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MOLECULAR AND GENETIC SUBTYPING OF BREAST CANCER: THE ERA OF PRECISION ONCOLOGY

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Abstract – *Objective:* *To examine and summarize the most discussed molecular targets for prognosis prediction in all histological subtypes of breast cancer.*

Materials and Methods: *The contemporary view on breast cancer pathology as heterogeneous disease has changed the therapeutic landscape from a "one size fits all" to a subtype specific treatment approach. We conducted a wide literature review in order to simplify the various findings associated with breast cancer molecular targets and the possible routine clinical implications in the future.*

Results: *The four intrinsic molecular subtypes of breast cancer are luminal A, luminal B, HER2/Neu-enriched and basal-like, with each subtype associated with a specific expression profile. Additionally, there are critical differences among the four molecular subtypes with regard to incidence, response to treatment, disease progression, survival, and imaging features: luminal A tumors have the most favorable prognosis of all breast cancer subtypes, whereas luminal B, HER2/Neu-enriched, and basal-like tumors have poorer clinical outcomes. Additionally, identification of expression-based tumor profiles most/least likely to respond to chemotherapy is changing the landscape of medical oncology.*

Conclusions: *Despite the significant prognostic improvements gained using current "individualized" therapeutic approaches, not all patients benefit as there are deeper sub-classes within the intrinsic subtypes which alter treatment responses. Thus, additional gene expression profiling of each subtype is essential in providing information about more accurate behavior of the different breast tumors, thus offering hope for an even more specific precision oncology. Such potential markers must not only demonstrate analytical and clinical validity along with clinical utility, but also provide wide availability and reproducibility.*

KEYWORDS: *Breast cancer, Molecular subtypes, Next generation sequencing, Breast tumor profiling, Liquid biopsy.*

THE CLINICAL AND HISTOLOGICAL SUBTYPES OF BREAST CANCER

The majority of breast cancers (around 2/3 of the cases) arise from the epithelial cells lining the lactiferous ducts and form the so-called ductal carcinoma. The remaining one-third of breast carcinomas have been shown to originate from the milk producing lobular epithelium, thus forming the so-called lobular carcinoma. Other less common histological groups are identified as inflammatory, medullary, apocrine, mucinous and tubular carcinomas (Figure 1)[1]. These subtypes, though rarer in occurrence, still have

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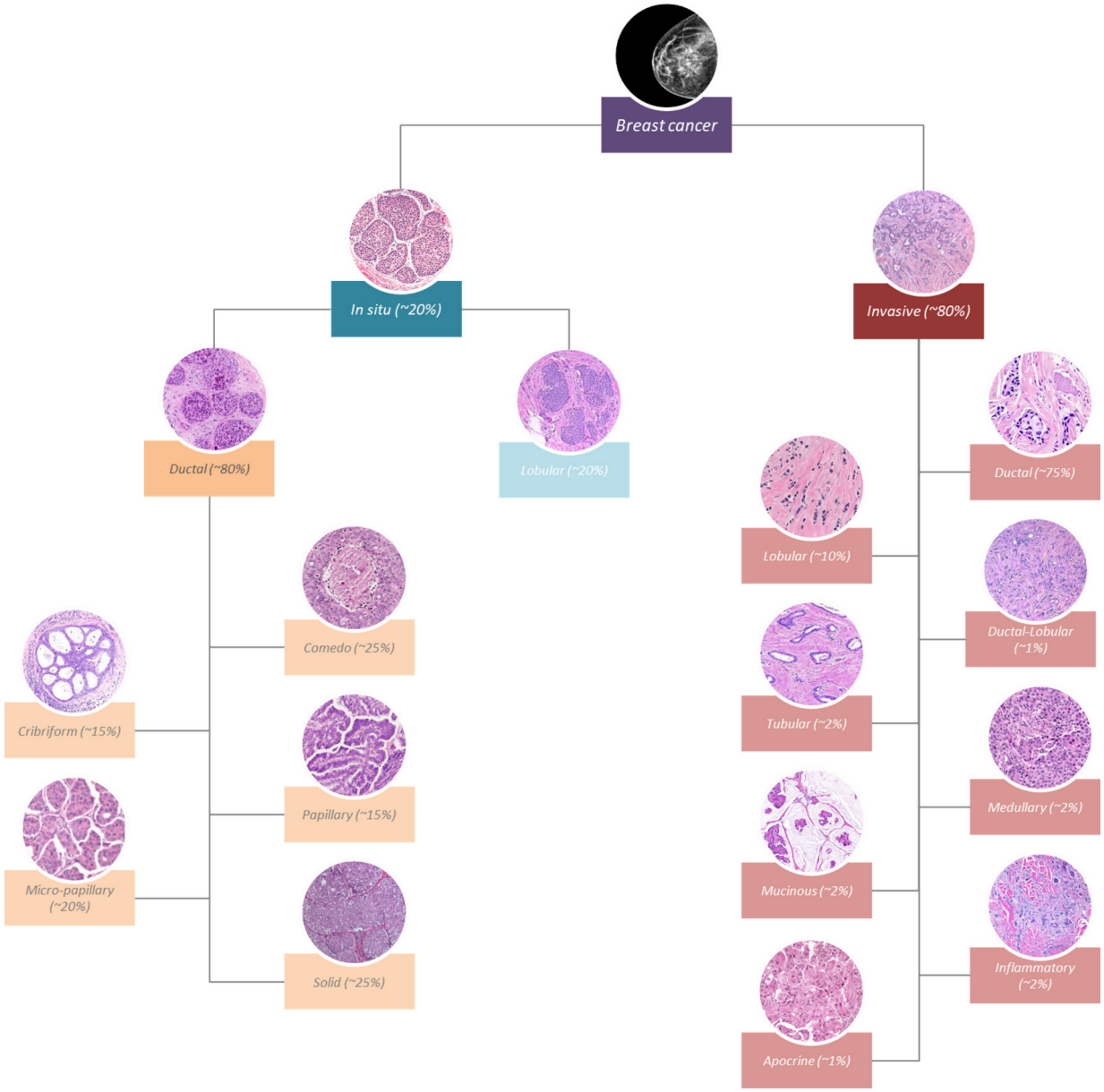

Fig. 1. Histological stratification of breast cancer. The majority of breast carcinomas arises from ductal epithelial cells (~75%) and tends to involve the surrounding connective tissues (invasive ductal carcinoma) and metastasize to the distant organs of the body. The subtypes listed indeed have an impact on clinical outcome, with some demonstrating better prognosis (mucinous) over others (inflammatory). The low percentage of in situ tumors (~20%) is attributed to the fact that screening programs are not organized worldwide in addition to the initial and long silent period this disease presents with.

a significant role in prognosis and treatment approaches. Previously, pure histological morphology was the "gold standard" in diagnosing and subsequent determination of the tumor type and grade, resulting in treatments relying mainly on surgery, radiation, and systemic chemotherapy. Sadly, these approaches were the only options which could be offered to breast cancer patients at the time and the achieved therapeutic outcomes being quite inconsistent.

MOLECULAR SIGNATURES

Since the introduction of neoadjuvant systemic chemotherapy regimens in the 70's and their current widespread application, breast cancer mortality has seen a significant reduction worldwide[2,3]. Nonetheless, despite these unified treatment protocols, many patients still do not receive optimal treatments and are either over or undertreated. Due to the advancements gained in molecular expres-

sion techniques, it was found why breast tumors with similar histopathological appearance can exhibit different clinical presentations, disease aggressiveness, treatment response and prognosis. The end of the 20th century saw the emergence of genomics and transcriptomics, which provided the necessary tools to simultaneously measure the expression of thousands of genes. In turn this has led to the identification of biology-based prognostic and predictive tumor profiles, several of which have been clinically validated and are currently used routinely. Thus, the pursue of a more patient centric approach, especially in the context of systemic therapies, had begun.

A prognostic factor, by definition, provides information on the clinical outcome, independent of therapy, at the time of diagnosis. Such markers are usually indicators of growth, invasion, and metastatic potential. By contrast, the information a predictive factor provides relates to the likelihood of response to a given therapeutic modality[4]. Such subtyping, in the context of breast cancer, allowed for the molecular characterization of the disease into intrinsic molecular variants (Figure 2), creating a paradigm shift in the clinical approach to treatment and prognosis (Figure 3)[5]. Gene expression patterns demonstrated that:

1) Luminal-like tumors have the highest incidence out of all breast cancers (~65%). They are characterized by a high genetic expression of the estrogen receptor (ER) in addition to other luminal epithelial genes, further dividing this sub-class into Luminal A and B based on high progesterone receptor (PR) and Ki-67 expressivity, respectively. Generally, luminal tumors, especially luminal A, have a more favorable prognosis[6].
2) HER2 (Human epiderma growth factor 2) enriched tumors, with an incidence of ~20%, are characterized by the amplification of the oncogene *ErbB2* in addition to having low levels of ER expression and are generally associated with a poor prognosis in the pre-targeted therapy era. Interestingly, about a third of HER2-enriched tumors are clinically HER2-negative[7].

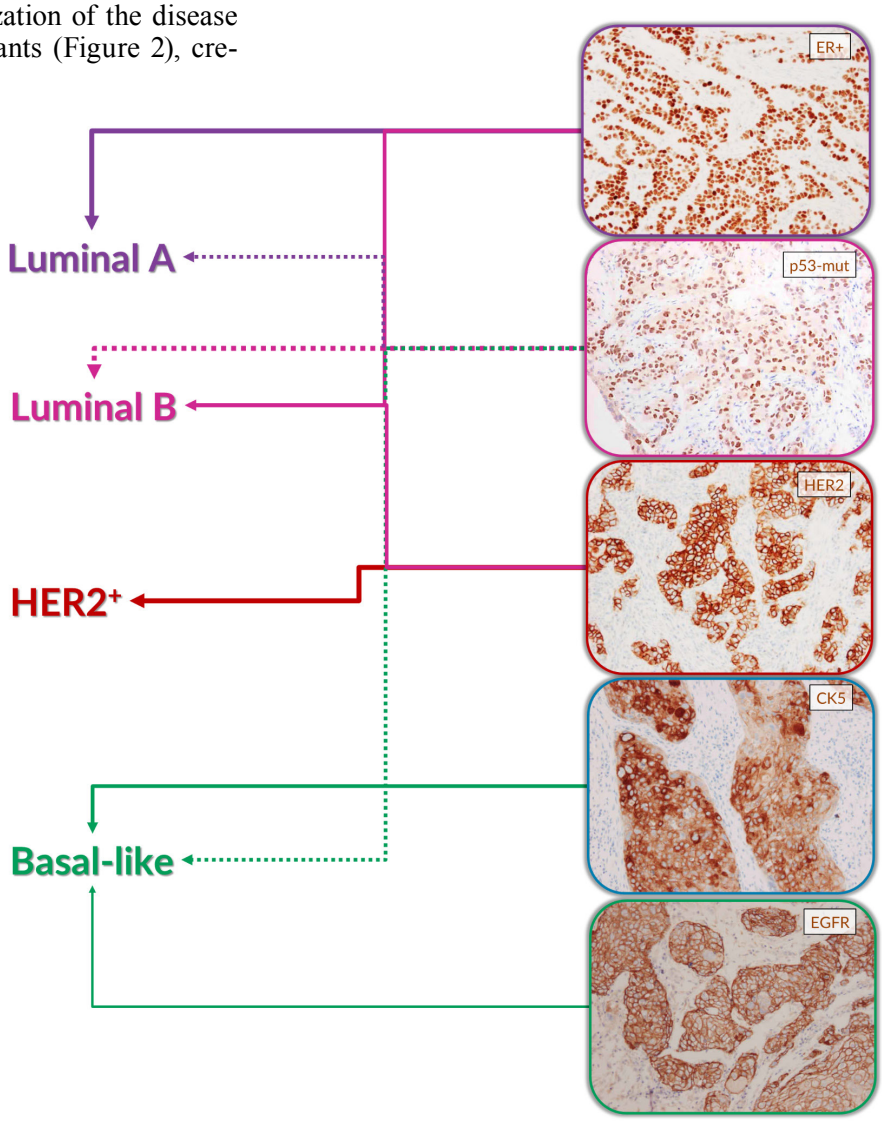

Fig. 2. The intrinsic molecular subtypes of breast cancer. Molecular portraits of breast cancer subtypes are listed on the left and examples of gene amplification (HER2 enrichment) and aberrant protein expression (p53, cytokeratin 5 and EGFR by IHC) are given. The importance of the connection is assessed by the correspondence in the connection of arrows. ER: estrogen receptor, EGFR: epidermal growth factor receptor.

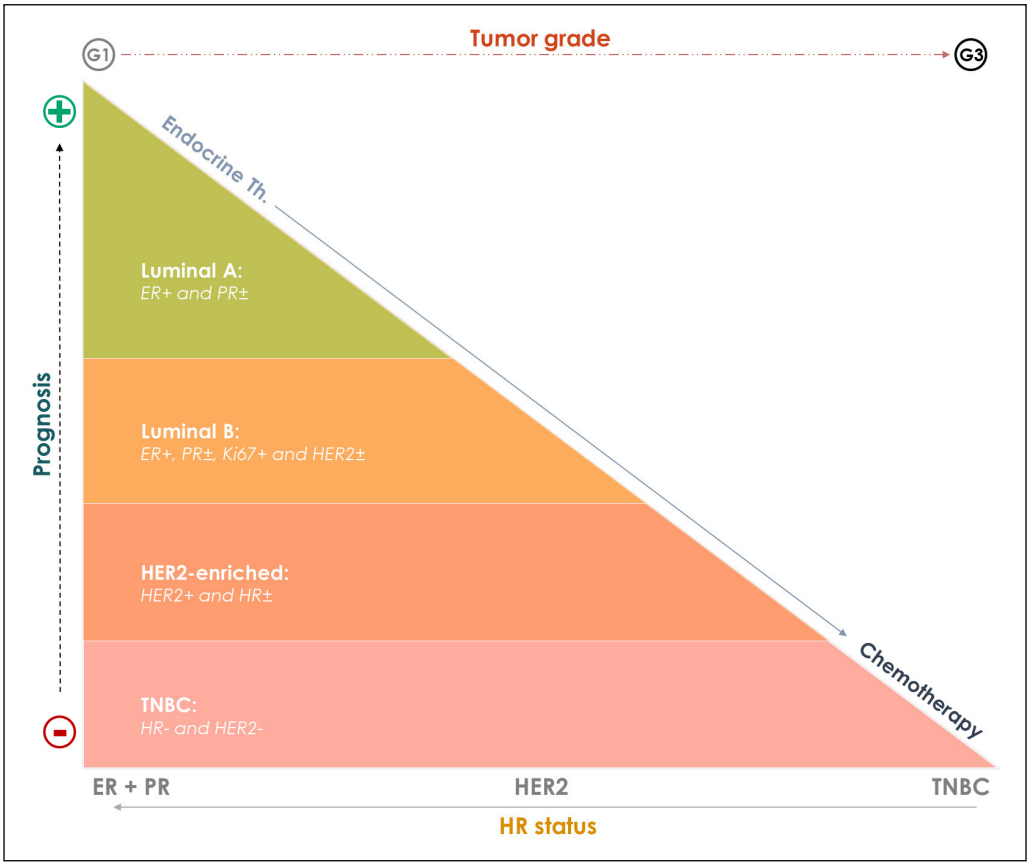

Fig. 3. Breast cancer subtypes, tumor grade and prognosis. The tumor grade reflects an inverse proportion to HR status. The prognosis in the Luminal A subtype is better due to a positive response to hormonal therapies. In contrast, TNBC shows higher tumor grade, lack of hormonal expression and is associated with a poorer prognosis. HR: Hormone receptor, HER2: Human epidermal growth factor receptor 2, TNBC: Triple-negative breast cancer.

3) Basal-like tumors, which comprise ~15% of all breast cancers, demonstrated expression profiles similar to basal myoepithelial cells. They often fail to express ER and many of the other genes generally associated with the presence of ER and are associated with higher incidence of p53 mutations, visceral metastases, higher risk of early recurrence and worse prognosis[8]. Other ER^{-ive} tumors include the claudin-low[9] and interferon-rich[10] subtypes.

With the increasing availability of large-scale genomic sequencing, the identification of expression-based tumor profiles most/least likely to respond to chemotherapy has become a reality. Such platforms are either RT-qPCR or microarray based with both providing adequate quantitative gene expression data[11-13]. However, profiling should be used on a case-by-case basis while using a single platform per patient in order to avoid discordant results. Some of the currently approved for clinical practice platforms are provided in Table 1[14,15]:

1) The Oncotype Dx 21-gene recurrence score (RS) - developed by reverse transcribing and then quantifying the 250 most promising candidate genes described in the literature. The resulting mathematical formula included 16 candidate and 5 reference genes and is currently used to predict relapse despite treatment with a selective estrogen receptor modulator in HR positive patients [16].
2) Predictor Analysis of Microarray 50 (PAM50) intrinsic subtype has an already established prognostic and predictive role in both nonmetastatic and metastatic breast cancer in identifying patients. It was designed to determine the intrinsic subtype of a cancer using only 50 prespecified genes via microarray technology and has shown encouraging results in predicting prognosis for node-negative breast cancer patients[17].
3) Another RNA-based prognostic assay, which utilizes RT-qPCR of 11 genes (including 3 reference genes) to calculate a prognostic score, is the EndoPredict (EP) test. This assay has

TABLE 1. Commercial panels for prognostic evaluation of BC patients using mRNA gene expression.

Panel	*Technology*	*Genes*
Oncotype DX	RT-qPCR	ACTB; BAG1; BCL2; BIRC5; CCNB1; CD68; CTSL2; ESR1; GAPDH; GRB7; GSTM1; GUS; HER2; Ki-67; MMP11; MYBL2; PGR; RPLPO; SCUBE2; STK15; TRFC
Mammaprint	NGS	AA555029_RC; ALDH4A1; AP2B1; AYTL2; BBC3; C16orf61; C20orf46; C9orf30; CCNE2; CDC42BPA; CDCA7; CENPA; COL4A2; DCK; DIAPH3; DTL; EBF4; ECT2; EGLN1; ESM1; EXT1; FGF18; FLT1; GMPS; GNAZ; GPR126; GPR180; GSTM3; HRASLS; IGFBP5; JHDM1D; KNTC2; LGP2; LIN9; LOC100131053; LOC100288906; LOC730018; MCM6; MELK; MMP9; MS4A7; MTDH; NMU; NUSAP1; ORC6L; OXCT1; PALM2; PECI; PITRM1; PRC1; QSCN6L1; RAB6B; RASSF7; RECQL5; RFC4; RTN4RL1; RUNDC1; SCUBE2; SERF1A; SLC2A3; STK32B; TGFB3; TSPYL5; UCHL5; WISP1; ZNF533
PAM50	Nanostring	ACTR3B; ANLN; BAG1; BCL2; BIRC5; BLVRA; CCNB1; CCNE1; CDC20; CDC6; CDCA1; CDH3; CENPF; CEP55; CXXC5; EGFR; ERBB2; ESR1; EXO1; FGFR4; FOXA1; FOXC1; GPR160; GRB7; KIF2C; KNTC2; KRT14; KRT17; KRT5; MAPT; MDM2; MELK; MIA; MKI-67; MLPH; MMP11; MYBL2; MYC; NAT1; ORC6L; PGR; PHGDH; PTTG1; RRM2; SFRP1; SLC39A6; TMEM45B; TYMS; UBE2C; UBE2T
EndoPredict	RT-qPCR	AZGP1; BIRC5; CALM2; DHCR7; HBB; IL6ST; MGP; OAZ1; RBBP8; RPL37A; STC2; UBE2C

Abbreviations: RT-qPCR, reverse transcriptase quantitative polymerase chain reaction; NGS, next-generation sequencing; PAM50, prediction analysis of microarray 50.

shown promise in the identification of patient subgroups with ER^{+ive}, $HER2^{-ive}$ tumors that have a very low risk of recurrence without adjuvant chemotherapy[18].

Current criteria for recommending genetic testing includes: triple negative breast cancers in women <60 years old, invasive carcinomas diagnosed in women <35 years of age or male breast cancer diagnosed at any age[19]. Moreover, studies have shown the advantages in gaining additional risk categories from such testing in early ER-positive, HER2-negative disease, thus allowing for better treatment optimization in patients harboring this sub-type of breast cancer[15]. Encouragingly, the field is undergoing constant evolution with intensive research efforts focusing to define the clinical utility and the indications for each of the prognostic profiles in routine practice and with the emergence of new testing panels and platforms, additional prognostic and predictive tumor profiles will likely be defined.

Areas of significant ongoing research are the elucidation of the genetic drivers (Table 2) responsible for tumor progression, drug resistance and metastases[20]. Current interests lie in identifying specific genomic landscapes that may give rise to novel cancer target therapies. Studies using next generation sequencing (NGS) have shown promising, prognostically significant, tumor subgroups in patients with both early and difficult to treat advanced diseases[21,22]. Breast cancer database analyses suggest that ~40 recurrent driver alterations exist, with alterations in *ERBB2*, germline *BRCA1/2* and *PIK3CA* demonstrating the highest level of evidence relating to antitumor activity and improved outcome in patients receiving the relevant targeted therapies[23]. A "real-world" setting study has demonstrated that even though some patients benefit from NGS analysis, the logistics and expenses are currently sub-optimal[24]. Thus, even though various NGS platforms are commercially available for analysis of breast tumors (e.g. mammaprint), routine clinical application is not yet fully supported and currently should be utilized on a case-by-case basis when additional information is needed in order to stratify the patient, based on risk profiles, in order to decide whether they are going to benefit from adjuvant chemotherapy.

A late event in the natural history of breast cancer, indicating a very poor prognosis, is the presence of overt metastases. In contrast, the much earlier detectable circulating tumor cells located in the bloodstream (defined as ≥1 cells/7.5 mL whole blood for early disease) and/or in the bone marrow, an early sign of tumor spread, have been associated with independent prognostic and predictive values, especially in patient groups presenting with a local disease[25]. Not only their quantity aids in estimating therapeutic outcome,

TABLE 2. Known breast cancer genetic drivers.

Gene	*Relative breast cancer Risk*	*Clinical Behavior*
ATM	x3	Breast MRI screening; consider RRM based on family history
BRCA1	x10	Breast MRI screening; recommend adnexectomy, discuss RRM
BRCA2	x10	Breast MRI screening; recommend adnexectomy, discuss RRM
CDH1	x5	Breast MRI screening; consider RRM based on family history
CHEK2	~x3	Breast MRI screening; consider colonoscopy every 5 years at 40, or 10 years before age of cancer diagnosis
NBN	~x3	Breast MRI screening
NF1	~x3	Breast MRI screening
PALB2	~x3	Breast MRI screening; discuss RRM
PTEN	~x5	Breast MRI screening; discuss RRM
STK11	~x5	Breast MRI screening
TP53	~x10	Breast MRI screening; discuss RRM; whole-body MRI, colonoscopy, complete blood count, and other tests

Several genetic mutations have been linked with an increased risk of breast cancer development. The table provides the most common culprits, the associated relative risk and current clinical practice recommendations. Based on the findings described in (20). *Abbreviations:* MRI: Magnetic resonance imaging, RRM: Risk reducing mastectomy. * = Relative risk calculated age varied between studies.

in both the adjuvant and neoadjuvant settings[26,27], but also epi/genetic profile analyses may add additional value. Interestingly, some of the mutated genes in breast cancer circulating cells (eg. *ER*, *PIK3CA*, *KRAS*, *ESR1*, *ERBB2* and *TP53)* are not aberrantly altered in the primary tumor samples, hinting towards biological heterogeneity, most likely a result of microenvironmental/metabolic differences and cellular adaption mechanisms[28]. However, their role in guiding routine clinical management has not been defined as evidence is scarce and besides linking cellular quantity to poorer prognosis, no new specific genetic patterns have been found thus far.

Currently the main prognostic criteria are based on disease stage and tumor morphology. Other factors like serum CA15-3 or CEA, can sometimes correlate with clinical or radiologically defined disease burden, but neither, can accurately predict therapeutic response[29]. The incorporation of intrinsic tumor subtypes aids in predicting therapeutic repose, nonetheless consistency is lacking. Via the utilization of a genomic analysis based multidisciplinary personalized treatment approaches, the possibility to attain maximum clinical benefits and improved outcomes in patients with either advanced stage disease or a rare tumor variant, is a reality [24]. Combining several of the above approaches may hone cancer therapies even more, providing accurately matched therapies to specific genomic landscapes. Unfortunately, there is a lack of well-defined tools allowing proper interpretation of genomic alterations detected by NGS when combined with protein expression of tumors [23]. Perhaps, convolutional neural network-based computer algorithms might provide a solution, as studies have successfully identified breast tumor features predictive of treatment efficacy[30].

CONCLUSIONS

The landscape of breast cancer molecular alterations is heterogenous. Utilization of some of the above-mentioned prognostic and predictive factors allows for a more detailed patient stratification and identification of matching therapies which would benefit individuals presenting with a specific disease subtype. At the same time, applying mentioned methods will protect patients presenting with a poor therapy-responding profile, ultimately sparing them from the unnecessary exposure to the potentially toxic and expensive therapies. It is a matter of time and continues research for protocol standardization and emergence of additional markers for deeper tumor subclassification in order to achieve accurate precision oncology, that is, targeting cancer therapies based on specific genetic profiles. Additional value may be brought by future applications of high-throughput analyses evaluating variations in tumor proteins, genome-wide germline variability and cellular metabolism.

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