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Personal Medicine Possible Treatment of Breast Cancer

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Abstract:

Personal medicine is based on purposeful treatment that, unlike traditional therapies, considers a person's genetic structure and medical history before establishing a treatment regimen. This science has made possible the improvement of "pharmacogenomic" knowledge, which identifies individuals who respond to a particular treatment based on their genotype information. The findings of the Cancer Genome Atlas Network show that each molecular endorsement of each BC is unique. Also, different responses to a given medication regimen have been reported among a similar group of breast cancer. Thus, personal medicine plays a role in the care of patients with breast cancer, in which a person's characteristics, including genetic characteristics, guide clinical decisions and are effective in choosing the right treatment for the patient at the right time.

INTRODUCTION

Somatic mutations cause more than 100 types of cancer in organs and sub-issues(1-4). After the census of human cancer genes in 2006, researchers found that 5 to 10 percent or more of the human genome was involved in oncogenesis(5). More accurate identification of cancer-causing genes expands cancer screening programs to identify «at-risk» patients and help these individuals correct their high-risk behaviors(6).

Recently, researchers observed differences in cancer in different people and decided to find a person-centered treatment approach to achieve a safer treatment for the disease(7). Personalized medicine is a new approach that focuses on the unique diagnosis and treatment of each human being. In this method, the characteristics of each person guide the path of diagnosis and treatment(8).

Progress in bioinformatics analysis and genome sequencing has led to the prevalence of Personalized medicine and, as a result, an increase in the recovery rate of cancer patients (Especially in metastatic non-small cell lung cancer and colorectal cancer). Studies have shown that Personalized medicine is more successful in patients with metastatic BC than in patients with non-small metastatic lung cancer and

colorectal cancer(7).

However, there are still obstacles to the widespread implementation of personal care among cancer patients. Our confined perceiving of cancer biology and the capability to recognize the molecular targets necessary for tumor plethora and progression are the most critical obstacles in this direction(9).

What is personal medicine?

There are different definitions of personalized medicine; for example, according to the U.S. Food and Drug Administration (FDA), personalized medicine is the choice of the best treatments based on cell surface proteins, the characteristics of proteins in the blood, and the genomic characteristics of the individual(10).

Elsewhere, the US National Institutes of Health (NIH) has highlighted the role of prevention and diagnosis in personal medicine, introducing personal medicine as a new medical method that involves using individuals' genetic characteristics to improve the prevention, diagnosis, and treatment of diseases(11). Personalized medicine can be considered as a kind of treatment suitable for each person, although the idea of personalized medicine is often exaggerated(12, 13).

Why is personalized medicine necessary to treat cancer?

Genetic, hereditary, or physical abnormalities may cause cancer. The leading cause of cancers is a lifestyle, infections, and environmental factors, and only 10 to 15% of cancers are inherited and familial. According to the characteristics of each person, the risk of cancer during a person's life can be determined(14). A cancer-disposing allele is rarely inherited in an autosomal-dominant method, collaboration to high cancer risk. It has also been observed that cancer occurs in people without a family history of cancer, so it can be concluded that non-genetic factors play a role in causing mutations or mutation-related changes(15). In addition to inherited variations in tumor genetics, inherited genetic several in genes that metabolize and process medicines impress treatment response. These variants may cause more toxicity with particular drugs(16). Modern personal medicine is based on the patient's medical history and genetic structure, but traditional personal medicine, which is based on environment and lifestyle, is the social condition of the patient's family history. In addition, in modern personal medicine, targeted therapy is vital, and in order to achieve it, it is vital that information be available on changed pathways and the components that contribute to cancer (15).

BC and personalized medicine

Undifferentiated breast tissue cells cause Breast Cancer (BC). This type of cancer is mainly a malignant tumor and spreads to other tissues such as bones, but in rare cases, it develops as a benign tumor called angiosarcoma or phyllodes tumor(17). Women are most likely to contract breast cancer, accounting for almost one-third of all malignancies among women(18). 1.5 million women are recognized with BC every year, matching to the World Health Organization (WHO), and the incidence rate is on the rise around the globe(19). Research confirms that preventative measures with minimal risk can benefit women with BRCA1 or BRCA2 gene mutations with identifiable highly penetrant mutations. According to Fackenthal and Olopade, BRCA1 and BRCA2 germline mutations are highly predictive of BC development and contribute to BC risk within a particular population, depending on their prevalence and penetrance(20).

A BRCA1 or BRCA2 mutation can be found in about 1 in 2 women who have two or more relatives with breast and/or ovarian cancer. Since one in 18 women with at least one relative who has a detectable mutation hold an inherited susceptibility to breast cancer, it's believed to be a multifactorial process. Unidentified genetic variants may be to blame(21, 22). A review of recent studies carried out in conjunction with large consortiums has able to the detection of new genes or genomic regions associated with BC susceptibility.

A number of genetic factors related to BC risk

have not been fully characterized, and are most likely the result of combinations of low-penetrance genetic variants that are common in societies. Using genome-wide association studies among European populations, these single nucleotide polymorphisms (SNPs) were identified in eight genes including TNRC9, LSP1, FGFR2, CASP8, MAP3K and rs10941679 on 5p12, and rs313281615 on 8q24, and rs13387042 on 2q35(23-29). An estimate by a polygenic pattern indicated that seven of the eight low-penetrance genes probably illustrate about 5% of the genetic risk for breast cancer, with the eighth SNP in 5p12 explaining the remaining 2% of the genetic risk. Studies suggest that the pathologic lineament of BC can be influenced by common genetic variants. As a result, deCODE has developed a test that identifies the seven original SNPs in breast cancer. There are five SNPs found in the genome-wide community studies (GWAS) (5p12, TNRC9, 2q35, 8q24, and FGFR2) that generally confer estrogen receptor-positive BC risk to postmenopausal white women of European descent, and it is evaluated that these seven markers report for 60% of all BCs (30, 31).

Interventions don't always succeed because of individual genetic differences and varying sensitivity to modifiable and environmental influences. It is increasingly evident that genetic susceptibility is the primary determinant of the response to intervention and prevention. In addition to behavior modification, these investigators apply a series of preventive measures, including primary detection and active monitoring for genetically vulnerable persons, noninvasive therapies for cancer in early-stage, and prophylactic and therapeutic interventions designed to slow disease development. In terms of health care, individualized preventive strategies can be designed and implemented based on the molecular characterization of breast cancer. The importance of personalized medicine when treatment patients with BC is illustrated by the role of CYP2D6 genotyping (polypeptide 6, cytochrome P450, subfamily D, family 2) (32). BC patients who have steroid receptor-positive disease are usually treated with tamoxifen (endocrine therapy). In addition to turning tamoxifen into its active metabolites, cytochrome P450 forms 4-hydroxytamoxifen and endoxifen(33).

When compared to tamoxifen, these metabolites have an affinity for the steroid receptor that is two orders of magnitude greater. Inhibiting proliferation is the main effect of these compounds. BC recurrence has been linked to CYP2D6 variants, severely impaired CYP2D6, and poor metabolizers(34). One could make intelligent clinical decisions about the use of powerful CYP2D6 inhibitors that could inactivate active metabolites. CYP2D6 genotyping is being used in pharmacogenomics-based approaches to

get a sense of a person's metabolizer phenotype; therefore, ethical issues must be addressed beforehand. Information about treatment strategies should be provided to patients and their caregivers. Patients with poor CYP2D6 metabolizing ability can benefit from raloxifene treatment(35).

Schroth et al. Provided recommendations for extensive coverage of the high-performance CYP2D6 and MALDI-TOF MS / CAN alleles (matrix laser repulsion mass spectrometry / copy number testing) to reduce phenotypic misalignment(36). As personalized medicine has increasingly been applied to BC treatment based on Erb-B2, promising results have been achieved(37, 38). Nevertheless, a report from a recent research study indicates that CYP2D6 should not be regarded as the sole guidance for tamoxifen dose determination (15, 39, 40). Pre- and permenopausal patients should not receive aromatase inhibitors, according to these investigators. Further study of other alleles than CYP2D6 and identifying patients who are responsive to tamoxifen has been recommended by Fleetman et al. (41). A metabolite of tamoxifen called norendoxifen has been identified as an increasingly promising lead compound as an anti-aromatase agent (42). The other presentations will emphasize the field of expression profiling as a current diagnostic tool and how Oncotype DX and MammPrint can be used for the

purpose of personalized medicine(15, 43, 44).

Taxonomy of BC based on immunohistochemistry

Using immunostaining, we routinely classify invasive ductal carcinomas based on expression of progesterone receptor (PR), human epidermal growth receptor 2 (HER2; alias c-ErbB-2 or, in rodents, Neu) and estrogen receptor (ER), also several cytokeratins (eg, CK5/6) and HER1(45). BC can be classified according to the differential expression of these protein biomarkers (Figure 1) and treated according to their therapeutic approach(46). 70% of invasive breast cancers express the estrogen receptor(47), and the majority also express the progesterone receptor(48, 49).

ER's signal transduction pathway appears intact in BC cells because PR levels are normal(50), but non-consistent ER and PR expression templates are often seen (ER-/PR+ and ER+/PR-). It has been shown that technological improvements have reduced the number of errors in immunohistochemical staining significantly, although many false-negative and false-positive results may still be encountered within the clinical practice for certain types of breast cancer(46, 51). It is generally accepted that the ER+ malignant neoplasms belong to a group called luminal cancers. In addition, these cancers can also be subtyped based on proliferation rate or their HER2 status, giving addition to the ER+/PR+/

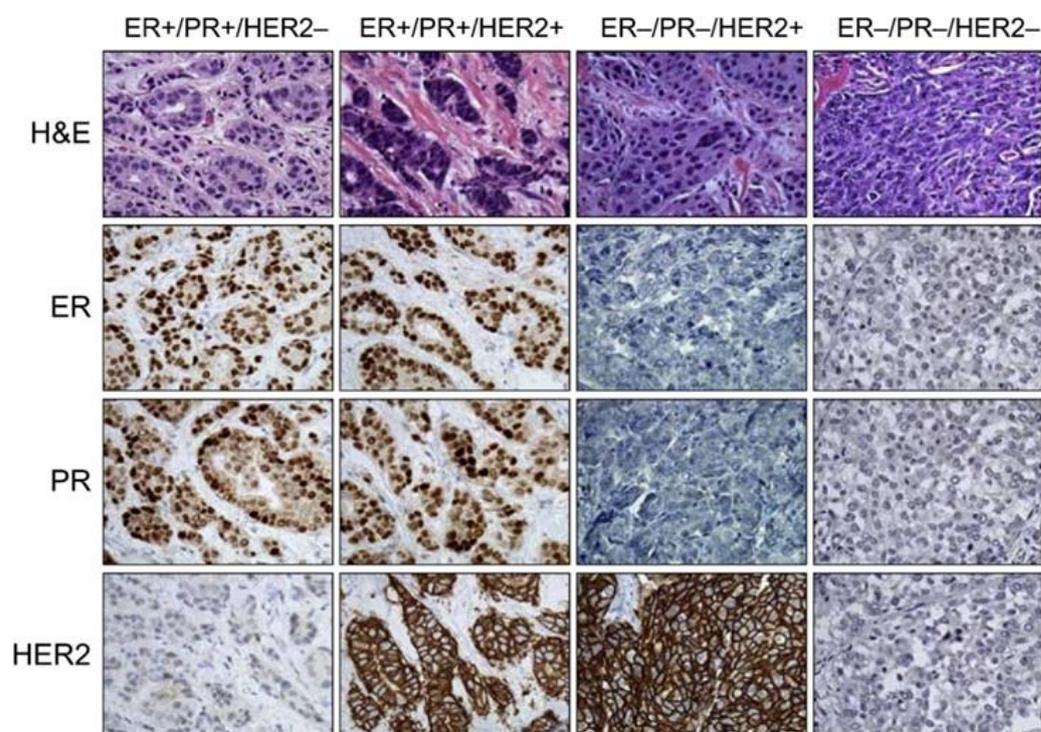


Fig 1. HER2, PR, ER, and expression levels are used to classify invasive breast cancer. There are examples of what constitutes an invasive BC according to the public clinical taxonomy. Histological changes are portrayed by using H&E staining; ER, PR, and HER2 expression are revealed by using immunohistochemistry. Cancers generally fall into four significant clinical categories: ER+/PR+/HER2+, ER+/PR+/HER2-, ER-/PR+/HER2+, and triple-negative ER-/PR-/HER2- [52].

HER2⁻ and ER⁺/PR⁺/HER2⁺ subtypes (Fig 1). The ER⁻ breast cancers are subclassified as HER2⁺ and triple-negative based on HER2 overexpression or gene reinforcement status, basal cytokeratin expression, and EGFR (HER1) expression, giving rise to ER⁻/PR⁻/HER2⁻ (triple-negative) subtypes and ER⁻/PR⁻/HER2⁺ (HER2-enriched) (Figure 1) (52).

Genomic Biomarkers

As Dowsett and Dunbier point out in their review, biomarkers can play an essential role in choosing the best treatment for BC patients. For instance, there have been two multigene expression profiles that have shown a superior capability to prognosticate and predict cancer (53). It has already been proven that Oncotype Dx, a 21-gene reverse transcription PCR-based test, can identify subsets of node-negative, estrogen receptor-positive patients who may benefit from a combination of chemotherapy and antiestrogen therapy (54). Studying tumors of node-negative women, not selected for estrogen receptor status, led to the development of the MammaPrint 70-gene signature (55, 56). Compared with patients who have experienced a relapse within the first 10 years, those whose tumors have been free of disease for ten years exhibit different characteristics. MammaPrint and Oncotype DX both allow BC patients with node-negative disease to be more accurately identified as the type of patient who does not require additional treatment, helping to prevent them from receiving harmful therapies. The two assays were approved by the FDA, and they are being evaluated for use in patients with node-negative breast cancer. In the next decade, genomic markers will most certainly become more predictive and prognostic, as well as older biomarkers such as Ki67 gaining traction. In addition to identifying biomarkers that predict response to special therapies, Oncotype Dx and MammaPrint are proving to be successful. It was discovered that transcriptional profiling could be applied to the analysis of genomic signatures of the tumour in order to predict the response to the T-FAC helper chemotherapy regimen by Hess and colleagues (57). Trastuzumab has been included as adjuvant therapy for the treating of HER2-positive BC over the past decade, and this has been significant. Combining the drug trastuzumab with chemotherapy to reduce recurrence rates has been shown to be very effective. Trastuzumab is a monoclonal antibody that targets the HER2 protein (58).

Developing drugs based on genomics

Pharmacogenomics is gaining increasing attention as a potential clinical tool, especially in oncology, where chemotherapy agents have a limited therapeutic window as well as intense drug toxicities that may pose life-threatening consequences. Women remain worried

about the short and long-term toxicities of treating even though improvements in helper chemotherapy have led to a significant decrease in relapse and mortality for breast cancer. As a consequence, the effects of modern chemotherapies are much greater in women with tumors that lack the estrogen receptor than in those that have estrogen receptors in their tumors, and some of them may no longer need chemotherapy. As an instance, the mortality risk for dose-dense cyclophosphamide/doxorubicin in conjunction with dose-dense paclitaxel (as in INT C9741) versus low-dose cyclophosphamide/doxorubicin/5-fluorouracil was reduced by 55% in women with estrogen receptor-negative tumors versus only 23% in estrogen receptor-positive tumors (59). It is therefore feasible that women with hormone receptor-negative BC could have a better outcome with the right composition of highly efficacious and less toxic chemotherapy. As pointed out by Tan et al., hormonal therapies may be more effective in certain populations by giving appropriate doses that take into account genetic variants that impact metabolizing enzymes. With the right compound of highly efficacious and less toxic chemotherapy, women with hormone receptor-negative BC may be able to find extra hope and victory in their battle against the disease. As pointed out by Tan et al., hormonal therapies may be more effective in certain populations by giving appropriate doses that take into account genetic variants that impact metabolizing enzymes (60).

Personalized BC Therapy: Future challenges and perspectives

With the advent of personalized medicine, the cost of treatment is also increasing, and health care is more costly when more experiments are done to recognize the illness and when customized treating is used. Personalized medicine will benefit the development of disease-prevention approaches in the long term since it provides information about an individual's health status and response to different interventions and treatments. Private health insurance covers genetic tests for only 5% of all patients. Under the current health care delivery system, this raises concerns about the effectiveness of personalized medicine in the United States. Personalized medicine costs are accounted for much smaller numbers of individuals than premiums are calculated for large populations. Large-population models need to be revised in order for personalized medicine to succeed. Precision diagnoses are less expensive in the long term, as they prevent unessential and ineffectual treatments, barricade adverse events, and deliver more efficient targeted therapies. The "pay for performance" concept will also be promoted as well as health care cost reductions. Further considerations to consider for implementing personalized medicine are ethical issues

Table 1. A summary of individual genetic factors that can be effective in the patient’s personal treatment

Genes	CASP8	SNP	rs13387042 on 2q35
	FGFR2		
	TNRC9		rs313281615 on 8q24
	MAP3K1		
	LSP1		rs10941679 on 5p12
	CYP2D6		
Biomarkers	ER	Molecular phenotype	ER+/PR+/HER2-
	PR		
	HER2		ER+/PR+/HER2+
	CK5/6		ER-/PR-/HER2+
	Ki67		ER-/PR-/HER2-

and genetic testing. Data concerning these topics should also be collected and analyzed.

In order to integrate data and draw reasonable consequence from it, a high degree of cooperation between specialists is required. In addition to customizing treatments and drugs based on a person’s unique characteristics, personalized medicine considers capacity to disease, somewhen years before the disease has fully developed (for example, before cancer has spread). Before personalized medicine can be implemented in action, additional perspectives of the infrastructure must be established. PLX4032 and ipilimumab are genetically-based drugs that have improved survival rates for patients with melanoma.

With the advancement of personalized medicine, denotation and therapeutic markets are expected to prosper. Additionally, other areas besides core products and services should benefit as well. The markets covered include complementary and alternative medicine, nutrition and wellness, fitness equipment, organic care, nutraceuticals, disease management, record data entry, and telemedicine.

Future research will be based on epidemiological studies that follow a “bench to bedside” approach. First-time clinical trials will experiment the newly discovered intermediation from preclinical trials. In this phase, population studies and clinical studies will be conducted to determine whether genetic and non-genetic factors are prevalent, associated, interacted, sensitive, specific, and predictive.

There are now recent findings from the Atlas of the Cancer Genome Network that indicate that individual breast cancers have distinct molecular characteristics whether they belong to the same molecular

classification or not, regardless of whether they are found next to other breast cancers (using cluster analysis) (61). This is similar to what has been proven for gene mutations, pathway activation, copy number changes, and proteomics data(61). There may also be molecular differences between BC groups that make treatment ineffective or lead to resistance to a treatment regimen(52).

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