

Review

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Review

miR125-Centered ceRNETs In Breast Cancer. Clinical, Molecular and Ethical Aspects in Personalized Medicine

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Abstract: According to the International Agency for Research on Cancer (IARC) of the World Health Organization (data of year 2020), Breast Cancer (BC) is one of the most common cancer types worldwide, with large geographical variations occurring between countries and world regions and highest incidence rates in countries that have undergone economic transition. The risk factors for BC include women ageing, genetic mutations, reproductive history, dense breast tissues, personal history of BC or specific non-cancerous breast diseases, family history of breast or ovarian cancer, previous treatment using radiation therapy, and exposure to hormone-like drugs such as diethylstilbestrol (DES). Additional risk factors include being overweight or having obesity after menopause, and taking hormones. MicroRNAs (miRNAs or miRs) are small non-coding RNA molecules that have an essential role in gene expression and are significantly linked to the tumor development and angiogenesis process in different types of cancer, including BC. In the last years, the knowledge about miRNAs role in BC has significantly improved, and complex interactions among coding and non-coding RNA has been elucidated. In this context, an increasing number of papers had been published regarding the role of miR-125 in BC. In this review, we summarize the state-of-the-art about this research topic in addition to elaborating on the need to set novel ethical and legal standards for the governance of such innovations in healthcare.

Keywords: breast cancer (BC); MicroRNAs (miRNAs); non-coding RNA; competing endogenous RNA (ceRNA); personalized medicine; ethical and legal challenges

1. Introduction

Breast Cancer (BC) is the most commonly diagnosed cancer type, accounting for 1 in 8 cancer diagnoses worldwide. Available data suggest that incidence and mortality in high-resource countries has been declining whereas incidence and mortality in low-resource countries has been increasing [1]. In 2020, there were about 2.3 million new cases of breast cancer globally and about 685,000 deaths from this disease, with large geographical variations observed between countries and world regions. Breast cancer incidence rates are highest in countries that have undergone economic transition, but transitioning countries carry a disproportionate share of breast cancer deaths [2]. In the United States, breast cancer alone is expected to account for 29% of all new cancers in women [3]. The 2018 GLOBOCAN (Global Cancer Data) data shows that age-standardized incidence rates (ASIR) of BC are strongly and positively associated with the Human Development Index (HDI) [4].

2. Clinical features of BC

2.1. Risk factors of BC

A variety of risk factors for breast cancer have been well-established by epidemiologic studies including race, ethnicity, family history of cancer, and genetic traits, as well as modifiable exposures such as increased alcohol consumption, physical inactivity, exogenous hormones, and certain female reproductive factors. Younger age at menarche, low parity, late menopause and older age at first full-term pregnancy may influence breast cancer risk through long-term effects on sex hormone levels or by other biological mechanisms, although recent studies suggest that triple negative breast cancers may have a distinct etiology [5]. Nearly one fourth of all BC cases are related to family history: women, whose mother or sister has a BC, are more prone to this disease [6]. In the past decades the incidence of pregnancy-

associated BC (PABC) increased [7]. Possible explanations are the trend to postpone childbearing and the general increase in the incidence of BC. Young patients with BC and not completed family planning should be referred for counseling about fertility preservation options before the initiation of adjuvant treatment. Both endogenous and exogenous estrogens are associated with the risk of breast cancer. The endogenous estrogen is usually produced by the ovary in premenopausal women and ovariectomy can reduce the risk of breast cancer. The main sources of exogenous estrogen are the oral contraceptives and the hormone replacement therapy (HRT) [8]. Modern lifestyles such as excessive alcohol consumption and too much dietary fat intake can increase the risk of BC as well. Alcohol consumption can elevate the level of estrogen-related hormones in the blood and trigger the estrogen receptor pathways [9].

Women that having extremely dense breast tissue is significantly associated with increased breast cancer risk compared to having scattered dense breast tissue [10]. In this scenario many patients in reproductive age and that have diagnosis of malignancies need to perform a fertility sparing surgery treatment (FST) [11–14] preserving their fertility by oocyte freezing before gonadotoxic treatments [15,16]. As known, a pregnancy following breast cancer does not have a negative impact on prognosis [17]. Women older than forty y.o. planning a family often need to recure to in vitro fertilization program (IVF) with not few pscycological implication in their infertile pathway to get pregnancy [18].

Currently available data disagree on the linkage between combined oral contraceptives (COCs) and other cancers, e.g. liver malignancy risk assessments. Hormonal contraceptives have been reported to increase the risk of not only hepatocellular carcinoma but also intrahepatic cholangiocarcinoma. Still, COCs safety and effectiveness has been recognized, and their effects are reversible. While patients who choose to rely on COCs for birth control ought to be warned of the possibility of carcinogenic side-effects, it should also be pointed out to them that COCs may also decrease the risks of endometrial, colorectal, and ovarian cancers [19,20].

The inherited susceptibility to BC is partially attributed to the mutations of BC-related genes such as BRCA1 and BRCA2 [21]. Additional genes that, during the years, had been implicated in BC pathogenesis include PTEN [22], TP53 [23], CDH1 [24], STK11 [25], CHEK2 [26], PALB2 [27], ATM [28], RAD51C [29], RAD51D [30], BARD1 [31], NF1 [32], BRIP1 [33], CASP8, CTLA4, NBN and, possibly, CYP19A1, TERT and XRCC3 [34].

2.2. BC diagnosis

BC is diagnosed via ultrasonography, which is a standard imaging procedure. In recent years, it has advanced to the point that it can now be used for breast imaging. Ultrasound is a technology used as a follow-up examination to clarify equivocal findings [35,36]. Mammography screening for malignancy is commonly used to detect the disease [37]. Breast MRI (magnetic resonance imaging) is used in conjunction with mammography as a support tool [38]; in this case, MRI can be helpful in deciding whether to have a breast-conserving mastectomy or surgery [39,40]. A biopsy is done when mammograms, other imaging tests, or a physical exam shows a breast change that may be cancer. A biopsy is presently the most affordable way to diagnose cancer. Surely, CT (computerized tomography) scans, MRIs, ultrasound, and PET (positron emission tomography) scans may also give information about extension and position of cancer in the body. Laboratory tests of cancer cells (from biopsy or surgery) and blood tests can also be used to help staging some types of cancer [41]. A recently developed technique is the Digital Breast Tomosynthesis (DBT), that is a subset of the mammography procedure, with the difference that the X-ray tube rotates around a narrow angle (15–60°) from the compressed breast tissue and produces 3D breast imaging information [42]. In the same way, the Contrast-enhanced mammography (CEDM) represents the angiogenic pattern of the masses, which depicts anatomical information of the tissue. The sensitivity of this procedure is high, about 85–90%, but it has a low specificity compared to conventional mammography; also, it has limitations in the diagnosis of ductal carcinoma of the breast [43].

Tumor vascularization depends on the size and severity of the pathology. There are disorders of vascular distribution in malignant breast lesions. Contrast-enhanced ultrasound (CEUS) is used in clinical research to observe different vascular structures. CEUS uses vein injection of gas microbubbles to improve the return of the waves [44]. In ultrasonography, the color Doppler estimates the local blood flow using mean Doppler shift coding in the region of interest, and colors it. Color Doppler imaging heavily depends on technical factors. Vascular flow sensitivity can be optimized through scale reduction by power Doppler imaging (with no flow direction) and by heightening color rate. Since breast lesions are relatively superficial, the vessels can be easily closed when squeezed between the transducer and chest wall [45].

Although MRI is not commonly used for BC imaging, it is a suitable method for screening patients with a high risk of BC (20–25%) [43]. According to the American Cancer Society (ACS), high-risk patients are recommended to be screened annually using MRI imaging. The measure of high risk is for those individuals with mutations in the BRCA1 and BRCA2 genes who have a history of chest radiotherapy at ages 10 to 30 years [46]. Each of these methods has

different subdivisions and their advantages and disadvantages have been discussed. Although there are ways to improve these methods, it should be kept in mind that with the simultaneous use of the capabilities of each imaging technique and their combination, early detection of BC can be significantly improved [47].

2.3. BC staging, grading and classification

The stage of a cancer gives information about its extension and spreading. In the TNM staging system, the acronym stands for tumor, node, metastasis and represents the standard classification of any cancer. The TNM staging system is the most common way to stage BC, too. Staging for breast cancer is very complex. Many different factors are considered before doctors can confirm the cancer stage, and on this basis an appropriate therapy is chosen. The TNMEIO system was suggested by the European Institute of Oncology (EIO) in an effort to include tumor characteristics affecting treatment decisions in the TNM system [48] (Table 1).

Table 1. TNM staging for BC.

Tumor		Node		Metastasis	
Tx	no primary tumor information	Nx	not assessable	Mx	not assessed
T0	no primary tumor evidence	N0	no clinically positive nodes	M0	no evidence
TIS	carcinoma <i>in-situ</i> (primary sites)	N1	single, ipsilateral, size <3 cm	M1	metastasis present at distance
T1	size <2 cm	N2a	single, ipsilateral, size 3-6 cm		
T2	size 2 to 4cm	N2b	multiple, ipsilateral, size <6 cm		
T3	size >4 cm	N3	massive/ipsilateral/bilateral/controlateral		
T4	size >4 cm, pterygoid muscle, base of tongue or skin involved	N3a	ipsilateral node(s), one more than 6 cm		
		N3b	bilateral		
		N4	controlateral		

Perou and Sorlie proposed the “Molecular Classification” terminology in BC for the first time in year 2000 with a comprehensive study showing the differences in gene expression; in this study, BC was divided into different subgroups according to various gene expression [49,50].

All breast cancers these days are tested for expression, or detectable effect, of the estrogen receptor (ER), progesterone receptor (PR) and HER2/neu proteins. These tests utilize principles of immunohistochemistry and once the status of these proteins it known, prognosis can be predicted, and appropriate novel therapies may be chosen for treatment. BC is usually, but not always, primarily classified by its histological appearance [51]. Some of the histological types include:

- Ductal Carcinoma in situ (DCIS). This is a very early form of cancer that has not spread. DCIS is a type of early BC inside of the ductal system that has not attacked the nearby tissue. It is one of the common types of non-invasive cancer.
- Infiltrating or invasive ductal carcinoma (IDC), i.e. the most widespread kind of BC. It begins in the milk ducts and can spread to surrounding tissues and eventually to other parts of the body.
- Medullary carcinoma. It constitutes roughly 15% of all BCs. Middle aged women are more likely to be affected. Cellular histology shows a resemblance to the brain medulla (gray matter).
- Lobular Carcinoma in situ (LCIS), recently renamed “lobular neoplasia”, i.e. a non-invasive and less common form of tumor. It is unlikely to turn into invasive cancer. LCIS is considered more akin to a “marker” that BC may develop.
- Infiltrating Lobular Carcinoma (ILC), i.e. the second most common type of BC after invasive ductal carcinoma. The cancer starts in the lobules or lobes and then spreads. Initial apparent thickening in the upper-outer section of the

breast is usually reported. Such carcinomas are usually positive for estrogen and progesterone receptors, and therefore hormone therapy can be a valid therapeutic option.

- Tubular carcinoma. The cancer cells come to resemble tiny tubules. Women aged 50 and older are typically affected. Adjuvant systemic therapy is an effective therapeutic option.
- Mucinous carcinoma or colloid. It is a somewhat rare and invasive BC that seldom spreads to the lymph nodes. The cancer cells are known to produce mucus. Jelly-like tumors result from the combination of mucous and cancer cells.
- Paget's disease. This leads to an eczema-like change in the skin of the nipple. Itchiness, scaling and oozing discharge from the nipple have been reported. An underlying BC is reported in 90% of patients with such symptoms have. Women in their 50s are most likely to be affected, although Paget's disease can happen at any age.
- Inflammatory breast cancer, i.e. a rare, yet rather aggressive type of BC, which can cause the blockage of the lymph vessels in breast skin. The cancer manifests itself over a rather large area blanketing the breast, rather than a lump, and causes swelling and inflammation.
- Triple negative breast cancer. Such an BC type is known to be negative for estrogen receptor (ER), progesterone receptor (PR) and HER2/neu proteins. The acronym HER stands for "human epidermal growth factor receptor")
- Metastatic breast cancer, i.e. a later BC stage which has metastasized to other organs (typically liver, brain, bones among others) [52].

Recently, the eighth edition of the American Joint Commission of Cancer (AJCC) staging system for BC approved major changes in the classification system, adopting an anatomy-based and histology-based subdivision built on the original TNM staging system and adding various biomarkers, to refine the prognostic information for better selection of therapy with improved outcome [53].

2.4. BC treatment

BC therapy involves a multidisciplinary approach comprising surgery, radiotherapy, neoadjuvant and adjuvant therapy. Effective therapy of BC requires maximum therapeutic efficacy [54]. There is increasing recognition that the care of a BC patient depends on highly individualized clinical features, including the stage at presentation, the biological subset of BC, the genetic factors that may underlie BC risk, the genomic signatures that advise treatment recommendations, the extent of response before surgery in patients who receive neoadjuvant therapy, and patient preferences. This customized approach to treatment requires integration of clinical care between patients and radiology, pathology, genetics, and surgical, medical and radiation oncology providers with relatively minor adverse effects and therefore better quality of life [55]. The main treatments for BC are:

- surgery
- radiotherapy
- chemotherapy
- hormone therapy
- targeted therapy
- Immunotherapy.
- Neoadjuvant systemic therapy for non-metastatic BC.

Chemotherapy, which combines DNA targeting drugs and microtubule poisons, is administrated to early, locally advanced, and metastatic BC. In the adjuvant setting, chemotherapy is used to kill remaining or spread cancer cells. In the neoadjuvant setting, chemotherapy is used to reduce tumor size and allow breast conservation.

Radiotherapy is an adjuvant treatment given to BC patients after surgery. Nearly half of all BCs are treated with radiotherapy alone or in combination with other treatments.

Neoadjuvant chemotherapy is broadly administered in early-stage breast cancer (EBC) and locally advanced BC. Such a therapeutic option can in fact result in better chances for breast-conserving surgery (BCS) by downstaging the disease and to determine tumor response to therapy [56]. Moreover, radiotherapy along with BCS has been shown to lead to higher long term overall survival rates and better local regional control, lowering local recurrence risks [57]. Therefore, patients with early stage BC, hypofractionated whole breast irradiation following breast conserving surgery now represent the standard of care based on randomized data with long-term efficacy and toxicity outcomes and post-mastectomy radiation therapy represents a standard approach for patients with locally advanced BC [58].

As for surgery treatments, mastectomy remains a valid surgical alternative in selected cases and is usually associated with immediate reconstructive procedures. New surgical procedures called "conservative mastectomies" are emerging as techniques that combine oncological safety and cosmesis by entirely removing the breast parenchyma sparing the breast skin and nipple-areola complex. Unfortunately, axillary lymph node status still constitute a critical point in the planning of adjuvant treatments, and a rather reliable predictor of local disease free and overall survival.

Moreover, currently no preoperative diagnostic tool can conclusively determine whether cancer cells have spread to the axillary lymphatic basins, hence there is no clarifying that point until after surgery completion [59]. Definitely, targeted therapy is the closest step to precision medicine that combines a companion biomarker with a specific treatment to select the right patient to treat. For example recently PARP (poly-ADP ribose polymerase) inhibitors are FDA-approved for people who were born with a mutation, or change, on the BRCA genes. The BC can be early-stage or metastatic and must be HER2-negative [60], immunotherapy is an emerging BC treatment. As for most treatments, immunotherapy is not beneficial to all patients, and its efficacy needs to be optimized through patient stratification and accurate predictive biomarkers.

The search for predictive biomarkers is an active field of research that includes genomic, proteomic and/or machine learning approaches. Endocrine therapy is the prevalent option for estrogen Receptors (ER)-positive BCs, since it is effective at inhibiting either estrogen production or ER signaling. Despite the high success rate of endocrine therapy, 20 to 50% of patients are reportedly resistant or develop resistance, particularly in metastatic disease. Documented resistance to endocrine therapy among ER-positive tumors seems to support the conclusion that evaluation of ER expression is not enough to reliably foresee treatment response [61]. Surely new predictive markers of sensitivity to selected therapies and innovative evaluation criteria to assess long-term treatment efficacy will be the essential prerequisites to address the biological complexity and heterogeneity of metastatic BC (MBC) [62].

3. Epigenetics of BC and the role of miR-125

3.1. microRNA: biogenesis and classification

MicroRNA (miRNA or miR) are short (20-25 nucleotides), single-stranded, non-coding RNA molecules whose main function is gene expression control, mainly silencing. They exert this downregulation by binding the 3' end of target mRNA(s) through sequence homology and promoting either their degradation or impairing their translation [63]. It is estimated that more than 2500 miRs are encoded in the human genome, regulating over 60% of human genes [64]; in addition, thanks to imperfect sequence pairing, they also can bind multiple targets, thus amplifying their intracellular action. They map in several genomic locations, either intra- or intergenic, and in the former case they may reside inside introns, exons or regulator sequences of other genes [65], either in the sense or in the antisense strand, making their classification a complex topic [66]. Their nomenclature is complex as well and mirrors their evolution and biogenesis [67]. miRNAs are usually transcribed by RNA polymerase II (Pol II) as independent transcription units or together with their hosting genes [68]. In the first case (canonical pathway, the most common), the transcript forms a hairpin structure by folding on itself, creating what is called a pri-miRNA which may contain one or more miR precursor(s), in this case forming a cluster. Once transcribed, the pri-miRNA is processed by the microprocessor complex, containing the ribonuclease Drosha and the RNA binding protein DiGeorge Syndrome Critical Region 8 (DGCR8), which cleaves it to produce the precursor-miRNA (pre-miRNA). The pre-miRNA is then exported to the cytoplasm through the action of Exportin5(XPO5)/RanGTP complex and further processed by the RNase III endonuclease Dicer to produce the mature miRNA duplex. Finally, either the 5p (at the 5' end) or 3p (at the 3' end) strands of the mature miRNA duplex is loaded into the Argonaute (AGO) family of proteins to form a miRNA-induced silencing complex (miRISC); notably, sometimes both strands – separately – can be used in this process, thus the proportion of AGO-loaded 5p or 3p strand varies greatly depending on the cell type, the cellular environment and on the biochemical characteristics of the sequence [69]. Multiple, non-canonical pathways of miRNA biogenesis exist as well [67]. These pathways may act on pri-miRNA either transcribed independently, or on those contained inside the introns/exons of other genes and generated during the splicing process (these splicing-derived miRNAs being called mirtrons) and can be broadly subdivided in Drosha/DGCR8-independent and Dicer-independent pathways; sometimes, importin 1 is used for their export in the cytoplasm [67]. However, in the end they all are loaded into the miRISC complex to proceed to their final maturation and exert their function.

Beyond the number identifier (usually higher for miRNA described chronologically later) additional nomenclature rules are established to identify unequivocally each miR [70,71]. miRNAs with almost identical sequence are identified by a progressive lowercase letter after the identification (ID) number (miR-XXXa, miR-XXXb, etc) while miR with identical sequence but mapping in different genomic locations are indicated by a progressive number separated from the ID number by a dash (i.e., miR-XXX-1, miR-XXX-2, etc). To further distinguish miRNAs of species, an additional three-letter code and a dash may be added at the beginning of the miR name (i.e., hsa-miR-XXX indicates a human -Homo sapiens – miR). Finally, the 5p and 3p notation described above is used when the two miRNAs are roughly equivalent in their intracellular amount; if one is significantly more abundant than the other, then the rarer has an asterisk at the end of its name (for example, miR-XXX-5p*).

3.2. The miR-125 family: molecular organization and roles in human pathology

miR-125 is a highly conserved family of microRNAs whose members had been found also in nematodes (named *lin-4* in 1993, the first miR described ever) [72]. The miR-125 family in *H. sapiens* includes three members, namely miR-125a, miR-125b-1 and miR-125b-2. MIR125A gene maps to chromosome 19q13.41 [73] and miR-125a is part of a cluster together with miR-99b and let-7e [74]. MIR125B1 gene maps to chromosome 11q24.1 and in this locus, it is part of a cluster including LET7A2 and MIR100 genes [74,75]; these miRNAs are inside the third intron of the MIR100HG gene [76]. Finally, MIR125B2 gene maps to chromosome 21q21.1 where it is included in a cluster together with the MIR99A and LET7C genes [74,75], inside intron 6 of MIR99AHG gene [76]. miR-125a and miR-125b differ only by a central diuridine insertion and a U-to-C change in miR-125a [77]. All members of the family show both 5p and 3p forms (Figure 1).

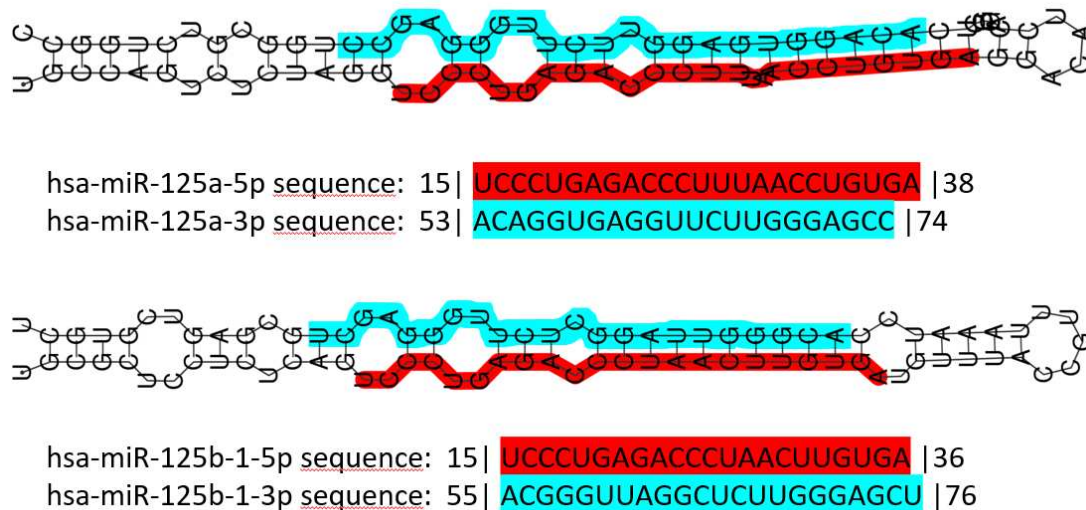


Figure 1. schematic representation of human miR-125 illustrating the structure of the pre-miRNA of both miR-125a and miR-125b, and their sequence. Color codes: red highlight for the 5p form, blue highlight for the 3p form. Numbers before and after the sequences indicate the number of nucleotides trimmed away from the mature miRNA. Data retrieved and partially modified from miRTarBase v9 update 2022 [78,79].

The miR-125 family is involved in several cell metabolic pathways controlling differentiation, proliferation, apoptosis, metastasis formation, drug resistance and immune system function because of targeting of messenger RNAs related to these cellular processes [80]. As described for miRNAs in general (see previous section), also miR-125 molecules have a complex behavior inside the cell, which mirrors their expression pattern in different tissues/cell types [78,79], their ample variety of targets [78,79], the intracellular role of their targets, and the way miR and mRNAs are either up- or down-regulated upon expression.

In the muscle, miR-125b action on insulin-like growth factor II (IGF-II) negatively regulates myoblast differentiation in vitro and muscle regeneration in vivo [81], while overexpression of miR-125b-5p protects skeletal muscle from atrophy in vitro and in vivo by targeting TRAF6 through inactivation of several ubiquitin-proteasome system (UPS)- and autophagy-lysosome system (ALS)-related proteins [82]; interestingly, the same interaction between miR-125b-5p and TRAF6 plays a critical role also in allergic asthma by modulating macrophage polarization [83] and in the myocardium, where it protects from ischaemia/reperfusion injury by preventing p53-mediated apoptotic signaling and suppressing TRAF6-mediated NF- κ B activation [84]. The same miR is also involved in smooth muscle phenotype [85] and in the proliferation and migration of vascular smooth muscle cells induced by platelet-derived growth factor BB by regulating the expression levels of AAMP (angio-associated migratory cell) and SRF (serum response factor) proteins [86]. Also, their role in cardiac muscle is well described in the literature. Beyond the above mentioned work [84], miR-125 family action is related to cardiomyocytes and the development of heart in embryonic mammals (reviewed in [87]); it regulates muscle-enriched transcription factors in cardiac and skeletal myocytes [88]; it can modulate cardiac progenitor cells proliferation and migration potential through the MALAT1/JMJD6 axis in hypoxia [89] while in the HO-TAIR/MMP2 axis miR-125 regulates cardiomyocytes proliferation and apoptosis under oxidative stress conditions [90]; it has been recently shown that cardiac-specific miR-125b deficiency induces perinatal death and cardiac hypertrophy [91]. Also miR-125a plays roles in cardiac muscle, by improving cardiac function and fibrosis and reducing inflammatory responses in DCM (diabetic cardiomyopathy) mice, although these data need further validation in man [92].

miR-125 is one of the most abundant microRNAs in the central nervous system (CNS) in mice and men [93]. In man, miR-125b promotes neuronal differentiation in human cells by repressing at least ten target mRNAs involved in those pathways – although in the same work the authors report a list of 164 deregulated genes, affecting several pathways [94] – and plays a key role for cocaine-induced PARP-1 expression (miR125 downregulation, inducing PARP-1 upregulation) [95]. It also regulates dendritic spine morphology and synaptic maturation [96]; it is implicated in synaptic plasticity [97]; it regulates neural stem/progenitor cell proliferation by targeting Musashi1 [98]; it promotes astrogliogenesis [99] and is involved in astrogliosis and glial cell proliferation [100]. miR-125b deregulation is linked to several brain disorders including Down syndrome [101], acute ischemic stroke [102,103] and Alzheimer's disease [104,105]. Recently, it has been shown that miR-125b-2 is imprinted in human but not mouse brain, where it regulates hippocampal circuit and function, and affects the hippocampal expression of Grin2a and NMDAR-mediated currents [106]. Its deregulation has been linked also to CNS tumor formation and growth, such as pediatric low-grade glioma [107], where it regulates cell growth and invasion; it regulates cell growth arrest and apoptosis of human neuroblastoma- and medulloblastoma-derived cell lines [108,109]; it inhibits cell apoptosis through p53 and p38MAPK-independent pathways in glioblastoma cells [110] and in glioma it targets BMF [111]. Finally, miR-125a-5p is up-regulated in myasthenia gravis (an autoimmune disease) thymuses [112].

In the immune system, miR-125 members regulate hematopoiesis, inflammation, and immune cell function. miR-125a controls stem cell homeostasis during hematopoiesis [113–115]; miR125 plays a role in immune cell identity [116]; miR-125b potentiates macrophage activation [117] and regulates their differentiation and polarization [118]; it is down-regulated during bacterial infections (reviewed in [119]). It is involved in periodontitis as well [120] and some authors report that miR-125a-5p modulates macrophage polarization by targeting E26 transformation-specific variant 6 gene during orthodontic tooth movement [121]. miR-125-5p targeting IL-6 R regulates macrophage inflammatory response and intestinal epithelial cell apoptosis in ulcerative colitis through JAK1/STAT3 and NF- κ B pathway [122]. miR-125b-1-3p is expressed in hMSCs-Ad exosomes and can promote T lymphocyte apoptosis and alleviate atherosclerosis (AS) by down-regulating BCL11B expression, thus providing potential molecular targets for the clinical treatment of AS [123].

3.3. miR-125 and cancer

One of the most studied topics is the role of miR-125 in cancer and beyond the above-mentioned tumors of the CNS, it is deregulated in several other tumors [124]. miR-125 is involved in neointimal hyperplasia [125]. In ovarian cancer cells Dahl and collaborators showed that overexpression of miR-125a induces conversion of highly invasive ovarian cancer cells from a mesenchymal to an epithelial morphology, suggesting miR-125a is a negative regulator of epithelial-to-mesenchymal transition (EMT) [126], while another study showed that ectopic expression of miR-125b in ovarian cancer cells induced cell cycle arrest and led to reduction in proliferation and clonal formation through the inhibition of the translation of BCL3 proto-oncogene mRNA [127]. Recently, a study on the same tumor cells revealed that serum miR-125b levels are a useful diagnostic biomarker to predict the responses to chemotherapy in patients, its expression being associated with FIGO stage, lymph node metastasis, and chemoresistance [128]. Huang and colleagues showed that miR-125b may act as a tumor suppressor in bladder urothelium by targeting E2F3, and its downregulation may contribute to tumorigenesis [129]. Use of miR-125b as a biomarker of bladder cancer in urine supernatant has been reported as well [130]. In the same tumor, hypoxia-regulated miRNAs include miR-125-3p [131]. miR-125 is also included in a panel of 8 miRNAs highly significant and consistently dysregulated for predicting survival in bladder cancer [132]. In hepatocellular carcinoma (HCC) it has been shown that the ectopic expression of miR-125a inhibits proliferation and metastasis by targeting MMP11 and VEGF [133], while others showed that ectopic expression of miR-125b reduces the cellular proliferation and cell cycle progression of HCC cells by targeting Mcl-1 and IL6R [134]. In another study the authors showed that miR-125b suppresses human liver cancer cell proliferation and metastasis by directly targeting oncogene LIN28B2 [135]. Additional miR-125 interactors in HCC had been identified in the years, including Pokemon [136], TRAF6 [137], hexokinase II [138] and FOXM1 [139]. As for the skin tumors, in melanoma, miR-125 controls the expression of NCAM [140] and c-Jun [141]; in cutaneous squamous cell carcinoma miR-125b controls the expression of MMP13 [142] and STAT3 [143]; in basal cell carcinoma, it is one of the most deregulated miRNAs [144]. The same altered pathway (miR-125b/STAT3) is also involved in osteosarcoma development [145,146], and in the same tumor additional pathways affected by miR-125 deregulation include ErbB2 [147] and BAP1 [148]. In lung cancer, miR-125 mutations significantly affect the survival of non-small cell lung cancer (NSCLC) patients [149] and its interactors include EGFR [150], HER2 [151] and MMP13 [152]. In pancreatic cancer miR-125 is deregulated as well [153,154] and NEDD9 is one of the recognized targets [155]. Also in prostate cancer miR-125 is deregulated [156–158] and its targets comprise BAK1 [159,160], p53 and PUMA [160]. A role of these miRNAs has been ascribed also in thyroid cancer, where it has been shown that miR-125b could directly act on Foxp3 expression by binding to its 3' UTR mRNA and inhibiting its expression; overexpression of miR-125b markedly sensitizes thyroid cancer cells to cisplatin treatment by inducing

autophagy through an Atg7 pathway in vitro and in vivo [161]. In gastric cancer it has been reported that miR-125b promotes cell migration and invasion by targeting PPP1CA-Rb signal pathways, resulting in a poor prognosis [162]. In colon cancer miR-125a-5p inhibits cell proliferation and induces apoptosis via targeting BCL2, BCL2L1 and MCL1 [163]. The use of miR-125b as a marker in clear-cell renal cell carcinoma has been explored as well, with good results [164]. Hematological malignancies are also a possible byproduct of miR-125 dysregulation; due to the ample literature available, we redirect the reader to specific and comprehensive reviews [74,80,165,166].

3.4. Role of miR-125 in BC

A relatively large amount of research findings are available regarding the role of miR-125 in BC. The reports showing altered expression of miRNAs in BC started to be published more than 20 years ago and the research is still running in search of an affordable diagnostic panel [167–172], and among the first targets recognized, we recall here ERBB2 and ERBB3 [173]. In 2011 Zhang and colleagues demonstrated the action of miR-125b on the regulation of the ETS1 proto-oncogene in human invasive breast cancer [174]. Rajabi et al. found that miR-125b, downregulated in BC, can reduce the expression of MUC1 (an oncoprotein), whose silencing causes DNA damage-induced apoptosis in cancer cells [175]. Tang and collaborators studied the effects of miR-125 deregulation on metastasis formation, finding that miR-125b induces metastasis by targeting STARD13 in MCF-7 and MDA-MB-231 breast cancer cells [176], in contrast with the tumor suppressive action described before. Using the same BC cell lines, Metheetraitrit and collaborators showed that forced expression of miR-125b results in radiosensitivity, as seen by reduced clonogenic survival, enhanced apoptotic activity and enhanced senescence post ionizing radiation treatment. Moreover, re-expression of c-JUN in MDA-MB-231 cells promoted radioresistance and abrogated miR-125-mediated radiosensitization, suggesting that overexpression of miR-125b causes sensibilization to γ -irradiation, indicating this miRNA as a possible target for adjuvant therapy [177]. In contrast, Wang and co-worker found an association between miR-125b expression and chemoresistance [178], again indicating an oncogenic role for this miRNA. In line with these last results, Zhou and collaborators found that miR-125b confers the resistance of BC cells to paclitaxel through suppression of pro-apoptotic Bcl-2 antagonist killer 1 (Bak1) expression [179]. He and collaborators studied the expression of miR-125a-5p/3p and miR-125b in 143 pairs of BC and normal adjacent tissues finding that miR-125a-5p and miR-125b were significantly down-regulated in BC tissue samples and that the expression level of miR-125a-5p was significantly higher in younger patients (<35 years) than in older ones, with a gradual reduction in miR-125a-5p expression was observed in BC tissue samples correlated to increasing age [180]. Recently, a paper showed the oncosuppressor role of miR-125b via the inhibition of proliferation, migration, and invasion of BC cells through targeting MMP11 protein [181].

3.5. Further mining miR-125 function in BC: competing endogenous RNA networks (ceRNets).

A fundamental way to control gene expression through miRNAs has been elucidated in recent years, consisting in the so called ceRNets. It has been shown that miRNAs are controllers of target mRNAs by altering their half-life or translation. However, they are also controlled, in many cases, by other long non-coding RNAs (lncRNA), or even other mRNAs, which “sponge” miRNAs through sequence homology, avoiding their interaction with mRNA targets [66]. In other words, lncRNA and mRNA compete for binding miRNAs; these two molecules form a competing endogenous RNA (ceRNA) couple. If the lncRNA efficiently sponges the miRNA, then miRNA inhibitory action is not accomplished, and the mRNA is regularly translated. In this case, the lncRNA (inhibitor of an inhibitor) has a function resembling that of an enhancer of gene expression. Hence, if the mRNA encodes an oncoprotein, the lncRNA has an oncogenic effect, while the miRNA has an oncosuppressive role. The same, with opposite effects, occurs in case of the mRNA coding an oncosuppressor. The three molecules, taken together, form what is currently known as a regulatory axis, and the sum of many axes creates the ceRNET. In the ceRNets, lncRNAs and mRNAs constitute the nodes of the network, while the miRNAs represent their connections. An increasing number of papers has been published in recent years depicting the increasing structure and complexity of the ceRNET in BC (see [182] and references therein), including the action of pseudogenes in this phenomenon. In fact, Welch and collaborators found that 309 pseudogenes exhibit significant differential expression among breast cancer subtypes and their expression pattern allows recognizing tumor samples from normal samples and discriminates the basal subtype from the luminal and Her2 subtypes; of them, 177 transcribed pseudogenes possess binding sites for co-expressed miRNAs that are also predicted to target their parent genes [183]. Recently, in a work by Zhu and collaborators the authors took advantage of the data available in exoRbase database and derived from exosomes of human BC samples [184]. Their study allowed to identify a ceRNA network including 19 mRNA nodes, 2 lncRNA nodes, 8 circular RNA nodes, and 41 miRNA connections. KEGG enrichment analysis showed that differentially expressed mRNA in the regulatory network are mainly enriched in the p53 signaling pathway.

Literature describing portions of a miR-125-centered ceRNET is constantly growing. It is likely that the miR-125 interactions with mRNAs described in the previous section will become axes of the growing BC ceRNET as well, as soon as the appropriate lncRNA is identified in the pathway. However, some axes have been already described and some of them, being interconnected, can be used to build a basic version of this network (Figure 2).

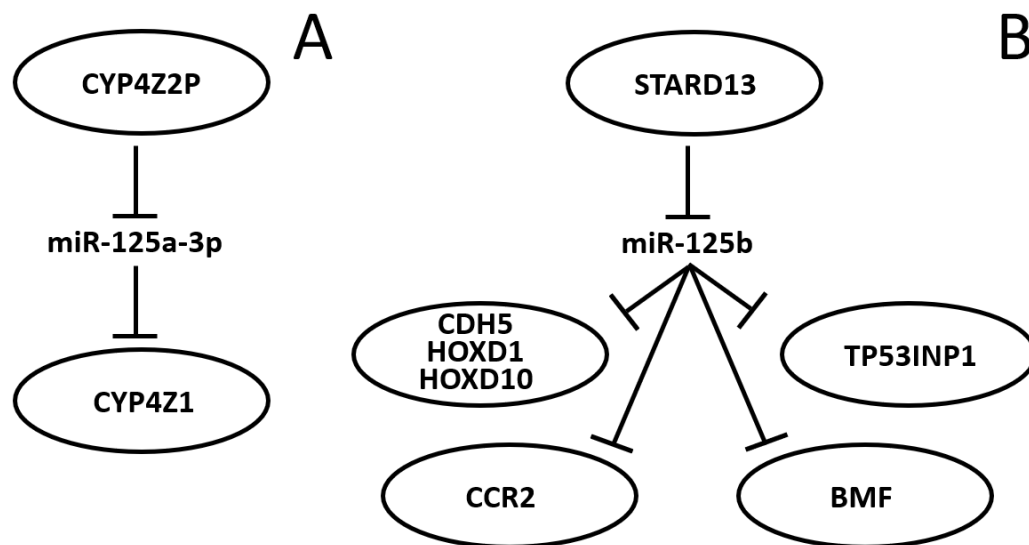


Figure 2. schematic representation of two miR-125-centered ceRNETs in BC. A: a simple ceRNET having only one axis, where a pseudogene mRNA (CYP4Z2P) inhibits miR-125a-3p action on the target mRNA (CYP4Z1) by sponging it, thus enhancing CYP4Z1 expression. B: a more complex ceRNET in which the interaction between miR-125b and STARD13 mRNA control the expression of multiple target mRNAs. See text for references and further explanations.

In 2004 Rieger and collaborators discovered a new human cytochrome P450 (CYP), termed CYP4Z1, which is specifically expressed in mammary gland and breast carcinoma [185]. They also found a transcribed pseudogene, named CYP4Z2P, that codes for a truncated CYP protein (340 amino acids vs. 505) with 96% identity to CYP4Z1. Both CYPs are highly expressed in breast cancer, although the expression level of CYP4Z2P is approximately 20 times lower than that of CYP4Z1 in mammary tissues, and barely expressed elsewhere. Later it was shown that increased expression of CYP4Z1 promotes tumor angiogenesis and growth in human breast cancer [186] and that CYP4Z2P 3'-UTR is involved in promoting breast cancer angiogenesis through the VEGF/VEGFR2 pathway [187]. In 2015 Zheng and collaborators showed that the action of CYP4Z2P 3'-UTR is sponging several miRNAs, including miR-125a-3p, and that this pseudogene acts as a ceRNA in respect to CYP4Z1, enhancing its expression levels [188,189]. They also showed that tumor angiogenesis is promoted by inducing the phosphorylation of ERK1/2 and PI3K/Akt pathways. The same group also showed later that the deregulation of these ceRNA also confer tamoxifen resistance in BC through the enhancement of the transcriptional activity of ER α via its phosphorylation dependent on cyclin-dependent kinase 3 (CDK3) [190]; that downregulation of CYP4Z1 or the CYP4Z2P 3'-UTR promotes cell apoptosis, mirroring the functions and modulating the expression of human telomerase reverse transcriptase (hTERT) [191]; and that the transcriptional factor six2 activates these CYPs ceRNET by directly binding to their promoters, thus activating the downstream PI3K/Akt and ERK1/2 pathways and consequently being involved not only in chemoresistance, but also regulating the stemness of BC cells [192,193].

STARD13 (StAR-related lipid transfer domain protein 13, also known as deleted in liver cancer 2 protein (DLC-2)) is a Rho GTPase-activating protein (GAP) that selectively activates RhoA and CDC42 and suppresses cell growth by inhibiting actin stress fiber assembly in hepatocellular carcinoma (HCC) [194]; this protein is ubiquitously expressed in normal tissues and downregulated in HCC. In mice, STARD13, promotes angiogenesis through the actions of RhoA [195]. Its role is well established in BC as well, where it act as a tumor suppressor gene [196], where it regulates cell motility and invasion [197], endothelial differentiation [198], metastasis formation [199,200], cell migration [201], and apoptosis [202]. It has also been shown that STARD13 exerts its function in BC through its participation to ceRNETs, such as the one involving positive TGF- β /miR-9 regulatory loop mediated by the STARD13/YAP axis [203], or the one involving hsa-miR-21-3p [204], or even the more complex network which involves 5 different miRNAs and that controls YAP/TAZ nuclear accumulation and transcriptional activity via modulation of Hippo and Rho-GTPase/F-actin signaling pathways [205]. A direct link between miR-125 and STARD13 has been described, too. Li and coworkers showed that

CDH5, HOXD1, and HOXD10 are putative STARD13 ceRNAs and display concordant patterns with STARD13 in different metastatic potential breast cancer cell lines and tissues; in addition, they also show that the 3' UTR of STARD13 mRNA can bind miR-125b (and also miR-9 and miR-10b, indicating that this mRNA may target multiple pathways simultaneously) [206], thus confirming their previous study about this interaction [207] and showing that the transcripts of the tumor suppressors genes CDH5, HOXD1, and HOXD10 inhibit BC metastasis in vitro and in vivo by competing with STARD13 mRNA for these three miRs. Interestingly, as mentioned before [205], CDH5, HOXD1 and HOXD10, together with STARD13, are BC players also in a different ceRNET, competing for a different set of miRNAs, indicating that STARD13 role in BC is very complex. In 2017 Hu and collaborators discovered another ceRNET axis in which STARD13 and miR-125b control the CCR2 (cysteine–cysteine chemokine receptor 2) expression levels [208]. In this case, they found that the CCR2 3' UTR harbors three miR-125 binding sites that both inhibits MDA-MB-231 and MCF-7 cell metastasis by repressing epithelial-mesenchymal transition (EMT) in vitro, and suppresses breast cancer metastasis in vivo, through the competition with STARD13 in a miR-125b-dependent and protein coding-independent manner. Another component of the same ceRNET is TP53INP1 (tumor protein p53-inducible nuclear protein 1). TP53INP1 is an antiproliferative and proapoptotic protein involved in cell stress response which acts as a dual regulator of transcription and autophagy and is modulated by p53 in response to stress; it also interacts with kinases HIPK2 and PKC δ , which phosphorylate p53, creating a positive feedback loop between p53 and TP53INP1 [209]. TP53INP1 is also involved in SPARC (secreted protein acidic and rich in cysteine) mediated-promotive effects on cancer cell migration and metastasis [210]. In 2018 Zheng et al. found a ceRNA interaction between STARD13 and TP53INP1 mediated by competitively binding to miR-125b in BC [211]. In this case STARD13 promotes upregulation of TP53INP1, causing the inhibition of BC cell metastasis through competitively binding to miR-125b thanks to the inhibition of SPARC gene expression. Later, Guo and co-workers also found a ceRNET axis in BC involving miR-125b, STARD13 and BMF (Bcl-2-modifying factor) [212]. BMF is a member of the BCL2 protein family and controls apoptosis in several cell types [213]. The authors [212] found that miR-125b directly binds the 3' UTR, and thus downregulates, BMF expression, and that STARD13, sponging miR-125b, upregulates BMF in BC both in vitro and in vivo. All together, these results may suggest novel therapies for BC treatment and aiding in selecting adequate drugs, depending on the molecular biology of the tumor, in perspective aiming at the goal of personalized medicine. Indeed, a recent work showed that tanshinone IIA (an effective component extracted from *Salvia miltiorrhiza* which regulates the stemness of tumor cells) attenuates this phenotype in BC cells, by downregulating miR-125b levels and upregulating its target gene STARD13, while miR-125b overexpression or STARD13 knockdown impairs the inhibitory effects of tanshinone IIA on the stemness of BC cells. [214].

3.6. Beyond clinical factors: new standards for a legally and ethically tenable implementation of personalized medicine

The broad-ranging and potentially revolutionary scope of personalized medicine has been well established and acknowledged universally. The notion of personalized medicine can be summarized as the medical model relying on characterization of individual patients' phenotypes and genotypes (e.g. the centerpiece of this article applied to breast cancer, molecular profiling, medical imaging, lifestyle data) for the ultimate purpose of configuring and modulating the most effective therapeutic pathways for any given individual patient with the right timing; personalized medicine as a prognostic avenue can identify and assess the predisposition to disease in order to delineate timely and individually outlined prevention strategies [215]. Such practices are extremely promising as far as the development of novel therapeutic avenues options is concerned, tailored to each patient's genetic make-up for maximum effectiveness. Such a breakthrough however is bound to give rise to a host of challenges from the legal, ethical, social and policy-making perspectives in order to guarantee the necessary standards of fairness, equitable access and non-discrimination among others [65,216]. New criteria need to be developed for the effective and equitable governance of personalized medicine, which must take into account key aspects such as individual privacy, the risk of stratification and discrimination of sub-populations segments on the basis of ethnicity, equal access opportunities, and how to ensure oversight for the fair allocation of funding [217]. As personalized medicine practices expand and further develop, they are likely to become increasingly mainstream, which will make ethical, legal and social implications all the more urgent to deal with, in order to guarantee te ethically sound implementation of such a major scientific breakthrough, which in conjunction with other technologies such as big data analysis and artificial intelligence has the potential to change healthcare at its very core [218]. Major European institutions have proven fully aware of such looming changes. The potential of personalized medicine has in fact been recognized in two highly relevant policy papers, focused on oncological diagnostics or therapeutics, advocating for personalized medicine to be fully harnessed and gradually implemented on a large scale for the sake of patients [219,220], despite the lingering difficulties linked to the still high level of uncertainty regarding outcomes [221]. The EU papers outline the key factors that can be instrumental in fulfilling the potential of personalized medicine, primarily a thoroughly structured, synergistic conjunction of health data and new technologies, in order to lay the groundwork for the comprehensive and well-balanced development of personalized medicine techniques [222].

The considerable potential of personalized and precision medicine to offer valuable oncological treatment options will be fulfilled through the elaboration of prevention and treatment pathways which will allow patients and doctors to identify the best-suited and most effective therapeutic course. Overall, such novel tailored approaches are likely to benefit healthcare systems to a substantial degree too, especially by reducing wasteful spending on trials and ineffective treatments and streamlining resource allocation more efficiently. In 2022, the EU plans took it upon itself to put in place new measures meant to make the most out of new innovative technologies based on AI, big data, and genomics. It is worth mentioning in that regard the so-called European Cancer Imaging Initiative, designed to implement and optimize the delivery of personalized medicine and innovative approaches through the application of new computer-aided tools [223,224]. Also deserving attention is the new Partnership on Personalized Medicine (also known as EP PerMed), phased in 2023 and funded by the EU’s chief funding program aimed at fostering research and development, Horizon Europe, which can rely on a budget of €95.5 billion. Among its priorities, EP PerMed is set to find common ground projects for public and private sector stakeholders, in order to define key objectives to direct research funding, harmonize the current broad range of personalized medicine approaches and strategies, develop new effective training blueprints, and support policy-makers. Just as importantly, it is considered a priority to provide support for longer life expectancy by increasing healthy life years and to contribute to guarantee the sustainability of each member state’s healthcare system [225]. Through a multidisciplinary concerted effort, EP PerMed will ultimately outline fundamental priorities to further research and education in personalized medicine, in addition to fostering cancer prevention, diagnosis, and therapeutic research endeavors. Rationalizing the implementation of personalized medicine by defining the roles of all parties involved in research, policy-making, industry and society at large will be vital for the purpose of ensuring such novel techniques and processes do not lose sight of the interests and rights of everyone, thus guaranteeing an ethically viable use for maximum benefit.

Table 2 describes the stakeholders at play and the expected outcomes for the harmonized development of personalized medicine initiatives in the European Union

Table 2. Summation of stakeholders’ roles and outcomes to be pursued through targeted measures aimed at personalized medicine development, uptake and awareness as defined by the European Partnership on Personalised Medicine.

Stakeholder(s) involved	Outcome(s) to be pursued
European countries/regions in cooperation with international partners	Broad-ranging collaborative research efforts for the development of innovative personalized medicine approaches regarding prevention, diagnosis and treatment
Healthcare authorities, policymakers	✓ Elaboration of evidence-based strategies and policy blueprints for the uptake of personalized medicine in national or regional healthcare systems ✓ Optimization of healthcare delivery and ensuring sustainability of healthcare systems through improved knowledge and understanding of the costs vs benefits ratio of personalized medicine
Healthcare industries and manufacturers, policymakers	✓ Timely transfer of research and innovation into markets, to be achieved through access to efficient measures and investments; ✓ Fostering the uptake of personalised medicine through the elaboration and implementation of innovative business models
Healthcare providers and professionals	Improvement of health outcomes, prevention of diseases and foster population health through the equitable and cost-effective implementation of personalized medicine
Connected local/regional ecosystems of stakeholders	Fostering the uptake of successful innovations in personalized medicine, in order to improve healthcare outcomes and strengthening European competitiveness
Citizens, patients and healthcare professionals	Broader knowledge of personalized medicine and resulting better involvement in its implementation through feedback

All stakeholders	Better cooperation and establishment of networks of national and regional knowledge and awareness-building hubs for personalized medicine.
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It will be ultimately essential to be able to rely on a clean-cut a set of criteria for the definition, delivery and oversight of personalized medicine-based approaches to be transposed in clinical and medical research settings. Other than the EU initiative, it is noteworthy how such a set of goals had already been acknowledged by the International Consortium for Personalized Medicine (ICPerMed), started in November 2016 [226,227]. The ICPerMed has laid out and described quite thoroughly the distinctive traits and features of personalized medicine and what it will finally come down to: the natural evolution of healthcare in the dawning age of biotechnology and big data. Such a broad-ranging breakthrough however certainly requires comprehensive adjustments and restructuring in the very modalities and processes through which healthcare is delivered. To that end, large-scale implementation calls for emphasizing training and new sets of skills for healthcare professionals, which will be able to rely on novel means and instruments to deliver care to their patients [228]. The path undertaken by the ICPerMed has been aided and supervised by European and international expert and specialist consultants in key research areas, who have greatly contributed to defining and weighing the opportunities and pitfalls posed by personalized medicine and identifying any particular concerns and management challenges [229]. To that end, as a preliminary step towards launching the partnership, the European Commission is set to outline a road map laying out in detail tailored preventive strategies and approaches [230]. The very real possibility that data may in all likelihood change healthcare at its core has been recognized and assessed by established European policies, both at the individual patient level and insofar as healthcare systems are concerned (the European Alliance for Personalized Medicine has issued in that respect a rather compelling report titled “Cooperating on Data: The Missing Element in Bringing Real Innovation to Europe’s Healthcare System” [231]). It is in fact worth considering that clinical studies, diagnostic results, medical records and patient information are but a part of the data sources available in healthcare. Completing the full transition towards the digitization of patient records is poised to be a major contributing factors in this highly consequential breakthrough. Comprehensive digital archives from which to collect and elaborate big data will be of utmost importance to that end. Data drawn from digital applications, wearable devices, and social media, will also be instrumental at providing information on environment- and lifestyle-related factors, socio-demographics, genomics, metabolomics, proteomics, radiomics, standardized electronic health records, or precision medicine platforms [232,233]. In order to outline an ethically and legally sound path towards the large-scale implementation of personalized medicine, it is necessary to streamline and optimize key aspects such as the management of biobanking and informed consent, confidentiality [234], access to treatment, clinical translation, and direct-to-consumer genetic testing. In addition, the stratification and genetic discrimination of sub-populations based on ethnicity will have to be prevented through the introduction of targeted measures [235,236]. Other hurdles which have been pointed out and need to be addressed have to do with the insufficient level of genetic literacy and substandard comprehension of personal and familial implications of germline and somatic genomic testing among patients, which may negatively affect the informed consent process [237]. An element of inequality may arise from each patient’s socioeconomic status, healthcare insurance policy (or level of coverage by the national healthcare system), and cancer care facilities [238]. Even though patients residing in countries with publicly funded universal healthcare are less likely to be affected by access inequalities, such systems often limit public coverage to treatments and techniques of already established efficacy [239]. In addition, seeking the highest possible degree of harmonization will prevent “healthcare tourism” practices, i.e. patients with adequate financial means traveling to countries where any given procedure is legally available [240,241]. Personalized medicine and its wide-ranging clinical applications will have to rely on full validation in terms of their efficacy and safety, and such a process will likely need larger study samples compared to more conventional procedures whose clinical value has already been acknowledged. That in turn may mean that personalized medicine techniques and therapeutic approaches may take longer to be acknowledged as fully evidence-based and approved for large-scale use [242]. Such implications can negatively affect the fair and equitable allocation of healthcare funding. The already mentioned European Union Communication issued in 2022 [219] in fact points to legal and ethical criteria as potentially difficult barriers to overcome, for the purpose of harnessing personalized medicine and the European Digital Strategy to their full capabilities. That principles holds true for many different innovations which open up new prospects, for instance, for transplant patients through regenerative medicine [243,244]. Lawsuits arising from negligence and malpractice charges [245] will probably become increasingly common as personalized medicine techniques do as well [246]. That however entails that medical procedures grow more complex, and as they do, the risk of litigation resulting from alleged medical malpractice will be ever more substantial [246]. The parties that could be held liable in such instances are not only the healthcare professionals implementing diagnostic and therapeutic actions, but range from manufacturing firms of genome sequencers and medical devices, laboratories, pharmaceutical companies, and healthcare facilities. The legal concept at the core of “genetic malpractice” is in fact the doctors’ failure to identify or accurately interpret

genetic testing. Such error-prone dynamics can be complicated even more by the lingering differences in the medical research community about the values, scope and timing of genetic testing when defining prognostic and therapeutic pathways, or whether such testing should be considered and carried out at all, and under what circumstances [227,246,247]. Research findings and case-law [245–247] are still inconclusive at this stage as to how and to what extent these new litigation profiles linked to clinical genomics-based personalized medicine will impact healthcare professionals and facilities. A major factor in determining how such legal actions end is surely the specific set of conditions, environmental and contributing factors specific to each case, in addition to the legal strategies chosen by plaintiffs, counselors, expert witnesses, and magistrates [248]. It appears therefore quite plausible that judicial decisions at first will have a major impact on the future incidence, sustainability, and frequency of such actions. Medical and legal analysts will in fact weigh such rulings and adjust their management and use of such techniques accordingly, by putting in place all necessary safeguards [249,250]. Current uncertainty makes it all the more urgent to rely on harmonized and widely agreed upon legislative, regulatory, and policy criteria, to be encapsulated in evidence-based guidelines and best practices specifying when and where genetic testing may be advisable, or even necessary, and when it is not (at least with the current level of knowledge) [251]. Such a degree of objectivity will provide valuable guidance based on sound scientific and clinical elements which will inform court decisions, thus protecting physicians and healthcare professionals from malpractice lawsuits which are often frivolous and harm the quality of care for everyone [252].

5. Conclusions

BC is a heterogeneous disease, thus patients that are histologically diagnosed with the same cancer type, might have different molecular characteristics, genetic mutations or tumor microenvironments that can deeply influence prognosis or treatment response. Consequently, the challenge in personalized medicine is to distinguish these diverse molecular characteristics, separate patients accordingly, and treat them using a tailored approach which considers all these features. Personalized medicine might profoundly improve patient outcomes thanks to diagnostic tests that can identify specific biomarkers, allowing doctors to select the most effective treatment for each patient, reducing the risk of adverse reactions and increasing the likelihood of a successful outcome. In this context, miR-125 and its targets are emerging as promising biomarkers in BC classification.

It is interesting to remark that, depending on the study, miR-125 has been described having either oncogenic or oncosuppressive role. However, this should not be surprising because of at least three reasons: cell changes in space and time, and miR regulation. First, different cancers – and sometimes also different stages of the same cancer, or even different populations of the same tumoral mass – have different metabolic needs [253,254]. So, in presence of both the same miRNA and corresponding mRNA target, the effect on the tumoral cell metabolism may significantly vary, allowing different spatial effects of miRNAs on the transcriptome. Second, the evolution of cancer during time is associated with alterations in the cancer cell proteome; new genes are activated, other genes are suppressed or lost (for example through aneuploidy [255,256] or copy number variations)[257–260] also as a response to the internal and external microenvironmental interactions [258–260]. This is obviously true also for every single cancer subpopulation (the space variable described before). Third, we recall here the organization of the miR-125b genes: this miRNA is transcribed from two different loci in the genome, which are under two different promoters[74], thus it is quite straightforward to hypothesize that the two copies are not fully interchangeable in their function despite their sequence identity, and they may be transcribed under different cellular conditions; consequently, different targets may be present at the time of miR-125 expression. In addition, the two clusters miR-125b is embedded in, are different; the transcription of the cluster as a single pri-miRNA using the same promoter suggests that these diverse miRNAs need to act in concert, thus the two different clusters, upon expression, likely modify the host cell proteome in different ways. As a consequence, it is possible to theorize that inconsistencies in the role of miR-125 (oncogene vs. oncosuppressor) might just reflect differences in the analyzed cells or in the used analytical protocols, more than real contradictions, thus further pushing researchers and physicians to characterize each patient at the molecular level. Indeed, some clues for this possibility have been showed for BC cell lines used to verify miR-125 function, where it has been shown that miR-125 is expressed in MCF-7 spheroids but not in MDA-MB-231 spheroids and that the unique cluster of miRNAs found in each cell type are associated with their chemoresistance properties and cancer progression, and most likely influencing the maintenance of the spheroid-enriched cancer stem cells properties [258]. Similar differences in different BC cell lines have been reported also by Ahram et al. who compared MDA-MB-453, MCF-7 and T47D cells finding that miR-125b is highly expressed in T47D cells and slightly downregulated in MDA-MB-453 cells, with all the predictable consequences related to their targets fate [261]. All together, these data underline the importance and complexity of the expression of miR-125 family members in the etiopathogenesis of BC, and the need to further and better characterize this biomarker in BC patients. Personalized medicine undoubtedly constitutes a broad-ranging breakthrough with huge potential to change healthcare to its very core. At the same time, such a potential constitutes such a breakthrough that the current sets of ethical, legal

and policy-making standards which provide us guidance today may be outpaced and ultimately inadequate. New criteria therefore need to be devised if we are to rely on equitable, effective healthcare for all.

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