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Systematic Review

Bioinformatics-Driven Personalized Medicine in Cancer: A Systematic Review of Advances in Diagnosis and Treatment

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Abstract
Cancer remains a global health challenge due to high morbidity, mortality, and tumor heterogeneity. Conventional diagnostic and therapeutic approaches are often insufficient, causing a shift in the paradigm toward personalized medicine. Bioinformatics, by integrating genomic, transcriptomic, proteomic, imaging, and clinical data, has become pivotal in precision oncology, enabling biomarker discovery, individualized therapy, and prognostic assessment. This systematic review followed PRISMA guidelines. PubMed, Scopus, Web of Science, and Google Scholar were searched up to May 2025. Eligible studies examined bioinformatics applications in cancer diagnosis, prognosis, or treatment personalization. Two independent reviewers performed screening and data extraction across 12 domains, including cancer type, study design, tools, findings, and challenges. Narrative synthesis and descriptive statistics were applied, and 18 studies from 8,133 records were included. Breast, lung, and liver cancers were most frequently investigated, respectively. The United States, Iran, and China were leading contributors. Commonly used platforms included TCGA, GEO, ENCODE, Cytoscape, STRING, and Reactome. Key biomarkers were TRIP13, STIL, NTRK2/3, FGFR2, VEGFA, and non-coding RNAs. Support vector machines, convolutional neural networks, LASSO regression, and deep learning achieved predictive accuracies of 85–95% for tumor subtyping, survival, and treatment response. The integration of multi-omics and imaging enhanced diagnostic precision and therapeutic stratification. Bioinformatics-driven personalized oncology is transitioning into clinical reality, improving biomarker discovery and individualized therapy. However, translation remains constrained by data standardization, interoperability, limited genomic diversity, and algorithm interpretability. Future research should prioritize explainable AI, federated learning, standardized multi-omic datasets, and international collaboration to ensure equitable, reproducible, and clinically meaningful precision oncology.

Keywords: Bioinformatics, Personalized medicine, Precision oncology, Cancer, Biomarkers, Machine learning, Multi-omics

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Background

Cancer encompasses a highly heterogeneous group of diseases characterized by uncontrolled cell proliferation, local tissue invasion, and—at advanced stages—distant metastasis.[1] Despite remarkable advances in molecular biology and clinical oncology, cancer remains one of the leading causes of morbidity and mortality worldwide, imposing a profound burden on public health systems.[2] For example, breast cancer (BC) is currently the most prevalent malignancy among women and accounts for approximately 16% of global female cancer deaths.[3] The clinical complexity of cancer arises not only from its potential to affect virtually any organ but also from extensive inter-tumoral and intra-tumoral heterogeneity, which continues to challenge both early detection and effective treatment strategies.[4]

Conventional diagnostic and therapeutic modalities, while improving survival in certain cancer types, are insufficient to comprehensively address this heterogeneity.[5] This limitation has driven the paradigm shift toward personalized medicine, which emphasizes tailoring diagnostic and therapeutic approaches to the unique molecular, genetic, and clinical characteristics of each patient rather than applying uniform, population-based protocols.[6,7] Closely aligned with this concept, precision medicine seeks to stratify patients into well-defined molecular subgroups in order to better predict disease course and optimize therapeutic response.[8] Overall, these approaches promise to enhance clinical outcomes while minimizing unnecessary toxicity.[9]

The successful realization of personalized oncology critically depends on the ability to integrate and interpret vast, multidimensional datasets.[10] Advances in bioinformatics, clinical informatics, and computational oncology have provided the essential infrastructure to transform raw genomic, proteomic, radiologic, and clinical data into actionable clinical knowledge.[11] In addition, artificial intelligence (AI) and machine learning (ML) techniques enable automated analysis of complex biomedical data, including high-resolution imaging and molecular biomarkers, thereby facilitating individualized decision-support systems.[12-14] Large-scale initiatives, such

as the Cancer Genome Atlas (TCGA) and NIH "All of Us" Research Program, have generated unprecedented volumes of high-throughput data; however, translating these resources into clinically relevant insights remains a substantial challenge, often referred to as the "knowledge gap".[15,16]

Despite numerous promising advances in bioinformatics, imaging informatics, and targeted therapeutics, their widespread translation of such resources into clinical oncology has been slow.[17] Barriers include poor interoperability among health information systems, lack of standardized data formats, concerns regarding data privacy, and limited awareness or training among healthcare professionals.[18-21] Furthermore, the existing body of literature lacks a comprehensive synthesis of how bioinformatics has been applied to personalized cancer medicine, which domains (diagnosis, prognosis, and treatment optimization) have been most extensively studied, and what critical gaps persist.[22]

Accordingly, a systematic review of current evidence is warranted to evaluate the role of bioinformatics in advancing personalized oncology. Such an effort can elucidate the state of the field, identify translational barriers, and highlight research priorities. Ultimately, integrating bioinformatics-driven approaches into oncology is expected to accelerate the transition toward a healthcare paradigm in which every cancer patient receives individualized, biology-informed, and optimally effective treatment.

Methods

Study Design

This study was designed as a systematic review conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The protocol was developed prior to the literature search and included predefined eligibility criteria, data extraction procedures, and analytical strategies to ensure methodological rigor and transparency.

Eligibility Criteria

The target population of this review consisted of all peer-reviewed scientific articles addressing the application of bioinformatics in personalized medicine for cancer up to April 2025. Studies were included if their full text was available (1) and if they were published in English (2), explicitly focused on bioinformatics in the context of cancer diagnosis, prognosis, or treatment personalization (3), and met established quality thresholds based on peer-reviewed publication and content relevance (4).

Information Sources and Search Strategy

A comprehensive literature search was performed in PubMed, Scopus, and Web of Science from inception until May 11, 2025. In addition, Google Scholar was searched to minimize publication bias and identify gray literature. To capture potentially relevant studies, the reference lists of included articles were manually screened, and forward citation tracking was performed. Moreover, an automated email alert system was established in the databases to identify newly published studies during the search period.

The search strategy combined controlled vocabulary (e.g., MeSH terms) and free-text keywords in three major domains:

(1#): ("Computational Biology" OR "Computational Biologies" OR "Computational Molecular Biology" OR "Computational Molecular Biologies" OR "Bio-Informatic" OR "Bio Informatic" OR "Bioinformatic")

(2#): ("Precision Medicine" OR "P Health" OR "P-Health" OR "Individualized Medicine" OR "Personalized Medicine" OR Theranostic" OR "Predictive Medicine")

(3#): (Cancer OR Neoplasm OR Malignant OR Malignancy OR Tumor OR Neoplasia OR Malignancies OR Benign)

The final search query was (1#) AND (2#) AND (3#).

Study Selection

All retrieved records were imported into EndNote reference management software, where duplicates were removed. Screening was performed in three stages: title screening, abstract screening, and full-text review.

At each stage, two independent reviewers assessed eligibility based on the inclusion and exclusion criteria. Discrepancies were resolved by consensus or, when necessary, by consultation with a third reviewer.

Data Extraction

The required data were extracted using a standardized data extraction form designed by the research team. The form included 12 domains: authors and year of publication, country, type of cancer, study aim, research design, bioinformatics tools/approaches, analytical methods, key findings, reported challenges, study population (demographics), publishing journal, and quality assessment.

The form was pretested on a small subset of articles and refined accordingly. Additionally, data entry was conducted using Microsoft Word and Excel version 2019.

Quality Assessment

To ensure content validity, the extraction form was reviewed by two domain experts in bioinformatics and health informatics methodology. Each included study was independently evaluated by two reviewers for methodological rigor and reporting quality. In addition, to assess methodological quality and risk of bias (RoB), a 13-item checklist was utilized, adapted from the QUADAS and the QAREL tools.

Data Synthesis and Analysis

The extracted data were analyzed through content analysis to identify thematic categories and recurring patterns across studies. Descriptive statistics (frequencies,

percentages, and cross-tabulations) were computed in Microsoft Excel to summarize study characteristics, cancer types, bioinformatics tools applied, and reported outcomes. Further, trends and distributions were visualized using charts and tables.

No meta-analysis was conducted due to the heterogeneity of study designs, data sources, and outcome measures. Instead, a narrative synthesis was undertaken to integrate findings, highlight advances in bioinformatics-driven personalized oncology, and identify persisting gaps and challenges.

Results

The initial database search retrieved 8,133 records. Overall, 3,421 unique articles remained after duplicate removal. Title screening by two independent reviewers excluded 3,012 records as irrelevant to the study scope, leaving 409 articles for abstract evaluation. Following abstract screening, 226 studies were excluded for not meeting the eligibility criteria. A total of 183 full-text articles were assessed, of which 165 were excluded after detailed evaluation. Ultimately, 18 studies met all the inclusion criteria and were included in the final synthesis (Figure 1).

Most studies had been conducted in hospital or clinical settings, reflecting the translational application of bioinformatics in real-world oncology practice. BC was the most frequently investigated malignancy, followed by lung cancer and liver cancer, highlighting their prominence in bioinformatics-based oncology research. The other cancer types, including gastric, ovarian, pancreatic, and head and neck cancers, were less frequently represented. In terms of geographic distribution, the United States contributed the largest number of studies, followed by Iran and China, with additional contributions from multinational collaborations, as well as Taiwan, Turkey, Singapore, and India. This distribution underscores the global engagement in bioinformatics-driven cancer research and the dominance of research output from high-resource settings (Figure 2).

The word cloud (Figure 3) illustrates the most frequently occurring terms across the included studies, demonstrating the central themes and methodological focuses in bioinformatics-driven oncology research. Prominent terms, such as "expression," "analysis," "medicine," and

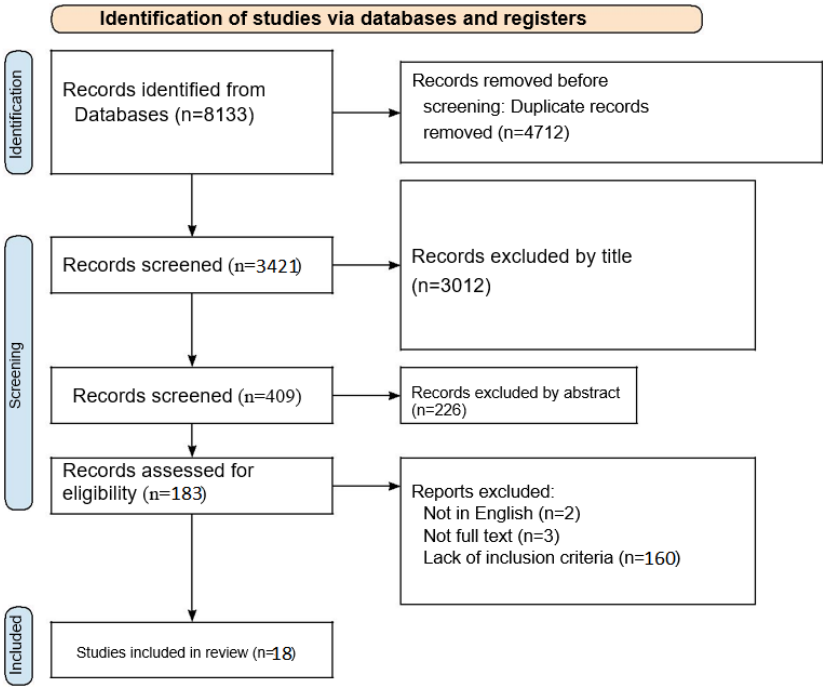

Figure 1. PRISMA Flow Diagram. *Note*. PRISMA: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses

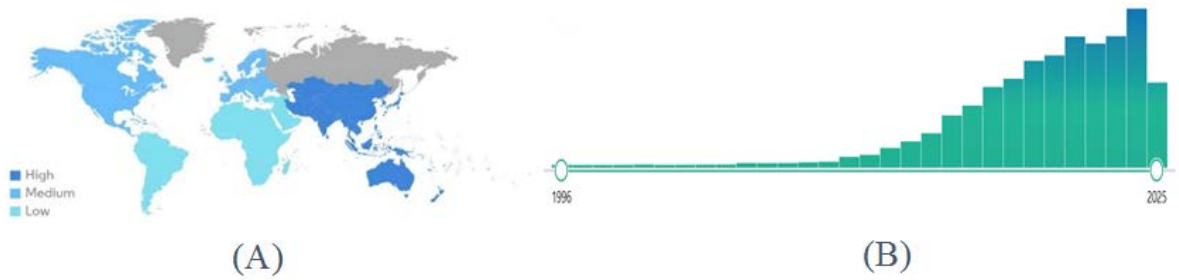

Figure 2. **(A)** Geographical Scope in the Subject of Bioinformatics in Personalized Medicine for Cancer and **(B)** The Growth Trend of Articles in the Field of Bioinformatics in Personalized Medicine for Cancer in Databases

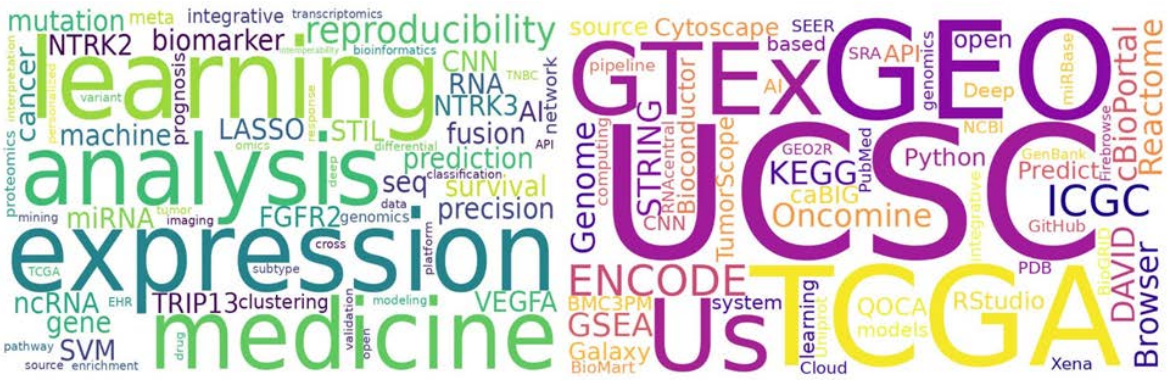

Figure 3. Word Cloud of Key Terms Extracted From the Included Studies

"learning," highlight the dominant role of gene expression profiling, computational analysis, and ML in precision cancer medicine. Repeatedly reported molecular targets included TRIP13, STIL, NTRK2/3, FGFR2, and VEGFA, as well as regulatory non-coding RNAs (ncRNAs), such as miR-21 and miR-145, underscoring their recurrent significance as diagnostic and prognostic biomarkers.

The visualization also emphasizes the widespread use of public genomic repositories and bioinformatics platforms, with TCGA, GEO, ENCODE, GTEx, UCSC, ICGC, and KEGG appearing as the most cited resources. Analytical pipelines and tools, such as Cytoscape, STRING, DAVID, Reactome, GSEA, Oncomine, and TumorScope, were also prominently represented, representing their application in pathway enrichment, network analysis, and predictive modeling.

Additionally, ML algorithms, including support vector machine (SVM), convolutional neural network (CNN), least absolute shrinkage and selection operator (LASSO), and deep learning approaches, were frequently mentioned, supporting their growing role in survival prediction, treatment response modeling, and tumor subtyping. The diversity of terms related to data reproducibility, integration, and open-source platforms indicates an increasing focus on standardization and accessibility in the field.

Overall, the word cloud demonstrates that bioinformatics research in oncology is characterized by a strong reliance on large-scale genomic data, ML algorithms, and integrative analytic frameworks, with the ultimate goal of advancing biomarker discovery, treatment personalization, and early cancer detection.

The analysis of the included studies revealed diverse research foci. The most common themes were as follows:

- Bioinformatics networks in cancer diagnosis and personalized medicine support, including integration with electronic health records to enhance patient care and safety
- Identification and validation of biomarkers, particularly involving ncRNAs, the miR-200 family, and related gene targets.
- Development of bioinformatics-driven approaches for drug selection, therapeutic optimization, and prediction of treatment outcomes
- Application of AI and ML for cancer detection, gene expression profiling, biomarker discovery, and predictive modeling
- Integration of genomic, transcriptomic, and imaging data to improve diagnostic accuracy and prognostic assessment
- Enhancement of personalized treatment strategies, including targeted drug selection, improved biomarker-based stratification, and quality-of-life improvement for cancer patients.

The reviewed studies employed a variety of bioinformatics processes, including:

- Algorithm development and computational modeling;
- Prediction of therapeutic response and treatment outcomes;
- Clinical validation and data standardization;
- Systems biology approaches to signaling pathways and therapeutic target identification;
- Design of integrative multi-omics databases;
- Automated imaging analysis and structural genomics;
- ML–based models for prognosis and treatment planning.

A recurrent theme was the emphasis on data integration across multiple layers (genomic, clinical, and imaging), highlighting the potential and challenges of multi-modal bioinformatics in oncology.

Despite promising advances, several challenges were consistently reported, including:

- Interoperability and standardization issues across health information systems;
- Regulatory and privacy concerns related to clinical and genomic data;
- Limited clinical adoption of bioinformatics tools due to technical complexity and insufficient training of healthcare professionals;
- Need for international collaboration and large-scale data sharing to enable robust, generalizable findings.

Table 1 presents further details of the included studies, including authors and year, country, aim of research, type of cancer, bioinformatics aspects, setting, included processes, methods, key findings, challenges, and

Table 1. Details of the Selected Studies in This Review

Authors and Year	Country	Aim of research	Type of cancer	Bioinformatics aspects	Setting	Included processes	Methods	Key findings	Challenges	Demographics
Iolanda Capone et al., 2022 [23]	Italy	Evaluation of bioinformatics tools for identifying fusion transcripts	Multiple (STT, lung, thyroid, and the like)	ADx, ARR, and SFU for RNA-seq from FFPE	Institutional Molecular Tumor Board	RNA extraction, RNA-seq, and fusion analysis	FusionPlex, FISH, RT-PCR, ADx, ARR, and SFU	High accuracy in STT; more suitable ARR in carcinoma.	Low RNA quality in FFPE and discrepancy with FISH	190 patients, 193 FFPE samples
Khorasani, Shahbazi, Mahdiyan - 2018 [24]	Iran	Investigation of miR-200 and target genes in prostate cancer	Prostate cancer	miRWalk, TargetScan, DAVID, and Cytoscape	In silico study	KEGG pathway analysis and gene targeting	Bioinformatics databases, network drawing, and performance analysis	E2F3, BCL2, and CCNE2 are the main targets.	The lack of data for some miRNAs leads to false results.	Without human population (data analysis)
Zurita AJ et al., 2020 [25]	USA	Evaluation of the use of HD-SCA technology for the identification, imaging, and biological-informational analysis of circulating tumor cells (CTCs) in the biological fluid of cancer patients	Breast, lung, prostate, and the like	ImageJ, Python, CTC morphometrics, and RNA-seq	USC Convergent Science Institute in Cancer	CTC isolation, staining, imaging, and analysis	HD-SCA, confocal microscopy, and single-cell RNA	Predicting treatment response through CTC analysis	Phenotypic diversity of CTC and difficulty in identification	129 NSCLC patients in one study, others different
Cheng, Moore, Greene – 2014 [26]	USA	The application of bioinformatics in the analysis of ncRNAs	Not cancer-specific (lncRNAs general)	Guilt-by-association, tiling arrays, and RNA-seq	Pacific Symposium on Biocomputing	Analysis of the structure, function, and localization of ncRNA	Machine learning models and analysis of the miRNA target	The extensive regulatory role of lncRNA in cancer	The statement below, lack of ML training data, and high diversity	Without a specific population; public bases.
Cheng et al., 2016 [27]	USA	Off-label drug suggestion in TNBC with ML	Triple negative BC	SVM, TCGA, CCLE, CTRP, and fusion data	Analysis of public data	GE, CNV, Mutation, and drug sensitivity analysis	SVM, AUC, KEGG, DAVID, and target matching algorithm	71.8% of patients have a treatment goal; Methotrexate, Olaparib	Elimination of potential goals and activating leaps	85 TNBC patients (TCGA), 18 cell lines
Ow, Tang, Kuznetsov – 2016 [28]	Singapore	Prediction of prognosis with PBVV and PSV models in HGSC	High-grade serous ovarian cancer	PBVV, PSV, TCGA, GEO, and Euclidean distance	Bioinformatics Institute, Singapore	Expression binarization, patient comparison	1D-DDg, SWVg, AWR, and Kaplan–Meier	PSV has higher accuracy in prediction compared to PBVV.	Need for precise normalization, challenging feature selection	TCGA (350), GSE9899, and GSE26712 (359)
Sinnarasan et al., 2023 [29]	India	Identification of biomarkers for stomach cancer using ML	Gastric cancer	DESeq2, Cytoscape, SVM-RFE, TCGA, and GEPIA	Pondicherry University	RNA-seq, DEG, PPI, ROC, and survival	SVM-RFE, STRING, GEPIA, and ClusterProfiler	TRIP13, KIF14, DTL, and EXO1 as biomarkers	Lack of clinical variables and insufficient laboratory confirmation	TCGA (407), PRJNA435914 (68), and PRJNA555737 (12)
Lai et al., 2024 [30]	China	A risk model for aging in LIHC using SRGs	Liver hepatocellular carcinoma	DESeq2, LASSO, KEGG, GO, and nomogram	Jinan University	Identification of SRGs, survival analysis, and model building	LASSO, Kaplan–Meier, Cox, ROC, and DCA	SOCS2, IGFBP3, and RACGAP1 are key biomarkers.	Need for more validation and limited generalizability	TCGA-LIHC (424) and PAAD (183)
Mohammadi et al., 2025 [31]	Iran	Evaluation of NTRK family in BC	BC	UALCAN, KM-plotter, STRING, Enrichr, and DGIdb	Iranian academic centers	Gene expression, genome alteration, survival, and targeted drugs	Welch t-test, log-rank, and bcGenExMiner	NTRK2/3 above expression = better prognosis	Tumor heterogeneity and need for in vivo validation	TCGA: 1101 patient
Ronquillo & Lester – 2022 [32]	USA	Precise medical status and genomic testing in All of Us	Multiple (breast, prostate, blood, and the like)	LOINC, OMOP, Python, R, and Jupyter	NIH All of Us	Extraction of genomic test data and their analysis	EHR mining and LOINC classification	Only 5.2% of cancer patients underwent genomic testing.	Lack of structural data and low racial diversity	5,678 cancer patients out of 315,297 people
Su et al., 2025 [33]	China	KRAS-wild-type profile in pancreatic cancer for precision treatment	KRAS wild-type pancreatic cancer	NGS (831 genes), RNA-seq, and CIBERSORT	Harbin Medical University	Jump analysis, fusion, treatment response, and survival	Hisat2, maftools, Kaplan–Meier, and IOBR	HRD related to platinum response and treatable fusions	Low validation without matched blood samples.	34 patients; 73.5% under 65 years old, different stages

Table 1. Continued.

Authors and Year	Country	Aim of research	Type of cancer	Bioinformatics aspects	Setting	Included processes	Methods	Key findings	Challenges	Demographics
Vakili et al., 2024 [34]	Canada, Portugal, KSA, and Poland	A comprehensive medical review in head and neck cancer with emphasis on miRNA	Head and neck cancer (HNSCC)	OncoMiR, GEO, DEGs, KEGG, TGF-β, and AI/ML	Collaborative international review	Review of miRNA, pathway, HPV, and EGFR	OncoMiR, meta-analysis and in silico validation	miR-21, miR-155, miR-145, and EGFR biomarkers	Lack of standardization of miRNA data	Multiple studies with hundreds of HNSCC patients
Lin et al., 2022 [35]	Taiwan	AI in precision medicine to improve cancer treatment	Multiple (colorectal, ovarian, lung, and skin)	AI, ML/DL, NLP, REVEL, DRAGEN, and QOCA	NCKU Hospital	NGS, RNA-seq, mutation signature, and single-cell model	CNN, SVM, CADD, UMAP, and DeconstructSigs	AI has improved prediction and the accuracy of treatment.	Complex interpretation of single-cell data, defect in EHR	Taiwanese patient data and TCGA
Agaoglu et al., 2022 [36]	Turkey	Differences in the interpretation of hereditary cancer variants between BIs and CGs	Hereditary cancers	SIFT, PolyPhen, ACMG, and SOPHiA DDM	University of Health Sciences, Turkey	NGS for 27 genes, comparing the interpretation of variants	ACMG criteria, PP3, PM1, and PP5	22.5% Disagreement; Conflicting Criteria	Lack of clinical data by BIs	285 patients; age: 46; 251 women
Winterhoff et al., 2022 [37]	USA and Germany	A molecular model for Bevacizumab response in ovarian cancer	Epithelial ovarian cancer	SVM, microarray, HITON-PC, MFAP2, and VEGFA	ICON7/OVAR-11 RCT, 2000 patients	RNA extraction, modeling, and validation	SVM, Cox regression, and NNFCV	A prediction of 10 months of additional survival for responders.	The complexity of the model requires phase III validation.	RCT with 2,000 patients with complete information
Peterson et al., 2023 [38]	USA	Prediction of NAT response in BC with a 4D model	Early BC	CNN (ResVNet), MRI, and pharmacokinetics	SimBioSys, Cincinnati University	MRI, segmentation, and response modeling	ROC, AUROC, Log-rank, and MAE	91.2% accuracy in predicting pCR	No examination of the lymph node and limited MRI	80 patients, mixed ethnicity, TNBC 22.5%
Jia et al., 2020 [39]	China	Identification of specific Luminal A and Basal-like genes	Luminal A, basal-like BC	Limma, edgeR, PPI, Cytoscape, KEGG, and GO	Inner Mongolia Medical University	Analysis of DEGs, PPI network, and gene survival	MCODE, cytoHubba, and PROGgeneV2	*NMUR1*, *CDC7*, and *STIL* are key genes.	Lack of laboratory validation	TCGA: 439 samples
Mokhtari et al., 2023 [40]	Iran and USA	BMC3PM for precise drug combination in BC	BC	Limma, CMAP, KEGG, IPPGE, and PHM	University of Tehran, Duke, and the like	RNA array, constructing the IPPGE profile, and health matrix	Spearman, KEGGgraph, and DC algorithm	β group drug combinations were more effective.	Lack of laboratory validation and data difference	6,173 patients and 312 healthy individuals , from GEO

Note. ncRNA: Non-coding ribonucleic acid; TNBC: Triple-negative breast cancer; ML: Machine learning; AI: Artificial intelligence; HGSC: High-grade serous carcinoma; LIHC: Liver hepatocellular carcinoma; SRG: Survival/senescence-related gene; NTRK: Neurotrophic tyrosine receptor kinase; miRNA: Micro ribonucleic acid; BI: Bioinformaticians; CG: Clinical geneticist; NAT: Neoadjuvant therapy; BMC3PM: Bioinformatics multidrug combination protocol for personalized precision medicine; STT: Soft tissue tumor; LncRNA: Long non-coding ribonucleic acid; KRAS: Kirsten rat sarcoma viral oncogene homolog; HNSCC: Head and neck squamous cell carcinoma; FFPE-RNA seq: Formalin-fixed paraffin-embedded ribonucleic acid sequencing; SVM: Support vector machine; TCGA: Cancer Genome Atlas; CCLE: Cancer Cell Line Encyclopedia; CTRP: The Cancer Therapeutics Response Portal; GEO: Geographic or geospatial; RFE: Recursive feature elimination; LASSO: Least absolute shrinkage and selection operator; KEGG: Kyoto Encyclopedia of Genes and Genomes; GO: Gene ontology; UALCAN: The University of Alabama at Birmingham CANcer data analysis portal; KM-plotter: Kaplan-Meier Plotter; STRING: Search Tool for the Retrieval of Interacting Genes/Proteins; DGIdb: Drug-Gene Interaction Database; OMOP: The Observational Medical Outcomes Partnership; CIBERSORT: Cell-type identification by estimating relative subsets of RNA transcripts; TGF-β: Transforming growth factor-beta; DL: Deep learning; NLP: Natural language processing; REVEL: Rare Exome Variant Ensemble Learner; DRAGEN: Dynamic Read Analysis for GENomics; SIFT: Sorting Intolerant From Tolerant; PolyPhen: Polymorphism phenotyping; DDM: Data-driven machine; HITON-PC: Parents and children; MFAP2: Microfibrillar-associated protein 2; VEGFA: Vascular endothelial growth factor A; CNN (ResVNet): Convolutional neural network; edgeR: Empirical Analysis of Digital Gene Expression Data in R; CMAP: Connectivity map; PHM: Primary health matrix; USC: University of Southern California; NIH All of Us: The All of Us Research Program, a long-term research initiative by the National Institutes of Health; NCKU Hospital: National Cheng Kung University Hospital; ICON7: The International Collaboration on Ovarian Neoplasms 7; RCT: Randomized controlled trial; GE: Gene expression; CNV: Copy number variation; HPV: Human papillomavirus; EGFR: Epidermal growth factor receptor; NGS: Next-generation sequencing; MRI: Magnetic resonance imaging; DEG: Differentially expressed gene; PPI: Protein-protein interaction; IPPGE: Immunofixation and protein electrophoresis; FISH: Fluorescence in situ hybridization; RT-PCR: Real-time polymerase chain reaction; ADx: Advanced diagnostics; ARR: Arriba; SFU: STAR-fusion; HD-SCA: High-definition or high-dimensional single-cell analysis; AUC: Area under the curve; DAVID: The Database for Annotation, Visualization, and Integrated Discovery; 1D-DDg: One-dimensional data-driven grouping; SWVg: Statistically weighted voting grouping; AWR: Advantage-weighted regression; STRING: Search Tool for the Retrieval of Interacting Genes/Proteins; GEPIA: Gene Expression Profiling Interactive Analysis; ROC: Receiver operating characteristic; DCA: Decision curve analysis; EHR: Electronic health record; LOINC: Logical Observation Identifiers Names and Codes; Hisat2: Hierarchical Indexing for Spliced Alignment of Transcripts 2; IOBR: Immuno-oncology biological research; OncoMiR: Oncogenic micro ribonucleic acid; CADD: Combined Annotation-Dependent Depletion; UMAP: Uniform manifold approximation and projection; ACMG: the American College of Medical Genetics and Genomics; NNFCV: Nested N-fold cross-validation; AUROC: Area under the receiver operating characteristic curve; MAE: Mean absolute error; MCODE: Molecular complex detection; DC: Difference of convex; ARR: Absolute risk reduction; E2F3: Early 2 Factor transcription factor 3; BCL2: B-cell lymphoma 2; CCNE2: Cyclin E2; PSV: Prognostic signature vector; PBVV: Prognostic binary variable vector; TRIP13: Thyroid hormone receptor interactor 13; KIF14: Kinesin family member 14; DTL: Denticleless E3 ubiquitin protein ligase homolog; EXO1: Exonuclease 1; SOCS2: Suppressor of cytokine signaling 2; IGFBP3: Insulin-like growth factor binding protein-3; RACGAP1: Rac guanosine triphosphate-activating protein 1; HRD: Homologous recombination deficiency; pCR: Pathologic complete response; NSCLC: Non-small cell lung cancer; BC: Breast cancer; PAAD: Pancreatic adenocarcinoma.

demographics.

The quality of the 18 studies included in this systematic review was evaluated using an integrated approach combining the QUADAS-2 and QAREL tools. Table 2 provides a comprehensive summary of RoB, applicability concerns, and reliability for each study. All studies were considered to have low RoB across the QUADAS-2 domains, including patient selection, index test, reference standard, and flow and timing. Similarly, applicability concerns were minimal, indicating that the included studies were methodologically appropriate and relevant to the research objectives. The QAREL assessment confirmed acceptable reliability for all studies, demonstrating that the study populations, examiners, test procedures, and statistical analyses were appropriate, reproducible, and consistently reported. Moreover, the Notes column highlights the methodological strengths of each study, such as the use of real clinical samples, multi-cohort validation, robust in silico analyses, and advanced bioinformatics and ML approaches. Overall, this quality assessment supports the inclusion of all studies in the review and indicates that the findings derived from these studies are reliable and methodologically sound. The integration of both tools provides a robust framework to ensure that the evidence synthesized in this review is based on high-quality and reproducible research.

Across the included studies, a consistent focus was placed on the identification of cancer-related genes and regulatory molecules, such as TRIP13, STIL, NTRK2/3, FGFR2, VEGFA, miR-21, and miR-145, which were reported as diagnostic or prognostic biomarkers in multiple tumor types, including breast, liver, gastric, and ovarian cancers. More than twelve studies specifically investigated these targets, highlighting their potential role in precision oncology.

In addition, ML approaches were widely applied, with over half of the studies employing at least one algorithm. Several methods (e.g., SVM, convolutional neural networks, LASSO, and deep neural networks) demonstrated strong predictive performance. Reported accuracies ranged from 85% to 95% for predicting treatment response, overall survival, or tumor subclassification. For example, the TumorScope model was evaluated in BC for predicting therapeutic response, while a LASSO-based model showed prognostic utility in liver cancer.

Several studies integrated genomic analyses into treatment selection strategies, including the use of combinatorial drug approaches in the BMC3PM framework and off-label drug recommendations for triple-negative BC. The findings consistently supported the role of bioinformatics in tailoring therapeutic options to individual molecular profiles. Furthermore, specific studies (e.g., Agaoglu et al[36]) emphasized variability in genetic variant interpretation among clinicians, underscoring the need for standardized frameworks.

Challenges related to data quality and accessibility were recurrent. For instance, Ronquillo et al[32] reported that only 5.2% of participants in the All of Us program had available genomic data, and multiple studies noted the lack of structured or standardized datasets. Most datasets originated from large public repositories (e.g., TCGA, GEO, and ENCODE), which predominantly represent Western populations. Laboratory-based analyses constituted the primary research setting.

Notably, the integration of genomic, clinical, and imaging data was shown to improve diagnostic accuracy and enhance clinical decision-making, particularly in studies from Taiwan and the United States employing hybrid AI frameworks. Novel therapeutic opportunities were also reported: for example, FGFR2 fusions in pancreatic cancer and biomarkers in KRAS-wild-type tumors were suggested as potential candidates for targeted therapy.

Collectively, the evidence indicates that bioinformatics offers powerful tools for identifying novel therapeutic targets, predicting treatment outcomes, and supporting precision medicine approaches in oncology. However, progress is limited by a number of challenges, such as a lack of structured data, insufficient algorithm interpretability, and restricted access to genomic datasets, highlighting the necessity of standardized infrastructures and international data-sharing initiatives.

Discussion

This review underlines the rapid evolution of bioinformatics and precision oncology, where advances in AI, ML, and integrative multi-omics are reshaping cancer diagnosis, prognosis, and therapeutic decision-making. Recent studies underscore the transformative role of combining genomics and AI to enable early detection, drug resistance prediction, and targeted therapy design. These approaches have demonstrated substantial clinical value, although challenges remain regarding data standardization, algorithmic interpretability, bias mitigation, and ethical governance.[41] Furthermore, integrating genomics with transcriptomics and proteomics has provided a more comprehensive understanding of tumor biology, thereby facilitating individualized treatment strategies.[42]

Advances in genomic bioinformatics have produced powerful platforms, including cBioPortal, GDC, GEO, and other pathway/network analysis tools, which are increasingly employed for biomarker identification and detection of cancer driver mutations. Such resources are central to tailoring treatments and predicting therapeutic response.[43] Emerging evidence suggests that AI significantly contributes to predicting responses to immunotherapy, identifying novel therapeutic targets (e.g., lncRNAs), and accelerating the discovery of precision oncology drugs. Despite this potential, critical issues regarding transparency, reproducibility, and ethical implementation persist.[44]

Integrating diverse molecular layers—including genomics, epigenomics, transcriptomics, and proteomics—has reinforced the concept of systems biology of cancer, yielding novel insights into disease

Table 2. Integrated Quality Assessment of Included Studies Using QUADAS-2 and QAREL Tools

Study (Author, Year)	Patient Selection — RoB	Patient Selection — Applicability	Index Test — RoB	Index Test — Applicability	Reference Standard — RoB	Reference Standard — Applicability	Flow and Timing — RoB	Overall QUADAS-2 RoB	Q1: Spectrum of Subjects	Q2: Spectrum of Examiners	Q3: Blinded?	Q4: Order Effects Avoided	Q5: Time Interval	Q6: Same test to all	Q7: Independent Interpretation	Q8: Examiner Training	Q9: Statistical Analysis Appropriate	Q10: Complete Reporting	Q11: Other Bias	QAREL Overall Reliability	Notes
Iolanda Capone et al., 2022 [23]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Real clinical FFPE samples; validated with reference standards
Khorasani, Shahbazi, Mahdiyan - 2018 [24]	Low	Low	Low	Low	N/A	N/A	N/A	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Robust in silico analysis with validated databases
Zurita AJ et al., 2020 [25]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Imaging and RNA-seq with high accuracy
Cheng, Moore, Greene – 2014 [26]	Low	Low	Low	Low	N/A	N/A	N/A	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Public datasets; validated ML approaches
Cheng et al., 2016 [27]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Integration of TCGA and CCLE with ML
Ow, Tang, Kuznetsov – 2016 [28]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Multi-dataset analysis; strong predictive modeling
Sinnarasan et al., 2023 [29]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	ML-based biomarker discovery; public dataset validation
Lai et al., 2024 [30]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Multi-cohort survival and risk modeling with LASSO
Mohammadi et al., 2025 [31]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Comprehensive NTRK evaluation in the TCGA cohort
Ronquillo & Lester – 2022 [32]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Rigorous EHR mining with LOINC standards
Su et al., 2025 [33]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Broad genomic sequencing; therapeutic correlation
Vakili et al., 2024 [34]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Comprehensive systematic review of miRNAs
Lin et al., 2022 [35]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	AI/ML application on multi-cancer datasets
Agaoglu et al., 2022 [36]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Bioinformatics evaluation of hereditary cancer variants
Winterhoff et al., 2022 [37]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Molecular modeling validated in large RCTs
Peterson et al., 2023 [38]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Advanced 4D modeling with high MRI predictive accuracy
Jia et al., 2020 [39]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	PPI network-based key gene identification
Mokhtari et al., 2023 [40]	Low	Low	Low	Low	Low	Low	Low	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good	Personalized drug modeling; large GEO datasets

Note. FFPE-RNA-seq: Formalin-fixed paraffin-embedded ribonucleic acid sequencing; TCGA: Cancer Genome Atlas; CCLE: Cancer Cell Line Encyclopedia; LASSO: Least absolute shrinkage and selection operator; NTRK: Neurotrophic tyrosine receptor kinase; EHR: Electronic health record; LOINC: Logical Observation Identifiers Names and Codes; miRNA: Micro ribonucleic acid; AI: Artificial intelligence; ML: Machine learning; RCT: Randomized controlled trial; MRI: Magnetic resonance imaging; PPI: Protein-protein interaction; GEO: Geographic or geospatial.

heterogeneity and treatment response [45]. Recent reviews have highlighted how AI can improve the integration of multi-omics data into pharmacological workflows, supporting drug prioritization and optimizing therapeutic choices.[46] Additionally, novel directions in oncology bioinformatics (e.g., counterfactual ML frameworks) offer interpretable and trustworthy treatment recommendations, bridging the gap between algorithmic predictions and clinical decision-making.[47] Moreover, federated learning has emerged as a promising approach for enabling collaborative research across multiple centers while preserving patient privacy, although reproducibility and harmonization remain challenges.[48]

A critical component of evaluating the robustness and translational potential of these approaches lies in the assessment of study quality. In this review, all included studies demonstrated low RoB and high applicability across QUADAS-2 domains, indicating rigorous patient selection, well-validated index tests, and reliable reference standards. In addition, most studies adhered to methodological best practices, including appropriate statistical analyses, blinded interpretation, and standardized examiner training, as reflected by consistent "Yes" responses across Q1–Q10 questions and "Good" overall QAREL reliability. Notably, the studies utilized diverse but high-quality datasets (i.e., clinical FFPE samples, public multi-omics repositories, imaging data, and robust in silico analyses), enhancing the credibility and generalizability of the findings. Furthermore, the low RoB across these studies supports the reliability of conclusions drawn regarding biomarker identification, ML-based treatment modeling, and multi-omics integration.

The findings of the present work closely align with these emerging trends in precision oncology. Specifically, the identification of key biomarkers, such as miR-21 and NTRK2/3, underscores the growing importance of advanced bioinformatics platforms in biomarker discovery.[43] Similarly, the application of ML for modeling treatment response parallels recent efforts in AI-driven prediction of immunotherapy outcomes and drug sensitivity.[41,44] Furthermore, the study's emphasis on integrating genomic, imaging, and clinical data conforms to the multi-omics paradigm, which is increasingly recognized as the cornerstone of precision oncology.[45,46] Models such as BMC3PM exemplify the development of counterfactual treatment recommendation frameworks designed to provide interpretable and clinically relevant decision support.[47] Considerations related to data sharing and patient privacy correspond to the adoption of federated learning approaches in oncology.[48] Finally, the predictive modeling of therapy response contributes to the broader movement toward AI-based adverse drug reaction prediction and personalized treatment selection.[49]

To further enhance the clinical utility and translational impact of such approaches, future research should focus on several key directions. First, the incorporation of federated and privacy-preserving ML frameworks is essential to enable multi-center validation without compromising patient confidentiality. Equally important is the advancement of explainable AI (XAI) methodologies to ensure that predictions remain interpretable and actionable for clinicians and patients. In addition, strengthening reproducibility and standardization through the use of large-scale, multi-omic, and multi-institutional datasets will be critical for achieving robust and generalizable findings. Ultimately, careful attention must be given to ethical and regulatory considerations to promote equitable and responsible deployment of AI-driven precision oncology. The consistently high methodological quality of the studies included in this review further emphasizes that future work built upon rigorous and transparent study designs is likely to yield clinically meaningful and trustworthy insights.

Conclusion

This systematic review demonstrated that bioinformatics has become a cornerstone of personalized oncology by enabling the integration of genomic, transcriptomic, proteomic, and imaging data into clinically actionable insights. Across the 18 included studies, consistent advances were identified in biomarker discovery (e.g., TRIP13, STIL, NTRK2/3, VEGFA, miR-21, and miR-145), ML–based predictive modeling, and bioinformatics-driven therapeutic optimization. These findings underscore the central role of computational tools in enhancing early detection, refining prognosis, and tailoring cancer treatment to the molecular and clinical profiles of individual patients. Importantly, the review highlights that ML and AI frameworks, including SVMs, CNNs, and deep learning algorithms, are achieving high predictive accuracy in survival and treatment response modeling. The integration of multi-omics data and electronic health records further improves diagnostic precision and supports decision-making at the bedside. It is worth mentioning that such approaches are not merely experimental but are increasingly positioned to reshape the clinical workflow in oncology. Several persistent challenges simultaneously hinder translation into routine practice, including limited interoperability of health information systems, variability in data quality, restricted access to diverse genomic datasets, and insufficient interpretability of complex algorithms. Moreover, most datasets originate from high-resource settings, raising concerns about the equity and generalizability of bioinformatics-driven models worldwide. Likewise, ethical and regulatory issues—particularly those related to privacy, transparency, and algorithmic bias— remain critical considerations. Taken together, the evidence indicates that bioinformatics-driven personalized medicine in cancer is no longer a theoretical aspiration but an emerging reality with tangible clinical benefits. To fully realize its potential, future research must prioritize federated and privacy-preserving learning frameworks, expand explainable AI methodologies, and strengthen reproducibility through standardized, multi-

center, and multi-omic datasets. Equally essential is fostering global collaboration to ensure inclusivity and equity in data sharing and application. In conclusion, bioinformatics provides powerful pathways to transform oncology into a truly personalized discipline—where prevention, diagnosis, and treatment are tailored to the unique molecular signatures of each patient. By addressing the current gaps in standardization, interpretability, and accessibility, the field can move decisively toward precision oncology that is not only innovative but also equitable, reproducible, and clinically impactful.

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