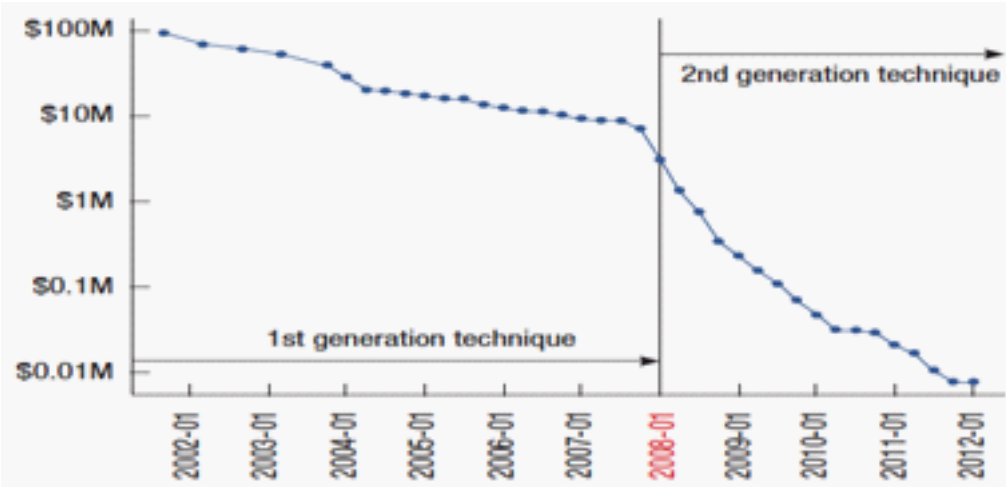

Figure 2: Cost of sequencing a human-sized genome. Note that a logarithmic scale is used on the Y-axis. The cost of sequencing rapidly decreased at an exponential rate from 2001 to 2007. The sudden drop in cost around January 2008 was due to sequencing technology geared up from the first generation ("Sanger-based" or dideoxy chain termination sequencing) to the second generation (or "next-generation"). The cost of sequencing has dramatically decreased since 2008. From Wetter strand KA. DNA sequencing costs: data from the NHGRI large-scale genome-sequencing program. http://www.genome.gov/sequencingcosts/ [81].

Several challenges must be overcome before this flood of profile data is successfully translated into clinical utilities for patients with breast cancer. Improved knowledge obtained using advanced profile technologies will not be sufficient for this purpose, but all stakeholders involved in personalised medicine should work together to take responsibility. Regulatory authorities should provide clear guidelines for evaluating and approving newly developed personalised drugs and

should validate the capabilities of the diagnostic devices that predict patient prognoses or drug responses. Medical educational institutions should prepare the next generation of physicians to use and interpret personal genetic information appropriately and responsibly. Finally, public and private insurers need to evaluate the clinical and economic utility of personalised drugs and devices to facilitate reimbursement.

References

1. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med. 2001; 7: 201-204.
2. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998; 279: 1200-1205.
3. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1997; 277: 301-306.
4. President's Council of Advisors on Science and Technology. Priorities for Personalized Medicine. Washington, DC: President's Council of Advisorson Science and Technology. 2008.
5. Pfizer. Think Science Now Perspective. Approaches to Cancer Care: the Promise of Personalized Medicine. New York: Pfizer. 2010.
6. Genetics home reference: Glossary. U.S. National Institutes of Health, U.S. National Library of Medicine. http://ghr.nlm.nih.gov/glossary=personalisedmedicine.Accessed July 1st. 2012.
7. Meadows M. Genomics and personalized medicine. FDA Consum. 2005; 39: 12-17.
8. Biomarkers Definitions Working Group.. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001; 69: 89-95.
9. Micheel C, Ball J; Institute of Medicine (U.S.). Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease. Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease. Washington, DC: National Academies Press. 2010.
10. NIH consensus conference. Treatment of early-stage breast cancer. JAMA. 1991; 265: 391-395.
11. Clark GM, Zborowski DM, Culbertson JL, Whitehead M, Savoie M, Seymour L, et al. Clinical utility of epidermal growth factor receptor expression for selecting patients with advanced non-small cell lung cancer for treatment with erlotinib. J Thorac Oncol. 2006; 1: 837-846.
12. Saez RA, McGuire WL, Clark GM. Prognostic factors in breast cancer. Semin Surg Oncol. 1989; 5: 102-110.
13. Nemoto T, Natarajan N, Bedwani R, Vana J, Murphy GP. Breast cancer in the medial half. Results of 1978 National Survey of the American College of Surgeons. Cancer. 1983; 51: 1333-1338.
14. Fisher B, Bauer M, Wickerham DL, Redmond CK, Fisher ER, Cruz AB, et al. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. An NSABP update. Cancer. 1983; 52: 1551-1557.
15. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer. 1989; 63: 181-187.
16. Rosen PP, Groshen S, Kinne DW, Norton L. Factors influencing prognosis in node-negative breast carcinoma: analysis of 767 T1N0M0/T2N0M0 patients with long-term follow-up. J ClinOncol. 1993; 11: 2090-2100.
17. Carstens PH, Greenberg RA, Francis D, Lyon H. Tubular carcinoma of the breast. A long term follow-up. Histopathology. 1985; 9: 271-280.
18. Clayton F. Pure mucinous carcinomas of breast: morphologic features and prognostic correlates. Hum Pathol. 1986; 17: 34-38.
19. Ridolfi RL, Rosen PP, Port A, Kinne D, Mike V. Medullary carcinoma of the breast: a clinicopathologic study with 10 year follow-up. Cancer. 1977; 40: 1365-1385.
20. Le Doussal V, Tubiana-Hulin M, Friedman S, Hacene K, Spyratos F, Brunet M. Prognostic value of histologic grade nuclear components of Scarff-Bloom-Richardson (SBR). An improved score modification based on a multivariate analysis of 1262 invasive ductal breast carcinomas. Cancer. 1989; 64: 1914-1921.
21. Le Doussal V, Tubiana-Hulin M, Friedman S, Hacene K, Spyratos F, Brunet M. Prognostic value of histologic grade nuclear components of Scarff-Bloom-Richardson (SBR). An improved score modification based on a multivariate analysis of 1262 invasive ductal breast carcinomas. Cancer. 1989; 64: 1914-1921.

22. Rosen PP, Groshen S, Saigo PE, Kinne DW, Hellman S. Pathological prognostic factors in stage I (T1N0M0) and stage II (T1N1M0) breastcarcinoma: a study of 644 patients with median follow-up of 18 years. JClinOncol. 1989; 7: 1239-1251.

23. Neville AM, Bettelheim R, Gelber RD, Save-Soderbergh J, Davis BW, Reed R, et al. Factors predicting treatment responsiveness and prognosis in node-negative breast cancer. The International (Ludwig) Breast Cancer Study Group. J ClinOncol. 1992; 10: 696-705.

24. Winstanley J, Cooke T, Murray GD, Platt-Higgins A, George WD, Holt S, et al. The long term prognostic significance of c-erbB-2 in primary breast cancer. Br J Cancer. 1991; 63: 447-450.

25. Borg A, Tandon AK, Sigurdsson H, Clark GM, Ferno M, Fuqua SA, et al. HER-2/neu amplification predicts poor survival in node-positive breast cancer. Cancer Res. 1990; 50: 4332-4337.

26. Paterson MC, Dietrich KD, Danyluk J, Paterson AH, Lees AW, Jamil N, et al. Correlation between c-erbB-2 amplification and risk of recurrent disease in node-negative breast cancer. Cancer Res. 1991; 51: 556-567.

27. Clark GM, McGuire WL. Follow-up study of HER-2/neu amplification in primary breast cancer. Cancer Res. 1991; 51: 944-948.

28. Nixon AJ, Neuberg D, Hayes DF, Gelman R, Connolly JL, Schnitt S, et al. Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. J Clin Oncol. 1994; 12: 888-894.

29. Albain KS, Allred DC, Clark GM. Breast cancer outcome and predictors of outcome: are there age differentials? J Natl Cancer Inst Monogr. 1994; 35-42.

30. Daly MB, Clark GM, McGuire WL. Breast cancer prognosis in a mixed Caucasian-Hispanic population. J Natl Cancer Inst. 1985; 74: 753-757.

31. Elledge RM, Clark GM, Chamness GC, Osborne CK. Tumor biologic factors and breast cancer prognosis among white, Hispanic, and black women in the United States. J Natl Cancer Inst. 1994; 86: 705-712.

32. Pierce L, Fowble B, Solin LJ, Schultz DJ, Rosser C, Goodman RL. Conservative surgery and radiation therapy in black women with early stage breast cancer. Patterns of failure and analysis of outcome. Cancer. 1992; 69: 2831-2841.

33. Oldenhuis CN, Oosting SF, Gietema JA, de Vries EG. Prognostic versus predictive value of biomarkers in oncology. Eur J Cancer. 2008; 44: 946-953.

34. Bentzen SM, Buffa FM, Wilson GD. Multiple biomarker tissue microarrays: bioinformatics and practical approaches. Cancer Metastasis Rev. 2008; 27: 481-494.

35. Clark GM. Prognostic factors versus predictive factors: Examples from a clinical trial of erlotinib. Mol Oncol. 2008; 1: 406-412.

36. Phan JH, Moffitt RA, Stokes TH, Liu J, Young AN, Nie S, et al. Convergence of biomarkers, bioinformatics and nanotechnology for individualized cancer treatment. Trends Biotechnol. 2009; 27: 350-358.

37. Drug information: drugs approved for different types of cancer. National Cancer Institute. 2012.

38. Drug information: drugs approved for breast cancer. National CancerInstitute. 2012.

39. Grann VR, Troxel AB, Zojwalla NJ, Jacobson JS, Hershman D, Neugut AI. Hormone receptor status and survival in a population-based cohort of patients with breast carcinoma. Cancer. 2005; 103: 2241-2251.

40. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005; 365: 1687-1717.

41. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005; 353: 1673-1684.

42. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy inHER2-positive breast cancer: a randomised controlled trial. Lancet. 2007; 369: 29-36.

43. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, Slamon DJ. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002; 20: 719-726.

44. Jones DS, Hofmann L, Quinn S. 21st Century Medicine: A New Model for Medical Education and Practice. Gig Harbor: The Institute for Functional Medicine. 2010; 23-87.

45. Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med. 1997; 336: 1401-1408.

46. BRCA1, BRCA2: cancer risk and genetic testing. National Cancer Institute. Accessed July 1st. 2012.

47. Drugs@FDA: FDA approved drug products. U.S. Food and Drug Administration. Accessed July 1st. 2012.

48. Hornberger J, Cosler LE, Lyman GH. Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer. Am J Manag Care. 2005; 11: 313-324.

49. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006; 24: 3726-3734.

50. Cronin M, Pho M, Dutta D, Stephans JC, Shak S, Kiefer MC, et al. Measurement of gene expression in archival paraffin-embedded tissues: development and performance of a 92-gene reverse transcriptase-polymerasechain reaction assay. Am J Pathol. 2004; 164: 35-42.

51. MammaPrintAgendia. Accessed July 1st. 2012.

52. Personalised Medicine Coalition. The Case for Personalised Medicine. 3rd edition. Washington, DC: Personalised Medicine Coalition. 2011.

53. Catchpoole DR, Kennedy P, Skillicorn DB, Simoff S. The curse of dimensionality: a blessing to personalized medicine. J Clin Oncol. 2010; 28: e723-724.

54. Cheng F, Cho SH, Lee JK. Multi-gene expression-based statistical approaches to predicting patients' clinical outcomes and responses. Methods Mol Biol. 2010; 620: 471-484.

55. Lee JK, Havaleshko DM, Cho H, Weinstein JN, Kaldjian EP, Karpovich J, et al. A strategy for predicting the chemosensitivity of human cancers and its application to drug discovery. Proc Natl Acad Sci U S A. 2007; 104: 13086-13091.

56. Smith SC, Baras AS, Dancik G, Ru Y, Ding KF, Moskaluk CA, et al. A20-gene model for molecular nodal staging of bladder cancer: development and prospective assessment. Lancet Oncol. 2011; 12: 137-143.

57. Staunton JE, Slonim DK, Coller HA, Tamayo P, Angelo MJ, Park J, et al. Chemosensitivity prediction by transcriptional profiling. Proc Natl Acad Sci U S A. 2001; 98: 10787-10792.

58. Neve RM, Chin K, Fridlyand J, Yeh J, Baehner FL, Fevr T, et al. A collection of breast cancer cell lines for the study of functionally distinct cancer subtypes. Cancer Cell. 2006; 10: 515-527.

59. Efron B, Tibshirani R, Storey JD, Tusher V. Empirical bayes analysis of amicroarray experiment. J Am Stat Assoc. 2001; 96: 1151-1160.

60. Dudoit R, Yang YH, Callow MJ, Speed TP. Statistical methods for identifying differentially expressed genes in replicated cDNA microarray experiments. Stat Sin. 2002; 12: 111-139.

61. Smyth GK. Linear models and empirical bayes methods for assessing differential expression in microarray experiments. Stat Appl Genet Mol Biol. 2004; 3: Article3.

62. Hu J, Wright FA. Assessing differential gene expression with small sample sizes in oligonucleotide arrays using a mean-variance model. Biometrics. 2007; 63: 41-49.

63. Lonnstedt I, Speed T. Replicated microarray data. Stat Sin. 2002; 12: 31-46. Newton MA, Kendziorski CM, Richmond CS, Blattner FR, Tsui KW. On differential variability of expression ratios: improving statistical inference about gene expression changes from microarray data. J ComputBiol. 2001; 8: 37-52.

64. Newton MA, Noueiry A, Sarkar D, Ahlquist P. Detecting differential gene expression with a semiparametric hierarchical mixture method. Biostatistics. 2004; 5: 155-176.

65. Wolfinger RD, Gibson G, Wolfinger ED, Bennett L, Hamadeh H, Bushel P, et al. Assessing gene significance from cDNA microarray expression data via mixed models. J Comput Biol. 2001; 8: 625-637.

66. Wang S1, Ethier S. A generalized likelihood ratio test to identify differentially expressed genes from microarray data. Bioinformatics. 2004; 20: 100-104.

67. Jain N, Thatte J, Braciale T, Ley K, O'Connell M, Lee JK. Local-pooled error pooled error test for identifying differentially expressed genes with a small number of replicated microarrays. Bioinformatics. 2003; 19: 1945-1951.

68. Golub TR, Slonim DK, Tamayo P, Huard C, Gaasenbeek M, Mesirov JP, et al. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science. 1999; 286: 531-537.

69. Brown MP, Grundy WN, Lin D, Cristianini N, Sugnet CW, Furey TS, et al. Knowledge-based analysis of microarray gene expression data by using support vector machines. Proc Natl Acad Sci U S A. 2000; 97: 262-267.

70. Brown MP, Grundy WN, Lin D, Cristianini N, Sugnet CW, Furey TS, et al. Knowledge-based analysis of microarray gene expression data by using support vector machines. Proc Natl Acad Sci USA. 2000; 97: 262-267.

71. Furey TS, Cristianini N, Duffy N, Bednarski DW, Schummer M, Haussler D. Support vector machine classification and validation of cancer tissue samples using microarray expression data. Bioinformatics. 2000; 16: 906-914.

72. Mukherjee S, Tamayo P, Slonim D, Verri A, Golub T, Mesirov JP, et al. Support Vector Machine Classification of Microarray Data. Cambridge: Massachusetts Institute of Technology. 1998.

73. West M, Blanchette C, Dressman H, Huang E, Ishida S, Spang R, et al. Predicting the clinical status of human breast cancer by using gene expression profiles. Proc Natl Acad Sci USA. 2001; 98: 11462-11467.

74. Nagji AS, Cho SH, Liu Y, Lee JK, Jones DR. Multigene expression-based predictors for sensitivity to Vorinostat and Velcade in non-small cell lung cancer. Mol Cancer Ther. 2010; 9: 2834-2843.

75. Culhane AC, Perriere G, Considine EC, Cotter TG, Higgins DG. Between-group analysis of microarray data. Bioinformatics. 2002; 18: 1600-1608.

76. Bradley AP. The use of the area under the ROC curve in the evaluation of machine learning algorithms. Pattern Recognit. 1997; 30: 1145-1159.

77. Hand DJ. Construction and Assessment of Classification Rules. Chichester: Wiley. 1997.

78. Soukup M, Lee JK. Developing optimal prediction models for cancer classification using gene expression data. J Bioinform Comput Biol. 2004; 1: 681-694.

79. Soukup M, Cho H, Lee JK. Robust classification modeling on microarray data using misclassification penalized posterior. Bioinformatics. 2005; 21: i423-430.

80. Buyse M, Sargent DJ, Grothey A, Matheson A, de Gramont A. Biomarkers and surrogate end points-the challenge of statistical validation. Nat Rev Clin Oncol. 2010; 7: 309-317.

81. DNA sequencing costs: data from the NHGRI large-scalegenome-sequencing program. Wetter strand KA. 2012.