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Bibliometric Analysis of Research Trends of Genomic Testing in Breast Cancer

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ABSTRACT

Introduction: Breast cancer is complex and heterogeneous because mutations can occur at the epigenome, transcriptome, or genome level. Therefore, breast cancer detection must cover the entire genome to identify mutated genes and study the hormonal and biochemical aspects of tumor cells through specific biomarkers so that the proper and effective therapy method can be determined to treat breast cancer.

Methods: This study is a literature review through metadata taken from Scopus and PubMed with the keywords "breast cancer," "diagnostic," and "genomic," obtained from as many as 35A0. The analysis was carried out in stages with the help of Biblioshiny from Rstudio software, then continued with VOSviewer.

Results: The study results showed a shift in the research theme on diagnostic and therapeutic methods for breast cancer, which is increasingly directed towards DNA genomic tests and deep neural networks. In addition, mapping with VOSviewer yielded a blue cluster associated with research on genetic mutations and genetic testing for breast cancer, a yellow cluster related to research on in situ hybridization techniques and neoadjuvant treatment, a red cluster associated with research on breast cancer subtypes and genomic analysis, and a green cluster related to research on breast cancer diagnosis and MammaPrint.

Keywords: Breast Cancer, Gene Mutation, Endocrine Treatment, Chemotherapy, Genomic Testing, MammaPrint

INTRODUCTION

Women are not only prominent supporters of male strength but also a source for the birth and success of future generations. This crucial role of women is relatively threatened by breast cancer, a malignant and complex cancer that is one of the leading causes of death in women (Lal et al., 2017; Meng et al., 2023). Breast cancer is complex because it is caused by many factors including changes at the genome level such as somatic mutations in non-coding genes such as GATA1 and MEN1, changes at the transcriptome level, such as mutations in long non-coding RNA (lncRNA) and micro-RNA (miRNA), and changes at the epigenome level such as DNA methylation, enhancers, and super-enhancers (Oliveira et al., 2022; Y. Zhang et al., 2021). The many factors that trigger changes at the genome, transcriptome, or epigenome level make breast cancer heterogeneous and have various subtypes.

One subtype of breast cancer is caused by mutations in several repair genes in the DNA damage response (DDR) pathway, such as BRCA1 and BRCA2. Damaged

double-stranded DNA can be repaired through conservative homologous recombination (HR). The BRCA1 and BRCA2 proteins are essential for double-stranded DNA repair through homologous recombination. The BRCA1 and BRCA2 genes that have undergone mutations result in variants in the nucleotide base sequences in both genes, which cause the BRCA1 and BRCA2 proteins to be transcribed into mRNA and then translated, which results in variations in the amino acid sequence so that they cannot interact with tumor suppressors, as well as for DNA repair and cell cycle regulators, thus increasing the risk of breast cancer (Lal et al., 2017; Lourenço et al., 2023). The mutated BRCA1 gene has pathogenic variants at c.110C>A and c.5205delA, while the mutated BRCA2 gene has pathogenic variants at c.3280A>T and c.3291dupT (Abdel Hamid et al., 2021). Moreover, patients with breast cancer were found to have the pathogenic variant c.5946delT found in exon 11 of the BRCA2 gene (Berhane et al., 2023).

The ERBB2 oncogene has also been identified as one of the causes of breast cancer. The ERBB2 gene located on the long arm of chromosome 17 encodes the human epidermal growth factor receptor 2 (HER2) protein. The ERBB2 gene that has been mutated into the ERBB2 oncogene has been identified as experiencing overexpression or amplification in around 15-20% of breast cancer patients (Ajabnoor et al., 2024b; Fatima et al., 2017). In addition, a moderate or high risk of developing breast cancer is also associated with ten genes, including ATM, BARD1, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, and TP53 (Palmer et al., 2020).

Breast cancer associated with gBRCA1pv in RNA-based prognostic tests with biomarkers is triple negative (Geyer Jr et al., 2022), while breast cancer associated with gBRCA2pv is confirmed with positive hormone receptors and negative human epidermal growth factor receptor 2 (HER2) (Alexandre et al., 2019; Exner et al., 2014; Schmidt, 2016). However, prognostic tests with predictive on hormone receptors (HR) such as positive Estrogen Response (ER), Progesterone Response (PR), and negative human epidermal growth factor receptor 2 (HER2) are still controversial. Potential prognostic and predictive markers in early and intermediate-risk breast cancer should consider several factors, including age, menopausal status, tumor size, lymph node status, lymph vascular invasion, histological grade, Ki-67 labeling index, genomic signatures such as genome-wide index (GGI), and intrinsic subtype (Gluz et al., 2016; Venetis et al., 2024).

Patients confirmed with breast cancer with hormone receptor-positive and human epidermal growth factor receptor 2 (HER2) negative indicators can be paired with genomic tests such as the MammaPrint test to measure the risk of breast cancer at a high or low level. If the patient is confirmed with high-risk breast cancer, chemotherapy can be recommended (Balic et al., 2019; Bou Zerdan et al., 2021; Caputo et al., 2020; Crozier et al., 2022a; Esserman et al., 2017; IE Krop et al., 2017; H. Liu et al., 2024). Meanwhile, if the patient is confirmed with low-risk breast cancer, it can be suggested to undergo other treatments such as hormonal therapy, for example, endocrine treatment by inhibiting the circulation of steroid hormones such as estrogen or progesterone, because both hormones will be captured by hormone receptors which will increase the expression of tumor cells in patients with breast cancer (Colomer et al., 2018; Hagemann, 2016)

MammaPrint is a diagnostic test that uses the expression levels of 70 genes, some of which are known to be biologically involved in tumor development and metastasis, so it can be used to predict high or low-risk breast cancer and assess the risk of recurrence in early-stage breast cancer (Amezcua-Gálvez et al., 2022; Drukker et al., 2014; Dubsky et al., 2021; Jahn et al., 2020; Westphal et al., 2022). In addition to MammaPrint, genomic tests can use the Oncotype DX assay. This multigene assay

utilizes reverse transcriptase polymerase chain reaction (RT-PCR) to measure the expression levels of 21 genes, consisting of 5 reference genes and 16 cancer genes related to hormones, HER2, proliferation, and invasion (Martínez-Herrera et al., 2024). In addition, genomic predictive tools for breast cancer can also be obtained by studying circulating tumor DNA (ct-DNA), namely single or double-stranded DNA released by tumor cells that can be detected in plasma and have been shown to closely reflect the mutation profile of primary tumors (S. Cheng et al., 2023). One of the results of studying circulating tumor DNA (ct-DNA) has successfully identified several genes that have mutations such as TP53, PI3K, and PIK3CA in the circulating tumor DNA (ct-DNA) studied (VA Nguyen Hoang et al., 2023). This study aims to analyze the bibliometrics of several genomic tests to complement clinical diagnostic tests so that they can provide a comprehensive picture of the causes, types of subtypes, and types of therapy chosen in treating breast cancer.

MATERIALS & METHODS

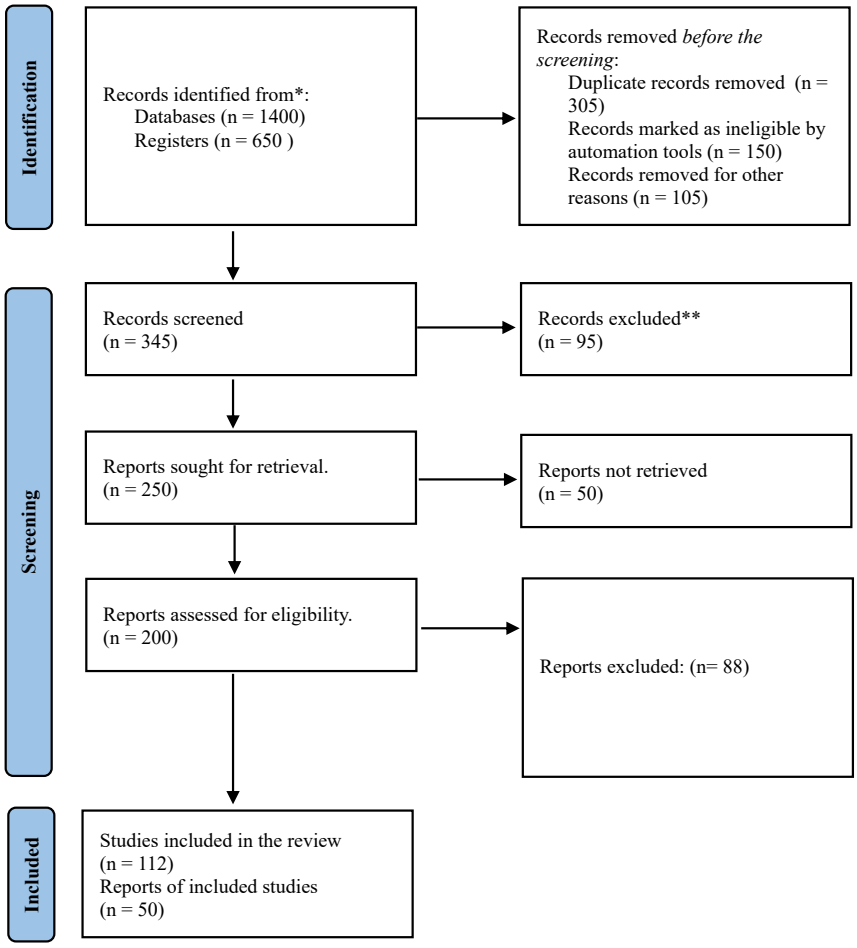

Figure 1. PRISMA analysis of literature review on breast cancer diagnosis

The search used Scopus, PubMed, and Google Scholar databases. The search was conducted to identify research papers discussing genetic diagnosis of breast cancer and MammaPrint. The search was conducted in August 2024, and various types of articles, including review articles, clinical trials, meta-analyses, and book chapters, were included in the search. The search was performed using the keywords "breast cancer," "diagnostic," and "genomic." No filters were applied based on species, language, gender, journal, age, or publication date. The study selection

process complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and a flowchart was created to illustrate this process. The collected data were exported to a text file in CSV format for easy analysis, especially in Rstudio Software. The results of the search metadata were then analyzed with the help of Bibliometric in the form of network visualization. Biblioshiny is a web-based computer program for comprehensive science mapping analysis. Citation analysis was performed on data obtained from the Dimension database using the same search terms used in the PubMed database.

Overlay visualization was performed using VOSviewer (https://www.vosviewer.com/). Examining research papers on academic stress involved a comprehensive analysis across multiple dimensions. First, the study investigated the publishing trends of research papers. Second, the most contributing authors and leading universities in the field were explored, highlighting significant contributors to breast cancer genetic diagnosis research and institutions at the forefront of this scientific pursuit. The third dimension involved the identification of the most frequently used keywords. Furthermore, the thematic evolution of breast cancer genetic diagnosis research was examined, seeking to understand how the focus and emphasis in this domain have evolved. Finally, a comprehensive evaluation was conducted to determine the most cited authors, sources, universities, and countries in the breast cancer genetic diagnosis literature.

RESULT

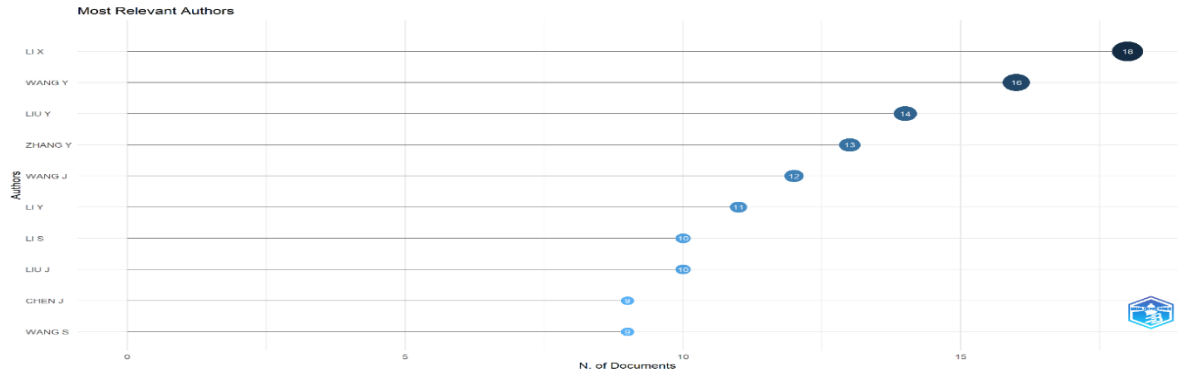

Figure 1. Relevance of the Author

The graph shows the list of the most relevant authors based on the number of documents they produced. The author with the most significant number of records is Li X, who has made 18 documents with discussions focusing on the application of genomic and proteomic technologies for precision diagnosis and subtype analysis of breast cancer (X. Li et al., 2019, 2022) and followed by Wang Y with 16 documents with several topics focusing on the development and application of advanced technologies such as machine learning, genomic sequencing, and bioinformatics for more personalized and targeted cancer diagnosis, prognosis, and therapy (Wang et al., 2019, 2023). Furthermore, Liu Y and Zhang Y contributed significantly with 14 and 13 documents, respectively. Other authors, such as Wang J, Li Y, and Li S, each contributed between 10 and 12 papers, while some others, such as Liu J, Chen J, and Wang S, have nine papers. The dominance of specific names, such as Li, Wang, and Liu, may indicate that these names are prevalent, especially in countries such as China, which is likely where most of this research originated. This suggests that the research field analyzed has a vital activity center in that country.

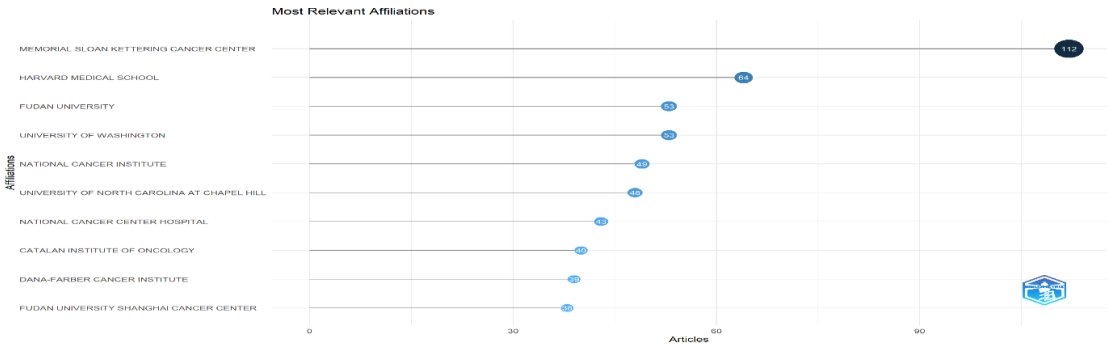

Figure 2. Publications from Several Universities

The graph above shows the most relevant institutions based on the number of articles they have published. Memorial Sloan Kettering Cancer Center emerged as the institution with the most significant contributions, with 112 articles. This indicates that the institution plays a vital role in the research discussed, especially in areas related to oncology or cancer (Penson et al., 2020; Yu et al., 2023), as the institution's name suggests. Harvard Medical School is in second place with 64 articles, followed by Fudan University and the University of Washington, with 53 articles. The fact that Fudan University, an institution in China, is ranked high alongside American institutions such as Harvard and the University of Washington reflects its essential role in global research, especially in health-related areas. Other institutions, such as the National Cancer Institute, the University of North Carolina at Chapel Hill, and the National Cancer Center Hospital, have significant contributions, ranging from 43 to 48 articles. These institutions have a connection to cancer research, indicating that their main research topics are focused on cancer or health-related areas (Camp et al., 2021). In addition, the Catalan Institute of Oncology and the Dana-Farber Cancer Institute are also on this list, indicating that there is active involvement from various countries in the research, reflecting international collaboration in understanding and addressing cancer (Pardo-Cea et al., 2024; Vargas-Parra et al., 2020).

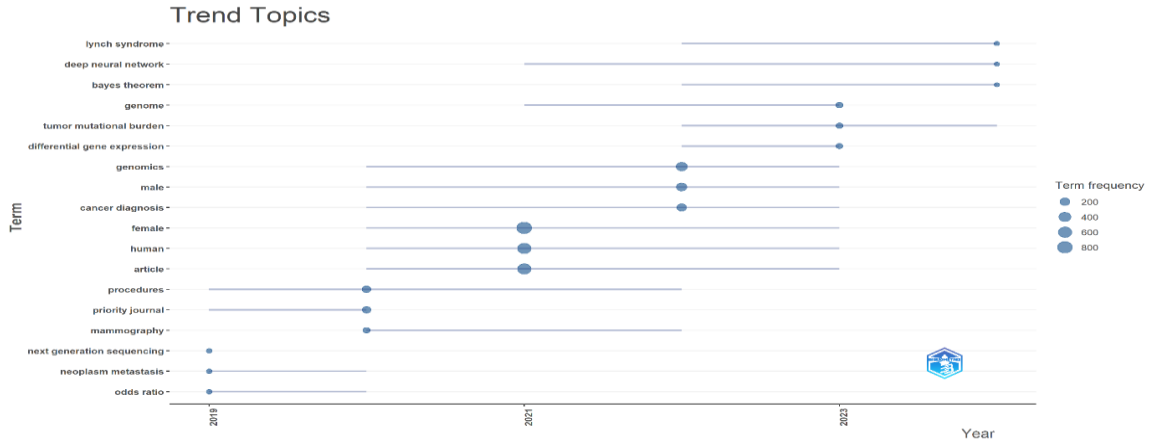

Figure 3. Trends in Research Topics

The figure above shows the trending topics from 2019 to 2023, with the size of the dots indicating the frequency of a particular term. This graph provides insight into the popularity of various issues in research or scientific publications from year to year. Some topics such as "lynch syndrome" (Ferrer-Avargues et al., 2021), "deep neural network" (Sathish Kumar et al., 2024), and "Bayes theorem" (Z. Zhang et al., 2022)

have maintained their popularity consistently from 2019 to 2023. This shows that these topics have high relevance and are a significant focus in academic discussions or research. In addition, topics such as "tumor mutational burden" (Xiao et al., 2021) and "differential gene expression" (Cyrta et al., 2022) have started to gain more attention in the following years, indicating an increase in interest in biomedical and genomics research.

The graphical visualization also shows how some topics, such as "next-generation sequencing" (Oranratnachai et al., 2023) and “neoplasm metastasis” (Byon et al., 2021) gained popularity early in the period but declined in later years. This suggests that these topics were once in the spotlight; new developments or changes in research focus have shifted scientists' attention to other issues. High-frequency nodes such as "male," "female," and "human" indicate that these keywords, although general, are still crucial in a more extensive research context, perhaps in demographic studies or population-based research. Overall, the graph reflects the changes in scientific research priorities and shows how some topics persist or decline over time.

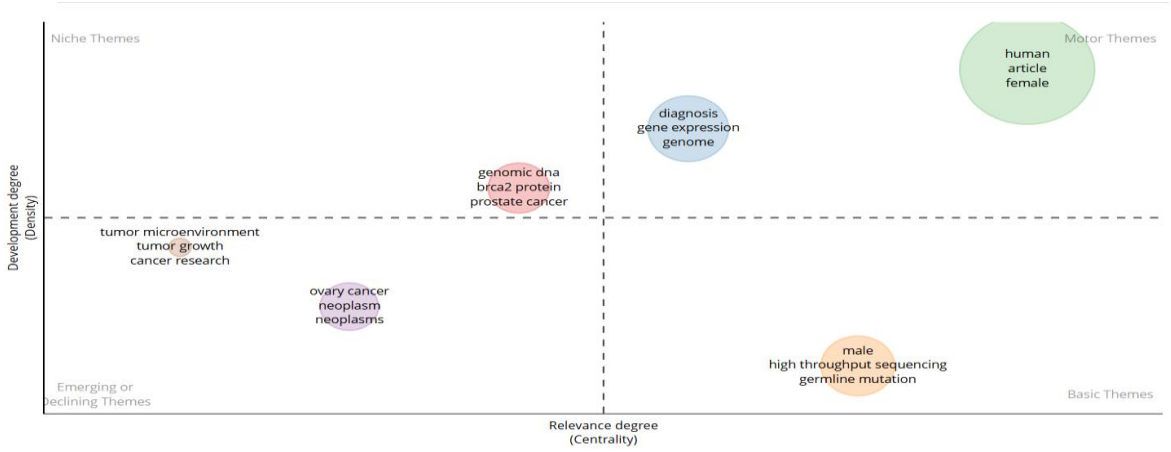

Figure 4. Thematic Map of Research

The image above depicts a theme map that maps various research topics based on two axes: Relevance Degree (Centrality) and Development Degree (Density). This map divides research topics into four quadrants, namely Motor Themes (main themes), Niche Themes (particular themes), and Development Degree (Density). Emerging or Declining Themes, and Basic Themes. Each of these quadrants provides insight into how the topics are positioned in the current research context, which helps researchers understand the importance of each theme and the level of maturity of thematic development.

In the upper right quadrant are Motor Themes, where topics such as "human," "article," and "female" show high relevance and development. This indicates that research focusing on humans, scientific articles, and gender roles, especially women, are central to significant and growing contemporary research. On the other hand, the lower left quadrant contains Emerging or Declining Themes such as "ovary cancer" (Høberg-Vetti et al., 2020), "neoplasm," and "neoplasms" (Romanelli et al., 2021), indicating these topics are in the early stages of development or may be starting to lose attention in the scientific literature. Meanwhile, the lower right quadrant displays Basic Themes such as “male,” “high throughput sequencing,” (Wojtaszewska et al., 2022), and "germline mutation" (Gervas et al., 2019), which, despite having high relevance in basic research, do not appear to be as active or rapidly developing as other themes. Overall,

this theme map offers a guide for researchers to assess research priorities and opportunities based on these themes' development dynamics and relevance in the scientific literature.

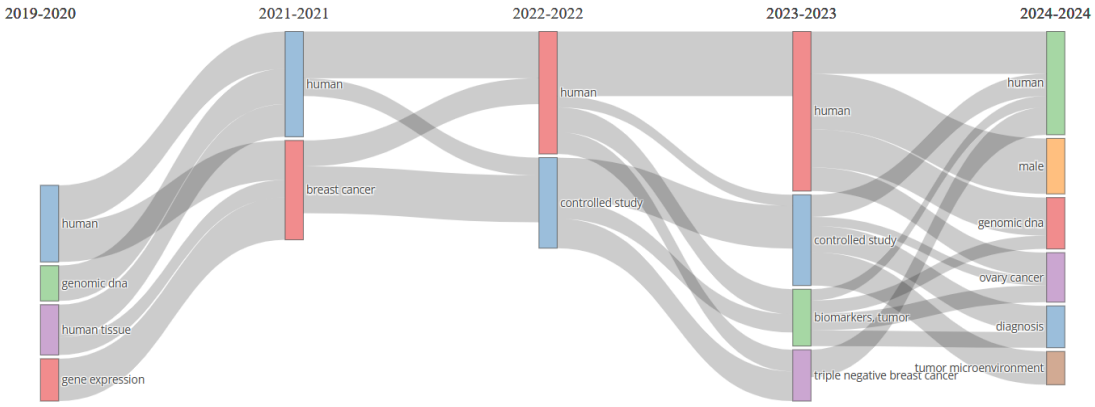

Figure 5. Evolution of Research Themes

The figure above shows a Sankey diagram that visualizes the development and interconnectedness of research topics from 2019 to 2024. This diagram illustrates how key research topics change, showing the evolutionary path from general terms to more specific topics. It also provides an overview of how research topic trends may emerge, grow, or decline in relevance over time. In the period 2019-2020, keywords such as "human," "genomic DNA" (Lee et al., 2024), "human tissue" (Rao et al., 2023), and “gene expression” (Bismeijer et al., 2020) dominated the research landscape. The term "human" emerged as a very central topic, indicating that much of the research at that time focused on studies involving human subjects. Research related to "genomic DNA" and "gene expression" also shows a great interest in genetics and molecular biology, where researchers are interested in understanding the genetic basis of various biological phenomena. "Human tissue" indicates that much research is focused on analyzing human tissue samples, which is essential in medical and biological studies.

Moving into 2021-2022, we see the emergence of the topic "breast cancer," indicating an increased focus on breast cancer as a significant area of research. This reflects increased awareness and funding for breast cancer research and the development of new diagnostic and therapeutic techniques. The topic "controlled studies" emerged this year, indicating that more structured and rigorous research methods are used more frequently in response to the need for more robust medical and scientific research validation. In 2023-2024, we see how "human" continues to be a persistent topic, indicating a consistent focus on human subjects. However, new issues such as "tumor microenvironment," (Tian et al., 2024) and “triple negative breast cancer” (van den Driest et al., 2024) are emerging, indicating a shift in research focus to more specific cancer types and tumor microenvironments that are becoming increasingly relevant in the context of personalized therapies. This suggests that cancer research has evolved from a more general focus to a more specific and targeted approach, perhaps due to advances in diagnostic technologies and a deeper understanding of cancer (Z. Zhang et al., 2022). Furthermore, the term "biomarkers, tumor" in 2023-2024 indicates an increasing focus on biological markers as tools for cancer diagnosis and monitoring. Research on tumor biomarkers is essential for developing personalized therapies, where

therapies can be tailored to the individual biological profile of the patient, increasing efficacy and reducing side effects (Cappetta et al., 2021; Pérez-Granado et al., 2019).

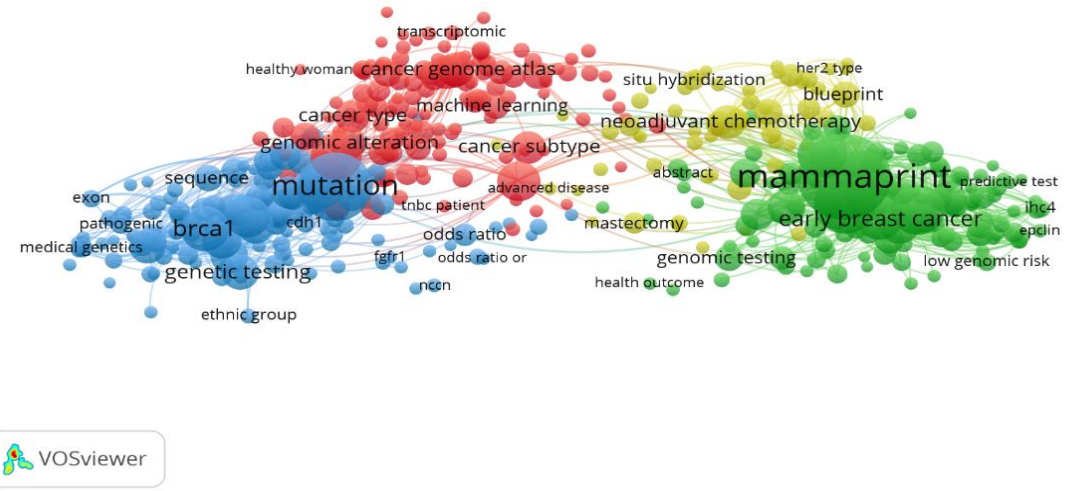

Figure 6. VOSviewer visualization

The visualization above shows the relationship between keywords related to research on MammaPrint and the identification of genetic diagnosis of breast cancer. In this visualization, several main clusters can be seen, represented by different colors, each depicting a group of keywords that are closely related to each other in relevant research.

The large green cluster on the right illustrates the main topics related to MammaPrint and early breast cancer diagnosis. Keywords such as "mammaprint," "early breast cancer," "genomic testing," "predictive test," and "low genomic risk" indicate a focus on the use of MammaPrint to determine prognosis and treatment plans for patients with early-stage breast cancer. MammaPrint is a genomic test that analyzes the expression of 70 genes to determine the risk of breast cancer recurrence (Crozier et al., 2022b; Mansani & Freitas-Junior, 2023). MammaPrint allows the identification of patients at low risk of recurrence, thereby sparing them from additional therapies that may not be needed and reducing exposure to side effects from excessive treatment (Kyalwazi et al., 2023).

The red cluster in the middle depicts research on genomic analysis and cancer subtyping. Keywords such as "cancer genome atlas," "machine learning," "cancer subtype," "genomic alteration," and "cancer type" indicate a more in-depth approach to understanding the genetic and molecular variations of breast cancer (Winn et al., 2020). Research in this cluster often involves extensive data analysis and machine-learning techniques to identify genetic patterns that may aid in the classification of breast cancer subtypes (van den Driest et al., 2024). This is important for developing more specific and effective therapies, as each cancer subtype may respond differently to different treatments. In addition, "machine learning" in genomic data analysis allows for large-scale data processing and interpretation, accelerating the discovery of critical genetic patterns (Lee et al., 2024).

The blue cluster on the left highlight topics about genetic mutations and genetic testing related to breast cancer. Keywords such as "mutation," "BRCA1," "genetic testing," "pathogenic," and "sequence" emphasize the importance of identifying specific genetic mutations that may increase the risk of breast cancer. BRCA1 and BRCA2 are the genes most commonly associated with increased risk of breast cancer (Bychkovsky et al., 2022). Genetic testing for these

mutations allows for early detection and preventive measures for individuals who carry these mutations, such as increased screening or prophylactic surgery (De Silva et al., 2023). Identifying these mutations is critical in breast cancer prevention and treatment strategies, as individuals carrying these mutations are at significantly higher risk of developing cancer (Bychkovsky et al., 2022; Martínez-Herrera et al., 2024).

Smaller yellow clusters show topics related to neoadjuvant therapy and in situ hybridization techniques. Keywords such as "neoadjuvant chemotherapy," "in situ hybridization," and "mastectomy" indicate research on preoperative (neoadjuvant) breast cancer treatment (Cao et al., 2021) and laboratory techniques used to analyze genes and proteins in tissue samples. Neoadjuvant treatment, which involves chemotherapy before surgery, aims to shrink the size of the tumor so that surgery can be performed more effectively and, perhaps, more conservatively (Schuch et al., 2024).

Overall, this visualization provides a comprehensive overview of the current research landscape in MammaPrint and genetic diagnosis of breast cancer. This research is critical to improving our understanding of breast cancer, developing better diagnostic tests, and providing more personalized and effective patient care. Combining genomic tests such as MammaPrint and genetic mutation analysis offers a powerful tool for clinicians to make more informed decisions about managing and caring for breast cancer patients (Vidula et al., 2023). By combining genomic information with clinical evaluation, MammaPrint helps improve treatment outcomes and quality of life for breast cancer patients and enables a more targeted and individualized approach to cancer treatment (Kolbinger et al., 2023).

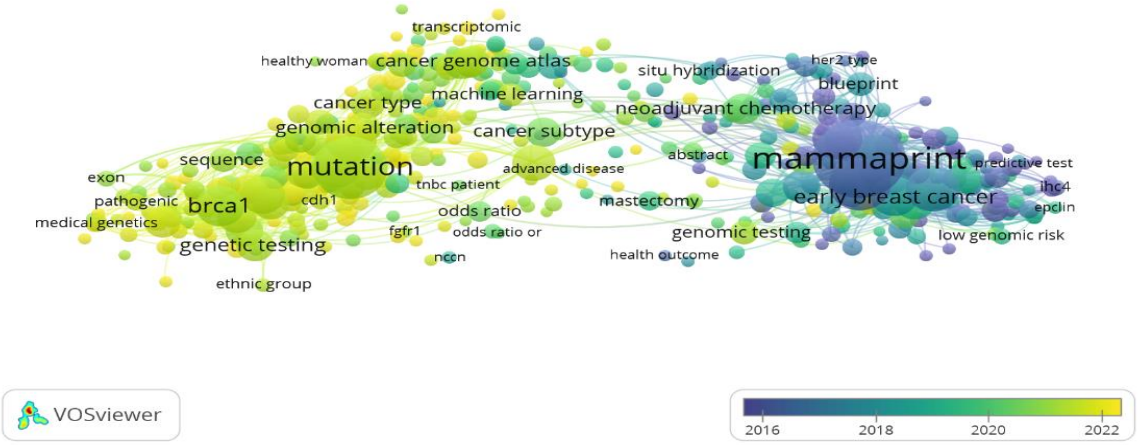

Figure 7. VOSviewer visualization

The figure above shows a network visualization of research topics using VOSviewer, depicting the relationship between different terms in the genomics and breast cancer fields and how the popularity of these terms evolved from 2016 to 2022. The colors in this figure indicate the period during which the topics gained attention, with yellow indicating newer terms (2022) and blue indicating older terms (2016). The terms "mutation" (W. Zhang et al., 2022) and "genetic testing" (Turza et al., 2022) are in the center of the graph with large node sizes, indicating that they were the most discussed topics and the main focus of research during that period. Terms such as "BRCA1," "genomic alteration," (Shi et al., 2022), and "cancer genome atlas" (Sathish Kumar et al., 2024) also show strong associations with the mutation and genomics themes, indicating intensive research in these areas, especially about cancer.

On the other hand, areas closer to the blue color, such as "mammaprint" and "early breast cancer," (V. Cheng et al., 2019),

reflect topics that have long been the focus of research but may be less relevant in recent research than other topics. However, "machine learning" appears in the yellower areas, indicating that integrating this new technology in genomics research has become increasingly important in recent years (Lee et al., 2024). This reflects the shift in research focus towards using advanced computational methods for genomics data analysis, which can help in more accurate prediction and diagnosis (Mishra & Bhoi, 2020). Overall, this graph reveals key topics in genomics and cancer research and provides insight into the evolution of research focus over the past few years, showing how the field continues to evolve with new technologies and scientific discoveries.

To complement the bibliometric visualization and provide a more comprehensive understanding of how these clusters translate into clinical and scientific practice, a systematic review of relevant studies was conducted. While the bibliometric mapping highlights the thematic evolution of genomic testing research, the tabulated evidence offers a structured overview of specific findings across the three dominant clusters, namely genetic mutations and testing (RQ1), genomic alterations and subtypes (RQ2), and genomic assays for early breast cancer such as MammaPrint (RQ3). This integration is essential because bibliometric data alone may capture research trends without sufficiently illustrating clinical applicability, whereas literature synthesis provides concrete evidence of how genomic assays have been validated, implemented, and challenged in real-world contexts. Therefore, the following tables summarize the key aspects and representative studies that reinforce the bibliometric findings, offering insights into both the scientific advancements and the persisting limitations of genomic testing in breast cancer.

Table 1. Research Aspects of Genomic Testing on Breast Cancer

Aspect	Details	Supporting References
Genetic Mutations and Testing (RQ1)	BRCA1/2, TP53, and *PIK3CA* mutations as main drivers; detection via NGS panels (e.g., MammaSeq) and ctDNA profiling.	AbdelHamid et al., 2021; Cheng et al., 2023; Vidula et al., 2023
Genomic Alterations and Cancer Subtypes (RQ2)	Identification of luminal A/B, HER2-enriched, and triple-negative breast cancer; based on mutational signatures and copy number variations.	Lal et al., 2017; Aftimos et al., 2021; Tsai et al., 2024
MammaPrint and Early Breast Cancer (RQ3)	70-gene signature test validated for prognosis and adjuvant therapy decisions; effective in avoiding overtreatment in low-risk patients.	n et al., 2017; Dubsky et al., 2021; Crozier et al., 2022
Clinical Integration	Genomic assays influence adjuvant chemotherapy recommendations; aid personalized strategies; cost-effectiveness proven in clinical cohorts.	Caputo et al., 2020; Mansani & Freitas-Junior, 2023; Simons et al., 2024
Challenges & Limitations	Barriers include high cost, limited adoption in low-resource settings, and need for guideline updates for NGS and multigene assays.	Rhiem et al., 2023; Fang et al., 2024
Future Directions	Expansion to broader panels (Oncotype DX, Prosigna PAM50, EndoPredict); integration of machine learning and multi-omics for precision oncology.	Chereda et al., 2024; Ji et al., 2024

The bibliometric results of this study are strongly supported by systematic findings summarized in Table 1, which highlight the interplay between genetic mutations, genomic alterations, and the clinical application of assays such as MammaPrint. Studies consistently show that BRCA1/2 and TP53 mutations remain central to breast cancer risk and are widely detected by next-generation sequencing technologies (AbdelHamid et al., 2021; Vidula et al., 2023). These findings resonate with the blue bibliometric cluster on genetic testing, underscoring the role of mutations as a

fundamental research focus. In addition, the red cluster emphasizing genomic alterations aligns with studies that describe the heterogeneity of breast cancer subtypes and their therapeutic implications (Aftimos et al., 2021; Tsai et al., 2024). Together, they confirm that genomic profiling not only advances scientific understanding but also directs therapeutic decisions. Thus, bibliometric mapping and literature review mutually reinforce the significance of genomic insights for precision oncology.

Table 2. Summary of Selected Studies Supporting Bibliometric Themes

Study	Cluster (RQ)	Purpose	Key Findings	Limitations
Esserman et al. (2017)	RQ3	Identify ultralow-risk breast cancer using MammaPrint	MammaPrint predicts long-term survival; avoids unnecessary chemotherapy in low-risk patients	Requires prospective validation in diverse cohorts
Dubsky et al. (2021)	RQ3	Clinical validation of MammaPrint in HR+ breast cancer	Independent predictor of metastasis and recurrence risk	Limited utility for chemotherapy benefit
Crozier et al. (2022)	RQ3	Compare biopsy vs. surgical specimens for MammaPrint	High concordance between biopsy and resection samples	Clinical uptake depends on accessibility
AbdelHamid et al. (2021)	RQ1	Detect BRCA1/2 variants in breast cancer	Identified pathogenic BRCA1/2 mutations strongly associated with breast cancer risk	Focused on specific population (Egyptian cohort)
Aftimos et al. (2021)	RQ2	Genomic/transcriptomic analysis of primaries & metastases	Identified heterogeneity between primaries and metastases; important for subtype therapy	Expensive sequencing, limited to study cohort
Vidula et al. (2023)	RQ1	Use of ctDNA in metastatic breast cancer	ctDNA profiling detected clinically actionable mutations	Limited to ER-positive metastatic cases
Fang et al. (2024)	RQ3	Genomic testing to refine axillary staging decisions	Genomic profiling helps omit unnecessary axillary surgery	Validation in larger samples needed

MammaPrint emerges as a critical tool in the green bibliometric cluster, particularly for early breast cancer, and this is corroborated by evidence in Table 2. The assay's 70-gene signature has been validated as a reliable predictor of recurrence and has shown strong clinical utility in avoiding overtreatment in low-risk patients (Esserman et al., 2017; Dubsky et al., 2021). Importantly, Crozier et al. (2022) demonstrated its reliability across both biopsy and surgical samples, which further enhances its applicability in routine practice. These results support the paradigm shift from generalized chemotherapy to personalized strategies, echoing bibliometric trends towards precision medicine. However, studies also underline the persistent barriers of cost and accessibility in different healthcare settings (Mansani & Freitas-Junior, 2023). Therefore, the integration of genomic testing in clinical guidelines remains an ongoing challenge despite its proven prognostic value.

The integration of bibliometric and systematic review perspectives highlights future directions for genomic testing research. On the one hand, genomic assays such as MammaPrint, Oncotype DX, and Prosigna PAM50 are being refined and expanded, while on the other hand, machine learning and multi-omics approaches are increasingly adopted to analyze complex genomic datasets (Chereda et al., 2024; Ji et al., 2024). These advancements are aligned with the bibliometric evidence showing emerging trends in computational approaches and biomarker discovery.

Nonetheless, limitations such as the high cost of sequencing technologies and the need for large-scale prospective validation remain barriers to universal adoption (Rhiem et al., 2023; Fang et al., 2024). Addressing these limitations is crucial to ensure that genomic testing benefits patients across diverse healthcare systems. Ultimately, the convergence of bibliometric analysis and literature review provides a comprehensive understanding of the trajectory of genomic testing in breast cancer and its promise for precision oncology.

DISCUSSION

The process of obtaining three main topics from data analysis is carried out through several systematic stages. First, relevant literature on breast cancer is collected from various scientific databases such as PubMed, Scopus, or Web of Science. This data is then imported into RStudio for initial bibliometric analysis. In RStudio, analysis identifies authors, institutions, and research topic trends based on existing publications. The graphs and visualizations generated from RStudio provide an overview of the distribution of authors, institutional contributions, and developments in research topics over the past few years.

Next, the data from the RStudio analysis was further processed using VOSviewer, a software used for network visualization of bibliometric data. VOSviewer maps frequently occurring keywords and displays the relationships between these keywords in the form of clusters. This visualization identified several main keyword clusters, indicating a close relationship between topics in breast cancer research. The three main clusters that emerged were genetic mutations and their testing (RQ1), genomic alterations and cancer subtypes (RQ2), and MammaPrint and genomic testing for early breast cancer (RQ3) obtained from selecting keywords relevant to the research topic. These three themes then became the main focus of further analysis, where the 50 most relevant journals on this topic were identified and used as the primary reference for further research. The following is a table of the 50 most relevant articles with the three main cluster topics:

No	Year	Type	RQ	No	Year	Type	RQ
1.	2016	Quantitative Experimental	RQ3 (Ma et al., 2016)	26.	2021	Quantitative Descriptive	RQ1 (AbdelHamid et al., 2021)
2.	2016	Quantitative	RQ3 (Beitsch et al., 2016)	27.	2021	Quantitative	RQ1 (Bekampytė et al., 2021)
3.	2016	Reviews	RQ3 (Hagemann, 2016a)	28.	2022	Qualitative	RQ1 (James et al., 2022)
4.	2016	Quantitative	RQ3 (RA Nunes et al., 2016)	29.	2022	Quantitative	RQ2 (Kaur et al., 2022)
5.	2016	Literature Review	RQ2 (Hagemann, 2016a)	30.	2022	Quantitative	RQ3 (Crozier et al., 2022b)
6.	2017	Case study	RQ3 (Fatima et al., 2017)	31.	2022	Quantitative	RQ3 (Amezcua-Gálvez et al., 2022)
7.	2017	Literature Review	RQ3 (AT Nunes et al., 2017)	32.	2023	Reviews	RQ3 (S. Li et al., 2023)
8.	2017	Review Analysis	RQ3 (I. Krop et al., 2017)	33.	2023	Reviews	RQ3 (Rhiem et al., 2023)
9.	2017	Reviews	RQ2 (Lal et al., 2017)	34.	2023	Quantitative	RQ1 (Rhiem et al., 2023)
10.	2017	Cohort Study	RQ3 (Esserman et al., 2017)	35.	2023	Quantitative Retrospective	RQ1 (Vidula et al., 2023)
11.	2018	Quantitative	RQ3 (M. Tsai et al., 2018)	36.	2023	Quantitative (Prospective Cohort)	RQ2 (V.-A. Nguyen Hoang et al., 2023)
12.	2018	Review of literature and	RQ2 (Suter & Pagani, 2018)	37.	2023	Quantitative Descriptive	RQ1 (Fernández-Castillejo et al., 2023)

		clinical data					
13.	2018	Review and Consensus	RQ2 (Colomer et al., 2018a)	38.	2023	Experimental	RQ2 (S. Cheng et al., 2023)
14.	2018	Literature Review	RQ3 (Vieira & Schmitt, 2018)	39.	2023	Survey	RQ1 (Lourenço et al., 2023)
15.	2019	Literature Review	RQ2 (McCart Reed et al., 2019)	40.	2023	Quantitative	RQ1 (Berhane et al., 2023b)
16.	2019	Reviews	RQ3 (Varga et al., 2019)	41.	2024	Quantitative	RQ2 (Jiang et al., 2024)
17.	2019	Systematic Review	RQ3 (Alexandre et al., 2019)	42.	2024	Quantitative	RQ3 (Fang et al., 2024)
18.	2019	Quantitative	RQ3 (Mittempergher et al., 2019)	43.	2024	Quantitative	RQ3 (Kim et al., 2024)
19.	2020	Case study	RQ1 (Minucci et al., 2020)	44.	2024	Quantitative Descriptive	RQ3 (van Olmen et al., 2024)
20.	2020	Literature Review	RQ3 (Caputo et al., 2020)	45.	2024	Quantitative	RQ2 (Chereda et al., 2024)
21.	2020	Quantitative	RQ1 (Mathias et al., 2020)	46.	2024	Quantitative	RQ3 (Drapalik et al., 2024)
22.	2020	Quantitative (Prospective Cohort)	RQ1 (Palmer et al., 2020)	47.	2024	Retrospective Analysis	RQ2 (Ajabnoor et al., 2024a)
23.	2021	Comparative Study	RQ2 (X. Liu et al., 2021)	48.	2024	Quantitative	RQ2 (Albain et al., 2024)
24.	2021	Quantitative	RQ2 (Aftimos et al., 2021)	49.	2024	Quantitative	RQ3 (Mansani et al., 2024)
25.	2021	Quantitative	RQ2 (Y. Zhang et al., 2021)	50.	2024	Quantitative	RQ3 ((Simons et al., 2024)

1. Genetic Mutations and Their Testing (RQ1)

One subtype of breast cancer is caused by mutations in several repair genes in the DNA damage response (DDR) pathway, such as BRCA1 and BRCA2. Damaged double-stranded DNA can be repaired through conservative homologous recombination (HR). The BRCA1 and BRCA2 proteins are essential for double-stranded DNA repair through homologous recombination. The BRCA1 and BRCA2 genes that have undergone mutations result in variants in the nucleotide base sequences in both genes, which cause the BRCA1 and BRCA2 proteins to be transcribed into mRNA and then translated, which results in variations in the amino acid sequence so that they cannot interact with tumor suppressors, as well as for DNA repair and cell cycle regulators, thus increasing the risk of breast cancer (Lal et al., 2017; Lourenço et al., 2023). The mutated BRCA1 gene has pathogenic variants at c.110C>A and c.5205delA, while the mutated BRCA2 gene has pathogenic variants at c.3280A>T and c.3291dupT (AbdelHamid et al., 2021). Moreover, patients with breast cancer were found to have the pathogenic variant c.5946delT found in exon 11 of the BRCA2 gene (Berhane et al., 2023).

Genetic mutations in breast cancer have become a primary focus of research due to their significant role in cancer development and their influence on treatment options (Markalunas et al., 2024). In this cluster, the studies analyzed underline the importance of identifying specific genetic mutations, such as BRCA1 and BRCA2, which are frequently associated with an increased risk of breast cancer. Several journals also highlight new methods for detecting these mutations, including Next-Generation Sequencing (NGS) technologies (Martínez-Herrera et al., 2024; W. Zhang et al., 2022) that can detect exact genetic variants. This not only helps in early diagnosis but also in

determining more personalized and effective therapeutic approaches.

Research in this cluster also includes the analysis of risk factors associated with genetic mutations. For example, the association between family history and breast cancer risk has been further strengthened by identifying mutations in the BRCA1/2 genes (Sunar et al., 2022). Studies have also shown that genetic testing is now an integral part of risk management (Vohra et al., 2022), especially for individuals with a family history of breast cancer. This testing provides valuable information about the probability of developing cancer and allows for preventive measures such as prophylactic mastectomy or intensive monitoring (Nishat et al., 2019). Genetic testing for mutations has also been a significant topic of discussion about its ethical and social implications. Several papers have addressed the challenges of accepting genetic testing in different populations, including risk perception, stigma, and privacy concerns (Jandoubi et al., 2024). In this context, it is essential to develop approaches that consider the patient's cultural and psychological aspects so that genetic testing can be carried out ethically and individually.

Gene mutations that cause breast cancer can also be caused by single nucleotide polymorphisms (SNPs) found in genes that encode proteins involved in cell cycle regulation and apoptosis. The TP53 gene encodes the p53 tumor suppressor protein involved in cell growth regulation, apoptosis, damage repair, and DNA recombination. The TP53 gene response to stress such as hypoxia, metabolite activation or oncogenes plays a role in maintaining genome stability. Polymorphisms in the TP53 gene in the form of rs1042522 cause cytosine to guanine transversion which results in the substitution of proline to arginine at codon 72 so that apoptosis occurs more quickly. The p53 regulated apoptosis inhibitor (PUMA) is a proapoptotic protein as a component of Bcl-2 3 (BBC3) binding. BBC3 is a moderator of apoptosis in response to the p53 tumor suppressor and other apoptotic stimuli such as unregulated oncogene expression, toxins, and growth factor deficiency. Polymorphism in the BBC3 gene in the form of rs2032809 causes the conversion of adenine to guanine in the gene promoter, thereby reducing the binding affinity of any transcription factor to the BBC3 promoter. Cyclin U encoded by the CCND1 gene is a key regulator in controlling the cell cycle that drives the conversion of cells from the G phase to the S phase. Polymorphism in the CCND1 gene in the form of rs9344 located at codon 241 results in alternative splicing. The EGFR gene encodes the epidermal growth factor receptor that drives cell cycle progression by activating signal transduction pathways. Polymorphism in the EGFR gene in the form of rs2227983 causes a guanine to adenine transition leading to an arginine to lysine substitution at codon 521 resulting in decreased receptor function, lower affinity for ligands, decreased growth stimulation, and induction of the proto-oncogenes MYC, FOS, and JUN (Bekampytė et al., 2021).

Overall, this cluster highlights significant advances in detecting and understanding genetic mutations in breast cancer (Rummel et al., 2020). With the advancement of technology and a better understanding of the molecular basis of cancer, genetic testing has become an essential tool in breast cancer management. It paves the way for a more personalized treatment approach and offers new hope to patients through earlier diagnosis and more effective therapeutic options (Lourenço et al., 2023).

2. Genome Alterations and Cancer Subtypes (RQ2)

Based on gene mutations in genomic changes, breast cancer is classified into three molecular cancer subtypes, namely luminal, HER2-enriched, and basal types. Luminal subtype cancer is divided into two, namely luminal A which can be treated only with endocrine hormone therapy and luminal B which must be treated using

chemotherapy. To differentiate luminal A and luminal B subtype cancers, the Ki-67 proliferation index can be used in addition to estrogen receptor (ER), progesterone (PR), and HER2 biomarkers (Amezcua-Gálvez et al., 2022).

Genomic alterations are changes at the DNA level that can alter gene expression and affect the behavior of cancer cells (Y.-F. Tsai et al., 2024). Research in this cluster focuses on identifying different genomic alterations associated with breast cancer subtypes. These subtypes, such as luminal A, luminal B, HER2-enriched, and triple-negative (Aftimos et al., 2021), have unique genetic characteristics that influence response to therapy and patient prognosis. Studies in this cluster also explore how genomic analysis can be used to classify breast cancers into these subtypes, which in turn guides more appropriate therapy choices.

A specific combination of genomic alterations defines each subtype. For example, the HER2-enriched subtype is characterized by amplification of the HER2 gene. In contrast, the triple-negative subtype often lacks expression of estrogen, progesterone, or HER2 receptors but may have mutations in genes such as TP53 (Basmadjian et al., 2024). A deeper understanding of these alterations allows for more targeted and effective therapeutic approaches. Technologies such as whole-exome sequencing and genomics have enhanced our understanding of the genomic variations within each subtype (Roman et al., 2020). Studies have also shown that despite common patterns, each subtype has significant heterogeneity, emphasizing the need for a personalized treatment approach (Ajabnoor et al., 2024b). Furthermore, identifying specific biomarkers for each subtype aids in early diagnosis and monitoring of therapeutic response.

Human epidermal growth factor 2 (HER2) protein is encoded by the ERBB2 oncogene located on the long arm of chromosome 17. Overexpression or amplification of HER2 occurs in breast cancer cells. Therefore, HER2 can be used as a predictive biomarker for response to agents targeting HER2. HER2 status is routinely tested by immunohistochemistry (IHC) and in situ hybridization (ISH) (Ajabnoor et al., 2024b). Positive HER2 biomarkers in patients with HER2 subtype breast cancer will be given trastuzumab or other HER2-targeted therapies. Positive ER/PR biomarkers in patients with HER2 subtype breast cancer will undergo endocrine hormone therapy (Lal et al., 2017).

Several journals in this cluster explore the relationship between genomic alterations and resistance to therapy (Rao et al., 2023). For example, mutations in the ESR1 gene have been associated with resistance to endocrine therapy in the luminal subtype. This study suggests that by identifying specific genomic alterations, clinicians can predict responses to treatment and tailor therapeutic strategies to overcome this resistance (Gebreslasie et al., 2019). Thus, a deeper understanding of genomic alterations may improve treatment efficacy and reduce the risk of recurrence (Y. Zhang et al., 2022). In addition, this cluster discusses developments in DNA sequencing technologies that allow for a more detailed analysis of genomic alterations. For example, exome sequencing and whole genome sequencing technologies have identified rare mutations that may have gone undetected with previous methods (Eisenstein, 2024). This opens up new opportunities for research and development of more specific therapies for rare and aggressive breast cancer subtypes.

In the clinical context, research on genomic alterations and breast cancer subtypes has made significant contributions to the development of more personalized therapies. With a better understanding of breast cancer's genetic heterogeneity, clinicians can make more precise and scientific decisions about treatment, which can ultimately improve patient outcomes. This shows that genomic research continues to be an essential foundation in the fight against breast cancer.

3. Genomic Testing for Early Breast Cancer (RQ3)

MammaPrint is one of the genomic testing tools used to evaluate the risk of recurrence of early-stage breast cancer (Mansani & Freitas-Junior, 2023). Research in this cluster highlights how MammaPrint and other genomic testing have transformed the approach to breast cancer management, particularly in determining the need for adjuvant chemotherapy (Ullah et al., 2023). This tool measures the expression of 70 genes associated with cell proliferation and metastatic potential, providing a more accurate risk profile for patients with early breast cancer (Crozier et al., 2022a).

Extensive clinical studies, such as MINDACT, have evaluated the effectiveness of MammaPrint in assisting therapeutic decisions (Rutgers et al., 2011). The results showed that patients with a low-risk profile based on MammaPrint can safely avoid chemotherapy without compromising long-term survival. This represents a paradigm shift in breast cancer treatment, from a "one-size-fits-all" approach to a more tailored therapy based on the individual's molecular profile. In addition to MammaPrint, other genomic tests, such as Oncotype DX, are used to assess risk and determine therapeutic strategies (Ji et al., 2024). The Oncotype Dx assay measures the expression of 21 genes, including 5 reference genes and 16 cancer-related genes related to hormones, HER2, invasion, and proliferation (Simons et al., 2024). The results of the Oncotype Dx assay are used to predict breast cancer recurrence and patient survival for 10 years after initial diagnosis and to predict the percentage of risk that requires patients to undergo chemotherapy (Caputo et al., 2020). Using these tests in clinical practice has improved prognostic and predictive accuracy, helping physicians and patients make more informed decisions. However, it is essential to note that these tests must be used with other clinical and pathological factors to obtain a complete picture of a patient's prognosis (Lux et al., 2022).

Several papers in this cluster have shown that using MammaPrint can reduce over-treatment, i.e., unnecessary chemotherapy given to low-risk patients. Thus, this test reduces the burden of potentially unnecessary therapy and the risk of chemotherapy-related side effects (Chowdhury et al., 2023). This suggests that genomic tests such as MammaPrint can provide significant clinical benefits, especially in the context of more personalized medicine. The use of MammaPrint has also been tested in various patient populations, including women with different tumor characteristics. Studies have shown that MammaPrint can be used effectively across different ethnic groups and tumor subtypes and provides flexibility in its application in the clinic (Retèl et al., 2020). Several studies have also explored the integration of MammaPrint with other clinical markers, such as tumor size and lymph node status, to provide more comprehensive risk stratification (Mampunye et al., 2021).

In this cluster, studies also highlight challenges and opportunities in the widespread adoption of genomic testing such as MammaPrint (Seguí et al., 2014). One of the main challenges is the cost and accessibility of this test, which may be a barrier in some countries with limited resources (X. Li et al., 2019). However, with increasing clinical evidence supporting the effectiveness of MammaPrint, it is hoped that the adoption of this genomic test will become more widespread, benefiting more patients with early breast cancer.

The Endo Predict assay is used to test 12 genes, namely 8 cancer genes, 3 normalization genes, and 1 control gene to add clinicopathological factors such as tumor size, nodal status and risk of breast cancer recurrence within 10 years (Amezcua-Gálvez et al., 2022).

Pro signa PAM50 measures the expression of 50 classifier genes and 5 control genes so that it can categorize four subtypes of breast cancer, namely luminal A, luminal B, HER2, and basal type (Alexandre et al.,

2019; Caputo et al., 2020). The Blue Print assay is also used to measure the expression of 80 signature genes to determine cancer subtypes such as luminal, HER2, and basal types (Mittempergher et al., 2019).

Genomic Grade Index (GGI) is a microarray that measures the expression of 97 genes to improve the classic histologic assessment of breast cancer. Meanwhile, Breast Cancer Index (BCI) is an assay derived from the expression of 11 genes using RT-PCR to predict risk over a period of up to 10 years and provide recommendations for endocrine hormone therapy for breast cancer patients with ER+ biomarkers (Caputo et al., 2020)

Graph Convolutional Neural Network (GNN) is used to classify patients based on the level of breast cancer they suffer from by utilizing gene expression profiles structured by protein-protein interaction networks (Chereda et al., 2024)

Genome Atlas of Breast Cancer (GABC) contains 10,172 abnormalities in non-coding genes including the genome in the form of single nucleotide polymorphisms (SNPs) and somatic mutations, the transcriptome in the form of lncRNA and miRNA, and the epigenome in the form of DNA methylation, enhancers and super-enhancers (Y. Zhang et al., 2021).

CONCLUSION

Bibliometric results related to breast cancer show a shift from using intrinsic detection of breast cancer subtypes with hormone receptor (HR) indicators, human epidermal growth factor receptor 2 (HER2), and other basal indicators to deciding on average therapy using chemotherapy. Along with the development of biochemical and genetic science and increasingly accurate research technology, it is now possible to study circulating tumor DNA (ct-DNA) released by tumor cells through reverse transcriptase polymerase chain reaction (RT-PCR) to identify mutated genes or design several biomarkers based on amino acid sequences in proteins or nitrogen base sequences in specific genes or the entire genome so that a comprehensive and factual picture is obtained regarding tumor development and risk levels to recommend several proportional and effective alternative therapies in treating breast cancer.

Declaration by Authors

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