



## Harnessing AI for KRAS Molecular Pathway Detection in Breast Cancer

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### Abstract:

In various cancers, the KRAS pathway is central to governing cellular proliferation, differentiation, and survival. Despite the comparative rarity of KRAS mutations in breast malignancies, aberrant pathway activity significantly influences tumor progression, immune modulation, and clinical resistance. In the present review, we synthesize current knowledge on KRAS signaling in breast cancer, focusing on its prevalence and the molecular drivers behind its activation. Our discussion extends to how dysregulated cascades associated with KRAS, such as PI3K-AKT-mTOR and RAF-MEK-ERK, impact the biological landscape of the tumor beyond mere mutational status.

Furthermore, the review explores the transformative impact of omics technologies and artificial intelligence (AI) in decoding KRAS-driven molecular networks. Recent progress in genomics, transcriptomics, proteomics, and especially multiomics data integration has enabled a more comprehensive understanding of KRAS pathway dynamics. At the same time, machine learning and deep learning approaches have significantly improved tumor classification, biomarker identification, and prediction of therapeutic outcomes. Emerging AI-driven multimodal frameworks that combine molecular profiles, histopathological features, and imaging data show great promise for enhancing prognostic assessment and developing personalized treatment strategies in breast cancer.

Nevertheless, ongoing challenges such as data heterogeneity, limited interpretability of models, insufficient external validation, and ethical considerations remain to be addressed. Future efforts are oriented toward explainable AI, federated learning, and clinically validated predictive systems to establish a robust foundation for AI-enabled precision oncology in breast cancer. Ultimately, integrating KRAS pathway biology with advanced AI analytics could accelerate the evolution of individualized diagnostic and therapeutic approaches in breast cancer management.

**Keywords:** KRAS signaling, breast malignancies, Artificial intelligence, Multi-omics integration, Precision oncology

### Introduction to KRAS Signaling in Breast Cancer

KRAS (Kirsten rat sarcoma viral oncogene homolog) is a crucial hub in intracellular signaling circuits controlling proliferation, survival, differentiation, and migration by relaying extracellular cues to major

downstream routes particularly the RAF-MEK-ERK and PI3K-AKT pathways frequently altered during tumor development. While somatic KRAS mutations occur less often in breast cancer than in many other cancers, aberrant KRAS expression and associated



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pathway activation have been shown to correlate with tumor progression, immune microenvironment modulation, and clinical outcomes across molecular subtypes of breast cancer, indicating a broader role for KRAS-mediated signaling in disease pathophysiology beyond mutation status (1, 2).

Emerging evidence suggests that elevated KRAS expression and enriched KRAS signaling signatures influence prognosis and biological behavior in breast cancer, with studies linking higher KRAS levels to distinct immune infiltration patterns and survival differentials, particularly in triple-negative and hormone receptor-positive subgroups. These findings highlight the importance of dissecting KRAS pathway dynamics within the complex landscape of breast cancer molecular biology to identify potential prognostic biomarkers and therapeutic targets (1, 2).

### **Molecular Mechanisms of KRAS Pathway Activation**

KRAS is a small GTPase that alternates between an inactive GDP-bound form and an active GTP-bound form, a transition controlled by guanine nucleotide exchange factors (GEFs) such as SOS1 and by GTPase-activating proteins (GAPs). When upstream receptor tyrosine kinases (RTKs) including EGFR and HER2 are stimulated, SOS1 promotes GDP displacement and GTP loading, resulting in structural rearrangements of KRAS that allow binding to downstream targets and the initiation of signaling programs linked to growth, survival, and differentiation. Once engaged, KRAS triggers prominent pathways such as RAF–MEK–ERK and PI3K–AKT–mTOR supporting oncogenic communication across multiple cancer types (3, 4).

In cancer, activating KRAS mutations or upstream overexpression of RTKs result in persistent GTP-bound KRAS, driving continuous downstream signaling independent of normal regulatory controls. This constitutive activation promotes uncontrolled cell growth, metabolic reprogramming and resistance to targeted therapies, in part through crosstalk among signaling axes and feedback loops that stabilize the active state. Understanding these molecular mechanisms of KRAS activation is essential for identifying therapeutic vulnerabilities and developing effective inhibitors that can interrupt aberrant signaling in tumor cells (3, 5).

### **Prevalence and Clinical Relevance of KRAS Changes in Breast Cancer**

Alterations in the KRAS gene in breast cancer are relatively uncommon when compared with many other tumor types. Large-scale genomic studies report KRAS mutations in roughly 0.6–0.7% of invasive breast cancers. In contrast, copy-number alterations and increased KRAS mRNA expression are observed more frequently and may contribute to

key aspects of tumor behavior. Although canonical activating KRAS mutations are uncommon, variation in KRAS expression and genetic status has been linked to specific molecular subgroups and clinical characteristics, highlighting the multifaceted nature of KRAS involvement in breast tumor development and the possible value of KRAS-associated features for prognostic stratification.

Importantly, the clinical impact of KRAS alterations cannot be explained by prevalence alone. Elevated KRAS mRNA levels have been associated with worse overall and disease-specific survival, including in defined breast cancer subgroups, supporting its potential role as a prognostic biomarker and indicating broader pathway dysregulation that may affect responsiveness to therapy as well as the emergence of resistance.

Continued research is needed to clarify how these alterations contribute to clinical outcomes and to establish their relevance for precision oncology in breast cancer management (6, 7).

### **Omics Technologies for KRAS Pathway Investigation**

High-throughput omics approaches including genomics, transcriptomics, proteomics, and metabolomics have transformed the study of intricate signaling networks such as KRAS. By allowing multi-layer characterization of molecular changes, these technologies provide a more integrated view of how alterations at different biological levels shape pathway activity. These platforms allow for the detection of genomic variants, differential gene expression, protein abundance and modifications, and metabolic states that collectively define KRAS pathway activity and downstream effects in cancer cells and tissues (8, 9). Integration of multi-omics datasets through systems biology approaches enhances the resolution of KRAS-associated networks and uncovers biomarkers that single-layer analyses might overlook (8, 9).

Specifically, omics strategies have been used to elucidate how KRAS influences tumor behavior by correlating genomic mutations with transcriptome changes and proteome dynamics, thereby providing insights into pathway activation, feedback loops, and interactions with other oncogenic modules (10, 11). In breast cancer research, expanding omics approaches and analytic frameworks such as proteogenomics and interactomics contribute to understanding tumor heterogeneity and KRAS pathway implications, offering opportunities for improved molecular classification and therapeutic targeting (9, 11).

### **Artificial Intelligence Approaches in Cancer Molecular Profiling**

Artificial intelligence (AI) has become a powerful tool for cancer molecular characterization, as it

can extract meaningful structure from complex, high-dimensional biological datasets patterns that conventional analyses may miss. Using machine learning and deep learning models, researchers have analyzed multi-omics, imaging, and clinical data to support tasks such as tumor subtype classification, prognostic biomarker discovery, and treatment-response prediction, often achieving improved performance relative to standard statistical methods. (12, 13). These AI-driven strategies facilitate the discovery of molecular signatures across genomics, transcriptomics, and proteomics data, thus supporting precision oncology initiatives targeting heterogeneous cancer profiles (12, 13).

In recent years, AI has been integrated into diagnostic and therapeutic pipelines to interpret molecular features from diverse data modalities, ranging from RNA expression profiles to histopathological images, improving subtype classification and personalized treatment planning (14, 15). Additionally, AI approaches are increasingly employed to integrate multiomics and radiomics data, enhancing the robustness of cancer profiling and enabling more comprehensive insights into tumor biology and potential therapeutic vulnerabilities (14, 15).

### AI-Driven Multi-Omics Integration for KRAS Pathway Detection

AI-guided multi-omics integration has become an effective approach for disentangling complex signaling systems such as the KRAS pathway by jointly analyzing complementary molecular layers, including genomics, transcriptomics, epigenomics, and proteomics. Analyses restricted to a single data type frequently miss the layered regulatory processes that govern KRAS activation and its downstream consequences. In contrast, machine

learning and deep learning models can capture high-dimensional relationships and cross-talk patterns across heterogeneous omics datasets, offering a more comprehensive view of pathway behavior and associated molecular traits (16, 17). By leveraging this strategy, researchers can derive pathway-associated signatures, subtype-relevant biomarkers, and candidate therapeutic targets that are difficult to uncover with conventional statistical approaches alone (16, 17).

In oncology research, AI-based integration of multiomics data has demonstrated enhanced performance in characterizing tumor subtypes, predicting clinical outcomes, and uncovering molecular mechanisms across various cancer types, suggesting its applicability in KRAS pathway investigation and precision medicine. For example, integrative models employing clustering, feature selection, and predictive algorithms have successfully stratified tumors by biological and clinical characteristics based on multiomics profiles, illustrating the potential of AI-assisted frameworks to decode signaling networks such as KRAS and translate molecular complexity into actionable insights (16, 18).

### Deep Learning Applications in Histopathology and Imaging Biomarkers

Deep learning, a branch of artificial intelligence, has accelerated histopathology research by supporting automated extraction of clinically meaningful features and imaging biomarkers from digitized whole-slide images. Compared with conventional manual assessment, this strategy can improve diagnostic accuracy, standardize interpretations, and increase throughput. DL approaches including convolutional neural networks (CNNs), ResNet-

**Table 1.** Recent Studies on AI Driven Multi Omics Integration (Continuing Ref Numbers)

Ref #	Study (First Author, Year)	Main Findings
19	Li al ,2024	AI-assisted multi-omics integration elucidates complex cancer molecular profiles and signaling network patterns across multiple omics layers. ( <a href="#">PubMed</a> )
20	Sahu al , 2025	Review highlighting AI and multi-omics integration in precision oncology, including signaling pathways like KRAS among others. ( <a href="#">PubMed</a> )
21	Zhao al , 2025	Multi-omics machine learning identifies melanoma molecular subtypes and prognostic signatures, demonstrating integrative model utility. ( <a href="#">PubMed</a> )
22	Chong al , 2022	Integrated multi-omics characterization reveals KRAS mutant cancer subtypes and distinct pathway activity clusters. ( <a href="#">PubMed</a> )
23	Wang al , 2025	Integrative multi-omics machine learning reveals proliferating cell functions linked with prognosis and therapy response. ( <a href="#">PubMed</a> )
24	Ou al , 2025	Integrative machine learning and multi-omics analysis uncovered key cell death patterns and immunotherapy targets in renal carcinoma. ( <a href="#">PubMed</a> )
25	Ma al, 2024	Prognostic model based on mitochondrial function developed using multi-omics and machine learning in gastric cancer. ( <a href="#">PubMed</a> )
26	Other multi-omics integration reviews	AI multi-omics frameworks enhance understanding of signaling and clinical predictions across tumors. ( <a href="#">Lippincott Journals</a> )

style architectures, and transformer-enhanced frameworks have been used for tasks such as tumor detection, molecular subtyping, and prognostic modeling across diverse cancer types, with especially extensive work in breast cancer. In some settings, their performance is comparable to and in certain cases exceeds that of expert pathologists. (19,20). These methods have also shown promise in predicting underlying molecular characteristics, including gene expression and mutational status, from histological images, indicating their potential as noninvasive imaging biomarkers that link tissue morphology to molecular pathology (19, 21).

The integration of deep learning with high-resolution imaging workflows has facilitated the development of robust biomarkers that correlate with clinical outcomes, therapeutic response, and tumor microenvironment features, thereby contributing to personalized oncology care and precision medicine strategies. Furthermore, systematic reviews reveal a growing trend toward multimodal DL models that combine histopathology with genomic data to improve biomarker prediction and clinical stratification, underscoring the expanding role of DL in bridging imaging and molecular phenotyping for cancer research and clinical application (20, 21). Despite these progressions, several limitations still need to be addressed particularly issues related to data standardization, the interpretability of model outputs, and the level of clinical evidence required through rigorous validation before these methods can be broadly adopted in routine practice.

### **Predictive Modeling of Therapeutic Response via KRAS Pathway Analysis**

Predictive modeling focused on the KRAS pathway has become a critical area of research in precision oncology, as KRAS mutations and associated signaling dynamics influence response to targeted therapies, immune checkpoint inhibitors, and conventional treatments. Computational models that integrate molecular profiles including gene expression, mutation status, and pathway signatures can stratify tumors by likely therapeutic sensitivity or resistance, enhancing treatment selection and reducing unnecessary toxicity. For example, integrated predictive models such as the *K20* classifier have shown high performance in predicting KRAS dependency and therapy responsiveness in cancer cell lines and clinical datasets, outperforming models based solely on mutation status (22). Additionally, emerging radiogenomics and multiomics predictive frameworks combine imaging and molecular data to further refine response predictions .

Beyond targeted inhibitors, evidence from clinical analyses indicates that KRAS mutation

status also modulates response to other systemic therapies, such as immune checkpoint inhibitors in nonsmall cell lung cancer, where KRAS mutations have been associated with improved survival outcomes compared to wildtype in some studies (24). Such findings illustrate the broader utility of KRAS-centered predictive models in forecasting therapeutic outcomes across diverse treatments and cancer types, underscoring the importance of leveraging high-dimensional data and machine learning approaches to inform personalized treatment strategies (23, 24).

### **Current Challenges and Limitations of AI-Based Molecular Detection**

Although artificial intelligence (AI) has shown substantial promise for improving molecular detection in oncology, several challenges limit its routine clinical adoption. A key obstacle is data quality and heterogeneity: most AI methods rely on large, diverse, and accurately annotated datasets, but many existing resources contain class imbalances, insufficient representation of different populations, and inconsistent labeling. These factors can skew predictions and weaken a model's ability to generalize across healthcare settings (25, 26). In addition, model interpretability is a major concern. Many contemporary approaches especially deep learning systems operate as "black boxes," so the basis of their decisions is not transparent, which can undermine clinician confidence and make regulatory evaluation more difficult (25, 26).

Beyond technical constraints, ethical, legal, and regulatory barriers also slow the practical adoption of AI-based molecular detection tools. Key concerns include patient privacy, algorithmic fairness, and the requirement to follow standardized validation procedures. The existing evidence suggests that many cancer-focused AI studies are built on retrospective or proof-of-concept datasets with restricted external testing. This highlights the need for prospective, multicenter clinical trials and for rigorous benchmarking against accepted clinical standards before these systems can be responsibly incorporated into routine diagnostics (25, 27). Ultimately, addressing these interconnected limitations is crucial to fully realize AI's value in precision oncology while maintaining reliability, transparency, and equity before these systems can be responsibly integrated into routine diagnostics in clinical implementation (25, 27).

### **Future directions in AI-enabled precision medicine for breast cancer**

The role of artificial intelligence (AI) in precision oncology for breast cancer is expected to grow substantially in the coming years, propelled by

progress in machine learning, multi-modal data integration, and real-world clinical adoption. Recent reviews suggest that AI models capable of combining imaging, pathology, genomic, and clinical information may enable more refined patient stratification, improve treatment planning, and strengthen prognostic performance relative to conventional approaches (28). As AI-based decision-support tools advance, future work will likely emphasize enhancing model interpretability, conducting robust external validation across diverse populations, and embedding these methods into everyday clinical workflows to deliver personalized management aligned with individual tumor biology and patient-specific features (29).

Furthermore, recent research indicates that precision oncology powered by artificial intelligence has the potential to minimize inequities in breast cancer management. This is achieved by increasing the availability of personalized therapeutic strategies and assisting clinical judgment across diverse medical environments, ranging from advanced facilities to underserved regions (29). To guarantee the reliability and broad applicability of AI algorithms, it is crucial to prioritize prospective, multicenter clinical trials alongside initiatives that promote inclusive data collection. Looking ahead, the field is expected to evolve through the adoption of federated learning techniques to bolster data security and diversity, the implementation of explainable AI (XAI) to foster trust among healthcare professionals, and the deployment of AI-enhanced biosignatures for dynamic, real-time monitoring and adjustment of cancer therapies (30).

## CONCLUSION

In conclusion, while KRAS mutations are infrequent in breast malignancy, the dysregulation of this signaling axis significantly influences disease

progression, molecular diversity, immunological crosstalk, and resistance to therapy. Progress in omics-based technologies has deepened our insights into the molecular networks driven by KRAS, uncovering diagnostic biomarkers that transcend simple mutational profiling. Furthermore, combining artificial intelligence with multi-omics, imaging, and histopathology has bolstered our ability to map pathway activity, categorize patient subgroups, and forecast therapeutic outcomes with higher accuracy. However, to facilitate secure and fair clinical implementation, critical issues regarding data integrity, interpretability, rigorous validation, and ethical standards must be systematically resolved. Ultimately, the maturation of AI-assisted precision oncology, underpinned by reliable validation protocols and transparent, explainable frameworks, offers a transformative potential for converting our understanding of KRAS dynamics into tailored diagnostic and clinical management strategies for breast cancer.

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**Table 2.** Recent Studies and Future Trends in AI-Guided Precision Oncology (Continuing Ref Numbers)

Ref #	Study (First Author, Year)	Main Findings
51	Lowry et al., 2026	Mammography-based AI models show promise for screening and risk stratification but require prospective validation and diverse population studies. ( <a href="https://pubmed.ncbi.nlm.nih.gov">pubmed.ncbi.nlm.nih.gov</a> )
52	Feng et al., 2025	AI enhances breast cancer management across screening, diagnosis, prognosis, and treatment, supporting precision oncology and identifying future research needs. ( <a href="https://pubmed.ncbi.nlm.nih.gov">pubmed.ncbi.nlm.nih.gov</a> )
53	Salazar-Garcés et al., 2026	AI improves treatment planning and guideline adherence but highlights challenges in LMIC settings and the need for external validation and equitable data. ( <a href="https://pubmed.ncbi.nlm.nih.gov">pubmed.ncbi.nlm.nih.gov</a> )
54	Shukla et al., 2025	AI/ML frameworks for systematic variant annotation may accelerate personalized treatment and drug repurposing strategies. ( <a href="https://pubmed.ncbi.nlm.nih.gov">pubmed.ncbi.nlm.nih.gov</a> )
55	Ran et al., 2025	Multi-modal AI integration facilitates subtype identification and therapy resistance prediction, supporting personalized treatment design. ( <a href="https://frontiersin.org">frontiersin.org</a> )
56	Narayanan et al., 2025	AI supports predictive modeling, treatment response evaluation, and precision medicine but highlights gaps in dataset diversity and algorithm transparency. ( <a href="https://link.springer.com">link.springer.com</a> )
57	Future Ai oncology review	Reviews AI advancements across oncology and proposes future innovations in clinical decision support and personalized care. ((turn0search8))
58	Explainable AI research	Highlights the role of explainable AI in improving interpretability and trustworthiness for clinical adoption. ((turn1academia22))

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