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DERLEME / REVIEW

New paradigms in breast cancer metastasis: the role of inherited genetic predisposition and molecular profiling

Meme kanseri metastazında yeni paradigmalar: kalıtsal genetik yatkınlık ve moleküler profillemenin rolü

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Abstract

While breast cancer retains its status as the most prevalent malignancy among women globally, the vast majority of mortality is attributable specifically to metastatic progression. Traditional oncology has historically viewed metastasis largely as a stochastic event, driven primarily by somatic mutations acquired during the evolution of the primary tumor. This review challenges that perspective by synthesizing emerging insights into how inherited susceptibility and somatic molecular evolution converge, alongside the role of next-generation liquid biopsy in surveillance. Key findings reveal that functional germline variants in the PCSK9 gene most notably rs562556 act by targeting the LRP1 receptor on tumor cells. This interaction suppresses metastasis-regulating genes such as XAF1 and USP18, thereby facilitating immune evasion and colonization. Parallel to this, deficiencies in DNA repair genes, including BRCA1/2, PALB2, and CHEK2, appear to facilitate dissemination by modulating tumor–immune dynamics via the cGAS–STING pathway. On the somatic front, recurrent mutations in PIK3CA, AKT1, and ESR1 are shown to cultivate an immunosuppressive tumor microenvironment, particularly through M2 macrophage polarization. Clinically, the evolution of liquid biopsy technologies specifically regarding ctDNA fragmentomic features and methylation signatures now permits the real-time tracking of minimal residual disease (MRD) and the early identification of therapeutic resistance. Ultimately, metastasis is not merely a reflection of somatic evolution but is deeply rooted in a heritable biological program. Integrating these discoveries offers a shifting paradigm for both understanding and managing metastatic breast cancer.

Keywords: Breast cancer, metastasis, ctDNA, liquid biopsy, genetic predisposition.

Öz

Meme kanseri, dünya genelinde kadınlarda en sık görülen malignite olma özelliğini korurken, mortalitenin birincil nedeni hala metastatik yayılımdır. Geleneksel onkoloji görüşü, metastazı büyük ölçüde primer tümörün evrimi sırasında kazanılan somatik mutasyonların rastgele (stokastik) bir sonucu olarak nitelendirmiştir. Ancak bu derleme, denklemin diğer tarafını; yani kalıtsal genetik mimarinin ve moleküler profillemenin metastatik süreçteki belirleyici rolünü mercek altına almayı amaçlamaktadır. Elde edilen veriler, *PCSK9* genindeki fonksiyonel varyantların (özellikle rs562556) tümör hücrelerinde LRP1 reseptörünü hedef alarak, *XAF1* ve *USP18* gibi metastaz baskılayıcı genleri susturduğunu ve immün kaçışı tetiklediğini göstermektedir. Buna paralel olarak *BRCA1/2*, *PALB2* ve *CHEK2* gibi DNA onarım genlerindeki defektlerin, cGAS–STING yolağını manipüle ederek yayılımı kolaylaştırdığı belirlenmiştir. Somatik düzeyde ise *PIK3CA*, *AKT1* ve *ESR1* mutasyonlarının, M2 makrofaj polarizasyonu üzerinden immünosüpresif bir mikroçevre inşa ettiği görülmektedir. Klinik tarafta ise sıvı biyopsi (ctDNA); özellikle fragmantasyon ve metilasyon imzaları sayesinde minimal rezidüel hastalığın (MRD) takibinde yeni bir standart sunmaktadır. Metastaz, sadece sonradan kazanılan somatik bir evrim değil, aynı zamanda kalıtsal bir biyolojik programın yansımasıdır. Bu derleme, kalıtsal yatkınlık, somatik moleküler evrim ve yeni nesil sıvı biyopsi stratejilerinin entegrasyonunu, klinik yönetimde güncel bir paradigma olarak sentezlemektedir.

Anahtar kelimeler: Meme kanseri, metastaz, ctDNA, sıvı biyopsi, genetik yatkınlık.

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women globally, but also continues to be a leading cause of cancer-related death[1]. The current therapeutic strategies have achieved a 5-year survival rate of more than 90% for patients with early-stage; however, this achievement is very different from that for disseminated (Stage IV) disease with a 5-year survival rate idling at 30%[2]. The biology of metastasis is remarkably ineffective and complex, and includes a process in which tumor cells must separate from the primary tumor, penetrate into the circulation, evade immune surveillance, extravasate into target organ parenchyma, and ultimately establish secondary colonies.

For a long time, scientists presumed that the accumulation of somatic mutations inside tumor cells was the main engine driving this complicated process. In contrast, a contemporary reinterpretation of Stephen Paget's 1889 "seed and soil" theory postulates that metastatic events are governed not only by the intrinsic metastatic potential of the cancer cell (the "seed"), but also by the physiological and genetic makeup of the host (the "soil"). Advances in the past few years, which have appeared in journals with the highest impact such as Nature, Cell, and Science, have led to a re-evaluation of how metastasis biology is governed, with a strong emphasis on the pivotal role of the patient's inherited genetic background. In this context, novel compo-nents, including homologous recombination deficiencies (HRD) and unexpected cross-talk between immune control and lipid metabolism, have emerged as decisive factors[3]. One of the more surprising results maybe is that a common germline variant in PCSK9 gene classically linked with cholesterol regulation is a major risk factor for metastasis in breast cancer patients[4,5] .Together these observations have more or less erased the traditional dichotomy of metabolic and oncogenic processes.

Yet, deciphering the molecular complexity of metastasis is of little value if it does not result in a therapeutic strategy. The era of precision medicine has been exemplified by the clinical significance of actionable somatic mutations (PIK3CA and ESR1)[3]as well as the possibility of monitoring these alterations in real time multilaterally through liquid biopsy (ctDNA)[6]. Several pivotal Phase III clinical trials, namely PADA-1, EMBER-3, and SERENA-6, have reported improved patient outcomes when treatment strategies are switched based on molecular profile[7–9]. As a result, the goal of this review is to provide an in depth overview of tumor intrinsic and extrinsic somatic processes driving metastatic dissemination, to delineate the immune and metabolic interactions within the tumor microenvironment, and explore how liquid biopsies might enable us to translate these findings into clinical applications.

INHERITED GENETIC PREDISPOSITION AND METASTASIS

Although BRCA1 and BRCA2 have traditionally dominated discussions of inherited breast cancer risk, increasingly we know that the genetic underpinnings of metastatic potential are far more complex than previously assumed [6]. The influence of germline variants is not limited to the initial mutational load of the tumor; rather, these genetic factors actively modulate how the tumor interacts with the immune system and the tumor's specific preference for distant tissues, or organotropism. Accordingly, in this section we review the nascent PCSK9 mutants in contrast to the well-established roles of canonical DNA repair genes in the metastatic cascade.

PCSK9 germline variants: the convergence of metabolism and metastasis

From a historical prospective PCSK9 has been considered to be found only in the lipid metabolism field and known mostly for controlling cholesterol level by degradation of LDL receptors (LDLR) on hepatocytes. Yet this established dogma has been upended in dramatic fashion by seminal work in Cell (2025), which describes PCSK9 not as a mere metabolic player, but as a metastatic driver in breast cancer. The rs562556 (V474I) Variant: The Surprising Metastatic Consequence Widespread among 70% of the European population, PCSK9 rs562556 (V474I) germline variant represents a paradoxical biology: although it does not lead to a full loss of enzyme function, it introduces some functional modifications which lead to a high risk of metastatic recurrence. Data from retrospective studies in a Swedish population bring this risk into sharp focus. Early breast cancer patients homozygous for this allele had 22% 15-year metastatic recurrence, compared with only 2% for non-carrier[4]. This extreme difference represents one of the most convincing evidence so far that the ability

for metastasize is not only influenced by somatic evolution, but by inherited genetics of the patient (Figure 1).

Molecular mechanism: LRP1–XAF1–USP18 axis

Attempts to explain the mechanistic basis of PCSK9-mediated metastasis have mainly focused on its interaction with the tumor cell surface receptor Low-density lipoprotein receptor-related protein 1 (LRP1)[4,5]. Under homeostatic condition, PCSK9 binds to LRP1 and induces its lysosomal degradation. The V474I mutant, by contrast, seems to magnify this activity possibly resulting from better binding stability or a partial gain-of-function leading to the extensive reduction of LRP1 from the membrane of the tumor cell. This decrease in membrane LRP1 induces a series of intracellular changes, which alter cell fate at a fundamental level (Figure 2).

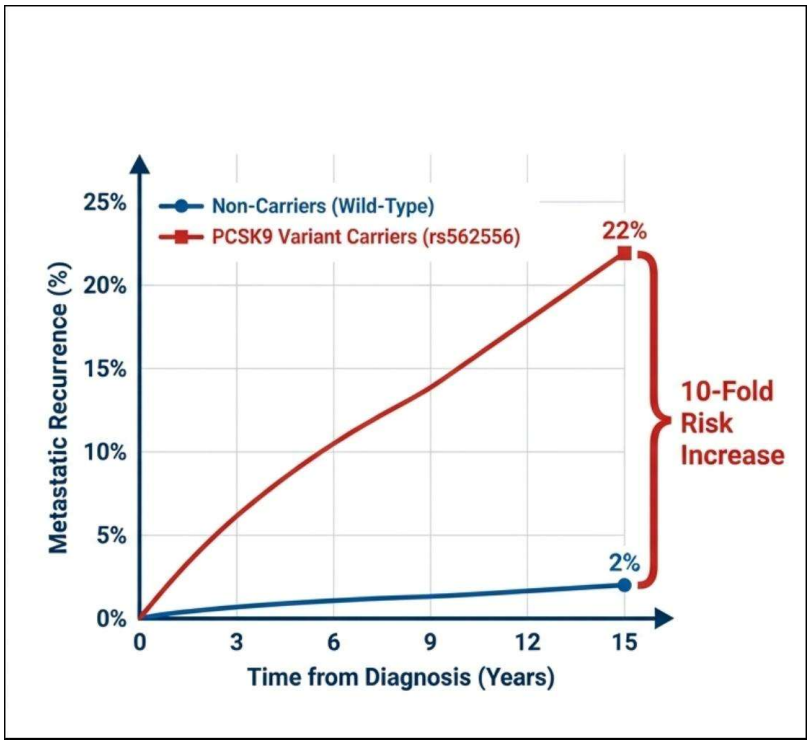

Figure 1. Impact of the inherited PCSK9 variant on metastatic recurrence.

Illustration of the noted disparity in rates of metastatic recurrence. The figures illustrate a 22% risk of recurrence over 15 years for carriers of the rs562556 PCSK9cc variant, as compared with 2% for non- carriers. This highlights the importance of heritable metabolic regulators in metastatic potential. (Adapted from [4] and redrawn using Notebooklm).

Mostly, the down-regulation prevents nuclear translocation of LRP1 intracellular domain (ICD), which is a fragment of LRP1 that acts as transcriptional regulator. Accordingly, the transcription of positive targets (e.g., XAF1 and USP18) that depend on LRP1 for their positive regulation, is blocked. The biological consequences are that:1 silencing of the pro-apoptotic tumor suppressor XAF1 confers resistance to anoikis (detachment-induced cell death) and 2 loss of USP18 negatively affects type I interferon signaling. The latter effect generates a metastatic-friendly niche because it reduces the surveillance capacity of NK and T cells in the niche. Such mechanistic insights have led to increased enthusiasm for the possible use of existing PCSK9 inhibitors, the monoclonal antibodies evolocuma and alirocumab, as antimetastatic adjuvants. In addition, preclinical data suggest a synergistic option, namely that PCSK9 blockade may increase the efficacy of anti-PD-1 immunotherapy (Table 1).

BRCA1/2: genomic instability and immune selection

Germline mutations in BRCA1 and BRCA2 severely impair homologous recombination (HR) repair, leading to a state of genomic instability that promotes tumor evolution and selection of metastatic clones[4]. An important consequence of this defect is the generation of cytoplasmic DNA fragments, or micronuclei, that chronically activate the cGAS–STING pathway. There is a paradoxical situation here: when this pathway is activated acutely it induces strong antitumor immunity mediated by type I interferons, whereas chronic activation leads to an inflammatory and immunosuppressive tumor microenvironment that promotes metastatic dissemination. Furthermore, distinct organotropism patterns arise with a striking overrepresentation of visceral metastases in BRCA2 carriers, providing further evidence for the gene-specific nature of metastatic spread.

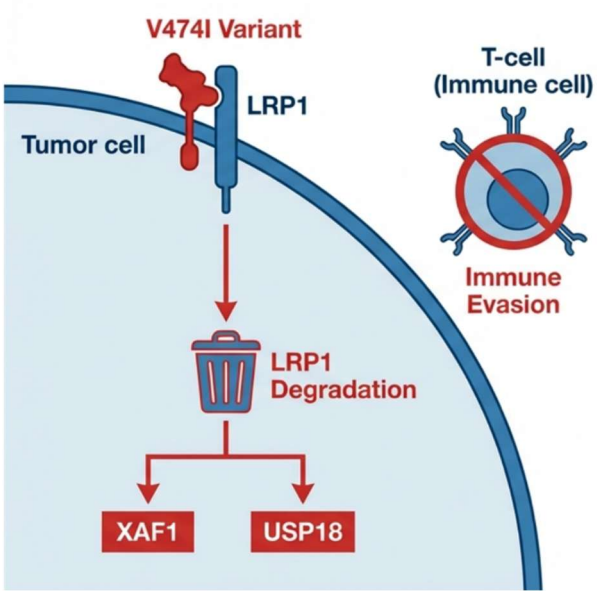

Figure 2. Molecular mechanism of PCSK9-driven metastasis.

Schematic illustration of the PCSK9-mediated metastatic axis. The illustration shows the V474I variant promotes the degradation of tumor cell LRP1, which in turn suppresses XAF1 and USP18. This allows the cascade to suppress the immune response, and promote tumor survival in the environment of metastasis. (Adapted from [4] and redrawn using Notebooklm).

Table 1. Inherited risk factors and PCSK9 mechanism [4,6]

Gene/Variant	Effect Mechanism	Metastatic Outcome
PCSK9 (V474I)	Increases degradation of the LRP1 receptor.	Immune escape, XAF1/USP18 loss increases metastasis risk by 2.3 times.
BRCA1/2	Defect in homologous recombination repair.	Genomic chaos, metastatic clone selection, and immune modulation.
CHEK2 (1100delC	Loss of G1/S checkpoint.	Prone to bone metastasis, especially in ER+ patients (68% of first metastases occur in bone).

PCSK9, Proprotein convertase subtilisin/kexin type 9; V474I, Valine to Isoleucine substitution at position 474; LRP1, Low-density lipoprotein receptor-related protein 1; XAF1, XIAP-associated factor 1; USP18, Ubiquitin specific peptidase 18; BRCA1/2, Breast cancer gene 1 and 2; CHEK2, Checkpoint kinase 2; ER+, Estrogen receptor positive.

Table 2. Molecular flow of the metastatic process[3,13,14]

Stage	Molecular Events and Genetic Factors	Result
1. Initiation (Germline)	**PCSK9 (V474I)**, **BRCA1/2**, **CHEK2**, **PALB2** genotypic background.	The tumor's initial immune profile and level of genomic instability are determined.
2. Immune Modulation	Loss of MHC-I/II, decreased T cell infiltration, M2 macrophage polarization.	Tumor escape from the immune system and shaping of the microenvironment.
3. Somatic Profiling	Acquisition of **PIK3CA**, **TP53**, **ESR1**, **AKT1** mutations.	Increased proliferation, treatment resistance, and acquisition of invasive properties.
4. Immune Evasion + EMT	Increased PD-L1, Activation of Epithelial-Mesenchymal Transition (EMT).	Acquisition of cell motility and invasion of the stroma.
5. Circulation	Circulating Tumor Cell (CTC) and ctDNA release.	Tumor cells entering the bloodstream and being transported to distant organs.
6. Colonization	Microenvironment adaptation (e.g., RANKL in bone, mitochondrial fission in the brain).	Formation of new tumor foci (metastases) in distant organs.

PALB2, Partner and localizer of BRCA2; MHC-I/II, Major histocompatibility complex classes I and II; M2, Alternatively activated macrophage; PIK3CA, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TP53, Tumor protein p53; ESR1, Estrogen receptor 1; AKT1, AKT serine/threonine kinase 1; PD-L1, Programmed death-ligand 1; EMT, Epithelial-mesenchymal transition; CTC, Circulating tumor cell; ctDNA, Circulating tumor DNA; RANKL, Receptor activator of nuclear factor kappa-B ligand.

CHEK2 mutations and predisposition to bone metastasis

Checkpoint Kinase 2 (CHEK2) acts as an essential protector of cell-cycle integrity and DNA damage response. However, this particular variant, the CHEK2 1100delC variant, goes beyond just conferring risk for estrogen receptor-positive breast cancer; it modulates metastatic behavior as well. The Mechanistic Basis for this Phenomenon is Often Referred to as the "Bone Marrow Vicious Cycle." CHEK2-deficient tumors are also impressively adaptable to the osseous niche. Through pathological crosstalk with stromal cells these tumors also induce RANKL that leads to osteoclast activation and subsequent aggressive bone resorption[3,10]. When the bone matrix breaks down, it unseals trapped growth factors chief among them TGF-β that signal back to the tumor cells and encourage their growth. This builds a positive-feedback loop that stabilizes metastatic colonization.

PALB2 and the tumor immune microenvironment

PALB2, serving as the molecular scaffold that connects BRCA1 and BRCA2, is essential for homologous recombination-mediated DNA repair. However, germline mutations in this gene induce a "BRCAness" phenotype, which has unique, and often profound, immunological consequences. Emerging evidence is revealing that the consequences of PALB2 deficiency include perturbation of cGAS–STING and interferon signaling[6]. This eviction is what makes the tumor microenvironment an immunologically "cold" fortress. As a result, this immunosuppressive terrain not only promotes the metastatic process but also constitutes a substantial obstacle to the success of immunotherapeutic modalities.

SOMATIC MUTATIONS AND THE EVOLUTION OF METASTASIS

But tumor biology is not studied in a vacuum; it builds upon the inherited genetic background and becomes more aggressive as somatic mutations are added. Such changes are also commonly clustered at particular genomic "hotspots" in metastatic breast cancer most prominently in the PI3K/AKT signaling axis, TP53, and the estrogen receptor gene ESR1. Together these alterations define how rapidly a

tumour divides, how it interacts with the immune system and whether it will respond to treatment.

PIK3CA mutations: roles in immune suppression

PIK3CA mutations, notably the H1047R and E545K hot spots, lead to constitutive activation of the PI3K pathway and occur in ~40% of estrogen receptor–positive breast cancers[3]. But they do more than just speed up cell growth. These mutations actively modify the tumor immune microenvironment by promoting PD-L1 expression on tumor cells, which blunt T-cell mediated cytotoxicity. Moreover, these factors promote the production of immunosuppressive cytokines including IL-10 and TGF-β, creating a niche permissive to liver metastasis. Clinically this knowledge has translated in PI3Kα inhibitors such as Alpelisib and Inavolisib becoming the standard of care, with the combined advantage of hitting the pathway and rescuing antitumour immunity.

AKT1 E17K mutation and macrophage polarization

The AKT1 E17K mutation is rare in breast cancer (3–5%) but has a disproportionate impact on metastatic behavior. It leads to constitutive pathway activation as a consequence of aberrant membrane targeting of AKT1. Most importantly, cells containing this particular change secrete high amount of chemokines, in particular CCL2. This secretion profile forces tumor-associated macrophages (TAMs) to adopt an M2, that is pro-tumorigenic, phenotype [3]M2 macrophages then promote angiogenesis and extracellular matrix remodeling, preparing the ground for metastatic seeding.

TP53 loss and the "cold" tumor microenvironment

In triple-negative breast cancer (TNBC), the platform that is a hub for information gathering, TP53 mutations are ubiquitous (present in about 80% of tumors), and p53 loss does more than simply impair genomic stability. It profoundly remodels the immune microenvironment. In particular, the loss of TP53 is associated with the downregulation of the STING pathway and the suppression of the type I interferon response [11]. This attenuation makes the tumor immunologically "invisible," creating a "cold" microenvironment that permits rampant metastatic dissemination.

ESR1 mutations: mechanisms of acquired resistance

Approximately 30-40% of patients with metastatic estrogen receptor–positive breast cancer develop ESR1 mutations under the selective pressure of aromatase inhibitor therapy, primarily in the ligand-binding domain (Y537S and D538G). These modifications provide the receptor with the capability to function in an estrogen-independent manner, enabling tumor cells to survive in hormone ablated environment – a feature commonly identified in bone and liver metastases. Although these mutations make the tumor resistant to standard endocrine therapies, they do not make it untreatable. Newer-generation oral selective estrogen receptor degraders (SERDs) such as Elacestrant, Camizestrant and Imlunestrant have demonstrated activity against this resistance mechanism [7–9].

TUMOR MICROENVIRONMENT AND METABOLIC ADAPTATION

Metastasis is not a single step which cancer cells perform alone; it is a multistep manipulation of the tumor by stromal and immune elements to form a permissive niche. To allow colonization, the metastatic niche must be actively modified by a series of events that transform it into a soil fostering survival, growth, and immune evasion.

Macrophages as metabolic benefactors

In this changed context, macrophages go beyond their classic role as immune regulators to become essential metabolic supporters. In lactate- and fatty acid–rich microenvironments, these cells provide the tumor with necessary growth factors (e.g., EGF and VEGF) [12] M2 phenotype-polarized macrophages, via their activation of the PI3K/AKT signaling pathway, also promote ECM remodeling a process that directly facilitates tumor invasion and metastastic seeding.

Mitochondrial dynamics and plasticity

The physical separation of tumor cells from the primary site induces a crisis of bioenergetics. Metastatic cells, to survive the journey through hostile environments, need to experience extensive mitochondrial reprogramming. In a demonstration of

this plasticity, recent results in Nature Cancer (2024) show that breast cancer cells that metastasize to the brain survive by increasing mitochondrial fission and fragmentation. By contrast, cells invading lymph nodes take on yet another metabolic profile, shifting their lipid metabolism to utilize the oleic-acid–rich environment of that particular niche[12]. Such metabolic flexibility is essential for life as it disseminates, and new developments uncouple this dilemma.

Epigenetic layers: lncRNAs and methylation

Control of metastasis extends from the static nucleotide sequence of DNA to the dynamic environment of epigenetics. Long non-coding ribonucleic acids (lncRNAs) have now been identified as multifaceted regulators that fine-tune genes associated with invasion, immune evasion, and organ tropism. At the same time, patterns of DNA methylation act as a molecular navigational system that, through driving changes in transcriptional programs and cell plasticity, influences the final place of a tumor's metastasis, or its organotropism[13]

LIQUID BIOPSY: A REVOLUTION IN REAL-TIME MONITORING OF METASTASIS

Conventional tissue biopsies frequently do not capture the entire heterogeneity of metastatic disease and are invasive, which limits the application of them in clinical practice. Circulating tumor DNA (ctDNA) has revolutionized the field by providing noninvasive, real-time monitoring of tumor genetics from a peripheral blood draw [13]. As a representative of dynamic molecular profile of cancer in all metastatic sites, ctDNA seems to be a promising approach for monitoring disease evolution.

ctDNA analysis methods and sensitivity

Two main strategies are employed for the analysis of ctDNA, each with its own benefits (Table 3). Tumor-Informed Approaches: In this approach, tumor tissue is sequenced initially to identify patient-specific mutations that are subsequently monitored in the blood (e.g., Signatera). The sensitivity of this technique is extremely high (up to 10^{-5}), and is therefore well suited for detection of minimal residual disease (MRD) and early relapse. Tumor-Naïve Approaches: In this approach, a fixed gene panel is applied directly to plasma without sequencing of the tumor (e.g., Guardant360). This strategy is the most applicable for treatment selection and comprehensive molecular profiling, with a reported sensitivity of moderate to high (0.1–1% VAF).

Emerging frontiers: fragmentomics and methylation profiling

Mutation-based analyses alone may not be sufficient to capture the full complexity of ctDNA biology. Fragmentomics: Tumor-derived DNA fragments are shorter and end in distinct end-motif signatures than DNA from normal cells. These biophysical experiments contribute to enhanced sensitivity and specificity of ctDNA detection[12]. Methylation Profiling: Tumor DNA has epigenetic signatures (including methylation of specific genomic locations) and so accurately predicting tissue of origin as well as improve early detection and risk stratification.

Table 3. Comparison of ctDNA detection methods[14].

Feature	ddPCR (Digital Drop PCR)	NGS (Panel) - Tumor Naive	WGS / Tumor-Informed
Target	Single, known mutations (e.g. *ESR1* Y537S)	Multiple genes (50-500 genes)	Personalized mutations
Sensitivity	Very High (0.01% VAF)	Medium-High (0.1-1 VAF)	Very High (ideal for MRD)
Cost	Low	Medium-High	High
Usage	Resistance mutation monitoring	Treatment selection, profile	Relapse monitoring, MRD
Advantages	Fast, inexpensive	Comprehensive profile	Highest sensitivity

:ddPCR, Droplet digital polymerase chain reaction; NGS, Next-generation sequencing; WGS, Whole genome sequencing; VAF, Variant allele frequency; MRD, Minimal/molecular residual disease; ESR1 Y537S, Estrogen receptor 1 mutation (Tyrosine to Serine at position 537).

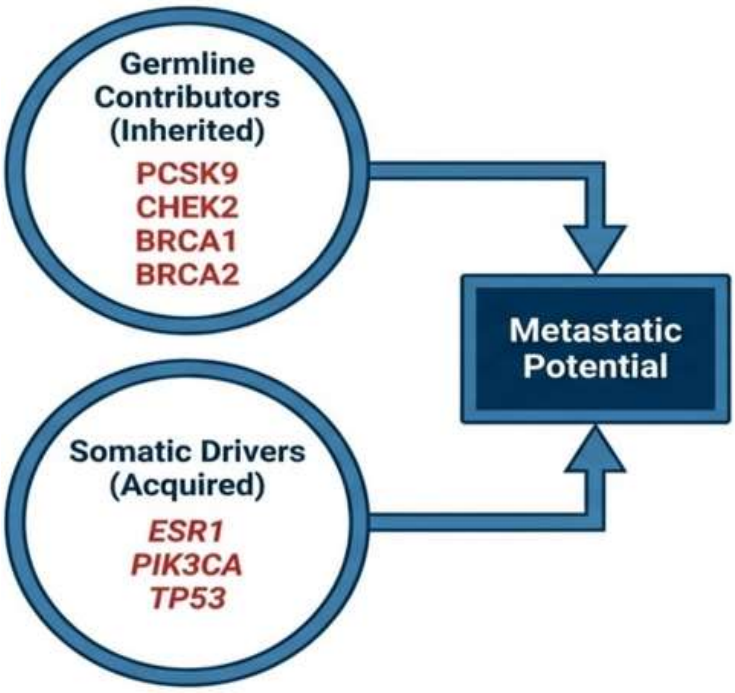

Figure 3. Genetic drivers of breast cancer metastasis.

Summary of genetic determinants of metastatic disease. The visualization integrates germline factors (PCSK9, CHEK2, BRCA1/2) and the main somatic drivers (ESR1, PIK3CA, TP53) and shows the point at which inherited and acquired events coalesce to determine metastatic capability. (Adapted from [6]and redrawn using Notebooklm).

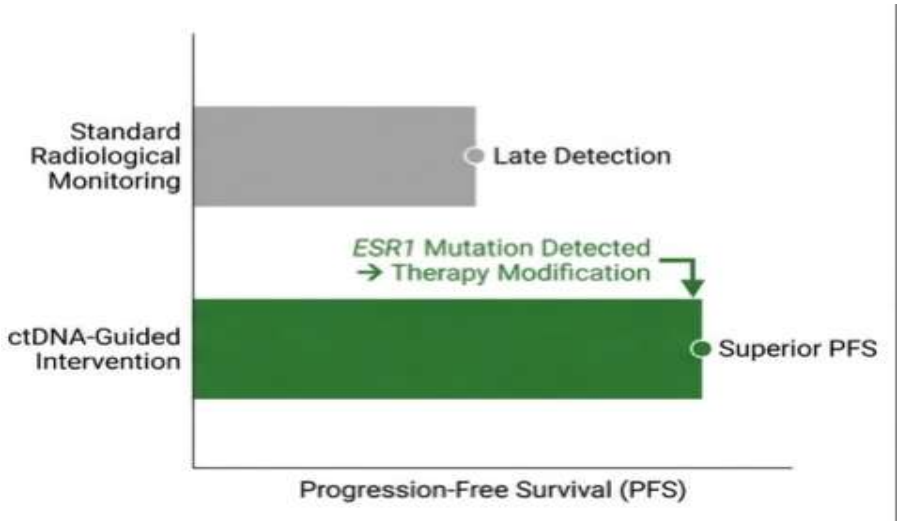

Figure 4. Clinical impact of ctDNA-guided therapy on patient outcomes.

Effect of ctDNA-guided intervention on survival. Consistent with this, results with therapy change in the PADA-1 and SERENA-6 trials according to early ctDNA detection of ESR1 mutations were superior in progression-free survival (PFS) compared with standard radiological monitoring approaches. (Adapted from [7] and redrawn using Notebooklm).

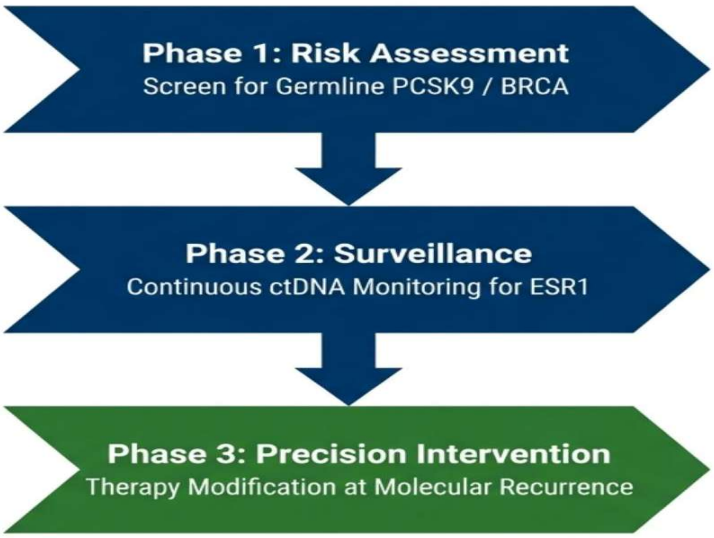

Figure 5. A new standard of care in oncology.

The second care delivery model that we proposed was an integrated care model. The sketch defines a state-of-the-art workflow for integrating baseline germline risk assessment with ongoing ctDNA surveillance, targeting intervention at the earliest evidence of molecular recurrence to maximize patient outcome. (Adapted from [1]and redrawn using Notebooklm).

Clinical application: lessons from PADA-1 and SERENA-6

The greatest clinical utility of ctDNA appears for the identification of molecular progression that is,a disease change that can be detected in the blood well before radiologic imaging identifies recurrent disease. PADA-1 Trial: In patients on an aromatase inhibitor + CDK4/6 inhibitor, switching therapy to fulvestrant when blood-based ESR1 mutations were rising prolonged progression-free survival twofold [7]. SERENA-6 Trial (2025): In a similar fashion, switching from ongoing endocrine therapy to Camizestrant in ctDNA-detected ESR1 mutation led to a statistically significant prolongation of PFS (HR = 0.44), demonstrating the clinical relevance of early treatment intervention[8] (Figure 4). EMBER-3 Trial (2024): The oral SERD Imlunestrant demonstrated an improvement in progression-free survival for patients with ESR1 mutations, confirming the utility of ctDNA guided-treatment modification[9].

DISCUSSION

The evidence collated in this review indicates that prioritizing a single genetic perturbation is not adequate for the analysis or treatment of metastatic breast cancer. Recently discovered germline risk factors for example the metastasis-promoting PCSK9 rs562556 variant demonstrate that metastasis is driven not only by tumor-intrinsic evolution but also by the host's metabolic and immunologic milieu[4,5]. Together, these findings offer a strong argument for the potential repositioning of PCSK9 inhibitors as anti-metastatic agents[4].

Looking to the future, it is expected that germline testing at diagnosis will move beyond BRCA-focused panels to include additional germline factors potentially predictive of metastatic risk. Simultaneously, the liquid biopsy field is quickly evolving toward integrated "multi-omic" solutions that leverage mutations, fragmentomics and methylation profiles, among others, to improve sensitivity and biological understanding[13]. The SERENA-6 and PADA-1 trials have demonstrated the clinical significance of intervening in molecular relapse (i.e., at a time when tumor evolution is detectable by ctDNA but has not yet manifested on radiographs)[7,8]. This approach will almost certainly alter what is considered standard oncology care, leading to earlier, molecularly guided treatment decisions.

CONCLUSION

The therapeutic options in metastatic breast cancer are currently being fundamentally reshaped. The addition of analysis for inherited markers in particular variants in PCSK9, as well as DNA repair deficiencies means that we can now identify patients at high risk with greater precision and at an earlier point than ever before[4,6]. Concurrently, the development of liquid biopsy techniques has provided clinicians with the means to track disease evolution inorganico, enabling adaptive therapeutic interventions as early as at the stage of molecular relapse[14]. In addition, the clinical activity registered with oral SERDs recently in ESR1-mutant disease more generally, provides a powerful confirmation of an overarching tenet: that as we better understand the underlying biologic underpinnings of metastasis, outcomes (therapeutic at least) continue to improve (Figure 5)

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