Predictive Pre-Cancerous Biomarkers in BRCA1/2 Mutation Carriers: From Tissue-Resident Pre-CAFs to Blood-Based Exosomal Cargo

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Abstract
BRCA1 and BRCA2 mutations are associated with a high lifetime risk of breast and ovarian cancer, and require close monitoring. The sensitivity of current imaging sense modality is limited, and the tissue biopsy is ethically and practically difficult in asymptomatic patients. Recent advances have identified a unique population of pre-cancer associated fibroblasts (pre-CAFs) that are characterised by dual overexpression of Podoplanin (PDPN) and CD10 (PodPDPN/CD10) in histologically normal breast tissue from BRCA1/2 carriers, the earliest stromal remodelling event prior to malignant transformation. This tissue-based signature offers insights into mechanisms, but is hampered by the need for invasive sampling for clinical use. This review summarizes the current state of the art of non-invasive liquid biopsy alternatives, such as soluble PDPN (sPDPN), cell-free DNA (cfDNA) methylation signatures, and, most promisingly, exosomal microRNA (miRNA) cargo. We emphasize that although circulating free miRNA is highly unstable, exosomal lipid bilayer vesicles provide biological protection and allow for paracrine/endocrine reprogramming of distant epithelial cells. The future of stromal biology and exosomal transcriptomics is one in which a simple blood test may be able to predict the onset of carcinogenesis in high-risk BRCA1/2 populations, leading to truly personalised prevention.

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1. Introduction

The identification of BRCA1 and BRCA2 tumour suppressor genes revolutionised hereditary cancer risk assessment. Breast cancer is the most common cancer in women globally, accounting for 5-15% of cases, and is associated with pathogenic variants mainly in the genes BRCA1 or BRCA2 [1]. Women with pathogenic BRCA2 mutations are at risk of developing breast cancer between 38% and 84% of the time, and at risk of developing ovarian cancer between 16.5% and 27.0% of the time. BRCA1 and BRCA2 are genes that code for proteins that repair DNA, which is essential for homologous recombination [2-4], and loss of these genes is associated with early onset and aggressive breast cancers. The clinical problem is, however, stark for those women who are carriers of these pathogenic mutations: prophylactic mastectomy is effective, but surgically morose; and standard imaging (mammography and MRI) misses the molecular precipice of transformation [5]. In high-risk women, annual magnetic resonance imaging (MRI) is the most sensitive screening test for early detection of breast cancer, but there are barriers to implementation [6]. The clinical need is great for predictive biomarkers, signals that can be detected in the systemic circulation that can predict the imminent tissue malignant conversion. The paradigm of carcinogenesis has changed from an epithelial-centric model to a stromal determinant (TME) model, with recent discoveries in the field. This review documents the discovery of a novel pre-cancerous stromal signature in BRCA carriers and the technical and biological approaches that have been developed to bring this knowledge into a practical, non-invasive blood-based test. 2. Overview: The Tissue-Based Signature,

PDPN and CD10 in Pre-CAFs 2.1. Biology of the Markers Podoplanin (PDPN) is a type-I transmembrane mucin-like glycoprotein that participates in actin cytoskeleton organisation, cell migration and platelet interaction with C-type lectin-like receptor 2 (CLEC-2) [8]. PDPN is a tumour cell-associated biomarker of plasticity in triple-negative breast cancer (TNBC) and has been shown to be synergistic with hypoxia-induced mesenchymal phenotypic shifts in the promotion of lymphatic dissemination and poor prognosis [9]. In breast cancer, PDPN is highly expressed in cancer-associated fibroblasts (CAFs) and is associated with poor clinical prognosis, suggesting its potential as a cancer prognostic marker and therapeutic target [10, 11]. CD10 is a type-II transmembrane zinc-dependent metalloprotease (also called neprilysin, membrane metallo-endopeptidase MME) that breaks down bioactive peptides such as enkephalins and natriuretic peptides [12]. CD10 is potentially involved in the progression of breast cancer, since it is expressed by CAFs in tumours with higher progression rate [13]. CD10 expression has been linked to negative ER status, increased tumoural grade and decreased patients' survival [13, 14].

The Pre-CAF Discovery in BRCA Carriers Studies of breast cancer risk reduction surgery specimens from women with the BRCA1/2 mutations, who did not have any clinical or pathological evidence of breast cancer, have recently led to the discovery of a very distinct type of stromal cell that does not exist in non-carrier controls of similar age [15-18]. These cells are known as pre-cancer associated fibroblasts (pre-CAFs) and have a specific surface molecular signature: PDPN^{high} and CD10^{+} [19]. This is paradigm shifting in three ways: Stromal Priming: It shows that mutations in BRCA allow a "fertile soil" to exist before epithelial transformation has occurred and before any malignant clones have formed (Figure 1). In this context, pre-neoplastic stromal cells stimulate the proliferation of epithelial cells and help to initiate cancer through BRCA1 [19].

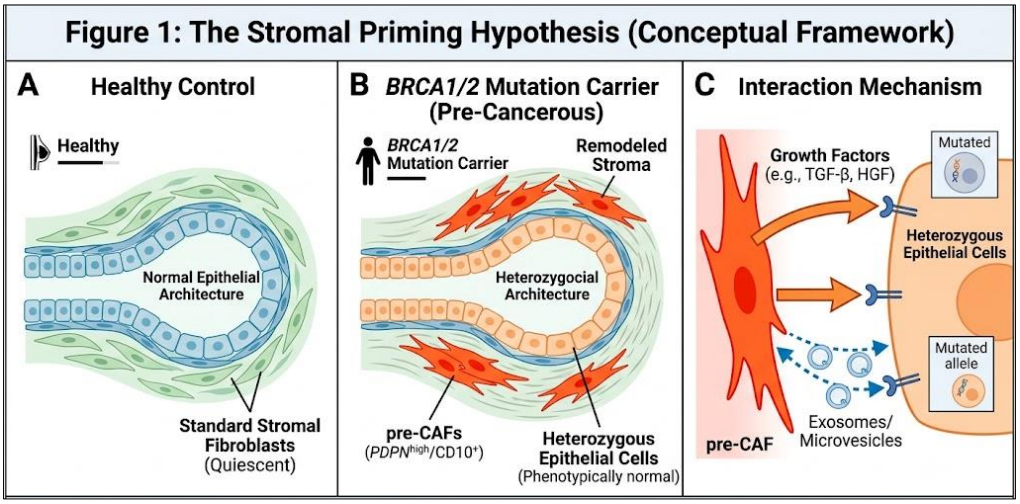

Fig 1: The diagram highlights that the 'fertile soil' (the stroma) is remodeled by the appearance of pre-CAFs, which occurs prior to any apparent malignant transformation of the adjacent epithelial cell, which establishes a pro-tumorigenic microenvironment.

Specificity: This dual-positivity for PDPN/CD10 was observed in all BRCA1 carriers and, for the first time, confirmed in BRCA2 carriers which indicates a common stromal response to DNA repair deficiency [20]. The marker is present years before imaging changes are detected and is a critical therapeutic time window [19] Pre-CAFs are found to be over-expression of PDPN, CD10 and PD-L2, which are associated with early stromal remodeling. Pre-CAFs with high levels of PDPN (PDPN^{high}/CD10^{+}) are found in the non-cancerous stromal components of tissues from BRCA1/2 patients [19, 20]. The results presented here pinpoint the critical role of the stromal microenvironment in the initiation of BRCA1/2 associated breast cancer and the need to explore epithelial and stromal changes together in cancer risk evaluation.

2. Technical Issues for tissue detection Flow cytometry is still considered to be the "gold standard" for quantification of these surface markers.

In practice, however, the ex vivo processing of solid breast tissue to obtain single cell suspensions, which is necessary to perform laser-based cytometry as summarised in Table 1, is the subject of intense debate in clinical practice.

Table 1

Step	Methodology	Duration / Conditions	Purpose
1.Mechanical	Mincing with a scalpel	Performed on ice; tissue diced into ~1 mm^3 pieces	Increase surface area for enzymatic action
2.Enzymetic	Collagenase + Hyaluronidase in digestion buffer	37°C incubation with gentle agitation (e.g., 1–2 hours)	Digestion of extracellular matrix (collagen and hyaluronic acid)
3.Mechanical	Vigorous pipetting (trituration)	Repeated aspiration through a serological pipette	Shear off the remaining cell clusters to achieve a single-cell suspension
4. Filtration	40–70 µm cell strainers	Pass the cell suspension through a strainer into a collection tube	Exclude debris and clumps to prevent cytometer clogging
5. Analysis	Flow cytometry (with IHC confirmation)	Stain with anti-PDPN and anti-CD10 antibodies; gating on live cells	Quantify PDPN/CD10 surface expression on stromal (fibroblast) population

The Clinical Barrier: Even though it is technically possible, healthy, asymptomatic BRCA carriers do not want to undergo invasive core needle or surgical biopsies. This logistical and ethical limitation requires the creation of non-invasive surrogate markers. Bilateral salpingo-oophorectomy (BSO) and mastectomy are risk reducing surgeries that can reduce the risk of breast and ovarian cancer [1, 21], but emotional, cultural and financial barriers can make it difficult for people to receive these surgeries.

3. From Solid to Liquid

The Peripheral Blood Paradigm Liquid biopsy (LB) is a minimally invasive method that involves the analysis of circulating tumour cells (CTCs), cell-free DNA (cfDNA), extracellular vesicles (EVs), and other biomarkers derived from the tumour in body fluids, which has revolutionized the management of breast cancer. These approaches provide additional possibilities for early detection, surveillance of treatment response, and elucidation of treatment resistance mechanisms [22-24]. Compared to tissue biopsies, liquid biopsies provide a unique clinical benefit: they are non-invasive, repeatable, and the accuracy is dependent on the spatial and timbral heterogeneity of the tumour, which means that they can be used for real-time monitoring, as demonstrated in Figure 2.

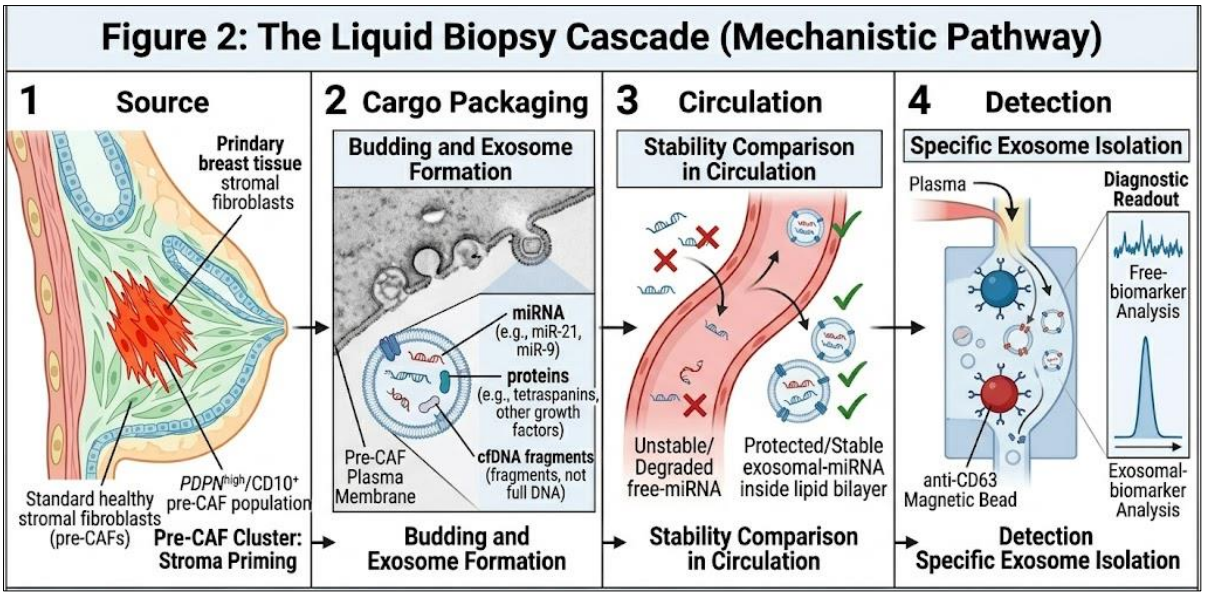

Fig 2: The Liquid Biopsy Cascade. Pathway from tissue-resident pre-CAFs to blood-based detection. Exosomes from stromal fibroblasts (PDPN^{hg}/CD10^{+} pre-CAFs) contain cfDNA fragments and miRNAs. Exosomal miRNAs are more resistant to degradation than free miRNAs, which are highly unstable. Specific exosome isolation (such as anti-CD63 capturing) allows non-invasive quantification of pre-CAF-derived cargo, pointing to the diagnostic potential of exosomal biomarkers as opposed to unstable free-floating analytes.

3.1. Soluble Proteins Soluble PDPN (sPDPN) has been investigated and shown to be significantly higher in plasma of breast cancer patients than in healthy controls. The plasma sPDPN level can be utilized as a novel index for the clinical stage, differentiation grade and metastasis status of breast cancer. Data on sPDPN elevation in the pre-cancerous phase in BRCA carriers are currently not available, but promising [25-27].

Likewise, a CAF secreted protein called Complement Factor B (CFB) has been linked to tumour inflammation. By using integrative traditional and AI approaches [28]. Recent studies corroborate the hypothesis that CFB is a genetically associated risk protein that may have a causal role and that is a prognostic and therapeutic biomarker both at the expression and mutation level in breast cancer [29]. There is a relationship between CFB and breast cancer risk and poor prognosis. More importantly, CFB elevation is not specific to BRCA1/2 carriers, and is a pan-cancer or general risk marker [29], which reduces its value for this group.

3.2. The study of cell-free DNA (cfDNA) and epigenetics.Research into cell-free DNA (cfDNA) and epigenetics.

This is the most advanced non-invasive strategy at present. Circulating cfDNA can be isolated and epigenetic changes can be analysed before the development of a tumour. Integrated clinical profiling of cfDNA methylation biomarkers holds great promise for improving breast cancer diagnosis, prognosis and personalised treatment (30). A study that combined genomic and epigenomic (fragmentomic and DNA methylation) features was conducted on 194 blood plasma samples from 88 BRCA1 and/or BRCA2 pathogenic variant carriers. In 71% of carriers who had active cancers detected by conventional surveillance, and in 56% of those with negative conventional surveillance results (in press), signals for cancer were detected.

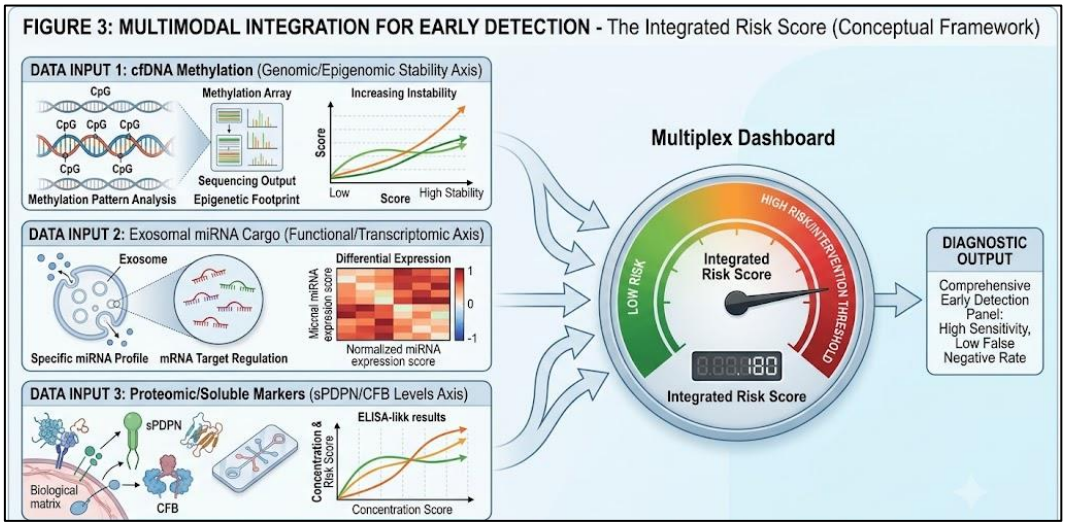

Fig 3: Multimodal Integration for Early Detection. Integrated risk score (cfDNA methylation analysis, exosomal miRNA profiling and soluble protein quantification (sPDPN/CFB)) for early cancer detection in high-risk individuals in a single multiplexed liquid biopsy panel.

Importantly, 43% of these signal-negative patients later had cancer within 2 years, indicating that cancers were detected early. In a separate study, 7,095 hypermethylated regions and 212 hypomethylated regions were identified in 25 BRCA germline mutation carriers compared to 19 controls using a technique called cfMeDIP-seq (cell-free Methylated DNA Immunoprecipitation and High-Throughput Sequencing). The regions were able to distinguish between BRCA positive and healthy samples with an AUC of 0.95, a sensitivity of 88% and a specificity of 94.74% [31].

4. Discussion

4.1. A Coherent Translational Pipeline

From Tissue to Blood The evidence collated in this review provides a new and unique translational pathway: Tissue discovery (pre-CAF) → Mechanistic understanding (stromal reprogramming) → Clinical translation (liquid biopsy) . This is a new paradigm for cancer prevention in high-risk populations. The discovery of the PDPNhigh/CD10+ pre-CAF signature in histologically normal breast tissue from BRCA1/2 carriers (De Leonardis et al., 2025) is a landmark discovery for three interrelated reasons [19]: First, it offers clear proof that stromal changes occur before epithelial changes, a notion that was previously only hypothesized but not shown at the single-cell level in human tissue [20]. Second, the acceptance of this signature in both BRCA1 and BRCA2 carriers indicates that there is a common stromal response to DNA repair deficiency, regardless of the tumour suppressor gene involved [52, 53]. Third, the temporal advantage (these cells are present years before imaging abnormalities are detected) provides a new therapeutic window for intervention that has not existed before [19].

This finding is a paradigm shift in decades-long oncology dogma of epithelial-centric carcinogenesis. The "second hit" hypothesis suggests that biallelic inactivation of BRCA1/2 is the rate limiting step in tumour initiation [52, 53]. The pre-CAF discovery, however, indicates that the stromal microenvironment may be the "first hit", setting up a "fertile soil" that allows the expansion and malignant transformation of already vulnerable heterozygous epithelial cells [19]. This conceptual shift has significant implications for basic research as well as clinical practice.

4.2. The inherent limitations of tissue-based detection.

Although the pre-CAF signature is a biological beauty, its clinical utility is limited by the need for invasive tissue sampling. Core-needle or surgical biopsies are core procedures, and are not recommended in the absence of radiological abnormalities, which is why asymptomatic BRCA carriers are reluctant to undergo them. This ethical and practical obstacle has stimulated a concerted effort to find blood-based surrogates that can interrogate the pre-neoplastic stroma without being invasive. Technical problems with the detection of tissues should not be underestimated. The pre-CAF quantification workflow (mechanical mincing, enzymatic digestion with collagenase/hyaluronidase, vigorous trituration, filtration through 40–70 µm strainers and flow cytometric analysis) is labour-intensive, time consuming and requires specialised equipment and expertise [55].

Furthermore, the processing may generate artefacts that can affect the accuracy of the measurement, such as the loss of fragile cell populations or changes in surface marker expression due to stress [56]. These technical challenges further highlight the need for non-invasive alternatives.

4.3. The Liquid Biopsy Landscape

Opportunities and challenges in oncology, liquid biopsy has become a revolutionary technology, providing the potential to track tumour dynamics via minimally invasive blood sampling serially. Each of the three main liquid biopsy compartments (circulating tumour DNA (ctDNA), circulating tumour cells (CTCs) and extracellular vesicles (EVs)) has its own advantages and disadvantages that need to be considered [57].

4.3.1. Soluble Proteins:

sPDPN and CFB The plasma level of soluble PDPN (sPDPN) has been shown to be significantly elevated in breast cancer patients compared to healthy controls, and to be associated with clinical stage, differentiation grade and metastasis status [25]. There are, however, two important caveats in its use as a predictive biomarker in BRCA carriers. First, it has been shown that sPDPN is elevated in established cancers, but not in the pre-cancer state. It is unclear if sPDPN increases in the pre-neoplastic asymptomatic stage of the disease, since there

is no longitudinal study to date that has examined this question. Second, sPDPN is not specific to BRCA-related tumours, as it is increased in a variety of cancers, which makes it less useful as a BRCA-specific predictive marker. Likewise, Complement Factor B (CFB) is a CAF-secreted protein that has been shown to have causal relevance to breast cancer risk via integrative Mendelian randomisation and multiomics analyses [29]. CFB elevation is not specific to BRCA1/2 carriers, however, and is likely a general risk marker for breast cancer, which is why it is not enough to be a predictive biomarker for this high-risk group.

4.3.2. cfDNA Methylation

The most advanced non-invasive strategy. The most advanced non-invasive approach to early cancer detection is currently cell-free DNA methylation analysis. Circulating cfDNA can be used to identify epigenetic changes that occur months to years before tumour development, by analyzing the methylation patterns of the DNA [31]. In the landmark study that combined genomic and epigenomic features (fragmentomic and DNA methylation) it was shown that cancer-associated signals could be detected in 71% of those carriers who had active cancers and importantly, 56% of those carriers who had negative surveillance results. Of those who had a negative result and who had a signal, 43% had a signal [58]. Subsequently diagnosed cancer within 2 years (indicating that cfDNA methylation signatures may be able to identify occult cancers before conventional imaging). The cfMeDIP-seq study also confirmed this method, with 7,095 hypermethylated and 212 hypomethylated regions distinguishing between BRCA carriers and healthy controls with an AUC of 0.95, sensitivity of 88% and specificity of 94.74% [31].

These findings have a biologically plausible mechanistic basis in the hypomethylation of genes involved in DNA repair and cell cycle regulation in breast cancers with mutations in BRCA1/2 [31]. This can allow for early diagnosis of cancer, minimal residual disease (MRD) detection and response to treatment monitoring, all in one blood draw. But there are limitations to cfDNA methylation analysis. The amount of tumour derived cfDNA in the blood is frequently very low, especially in early or pre-neoplastic disease states [31], and thus very sensitive detection methods are needed. Furthermore, it is difficult to determine the exact source of the methylated cfDNA fragments since other organs may also be a source of the circulating pool [59]. The challenges underscore the need for complementary approaches.

4.3.3. Exosomal miRNAs: Nature's Biologically Elegant Solution.

Exosomal miRNAs are the most theoretically elegant approach to the non-invasive detection of pre-CAF activity. All cell types release exosomes, which are vesicles containing miRNA cargo and are protected by a lipid bilayer, thus offering a stable, biologically protected vehicle for miRNA cargo [60-62]. MiRNAs are protected from enzymatic degradation by the lipid membrane and are detectable in plasma with high stability [37].

In contrast to free miRNAs, which are extremely unstable and have high inter-assay variability [34], exosomal miRNAs are very stable and can be reliably quantified. The biological significance of exosomal miRNAs is also of great interest. Pre-CAFs secrete exosomes that are taken up by distant epithelial cells, facilitating paracrine and endocrine communication [19].

Exosomal miRNAs (such as miR-21, miR-9, miR-200) are delivered into recipient cells and are able to inhibit tumour-suppressor genes or promote survival pathways [38, 63]. The idea that this pre-CAF-derived exosomal cargo may be sufficient to drive a vulnerable, heterozygous epithelial cell toward malignancy without the need for a second somatic mutation, though not yet demonstrated in vivo, is biologically plausible and experimentally tractable. Distinct exosomal miRNA signatures have already been identified in the plasma of BRCA1 carriers years prior to diagnosis in proof-of-concept studies [50]. The cargo of exosomes, such as miRNAs and proteins, is frequently linked to patient prognosis and can give clues to the aggressiveness of the tumour and survival rates, which can help to assess patient risk [64, 65].

The exosomal biomarkers have exhibited excellent diagnostic performance, such as a 4-miRNA EV panel, which exhibited a sensitivity of 98% and a specificity of 96% in the diagnosis of breast cancer [66]. This makes exosomal miRNAs ideal candidates for liquid biopsy biomarkers.

4.4. The Holy Grail

PDPN/CD10-specific Exosomes Pre-CAF biology and exosomal transcriptomics converge towards the ultimate translational goal of isolating PDPN/CD10-specific exosomes from peripheral blood. This would be a real "liquid biopsy of the stroma" allowing for serial monitoring of the pre-neoplastic niche in BRCA carriers without any invasive procedures.

The technology to do this is already in place. Exosomes can now be isolated using generic surface markers, such as CD63 and CD81, on microfluidic chips that are well established and commercially available [67, 69]. The next step is to develop this technology to capture exosomes that express both PDPN and CD10, the surface signature of pre-CAFs.

A number of research groups are working on the development of these platforms, and preliminary prototypes have shown that multiplexed capture of exosomes, by tissue-specific markers, is feasible [70]. But there are still challenges to be addressed.

First, PDPN is expressed by several cell types such as cancer cells, lymphatic endothelial cells and other stromal cells [71]. It will be important to carefully validate the origin of PDPN/CD10-positive exosomes in the circulation, specifically from breast pre-CAFs, rather than from other PDPN expressing tissues, which will require the use of animal models with tissue specific reporter systems.

Second, the sensitivity of such an assay should be high enough to detect pre-CAF-derived exosomes in the early pre-neoplastic stage, where the number of pre-CAFs might be small.

Third, the isolation protocols, normalisation strategies and quality control measures need to be standardised prior to clinical implementation.

4.5. A Multi-Analyte Predictive Panel

The future of risk stratification with the complexity of cancer biology, a single analyte is not likely to be enough to give you predictive power. The future is probably in an integrated risk score that integrates complementary biological data. Tracking epigenetic drift would give an indication of global genomic instability and early clonal expansion (30). The quantification of exosomal miRNA cargo would reflect the activity of the pre-CAF niche (72) and capture the functional

biological communication between the stroma and epithelium.

4.6. Proteomic Profiling

The measurement of sPDPN in conjunction with other stromal mediators such as CFB, cytokines, and growth factors would give a complementary measure of the proteomic environment [26, 27, 73]. The combination of these different types of data would necessitate advanced computational methods, such as machine learning algorithms that can detect multi-dimensional signatures that are highly sensitive and specific to the prediction of imminent transformation [74]. These strategies have been effective in other cancer settings and are appropriate for the current situation.

4.6.1. Standardisation Challenges

The direction to clinical validation exosomal research needs to address key technical standardisation challenges prior to clinical implementation: First of all, the traditional gold standard exosome isolation method, Ultracentrifugation, is time-consuming, requires large sample volume and has variable results [62, 75]. Commercial precipitation and affinity-based kits provide convenience, but are not uniform in purity, yield, and reproducibility [76, 77]. There is a great need for consensus guidelines for recommended isolation methods for specific applications in the field.

4.6.2. Normalisation Strategies

No consensus normaliser exists for exosomal miRNA studies. Some researchers employ synthetic miRNAs (e.g., cel-miR-39) that are spiked into the RNA sample [74], and others use endogenous reference genes (e.g., U6, miR-16) [78]. Results can vary widely depending on the normaliser used, and can be contradictory between studies.

4.6.3. Haemolysis Contamination

even low levels of haemolysis can cause an overestimation of miRNA levels due to the release of high amounts of erythrocyte-derived miRNAs (e.g., miR-451) into the plasma [79]. Good quality control is critical for reproducible results, and should include measures to identify and reject homolysed samples.

4.6.4. Inter-Laboratory Variability

There is a high inter-laboratory variability, which is due to differences in sample collection, processing, storage and analysis protocols [80]. Standardised operating procedures and external quality assessment programmes are crucial for clinical validation.

4.7. Ethical and practical issues in clinical implementation.

The medical profession needs to be ready for the consequences of telling a healthy 30-year-old that they are a BRCA carrier and have a positive blood test for pre-cancer. This shifts the paradigm from reactive oncology to proactive risk-mitigating intervention.

Psychosocial Impact: The psychological impact of having molecular evidence of pre-cancerous changes, but no imaging correlate, should be carefully managed.

The infrastructure of genetic counselling will have to be expanded to provide for this new layer of predictive information.

Clinical Management: A positive test would present challenging clinical questions. If it does, should it lead to more frequent imaging? Does it warrant consideration of chemoprevention? Does it affect the timing of prophylactic surgery? Prospective trials will be needed to define evidence-based management algorithms.

Chemoprevention Opportunities: The PDPN/CD10 stromal axis could be a target for chemoprevention. Selective oestrogen receptor modulators (SERMs) and aromatase inhibitors have demonstrated chemopreventive effects in BRCA carriers, but uptake has been low because of concerns about efficacy and side effects. A future direction is the development of targeted therapies specifically directed at pre-CAFs, either by blocking the function of PDPN or by blocking downstream signalling pathways.

Health Economics: The cost-effectiveness of predictive blood-based screening needs to be assessed. If these tests could detect people who are likely to develop cancer in the near future, the cost of late-stage treatment could be enormous.

4.8. Limitations

This review has a number of limitations that should be noted. First, the field of pre-CAF biology is still in its infancy and most results come from a small number of studies with small sample sizes. Second, the evidence of exosomal signatures in BRCA carriers is based on cross sectional studies, and there is no definitive prospective validation. Third, the difficulty of isolating tissue-specific exosomes from the circulation is still a challenge. Fourth, the ethical and practical considerations of predictive testing of healthy individuals have not been thoroughly examined.

4.9. Concluding Synthesis

The combination of stromal biology, exosomal transcriptomics, and advanced microfluidics will usher in a new era of the ability to predict impending carcinogenesis in high-risk BRCA1/2 individuals with a simple blood test. The discovery of the PDPNhigh/CD10+. pre-CAF signature has given a precise biological target, and advances in liquid biopsy technologies have given the tools to interrogate this target non-invasively. The journey from tissue discovery to clinical translation is now well underway. Technical standardisation, clinical validation and ethical implementation are still significant but achievable challenges. The ultimate goal for the millions of women around the world who carry the BRCA1/2 mutations is transformative: cancer will not only be detected earlier, but predicted and prevented.

Declarations

Ethical approval. not applicable. The cell line were established in long term in the Oxford Brookes University laboratories and tested for mycoplasma.

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