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A scoping review and bibliometric analysis (ScoRBA) of machine learning in genetic data analysis: unveiling the transformative potential

Authors: Wan Nur Amalina Zakaria[1,*]; Haikal Zahiruddin[2]; Zuriani Ahmad Zukarnain[2]; Adi Wijaya[3]

Affiliations: [1]Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kubang Kerian, 16150, Kelantan, Malaysia; [2]Faculty of Computer and Mathematical Sciences, Universiti Teknologi MARA Kelantan, 18500 Bukit Ilmu, Machang, Kelantan, Malaysia; [3]Department of Health Information Management, Universitas Indonesia Maju, Jakarta 12610, Indonesia

ABSTRACT

This study uses scoping review and bibliometric analysis; ScoRBA, to comprehensively highlight the recurrent themes linked to machine learning (ML) applications in genetic data analytics. Using relevant documents and the VOSviewer software, co-occurrence keywords analysis was performed. The important domains identified are Cancer Genomics, Bioinformatics, Precision Medicine, Disease Biomarkers, and Genetic Algorithms. These domains benefit from ML's data-driven insights, which have the potential to revolutionize healthcare and biomedical research. The study reveals a surge in research publications and citations in recent years, indicating the growing importance of ML in genetic data analysis. It identifies research gaps and challenges within each domain, offering recommendations for future investigations. This review emphasizes the potential for personalized, data-driven healthcare by highlighting the power of ML and advanced computational methods. By addressing the identified research gaps and following the proposed recommendations, these interdisciplinary fields promise to improve disease diagnosis, prognosis, and treatment, while deepening our understanding of human biology. In conclusion, this study provides an overview of the application of ML in genetic data analysis, highlighting its pattern, advances, gaps and future directions.

Keywords: Bioinformatics, genomics, biomarkers, machine learning, precision medicine

INTRODUCTION

In recent years, due to technological advancements and the explosion of large-scale genomic data, the field of genetics have undergone through a transformative evolution. Enabling the successful development of pipelines and tools for preprocessing and analyzing raw genetic data, significantly improving accessibility for research and analysis [1]. Significantly, advanced computational techniques, including generative models like generative adversarial networks (GANs)

***Corresponding author:** Wan Nur Amalina Zakaria, Lecturer, Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kubang Kerian, 16150, Kelantan, Malaysia, email: dr_amalina@usm.my; **Potential Conflicts of Interest (CoI):** All authors: no potential conflicts of interest disclosed; **Funding:** All authors: no funding has been sought or gained for this project; **Academic Integrity.** All authors confirm that they have made substantial academic contributions to this manuscript as defined by the ICMJE; **Ethics of human subject participation:** The study was approved by the local Institutional Review Board. Informed consent was sought and gained where applicable; **Originality:** All authors: this manuscript is original has not been published elsewhere; **Review:** This manuscript was peer-reviewed by three reviewers in a double-blind review process.

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and restricted Boltzmann machines (RBMs), have been employed to construct synthetic genomes. This approach facilitates the exploration of varied genomic datasets while adhering to ethical considerations [2].

Computational tools such as TelFinder can now detect telomeric motif sequences, shedding light on telomere composition and evolution [3]. Artificial Neural Networks (ANNs) have been employed to classify and scrutinize J-domain proteins (JDPs), revealing coevolution patterns between J-domains and their Hsp70 partners for specific cellular functions [4]. Statistical methodologies, exemplified by Cloud Infrastructure for Microbial Bioinformatics (CLIMB), parse genomic data to pinpoint condition-specific patterns, enhancing our understanding of tissue specificity and cell differentiation [5]. Furthermore, machine learning (ML) applications have proven invaluable in gene expression data analysis, genetic analysis of complex phenotypes, and single-cell omics data analysis [6,7]. ML methods play a pivotal role in genome-wide association studies (GWAS) [8], copy number variation (CNV), single nucleotide variant (SNV) calling [9], and epigenome-wide association studies (EWAS) [10]. Therefore, ML applications have been developed for post-GWAS prioritization [11]. For instance, a tree-based ML method might supplement the disease-related SNV acquired from other population genomic techniques such as GWAS, with a crucial layer of knowledge [12].

EWAS, on the other hand, uses array-based assays to test whether DNA methylation (DNAm) at particular CpG sites is associated with a disease [13]. Because of technical limitations [14] and limited CpGs tested with EWAS, ML is used to identify additional CpGs on a genome-wide scale [15]. CNVs from exome sequencing are becoming a common method for genetic testing [16-20], even though the clinical efficacy of microarrays has not decreased [21]. CNVs require the expertise of qualified clinical specialists to interpret in a clinically sophisticated manner. To avoid looking through enormous genomic databases, several ML techniques and general guidelines have been put out for the accurate detection of CNVs from exome sequencing [22]. ML is also instrumental in high-throughput chromosome conformation capture (Hi-C) data analysis, transcription factor binding site inference, and single-cell RNA-seq data analysis [23]. These approaches exhibit great potential for biomarker identification, disease outcome prediction, and advancing precision medicine.

The incorporation of ML techniques into genetic research effectively identifies genetic markers and predicts disease susceptibility [24]. Deep learning algorithms and ML methods are applied across multiple facets of genomics, offering insights into rare hereditary immune diseases [25]. The marriage of ML with genetics and genomics holds the promise of revolutionizing our understanding of human genetic variation and disease causation [26]. While these advancements have reshaped genetics research, a comprehensive analysis or review is urgently needed to map the existing research terrain and identify gaps in the utilization of ML methodologies in genetic data analysis. Though ML techniques have revolutionized various genomics aspects [6-10], there remains a lack of systematic exploration in this dynamic field. To bridge the existing gap and provide a comprehensive overview of this rapidly evolving research domain, this study proposes a meticulous scoping review and bibliometric analysis, denoted as ScoRBA [27]. This approach aims to systematically outline prevailing themes related to ML applications in genetic data analyses, contributing to a deeper understanding of the research landscape and guiding future investigations in this promising field.

METHODS

In this study, a ScoRBA procedure that closely adheres to the five-step scoping review protocol established by Arksey and O'Malley was performed [28]. The research commenced with the formulation of a primary inquiry aimed at exploring the landscape of literature concerning genetic data and ML.

On September 18, 2023, a comprehensive literature search was conducted utilizing Scopus' database. Given Scopus' extensive coverage of academic publications, it was selected as the primary data source [29,30]. The study's search queries incorporated the following terms: TITLE ("machine learning algorithm" OR "deep learning" OR "artificial intelligence") AND TITLE (gene OR genetic OR genom* OR exome). To ensure precision, the search field was restricted to "Title" only while still including all articles without limitations, ensuring the inclusion of all relevant research. The search yielded 1045 documents related to "machine learning" and "genetic data."

The search strategy and data collection procedures used in this study are modified from the PRISMA flow diagram as shown in Figure 1 [31].

The exported metadata, encompassing publication details and keywords, in Comma-Separated Values (.csv) format. This dataset was subjected to co-occurrence keyword analysis using VOSviewer version 1.6.17 to unveil prevalent patterns and themes [32]. Using VOSViewer's clustering algorithms, the resultant visualization map shows the terms or keywords. The term occurrence in visualization map shows the frequency of occurrence of specific keywords. The keywords are shown as different-sized nodes based on the frequency records for each keyword. Furthermore, the map displays how frequently the keywords occur close to each other. The formation of text clusters is significantly influenced by the co-occurrence of keywords within a text network as shown in the result section. The analysis involved summarizing and collating information about the selected articles and the ML models employed in genetic data analysis, organized under discerned clusters or themes. Additionally, the study examined publication trends to gauge the broader growth and impact of research within this field. This involved analyzing the number of annual publications and citations in the area. By quantifying these trends, the study aims to highlight the expanding influence and evolving focus within the research area.

RESULTS

Trends in publications and citations: The dataset reveals a compelling temporal evolution of events in the domain of ML applied to genetic data analysis. Notably, the years from 2014 to 2022 witnessed a remarkable surge in these events, with a staggering increase from 4 documents in 2014 to 256 documents in 2022. This exponential growth signifies the increasing significance and interest in the intersection of ML and genetics, possibly driven by advances in technology and data availability.

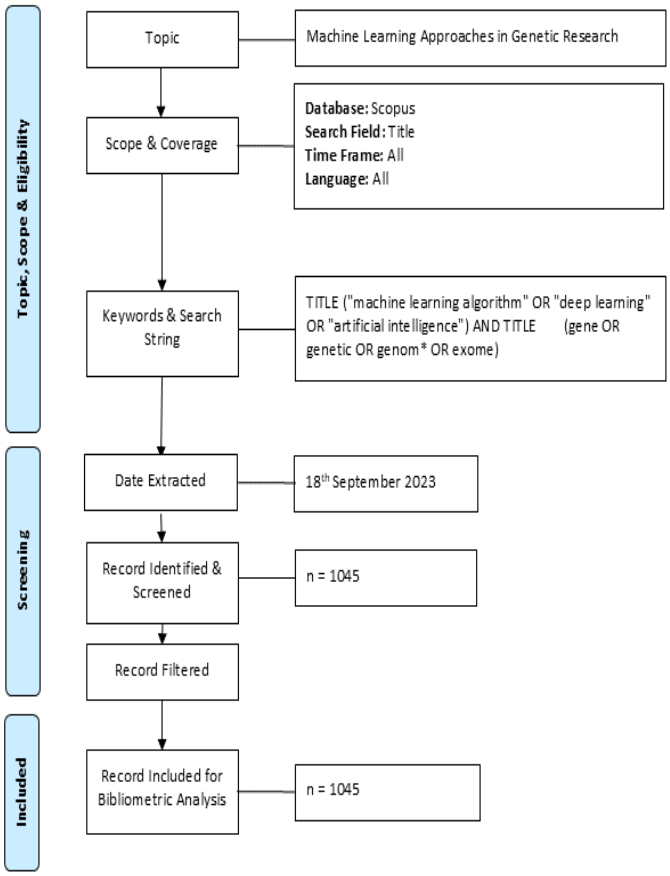

Figure 1: PRISMA flow diagram of the search strategy and data collection steps [31]

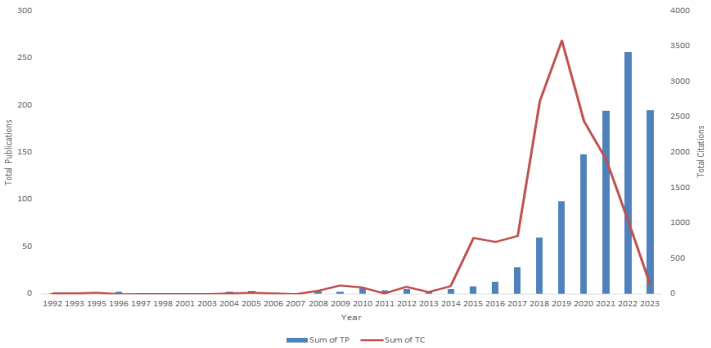

Figure 2: Publication trends and citations in the domain of ML applied to genetic data analysis Total Publication (TP) and Total Citation (TC)

Table 1: Results of the PAGER analysis of the ML and genetic research [35]

Pattern	Advances	Research Gaps	Evidence for Practice	Research Recommendations
Cancer Genomics	Predicting treatment responses, early cancer diagnosis, treatment, and personalized medicine	Follow-up studies on metastatic cancer, detecting driver mutations, integration into clinical practice, and method reliability	ML's potential, databases like CancerSysDB, ML's role in genomic classification, and predicting cancer phenotypes	▪ Explore robust methods for data analysis ▪ Integrate with big data mining ▪ Explore ML in cancer genomics classification ▪ Address data-related questions
Bioinformatics	Understanding transposable elements, identifying disease biomarkers, cancer research, and multi-faceted analyses	Effectiveness of Anderson Acceleration (AA), lack of standardized big data tools, and unable to predict the biological activity of natural products	ML's role in analyzing biological data, multi-modal data analysis, and translational bioinformatics	▪ Advance ML techniques for disease prediction ▪ Explore ML in biological data analysis, ▪ Integrate with omics technologies ▪ Address data management challenges
Precision Medicine	Analyzing complex biological data, personalized treatments, and disease subtype identification	Dependence on experimentally determined structures, biomarkers identification, deep learning datasets, as well as security/privacy concerns	Impact of ML in diagnostics, data-driven diagnostics, and challenges to address	▪ Improve ML models' transparency ▪ Enhance deep learning datasets ▪ Address biomarker identification, and security/privacy concerns
Disease Biomarkers	Identifying disease-specific biomarkers, early detection, and patient care	Limited neuropsychiatric symptoms (NPS) analysis, novel biomarkers, interpretable ML models, and quality metabolomics data	ML for complex pattern detection, predictive models for diagnosis, and molecular biomarker identification	▪ Address NPS analysis ▪ Explore new biomarkers ▪ Develop interpretable ML models ▪ Improve metabolomics data quality
Genetic Algorithms	Supervised and unsupervised learning in healthcare, and optimization problems	Relationships between solution size, operator complexity, variance error, combinatorial problems, and optimization problems	Applications in radiology, drug development, and function optimization	▪ Develop new recommendation systems ▪ Improve GAs for function optimization ▪ Explore hybrid algorithms ▪ Enhance genetic operators' integration

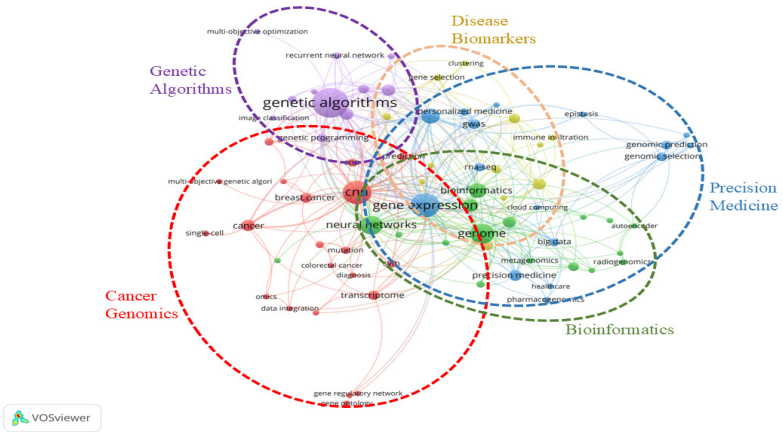

Figure 3: Co-occurrence of author keywords. 77 out of 2170 keywords met the threshold of a minimum of four occurrences

The year 2017 stands out as a pivotal point, with a sudden jump to 28 documents, indicating a significant shift in the field. This surge suggests a substantial shift and growing interest in integrating ML techniques with genetic and genomic data. Several factors contributed to this shift. Technological advancements, such as continuous improvements in high-throughput genomic technologies and computational power, made it feasible to handle and analyze large-scale genetic data more efficiently [33]. Researchers increasingly applied ML methods to tackle complex problems in genetics, such as predicting rare genetic disorders and analyzing noncoding regions of the genome, thereby enhancing diagnostic yields and research outcomes [34]. Additionally, the accumulation and availability of abundant genetic and genomic data facilitated more extensive research and exploration, enabling scientists to develop and refine ML models tailored to genetic data. These factors collectively contributed to the notable increase in research output, highlighting 2017 as a transformative year in this interdisciplinary field. However, the most recent data for 2023 shows a slight decline to 195 documents due to incomplete years.

Similarly, the total number of citations was 109 in 2014 and showed a gradual increase over the years with only a slight drop in 2016. A notable increase occurred from 2017 onwards, with total citations reaching 2719 in 2018 and 3582 in 2019. This suggests a significant expansion in this dimension of the domain, possibly indicating increased complexity, coverage, or engagement.

Keyword co-occurrence analysis: The co-occurrence keywords analysis using VOSviewer software identified five clusters. Figure 3 shows all the five clusters: Cancer Genomics, Bioinformatics, Precision Medicine, Disease Biomarkers, and Genetic Algorithms (GAs). These clusters highlight the integration of advanced technologies and analytical methods to enhance our understanding and treatment of diseases. These clusters (patterns) were later used as a basis for further discussion.

DISCUSSION

This discussion delves into the pattern, advances, research gaps, evidence for practice, and research recommendations (PAGER) in the domains of Cancer Genomics, Bioinformatics, Precision Medicine, Disease Biomarkers, and Genetic Algorithms (GAs) (Table 1).

The intersection of cancer genomics and machine learning (ML) has ushered in a new era in cancer research and clinical practices, offering transformative potential in diagnosis, prognosis, and treatment prediction [36,37]. AI and ML algorithms now play crucial roles in predicting treatment responses, facilitating early cancer detection, and enhancing prognosis accuracy. This progress is further fueled by open-source healthcare datasets and next-generation sequencing technology, enabling detailed genomic analysis, including microRNA and RNA-seq profiling [38].

ML techniques, such as Support Vector Machine classifiers, exhibit promise in accurately classifying cancer types and predicting clinical metrics [39]. Computational methods aid in somatic mutation detection, thereby improving cancer prognosis and

guiding targeted therapy decision [40]. However, despite these advancements, critical research gaps persist, highlighting for further investigation.

Research must delve into metastatic cancer with symmetrically handled data, enabling a comprehensive understanding of disease progression and treatment responses. Additionally, precise detection of driver mutations, for tailoring treatments to individual patients, emphasizing the importance of integrating academic insights into clinical practice. Moreover, questions regarding the nature of data, method efficacy, tool reliability, and economic feasibility must be addressed to ensure the practicality and efficacy of ML-driven cancer genomics applications [41-45].

While ML and AI's hold tremendous promise in cancer genomics, several challenges must be overcome before widespread clinical implementation [46]. Understanding the theoretical foundations of deep learning, addressing algorithmic opacity, and ensuring the quality of medical data used for ML model training are crucial steps in this process [47]. Databases like CancerSysDB provide valuable resources for accessing cancer-related data, while ML techniques combined with topological analysis of genomic data offer new avenues for predicting cancer phenotypes [48].

Looking ahead, future research in cancer genomics and ML should prioritize robust methods for analyzing vast genomic data, integrating big data mining approaches, and exploring ML algorithms for classification and subtyping. Additionally, improving understanding of cancer biology and drug discovery through ML-driven research efforts will further advance personalized medicine and precision oncology [49,50].

Addressing these research gaps is paramount for realizing the full potential of cancer genomics and ML in improving patient outcomes, guiding treatment decisions, and advancing our understanding of cancer biology. By leveraging ML-driven approaches and interdisciplinary collaboration, progress towards a more effective cancer prevention, diagnosis, and treatment strategies can be made.

The fusion of bioinformatics and ML has not only reshaped biology and healthcare paradigms but also revolutionized our understanding of complex biological processes [51]. ML algorithms play a crucial role in analyzing biological data, aiding in disease identification, and unraveling intricate aspects such as transposable elements and their regulatory mechanisms. This contribution extends to genome evolution, development, diseases, and drug resistance, enriching our comprehension of these critical areas [52]. The synergy between bioinformatics and ML enables systematic cancer analysis, fostering data-driven research and innovative approaches in prognosis, prediction, and treatment [53]. However, several research gaps persist, including the assessment of Anderson Acceleration in classical ML classifiers, the lack of standardized big data architectures for bioinformatics challenges, and the need for ML methods predicting biological activity based on biosynthetic gene clusters [54-56]. Anderson Acceleration, renowned for enhancing the convergence of gradient descent algorithms, exhibits potential in training bioinformatic-based ML [54].

The integration of bioinformatics and ML into clinical settings is essential for evidence-based practice [57]. ML's application in bioinformatics spans various domains such as microarrays, genomics, proteomics, and text mining, facilitating high-throughput biological data analysis and data-driven predictions [58]. Future research endeavors should prioritize ML techniques for predicting obesity and chronic diseases [59], delve deeper into ML algorithms for bioinformatics analysis, integrate computational methods in cancer biology, and address challenges associated with data management and storage in ML algorithms [60,61].

Addressing these research gaps is paramount for advancing personalized medicine, precision diagnostics, and targeted therapeutics. Enhancing ML algorithms' capabilities in analyzing biological data not only enhances our understanding of disease mechanisms but also paves the way for novel interventions and treatment strategies. Standardizing big data architectures in bioinformatics can streamline research efforts and foster collaboration across disciplines, leading to more robust and reproducible findings. Moreover, integrating ML into clinical practice empowers healthcare professionals with data-driven insights, enabling more accurate diagnoses, personalized treatments, and improved patient outcomes. By bridging these gaps, the full potential of bioinformatics and ML in revolutionizing healthcare delivery and the future of medicine can be realized.

The synergy between precision medicine and ML has propelled significant advancements, particularly in the analysis of complex biological data, thereby impacting structural biology and precision medicine research [62]. However, challenges persists, such as accurately predicting complex protein structures, reliance on experimentally determined structures, and concerns regarding security and privacy [63]. Precision medicine endeavors to tailor treatment based on genetic and environmental factors, laveraging ML for data-driven diagnostics [64]. Yet, challenges remain in identifying biomarkers for heterogeneous diseases, enhancing deep learning datasets and exploring ML's potential in clinical trial design [65,66].

Practical evidence underscores ML's capacity to deliver personalized treatments and improve diagnostics [67]. Nonetheless, challenges such as comprehending deep learning theory, addressing algorithmic opacity, and ensuring data quality must be resolved to successful integrate ML into clinical settings [68-70]. The fusion of precision medicine with ML offers promising prospects for personalized treatments, refined diagnoses, and enhanced disease prevention and management [71-73].

Addressing these challenges is paramount for realizing the full potential of precision medicine and ML. Accurate prediction of complex protein structures and the identification of biomarkers for heterogeneous diseases are critical for advancing personalized treatments and diagnostics. Moreover, overcoming algorithmic opacity and ensuring data quality are essential for establishing trust in ML-driven clinical decision-making. By addressing these gaps, it unlock the transformative potential of precision medicine and ML to usher in a new era of personalized healthcare tailored to individual patients' needs and characteristics.

Advancements in disease biomarkers and ML have opened up avenues for personalized medicine with profound implications for patient care. ML, coupled with high-throughput assays and computational techniques, has empowered the identification of tumor-specific signatures, offering insights into patient responses and aiding in tailored therapies [74]. Moreover, ML excels in predicting neurodegenerative diseases by laveraging clinical and genetic biomarkers for early detection and personalized treatment strategies [75]. However, several challenges persist, including limited analysis of neuropsychiatric symptoms, the necessity for novel biomarkers, and the demand for interpretable ML models to navigate complex metabolomics data [76-78].

While ML techniques excel in discerning complex patterns within disease biomarkers, transparency remains an issue [79]. Explainable AI (XAI) methods offer a promising solution by providing insights into ML algorithms, enhancing their applicable [80]. In the realm of disease biomarkers, XAI methods such as Layer-wise relevance propagation (LRP), VGG-16, and CNN [81] can analyze and interpret results obtained from ML algorithms, shedding light on decision making processes [81]. LRP, for instance, operates by propagating the prediction backwards in the neural network using specialized propagation rules, offering valuable insights into model prediction across various data modalities [82,83].

ML approaches have significantly contributed to disease biomarker identification, paving the way for personalized medicine and diagnostics [84,85]. However, challenges such as opacity in decision-making and data quality must be addressed to seamlessly integrate ML into clinical practice [86]. By tackling these challenges and enhancing transparency in ML models, healthcare practitioners can leverage the full potential of ML in disease biomarker identification, ultimately improving patient outcomes and revolutionizing personalized medicine.

Advancements in Genetic Algorithms (GAs) and ML have transformed medicine, offering solutions and predictive models with significant impacts on patient care [87]. ML applications in healthcare range from risk prediction models to discovery of unknown disease subtypes [88,89]. However, crucial research gaps persist, such as the need for a broader vision of GAs, understanding Genetic Programming (GP) relationships, and addressing problems in combinatorial and optimization challenges [90].

GAs have already shown promise in optimizing drug therapy decisions and contributing to drug development [91], but expanding their applications could revolutionize treatment protocols and resource allocation in healthcare. Additionally, improving our understanding of GP relationships can refine GAs for medical imaging analysis and drug discovery.

Addressing combinatorial and optimization challenges is essential for streamlining healthcare processes and resource utilization. Practical applications of GAs and ML, such as personalized dietary recommendations [92], medical check-up processes [93] and patient assignments [94], highlight their real-world impact.

Future research should focus on developing personalized recommendation systems, improving function optimization in GAs, exploring hybrid algorithms, and enhancing genetic operators' integration [95,96]. By addressing these gaps, it can drive innovation in healthcare delivery and improve patient outcomes.

CONCLUSION

This review study comprehensively examines cancer genomics, bioinformatics, precision medicine, disease biomarkers, and GAs, revealing significant advances, critical research gaps, and forward-looking recommendations in each area. These findings collectively underscore the transformative potential of interdisciplinary approaches rooted in ML and advanced computational methods, offering personalized, data-driven healthcare solutions. By addressing identified gaps, such as the need for precise driver mutation detection and interpretable ML models, the study hopes to overcome current challenges in the field and propel advancements in disease diagnosis, prognosis, and treatment. Looking ahead, future research should prioritize robust methods for genomic data analysis, enhance algorithmic transparency, and integrate computational approaches into clinical practice to drive further progress in improving patient outcomes.

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