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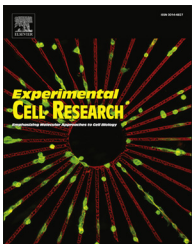

Review Article

# Individualizing breast cancer treatment—The dawn of personalized medicine

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ABSTRACT

Identification of breast cancer not being a single disease but backed by multiple heterogeneous oncogenic subpopulations is of growing interest in developing personalized therapies to provide optimal outcomes. Through this review, we bring attention to evolution of tumor and microenvironment heterogeneity as a predominant challenge in stratifying therapies. Establishment of a 'precancer niche' serves as a prerequisite for genetically initiated cells to survive and promote neoplastic evolution towards clinically established cancer through development of tumor and its microenvironment. Additionally, continuous evolutionary interplay between tumor and recruited stromal cells along with many other components in the tumor microenvironment adds up to further complexity in developing targeted therapies. However, through continued excellence in developing high throughput technologies including the advent of single-nucleus sequencing, which makes it possible to sequence individual tumor cells, leads to improved abilities in decoding the heterogenic perturbations through reconstruction of tumor evolutionary lineages. Furthermore, simple liquid-biopsies in form of enumeration/characterization of circulating tumor cells and tumor microvesicles found in peripheral circulation, shed from distinct tumor lesions, show great promise as prospective biomarkers towards better prognosis in tailoring individualized therapies to breast cancer patients. Lastly, by means of network medicinal approaches, it is seemingly possible to develop a map of the cell's intricate wiring network, helping to identify appropriate interconnected protein networks through which the disease spreads, offering a more patient-specific outcome. Although these therapeutic interventions through designing personalized oncology-based trials are promising, owing to continuous tumor evolution, targeting genome instability survival pathways might become an economically viable alternative.





## Contents



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## Introduction

Breast cancer, the most common form of cancer in women, an estimated 232,340 new cases and 39,620 deaths in 2013 in the US alone [1] with worldwide more than 1,300,000 cases and 450,000 deaths each year [2] was first documented in ancient Egyptian writings, the Edwin Smith Papyrus (copy of trauma surgery) where 8 cases of breast malignancy were recorded. Treatments at that time were restricted to cauterization of the breast at the tumor site until the late seventeenth century when French surgeon Jean Louis Petit and Scottish surgeon Benjamin Bell were able to remove the diseased breast tissue and lymph node along with the malignant tumor. This was initially followed by mastectomy and then, with subsequent impressive therapies such as lumpectomy, chemo and radiotherapy, providing better treatment options; increasing average survival rates of breast cancer patients. Interestingly, in spite of enormous failure rate and lethal side effects, chemotherapy still finds the widest application in terms of treatment amongst all established therapies. Prominent chemotherapeutic drugs including doxorubicin, cisplatin, gemcitabine, bevacizumab and trastuzumab are in practice today for breast cancer management. However, worldwide usages of all established cancer therapies have reported substantial inter-patient differences in therapeutic response. Any particular therapy can prove to be effective in some patients but ineffective in others with some experiencing adverse drug reactions (ADRs) resulting in patient morbidity and mortality, while some remain unaffected [3]. Even the blockbuster drugs (generating more than $1 billion dollar annually) show efficacies in 40–60% of the patients whereas 50% (estimated) of cancer patients fail to get benefited from chemotherapy. Reasons include intrinsic or acquired multidrug resistance (MDR) [4,5], DNA polymorphisms [6] and most importantly the presence of inter-tumor heterogenic subpopulations, responding to radio, chemo and targeted therapies differently amongst different individuals within the same cancer type. This inter-individual difference in response to drug treatment thus strongly commends a paradigm shift from "One Drug Fits All" strategy towards "Personalized Medicine". This can be achieved through identifying genetic variants of the same disease and tailoring targeted therapies towards the entire spectrum of mutations that collectively represent individual tumor sub-populations [7,8], providing improved therapeutic outcomes.

## Science driving personalized breast cancer therapies – advancements and future perspectives

*Identifying novel genetic subsets of breast cancer genome: disease stratification*

Of late, breast cancer is considered not to be a single disease but a conglomerate of multiple subsets of genetically definable or molecularly distinct syndromes, exhibiting different natural histories requiring different treatments for every patient or a particular patient group. Thus a continuous approach has been to decode the heterogeneity into better characterized smaller subsets to be used in predicting therapeutic and prognostic outcomes making way for personalized therapies [9]. Presently, this heterogeneity is categorized clinically into estrogen receptor positive ($ER^+$), human epidermal growth factor receptor 2 (HER2; also called ERBB2 or neu) positive ($HER2^+$) and triple-negative ($ER^-$, progesterone receptor negative ($PR^-$) and $HER2^-$) [2,10] with six independent intrinsic molecular subtypes such as normal-like, HER2-enriched (HER2E), luminal (A and B), basal A/basal-like and basal B/claudin-low being reported in the past few years [10–12]. Although a standard approach towards classifying breast cancers relies on gene expression patterns, immunohistochemistry (IHC) based classification is preferred many a time (Fig. 1) [13] due to high expense and technical difficulties involved with gene expression methods. However, to bring greater clarity into the robustness of sensitive and accurate sub-classifications, different approaches such as pathway-assisted clustering of plasma samples of breast cancers [14] and newly developed three-gene subtype classification model (SCM), SCMGENE have been explained [15]; elucidating lesser variability and simplicity over other complex classifiers.

The molecular architecture of breast cancer genome is however revisited again and again with the help of high-throughput technologies such as the ever-evolving next-generation sequencing (NGS) shown in Figs. 2 and 3 [16], to extract the quantum of

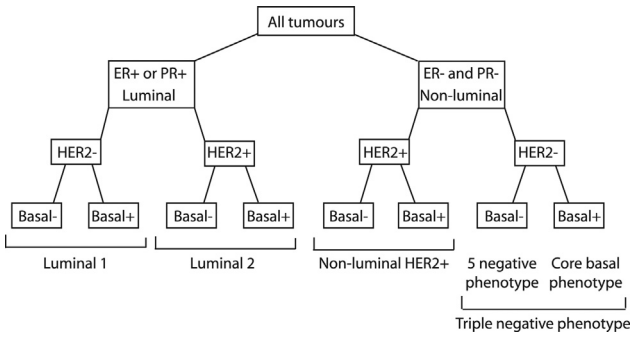


**Fig. 1 – IHC based breast cancer subtype classification. Two major subtypes are the luminal (ER+ or PR+) and non-luminal tumors (ER- and PR-). These are further sub-classified into luminal 1 (HER2-), luminal 2 (HER2+), non-luminal HER2+ and triple-negative phenotype (TNP). The luminal 1 and 2 types were further sub-classified into luminal basal-, luminal basal+ and the TNP into core basal group (CBP: CK5/6 or EGFR+) and 5 negative phenotype (5NP: ER-, PR-, HER2-, cytokeratin (CK) 5/6-, and EGFR-) (Reprinted from Public Library of Science: [Plos Medicine] Blows et al. [13]).**



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