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# Genetic Diversity and Mutation Frequency Databases in Ethnic Populations: Systematic Review

Shumaila Khan<sup>1\*</sup>, PhD; Mahmood Alam<sup>2\*</sup>, PhD; Iqbal Qasim<sup>3</sup>, PhD; Shahnaz Khan<sup>4</sup>, PhD; Wahab Khan<sup>5</sup>, PhD; Orken Mamyrbayev<sup>6</sup>, PhD; Ainur Akhmediyarova<sup>7\*</sup>, PhD; Nurzhan Mukazhanov<sup>7\*</sup>, PhD; Zhibek Alibiyeva,<sup>7\*</sup>, PhD

<sup>1</sup>Department of Computer Science, University of Science and Technology Bannu, Bannu Township, Bannu, Pakistan

<sup>2</sup>Faculty of Business, Law and Social Sciences, Birmingham City University, Birmingham, United Kingdom

<sup>3</sup>Hertfordshire Business School, University of Hertfordshire, Hatfield, United Kingdom

<sup>4</sup>Department of Chemistry, University of Science and Technology Bannu, Bannu, Pakistan

<sup>5</sup>Faculty of Computing and Informatics, Multimedia University, Cyberjaya, Malaysia

<sup>6</sup>Institute of Information and Computational Technologies, Satbayev University, Almaty, Kazakhstan

<sup>7</sup>Institute of Automation and Information Technologies, Satbayev University, Almaty, Kazakhstan

\*these authors contributed equally

#### **Corresponding Author:**

Shumaila Khan, PhD

Department of Computer Science, University of Science and Technology Bannu, Bannu Township, Bannu, Pakistan

# Abstract

**Background:** National and ethnic mutation frequency databases (NEMDBs) play a crucial role in documenting gene variations across populations, offering invaluable insights for gene mutation research and the advancement of precision medicine. These databases provide an essential resource for understanding genetic diversity and its implications for health and disease across different ethnic groups.

**Objective:** The aim of this study is to systematically evaluate 42 NEMDBs to (1) quantify gaps in standardization (70% nonstandard formats, 50% outdated data), (2) propose artificial intelligence/linked open data solutions for interoperability, and (3) highlight clinical implications for precision medicine across NEMDBs.

**Methods:** A systematic approach was used to assess the databases based on several criteria, including data collection methods, system design, and querying mechanisms. We analyzed the accessibility and user-centric features of each database, noting their ability to integrate with other systems and their role in advancing genetic disorder research. The review also addressed standardization and data quality challenges prevalent in current NEMDBs.

**Results:** The analysis of 42 NEMDBs revealed significant issues, with 70% (29/42) lacking standardized data formats and 60% (25/42) having notable gaps in the cross-comparison of genetic variations, and 50% (21/42) of the databases contained incomplete or outdated data, limiting their clinical utility. However, databases developed on open-source platforms, such as LOVD, showed a 40% increase in usability for researchers, highlighting the benefits of using flexible, open-access systems.

**Conclusions:** We propose cloud-based platforms and linked open data frameworks to address critical gaps in standardization (70% of databases) and outdated data (50%) alongside artificial intelligence–driven models for improved interoperability. These solutions prioritize user-centric design to effectively serve clinicians, researchers, and public stakeholders.

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#### **KEYWORDS**

ethnic-specific mutation frequency databases; genetic diversity; mutation disorder; inherited disease

## Introduction

#### Background

Recent advancements in genomic techniques, such as next-generation sequencing and clustered regularly interspaced short palindromic repeats technology, have revolutionized the identification of gene mutations associated with disease, enabling precise disease diagnosis and personalized treatment

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strategies. Completing the human genome sequence played a

significant role in detecting gene mutations that cause diseases,



Mutation databases are critical web-based repositories that aggregate genomic variant data for specific populations or ethnic groups, enhancing the understanding of genetic diversity and its association with the disease. Central databases, including Online Mendelian Inheritance in Man (OMIM) [4] and the Human Gene Mutation Database (HGMD) [5], primarily catalog published mutations and may not fully represent the genetic diversity of different populations [6,7]. On the other hand, locus-specific databases (LSDBs) focus on specific loci but may not gather information about a particular nation or ethnicity [8].

Other databases, like national and ethnic mutation frequency databases (NEMDBs), were developed to fill these gaps by recording the mutation spectrum observed for any gene (or multiple genes) associated with a genetic disorder for specific populations or ethnic groups worldwide. These databases are crucial for comprehending genetic variations related to diseases and facilitating targeted genetic testing and personalized medicine [9]. Regarding advancement in genomic analysis technologies, many NEMDBs face issues related to standardization, data quality, and accessibility. For example, the Human Genome Variation Society (HGVS) maintains a dedicated website; an inspection by the authors on March 12, 2024, revealed that while the page comprises 11 links, only 4 are functional, as compared to LSDBs, which contain 1646 links, and the total number of mutations was found to be 145,964. Most NEMDBs are outdated and have limited content, hindering their effectiveness in clinical and research settings [10].

Given the reliance of researchers and health care professionals on internet-enabled tools for accessing mutation data, there is a need for engineering-driven solutions to enhance further database accessibility, data standardization, and cross-platform data integration. This paper addresses the challenges by proposing an artificial intelligence-driven mutation prediction model and the linked open data (LOD) frameworks to improve data sharing, query efficacy, and interoperability within gene databases. By focusing on web-based user-centric designs, the objective is to optimize the usability of NEMDBs for health care professionals, researchers, and the general public, thereby advancing digital health solutions and improving outcomes in genetic research. By identifying the challenges and limitations associated with NEMDBs, we seek to provide actionable recommendations for enhancing their development and usability. The key contributions of the review are as follows:

- This systematic review examined 42 NEMDBs to a). analyze their design frameworks, methods of data collection, and querying capabilities; and b). identified critical gaps, including 70% (29/42) lack standardized formats, 60% (25/42) lack cross-ethnic comparisons, and 50% (21/42) have outdated data.
- To improve interoperability, engineering-driven recommendations include cloud platforms, artificial intelligence models, and LOD frameworks.
- A user-centric analysis to enhance accessibility for clinicians, researchers, and the public.

The rest of the article is organized as follows: the Related Works section presents a literature study and comprehensive review of available NEMDBs and other databases. The Methods section defines the systematic literature review approach and outlines the objectives. The Discussion section provides conclusions and future recommendations. Finally, the Conclusion section summarizes the review.

#### **Related Works**

Recent scientific developments have brought about the emergence of bioinformatics, a multidisciplinary field that combines molecular biology, information technology, computer science, and mathematics to form a single discipline [11]. Bioinformatics encompasses various tasks such as database design, categorization, protein structure prediction, RNA folding, and mutation mapping. These systems are essential for organizing and managing biological data within structured and persistent databases critical in retrieving, updating, storing, and querying information.

A significant milestone in bioinformatics history was Margaret Dayhoff's establishment of one of the first protein sequence databases in the 1960s; GenBank was developed in the 1980s and became the first nucleotide sequence database [12]. Similarly, mutation databases aim to make such data readily accessible to medical professionals, researchers, and clinicians studying genetic variations [13]. Recent advancements in developing integrated databases that include diverse ethnic mutation frequencies highlight the need for more inclusive data collection methods and internet-enabled platforms to bridge the genetic diversity gap [14].

PubMed, hosted by the National Center for Biotechnology Information (NCBI) since 1997, is a prominent scientific database containing several medical-related articles [15]. PubMed gives access to 38 databases concerning biomedical research and the analysis of erratic genetic diseases. Other repositories, such as MeSH (Medical Subject Headings), Institute for Scientific Information (ISI) Web of Science, and Medical Literature Analysis and Retrieval System Online (MEDLINE), provide comprehensive data about a particular gene and disease and are accessible to the public [9]. PubMed is one of the most influential bioinformatics resources, featuring web-based systems like PubMed Assistant [16], AliBaba [17], and PubMed-Ex. These enhance functionality through keyword highlighting, citation management, and semantic enrichment of biomedical entities extracted from text [18].

Similarly, the National Institutes of Health established the NCBI in 1988 as a centralized system for accessing diverse resources and databases via the NCBI website. The primary resources in the NCBI include the Database of Short Genetic Variations, the Database of Genomic Structural Variation, Entrez (an integrated database retrieval system that gives access to a diverse set of 35 databases), the Clone database (Clone DB), the BioProject Database [9,19], and the clinical central variant database (ClinVar). Table 1 summarizes the primary databases supported by NCBI, emphasizing their role in providing internet-enabled access to genomic data for researchers and health care professionals. Such internet-enabled systems streamline the extraction and analysis of gene mutation content and support

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collaborative research by facilitating data sharing across diverse platforms. However, challenges like data fragmentation, a lack of standardization, and accessibility limitations persist. Addressing these challenges requires leveraging artificial intelligence–based tools and LOD frameworks to improve data integration and usability. Enhancing the functionality of these systems will advance precision medicine and support clinical decision-making through electronic health applications.



Table . NCBI<sup>a</sup> databases.

References	Database Name	Brief description
Bianco et al [9]	Bio Project Database	The database allows users to submit detailed re- search studies from intensive genome sequences projects to huge worldwide associations.
Bianco et al [9]	BioSample Database	The Biosample Database is a new resource that annotates biological samples used in various NCBI-submitted studies, including genome-wide association studies, epigenetics, genomics se- quencing, and microarrays.
Landrum et al [3]	Clinical variant database (ClinVar)	ClinVar is a database that contains human genom- ic variants and their relevant disease. The database is publicly available.
Sayers et al [20]	PopSet Database	This database contains different sets of data that were submitted to GenBank. The data includes gene-related sequence data and their alignments with specific population, phylogenetics, muta- tion, and ecosystem studies.
Sayers et al [20]	Clone database (Clone DB)	The database incorporates clones and library in- formation, including sequence data, map posi- tions, and information distribution. It also offers filtering by organism and vector types.
Sayers et al [20]	MMDB (Molecular Modeling Database)	It details sequence alignments and profiles repre- senting protein spheres preserved in molecule evolution.
Boguski et al [21]	Database of expressed sequence tags (dbEST) Nucleotide EST Database	This database collects sequence tags and includes details about complementary DNA (transcript) sequences. dbEST is accessible directly via the Nucleotide EST Database.
Church et al [22]	Database of Genomic Structural Variation (db-Var)	It was designed to collect details about large- scale genomic variation, including large inser- tions, deletions, translocations, and inversions. It also contains the relationships of different variants to their phenotype.
Louhichi et al [23]	Entrez	Entrez is a rich database that integrates informa- tion from 35 databases containing over 570 mil- lion biological data records. The database pro- vides a graphical representation of sequences and chromosome maps, which is considered favorable in genetic research.
Mailman et al [24] and GAIN Collaborative Re- search Group et al [25]	Databases of Genotypes and Phenotypes (dbGaP)	The database contains information about geno- type and phenotype. The information is gathered using studies such as genome-wide association studies, medical resequencing, and molecular diagnostic assays.
Sherry et al [26]	Database of Short Genetic Variations (dbSNP)	This database, similar to HapMap, was developed to support large-scale polymorphism detection. It has since been updated and now also includes other variant types, such as insertions/deletions, microsatellites, and nonpolymorphic variants.
Sherry et al [26]	Database of Major Histocompatibility Complex (dbMHC)	dbMHC hosts two key resources: (1) an interac- tive alignment viewer for HLA (Human Leuko- cyte Antigen) and related genes
		and the Major Histocompatibility Microsatellite Database.

<sup>a</sup>NCBI: National Center for Biotechnology Information.

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Mutation databases are a knowledge base where allelic variations are defined and assigned to an explicit gene. Generally, 3 types of databases are accessible, that is, central, locus, and ethnic databases [27]. The primary mutation database comprises shared genome variation information and tools to analyze previously collected data.

#### **Central Databases**

The first mutation database, OMIM, was initiated in the 1970s by Professor Victor McKusick. OMIM primarily focuses on significant mutations, containing information about phenotypes, gene function, and allelic variants, which is helpful for researchers, students, and clinicians [4]. The website has been frequently updated and can be easily accessed. As of February 7, 2024, the updated version of OMIM consists of approximately 26,057 entries, each identified by a unique 6-digit number. Entries are categorized into phenotype and gene entries, detailing allelic variants, clinical synopses, and gene map loci. Content undergoes peer review and curation by journals and researchers, ensuring reliability and accuracy.

Another well-known database is HGMD, established in 1996 to study mutation disorders in human genetics [28]. With the higher rate of quality mutation records, HGMD acquired a broader position as the central mutation database. HGMD provides all known gene lesions causing human inherited diseases published in the peer-reviewed literature. The data provided by HGMD have been extensively used in international collaborative research projects and clinical settings [29], significantly advancing our understanding of mutational spectra in human genetics. HGMD offers a comprehensive database of mutations responsible for inherited human diseases, including their location, frequency, and the local DNA environment [30].

Recently, next-generation sequencing technologies and artificial intelligence algorithms have significantly enhanced the capabilities of central mutation databases. For example, HGMD has incorporated artificial intelligence–driven predictive models to improve the detection of gene variants and accelerate the identification of novel mutations [28]. These advancements allow for faster processing of large-scale genomic datasets, contributing to more accurate predictions in clinical genomics and personalized treatments. By leveraging such technologies, mutation databases like HGMD provide researchers with advanced tools for detecting causative mutations, enabling more efficient research and clinical diagnostic workflows.

HGMD updates its database frequently to ensure that the information provided is up to date and accurate. HGMD is accessible in two versions. The public version of HGMD [6] is freely accessible by registered users from academic institutions. The professional version is offered for commercial and educational/nonprofit users by subscribing to BIOBASE GmbH and under license via QIAGEN Inc [31]. The professional version of HGMD provides users with a feedback function in case of missing or new data and allows them to request changes or ask for an analysis of listed variants. In addition, the professional version of HGMD offers more advanced features than the public version. The latest version of HGMD was

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released in 2017, and statistics from April 2021 showed that the database contained 352,731 gene lesion entries in the HGMD Professional release, of which 234,987 entries were manually curated from academic and nonprofit sources and published journals.

#### LSDBs

LSDBs, which originated in 1976, were the first comprehensive databases documenting mutations at specific gene loci. The earliest example involved hemoglobin mutations, which were initially published as part of the Syllabus of Human Hemoglobin Variants. These databases are commonly used in DNA-based diagnosis to give clinicians, scientists, and patients an up-to-date overview of genetic variants. Their key objectives include quality data collection, validation, estimation, and transparency. Distinct from central databases, LSDBs are publicly accessible and supported by academic researchers who aim to share genetic information broadly. These databases, governed by experts in specific gene mutations or families, provide a specialized focus on different variations of a single gene. Expert curation ensures accuracy and relevance, with LSDBs often linking to clinical databases like PubMed/MEDLINE [32]. information Maintaining standard data fields such as exon number and mutation description, LSDBs ensure quality data submission [33,34]. They source information from direct submissions, published literature, and other variant databases like OMIM, the Database of Short Genetic Variations, and HGMD. PubMed is a primary tool for gene-related article searches, enhancing data completeness [35].

Generally, the genetic database system has been supported by various "LSDBs-in-a-box" over time. This approach was used as a solution intended to achieve the aim of database creation and has encompassed Universal Mutation Database [36], MUTbase [37], Mutation Storage and Retrieval (MuStaRt) [38], and LOVD [39].

LOVD [39], the widely accepted LSDB-in-a-box tool, is the most popular and freely available solution. LOVD was released in December 2012 and has been updated over time. LOVD 3.0 is mainly used as a tool for gene-centric groups and for displaying DNA variants. In addition, it provides space for storing patient-centric and next-generation sequencing data, even of variants that lie outside of genes. A desirable feature of LOVD is that its creators have established a database for most human protein-coding genes on their servers [40] and have invited interested parties to assume responsibility for maintaining databases for one or more genes of interest.

Databases like OMIM and HGMD have become indispensable genetic counseling and diagnosis tools in clinical settings. Clinicians regularly access these databases to identify gene mutations relevant to a patient's condition, allowing them to tailor treatments based on specific genetic profiles. Accessing relevant mutation data in real time facilitates personalized medicine, where treatment plans are developed based on individual genetic makeup. The accessibility and reliability of mutation databases have revolutionized how genetic diseases are diagnosed and treated, significantly improving health care outcomes for patients with inherited disorders.

#### **NEMDBs**

Various genetic disorders exhibit diverse mutation spectrums among specific population groups, providing researchers with valuable insight into genetic diversity. NEMDBs emerged to address this diversity, capturing the genetic heterogeneity of a particular ethnic group [12]. The HGVS maintains a catalog of central databases, LSDBs, and NEMDBs. These regional or ethnic databases offer valuable information on population genetic history, genetic testing, and gene-disease associations.

Figure 1 shows the architecture of the NEMDBs, representing 3 main architectural approaches: Ethnic and National database Operating Software (ETHNOS)–based architecture, 3-tier

architecture, and LOVD architecture. ETHNOS-based design provides a decentralized approach, with data distributed across nodes representing different locations, institutions, or groups. Some NEMDBs use a 3-tier architecture for efficient data management, comprising the display layer, application/logic layer, and data layer. On the other hand, LOVD architecture, an open-source platform, integrates separate modules for specialized functions like data submission, storage, and retrieval. The LOVD design provides effective administration and mutation-related data accessibility inside the NEMDB, offering a standardized and dependable platform for researchers and medical practitioners.



The genetic diversity captured in NEMDBs allows researchers to develop targeted strategies for detecting and diagnosing genetic disorders. By reviewing mutation patterns within and between populations, NEMDBs play a crucial role in stratifying national molecular diagnostic services and studying human demographic history, admixture patterns, and gene/mutation flow [41]. Such databases aim to identify novel mutations in ethnic-specific groups through coordinated genetic testing [42].

Recent developments in NEMDBs have enhanced their role in precision medicine. Databases focusing on underrepresented populations, such as those in Africa and Southeast Asia, have advanced precision medicine by identifying population-specific mutation patterns. This focus is particularly crucial for preventing prevalent diseases within specific populations. For example, the African Genome Variation Project and the Indian Genome Variation Database have provided data supporting personalized health care initiatives [42]. These databases play a pivotal role in stratifying national molecular diagnostic services, especially for ethnic groups with a higher predisposition to certain genetic conditions, such as cystic fibrosis in Caucasians, hemochromatosis in Jews, and thalassemia in people of Mediterranean and Southeast Asian descent [43,44].

The ethnic databases are broadly categorized into two groups, that is, National Mutation Genetic Databases (NMDBs) and NEMDBs. [45]. NMDBs primarily record existing gene mutations within specific ethnic populations, though they may include limited frequency data. NEMDBs, on the other hand, track inherited mutation frequencies across various ethnic groups and provide a broader view of global genetic diversity [45,46]. Examples of NEMDBs are listed in Table 2.

Table . National and ethnic mutation frequency databases.

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References	Database	Brief description
Peltonen et al [47]	Finnish Disease Heritage, 2002	This database contains comprehensive informa- tion about gene mutations in the Finnish popula- tion. Mutant allele frequencies are typically re- ported for Finnish mutations with multiple exter- nal links (Online Mendelian Inheritance in Man, GeneTests) and references. The database was initially published in 2004 and has since been updated with additional genes and mutation dis- orders. This database was designed using the LOVD platform.
Patrinos et al [12]	The Iranian National Mutation Frequency Database, 2006; Cypriot National Mutation Fre- quency Database, 2006	Here, 2 similar databases are presented, one for the population of Cyprus and the other for the Iranian population. These databases facilitate mutation screening and the establishment of gene-related services. Both of the databases were developed using the ETHNOS <sup>a</sup> platform.
Bianco et al [9]	Hellenic National Mutation Database, 2005	This database aims to provide qualitative and updated reports of genetic disorders in the Greek population. It reports diseases and related infor- mation for the Hellenic (Greek) population.
Zlotogora et al [48]	Israeli National Genetic Database	The Israeli National Genetic Database was devel- oped using the Electronic Tool for Human Na- tional and Ethnic Mutation Frequency Databases (ETHNOS) platform. This resource includes the Israeli National and Ethnic Mutation Frequency Database (NEMDB), which provides a detailed list of registered laboratories offering genetic testing services for the Israeli population through a dedicated query interface
Nakouzi et al [49]	The Lebanese National Mutation Frequency Database, 2006	This database was designed to analyze the genet- ic diseases in the population of Lebanon.
Sefiani et al [50]	The Moroccan Human Mutation Database, 2010	This database was developed to report the various mutation disorders found in the population of Morocco. A book chapter containing the details of various genetic disorders has also been pub- lished.
Ruangrit et al [51]	Thailand Human Mutation and Variation Database, 2008	ThaiMUT is an online ethnic database reporting mutation disorders in Thailand's population. This database presents different published and unpub- lished gene disorders and related diseases inves- tigated in Thailand.
Pradhan et al [52]	Indian Genetic Disease Database, 2010	A database that integrates gene-related diseases in the Indian population. Domain experts have curated the diseases of this database. The database was developed using a 3-tier architec- ture.
Qasim et al [42]	Pakistan Genetic Mutation Database	The database contains information about different disorders occurring in the Pakistani population. It currently has two versions, including the public version, which uses a relational database, and a second version that was developed using ontolo- gy as a knowledge base.
Romdhane et al [53]	Tunisian National Mutation Frequency Database	This database was developed to collect data about the different genetic disorders found in the Tunisian population.
Tadmouri et al [54]	CTGA <sup>b</sup> , 2006	The CTGA database is an open-access repository of information and findings on human gene variations and inherited, heritable genetic disor- ders in Arabs; it is constantly updated.



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References	Database	Brief description
Horaitis et al [27]	Singapore Human Mutation Database, 2006	The database contains mutations found in Singa- pore for Mendelian diseases. It presents mutation disorders and the frequency of polymorphisms examined based on phenotypes.
Rajab et al [55]	Oman Genetic Mutation Database, 2015	The database was developed to collect and man- age the mutations found in the Oman population. The mutations were collected from this database's scientific literature and service provi- sion.

<sup>a</sup>ETHNOS: Ethnic and National database Operating Software. <sup>b</sup>CTGA: Catalog of Arab Disease Mutation Database.

### Methods

#### Overview

For this study, we conducted a systematic literature review to analyze the structure, usability, and challenges of NEMDBs. The review focused on web-based databases and tools, ensuring inclusive extraction of relevant research content on homogeneity, data sources, and cross-comparisons within NEMDBs. Figure 2 demonstrates the step-by-step selection process used in this research, presenting the systematic literature review approach by outlining objectives for extracting and analyzing relevant information. The quality verification stage involved assessing the selected papers' validity and ensuring the extraction results' reproducibility. Finally, in the last part of the guideline, we extracted data from the identified documents to address the research question, visually present the data, and explain significant terms and relevant papers. By adopting a systematic web-based approach, this study ensures a rigorous and comprehensive analysis of NEMDB frameworks, aligning with the scope of digital health informatics.



#### Search Strings and Data Sources

To conduct a thorough literature search, various well-known databases were used to find the relevant research studies on NEMDBs. The search was performed across NCBI, PubMed/MEDLINE, and Web of Science databases to identify the most relevant research published between 1990 and 2023. The search strings used for literature searching included "mutation repository," "human mutation database," "genomic variation databases," "informed consent," and "empirical studies." The scope of the study was extended to integrate other databases, including the OMIM, LSDBs, and HGMD, to provide a comprehensive analysis of available resources in the field of genetic mutations and ethnic frequencies.

#### Selection of Studies

The literature selection was based on noticeably defined inclusion and exclusion criteria, explicitly addressing the review's objectives. Reviews provide comprehensive descriptions and analysis of the available NEMDBs [8,12,45], emphasizing their characteristics, functions, and importance in investigating genetic variants within specific population groups. This review included papers if they satisfied the following criteria.

Inclusion criteria were as follows:

• The paper was published in a peer-reviewed journal and contains insight into the design, structure, and content of NEMDBs.

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- NEMDBs were discussed in research publications, reviews, or survey studies about genetic diseases or population genetics.
- Papers that explored the gene variations and mutations related to a specific group of the ethnic population.
- Papers that only considered published and active NEMDBs that are publicly available.
- Studies that presented the protocols and methods used for data curation and quality control in NEMDBs.

Exclusion criteria were as follows:

- Papers that did not focus on ethnic-specific mutation databases.
- Research studies unrelated to mutation disorders, ethnic diseases, or gene variations.
- Studies that relied on generic genomic databases without emphasizing NEMDBs.
- Papers having minimal empirical proof or practical use.

A total of 420 articles were retrieved from Web of Science, NCBI PubMed, and Google Scholar.

Figure 3. Risk of bias assessment of the selected studies.

#### **Quality Verification**

In order to ensure the rigor and reliability of this review, a comprehensive risk of bias assessment was conducted. The articles were evaluated using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist. This process involved reviewing each study against PRISMA criteria assess completeness, transparency, to and methodological accuracy. We adhered to the Risk of Bias 2 guidelines for bias assessment, using the Robvis visualization tool. Each article was placed into one of three response categories-"High," "Low," or "Some concern"-based on its adherence to quality criteria.

For each study domain, an overall summary rating was calculated and visually represented in Figure 3, which outlines the risk level associated with each reviewed source. The highest proportion of "High Risk" ratings arose from the randomization process, indicating important issues with study designs in this area. On the contrary, bias due to deviations from intended interventions showed a relatively balanced distribution across the categories, with many studies achieving a "Low Risk" rating.



For bias due to missing outcome data, there was a more mixed distribution, with several studies flagged under both the "High" and "Some Concern" categories. The domain of bias in measuring the outcome revealed that most studies were categorized as "Low Risk," indicating reliable measurement practices in most cases. However, bias in the selection of reported results presented considerable concerns, with many studies rated as "High Risk." These findings were consolidated in the overall risk of bias evaluation, highlighting that many studies demonstrated high-risk characteristics. This visualization provided a transparent assessment of study quality, presenting a clear representation of the reliability of the data used in this review.

EndNote (version 20.5; Clarivate Plc), an automatic reference generator tool, was used to certify consistent citation and organization of the sources. The included articles were evaluated against all items on the PRISMA checklist to ensure adherence to best practices in the systematic review methodology.

#### **Data Extraction and Analysis**

The data extraction process involved a thorough review of each paper, focusing on identifying essential information relevant to

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the objectives of this review. Reviewers used "yes," "no," or "partial" responses to indicate the extent to which the review adheres to the checklist items. Detailed comments were provided to explain decisions, especially in cases where articles only partially met the checklist criteria. The extracted data were categorized and analyzed based on the homogeneity, structure, and user-centric design of the NEMDBs. The analysis focused on the consistency of mutation data within different databases. It evaluated how these databases are structured to serve their intended user groups, such as health care professionals, researchers, and the general public. The results were synthesized to recognize trends and potential gaps in NEMDB design and application.

## Results

#### Overview

This systematic review examines biological databases and their role in storing and organizing persistent data related to mutations and diseases of specific genes (an overview of the selection process is provided in Figure 4). These databases serve as knowledge bases and require curation by experts to maintain

the accuracy and relevance of the information. Most mutation databases had web-based access that shows and describes the contents and a minimum set of cross-references (active links) to access detailed information. Usually, these databases have links to central mutation knowledge bases for genetic variation (eg, NCBI, OMIM, and HGMD for clinical data; PubMed/MEDLINE for published references; and GenBank/European Molecular Biology Laboratory/DNA Databank of Japan for detailed DNA sequence information) [9]. They use different methods and techniques for collecting mutation-related information and database schemes and querying strings/options for retrieving data. These databases were created over various periods, as illustrated in Figure 5, and use their own developed platform, with most linked to central databases. The details about the methods and materials are given in the subsequent sections. Data from NEMDBs can be analyzed based on factors such as data quality and consistency, querying capabilities, database system/design, and the scope of disease content.

**Figure 4.** An overview of the study selection process following the PRISMA 2020 workflow. The flowchart presents the steps involved in the identification, screening, eligibility, and inclusion of studies in the systematic review. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses. \*Duplicates were removed using EndNote X20.5 and manual screening. \*\*Some articles appeared in multiple databases and were counted once during deduplication.





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Figure 5. A catalog of NEMDBs. NEMDBs: national and ethnic mutation frequency databases.



#### System Design and Data Accessibility

The design of mutation databases is user-friendly and provides free data accessibility, although some databases may require registration for access. A registration check ensures the user adheres to data submission, privacy, and authenticity guidelines. Consequently, a universal database management system platform fulfilling essential database requirements-including a friendly interface, the searching/querying option, and some privileges for curators-becomes necessary. Despite these advancements, the software was designed based on foundational systems such as ETHNOS, specifically for managing mutation databases. The ETHNOS-based software is used to satisfy the essential requirement of the NMDBs. They provide services to all those researchers who wish to implement the software for their database development purposes (detailed information can be found on the database website) [12,46]. ETHNOS supported the creation of various databases (ie, Hellenic, Cypriot, Iranian, Lebanese, and Serbian NEMDBs). However, ETHNOS could not handle greater querying capacity and larger datasets [12,13,56].

The Frequency of the Inherited Disorders database (FINDbase), a relational database established on an upgraded version of ETHNOS software capable of handling larger datasets, refers

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to the frequency of low alleles leading to inherited disorders in various ethnic populations worldwide [57]. FINDbase is an inclusive web-based resource supporting the occurrence of clinically relevant genomic variation allele frequency information, serving a well-defined scientific discipline. It offers modules for causative genomic variants and pharmacogenomics (PGx) biomarkers, with data collection focusing on expanding PGx datasets in European and other populations. FINDbase aims to interlink the PGx data module to DruGeVar [58], another genomic data resource.

Moreover, specific databases are based on a 3-tier architecture model (user/client, application server/web interface, and relational database management system), while others use the LOVD platform [39]. LOVD was initially designed for creating and maintaining web-based LSDBs. It is platform-independent software that uses PHP and MySQL only. The LOVD software has many variations, including LOVD v.2.0 [59] and LOVD v.3.0, following the HGVS. The front ends of all databases are based on HTML, with some JavaScript, PHP, and ASP.Net, and they rely on Cascading Style Sheets support. The primary purpose of LOVD is to facilitate the curators by providing flexible tools for gene mutation and the display of DNA variants. LOVD v.3.0 was updated on May 30, 2024. The data can be retrieved by using the LOVD application programming interface.

#### **Quality Data Collection**

The process of data collection is essential in the mutation database development phase, involving data collection from different sources such as PubMed, peer-reviewed and scientific literature, meeting reports, and experts and genetic services [60]. Table 3 shows the various data collection methods that the mutation databases use for gathering mutation-related information. Data can also be identified through automated text mining and manual journal screening and linking the unpublished mutation data presented in publicly available LSDBs; for example, the mutation databases may have a link

to the HGMD database that facilitates users with access to LSDBs, for both published and unpublished materials [5].

Table 3 shows the system design, data collection, and quality of the available NEMDBs. This table also holds the data-querying facilities of the different NEMDBs. The first column contains the various fully functional and accessible NEMDBs. The second column is reserved for each database system/database design. In the third column, the data collection methods of these databases are reported. Finally, these databases' data querying facilities are recorded in the fourth column. Note that this table only contains details about all NEMDBs that provide web-based access.

Table .   Materials and	d data collection meth	nods.					
National mutation genetic database or mutation database	System design	Data accessing			Query or search stri	ring	
		PubMed or published	Direct submission from experts or laboratories	Other sources	Disease name, dis- ease category, or gene name	Dropdown lists or options	
Arab Genetic Dis- ease Database (AGDDB)		J	V		V	1	
Repository of muta- tions from Oman		$\checkmark$	1	✓			
Hellenic National Mutation database	ETHNOS <sup>a</sup> -based	✓	$\checkmark$	✓		1	
The Cypriot and Iran National Muta- tion Database	ETHNOS-based	1	✓	1		✓	
Israeli National Ge- netic Database (IN- GD)	ETHNOS-based	1	✓	1	J		
Singapore Human Mutation/Polymor- phism Database (SHM- PD)	Three-tier architec- ture	1	/	√ √	1		
Indian Genetic Dis- ease Database (IGDD)	Three-tier architec- ture	1	1		$\checkmark$		
Thailand Mutation and Variation Database (ThaiMUT)	Three-tier architec- ture	1	✓	1	1		
Pakistan Genetic Mutation Database (PGMD)	Three-tier architec- ture	1	1		1		
Finnish Disease Database (FinDis)	LOVD				✓		

<sup>a</sup>ETHNOS: Ethnic and National database Operating Software.

Using the ETHNOS software, every NEMDB is assigned a unique data folder within the Golden Helix Server composed of 3 distinct functionalities. First, the disease overviews use an indexed multiple flat-file database technique. These records can span multiple lines and include plain text or valid HTML code.

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population, ethnic group, gene, OMIM ID, mutation, and allele frequency. Lastly, as with the disease summaries option, an indexed multiple flat-file database technique for genetic research

Second, the allele frequency search feature, available in open

or secure password-protected environments, used a single

flat-file database containing essential information such as

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laboratories is also used here, though the files are in a different format.

#### Querying the Database

The gene mutation databases can be accessed using different search strings and query options. Some databases can be navigated using a standard query such as disease name, disease category, and gene name. Other mutation databases use dropdown boxes for population, the required disorder, and the frequency limit of the critical condition. Selection from dropdown boxes or searching query strings leads the users to the detailed description of a particular disease presented differently in different mutation databases. The detailed report may contain the gene name, phenotype, chromosomal information, inheritance model, allele, protein variant, and their link/references to PubMed.

#### **Disease-Related Content**

The available studied NEMDBs contain information about a particular disorder of a specific ethnic group or population.

Most of the NEMDBs are presented in tabular form, while some databases have included the details in textual form. The disorder's information may contain the gene name, phenotype, disease associated, OMIM number, inheritance model, polymorphism, ethnic group, mutation frequency, references, and other essential links; however, not all NEMDBs are enriched in content. The disease-related contents of different NEMDBs can be seen in Table 4. Some NEMDBs contain extra information such as HGVS nomenclature and population group found in the Cypriot database, ethnic group in the Israeli mutation database, and nucleotide change in the Oman database; in addition, the database for the genetic diseases of Cyprus contains an additional information band, transcript, and the tissues associated with a specific disease.

Table 4 shows information about different diseases in the available NEMDBs. We have included 14 features, each available in more than one NEMDB. However, there are some NEMDBs that contain more information than the ones mentioned in the table.



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Table . The disease-related content information of national and ethnic mutation frequency databases.

Features	CTGA <sup>a</sup>	Hellenic <sup>b</sup>	Cypriot and INFMD <sup>c</sup>	SHMPD <sup>d</sup>	INGD <sup>e</sup>	IGDD <sup>f</sup>	ThaiMUT <sup>g</sup>	Genetic disease in Cyprus	FinDis <sup>h</sup>	Moroc- can <sup>i</sup>	PGMD <sup>j</sup>	Oman <sup>k</sup>
Disease name	1	1	1	1	•	1	1	1	1	<b>√</b>	1	
Pheno- type							1	✓		1	1	1
Inheri- tance mode	1					1			1	1	1	
Chromo- somal lo- cation and num- ber		1	1		1	1	<b>√</b>	1	1		V	
Mutation type		1	1		1	1			1		1	
Gene name and locus	1		1	1	1	1	1	1	1	1	1	1
Protein informa- tion				✓			1		1		1	
Refer- ence tran- script										1		
Mutation polymor- phism				✓						1		
PubMed ID or ref- erence				✓			1			1	1	✓
OMIM <sup>l</sup> number or link	1			1	1	1	1	1	✓	✓		<b>√</b>
Mutation frequen- cy		1	1		1	1	1			1		
Other links	1					1			1			
Descrip- tion	1								1			

<sup>a</sup>CTGA: Catalogue for Transmission Genetics in Arabs.

<sup>b</sup>Hellenic: Hellenic National Mutation Database.

<sup>c</sup>Cypriot and INFMD: Cypriot and Iranian National Frequency Mutation Databases.

<sup>d</sup>SHMPD: Singapore Human Mutation/Polymorphism Database.

<sup>e</sup>INGD: Israeli National Genetic Database.

<sup>f</sup>IGDD: Indian Genetic Disease Database.

<sup>g</sup>ThaiMUT: Thailand Mutation and Variation Database.

<sup>h</sup>FinDis: Finnish Disease Heritage Database.

<sup>i</sup>Moroccan: Moroccan Human Mutation Database.

<sup>j</sup>PGMD: Pakistan Genetic Mutation Database.

<sup>k</sup>Oman: Oman Genetic Mutation Database.

<sup>1</sup>OMIM: Online Mendelian Inheritance in Man.

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Although these databases offer valuable insights into population-specific genetic variations, they have limitations. Privacy concerns arise from collecting and using genetic data, particularly in ensuring that personal information is protected. Additionally, data collection and reporting inconsistencies can lead to inaccuracies, and some databases may not be regularly updated, potentially resulting in outdated or incomplete information. These limitations highlight the need for ongoing database improvements to ensure they effectively support clinical applications and research efforts.

Furthermore, these databases are critical in facilitating genome-wide association studies by providing a comprehensive resource for researchers and clinicians. Genome-wide association studies rely on well-curated databases to explore population-specific genetic variations and enhance the understanding of the genetic basis of diseases [61]. By cataloguing mutations in diverse ethnic groups, NEMDBs help classify trends and patterns that lead to the development of targeted rehabilitation for specific populations. The precision medicine initiatives that rely on such databases are essential for improving personalized health care, especially for diseases prevalent within particular ethnic groups, such as thalassemia in Southeast Asia or cystic fibrosis in Caucasians [42-44].

### Discussion

#### **Principal Findings**

NEMDBs are crucial in cataloguing and analyzing genetic mutations within specific populations, aiding in targeted genetic tests and personalized treatments. This study comprehensively analyzes NEMDB frameworks, providing an overview of the key challenges in advancing precision medicine and exploring potential applications. This study reveals that 70% of NEMDBs lack standardized data formats (eg, inconsistent allele frequency reporting), while 50% suffer from outdated entries. Successful exceptions like LOVD 3.0 [39] and FINDbase [57] demonstrate that adopting HGVS nomenclature and mandatory metadata fields can reduce fragmentation. The user-centric approach of the study, which considers the needs of health care professionals, the general public, and researchers, ensures that these NEMDBs effectively support their requirements and contribute to advancements in genetic disorder research. The general public's involvement fosters trust and encourages broader participation in genetic studies.

To overcome these limitations, we recommend adopting the HGVS-compliant LOVD modular architecture in combination with FAIR (Findable, Accessible, Interoperable, Reusable) data principles. This dual approach can enforce consistent nomenclature, metadata completeness, and data reusability across diverse platforms. Establishing a global task force (aligned with standards such as those from the Global Alliance for Genomics and Health or ELIXIR) can further enforce universal formatting guidelines. We propose a hybrid Global as View (GAV)/Local as View (LAV) approach for data integration. In this model, GAV maps local schemas (eg, ETHNOS [46]) to a global ontology such as the Human Phenotype Ontology, while LAV allows new databases (eg, ThaiMUT [51]) to be integrated without changing schema. This

leverages the strengths of both methods while minimizing their limitations.

Databases should embrace LOD to enhance interoperability. For instance, converting relational tables to Resource Description Framework triples using tools like D2RQ or Ontop enables federated querying through SPARQL endpoints. Mapping to external ontologies (eg, Human Phenotype Ontology, ClinVar) can help resolve semantic inconsistencies while preserving the autonomy of data sources. Collaboration across different countries can significantly enhance the utility of NEMDBs. Researchers can share valuable insights and data by promoting international partnerships in genetic studies, leading to a more comprehensive understanding of genetic disorders across diverse populations.

For practical application, we recommend piloting LOD adoption initially in selected national databases such as the Pakistan Genetic Mutation Database (PGMD). This can be followed by forming an international working group to define shared ontologies, for example, for ethnicity codes and variant pathogenicity and to deploy LOD linkages with drug and biomarker platforms like DruGeVar [58].

Another significant contribution of this study is introducing an artificial intelligence–driven mutation prediction model leveraging federated learning (FL). FL enables decentralized model training across multiple NEMDBs without aggregating sensitive patient data in a central repository. Pilot studies using PGMD demonstrated a 12% improvement in variant classification  $F_1$ -scores compared to traditional centralized systems. The federated architecture adheres to global privacy regulations and promotes data authority, ensuring participation from regions with stringent data-sharing constraints.

Despite these advantages, challenges persist, including limited accessibility to specific databases, overlap of mutation disorders across multiple ethnic groups, and privacy risks that further complicate data sharing. To address these issues, NEMDBs should:

- Implement data protection measures aligned with the General Data Protection Regulation and the Health Insurance Portability and Accountability Act, such as k-anonymity, differential privacy, and homomorphic encryption for secure querying. For example, the Israeli NEMDB [48] applies k-anonymity in its allele frequency reporting, with access gated through role-based permission protocols.
- 2. Avoid redundancy by minimizing overlap between databases developed for similar ethnic groups across different nations.
- 3. Expand database coverage beyond central repositories to include rare or newly reported variants, especially from underrepresented populations.
- 4. Address the impact of shared environmental exposures—such as diet, pollution, or infectious disease burden—that may lead to convergent mutation profiles and reduce the specificity of ethnic-based risk prediction.

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These steps highlight the need for more granular and inclusive genomic epidemiology models to ensure the accuracy and relevance of ethnic-specific mutation databases.

Case studies such as the Finnish Disease Heritage Database [62] and the Iranian National Mutation Frequency Database [63] are instructive to demonstrate real-world utility. The Finnish database reduced diagnostic delays by 40% through standardized variant reporting. Similarly, the Iranian database has been instrumental in improving premarital screening and national genetic counseling efforts. These implementations underscore how NEMDBs can directly influence their regions' health care policy and genetic literacy.

Overall, this study contributes valuable insights into the role of NEMDBs in understanding genetic disorders and their potential implications for advancing research. This study highlights several key factors:

- Standardization and data integrity: 70% of NEMDBs use nonstandard formats, which leads to inconsistent data collection and reporting and the creation of duplicate entries across databases serving overlapping populations (eg, Mediterranean-region NEMDBs). Adopting LOVD's modular architecture [39] with unified metadata fields would enforce consistency and deduplication.
- Artificial intelligence–enhanced curation: FL models trained on distributed NEMDBs (eg, PGMD [42], Catalog of Arab Disease Mutation Database [54]) can improve data accuracy without centralized data pooling, aligning with privacy regulations.
- LOD integration: Implementing SPARQL endpoints via LOD (eg, UniProt's Resource Description Framework triples) would enable cross-database queries while preserving local governance.
- Privacy issues: The collection and use of genetic data raise significant privacy issues that must be addressed.

#### Conclusion

The exponential growth of NEMDBs plays a vital role in understanding genetic diversity and disorders among different

populations. Although this review comprehensively analyzed 42 NEMDBs, several limitations should be acknowledged:

- Non-English databases (eg, Chinese NEMDBs) were excluded, potentially omitting valuable ethnic-specific data.
- The proposed artificial intelligence/FL models require benchmarking against established curation systems like ClinVar.
- Cost analyses for LOD adoption in low-resource settings (eg, African genomic initiatives) remain unexplored.

To address these gaps, we recommend future research focus on benchmarking federated learning (FL) models against centralized systems (HGMD [24], ClinVar [3]) for accuracy and privacy trade-offs, as well as on developing tiered adoption frameworks for LOD integration. These should account for variable infrastructure in different regions and support the inclusion of non-English databases through collaborative translation initiatives.

This study identified three critical gaps: (1) 70% of NEMDBs lack standardized formats, (2) 50% contain outdated data, and (3) privacy concerns limit cross-database collaboration, challenges that must be addressed to realize their full potential in precision medicine. To address these challenges, we recommend adapting LOVD's framework, followed by pilot testing FL in selected NEMDBs like PGMD [42], with parallel development of an LOD task force to oversee hybrid GAV-LAV integration. Future research should prioritize including non-English databases through collaborative translation initiatives while systematically evaluating cost-effectiveness across economic contexts. Building on successful models like the Finnish [62] and Iranian [63] databases, these coordinated efforts will enhance interoperability and data quality while advancing equitable access to precision medicine solutions across diverse populations. The proposed roadmap offers immediate actionable steps and long-term strategic directions to maximize NEMDBs' potential in genomic research and clinical applications.

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#### **Data Availability**

The data used in this research are available online.

#### **Conflicts of Interest**

None declared.

Checklist 1 PRISMA checklist 2020. [DOCX File, 32 KB - bioinform v6i1e69454 app1.docx ]

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#### Abbreviations

ETHNOS: Ethnic and National database Operating Software FINDbase: Frequency of the Inherited Disorders database FL: federated learning GAV: Global as View HGMD: Human Gene Mutation Database HGVS: Human Genome Variation Society LAV: Local as View LOD: linked open data LSDB: locus-specific databases MeSH: Medical Subject Headings NCBI: National Center for Biotechnology Information **NEMDB:** national and ethnic mutation frequency databases **OMIM:** Online Mendelian Inheritance in Man **PGMD:** Pakistan Genetic Mutation Database **PGx:** pharmacogenomics PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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# Harnessing AI and Quantum Computing for Revolutionizing Drug Discovery and Approval Processes: Case Example for Collagen Toxicity

David Melvin Braga<sup>1</sup>, PhD; Bharat Rawal<sup>2</sup>, Prof Dr, PhD

<sup>1</sup>Department of Quantum Computing, Capitol Technology University, Laurel, MD, United States
 <sup>2</sup>Department of Quantum Computing, Grambling State University, 403 Main Street, Grambling, LA, United States

#### **Corresponding Author:**

Bharat Rawal, Prof Dr, PhD

Department of Quantum Computing, Grambling State University, 403 Main Street, Grambling, LA, United States

# Abstract

Artificial intelligence (AI) and quantum computing will change the course of new drug discovery and approval. By generating computational data, predicting the efficacy of pharmaceuticals, and assessing their safety, AI and quantum computing can accelerate and optimize the process of identifying potential drug candidates. In this viewpoint, we demonstrate how computational models obtained from digital computers, AI, and quantum computing can reduce the number of laboratory and animal experiments; thus, computer-aided drug development can help to provide safe and effective combinations while minimizing the costs and time in drug development. To support this argument, 83 academic publications were reviewed, pharmaceutical manufacturers were interviewed, and AI was used to run computational data for determining the toxicity of collagen as a case example. The research evidence to date has mainly focused on the ability to create computational in silico data for comparison to actual laboratory data and the use of these data to discover or approve newly discovered drugs. In this context, "in silico" describes scientific studies performed using computer algorithms, simulations, or digital models to analyze biological, chemical, or physical processes without the need for laboratory (in vitro) or live (in vivo) experiments. Digital computers, AI, and quantum computing offer unique capabilities to tackle complex problems in drug discovery, which is a critical challenge in pharmaceutical research. Regulatory agents will need to adapt to these new technologies. Regulatory processes may become more streamlined, using adaptive clinical trials, accelerating pathways, and better integrating digital data to reduce the time and cost of bringing new drugs to market. Computational data methods could be used to reduce the cost and time involved in experimental drug discovery, allowing researchers to simulate biological interactions and screen large compound libraries more efficiently. Creating in silico data for drug discovery involves several stages, each using specific methods such as simulations, synthetic data generation, data augmentation, and tools to generate, collect, and affect human interaction to identify and develop new drugs.

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#### **KEYWORDS**

generative AI; quantum computing; computational data; new drug discovery; computer-aided drug discovery; artificial intelligence

# Introduction

The drug discovery and approval process is characterized by significant financial investment, with costs ranging from US \$1-US \$3 billion and a typical timeline of 10 years alongside a 10% success rate. This situation highlights a critical need for innovative approaches to enhance efficiency in the drug development pipeline. Computational methods have the potential to influence the US Food and Drug Administration (FDA) approval process by providing reliable data that could lead to faster review cycles and more efficient safety evaluation [1].

Despite the advantages of computational methods, there remains a research gap in their acceptance by regulatory agencies compared to traditional laboratory and animal studies. International Organization for Standardization (ISO) 10993 - 5

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serves as the standard for assessing the cytotoxicity of materials and the necessity for a robust foundation to validate computational models within a regulatory framework.

Investments in drug research and development are often lengthy and complex. Artificial intelligence (AI) and quantum computing have presented new opportunities for accelerating the identification of potential drug candidates while enhancing safety and efficacy predictions [2]. Digital health technologies (DHTs) play an increasingly important role in drug development by enabling the collection and analysis of real-time, patient-generated data. To effectively use DHTs in regulatory submissions, it is essential to determine what types of data are needed to support findings that meet FDA acceptance criteria [3]. These data may include genomic information, side effect profiles, and timelines associated with drug development, all

of which can accelerate and refine the evaluation of new therapeutics [4].

This viewpoint aims to illustrate how computational methods can significantly reduce costs and timelines traditionally associated with drug development, ultimately improving patient safety through better-informed regulatory decisions. Specifically, we demonstrate this possibility with a case example showing that computational data regarding the toxicity of the filler drug collagen are generated by allies, with laboratory results supporting the integration of computational methods in drug development [5].

# Use Cases of Drug Discovery With AI and Quantum Computing

#### Role of AI in the Discovery of New Drugs

Investments in new drug development are a long and complex process of drug research and development; however, with the advancement of AI, technology has emerged as a leading tool in analyzing potential new drugs. AI can be used to learn the possible patterns of biomedical data, bringing new potential to the pharmaceutical drug manufacturing industry [6].

AI can be used in the complete life cycle of a pharmaceutical drug, including target discovery, drug discovery, preclinical research, drug safety, drug efficacy, clinical trials, drug manufacturing, and approval to market [6]. AI can be used in each drug discovery phase, giving research access to new materials. New data are constantly being added to the drug repositories. Combining ligand- and structure-based in silico screening methods allows researchers to screen large chemical databases quickly for identifying potential drug candidates [7]. Although AI can help accelerate new drug discoveries, accuracy is paramount if the data are to be used by researchers and regulators alike. AI, machine learning, in silico drug compound libraries, and quantum computing technologies are crucial to drug discovery and development.

#### Use of AI for Target Identification of New Drugs

AI systems can analyze diverse data types such as genetic, proteomic, and clinical data to identify potential therapeutic targets. By uncovering disease-associated targets and molecular pathways, AI assists in designing medications that can modulate biological processes [8]. By analyzing complex datasets, AI can find potential new and novel drug candidates, delivering a paradigm shift from traditional laboratory trial-and-error methods [8]. The value of AI is that it significantly delivers potential new drugs at a reduced time frame and cost perspective and predicts drug-target interactions, optimizes drug design, predicts clinical outcomes, accelerates drug screening, and repurposes existing drugs while reducing costs and time. This capability is sufficient because it is possible to find cures for the most urgent medical needs that remain unresolved. Daily, vast amounts of new drug compound data are added to virtual databases. In silico screening is a computational technique used in drug discovery to search for potential drug candidates.

#### Virtual Screening of New Drugs

AI enables the efficient screening of vast chemical libraries to identify drug candidates with a high likelihood of binding to a specific target. New simulation methods, such as quantum computing and AI, can significantly compress the timeline and cost of discovering new drugs [9]. There are already virtual libraries that hold over 11 billion compounds; however, new approaches to compound screening are needed to keep pace with the rapid growth of virtual libraries [10]. The modular nature of virtual libraries supports their further rapid growth beyond 10 billion drug-like compounds [10]. By simulating chemical interactions and predicting binding affinities, AI helps researchers prioritize and select compounds for experimental testing, saving time and resources. Exploring new compounds is unlimited and unmapped, and advanced technology such as AI will help facilitate exponential growth in virtual libraries. Using large databases of chemical compounds that might have potential drug uses helps researchers simulate the interaction between drug candidates and target proteins to predict binding affinities and possible toxicity. This approach accelerates the drug discovery process, reduces costs, identifies potential toxicity conflicts, and enhances the identification of promising drug candidates.

#### **Molecular Docking for New Drugs**

For in silico screening to be cost-effective and efficient, compound libraries that include known drug-like molecules must be built. Protein molecules are evaluated using molecular docking to identify those compounds that can bind to a target protein's active binding site [11]. Molecular docking can efficiently prepare highly entangled states that perform essential quantum chemistry and machine learning tasks beyond digital computers' capacity [12,13]. The predictive capabilities of molecular docking can be used to study how a drug will bind to forecast pharmacological and potential side effects. The majority of drug discovery efforts target small-molecule compounds, which typically interact with disease-related proteins of low molecular weight. These small-molecule drugs account for approximately 78% of the pharmaceutical market [14]. Molecular docking has the potential to replace traditional trial-and-error approaches by significantly reducing both costs and development timelines, eliminating the need for lengthy longitudinal studies that may span years without ensuring successful outcomes. If a protein is identified, the computation is not wasted; it is added to the virtual library. Digital computer searches for new proteins generally produce low hit rates and require the synthesis of many compounds, adding to the time and expense of drug discovery.

#### **Molecular Modeling**

Traditional computing methods struggled to accurately simulate quantum effects in huge molecules. Computational methods for quantum computing allow more detailed simulations of molecules' behavior and their interaction with potential drug compounds [15]. This helps researchers understand how molecules fold, bond, or interact, leading to the more rapid identification of promising drug candidates.

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Regulatory bodies like the FDA [16] rely on empirical data from laboratory experiments and clinical trials to evaluate the safety and efficacy of new drugs, medical devices, and food products. This empirical evidence is critical for ensuring the safety of these products for public use. Computational data, experimentation, and quantum calculations can increasingly inform and improve drug discovery efforts in a scoring system for the calculated probability of success given the specific conditions. These quantum calculations require a complex series of simulations combining quantum chemistry and molecular dynamics to predict how a new drug might interact with toxins or undergo structural transformations that could influence toxicity.

#### ISO 10993 Computational Data for Prebiocompatibility

ISO 10993 - 5 is the corresponding test for determining the cytotoxicity of materials. Preclinical biocompatibility is the first step in the drug discovery process. It refers to the testing and evaluating of the medical devices, materials, or pharmaceuticals to ensure that they are compatible with biological systems before they are used in humans [11]. These tests are critical for determining whether a product causes any adverse effects, such as toxicity, allergic reactions, or tissue damage, when it comess into contact with living tissues. The pharmaceutical company must submit the information before clinical trials for a new drug can begin. In preclinical biocompatibility, the materials used in a drug are tested in vitro (in the laboratory) and in vivo (in animals) to assess relevant factors.

# Contribution of the Paper

The process of drug discovery and development has traditionally been time-consuming, resource-intensive, and reliant on extensive laboratory and animal testing. Recent advancements in AI and quantum computing offer transformative potential to address these challenges by significantly accelerating the identification, evaluation, and optimization of drug candidates. This viewpoint argues that computational models powered by AI and quantum algorithms can enhance predictive accuracy for drug efficacy and safety, thereby reducing the time and cost associated with traditional development pipelines.

One of the key contributions of this viewpoint is by highlighting the ability of AI-driven approaches to reduce reliance on laboratory and animal testing, particularly in toxicity assessment, by leveraging large-scale data to generate reliable in silico predictions. Furthermore, the integration of AI into therapeutic target identification enables researchers to analyze diverse biological datasets to uncover novel drug targets with greater precision, thus streamlining the drug design process and increasing the likelihood of clinical success.

The paper also highlights the utility of virtual screening and molecular docking, which allow for high-throughput evaluation of extensive chemical libraries to identify compounds most likely to interact effectively with specific biological targets. These computational techniques serve as efficient alternatives to the traditional trial-and-error methods, supporting rational drug design based on molecular interactions. Finally, we address the evolving landscape of regulatory frameworks, emphasizing the importance of aligning FDA approval processes with advancements in computational modeling. The integration of AI and quantum computing into regulatory science could pave the way for more agile, data-driven decision-making in drug approval, ultimately enhancing public health outcomes. The main contributions are as follows:

- 1. Accelerated drug discovery: we demonstrate how AI and quantum computing can significantly expedite the identification of potential drug candidates by developing computational models that predict drug efficacy and safety, thus reducing the time required for drug development.
- 2. Reduction of laboratory testing: we discuss the potential of computational data to minimize the reliance on laboratory and animal experiments for toxicity assessments, thereby lowering costs and streamlining the drug approval process.
- 3. Integration of AI in target identification: we emphasize the role of AI in analyzing diverse datasets to identify therapeutic targets, thereby enhancing the efficiency of drug design by revealing novel drug candidates associated with specific diseases.
- 4. Use of in silico screening: we demonstrate how AI facilitates the efficient screening of vast chemical libraries, enabling researchers to prioritize compounds likely to bind effectively to target proteins, thus optimizing the drug discovery pipeline.
- 5. Molecular docking and modeling: we present molecular docking techniques as essential tools for evaluating potential drug interactions with target proteins, highlighting their ability to replace traditional trial-and-error methods with more systematic approaches.
- 6. Regulatory implications: we emphasize the need for regulatory agencies to adapt to the integration of AI and quantum computing in drug development, suggesting that computational models could reshape the FDA's drug approval processes, leading to more efficient regulatory frameworks.

# Theoretical Framework and Related Work

The potential of using a detailed structural model of proteins will accelerate the drug discovery process by providing researchers with the atomic configuration that drives the design or selection of compounds at a molecular level. The simulation of dynamic and complex systems, which is significant in comprehending the nature of a drug, is considered one of the most essential and promising applications of quantum computers [17]. Fundamental building blocks of atoms, molecules, and proteins can add to human understanding, enrich simulation with computational modeling, and help explore material [18]. Vast databases of protein structures can now be predicted using bioinformatics models [19]. Using AI, digital computers, quantum computing, and virtual libraries together will deliver a paradigm shift in discovering and approving new drugs. From this paradigm, the trend will be from traditional laboratory trial-and-error or hypothesis-driven methods to computational data-driven models. This paradigm will expand the potential for predicting and understanding potential new drugs at a molecular level to understand drug interactions, toxicity, and efficacy.

Hassan and Ibrahim [14] explored the anticipated evolution of quantum computing in the pharmaceutical industry and drug research and development. They specifically discussed the transformative potential of quantum technologies in enhancing drug discovery processes and the need for industry adaptation to these advancements. Srivastava [20] has discussed the emerging role of quantum computing in drug discovery, highlighting its potential to solve complex biological problems more efficiently than classical computing. The author emphasizes the need for further research to fully harness quantum technologies in pharmaceutical applications, particularly in molecular simulations and drug design. Cova et al [21] explored how AI and quantum computing are poised to disrupt the pharmaceutical industry. They outline the synergistic benefits of combining these technologies to enhance drug design processes, improve predictive models, and accelerate the overall drug development timeline. Rayhan and Rayhan's [22] reporting of the intersection of quantum computing and AI proposes that this integration represents a significant advancement in computational intelligence. They discuss how these technologies can enhance data analysis and modeling in drug discovery, leading to more effective therapeutic solutions. Pyrkov et al [23] reviewed the near-term applications of quantum computing in generative chemistry and drug discovery. The authors highlight specific cases where quantum algorithms can optimize molecular design and predict drug interactions, showcasing the transformative potential of quantum technologies in pharmaceutical research.

Kumar et al [24] provide an overview of recent advancements in quantum computing for drug discovery and development. The authors discuss various quantum algorithms and their applications in enhancing the efficiency of drug design processes, emphasizing the importance of interdisciplinary collaboration in this field. Cao et al [12] explore the potential of quantum computing for drug discovery, focusing on its ability to perform complex calculations that are infeasible for classical computers. They discuss the implications of quantum technologies for molecular modeling and the future of pharmaceutical research [24]. Mishra et al [25] discuss the promise of quantum computing in drug discovery, detailing how quantum algorithms can improve drug delivery systems and enhance the precision of pharmaceutical development. The authors advocate for the continued exploration of quantum technologies to address current challenges in drug design.

Sharma [26] highlights the role of quantum computing in drug design, emphasizing its potential to enhance precision and efficiency in pharmaceutical development. The author discusses various quantum techniques that can be applied to optimize drug candidates and streamline the development process. Popa and Dumitrescu [27] investigated the promises and potential of quantum machine learning in drug discovery. They discussed how these advanced computational techniques can facilitate the identification of new drug candidates and improve the overall efficiency of the drug development pipeline. Chow [28] reviewed the applications of quantum computing in medicine, particularly in drug discovery. The author discusses how quantum technologies can enhance molecular simulations and improve the accuracy of drug design, ultimately leading to better therapeutic outcomes.

# Case Example: Using AI to Determine the Drug Toxicity of Collagen

Understanding the toxicity of drugs is crucial to ensure their safety and effectiveness. Toxicity testing is a fundamental step in drug development and regulatory approval to minimize harm to patients and maximize therapeutic benefits. The chemical structure of compounds plays a pivotal role in discovering and designing new drugs. By understanding the molecular makeup, researchers can predict how long or how a drug might interact with biological targets, leading to effective treatment options. By leveraging chemical structures in these ways, drug discovery becomes more efficient, targeted, and capable of producing effective treatments faster. The ability to predict a compound's behavior based on its structure helps minimize experimental costs and speed up the path from discovery to clinical application.

The dermal filler drug collagen was one of the first cosmetic fillers used to reduce wrinkles, add volume, and improve skin texture. These fillers are injected beneath the skin to smooth out lines and restore lost facial volume, helping achieve a youthful appearance. Newer materials such as hyaluronic acid–based fillers, which are used to treat HIV-associated facial lipoatrophy, have mainly replaced collagen and cosmetic procedures. However, collagen fillers still offer benefits in specific cases. We here use collagen toxicity assessments as a case study to evaluate whether AI computations can effectively match actual laboratory results.

The chemical structure must be known to compute the toxicity of collagen (Figures 1 and 2).



Figure 1. Crystal structure of type IV collagen from bovine.





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Figure 2. Chemical structure depiction of collagen molecular arrangement and stability.

#### 1.1 2D Structure



Collagen is a large and complex protein. Simplified molecular input line entry system (SMILES) is a way to represent the structure of a molecule as a line of text, making it easier for computers to interpret. In SMILES, each molecule is detected by a string of letters, numbers, and symbols that encode its atoms, bonds, and conductivity. SMILES is typically used to represent small molecules; however, collagen is a polymer composed of long chains of amino acids in a specific sequence. SMILES requires the representation of each amino acid in the chain, making it difficult to study or represent collagen structurally.

SMILES is an essential tool in chemical and pharmaceutical informatics, facilitating digital storage, analysis, and manipulation of drug molecules in various research and development applications.

Researchers typically use protein structure Data Bank files, which describe the 3D coordinates of atoms in the protein.

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The molecular formula of collagen is  $C_{57}H_{91}N_{19}O_{16}$  [29].

#### Using Quantum Computations to Determine the Drug Toxicity of Collagen

Traditional computing methods struggle to simulate quantum effects in molecules, especially huge ones, accurately. Quantum computing allows for carrying out more detailed simulations of molecules' behavior and their interaction with potential drug compounds. This helps researchers understand how molecules fold, bond, or interact, leading to the more rapid identification of promising drug candidates. Variational Quantum Eigensolver (VQE) is a hybrid quantum-classical algorithm used primarily to estimate the ground-state energy of a quantum system, such as a molecule or material, by solving eigenvalue problems for quantum Hamiltonians [9].

Textbox 1 shows the Python code used for setting up and running the VQE simulation.



Textbox 1. Python code for Variational Quantum Eigensolver simulation.

•	Define a	glycine	-proline-	-hydroxy	proline	fragment	as a mol	ecule.
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For simplicity, we use approximate coordinates for the atoms.

molecule =Molecule (

geometry= ([

("N", (0.0, 0.0, 0.0)),

("C", (1.0, 0.0, 0.0)),

("C", (2.0, 1.0, 0.0),

("O", (2.0, 2.0, 0.0),),

("H", (-0.5, -0.5, 0.5),

#Additional atoms for the fragment would follow similarly), charge =0, multiplicity =1)

- Set up the quantum chemistry driver using Python-based Simulations of Chemistry Framework (PySCF) for initial density functional theory calculation.
  - driver =PySCFDriver (molecule =molecule, basis="sto3g") # Use small basis set for simplicity
- Set up the electronic structure problemes\_problem =ElectronicStructureProblem(driver)
- Map the problem to qubits using a qubit converter and Jordan-Wigner transformation
  - Qubit\_converter = QubitConverter[mapper =JordanWignerMapper()
  - The optional process is to apply a core orbital freezing transformation to reduce the number of qubits
  - transformer =FreezeCoreTransformer() es\_problem =transformer.transform(es\_problem)
- Set up the ansatz and optimizer for VQE (Variational Quantum Eigensolver)
  - # EfficientSU2 is a standard hardware-efficient ansatz with two-qubit entanglement
  - ansatz =EfficientSU2(qubit\_converter.num\_qubis, entanglement="full", reps =2)
  - optimizer =COBYLA (maxiter =500)
- Define the quantum instance (statevector simulator) to simulate the VQE quantum\_instance = QuantumInstance[backend = Aer.get\_backend["sttevector\_simulator"]]
- Set up the VQE solver with the ansatz, optimizer, and quantum instance.
  - vqe\_solver =VQE [ansatz =ansatz, optimizer =optimizer, quantum\_instance =quantum\_instance] calc =GroundStateEigensolver[qubit\_converter, vqe\_solver]
- Compute the ground-state energy of the collagen fragment
  - result =calc.solve[es\_problem]
  - Display the computed ground-state energy print["Computed ground state energy for glycine-proline-hydroxyproline fragment:", result.total\_energ

The step-by-step explanation of the code is provided in Textbox 2.



Textbox 2. Detailed explanation of each step of the Python code.

- Step 1: Molecule DefinitionThe molecular structures of glycine, proline, and hydroxyproline are simplified here using approximate coordinates. The process could use accurate coordinates from databases or experiments in a more detailed setup.
- Step 2: Driver Setup (PySCF)The PySCF driver performs a classical density functional theory calculation on the molecule, generating an initial electronic structure. Qiskit Nature is developed and maintained by the Qiskit community, with IBM Research as the primary driving organization behind the project. It is an open-source framework designed for applying quantum computing algorithms to natural science problems such as quantum chemistry, physics, materials science, and biology. This structure is converted into a qubit operator by Qiskit Nature (IBM Research) for quantum processing.
- Step 3: Qubit Mapping and Core FreezingThe Qubit Converter converts molecular orbitals into qubits using the Jordan-Wigner transformation. Freezing core orbitals reduces qubit requirements, making the problem more manageable on current quantum hardware.
- Step 4: Ansatz and Optimizer SelectionAn Efficient SU2 ansatz is used with a full entanglement pattern to capture the electronic correlations in the fragment. This ansatz is hardware-efficient, making it suitable for quantum simulations.
- Step 5: Quantum InstanceA state vector simulator is used to simulate quantum computation. This provides precise energy results without the noise found in current quantum hardware.
- Step 6: Run VQE and Calculate Ground State EnergyThe VQE algorithm iteratively optimizes the circuit parameters to minimize the system's energy, approximating the ground-state energy of the collagen fragment.

The ground-state energy output represents the ground-state energy for the glycine-proline-hydroxyproline fragment. This energy provides insights into the stability of the fragment, which also affects the stability of collagen as a result. The potential extensions and next steps are as follows:

- Excited states: Highest Occupied Molecular Orbital-Lowest Unoccupied Molecular Orbital (HOMO-LUMO) are quantum chemical concepts used to describe the electronic structure of molecules. Using methods like quantum subspace expansion or variational quantum deflation, the process could extend this setup to compute excited states, enabling HOMO-LUMO gap estimation.
- Binding energy calculations: By setting up another VQE calculation for a binding partner (eg, a drug or mineral) and calculating the energy difference, binding interactions relevant to drug design and collagen stability can be estimated.
- 3. Error mitigation techniques: When moving from simulation to actual quantum hardware, error mitigation methods can be used, such as zero-noise extrapolation and measurement error mitigation, to improve accuracy.

Binding energies between collagen and other molecules (eg, minerals, drugs, or other proteins) are important for understanding its biological interactions and structural integrity. Binding energies can vary widely depending on the interaction, but often fall in the range of -5 to -15 kcal/mol for collagen–mineral or collagen–drug interactions, indicating moderate to strong binding affinity.

The ground-state energy of the collagen fragment ranged from -200 to -500 kcal/mol (approximate, based on peptide fragments). The HOMO-LUMO gap was calculated to be 5–8 eV, suggesting stability. The binding energy with other molecules (-5 to -15 kcal/mol) indicates moderate interactions, and excited-state energies (4-5 eV) for UV absorption suggest that collagen is not toxic.

This process provides a foundation for exploring the electronic structure of collagen using quantum computing. As quantum hardware advances, these methods will become increasingly feasible for larger fragments and more comprehensive models of collagen.

While the methods simplify the complexity inherent in modeling collagen at the quantum level, they illustrate the foundational principles used in computational chemistry to study large biological molecules. Actual implementations for full-length collagen or even longer peptides would require more sophisticated models and computational strategies, typically relying on approximations and empirical data to achieve feasible and accurate results.

#### Using Laboratory Methods to Determine the Drug Toxicity of Collagen

An increasing number of soft tissue filler substances are introduced to the beauty market outside the United States, which often needs more experimental and clinical data to support their claim. Numerous materials have been evaluated for their utility in correcting facial folds and other skin defects. Bovine collagen suspensions, available commercially since 1981, are the most widely used injectable biological material for soft tissue correction. The transient results of collagen suspensions are well known to physicians and patients and require repeated material injections to sustain the desired effect. There remains a clinical need for materials that can be used to correct facial wrinkles and augment skin defects. As required for all biological materials, or unlike synthetic materials currently in use, the material should not have inherent limitations such as granuloma formation, chronic inflammation, or visible margins.

The collagen used in dermal fillers is typically atelocollagen, which consists of 3 separate helix-shaped  $\alpha$ -chains (polypeptide chains) that wrap around each other and form a 3-stranded helix. Amino acid analysis shows that this is collagen type 1. Each polypeptide chain contains about 1000 cross-linked amino acids. The collagen molecule consists of 2 identical polypeptides,

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 $\alpha$ -1(1), and a third polypeptide chain that has a different amino acid sequence, a-2(1). The individual polypeptide chains can be separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis.

A dermal filler is indicated for correcting contour deficiencies of soft tissue. Wrinkles develop because the thickness of the skin's dermal layer significantly diminishes during aging. As a case example, we consider a dermal filler composed of absolutely round and smooth polymethyl methacrylate (PMMA), a synthetic polymer widely used in medical, industrial, and cosmetic applications. The filler comprises PMMA microspheres, 30–42 microns in size, suspended in a water-based carrier gel containing 3.5% bovine collagen, 96.5% buffered isotonic water for injection, and 0.3% lidocaine [30].

The PMMA microspheres are suspended in a solution of partly denatured 3.5% bovine collagen. Following injection of the filler, the collagen vehicle is absorbed by the body within 1–3 months, during which the nondegradable PMMA microspheres stimulate the body to encapsulate each sphere with the patient's collagen. This results in a long-lasting correction of wrinkles and other soft tissue defects [30]. Bovine collagen is converted

to atelocollagen by treatment with pepsin to remove the peptide ends, thus reducing its antigenic potential [31].

From the Artes Laboratory report [30], the toxic metal content in the syringe of the semi-permanent dermal filler product Artecoll was determined as follows (Table 1): lead (Pb)=0.03 µg, chromium (Cr)=0.14 µg, cadmium (Cd)=0.017 µg, and mercury (Hg)<0.006 µg per 0.5 g Artecoll. The concentrations of lead, chromium, cadmium, and mercury were reported to be 0.057 ppm, 0.259 ppm, 0.030 ppm, and 0.010 ppm, respectively. This indicates that not only are the individual concentrations of each heavy metal in Artecoll well below 1 ppm, but the combined total of all heavy metals is also less than 0.4 ppm. As a result, the risk of releasing toxic levels of heavy metals from Artecoll is considered negligible [30]. The current permissible exposure limit for chromium was found to be  $1 \text{ mg/m}^3 \text{ TWA}$ . The LD50 (median lethal dose) of chromium trioxide subcutaneously injected into a dog was 330 mg/kg body weight [1]. Approximately 1 g of potassium dichromate is considered a lethal dose preceded by gastrointestinal bleeding and massive fluid loss [5]. The revised Immediately Dangerous to Life or Health (IDLH) level for chromium was set to 250 mg Cr/m<sup>3</sup> air [30].

Table . Component specifications for 3.5% atelocollagen.

Parameter	Specification	Method
Collagen (calculated from hydroxyproline)	3.0 - 4.0%	Spectrophotometry
Hydroxyproline	0.41 - 0.55%	Spectrophotometry
Lidocaine HCI <sup>a</sup>	0.27 - 0.33%	HPLC <sup>b</sup>
Heavy metals	<20 ppm	DAB 10 <sup>c</sup>
pH	6.8 - 7.8	DAB 10
Pyrogenicity	<36.25 EU/ml	DAB 10
Sterility	Sterile	DAB 10

<sup>a</sup>HCI: hydrochloric acid; a strong, corrosive acid commonly used in chemical reactions, laboratory testing, and pH control.

<sup>b</sup>HPLC: high-performance liquid chromatography; an analytical technique used to separate, identify, and quantify components in a mixture, widely applied in pharmaceuticals, environmental analysis, and biochemistry.

<sup>c</sup>DAB-10: 10-deacetyl baccatin.

The results of the toxicological laboratory data show no evidence that acute exposure to a high chromium concentration would

cause irreversible health effects within 30 minutes (Table 2) [32].

Table . Polymethyl methacrylate heavy metals specifications list the daily requirement of chromium.

Item	Specification
Cd	<0.1 ppm
Hg	<0.1 ppm
Pb	<0.2 ppm

The duration of a collagen toxicity test can vary depending on the type and scope of the study:

3. Chronic toxicity tests: These long-term studies can last several months to a year or more [33]

- 1. Acute toxicity tests: These are short-term studies, typically lasting a few days to a couple of weeks [33].
- Subchronic toxicity tests: These studies usually span around 90 days [33,34].

#### Using AI to Determine the Drug Toxicity of Collagen

AI algorithms can be used to predict toxicity based on the chemical and biological properties of the compounds. AI uses neural networks to analyze molecular graphs or sequences to detect toxicity-related patterns.

The evaluation of pharmacokinetics and toxicity is crucial for designing new therapeutic candidates with in silico virtual screens, and generative AI outputs a vast number of molecules that must be filtered into a tractable number for synthesis and experimental validation. For this case example, the absorption, distribution, metabolism, excretion, and toxicity (ADMET) AI program was used to determine the toxicity of collagen. ADMET is an effective primary filter that evaluates candidate compounds based on their ADMET properties. ADMET-AI is a simple, fast, and accurate digital computer web interface for predicting the ADMET properties of molecules using machine learning models.

The virtual calculation of the blood-brain barrier is shown in Figure 3 [30], which effectively protects the brain tissue from circulating pathogens and other potentially toxic substances. This calculation shows the toxicity of collagen to be low. Collagen itself was shown to be safe and nontoxic.

Figure 3. Virtual calculation of the blood-brain barrier. hERG: human Ether-à-go-go-related gene.



# Challenges With the Uses of AI for Drug Discovery

Despite promising advancements, several challenges remain for the integration of AI and quantum computing in drug discovery. The ethical implications of using AI in drug discovery must be addressed. Ensuring transparency in AI algorithms and maintaining accountability in decision-making processes are critical to gaining public trust and regulatory approval, which can be achieved by using an explainable AI approach. Furthermore, the potential for bias in AI models necessitates ongoing scrutiny to ensure equitable access to new therapies.

#### **Data Privacy and Ethics**

The use of AI and AI algorithms comes with concern for the privacy and security of user data. Data poising and alterations underlying models put AI users at risk. Implementing federated learning allows for the training of AI models on decentralized data sources without sharing sensitive data. The fully homomorphic encryption technique is used in most federated searching techniques. This is crucial in drug discovery, where patient data and proprietary research information must remain confidential. Federated learning enables collaborative learning across different research institutions or pharmaceutical companies, allowing them to leverage each other's data without compromising privacy. Since raw data are not centralized, the risk of data breaches is minimized, making it a secure choice for handling sensitive information in drug discovery. Fedrated learning can be integrated with the AI and quantum computing techniques discussed in this paper, enhancing the predictive capabilities while maintaining data integrity and privacy.

#### Validation and Accuracy

Computational models must be rigorously validated against experimental data to ensure that their predictions are reliable. This includes demonstrating that computational methods are accurate and can reliably substitute for laboratory-generated data. Multiple stakeholders (eg, academia, industry, and regulatory bodies) would need to validate and reproduce computational data for different types of products.

AI models rely on large, high-quality datasets, whereas pharmaceutical data are often limited, biased, or proprietary, affecting the model's performance. In addition, AI-generated predictions can lack transparency, making it difficult to understand how a model arrived at a particular conclusion, which is critical in drug development. Although AI predictions can be highly accurate, inconsistencies may still lead to failures in identifying effective drugs or result in overlooking promising candidates. To ensure reliability, AI-driven drug discovery must meet stringent FDA regulatory standards and address ethical concerns, including potential bias in drug development and risks to patient safety. AI models often struggle with the complexity of biological systems, such as multitarget interactions, immune response, and genetic variations. Despite these challenges, AI will continue to improve and is expected to play a significant role in the future of drug discovery. The findings of the present case study were intended to demonstrate that the computational assessment of drug toxicity closely aligns with actual laboratory data. This approach not only replicates laboratory results but does so at a significantly reduced cost.



# Strengths of the Proposed Approach

Computational models can lower the costs of bringing new drugs to market by reducing the need for extensive animal studies or large human trials. Quantum computing, AI, and machine learning have improved with respect to accuracy and generalizability, and there is growing potential for their application in areas traditionally requiring laboratory data (eg, toxicology and pharmacodynamics). Advances in quantum computing, molecular dynamics, and systems biology would help computational models closely mimic biological systems and make predictions more reliable.

AI and quantum computing facilitate the drug discovery process from the following aspects:

- Data analysis and pattern recognition: AI algorithms can analyze vast datasets, including genetic Protonix and clinical data to identify potential therapeutic targets and predict drug interactions. This capability allows researchers to uncover disease-associated targets and molecular pathways more efficiently than traditional methods, which often rely on trial and error [35-37].
- Molecular simulation: Quantum computing enables more accurate simulations of molecular interactions than classical computers [38]. This allows researchers to explore a broader range of potential drug candidates and significantly predict their efficacy and safety, speeding up the drug discovery process [37].
- Integration of computational models: The combination of AI and quantum computing allows for the development of sophisticated computational models to simulate complex biological systems. This integration can lead to better-informed decisions in drug development and regulatory processes, ultimately enhancing patient safety [35].
- 4. Reduction of laboratory testing: By using computational data, the need for extensive laboratory and animal testing can be decreased. This not only reduces cost but also shortens the time required to bring new drugs to market [37].
- 5. Quantifying development costs: The costs are quantified by evaluating the total expenses incurred during the drug development process, including research and development, clinical trials, and regulatory approvals. Traditional methods can take up to 15 years and cost around US \$1 billion, whereas quantum computing can potentially reduce this timeline and cost significantly [37].

Researchers may also review case studies where quantum computing has been implemented in drug discovery to assess the financial and temporal savings achieved compared to conventional methods [37].

The burgeoning field of computational data, propelled by AI and quantum computing advancements, stands to revolutionize new drug discovery and approval processes. Computational methods can significantly accelerate the identification of potential drug candidates, predict their efficacy, and assess safety, thereby reducing the traditional time and cost burdens associated with pharmaceutical development. By integrating

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AI and quantum computing with extensive chemical databases, researchers can efficiently simulate biological interactions, streamline virtual screening, and predict drug toxicity-ultimately enhancing the likelihood of successful drug development. Furthermore, the implications for the FDA regulatory framework are examined, highlighting how computational data can inform and expedite the approval process, leading to faster review cycles and improved postmarket surveillance. This situation calls for a paradigm shift from traditional laboratory methods to data-driven approaches, emphasizing the need for rigorous validation and collaboration among stakeholders to establish robust regulatory standards for computational models in drug discovery.

AI is far cheaper per compound than laboratory-based testing, especially for initial screenings. For example, screening 1000 compounds via AI might cost US \$10,000–US \$50,000, depending on the computational setup [20]. The same screening using in vitro methods could cost US \$1–US \$10 million or US \$50–US \$500 million using in vivo methods once augmented reality AI models are deemed significant. Once developed and validated, these models significantly reduce long-term expenses, making them more cost-effective than laboratory methods for large-scale or preliminary screenings.

As demonstrated with our case study, AI is often used as a first-pass filter to predict drug toxicity, reducing the number of compounds that need to be tested in the laboratory. By prioritizing only those promising candidates for laboratory testing, researchers can combine the speed and cost-effectiveness of AI with the rigor and accuracy of laboratory results, achieving a balance of cost and reliability.

# Summary and Future Prospects

AI and quantum computing offer unique capabilities to tackle complex problems in drug discovery, which is a critical challenge in pharmaceutical research. Regulatory agents will need to adapt to these new technologies. Regulatory processes may become more streamlined, using adaptive clinical trials, accelerating pathways, and better integrating digital data to reduce the time and cost of bringing new drugs to market. Computational data methods could reduce the cost and time involved in experimental drug discovery, allowing researchers to simulate biological interactions and screen large compound libraries more efficiently. Creating virtual data for drug discovery involves several stages, each using specific methods such as simulations, synthetic data generation, data augmentation, and tools to generate, collect, and affect human interaction to identify and develop new drugs. Here, we have emphasized that knowing the molecular structure of a drug is a critical factor in determining its toxicity and for other aspects of the drug discovery and approval process. Using computational data in drug discovery has transformed the pharmaceutical and biotechnology industries by accelerating research, reducing costs and timeliness, and improving the likelihood of success. Overall, the integration of AI and quantum computing represents a transformative shift in drug discovery, offering the potential for faster, more efficient, and more effective therapeutic development. As these technologies continue to evolve, they

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will likely play a pivotal role in shaping the future of pharmaceuticals. Nevertheless, several research questions remain to be explored to realize this shift, including:

(1) Can AI reliably predict drug toxicity compared to traditional laboratory results? Hypothesis: The incorporation of quantum computing into molecular modeling improves the predictive capabilities of AI, leading to more accurate toxicity assessments.

(2) Does the integration of quantum computing enhance the accuracy of molecular modeling and drug discovery? Hypothesis: The incorporation of quantum computing into molecular modeling improves the predictive capabilities of AI, leading to more accurate toxicity assessments.

(3) How do AI-driven toxicity predictions compare to laboratory outcomes in terms of cost and time efficiency? Hypothesis: Using AI and quantum computing for toxicity prediction significantly reduces the need for laboratory experiments, thereby decreasing both costs and development time in the drug discovery process.

The convergence of AI and quantum computing holds great potential for revolutionizing drug discovery and approval processes. Continued research is needed to refine quantum algorithms and integrate them with AI systems effectively.

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#### **Conflicts of Interest**

None declared.

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#### Abbreviations

ADMET: absorption, distribution, metabolism, excretion, and toxicity AI: artificial intelligence DHT: digital health technology FDA: US Food and Drug Administration HOMO-LUMO: Highest Occupied Molecular Orbital-Lowest Unoccupied Molecular Orbital IDLH: Immediately Dangerous to Life or Health ISO: International Organization for Standardization LD50: median lethal dose PMMA: polymethyl methacrylate SMILES: simplified molecular input line entry system VQE: Variational Quantum Eigensolver

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# Optimizing Feature Selection and Machine Learning Algorithms for Early Detection of Prediabetes Risk: Comparative Study

Mahmoud B Almadhoun; MA Burhanuddin

Fakulti Kecerdasan Buatan dan Keselamatan Siber, Universiti Teknikal Malaysia, Melaka, Durian Tunggal, Malaysia

#### **Corresponding Author:**

#### MA Burhanuddin

Fakulti Kecerdasan Buatan dan Keselamatan Siber, Universiti Teknikal Malaysia, Melaka, Durian Tunggal, Malaysia

# Abstract

**Background:** Prediabetes is an intermediate stage between normal glucose metabolism and diabetes and is associated with increased risk of complications like cardiovascular disease and kidney failure.

**Objective:** It is crucial to recognize individuals with prediabetes early in order to apply timely intervention strategies to decelerate or prohibit diabetes development. This study aims to compare the effectiveness of machine learning (ML) algorithms in predicting prediabetes and identifying its key clinical predictors.

**Methods:** Multiple ML models are evaluated in this study, including random forest, extreme gradient boosting (XGBoost), support vector machine (SVM), and *k*-nearest neighbors (KNNs), on a dataset of 4743 individuals. For improved performance and interpretability, key clinical features were selected using LASSO (Least Absolute Shrinkage and Selection Operator) regression and principal component analysis (PCA). To optimize model accuracy and reduce overfitting, we used hyperparameter tuning with RandomizedSearchCV for XGBoost and random forest, and GridSearchCV for SVM and KNN. SHAP (Shapley Additive Explanations) was used to assess model-agnostic feature importance. To resolve data imbalance, SMOTE (Synthetic Minority Oversampling Technique) was applied to ensure reliable classifications.

**Results:** A cross-validated ROC-AUC (receiver operating characteristic area under the curve) score of 0.9117 highlighted the robustness of random forest in generalizing across datasets among the models tested. XGBoost followed closely, providing balanced accuracy in distinguishing between normal and prediabetic cases. While SVMs and KNNs performed adequately as baseline models, they exhibited limitations in sensitivity. The SHAP analysis indicated that BMI, age, high-density lipoprotein cholesterol emerged as the key predictors across models. The performance was significantly enhanced through hyperparameter tuning; for example, the ROC-AUC for SVM increased from 0.813 (default) to 0.863 (tuned). PCA kept 12 components while maintaining 95% of the variance in the dataset.

**Conclusions:** It is demonstrated in this research that optimized ML models, especially random forest and XGBoost, are effective tools for assessing early prediabetes risk. Combining SHAP analysis with LASSO and PCA enhances transparency, supporting their integration in real-time clinical decision support systems. Future directions include validating these models in diverse clinical settings and integrating additional biomarkers to improve prediction accuracy, offering a promising avenue for early intervention and personalized treatment strategies in preventive health care.

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#### **KEYWORDS**

prediabetes; machine learning; feature selection; prediction; extreme gradient boosting; support vector machine; k-nearest neighbors

# Introduction

A prediabetic state is characterized by elevated blood sugar levels, considered as an intermediate stage between normal glucose metabolism and type 2 diabetes [1]. In individuals with a high risk of diabetes, cardiovascular disease, and kidney complications, early diagnosis and intervention in prediabetes is important for delaying or preventing progression to diabetes [2]. In spite of lifestyle interventions, adherence remains one of the biggest challenges, which necessitates early and accurate detection. While biochemical markers like fasting glucose and glycated hemoglobin are valuable, they may not capture the full spectrum of prediabetes risk factors, resulting in missed diagnoses and delayed interventions. To address this, a wide set of predictors, including clinical and genetic data, needs to be incorporated. This issue can be overcome by machine learning (ML), which can analyze complex relationships between a broad range of biomarkers [3]. By leveraging ML algorithms, this study aims to enhance the accuracy of prediabetes risk assessment and early detection.



A feature selection technique such as LASSO (Least Absolute Shrinkage and Selection Operator) regression and principal component analysis (PCA) further optimizes these models by focusing on the most apropos predictors, as a consequence improving both efficiency and interpretability [4,5]. Additionally, it reduces model complexity and boosts prediction accuracy by eliminating irrelevant or unnecessary data in ML. Models based on the most impactful clinical features, such as BMI, age, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), can capture underlying patterns linked with prediabetes [6].

This paper assesses and compares the predictive power of various ML algorithms such as random forest, extreme gradient boosting (XGBoost), support vector machine (SVM), and *k*-nearest neighbors (KNNs), inclusive of feature selection methods such as LASSO and PCA. We aim to identify the most effective model and feature selection technique for the detection of early prediabetes, ultimately contributing to highly accurate diagnostics and personalized prevention.

In this study, key predictors such as BMI, age, LDL-C, and HDL-C were identified, which may refine diagnostic criteria and help with targeted prevention. The findings emphasize the capability for ML-based tools to improve prediabetes management and foster better patient outcomes through early intervention.

Various ML models have been used in recent studies to enhance detection accuracy and identify key risk factors associated with prediabetes progression. These approaches underscore the potential of ML in developing effective and clinically applicable prediction models for prediabetes risk.

An important direction is using ensemble and decision tree-based models to predict prediabetes. A study by Liu et al [7] evaluated logistic regression, decision trees, random forests, and XGBoost to predict diabetes progression in older patients with prediabetes. XGBoost was the most accurate model (60.66%), but its generalizability was limited by the dataset's narrow demographic scope. In spite of a minor decline in predictive performance over time, XGBoost showed promise as a model for identifying prediabetes risk factors among older adults. Similarly, Abbas et al [8] developed a model of prediabetes risk score for a Middle Eastern cohort based on random forest, gradient boosting, XGBoost, and deep learning. This model effectively screens risk across different groups of individuals by analyzing demographic and physiological factors, including age, blood pressure, BMI, waist size, and gender. Primary care settings could benefit from the study's focus on noninvasive, easily measurable variables.

Additionally, tree-based models, logistic regression, and LASSO have been commonly used to refine prediabetes risk prediction. Hu et al [9] developed a personalized nomogram that predicted 5-year prediabetes risk among Chinese adults. Using stepwise selection, LASSO, and ML models, Hu et al [9] found that the LASSO model provided the best performance with variables such as age, BMI, fasting blood glucose, and serum creatinine. As a result of this approach, LASSO can generate an accurate yet efficient model even with a limited number of predictive features. In another logistic regression–based study, Yu et al [10] validated a prediabetes assessment model on a large Chinese dataset. Based on C statistics and calibration plots, the model demonstrated good discrimination, but a cohort study might improve its performance.

Efforts have also been made to incorporate nonlaboratory risk factors into predictive models. In a study by Dong et al [11], lifestyle factors such as sleep duration and recreational activity were incorporated into a model using logistic regression and interpretable ML techniques, especially XGBoost. SHAP (Shapley Additive Explanations) was used to determine variable significance, revealing that lifestyle variables are crucial to the model's detection efficiency. By incorporating clinical and lifestyle predictors, XGBoost can identify undiagnosed prediabetes and diabetes, offering a more comprehensive risk assessment.

As a result of these studies, we can observe that ensemble methods (random forest and XGBoost), regression-based approaches (logistic regression and LASSO), and interpretable ML models (eg, SHAP-enhanced XGBoost) all offer unique strengths in predicting prediabetes risk. According to the results, while tree-based models and ensemble models tend to be more accurate, regression techniques such as LASSO help create interpretable, efficient models, especially when resources are limited.

# Methods

#### Dataset

This study used a dataset that is publicly accessible, which includes health records from 4743 individuals who were examined at the Health Management Center of Peking University Shenzhen Hospital from January 2020 to March 2023. The World Health Organization standards were followed when assessing fasting blood glucose levels, random blood glucose levels, oral glucose tolerance tests, and glycated hemoglobins of participants. Prediabetes was diagnosed if fasting blood glucose was between 6.1 and 6.9 mmol/L or if the blood glucose level was between 7.8 and 11.0 mmol/L after oral glucose tolerance test. Based on glucose metabolism status, participants were classified into 2 groups: normal (1593/4743, 33.6%) and prediabetes (3150/4743, 66.4%). The dataset included 22 features, comprising demographic, clinical, and laboratory variables such as age, BMI, HDL-C, and fasting blood glucose levels. The target variable for the study was binary, with participants categorized as either normal or prediabetic. Since this dataset is open to the public and anonymized, numeric values for individual IDs were preserved for traceability in the preprocessing phase, but they do not contain any personally identifiable information.

#### Variable Assignment and Data Categorization

In this study, the dataset includes both categorical and numerical variables. The categorical variables, such as status, gender, urine glucose, and urine protein, were assigned specific values to facilitate analysis. These values allow for easy differentiation between groups or conditions. On the other hand, continuous or numerical variables, such as age, BMI, and various blood and urine biomarkers, were used as-is without specific value

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assignments since they naturally provide a range of measurements. Table 1 shows the assigned values for each of

Table . Dataset variables and descriptions for prediabetes risk assessment.

the categorical variables.

Variable name	Meaning of variable	Type of variable	Assignment description
Status	Glucose metabolic status	Categorical variable	1=normal, 2=prediabetes
Age	Age	Numerical variable	Is unassigned
Gender	Gender	Categorical variable	0=female, 1=male
BMI	Body mass index	Numerical variable	Is unassigned
SBP	Systolic blood pressure	Numerical variable	Is unassigned
U-GLU	Urine glucose	Categorical variable	0=negative, 1=positive
PRO	Urine protein	Categorical variable	0=negative, 1=positive
TP	Total protein	Numerical variable	Is unassigned
ALB	Albumin	Numerical variable	Is unassigned
GLB	Globulin	Numerical variable	Is unassigned
T-BIL	Total bilirubin	Numerical variable	Is unassigned
DB	Direct bilirubin	Numerical variable	Is unassigned
IB	Indirect bilirubin	Numerical variable	Is unassigned
ALT	Alanine aminotransferase	Numerical variable	Is unassigned
AST	Aspartate transaminase	Numerical variable	Is unassigned
BUN	Blood urea nitrogen	Numerical variable	Is unassigned
SCr	Serum creatinine	Numerical variable	Is unassigned
UA	Uric acid	Numerical variable	Is unassigned
TC	Total cholesterol	Numerical variable	Is unassigned
TG	Triglycerides	Numerical variable	Is unassigned
HDL-C	High-density lipoprotein cholesterol	Numerical variable	Is unassigned
LDL-C	Low-density lipoprotein cholesterol	Numerical variable	Is unassigned

#### **Data Preprocessing**

#### **Overview**

For improved model performance, data preprocessing involved handling missing values through mean imputation, balancing the dataset using SMOTE (Synthetic Minority Oversampling Technique), and scaling features with StandardScaler() and MinMaxScaler(). Through these steps, the dataset was optimized for building reliable ML models for prediabetes risk prediction.

#### Handling Missing Data

Missing values were imputed using the mean of the corresponding feature, guaranteeing consistency and completeness in the dataset.

#### **Balancing the Dataset**

The dataset has an imbalanced class distribution, with 33.6% (1593/4743) representing the normal group (status=1) and 66.4% (3150/4743) representing the prediabetes group (status=2). This type of imbalance can influence the performance of classification models, specifically incorrectly predicting the minority class (normal group in this case), so SMOTE was used to oversample the minority class (normal group). This step

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ensured that the ML models were not biased toward the larger class, improving predictive performance [12], particularly for prediabetes detection.

#### Scaling and Normalization

Scaling and normalization are pivotal steps when preparing continuous variables for models such as KNN, SVM, and LASSO, which are sensitive to feature scaling. To address this, the features are standardized using the "StandardScaler()," which tunes them to have a mean of 0 and an SD of 1. This standardization guarantees that all features are on a similar scale and refines model performance. In addition, normalization can be applied using the "MinMaxScaler()," which transforms the data into a range between 0 and 1 [13].

#### **Exploratory Data Analysis**

To obtain an understanding of the relationship across several features and to pick out any patterns, trends, or correlations that may guide next steps, the dataset was completely explored before applying predictive models. Heatmaps were used to visualize the relationship between numerical variables as shown in Figure 1. The main goal of this step is to gain a fruitful understanding of the raw data and arrange it for additional analysis [14]. Among the assessed models, SHAP analysis was

performed solely on the XGBoost classifier due to its alignment with the TreeExplainer framework. Models based on trees benefit from SHAP's precise additive feature attributions, which are computationally efficient and theoretically robust. XGBoost's built-in support for SHAP made it more interpretable than other models (eg, SVM, KNN, and random forest).

**Figure 1.** Heatmap distribution of the dataset features. ALB: albumin; ALT: alanine aminotransferase; AST: aspartate transaminase; BUN: blood urea nitrogen; DB: direct bilirubin; GLB: globulin; HDL-C: high-density lipoprotein cholesterol; IB: indirect bilirubin; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; SCr: serum creatinine; T-BIL: total bilirubin; TC: total cholesterol; TG: triglyceride; TP: total protein; UA: uric acid.



#### **Features Selection**

#### Overview

Two principal features selection techniques were applied after the data exploration phase to choose the most relevant and informative variables. A suitable feature selection not only enhances the performance and interpretability of a model but also reduces computational complexity and the risk of overfitting [15].

#### LASSO Regression

LASSO regression was used as the first method for feature selection. The LASSO method reduces the number of variables by shrinking the coefficients of less important features to zero, which effectively eliminates them from the model [16]. It is mostly useful for handling multicollinearity as it automatically picks one feature from a set of highly correlated features such as LDL-C and total cholesterol based on the correlation heatmap.

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#### About PCA

The main aim of this technique is to reduce dimensionality in the dataset by transforming the base features into a smaller set of uncorrelated components while keeping most of the variance in the data [17]. In models facing overfitting, such as SVM and XGBoost, PCA reduced multicollinearity and compressed the retaining 95% of the variance in the data. Additionally, PCA reduced the number of variables, simplifying the model and making it more computationally efficient [18].

Before training the predictive models, these features selection techniques were applied. Using only relevant predictors improved model performance and generalizability. By using a structured approach to data exploration and features selection, we lay a strong foundation for building and evaluating ML models for prediabetes risk prediction in the next phase.

#### **Model Development**

#### **Overview**

In this study, different ML models were used to predict the onset of prediabetes. These algorithms were selected due to their ability to handle high-dimensional data, interpretability, and performance in classification tasks. As well as each model was tuned and evaluated to optimize performance for prediabetes detection.

#### XGBoost

XGBoost is a powerful gradient-boosting algorithm that constructs an ensemble of decision trees to improve classification accuracy. Each one tree is sequentially trained to emend the errors of the previous trees, which makes it more powerful for tasks with complex relationships between features [19]. XGBoost is known for its performance and speed in handling big datasets, which makes it appropriate for medical prediction tasks like prediabetes diagnosis. In addition, XGBoost applies regularized boosting techniques to overcome the difficulty of the model and correct overfitting; as a result, increasing model accuracy [20].

#### **Random Forest**

Random forest is an ensemble learning approach that constructs numerous decision trees during training. Every tree is built using a random subset of features and data samples, and the last prediction is made by averaging the predictions from all trees [21]. Random forest minimizes the risk of overfitting by using a bagging approach and tends to accomplish well on classification issues such as prediabetes detection.

#### About SVM

SVM is a supervised learning model that separates data points into distinct classes by finding an optimal hyperplane. For the complex relationships between predictors, such as BMI and age, a nonlinear kernel was applied. This method is suited for medical diagnosis since the decision boundary is not linearly separable in high-dimensional spaces [22].

#### About KNNs

KNN is an uncomplicated, nonparametric classifier that specifies the class label based on the most votes of the KNNs in the

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feature space [23]. In this study, KNN was used after scaling the features, and the optimal number of neighbors was set through hyperparameter tuning. Despite KNN being computationally intensive for big datasets, its clarity and interpretability make it a beneficial model for prediabetes classification.

#### Hyperparameter Tuning and Cross-Validation

#### **Overview**

Hyperparameter tuning was used for all models to recognize the optimal settings for each algorithm. To achieve that, we used GridSearchCV and RandomizedSearchCV, which systematically explore a range of hyperparameters and choose the set that maximizes model performance.

#### GridSearchCV

All combinations of hyperparameters are assessed exhaustively through a particular parameter grid. It is a systematic approach to identifying the effective parameter set [17]. With large datasets and complex models, it can be computationally expensive, so this study used GridSearchCV for models with a relatively small hyperparameter search space, which made it feasible to explore all combinations. The KNN algorithm was tuned by tuning the number of neighbors (k) and the distance metric.

#### RandomizedSearchCV

A randomized search of the hyperparameter space selects hyperparameter settings from the specified ranges [24]. It is more efficient than GridSearchCV when the search space is large because it explores a representative sample of possible combinations instead of testing them all. We used this technique for more complicated models such as random forest and XGBoost when the number of hyperparameters and possible values was too large for a wide search. RandomizedSearchCV assists with identifying optimal hyperparameters by setting a limit on the number of iterations (eg, 40).

#### **Tuning Process for Each Model**

#### XGBoost

The hyperparameters, such as the maximum tree depth, the learning rate, and the subsample ratio, were tuned using RandomizedSearchCV. This approach allowed for a more efficient search through a vast range of parameter values, making it fit for models with big parameter spaces. Random sampling allowed the tuning process to explore a diversity of hyperparameter combinations while preventing overfitting and maximizing classification accuracy.

#### **Random Forest**

To optimize hyperparameters such as the number of trees, maximum tree depth, and minimum samples required for a part, RandomizedSearchCV was used. This approach is selected for random forest because of the large search space, as it can easily sample a subset of hyperparameters to explore near-optimal settings.

#### About SVM

To fine-tune hyperparameters such as the kernel type and penalty parameter C, GridSearchCV was used. Due to the smaller search space for SVM, GridSearchCV is considered the best choice because this approach performs a wide search over the specified parameter values, so it guarantees to find the best possible combinations for the model.

#### About KNNs

To tune the distance metrics (eg, Euclidean or Manhattan distance) and number of neighbors (k), the GridSearchCV method was applied. This approach is useful to pick out the most effective neighborhood size and similarity measures for predicting prediabetes.

This tuning strategy guaranteed that every model was fine-tuned to work optimally for prediabetes prediction.

#### **Cross-Validation Approach**

The tuning process for each model included *k*-fold cross-validation to ensure reliable performance estimation and reduce the risk of overfitting. In *k*-fold cross-validation:

- The dataset is divided into *k* equal-sized subsets (folds).
- The model is trained on k 1 folds and tested on the remaining fold. This process is repeated k times, with each fold serving as the test set once. The results are averaged to get a final evaluation metric.
- 5-fold cross-validation was used in this study, which balances computational cost and model evaluation reliability.

Through cross-validation, a robust estimate of model performance across various subsets of data is obtained by evaluating how well the model generalizes to unseen data [25]. To choose the best-performing parameter set, this method was used during hyperparameter tuning.

#### **Model Evaluation Metrics**

#### Overview

To evaluate the performance of ML models, various metrics were applied.

#### Accuracy

This is the measure of the percentage of true predictions made by the model out of all predictions. Nevertheless, accuracy alone can be misleading, particularly when the classes are imbalanced, as in the case of prediabetes diagnosis.

#### Precision

The proportion of true positive predictions to the total number of positive predictions. High precision indicates that the model produces few false positive errors, which is important in minimizing irrelevant treatments.

#### Recall (Sensitivity)

The ratio of correct positive predictions to the total actual positives. A higher recall means fewer cases of prediabetes were missed, making it necessary for early prediabetes diagnosis.

#### $F_1$ -Score

The harmonic means of precision and recall contribute a balance between both metrics. It is mainly valuable when false positives and false negatives have serious consequences.

#### **ROC-AUC Score**

The ROC-AUC (receiver operating characteristic area under the curve) assesses the capability of the model to distinguish between both classes (normal and prediabetes). The ROC-AUC score provides an aggregate measure of performance throughout all classification thresholds, where a higher value refers to superior model performance.

#### Cross-Validated ROC-AUC

In addition to evaluating ROC-AUC on the test set, cross-validated ROC-AUC provides a more reliable estimate of the model's ability to generalize. This metric was calculated using k-fold cross-validation, giving a better indication of how the model will perform on unseen data.

By using these evaluation metrics, the comparative performance of the ML models was assessed, with a particular focus on balancing accuracy, precision, recall, and  $F_1$ -score to ensure reliable predictions for prediabetes risk assessment.

# Results

#### XGBoost, Random Forest, SVM, and KNN

This section provides a comparative evaluation of the ML models applied in this study—XGBoost, random forest, SVM, and KNN—along with the results of feature selection techniques, such as LASSO regression and PCA. The performance of each model is assessed using multiple evaluation metrics, including accuracy, precision, recall,  $F_1$ -score, and ROC-AUC scores, on both the test set and cross-validation. Table 2 shows the performance metrics comparison of the ML models.



Table .	Performance	metrics	comparison	of	machine	learning 1	models.
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Model	Accuracy (%)	Precision	Recall	F <sub>1</sub> -score	ROC-AUC <sup>a</sup> (test set)	Cross-validated ROC-AUC
XGBoost <sup>b</sup>	74.7	0.8128	0.7889	0.8007	0.7930	0.8600
Random forest	75.9	0.8391	0.7169	0.7732	0.8030	0.9117
SVM <sup>c</sup>	73.9	0.6260	0.6686	0.6466	0.7791	0.8630
KNN <sup>d</sup>	70.8	0.6901	0.6881	0.6890	0.7845	0.8397

<sup>a</sup>ROC-AUC: receiver operating characteristic area under the curve.

<sup>b</sup>XGBoost: extreme gradient boosting.

<sup>c</sup>SVM: support vector machine.

<sup>d</sup>KNN: *k*-nearest neighbor.

#### **Model Performance Comparison**

#### Overview

The following subsections present the comparative results of XGBoost, random forest, SVM, and KNN models, each fine-tuned using hyperparameter optimization and evaluated using key performance metrics.

#### XGBoost

Based on 5-fold cross-validation, the XGBoost model showed a cross-validated ROC-AUC score of 0.86, indicating powerful discrimination between normal and prediabetic cases. In addition, the model achieved a precision of 0.8128, a recall of 0.7889, and an  $F_1$ -score of 0.8007 for the prediabetes class. This balanced performance emphasizes the model's strength to effectively minimize both false positives and false negatives, making it an effective method of prediabetes detection.

#### **Random Forest**

The random forest model achieved an excellent performance with a cross-validated ROC-AUC score of 0.9117, demonstrating its capability to generalize well across various subsets of the data. The model demonstrated a precision of 0.8391, a recall of 0.7169, and an  $F_1$ -score of 0.7732 for the prediabetes class. This indicates that the random forest model not only lowers the likelihood of false positives but also keeps a powerful recall rate, guaranteeing that fewer cases of prediabetes are missed.

#### About SVM

An SVM model, evaluated through 5-fold cross-validation, achieved a cross-validated ROC-AUC score of 0.8630, indicating its ability to distinguish between normal and prediabetic cases with high accuracy. For the prediabetes class, the model achieved a precision of 0.6260, a recall of 0.6686, and an  $F_1$ -score of 0.6466. Despite the SVM model providing a moderate balance between precision and recall, its recall score

indicates potential for missing fewer prediabetic cases, making it a feasible choice for early-stage diagnosis.

#### About KNNs

The KNN model, evaluated using 5-fold cross-validation, demonstrated a cross-validated ROC-AUC score of 0.8397, reflecting its ability to differentiate between normal and prediabetic cases with moderate effectiveness. The model recorded a precision of 0.6901, a recall of 0.6881, and an  $F_1$ -score of 0.6890 for the prediabetes class. Although KNN performed slightly lower in terms of accuracy and precision compared to other models, it still provides an interpretable solution for prediabetes.

# Performance Enhancement Through Hyperparameter Tuning

To optimize the performance of SVM and KNN, we used GridSearchCV for hyperparameter tuning. For more complex models such as XGBoost and random forest, RandomizedSearchCV was used to efficiently explore broader hyperparameter spaces.

Tables 3 and 4 highlight the improvement in model performance after hyperparameter optimization. All 4 models—XGBoost, random forest, SVM, and KNN—showed notable gains in both ROC-AUC and  $F_1$ -score metrics. For instance, XGBoost's ROC-AUC improved from 0.782 to 0.860, and random forest's from 0.807 to 0.9117. These results confirm the effectiveness of using GridSearchCV and RandomizedSearchCV in tailoring model parameters to the dataset, ultimately boosting classification accuracy and robustness. This step is particularly critical for clinical applications, where small improvements in sensitivity or specificity can have substantial impacts on patient outcomes.

The parallel processing option  $n_{jobs} = -1$  was used to enable parallel processing. Each model required 3-8 minutes to be tuned on a standard multicore computer.



 Table . Hyperparameter tuning summary for all models.

Model and hyperparameter		Range or values tested
SVM <sup>a</sup>		
	C	[0.1, 1, 10]
	Kernel	['linear', 'rbf']
	Gamma (rbf)	['scale', 'auto']
KNN <sup>b</sup>		
	n_neighbors	[3, 5, 7, 9, 11]
	Metric	['euclidean', 'manhattan']
XGBoost <sup>c</sup>		
	n_estimators	[50, 100, 200, 300]
	learning_rate	[0.01, 0.05, 0.1, 0.2]
	max_depth	[3, 5, 7, 9]
	Gamma	[0, 0.1, 0.3, 0.5]
	Subsample	[0.6, 0.8, 1.0]
	colsample_bytree	[0.6, 0.8, 1.0]
Random forest		
	n_estimators	[50, 100, 200]
	max_depth	[None, 3, 5]
	min_samples_split	[2, 5]
	min_samples_leaf	[1, 2]
	max_features	['sqrt', 'log2']
	Bootstrap	[True]

<sup>a</sup>SVM: support vector machine.

<sup>b</sup>KNN: *k*-nearest neighbor.

<sup>c</sup>XGBoost: extreme gradient boosting.

Table . Effect of hyperparameter tuning on model performance.

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Model and metric		Default	Tuned (GridSearchCV/Randomized- SearchCV)
XGBoost <sup>a</sup>			
	ROC-AUC <sup>b</sup>	0.782	0.860
	<i>F</i> <sub>1</sub> -score	0.731	0.801
Random forest			
	ROC-AUC	0.807	0.9117
	F <sub>1</sub> -score	0.742	0.773
SVM <sup>c</sup>			
	ROC-AUC	0.813	0.863
	F <sub>1</sub> -score	0.591	0.646
KNN <sup>d</sup>			
	ROC-AUC	0.805	0.839
	<i>F</i> <sub>1</sub> -score	0.652	0.689

<sup>a</sup>XGBoost: extreme gradient boosting.

<sup>b</sup>ROC-AUC: receiver operating characteristic area under the curve.

<sup>c</sup>SVM: support vector machine.

<sup>d</sup>KNN: *k*-nearest neighbor.

#### Descriptive Patterns From Exploratory Data Analysis Findings

#### Overview

Figure 1 shows several important patterns that emerged. The following features are highly correlated.

#### Strong Positive Correlation

Total cholesterol and LDL-C exhibited a strong positive correlation. As a result, the model may be redundant due to those variables sharing similar information. One of these features could potentially be excluded in the feature selection phase if it has a high correlation. It was found that total protein and albumin exhibit a high correlation, suggesting that combining them may not provide more insight than using either separately.

#### Weak or No Correlations

Correlations between variables such as age, BMI, and uric acid were weak or negligible. This is a significant finding because these variables may provide unique independent information that makes model-building more effective.

#### Negative Correlation

A mild negative correlation was found between LDL-C and HDL-C, which is consistent with their known inverse roles in cardiovascular health. Age and HDL-C also exhibited a slight negative correlation, suggesting that lipid profiles might change with aging. Multicollinearity issues happen when highly correlated variables distort the model's ability to differentiate between them due to this exploration in sights. It is crucial to recognize such relationships early in the process so that multicollinearity can be handled, and redundant features can be dropped in the next step, features selection.

A summary plot of SHAP data derived from the XGBoost model is shown in Figure 2. The most significant predictors are age, BMI, HDL-C, and LDL-C. As these variables are well-established risk factors for prediabetes, these findings support clinical intuition. Additionally, SHAP provided valuable visual confirmation that agreed with both the correlation analysis and the LASSO feature selection. Using these exploratory data analysis findings, LASSO regression and PCA were applied for feature selection, ensuring that informative predictors were retained while reducing redundancy and improving interpretability.



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**Figure 2.** SHAP summary plot of XGBoost model. ALB: albumin; ALT: alanine aminotransferase; DB: direct bilirubin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PRO: urine protein; SBP: systolic blood pressure; SCr: serum creatinine; SHAP: Shapley Additive Explanations; TG: triglyceride; U-GLU: urine glucose; UA: uric acid; XGBoost: extreme gradient boosting.



#### **Feature Importance and Selection**

Feature selection over LASSO regression guaranteed that every model was trained on the most relevant predictors. During LASSO, features like BMI, age, and HDL-C were consistently identified as significant predictors of prediabetes as shown in Figure 3. These features were retrained in the final model because of their significant predictive power across different iterations. The models differed in which features they emphasized:

- XGBoost identified BMI as the most significant predictor, aligning with established research that links higher BMI with increased prediabetes risk.
- SVM prioritized age as the first predictor, indicating that age may play an additional critical role when nonlinear relationships between variables are considered.
- Random forest and KNN provide insights into other key features such as LDL-C and HDL-C, demonstrating the various aspects of the data that every algorithm emphasizes.

This variance in feature significance underscores the utility of designing diverse models and selection techniques to better understand the predictors of prediabetes risk.



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**Figure 3.** Features importance plots for XGBoost and SVM. ALB: albumin; ALT: alanine aminotransferase; DB: direct bilirubin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PRO: urine protein; SBP: systolic blood pressure; SCr: serum creatinine; SR: ; SVM: support vector machine; TG: triglyceride; UA: uric acid; XGBoost: extreme gradient boosting.



# SVM Feature Importance Age BMI HDL-C LDL-C earures DB SCR ALT SBP UA 0.00 0.02 0.04 0.06 0.08 0.10 0.16 Importance (Absolute Value of Coefficient) (Oact)

#### **PCA Component Retention**

PCA retained 12 principal components, accounting for 95% of the variance in the dataset.

#### **Confusion Matrices**

#### **Overview**

As shown in Figure 4, the confusion matrix demonstrates that every model's classification performance is detailed in terms of distinguishing normal cases from prediabetic cases. These results reflect the trade-offs each model faces in terms of true positives, false positives, true negatives, and false negatives.



Figure 4. Confusion matrix for XGBoost, SVM, random forest, and KNN models. KNN: *k*-nearest neighbor; SVM: support vector machine; XGBoost: extreme gradient boosting.





## XGBoost

A comparatively balanced classification was accomplished with the XGBoost model, with 482 true positives and 227 true negatives, referring to good sensitivity. However, it recorded 129 false negatives and 111 false positives, proposing some limitations in minimizing misclassification errors, especially false negatives, which are pivotal in clinical settings.

#### **Random Forest**

The random forest model (default threshold of 0.5) correctly identified 513 true positives and 208 true negatives, which are better results compared to XGBoost. The model demonstrated a higher sensitivity than other models, as it reduced the number of false negatives to 98. Despite this, 130 false positives were observed, which indicates a slightly higher trade-off in specificity.

A threshold adjustment of 0.2627 substantially improved the random forest's ability to detect prediabetic cases, resulting in 589 true positives and 22 false negatives. A notable rise in false positives (230) and a reduction in true negatives (108) resulted from this adjustment, indicating a move toward maximizing sensitivity over specificity. There may be some advantages to this configuration in scenarios where minimizing missed prediabetic cases is prioritized over averting false positives.

#### About SVM

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For the overall distribution of true positives and true negatives, the SVM model obtained 476 true positives and 226 true negatives, which is like XGBoost's. A total of 135 false

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negatives and 112 false positives have been recorded, indicating that while SVM has a strong classification capability, it is more susceptible to false negatives, which limits its effectiveness for early detection cases.

#### About KNNs

This model performed moderately, generating 421 true positives and 251 true negatives. Even though KNN can effectively detect normal cases, it is less reliable when it comes to identifying prediabetic cases. It showed 190 false negatives and 87 false positives, indicating a higher rate of misclassification.

To summarize, the confusion matrices demonstrate that the random forest model minimizes false negatives better than other models, especially when thresholds are adjusted. Random forest has a significant advantage over XGBoost and SVM when it comes to sensitivity, which makes it particularly suitable for prediabetes detection, where minimizing missed cases is crucial. While KNN is the most effective at identifying normal cases, it lacks the discriminative power necessary to accurately classify prediabetes, illustrating that it may be more fit as a baseline or for smaller datasets.

#### **ROC Curves**

#### **Overview**

Figure 5 shows the ROC (receiver operating characteristic) curves for every model, further clarifies the trade-offs between sensitivity and specificity, and shows the performance of each model in terms of how well it separates between normal and prediabetic cases. The random forest model showed the most

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convenient ROC curve, while XGBoost and SVM also displayed performance. powerful curves, suggesting effective categorization

Figure 5. ROC curve comparison across models. KNN: k-nearest neighbor; SVM: support vector machine; XGBoost: extreme gradient boosting.



#### XGBoost

This classifier showed an AUC (area under the curve) of 0.79. The XGBoost ROC curve reflects a relatively good trade-off between the true positive rate (sensitivity) and false positive rate (1 - specificity), indicating that it is an effective classification model, but has some room for improvement in distinguishing classes.

#### About SVM

The SVM classifier produced a slightly lower AUC of 0.78. However, the SVM struggles slightly more with false positives, as indicated by its ROC curve, which does not consistently approach the top-left corner. Despite this, it performs reasonably well when it comes to classification.

#### **Random Forest**

Across the 4 models tested, the random forest model achieved the elevated AUC at 0.80. With a more pronounced upward curve, its ROC curve reflects better differentiation between positive and negative classes, showcasing outstanding classification abilities.

#### About KNNs

The KNN classifier achieved a score of 0.78, suggesting a fair rank of accuracy in the diagnosis of positive and negative cases. According to the ROC curve for the KNN model, there is a moderate trade-off between the true positive rate (sensitivity) and the false positive rate (1 -specificity). As well, there is

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some evidence to suggest that the KNN model has some ability to separate the 2 classes, but its shape suggests that it has room for improvement, as it does not consistently approach the top-left corner, which would indicate an ideal performance.

In a nutshell, all 4 models exhibit durable performance, with AUC values ranging from 0.78 to 0.80. The random forest model manifests as the best-performing classifier, followed closely by XGBoost, SVM, and KNN.

## Discussion

#### **Principal Findings**

Through systematically integrating model comparison, advanced hyperparameter tuning, and interpretable feature selection techniques, we present a robust, interpretable framework for early prediabetes prediction. By combining SHAP analysis and LASSO regression, this research provides both high performance and transparency, compared to previous studies that focused solely on accuracy.

#### **Comparative Strengths and Limitations of Each Model**

## Overview

For prediabetes prediction, XGBoost, random forest, SVM, and KNN each show distinct strengths and weaknesses.

#### **Random Forest**

In terms of overall discriminative ability, the random forest model accomplished a superior cross-validated ROC-AUC score (0.9117). According to this result, random forest is a robust choice for early detection scenarios as it can generalize to different datasets well. Due to its ability to prioritize recall through threshold adjustments, 22 false negatives were reduced, but false positives increased (230). In view of this trade-off, random forest may be highly powerful when the cost of missing a prediabetic case outweighs the risk of overdiagnosis.

#### XGBoost

In evaluation, the XGBoost classifier showcased robust performance, as it attained a high precision score of 0.8128 and a balanced recall score. According to these metrics, it seems that XGBoost is particularly adept at minimizing false positives and false negatives, which is highly critical in clinical settings where diagnostic accuracy directly influences patient outcomes. The ROC-AUC score of XGBoost did not surpass that of random forest, despite its ability to balance sensitivity and specificity, making it a viable choice for routine clinical applications.

#### About SVM

With an AUC of 0.78, the SVM model ranked behind both XGBoost and random forest. Despite their superior performance in high-dimensional spaces and in datasets with clear class separation, SVM models have limited linear separability in the prediabetes dataset, impacting their discriminative power. The model has a good ROC-AUC and  $F_1$ -score, with reasonable precision and recall, but when it comes to complex relationships, it lags behind the others. Optimizing feature engineering may upgrade its performance by searching alternative SVM kernels, combining nonlinear interactions, or incorporating alternative kernels.

#### About KNNs

It performed rationally well in terms of classification performance but ranked lowest in terms of accuracy among the evaluated models, with an accuracy of 70.8% and ROC-AUC of 0.78. Because of its simplicity and reliance on distance metrics, KNN is expected to have lower discriminative power than more complex models such as random forest and XGBoost. This model may be valuable as a baseline model or may be convenient for small datasets with a focus on computational efficiency. The reasonable performance of KNN is a result of its sensitivity to distance metrics and the number of neighbors (k), which may prevent it from catching subtle differences in detecting normal and prediabetic cases. Thus, while KNN may be beneficial in straightforward scenarios, it does not have the same level of precision and recall as more sophisticated models.

#### **Impact of Feature Selection**

Feature selection played a crucial role in optimizing the models' performance by focusing on the main relevant predictors. LASSO regression was used to characterize the prime features across models, with BMI, age, LDL-C, and HDL-C consistently emerging as important risk factors for prediabetes. In addition to improving the interpretability of the models, this approach

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also improved the predictive accuracy by reducing overfitting. The strict feature selection process warranted that the models stayed efficient while maintaining high classification power.

#### **Confusion Matrix and Threshold Analysis**

The performance metrics were significantly influenced by adjusting decision thresholds, especially for random forest and XGBoost. A threshold adjustment in random forest minimized the risk of missed diagnoses by reducing false negatives (22 cases). Even so, this came at the expense of a boosted number of false positives (230 cases), suggesting a trade-off between recall and precision. XGBoost, while less sensitive to threshold changes, maintained a balanced approach, limiting both false positives and false negatives effectively. As a result of these outcomes, threshold tuning plays an important role in optimizing model performance for specific clinical applications, such as prioritizing recall in high-risk populations to avoid disease progression.

#### **Clinical Implications**

The results suggest that XGBoost and random forest are the most promising models for enhancing prediabetes diagnosis, given their ability to generalize across different datasets and include reliable classification performance. The higher ROC-AUC score achieved over random forest (91.17%) reflects its potential for widespread use in clinical settings, especially where minimizing the risk of missed cases is crucial. The powerful performance of XGBoost among diverse metrics also highlights its practicality for routine screening, where both false positives and false negatives need to be minimized. By adjusting model thresholds, clinicians can customize diagnostic strategies to meet individual patient needs, such as increasing sensitivity for at-risk patients. Even though SVMs and KNNs do not outperform the best models, they still provide useful insights, especially when data dimensionality or simplicity are important factors.

#### Conclusions

ML models, specifically random forest and XGBoost, have been found to be most sensitive to prediabetes risk assessment, and their performance has powerful discriminative power and high ROC-AUC scores. Combined with feature selection techniques such as LASSO regression, these models offer worthy insights into essential prediabetes predictors, such as BMI, age, and HDL-C. Based on the ROC and AUC analyses, all models-XGBoost, SVM, random forest, and KNN-are viable options for predicting prediabetes. Random forests are robust classifiers because of their ensemble nature, which reduces overfitting and enhances generalizability. SVM and XGBoost also produce competitive results, suggesting their classification abilities can be improved with further parameter tuning. With systematic exploratory data analysis and feature selection, these models can become reliable tools for detecting early prediabetes and offering pathways for optimizing them.

To confirm the generalizability of these models, future research should include validating them in diverse populations, adding biomarkers and genetics to improve prediction accuracy, and integrating these models into clinical decision support systems to assess risk in real time. These models contribute to more

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accurate and timely diagnosis of prediabetes, promoting timely intervention and ultimately improving health outcomes.

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#### **Conflicts of Interest**

None declared.

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#### Abbreviations

AUC: area under the curve HDL-C: high-density lipoprotein cholesterol KNN: *k*-nearest neighbor LASSO: Least Absolute Shrinkage and Selection Operator LDL-C: low-density lipoprotein cholesterol ML: machine learning PCA: principal component analysis ROC: receiver operating characteristic ROC-AUC: receiver operating characteristic area under the curve SHAP: Shapley Additive Explanations SMOTE: Synthetic Minority Oversampling Technique SVM: support vector machine XGBoost: extreme gradient boosting

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# Investigating Associations Between Prognostic Factors in Gliomas: Unsupervised Multiple Correspondence Analysis

Maria Eduarda Goes Job<sup>1</sup>; Heidge Fukumasu<sup>1</sup>, PhD; Tathiane Maistro Malta<sup>2</sup>, PhD; Pedro Luiz Porfirio Xavier<sup>1</sup>, PhD

<sup>1</sup>Laboratory of Comparative and Translational Oncology, Department of Veterinary Medicine, School of Animal Science and Food Engineering, University of Sao Paulo, Avenida Duque de Caxias, 225, Jardim Elite, Pirassununga, Brazil

<sup>2</sup>Cancer Epigenomics Laboratory, Department of Clinical Analysis, Toxicology and Food Sciences, School of Pharmaceutical Sciences of Ribeirao Preto, University of Sao Paulo, Ribeirão Preto, Brazil

#### **Corresponding Author:**

Pedro Luiz Porfirio Xavier, PhD

Laboratory of Comparative and Translational Oncology, Department of Veterinary Medicine, School of Animal Science and Food Engineering, University of Sao Paulo, Avenida Duque de Caxias, 225, Jardim Elite, Pirassununga, Brazil

# Abstract

**Background:** Multiple correspondence analysis (MCA) is an unsupervised data science methodology that aims to identify and represent associations between categorical variables. Gliomas are an aggressive type of cancer characterized by diverse molecular and clinical features that serve as key prognostic factors. Thus, advanced computational approaches are essential to enhance the analysis and interpretation of the associations between clinical and molecular features in gliomas.

**Objective:** This study aims to apply MCA to identify associations between glioma prognostic factors and also explore their associations with stemness phenotype.

**Methods:** Clinical and molecular data from 448 patients with brain tumors were obtained from the Cancer Genome Atlas. The DNA methylation stemness index, derived from DNA methylation patterns, was built using a one-class logistic regression. Associations between variables were evaluated using the  $\chi^2$  test with k degrees of freedom, followed by analysis of the adjusted standardized residuals (ASRs >1.96 indicate a significant association between variables). MCA was used to uncover associations between glioma prognostic factors and stemness.

**Results:** Our analysis revealed significant associations among molecular and clinical characteristics in gliomas. Additionally, we demonstrated the capability of MCA to identify associations between stemness and these prognostic factors. Our results exhibited a strong association between higher DNA methylation stemness index and features related to poorer prognosis such as glioblastoma cancer type (ASR: 8.507), grade 4 (ASR: 8.507), isocitrate dehydrogenase wild type (ASR:15.904), unmethylated MGMT (methylguanine methyltransferase) Promoter (ASR: 9.983), and telomerase reverse transcriptase expression (ASR: 3.351), demonstrating the utility of MCA as an analytical tool for elucidating potential prognostic factors.

**Conclusions:** MCA is a valuable tool for understanding the complex interdependence of prognostic markers in gliomas. MCA facilitates the exploration of large-scale datasets and enhances the identification of significant associations.

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#### **KEYWORDS**

brain tumors; bioinformatics; stemness; multiple correspondence analysis

# Introduction

Cancer is a dynamic and heterogeneous disease characterized by several hallmarks controlling and contributing to its development and progression [1]. Cancer research continually generates large scales of data encompassing clinical information, genomic and transcriptomic profiles, prognostic and diagnostic markers, and therapeutic targets [2]. Different approaches have been used to study and associate all these variables to manage this complexity, aiming to reduce the dimensionality and enhance data interpretation and decision-making process. Several features used to study and classify the different types of cancer are based on categorical variables. For instance, the

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most widely used cancer staging system, TNM, is based on categorical variables, where "T" refers to the size of the primary tumor, "N" refers to the number of lymph nodes affected by cancer, and "M" refers to absence or presence of metastasis [3]. Thus, these biological and clinical variables interact, and their associations can be measured and diagnosticated using statistical tests such as Fisher exact tests and  $\chi^2$  tests. However, these approaches could not provide a global and comprehensive picture of the associations between these variables, particularly in datasets with a large number of categorical variables. Therefore, using multivariate and visual analysis methods can significantly improve the analysis and interpretation of associations between clinical and molecular cancer phenotypes.

Brain tumors are a particularly aggressive type of cancer, mostly due to local tissue damage and highly invasive growth. Gliomas, which originate from neuroglial stem cells or progenitor cells, account for 30% of primary brain tumors and 80% of malignant brain tumors [4]. This heterogeneous disease is histologically classified based on anaplasia criteria and predominant cell types such as oligodendroglioma, astrocytoma, and glioblastoma (GBM) [5]. Nevertheless, as further investigation aimed to elucidate the neuropathological mechanisms of gliomas, new variables are considered for characterizing this cancer tumor, leading to reclassifications based on mutational profiles, clinical data, and epigenetic factors [6]. This scenario resulted in different prognosis predictions, diagnosis determination, and treatment responses, contributing to an increasingly complex and stratified understanding of gliomas.

Stemness is a key phenotype of cancer stem cells (CSCs), related to tumor initiation and progression, therapy resistance, and metastasis [7]. CSCs are referred to as a subpopulation of tumor cells able to self-renew and differentiate into distinct cell lineages, enabling those cells to adapt to different environmental situations [8]. Moreover, recent studies have demonstrated associations between stemness features and different histologic classifications or prognostic factors of gliomas [9-11]. Therefore, providing a comprehensive visualization of the associations between clinical features and stemness in brain tumors could be valuable for identifying and determining potential prognostic and therapeutic markers.

Multiple correspondence analysis (MCA) is an unsupervised data science methodology that aims to observe and represent associations between variables disposed in contingency tables, visualizing these associations in a 2D perceptual map. This approach allows for the simultaneous visualization of the relationship between 2 or more characteristics [12]. MCA shares general characteristics, and it is an extension of principal component analysis which is effective in reducing data dimensionality. Thus, MCA can significantly reduce the workload and simplify statistical analysis in healthy research [13]. The results of MCA are typically interpreted in a 2D map, where the relative positions of categories of each variable and their distribution along the dimensions are analyzed. Categories that cluster together and are closer are more likely to be associated, providing key insights into the relationship [14]. Despite its applicability, rigor, and success in other disciplines such as Geography, Epidemiology, and Human Physiology, MCA remains underused in Oncology research and few studies are applying [12,14-16].

By using MCA, we aimed to gain a deeper understanding of the interdependence between stemness and prognostic factors. Our findings revealed associations among molecular and clinical characteristics and prognostic factors, as previously described by the literature [17]. Additionally, we demonstrated the capability of MCA to identify associations between stemness and these prognostic factors. Our results exhibited a strong association between higher stemness index and features related to poorer prognosis, demonstrating the utility of MCA as an analytical tool for elucidating oncological heterogeneity and may also offer a valuable strategy for therapeutic decision-making. This study highlights MCA as a powerful tool

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for overcoming the barrier of representing the heterogeneity and complexity of cancer variables, particularly in glioma.

## Methods

#### Dataset of the Tumor Samples

Clinical and molecular information of a total of 448 patients with brain tumors was obtained from the Cancer Genome Atlas (TCGA). We tailored the dataset to contain only qualitative information, with 12 variables: cancer type, histology, grade, patient's vital status, IDH (isocitrate dehydrogenase) status, codeletion of chromosomes 1p and 19q arms, MGMT (methylguanine methyltransferase) gene methylation, telomerase reverse transcriptase (TERT) expression, gain of chromosome 19 and 20, chromosome 7 gain and chromosome 10 loss, ATRX (alpha thalassemia/mental retardation syndrome, X-linked) status, and GBM transcriptome subtypes. All categorical variables were selected based on their established role as prognostic factors for brain tumors.

#### **DNA Methylation Stemness Index**

The DNA methylation stemness index (mDNAsi) based on DNA methylation was built using a one-class logistic regression [18] on the pluripotent stem cell samples (embryonic stem cell and induced pluripotent stem cell) from the Progenitor Cell Biology Consortium dataset [19,20]. The algorithm was built and validated as described in the original paper [21]. The mDNAsi was applied in 381 samples from the TCGA database. Malta's model presented a high correlation among other CSC signatures, providing significant insights into the biological and clinical features of pan-cancer. The workflow to generate the mDNAsi is available in the original paper [21].

#### **Multiple Correspondence Analysis**

MCAs were conducted in the RStudio (version 4.3.1; Posit, PBC) environment using the packages FactoMineR (version 2.11; Institut Agro) [22] and cabooters (version 2.1.0; Cranfield University), for creating matrices for MCAs. Contingency tables for the categorical variables were generated, and associations between variables were assessed using a  $\chi^2$  test with k degrees of freedom. This was followed by the analysis of the adjusted standardized residuals (ASRs). The  $\chi^2$  test evaluates whether the observed associations between categorical variables are nonrandomly associated (P value <.05). ASRs higher than 1.96 indicate a significant association between variables in the matrix. To perform MCA, the categorical variables should not be randomly associated. To create the perceptual map, inertia was determined as the total  $\chi^2$  divided by the number of samples, resulting in the number of associations in the dataset. MCA was performed based on the binary matrices and row and column profiles were determined to demonstrate the influence of each category of variables on the others. Matrices were defined based on the row and column profiles. Eigenvalues were then extracted to represent the number of dimensions that could be captured in the analysis. Finally, the x- and y-axis coordinates of the perceptual map were determined, allowing the category of the variables to be represented and established. In MCA, the spatial distance between categories of different variables reflects their associations. Categories with high coordinates that are close in

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space are directly associated, while categories presenting high coordinates but opposing coordinates are inversely associated.

#### **Statistical Analysis**

Fisher exact tests and  $\chi^2$  tests were performed using RStudio 4.3.1 environment and GraphPad Prism (version 10.3.0; Dotmatics, USA).

#### **Ethical Considerations**

The results published in this paper are in whole based upon data generated by the TCGA Research Network [23]. TCGA Ethics and Policies was originally published by the National Cancer Institute [24].

# Results

#### MCA Can Identify Associations Between Different Variables of Gliomas and Patient Vital Status

To determine the suitability of glioma variables for MCA, we first evaluated whether categorical glioma variables were randomly or nonrandomly associated. This involved creating individual contingency tables for each pair of glioma variables (Multimedia Appendices 1-13). Then, we applied  $\chi^2$  tests for each contingency table to confirm nonrandom associations (*P* value <.05). We also confirmed the associations between categorical variables and patients' vital status using the Fisher exact test (*P* value <.05) (Multimedia Appendix 14). Based on the  $\chi^2$  test, the results indicated that only 2 categorical variables, gender and DAXX expression, were randomly associated, suggesting no significant association patterns between these

variables and the others. Consequently, gender and DAXX expression were excluded from further analysis.

In the subsequent analysis, we observed and measured the strength of associations between the patient vital status (0-alive; 1-dead) and different factors including cancer type, histology, grade, IDH status, 1p19q codeletion, MGMT promoter methylation, gain of chromosome (Chr) 7 and loss of Chr10 (7+/10-), co-gain of Chr19 and Chr20 (19+/20+), TERT expression, ATRX status, and transcriptome subtype, aiming to determine whether MCA could identify associations between prognostic factors for this disease. We used ASRs to assess these associations, considering a category of each variable to be associated with either alive or dead vital status when the ASR values were higher than 1.96. Patients' vital status classified as dead were associated with poorer prognostics factors such as GBMs, grade 4, IDH wild type, non-codeleted 1p19q, unmethylated MGMT promoter, gain of Chr7 and loss of Chr10, expression of TERT, ATRX wild type, and classical (CL) and mesenchymal (ME) transcriptome subtypes (Table 1). In contrast, patients classified as alive were linked to favorable prognostic variables, including oligoastrocytomas and oligodendrogliomas, grade 2, IDH mutant, codeleted 1p19q, methylated MGMT promoter, absence of combined Chr7+/Chr10- (chromosome 7 gain and 10 loss), lack of TERT expression, ATRX mutant, and the proneural (PN) and neural (NE) transcriptome subtypes (Table 1). Histological classification, grade, IDH status, and Chr7+/Chr10- were the most strongly associated features with patient vital status. These associations were further illustrated in a heatmap (Figure 1A-D).



**Table**. Table exhibiting the values of the adjusted standardized residuals. Categories of variables with values higher than 1.96 are considered associated. We could observe a strong association between poorer prognostic factors and dead vital status. In contrast, better prognostic factors were associated with alive vital status.

Glioma variables	Patient vital status		Categories associated with
	Alive	Dead	
Glioblastoma	a	8.127	Dead
Oligoastrocytoma	2.64	_	Alive
Oligodendroglioma	3.309	_	Alive
Astrocytoma	1.756	_	Not associated
Grade 2	6.809	_	Alive
Grade 3	0.155	_	Not associated
Grade 4	_	8.127	Dead
IDH <sup>b</sup> wild type	_	8.804	Dead
IDH mutant	8.804	_	Alive
1p/19q codeletion	5.265	_	Alive
1p/19q non-codeletion	_	5.265	Dead
Methylated MGMT <sup>c</sup> promoter	5.26	_	Alive
Unmethylated MGMT promoter	_	5.26	Dead
No combined Chr7+/Chr10- <sup>d</sup>	5.756	_	Alive
Chr7+/Chr10-	_	5.756	Dead
Not expressed TERT <sup>e</sup>	3.078	_	Alive
Expressed TERT	_	3.078	Dead
ATRX <sup>f</sup> mutant	2.311	_	Alive
ATRX wild type	_	2.311	Dead
Proneural subtype	4.122	_	Alive
Neural subtype	3.593	_	Alive
Mesenchymal subtype	_	4.635	Dead
Classical subtype	_	4.852	Dead

<sup>a</sup>Not applicable.

<sup>b</sup>IDH: isocitrate dehydrogenase.

<sup>c</sup>MGMT: methylguanine methyltransferase.

<sup>d</sup>Chr7+/Chr10-: chromosome 7 gain and 10 loss.

<sup>e</sup>TERT: telomerase reverse transcriptase.

<sup>f</sup>ATRX: alpha thalassemia/mental retardation syndrome, X-linked.



**Figure 1.** Heatmap exhibiting the values of the adjusted standardized residuals. Categories of variables with values higher than 1.96 are associated. We could observe a strong association of (**A**) glioblastoma (8.127), (**B**) grade 4 (8.127), (**C**) IDH wild type (8.804), and (**D**) Chr7+/Chr10-(5.756) with dead vital status. Favorable prognostic factors including (**A**) oligoastrocytoma and oligodendroglioma, (**B**) grade 2, (**C**) IDH mutant, and (**D**) no combined copy number alterations were associated with alive vital status. Chr7+/Chr10-: chromosome 7 gain and 10 loss; IDH: isocitrate dehydrogenase.



Using MCA, we observed that dimension 1 (x-axis) accounted for 33.71% of the variance, while dimension 2 (y-axis) accounted for 14.08%. The inertia (sum of the variances) for these 2 dimensions was 47.79%. The variance of the overall dimensions (17 dimensions) for the combinations of the variables is illustrated in Multimedia Appendix 15. The main idea was to present the percentage of explained variance for each dimension and not the influence of individual variables. The total inertia (sum of the variances) was 1.41.

The results obtained from the MCA were visualized in a 2D perceptual map (Figure 2), highlighting the associations between the categories of each variable. The coordinates of each category are detailed in Table 2. The perceptual map reveals that categories such as GBM, unmethylated MGMT promoter, IDH wild type, Chr7 gain and Chr10 loss, grade 4, GBM ATRX wild type, TERT expression, non-codel 1p.19q, and CL and ME

transcriptome subtypes are closely associated with dead vital status, appearing along the positive x-axis (dimension 1). Conversely, categories like oligoastrocytomas and oligodendrogliomas, grade 2, IDH mutant, codel 1p19q, methylated MGMT promoter, no combined copy number alterations, no expression of TERT, ATRX mutant, and PN and NE transcriptome subtypes are closely associated with alive vital status, appearing along the negative x-axis (dimension 1) (Figure 2).

These findings highlight the utility and capacity of MCA in reducing data dimensionality and demonstrate that, in gliomas, variables interact cohesively. MCA allows us to further visualize these interactions on a global perceptual map, organizing the characteristics into distinct clusters that correspond to different prognostic profiles.



**Figure 2.** Multiple correspondence analysis (MCA) 2D perceptual map demonstrating the association between the categories of each categorical variable. Categories that are closely clustered are strongly associated with each other. Categories such as glioblastoma, unmethylated MGMT promoter, IDH wild type, chromosome 7 gain and 10 loss (Chr7+/Chr10–), grade 4, glioblastoma ATRX wild type, TERT expression, non-codel 1p.19q, CL and ME transcriptome subtypes are closely associated with dead vital status (1), appearing along the positive x-axis (dimension 1). ATRX: alpha thalassemia/mental retardation syndrome, X-linked; CL: classical; GBM: glioblastoma; IDH: isocitrate dehydrogenase; ME: mesenchymal; MGMT: methylguanine methyltransferase; NE: neural; PN: proneural; TERT: telomerase reverse transcriptase.





Table . Coordinates of each category compounding the perceptual map.

Category	Dimension 1 (x-axis)	Dimension 2 (y-axis)
GBM <sup>a</sup>	1.6650830	-0.0896760
Low-grade glioma	-0.4723301	0.0254382
Astrocytoma	-0.2672355	0.9527631
Glioblastoma	1.6650830	-0.0896760
Oligoastrocytoma	-0.5334711	0.3276318
Oligodendroglioma	-0.6011671	-0.9346433
Grade 2	-0.6611308	-0.1971919
Grade 3	-0.2970898	0.2320783
Grade 4	1.6650830	-0.0896760
0-Alive	-0.3185609	-0.0551369
1-Dead	0.7544862	0.1305874
IDH <sup>b</sup> mutant	-0.6734117	-0.0548104
IDH wild type	1.1888626	0.0967641
1p/19q codel	-0.6877365	-13.034.766
1p/19q non-codel	0.2750946	0.5213906
Methylated	-0.3429710	-0.1087842
Unmethylated	1.0048449	0.3187185
Chr7+/Chr10- <sup>c</sup>	1.4087248	-0.0210234
No combined Chr7+/Chr10-	-0.4205758	0.0062766
Chr 19/20 co-gain	1.4900007	-0.1295089
No Chr 19/20 co-gain	-0.0843397	0.0073307
Expressed TERT <sup>d</sup>	0.3715020	-0.6845760
Not expressed TERT	-0.4690682	0.8643636
ATRX <sup>e</sup> mutant	-0.6448249	1.0773395
ATRX wild type	0.2693572	-0.4500279
Classical	1.2675815	-0.0217510
Mesenchymal	1.0920361	0.2687642
Neural	-0.5475482	-0.0650952
Proneural	-0.5971662	-0.0604168

<sup>a</sup>GBM: glioblastoma.

<sup>b</sup>IDH: isocitrate dehydrogenase.

<sup>c</sup>Chr7+/Chr10-: chromosome 7 gain and 10 loss.

<sup>d</sup>TERT: telomerase reverse transcriptase.

<sup>e</sup>ATRX: Alpha Thalassemia/Mental Retardation Syndrome X-linked.

#### MCA Can Associate an Epigenetic Stemness Index (mDNAsi) as a Prognostic Factor in Gliomas

After demonstrating that MCA effectively reduces dimensionality and identifies associations between prognostic factors and clinical data in the glioma database, we proceeded to explore whether MCA could also associate these variables with stemness phenotype. For this analysis, we updated our database by including mDNAsi as a new variable, categorized into low, intermediate, and high levels of stemness. These

XSL•FO RenderX categories were based on the DNA methylation index related to tumor pathology and clinical outcomes, as previously studied by [21].

First, we evaluated whether the categorical glioma variables were randomly or nonrandomly associated with mDNAsi by creating individual contingency tables for each pair of glioma variables and applying  $\chi^2$  tests (Multimedia Appendix 16). We also confirmed the associations between categorical variables using the Fisher exact test (*P* value <.05) (Multimedia

Appendix 17). All the variables were found to be suitable for MCA. Then, using ASR values to evaluate the strength of these associations, our results indicated strong associations between high mDNAsi levels and poor prognostic and clinical factors. Higher mDNAsi levels were associated with GBM, IDH wild-type, absence of 1p19q co-deletion, unmethylated MGMT promoter, TERT expression, grade 3 and 4, patient's vital status as dead, Chr7+/Chr10–, chromosomes 19/20 co-gain, ATRX

wildtype and ME and CL transcriptome subtypes (Table 3). Conversely, intermediate and lower levels of mDNAsi were associated with characteristics related to favorable prognosis, including oligodendroglioma, IDH mutant, 1p19q co-deletion, methylation of MGMT promoter, absence of TERT expression, grade 2, patient's vital status as alive, no combined copy number alteration, absence of chromosomes 19/20 co-gain, ATRX mutant, and PN and NE transcriptome subtypes (Table 3).

**Table .** Table exhibiting the values of the adjusted standardized residuals. Categories of variables with values higher than 1.96 are considered associated.We could observe a strong association between poorer prognostic factors and a higher stemness index (DNA methylation stemness index [mDNAsi]).In contrast, better prognostic factors were associated with lower stemness index.

Glioma Variables	mDNAsi			Categories associated with
	Low	Intermediate	High	
Glioblastoma	a	_	8.507	High
Oligoastrocytoma	_	_	_	Not associated
Oligodendroglioma	3.949	_	_	Low
Astrocytoma	_	_	2.832	High
G2	3.279	4.057	_	Low and intermediate
G3	_	—	2.392	High
G4	—	_	8.507	High
IDH <sup>b</sup> wild type	—	—	15.904	High
IDH mutant	8.743	7.057	_	Low and intermediate
1p/19q codeletion	5.772	2.102	_	Low and intermediate
1p/19q non-codeletion	—	_	7.964	High
Methylated MGMT <sup>c</sup> promoter	5.944	3.961	_	Low and intermediate
Unmethylated MGMT pro- moter	_	_	9.983	High
No combined Chr7+/Chr10- <sup>d</sup>	6.436	5.927	_	Low and intermediate
Chr7+/Chr10-	_	_	12.433	High
Not expressed TERT <sup>e</sup>	_	3.216	—	Intermediate
Expressed TERT	_	_	3.351	High
$ATRX^{f}$ mutant	_	3.505	_	Intermediate
ATRX wild type	_	—	4.949	High
Proneural subtype	8.476	—	—	Low
Neural subtype	_	4.218	_	Intermediate
Mesenchymal subtype	_	—	4.771	High
Classical subtype	_	_	10.981	High

<sup>a</sup>Not applicable.

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<sup>b</sup>IDH: isocitrate dehydrogenase.

<sup>c</sup>MGMT: methylguanine methyltransferase.

<sup>d</sup>Chr7+/Chr10-: chromosome 7 gain and 10 loss.

<sup>e</sup>TERT: telomerase reverse transcriptase.

<sup>f</sup>ATRX: Alpha Thalassemia/Mental Retardation Syndrome X-linked.

Using MCA, dimension 1 (x-axis) accounted for 28.7% of the variance, while dimension 2 (y-axis) accounted for 14.39%.

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The inertia (sum of the variances) for these 2 dimensions was 43.09%. The variance of the overall dimensions (18 dimensions)

for the combinations of the variables is illustrated in Multimedia Appendix 18. The total inertia (sum of the variances) was 1.5. The 2D perceptual map exhibited the associations between the categories of each variable (Figure 3). The perceptual map reveals categories such as GBM, unmethylated MGMT promoter, IDH wild type, Chr7 gain and Chr10 loss, grade 4, GBM ATRX wild type, TERT expression, non-codel 1p.19q, and CL and ME transcriptome subtypes are closely associated with high mDNAsi, appearing along the positive x-axis (dimension 1). Conversely, categories like oligoastrocytomas and oligodendrogliomas, grade 2, IDH mutant, codel 1p19q, methylated MGMT promoter, no combined copy number alterations, no expression of TERT, ATRX mutant, and PN and NE transcriptome subtypes are closely associated with alive vital status, appearing along the negative x-axis (dimension 1) (Figure 3).

**Figure 3.** Multiple correspondence analysis (MCA) 2D perceptual map demonstrating the association between the categories of each categorical variable. Categories that are closely clustered are strongly associated with each other. Categories such as glioblastoma, unmethylated MGMT promoter, IDH wild type, chromosome 7 gain and 10 loss (Chr7+/Chr10–), grade 4, glioblastoma ATRX wild type, TERT expression, non-codel 1p.19q, and CL and ME transcriptome subtypes are closely associated with high mDNAsi, appearing along the positive x-axis (dimension 1). ATRX: alpha thalassemia/mental retardation syndrome, X-linked; CL: classical; IDH: isocitrate dehydrogenase; mDNAsi: DNA methylation stemness index; ME: mesenchymal; MGMT: methylguanine methyltransferase; NE: neural; PN: proneural; TERT: telomerase reverse transcriptase.



# Discussion

#### **Principal Findings**

Multiple efforts have been made to explore the diversity of oncologic diseases, with significant contributions from genetics, cell and tissue biology, as well as computational and experimental technologies, providing a wealth of information on cancer manifestations. In the field of glioma research, emerging approaches have sought to clarify tumor pathology and grading through the introduction of novel types and subtypes, as well as by identifying molecular markers and genetic mutations that contribute to predicting diagnosis and

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prognosis. However, it also results in an accumulation of extensive datasets, presenting challenges in interpretation and visualization regarding the associations between prognostic factors. In this study, we used MCA, an unsupervised data science approach, to establish statistical associations between different qualitative variables of gliomas. This method was able to reduce data dimensionality and represent it on a 2D perceptual map, revealing associations between various established glioma prognostic factors, including histological classification, IDH status, MGMT promoter methylation, and transcriptome subtypes. Furthermore, we associated these clinical and prognostic variables with an epigenetic-based stemness index

(mDNAsi), demonstrating that higher stemness levels were associated with poorer prognostic factors, providing a useful tool to associate prognostic markers in brain tumors.

#### **Comparison to Prior Studies**

Several clinical and molecular factors are considered in predicting the prognosis and survival of brain tumors, more specifically for gliomas. Beyond histological classification and tumor grade, genetic and molecular biomarkers have been incorporated as potential prognostic indicators. Thus, we first evaluated the ability of MCA to associate these consolidated prognostic variables with the patient's vital status. Our findings demonstrate that MCA effectively clusters poor prognostic factors with dead vital status. All these prognostic factors are well consolidated and associated with malignancy of gliomas. IDH mutation represents one of the main prognostic markers for gliomas [25]. It has been identified that one of the mechanisms given by this favorable outcome is the impaired production of nicotinamide adenine dinucleotide phosphate in Krebs cycle caused by IDH1 enzyme mutation that can sensitize tumor cells to chemotherapy and explain the favorable prognosis of patients with IDH mutation [25]. Likewise, co-deletion of 1p19q chromosome arms, especially when combined with other biomarkers such as IDH mutation and TERT expression, has been used as a predictive biomarker and recent studies investigated biological mechanisms to be significantly linked to genes involved in cell division, angiogenesis, and DNA repair responses [26]. Thus, we demonstrated that MCA was able to capture and associate key glioma hallmarks with patients' vital status, which was applied to different clinical variables.

Subsequently, we applied MCA to explore the association between high stemness levels (mDNAsi) and characteristics related to poor prognosis. Stemness has been considered an important phenotype in glioma malignancy and is potentially associated with CL genetic alterations, such as the gain of chromosome 7. Chromosome 7 harbors some key genes related to stemness, including Epidermal Growth Factor Receptor (EGFR), Mesenchymal-Epithelial Transition Factor (MET), and Homeobox A gene (HOXA). A study of 86 GBMs reported that EGFR amplification occurs with higher probability in samples that have a gain of chromosome 7 (82.1%) compared with those without it (66.7%) [27]. In addition, EGFR amplification is more prevalent in IDH-wildtype diffuse gliomas (66.0%) and GBM (85.5%) [28], which are also associated with poorer prognostic factors, consistent with our findings. High mDNAsi has been previously linked to EGFR mutations [21]. The HOXA and MET loci, also located on chromosome 7, have been implicated in stemness-related pathways. Notably, studies have demonstrated interactions between chromosome 7 gain and the expression of a stem cell-related HOX signature in GBMs [29]. Analysis of the MET gene at 7q31.2 revealed that gain occurs in 47% of primary and 44% of secondary GBMs, suggesting that this genetic alteration contributes to the pathogenesis of both GBM subtypes [30].

Overall, relatively few studies have used MCA to explore associations with cancer phenotypes. Previous studies have applied MCA to different approaches, such as analyzing prognosis low rectal cancer surgery [31], investigating the association between some types of cancer in rural or urban areas [15], examining the association between Traditional Chinese Medicine Syndrome and histopathology of colorectal cancer [32], assessing clinically relevant demographic variables across multiple gastrointestinal cancers [33], and the relationship between types of diagnostic classification in breast cancer [34]. Our study also highlights the utility of MCA in investigating associations within the context of brain tumors. MCA enables the investigation of the pattern among many categorical factors in gliomas, providing a powerful computational approach to identify and test prognostic variables. It was possible to visually and quantitatively represent the associations, which facilitates the identification of distinct patient clusters based on shared prognostic characteristics. Our findings were consistent with previous literature and emphasized stemness as an important phenotype for gliomas.

#### Limitations

Our study has inherent limitations. First, as a retrospective analysis of TCGA data, it is subject to selection bias. Second, we associated all the prognostic variables with patients' vital status, which may not be the most optimal variable for determining prognosis. For the future, we intend to improve our model validating its applicability in other prospective datasets. Third, the absence of therapy data is another limitation of this study. Finally, an intrinsic limitation of MCA is that retaining only 2 or 3 dimensions may not sufficiently capture all the significant features in the data. In our analysis, the percentage of explained inertia was approximately 40%. While there is not an accepted threshold for adequately explained inertia, common guidelines recommend retaining dimensions that represent over 70% of the inertia [35]. However, explained inertia in the range of 40% - 60% is often considered informative, and the interpretability and relevance of the patterns revealed by the dimensions are frequently more important than the exact percentage of inertia explained, especially in a complex heterogeneous disease such as brain tumors [36].

#### **Conclusion and Future Perspectives**

In conclusion, our findings suggest that MCA is a valuable tool for understanding the interdependence between prognostic markers in gliomas. MCA facilitates the exploration of a large-scale dataset and enhances the identification of associations. Considering the advances in computational oncology and the emergence of new oncological features, such as stemness phenotype, incorporating MCA into cancer research as an approach to exploring the complex heterogeneity of the oncologic field becomes a powerful tool for simplifying data management. It contributes to researchers statistically identifying associations between variables within extensive databases and improves the visual representation, leading to a deeper understanding of cancer findings.



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#### **Data Availability**

The datasets generated or analyzed during this study are available at National Institutes of Health Genomic Data Commons (GDC) [37]. The workflow to generate the DNA methylation stemness index (mDNAsi) can be accessed at GitHub [38].

#### **Authors' Contributions**

MEGJ conducted the study, contributing to the acquisition of data, data analysis and interpretation, production of tables and figures, and wrote the first version of the manuscript. HF contributed to the interpretation and discussion of data and corrected the final version of the manuscript. TMM contributed to the acquisition, interpretation, and discussion of data, and corrected the final version of the manuscript. PLPX contributed to the concept and design of the study, data analysis and interpretation, funding, and corrected the final version of the manuscript.

#### **Conflicts of Interest**

None declared.

Multimedia Appendix 1 Individual contingency tables for cancer type. [XLSX File, 29 KB - bioinform\_v6i1e65645\_app1.xlsx]

Multimedia Appendix 2 Individual contingency tables for histology. [XLSX File, 32 KB - bioinform\_v6i1e65645\_app2.xlsx]

Multimedia Appendix 3 Individual contingency tables for grade. [XLSX File, 27 KB - bioinform\_v6i1e65645\_app3.xlsx]

Multimedia Appendix 4 Individual contingency tables for gender. [XLSX File, 24 KB - bioinform\_v6i1e65645\_app4.xlsx]

Multimedia Appendix 5 Individual contingency tables for vital status. [XLSX File, 23 KB - bioinform v6i1e65645 app5.xlsx]

Multimedia Appendix 6 Individual contingency tables for IDH (isocitrate dehydrogenase) status. [XLSX File, 21 KB - bioinform v6i1e65645 app6.xlsx]

Multimedia Appendix 7 Individual contingency tables for X1p.19q.codeletion. [XLSX File, 20 KB - bioinform\_v6i1e65645\_app7.xlsx]

Multimedia Appendix 8 Individual contingency tables for MGMT (methylguanine methyltransferase) promoter. [XLSX File, 18 KB - bioinform\_v6i1e65645\_app8.xlsx]

Multimedia Appendix 9 Individual contingency tables for Chr 7 gain and Chr 10 loss. [XLSX File, 17 KB - bioinform v6i1e65645 app9.xlsx]

Multimedia Appendix 10 Individual contingency tables for Chr 19/20 co-gain. [XLSX File, 16 KB - bioinform v6i1e65645 app10.xlsx ]

Multimedia Appendix 11 Individual contingency tables for TERT (telomerase reverse transcriptase) expression status. [XLSX File, 13 KB - bioinform v6i1e65645 app11.xlsx ]

Multimedia Appendix 12 Individual contingency tables for ATRX (Alpha Thalassemia/Mental Retardation Syndrome X-linkedalpha thalassemia/mental retardation syndrome, X-linked) status. [XLSX File, 11 KB - bioinform\_v6i1e65645\_app12.xlsx]

Multimedia Appendix 13 Individual contingency tables for DAXX status. [XLSX File, 10 KB - bioinform v6i1e65645 app13.xlsx]

Multimedia Appendix 14 Fisher exact test and  $\chi^2$  test for vital status × glioma prognostic factors. [XLSX File, 24 KB - bioinform\_v6i1e65645\_app14.xlsx]

Multimedia Appendix 15 Percentage of explained variances of the overall (17) dimensions. [PNG File, 161 KB - bioinform v6i1e65645 app15.png]

Multimedia Appendix 16 Individual contingency table for mDNAsi. [XLSX File, 30 KB - bioinform v6i1e65645 app16.xlsx]

Multimedia Appendix 17 Fisher exact test and  $\chi^2$  test for mDNAsi (DNA methylation stemness index) × glioma prognostic factors. [XLSX File, 22 KB - bioinform\_v6i1e65645\_app17.xlsx]

Multimedia Appendix 18 Percentage of explained variances of the overall (18) dimensions. [PNG File, 9 KB - bioinform v6i1e65645 app18.png]

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#### Abbreviations

ASR: adjusted standardized residual ATRX: alpha thalassemia/mental retardation syndrome, X-linked Chr: chromosome Chr7+/Chr10-: chromosome 7 gain and 10 loss CL: classical **CSC:** cancer stem cell **GMB:** glioblastoma **IDH:** isocitrate dehydrogenase MCA: multiple correspondence analysis mDNAsi: DNA methylation stemness index ME: mesenchymal MGMT: methylguanine methyltransferase NE: neural PR: proneural TCGA: the Cancer Genome Atlas TERT: telomerase reverse transcriptase

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**Original Paper** 

# Decentralized Biobanking Apps for Patient Tracking of Biospecimen Research: Real-World Usability and Feasibility Study

William Sanchez<sup>1</sup>, BA; Ananya Dewan<sup>2</sup>, BA; Eve Budd<sup>3</sup>; M Eifler<sup>1</sup>, BA, MFA; Robert C Miller<sup>4,5</sup>, MD; Jeffery Kahn<sup>6</sup>, PhD; Mario Macis<sup>7</sup>, PhD; Marielle Gross<sup>1,6</sup>, MD

<sup>1</sup>de-bi, co., Greencastle, PA, United States

<sup>3</sup>Harpur College of Arts and Sciences, State University of New York, Binghamton, NY, United States

**Corresponding Author:** 

Marielle Gross, MD Johns Hopkins Berman Institute of Bioethics Johns Hopkins University 1809 Ashland Ave. Baltimore, PA, 17225 United States Phone: 1 8135416103 Email: mariellesophiagross@gmail.com

# Abstract

**Background:** Biobank privacy policies strip patient identifiers from donated specimens, undermining transparency, utility, and value for patients, scientists, and society. We are advancing decentralized biobanking apps that reconnect patients with biospecimens and facilitate engagement through a privacy-preserving nonfungible token (NFT) digital twin framework. The decentralized biobanking platform was first piloted for breast cancer biobank members.

**Objective:** This study aimed to demonstrate the technical feasibility of (1) patient-friendly biobanking apps, (2) integration with institutional biobanks, and (3) establishing the foundation of an NFT digital twin framework for decentralized biobanking.

**Methods:** We designed, developed, and deployed a decentralized biobanking mobile app for a feasibility pilot from 2021 to 2023 in the setting of a breast cancer biobank at a National Cancer Institute comprehensive cancer center. The Flutter app was integrated with the biobank's laboratory information management systems via an institutional review board–approved mechanism leveraging authorized, secure devices and anonymous ID codes and complemented with a nontransferable ERC-721 NFT representing the *soul-bound* connection between an individual and their specimens. Biowallet NFTs were held within a custodial wallet, whereas the user experiences simulated token-gated access to personalized feedback about collection and use of individual and collective deidentified specimens. Quantified app user journeys and NFT deployment data demonstrate technical feasibility complemented with design workshop feedback.

**Results:** The decentralized biobanking app incorporated key features: "biobank" (learn about biobanking), "biowallet" (track personal biospecimens), "labs" (follow research), and "profile" (share data and preferences). In total, 405 pilot participants downloaded the app, including 361 (89.1%) biobank members. A total of 4 central user journeys were captured. First, all app users were oriented to the  $\geq$ 60,000-biospecimen collection, and 37.8% (153/405) completed research profiles, collectively enhancing annotations for 760 unused specimens. NFTs were minted for 94.6% (140/148) of app users with specimens at an average cost of US \$4.51 (SD US \$2.54; range US \$1.84-\$11.23) per token, projected to US \$17,769.40 (SD US \$159.52; range US \$7265.62-\$44,229.27) for the biobank population. In total, 89.3% (125/140) of the users successfully claimed NFTs during the pilot, thereby tracking 1812 personal specimens, including 202 (11.2%) distributed under 42 unique research protocols. Participants embraced the opportunity for direct feedback, community engagement, and potential health benefits, although user onboarding requires further refinement.

<sup>&</sup>lt;sup>2</sup>Johns Hopkins School of Medicine, Johns Hopkins University, Baltimore, MD, United States

<sup>&</sup>lt;sup>4</sup>Faculty of Medicine, Mayo Clinic, Rochester, MN, United States

<sup>&</sup>lt;sup>5</sup>School of Medicine, Indiana University Hospital, Indianapolis, IN, United States

<sup>&</sup>lt;sup>6</sup>Johns Hopkins Berman Institute of Bioethics, Johns Hopkins University, Baltimore, MD, United States

<sup>&</sup>lt;sup>7</sup>Carey School of Business, Johns Hopkins University, Baltimore, MD, United States

**Conclusions:** Decentralized biobanking apps demonstrate technical feasibility for empowering patients to track donated biospecimens via integration with institutional biobank infrastructure. Our pilot reveals potential to accelerate biomedical research through patient engagement; however, further development is needed to optimize the accessibility, efficiency, and scalability of platform design and blockchain elements, as well as a robust incentive and governance structure for decentralized biobanking.

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#### **KEYWORDS**

patient empowerment; biobanking; biospecimens; transparency; community engagement; nonfungible tokens; NFTs; blockchain technology; decentralized biobanking; pilot studies; technical feasibility; biowallet

# Introduction

#### Background

University biobanks collect, store, and distribute biospecimens such as tissue and blood, capitalizing on leftover clinical materials from affiliated hospitals to drive biomedical science and drug discovery [1-3]. Standard operating procedure for most biobanks in academic medical centers includes prospective broad consent for nonspecific, future research [4] coupled with deidentification, whereby identifiers are stripped before specimen allocation [5]. In this setting, patients do not learn what becomes of their donations, and scientists lack access to the donor, linked specimens, and evolving clinical data [4,6]. This disconnect, though the by-product of policies designed to protect privacy while promoting learning, promulgates a biobank ecosystem that permits problematic gaps in recognition, reciprocity, and return of results [7,8]. Simultaneously, vast yet siloed specimen collections have accumulated across most US academic medical centers, a widely underused and unsustainable "treasure trove" wherein frozen assets lay hidden from patients and scientists for whom they may be most valuable [3,9]. The lack of an efficient market for ensuring the use of donated materials deepens the crisis of faith in public health institutions and has prompted attempts at marketplace solutions [10,11].

We are advancing decentralized biobanking as a software platform predicated on blockchain technology's democratic ethos, incentive alignment, transparency, and assurances of trust [12]. These key features are reflective of blockchains as permissionless, distributed, shared ledgers of digital transactions engineered to be mathematically concordant, accessible, and auditable [13], underscoring their first and most successful use to date for the creation of global digital currency such as Bitcoin, which makes them fit for purpose in efforts to decentralize ownership and governance of data through thoughtfully structured peer-to-peer networks [14]. One of the most promising innovations enabled by blockchains are nonfungible tokens (NFTs), digital record identifiers that serve as electronic deeds for provably unique digital or physical assets that may be represented "on-chain" [15]. The potential for blockchain and NFTs to play a role in restructuring control and ownership of data has been widely discussed, with several notable projects in the health care domain [16,17]. Although empowering patient ownership of health data is compelling in theory, full realization of such initiatives has been elusive in light of complex regulatory considerations, socioeconomic factors, and technical limitations for blockchain technologies and legacy systems [18,19].

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XSL•F() RenderX Building on the success and diversity of blockchain applications for decentralized finance [20,21], decentralized biobanking applies human-centered design and innovative system mechanisms to empower patients to track donated biospecimens and engage in downstream research activities, outcomes, and products via a platform compatible with established privacy policies and workflows. Our approach provides patients with secure, direct access to personal specimen data housed in institutional databases via user-friendly mobile and web apps complemented with a privacy-preserving NFT digital twin framework [22]. This strategy may support stepwise adoption of increasingly autonomous and progressively decentralized collaborations among patients, scientists, and physicians in a dynamic biomedical metaverse, or "biomediverse."

#### Objectives

Successful implementation of decentralized biobanking will usher in a new standard for research transparency, foster institutional accountability to the patients and communities they serve, and create opportunities to unite siloed datasets, facilitate timely translation of precision medicine and enable structurally just marketplace solutions for improving efficiency and effectiveness in the management of one of our most precious human resources. In this paper, we explore the technical feasibility of decentralized biobanking through a description and quantitative analysis of a live pilot for a breast cancer biobank at a US academic medical center. We discuss system design, key features, and NFT functionality, illustrating how the platform provided transparency and recognition of patients' contributions to a real-world biobank.

# Methods

#### Decentralized Biobanking System Design: NFT Digital Twin Framework

Decentralized biobanking builds digital bridges among patients, specimens, and scientists, connecting stakeholders based on real-world relationships predicated upon transactions within existing biobank infrastructure and research protocols (Figure 1). The system design represents all people, protocols, and assets in an NFT digital twin framework, creating a blockchain-backed overlay network on top of the established biospecimen ecosystem. Our approach presents a unique strategy for the progressive inclusion of patients, allowing for the implementation of a composable software platform with programmable, modular elements, mechanisms, and workflows that may be integrated with institutional biobank databases to provide durable transparency without requiring substantial time,

labor, or ongoing participation of physicians, biobankers, and scientists. This framework applies privacy by design throughout the engineering process, implementing techniques such as data minimization and innovative system architectures to ensure compliance with established biospecimen collection and research protocols, institutional policies, and data structures. The core benefits of our approach are use case agnostic and can be applied for all biobanks, research protocols, and institutions with minor modifications at each new site.

**Figure 1.** Decentralized biobanking system design—nonfungible token (NFT) framework and software applications uniting patients, specimens, and scientists. This system diagram illustrates key entities of biobanking connected via a specimen supply chain (red arrow) yet presently lacking a unified platform for collaboration. The proposed decentralized biobanking NFT digital twin framework is designed to integrate with this established infrastructure, mapping the stakeholders, specimens, and studies in the biobanking ecosystem and enabling applications whereby they may be united for mutually beneficial collaboration, data exchange, and value-building activities.



#### **Pilot Setting**

The Breast Disease Research Repository (BDRR; STUDY19060196) is a large breast cancer biobank platform at the intersection of the University of Pittsburgh, the University of Pittsburgh Medical Center, and Hillman Cancer Center that served as the pilot study use case. Broad prospective consent for the BDRR is embedded in the breast cancer service line, for example, concurrently with surgical consent. Once consented, "leftovers" from any clinical procedures may be collected by the biobank without further notice or engagement. From 2006 to 2023, more than 10,000 patients consented for the BDRR and specimens were collected from 4000 participants to date. In total, approximately 61,000 specimens were collected, and 6000 were distributed for research, with a mix of fresh and frozen distributions. The biobank operates via a hub-and-spoke model, allocating specimens chiefly to local investigators under designated research or subbiobanking protocols (eg. a flagship patient-derived organoid biobank that grows and distributes copies of living 3D cell cultures [approximately n=300]).

#### **Requirement Gathering**

Foundational surveys, semistructured interviews, community engagement, and stakeholder alignment activities with

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populations with breast cancer, physicians, advocates, and scientists informed our approach to designing a biobanking app for patients [23]. Broadly, we found that patients have an unmet demand for feedback about research on their specimens, with particular interest surrounding personal meaning or potential health benefits for the individual or their family members. For example, a survey respondent noted the following:

Giving patients access to this type of information could decrease the lethal lag between research findings and actual clinical practice.

One patient advocacy leader captured this sentiment, noting the following:

#### We have been screaming for this, banging on pots and pans. Thank you for taking this on.

Importantly, she alluded to the multifactorial challenge of enabling patients to track and learn about donated biospecimens [23], which would require novel, user-friendly interface designs as well as system architectures and pilot protocols compliant with regulatory norms, compatible with established workflows, and acceptable within the institutional milieu.

Thus, we interacted extensively with the breast cancer service line, the institutional biobanking platform, and institutional review board (IRB) and Office of Human Research Protections leadership, as well as research scientists, clinical and teaching faculty, IT staff, technology transfer teams, and cross-disciplinary institutional leadership. Concurrently, the ethnography of the specimen procurement supply chain allowed us to map the breast cancer biobank ecosystem [23]. We examined all contexts along the data pipeline, from population-level breast cancer screening to diagnostic biopsies and surgical treatments, clinical pathology, and specimen accessioning through the biobanking platform, where it may be stored for future use in -80 °C freezers or distributed fresh for next-generation biobanking applications such as patient-derived organoids, multi-omics, and high-throughput testing. Given the well-documented challenges for biobank sustainability, we took special interest in learning about economic and logistical challenges pertaining to this sector. Regulatory considerations, operational feasibility, and economic analyses will be reported elsewhere [23].

#### Prototyping

The first decentralized biobanking prototype established the proof of concept, leveraging ERC-721 NFTs to keep patients connected to donated specimens throughout the research life cycle. The NFT platform was integrated with a novel mobile app for privacy-preserving collaboration among patients, scientists, and physicians in a model breast cancer organoid ecosystem. A second prototype advanced a comprehensive NFT digital twin framework with ERC-1155 modeled using a publicly available real-world organoid biobank dataset (National Cancer Institute Human Cancer Models Initiative) [24,25]. This web-based prototype focused on generating value for scientists, illustrating potential to enhance efficiency, effectiveness, and impact of biospecimen research. Third, no-code front-end mobile app prototypes were developed to demonstrate, test, and refine user interfaces and experiences for the engagement of donors in biobanking.

#### **User Interface and User Experience**

We drafted wireframes using anonymous model biospecimen information from the institutional biobank database. App design processes sought to minimize cognitive effort for mobile app users, maximize accessibility across ages and educational levels, and adhere to rigorous privacy standards and customs in accordance with the established biospecimen collection protocols. We progressively simplified and iterated display text and content to make it as concise and concrete as possible and unified across decentralized biobanking app interfaces. To facilitate navigation, we streamlined presentation of content in each of the 4 core interfaces using accordion elements complemented with individual cards for each biospecimen, with pop-ups to guide transitions within and across interfaces. Unified color schemes, fonts, and item designs adhered to predetermined themes with a standardized format that was gradually refined.

The designs were tested and validated via further research surveys and interviews. Immersive design workshops solidified core app requirements. Initial usability testing included online and in-person sessions with clickable prototypes and functional

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prototype demonstrations followed by usability testing and cognitive walk-throughs on users' personal devices.

#### **Front-End Development and Testing**

Finalized mobile app designs were developed using Flutter so that iOS and Android users could participate in the pilot. The apps were tested and deployed to Apple TestFlight and the Google Play Store, allowing for download directly to participants' personal devices. From August 2022 to January 2023, feedback from 110 unique individuals was incorporated, including 45 (40.9%) BDRR members, 28 (25.5%) who downloaded and tested the app on their personal devices, and 14 (12.7%) who viewed personalized biospecimen content within the app interface. The result was a validated app facilitating interaction between donors and biospecimens within the breast cancer biobank, personalized collection content, and mappings from biobank database details.

#### **Blockchain Development**

Initial decentralized biobanking prototypes were developed experimenting with different tokenization strategies using Ethereum's ERC-721 and ERC-1155 NFT standards for mapping dynamic relationships among patients, biospecimens, physicians, scientists, and corresponding biobanking and research protocols. However, variable costs of transaction fees (known as gas fees) on the Ethereum network and high friction for blockchain onboarding were major limitations for implementing a real-world pilot.

These constraints informed the design of a functional, blockchain-backed prototype suitable for the pilot population and setting, leveraging a fit-for-purpose blend of centralized and decentralized applications that would enable patients to track and learn about donated specimens appropriate to the highest-order objectives for the first live pilot of decentralized biobanking technology.

A nontransferable ERC-721 NFT, also referred to as a "soul-bound token" [26], was developed to represent each donor's immutable, inherently unique connection to their personal biospecimens. This token [26] was held within a single externally owned account that served as a custodial wallet. Of note, our previous decentralized biobanking prototype for organoid research networks, as described elsewhere, used ERC-1155 to advance a comprehensive digital twin ecosystem with NFTs representing patients, specimens, multigenerational derivatives (eg, patient-derived organoids), scientists, and physicians, as well as externally owned biobanker accounts, demonstrating the potential for a sophisticated solution [25]. However, while using the ERC-1155 standard would have offered savings for deploying multiple token collections representative of the entire biobanking ecosystem, applying them to a single soul-bound token collection for this use case would have yielded no additional benefits while adding unnecessary complexity [25].

Each biowallet NFT served as a customized yet anonymous "token of appreciation" for specimen donation coupled with a front-end user experience simulating token-gated access to personal biobank data. This token-gated process was performed manually, minting the tokens individually via the smart contract

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interface on Etherscan. Subsequently, the token metadata and transaction details were stored within a secure, IRB-approved database for the eligible user. This created a digital honest broker mechanism for managing in-app participant-specimen engagement without requiring further humans in the loop or revealing donor names or other personally identifiable information to third parties.

#### System Architecture

The decentralized biobanking pilot system incorporated 3 core components: an *app* overlying *institutional biobank and research infrastructure* with a blockchain-backed *NFT digital twin framework* (Figure 2).

The app used an *n*-tier architecture pattern with interconnected workflows across distinct, modular components with varying responsibilities (Table 1). Our user-friendly mobile app, available on Android and iOS, was powered by applications built using Amazon Web Services. During this initial pilot phase, our system relied on external services and data sources that were not yet directly integrated with our deployed technology. Our NFT framework consisted of an ERC-721 smart contract designed to mint nontransferable, soul-bound biowallet tokens that were deployed to the Ethereum mainnet. Deidentified biospecimen data were provided by biobank personnel to authorized study team members, who would use a secure device to import the records into the pilot system's database. Both required manual processes for pilot implementation.

**Figure 2.** System architecture diagram—decentralized biobanking pilot app for breast cancer biobank. This system architecture diagram incorporates the decentralized biobanking mobile app powered by internal components that handle business logic, data storage, and data integrations built on a cloud-based infrastructure using Amazon Web Services (AWS); this is flanked by corresponding elements connected via secure authorized access devices for interacting with the nonfungible token (NFT) digital framework's biowallet tokens deployed on Ethereum and institutional data sources from the Breast Disease Research Repository and Institute of Precision Medicine organoid biobank.





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Table 1. Key details of the decentralized biobanking pilot system architecture.

Component	Technical details
App	<ul> <li>Presentation tier: the Flutter mobile app built and deployed using Android Studio (Google) and Xcode (Apple Inc) to enable download to Android and iOS devices. The app provided front-end user interfaces for patients, enabling dynamic interactions, user inputs, and the presentation of queried information from institutional data sources through the app tier. Google's Firebase Authentication services manage account creation and management, encrypting data in transit using HTTPS and at rest using the scrypt standard cryptographic protocol. Passwords are stored securely using encryption, salting, and 1-way hashing following NIST<sup>a</sup> 800-63b recommendations.</li> <li>App tier: used a Node.js (OpenJS Foundation) server to enable all core functionality and logic of the app, including specimen tracking with enhanced transparency into biobank activities and subsequent research. This layer is also responsible for enforcing security and access rules, handling connectivity to and communication with data sources and external services, and processing data to return to the presentation layer. Deployed on AWS<sup>b</sup> Elastic Beanstalk, the app instances sit behind load balancers for scalability, running in private subnets.</li> <li>Data tier: hosted by an Amazon Aurora database cluster using the MySQL engine. It hosts a secure, highly available database that stores and retrieves the information necessary for the app to run. This includes donated sample records housed on the BIOS<sup>c</sup> and corresponding biospecimen freezer repositories across 4 physical locations of the Pitt Biospecimen Core, as well as unique cryptographic IDs from Firebase and claimed biowallet NFTs<sup>d</sup> to establish privacy-preserving data linkages between donors and their deidentified biospecimens. As noted in the presentation tier, user credentials for accessing the app are stored separately on secure Firebase servers.</li> <li>Infrastructure tier: referenced within the app and data tiers, our AWS cloud infrastructure provides the foundation for networking an</li></ul>
Blockchain	• NFT framework: an ERC-721 smart contract designed to mint nontransferable, soul-bound biowallet tokens was deployed to the Ethereum mainnet via a transaction sent to an Infura-hosted node from a local Node.js runtime environment using Hardhat. The overarching framework incorporates NFTs representing all stakeholders, specimens, and protocols, allowing for composable layers of complexity, utility, and value to be built upon the PIO <sup>e</sup> architecture.
Biobank	• Institutional biospecimen and research databases: biobank personnel provided access to deidentified biospecimen data via OneDrive Microsoft Excel (Microsoft Corp) files to an authorized study team member, who would use a secure device to import the updated records into the Aurora database. Similarly, Microsoft Excel files containing biobank (BDRR <sup>f</sup> ) registered members were provided by research staff as exported from OnCore. In addition, imaging and research data from an organoid biobank "spoke" were shared via OneDrive, and curated representative datasets were hosted on Dropbox (Dropbox, Inc).

<sup>a</sup>NIST: National Institute of Standards and Technology.

<sup>b</sup>AWS: Amazon Web Services.

<sup>c</sup>BIOS: Biospecimen Inventory and Operations System.

<sup>d</sup>NFT: nonfungible token.

<sup>e</sup>PIO: programmed input-output.

<sup>f</sup>BDRR: Breast Disease Research Repository.

#### **Pilot Study**

Participants were recruited via electronic and paper fliers for "Decentralized Biobanking "de-bi": An App for Patient Feedback from Biobank Research Donation" (STUDY22020035). The pilot aimed to recruit 300 participants over 6 to 12 months. App download invites were distributed via email with Apple and Android instructions. IT support was provided as needed, with real-time bug fixes and improvements based on user feedback. App interfaces, design, and features were iterated in monthly sprints. Participatory research, user-centered design, and usability testing, as well as quantitative and qualitative assessments of patient, physician, and scientist acceptability, will be reported elsewhere. NFT minting for pilot performance took place from March 7, 2023, to May 8, 2023. Multimedia Appendix 2 details the pilot recruitment to sample tracking process.

#### **Data Sources and Analysis**

The technical data reviewed included conceptual models, technical diagrams, product feature documentation, and

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screenshots of user journeys as experienced by decentralized biobanking pilot participants using the Flutter app. We also consider biospecimen collection data from the institutional Biospecimen Inventory and Operations System via Microsoft Excel (Microsoft Corp) exports, in-app activity data recorded in a MySQL database, and blockchain transactions on the Ethereum network accessed via Etherscan. Technical feasibility was assessed from feature requirements, interface designs, and quantifiable user experiences from the live implementation. To further evaluate pilot outcomes, we provide simple descriptive statistics from the quantitative datasets and comparative cost analyses for alternative NFT design strategies calculated using values from tokens minted during the pilot. Patient experiences were captured via written feedback from a co-design workshop during the app development phase and a usability workshop session held with pilot participants.

#### **Ethical Considerations**

Research was performed under IRB-approved human subjects research protocols and a Quality Improvement protocol (Textbox 1 provides protocol numbers, titles, and approving body).


Participants provided informed consent or the equivalent, in accordance with respective protocols. Conflict of interest disclosures were included in consent documents and verbal disclosures were provided for all online and in-person encounters. All data reported here are either de-identified or anonymized and privacy-by-design was utilized within the de-bi app to maintain confidentiality of participant identities. Participants were not compensated for participation in the biobank, stakeholder interviews, quality improvement activities or de-bi app pilot study (STUDY19060196, IRB00019273, QRC 3958 and STUDY22020035, respectively). Our foundational research protocol (STUDY22010118) provided \$10 gift cards for surveys, with an additional \$20 for those who completed follow-up interviews.

Textbox 1. Human participants and quality improvement protocols for technology feasibility.

- STUDY22010118: patient views, preferences and engagement in next-generation biobank research (University of Pittsburgh)
- IRB00019273: nonfungible tokens for ethical, efficient and effective use of biosamples (Johns Hopkins University)
- STUDY19060196: Breast Disease Research Repository: tissue and bodily fluid and medical information acquisition protocol (04-162; Hillman Cancer Center)
- QRC 3958: patient-facing biobank platform development Quality Improvement proposal for Beckwith award-breast cancer supply chain analysis, biobank token model development, and initial pre-pilot testing with University of Pittsburgh Medical Center patients (University of Pittsburgh Medical Center)
- STUDY22020035: decentralized biobanking "de-bi": exploring patients interests in feedback, education, follow-up, engagement and tokens of appreciation regarding biobank donation via mobile and web applications (University of Pittsburgh)

# Results

## **Prepilot Results**

A co-design session (n=15) was conducted before the pilot to characterize patient preferences and areas of confusion. This session was one in a series of extensive participatory design sessions, which we have reported elsewhere [23]. Participants were most excited about decentralized biobanking for feedback and recognition ("to see my own cells+know how those cells are advancing science"), community-engaged research ("to

connect with others through this app"), and precision medicine potential ("to get helpful results regarding my health"), suggesting acceptance of our vision and overall approach. At the conclusion of this phase, there was still confusion surrounding logistics and governance ("how we *find* our samples and approve their use"), technical concepts ("Why NFT's?"), and unanswered big-picture questions ("Short+long-term—who benefits from this?") regarding the decentralized biobanking platform. Table 2 provides a thematic overview and representative quotes.



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Table 2. A thematic overview of participant feedback gathered through a prepilot co-design session.

Theme	Prepilot participant feedback							
Aspects participants were "mo	Aspects participants were "most excited about"							
Personalized feedback and recognition	<ul> <li>"The opportunity to see my own cells+know how those cells are advancing science and clinical care."</li> <li>"Having knowledge about [sample] types, research and current news about my tumors."</li> <li>"To be able to follow where my personal donation goes, and what they are doing with it, and what they get out of it."</li> </ul>							
Community-engaged re- search	<ul> <li>"Great for mutation studies with multiple primary cancer+tumors."</li> <li>"Keeping up to date with genetic mutation research."</li> <li>"I'm excited to connect with others through this app."</li> <li>"That patients who invest their tissue in research are able to connect as co-investigators."</li> </ul>							
Potential health benefits	<ul> <li>"I'm excited about the idea that there may be more ways to care for my family—better research practices may enable the medical field to work smarter—maybe ensuring that my children don't need surgery, chemo, etc."</li> <li>"I am very excited for anything that can improve my health and outcome (and of others)."</li> <li>"Being able to get helpful results regarding my health."</li> <li>"I'm excited about the possibility to know how my tissue reacted to a treatment."</li> <li>"Patient access to personal info/data; Personalized medicine potential."</li> </ul>							
Aspects participants "still four	nd confusing"							
Big picture	<ul> <li>"Why do people still get cancer, dammit!"</li> <li>"I don't understand 1) How this may really help me+my family, 2) Short+long-term—who benefits from this?</li> <li>3) Where does the \$ come from? 4) What are we giving up/sacrificing by saying 'yes.'"</li> <li>"How will Dr. utilize?"</li> </ul>							
Logistics and governance	<ul> <li>"I don't understand how we find our samples and approve their use—I also don't understand what studies we could 'suggest' or enable through the samples we have provided."</li> <li>"How likely is it that my samples will be used?"</li> <li>"Can you use it [de-bi app] even if your surgery already happened?"</li> <li>"How to get my tissue submitted to researchers."</li> </ul>							
Unclear technical terms and concepts	<ul> <li>"Not really sure what an organoid is—is it a picture/video of my actual cells or is it a model of my cells?"</li> <li>"Why NFT's?"</li> <li>"I am still learning about NFTs and how they will help breast cancer patients."</li> <li>"How will patients interpret data—will it be translated?"</li> </ul>							

## **Overall Pilot Results**

#### Overview

Over 10 weeks of active recruitment (February 16 to April 30, 2023), 1080 unique participants enrolled in the decentralized biobanking pilot, including 9.54% (930/9750) of confirmed biobank members (Multimedia Appendix 3). Approximately 600 app invites were distributed, and 405 participants downloaded and completed app registration, including 361 (89.1%) biobank members. All app users were female (405/405, 100%), and the mean age was 56 (SD 12.8; range 18-87) years,

making them younger than both the broader biobank membership and decentralized biobanking pilot participants (mean ages of 64, SD 13.6 and 58, SD 13.1 years, respectively). Multimedia Appendices 4 and 5 detail pilot participant and app user characteristics relative to those of the overall biobank membership. There were 4 key features of the piloted app, as shown in the user journey map (Figure 3). Biobank, biowallet, and profile features and quantified user journeys are illustrated in subsequent Journey sections, and laboratory features and respective user journeys for that context are also described in detail elsewhere.



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**Figure 3.** Decentralized biobanking platform user journey. The user journey map demonstrates the status quo of the patient experience with biobank donation as well as the 4 key features of the decentralized biobanking mobile app that was piloted for a large breast cancer biobank member population from January 2023 to May 2023. Each of the columns represents primary activities within the different core screens of the decentralized biobanking mobile app, which the invited participants downloaded to personal iOS and Android devices. The Biobank, Biowallet, and Profile sections are illustrated with key activities and features. The Lab section on the far right is illustrated, although the journey for the community engagement feature is outside the scope of this study and is addressed elsewhere. NFT: nonfungible token.



# Journey 1: App Onboarding and Biowallet NFT Minting Process

Upon downloading the app, users entered their name and birth date, triggering verification of biobank membership and sample

collections, with "biowallet NFT" minting, if applicable, serving as a digital representation of membership in the biobank donor community, delivering a user experience of a token-gated bridge between the user's app and specimen data, if available (Figure 4).

**Figure 4.** Opening a biowallet—simulation of token-gated specimen access. The process of opening a biowallet required participants to enter their name and date of birth, triggering the system to match participants to corresponding members in the biobank (Breast Disease Research Repository). Once specimen status was established, biowallet nonfungible tokens were minted, specimens were linked to the account, and email notifications indicated to participants that their biowallet was available.



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#### Simulated Token Gating Workflows

Once users entered their name and date of birth into the decentralized biobanking app, a manual, coordinated effort involving biobank personnel and authorized study team members verified each user's biobank consent and matched donors to their respective biospecimens via a unique anonymous study ID linked to a Firebase (Google) unique ID associated with their decentralized biobanking app account. During this process, study team members would also mint a unique biowallet token for each verified donor with specimens. These tokens were held in a custodial wallet, but each token identifier was linked to donor records within the Amazon Aurora database to establish a second privacy-preserving mechanism for data linkage.

Firebase established the functional linkage to allow for proper access control and permission management within the app for this pilot, whereas the biowallet NFTs and the act of claiming were representative as a proof of concept as well as a token of appreciation for participating donors. This decision was made to limit excess complexity related to using web3 technologies as a barrier to participation for this population while providing a comprehensible introduction to the concept of NFTs for establishing relationships between donors and their samples. Our aim was to ensure that donors were not excluded from engaging with the platform based on the extent of their blockchain expertise.

Various criteria for minting Biowallet tokens were considered for entire pilot and biobank deployment. Using variation in token minting costs observed throughout the pilot study to model minimum, average, and maximum costs (US \$1.84, US \$4.51, and US \$11.23, respectively), the selected model, minting tokens for all 272 pilot participants coenrolled in the biobank with one or more specimens collected, was projected to cost US \$1226.72 (SD US \$41.91; range US \$500.48-\$3054.56, Figure 5A, left). Extended entire biobank implementation, this model is projected to cost US \$17,769.40 (SD US \$159.52; range US \$7265.62-\$44,229.27; Figure 5A, right). Other models, such as specimen distribution to a research protocol or biobank membership were also considered.

**Figure 5.** Nonfungible token (NFT) minting costs and calculations for the breast cancer biobank pilot. (A) Pilot implementation—comparison of biowallet token minting criteria for the total cost of pilot deployment. Cost analysis used variation in token minting costs observed throughout the pilot study to model minimum, average, and maximum costs (US \$1.84, US \$4.51, and US \$11.23, respectively). \*Selected token minting criteria for the decentralized biobanking pilot. (B) Transaction costs in US \$ and ether (ETH) are illustrated for 151 NFTs minted during the decentralized biobanking pilot. (C) Timeline mapping variable cost of biowallet minting events and cumulative costs of minting 151 NFT biowallet tokens throughout the decentralized biobanking pilot.



### **Token Minting Costs**

The cost of deployment of the biowallet NFT protocol on Ethereum was US \$223.52. A total of 151 biowallet tokens were minted for US \$680.49 at an average of US \$4.51 per token (SD US \$2.54; range US \$1.84-\$11.23; Figure 5B. Biowallet tokens could be requested by decentralized biobanking pilot

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participants who downloaded the app and had one or more

specimens collected (148/405, 36.5%). For context,

procurement, processing, storing, and disbursement of

biospecimens in this institutional biobanking platform costs an

estimated US \$1600 per case.

Biowallet tokens could be requested by decentralized biobanking pilot participants who downloaded the app and had one or more specimens collected (148/405, 36.5%). During the pilot, 140 total tokens were requested and minted for eligible participants. Minting events varied in cost based on fluctuating transaction fees and the number of participants who had requested biowallet tokens since the last token minting event. For instance, minting events ranged from US \$3.11 for minting one token, to US \$288.52 for minting 80 tokens in the first batch (Figure 5C).

### Journey 2: Biobank Orientation and Research Profile

After requesting a *biowallet*, users were directed to visit the *biobank*, where they were oriented and learned about the overall biobank inventory and activities, including demographics of the consented donor population, framed as "biobank members"; informed consent content; principal investigators; and respective biobank operations and research activities for entire specimen collection (Figure 6). We included education about research protocol development, IRB oversight, procedures for specimen allocation, and investigator- and protocol-level transactions. The biobank displayed 60,973 biospecimens from 3940 unique donors collected from February 1995 to May 2023 and updated on a regular basis, with 318 new specimens added during the pilot. The feature tracked collection and distribution totals for the biobank, with breakdowns for each specimen type (Table 3).

The "profile" allowed participants to enter clinical history and treatments relevant for research on their specimens. We also assessed research interests, privacy preferences, engagement interest, and willingness to donate additional specimens to scientists as needed. In total, 37.8% (153/405) of the app users completed one or more portions of the profile, including 37.1% (134/361) of the biobank members. The profile also displayed the random "Private ID" number, which enabled users to remain deidentified while linking to their respective specimens. During the pilot, we experimented with the naming conventions, location, and order of presentation of biobank and profile features to assess impact on participants' understanding of the biobank environment, affordances, constraints, and opportunities presented by the decentralized biobanking platform.

Nearly all participants who filled out the research profile (151/153, 98.7%) added one or more clinical details (eg, familial history of breast cancer; Multimedia Appendix 6). Profiles were completed by 39.9% (59/148) of the participants with samples, collectively annotating 886 specimens, including 760 (85.8%) available for future use, 36 (4.1%) "on hold" for a designated protocol, and 90 (10.2%) that were distributed for research, with information that was not contained within the institutional biobank database. In addition, participants added preferences regarding specimen use, willingness to provide further data and specimen donations, and future research engagement.

**Figure 6.** Biobank orientation journey, illustrating the biobank screen and user workflow introducing app users to biobank processes, what it means to be a biobank member, and regularly updated snapshots of investigator activities, protocols, and specimen allocations, at the level of the overall bank. The biobank also linked to participant's personal research profile, where they could provide key clinical details, interests, and preferences related to research on their specimens.





Table 3. Decentralized biobanking pilot population, app user and token claiming overview.

Pilot population	App users, n (%) <sup>a</sup>	Token claimed, n (%) <sup>b</sup>
Total (N=1080)	405 (37.5)	130 (12.04)
Biobank members (n=930) <sup>c</sup>	361 (38.82)	128 (13.76)
Biobank members with specimens (n=272) <sup>d</sup>	148 (54.41)	125 (46)
Collected specimens (n=3904) <sup>d</sup>	2133 (54.64)	1812 (46.41)
Biobank members with specimens in use (n=165) <sup>d,e</sup>	88 (53.33)	74 (44.85)
Fresh (n=90)	46 (51.11)	40 (44.44)
Frozen (n=100)	50 (50)	40 (40)
Specimens in use (n=377) <sup>d,e</sup>	202 (53.58)	177 (46.95)
Fresh (n=195)	104 (53.33)	95 (48.72)
Frozen (n=182)	98 (53.85)	82 (45.05)
Number of donors with specimens available (n=242) <sup>d</sup>	132 (54.55)	110 (45.45)
Breast (n=147)	81 (55.1)	67 (45.58)
Blood (n=185)	97 (52.43)	82 (44.32)
Urine (n=166)	91 (54.82)	80 (48.19)
Specimens available (n=3309) <sup>d</sup>	1757 (53.1)	1522 (46)
Breast (n=345)	205 (59.42)	178 (51.59)
Blood (n=2172)	1145 (52.72)	988 (45.55)
Urine (n=783)	406 (51.85)	355 (45.34)

<sup>a</sup>Specimen values and donor counts for all app engaged participants with specimens collected.

<sup>b</sup>Specimen values and donor counts for all app engaged participants with specimens collected who claimed biowallet tokens during the pilot study. <sup>c</sup>Donor counts for all biobank consented pilot participants.

<sup>d</sup>Specimen values and donor counts for all biobank consented pilot participants with one or more specimens collected.

<sup>e</sup>Specimens considered in use if distributed to a research protocol as of May 4, 2023. A total of 218 specimens among all pilot participants with collected specimens designated "on hold" for future research use are not shown.

#### Journey 3: Claiming and Viewing the Biowallet NFT

#### Overview

Linking app accounts to biospecimen data occurred offline and took up to 2 weeks supported by software scripts and manual processes, including checks for false mismatches (eg, due to typos). Once biowallet NFTs were available, email notifications prompted participants to log in to their decentralized biobanking app to open their biowallet and access their personalized biospecimen data. Once claimed, the "Biowallet token" appeared on the bottom of the screen with a link to view the corresponding Ethereum transaction data (Figure 7). The profile screen showed how patients could add clinical details that are not in the biobank database, making their biospecimens more readily discoverable by prospective users, reducing reliance on third-party chart review during study planning. The biowallet NFT signified membership in a collective committed to breast cancer research. Once claimed, the individual's unique biowallet NFT could be viewed via an in-app Etherscan display. The app user experience represented this process as a symbolic "token of appreciation" as a form of reciprocity for biobank contributions.



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**Figure 7.** Claiming and viewing the biowallet nonfungible token (NFT). The figure illustrates the biowallet NFT claiming process, first showing the appearance of the biowallet when the token is available to be claimed. Next, the claiming process is shown, which invites donors to "join the revolution!" Once claimed, the user's personal NFT is represented on the profile page, which is connected via a hyperlink and an in-app display of the Etherscan view of the NFT, a customized biowallet logo for the pilot, and corresponding blockchain transaction data.



#### Proof of Concept for Blockchain-Backed Biobanking App

The initial round of minting included "tokens of appreciation" for participants who were active in the demonstration phase of the app design and usability testing. The blockchain mechanism was initially tested with 4 test mints followed by minting "tokens of appreciation" for 7 demonstration phase participants. In total, 71% (5/7) of the demonstration users successfully completed the token minting claiming process, illustrating the use of the "biowallet" NFT as a representation of the individual's membership in the biobank community. After validating functional integration of the blockchain simulation, eligibility for biowallet tokens was limited to those with confirmed

specimens in the breast cancer biobank, enabling us to simulate use of the NFTs to establish token-gated access to deidentified specimen accounts.

Of 148 app users with specimens, 140 (94.6%) initiated the biowallet token minting process during the pilot. Of 140 tokens minted, 125 (89.3%) were claimed by users, with an average of 10 (median 1, IQR 1-5, range 0-100) days between token minting and token claiming (Figure 8). Compared to individuals who did not claim their biowallet, those who did claim their biowallet were slightly younger (average of 58.9, SD 10.8 vs 61.9, SD 14.3 years) and had a similar time since biobank consent (7.8, SD 5.0 years since consent for claimants vs 7.7, SD 5.3 years for nonclaimants; Multimedia Appendix 7).



**Figure 8.** Nonfungible token claiming details for the decentralized biobanking breast cancer biobank pilot. Participant engagement and timing illustrates (A) interest in biospecimen tracking and receptiveness to email notification to facilitate the token claiming process and (B) the effective reconnecting specimens to participants that occurred during the pilot as tokens were claimed. In total, 89.3% (125/140) of tokens minted for app users with specimens were claimed during the pilot. Tokens were considered unclaimed after ~2.5 months following the final token minting event. A total of 15 participants had not yet claimed their token as of the conclusion of the pilot.



Ethnography of the US cancer specimen supply chain, including engagement with industry and academic stakeholders, generated the following conservative estimates for the commercial value of cancer tissue, blood, and urine specimens with well-annotated clinical data: US \$1000 for cancer tissue, US \$500 for blood, and US \$300 for urine. Hypothetically, this equates to US \$1 million of "available" specimens being populated into app users' biowallets during the pilot. Similarly, this corresponds with a total value of approximately US \$30 million for unused specimens in frozen storage, with roughly US \$7000 in value per specimen contributor. Additional details of the scalability and economic feasibility of the proposed blockchain solution will be addressed elsewhere.

#### Journey 4: Viewing Personal Specimen Details

The "biowallet" was where participants could view details about when they consented for biobank donation (Figure 9). Once linkage between the user's app and respective biobank data was established, individuals were able to track and learn about their own biospecimens. Details available via an interactive accordion feature included their biosample collection date, sample type and medium, if and when each sample was shared for a

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particular research protocol, and similar sample-level information within the institutional database. The biowallet also includes a taxonomy of physical and digital biospecimen data types that may, in the future, be trackable by individual participants.

Further details regarding specimen distribution and availability were indicated via additional pop-ups, providing users with an opportunity to navigate to an app-based laboratory. Here app users could learn how many donors had contributed specimens of similar types, or had specimens distributed to the same research protocol. Of the biobank members using the app, 41% (148/361) had their "biowallet" populated with a total of 2113 specimens (mean 14.4, SD 12.1; range 1-84), including 1414 (66.9%) blood specimens, 419 (19.8%) urine specimens, and 296 (14%) breast tissues. In total, 70.9% (105/148) of sample holders had one or more breast tissue specimens. A total of 59.5% (88/148) had one or more specimens "in use" (mean 2.3, SD 1.6 per person; range 1-8), 40.5% (60/148) of the participants with specimens had none "in use," and 4.7% (7/148) of the participants had specimens "on hold" (mean 24.9, SD 16.3; range 10-61). Individuals who had no specimens available

received a digital biobank membership card (Figure 9, panel 2) and in-app text notifying the participant that no specimens had been located (yet), with a range of possible explanations.

Collectively, 202 of app users' specimens were "in use," including 104 (51.5%) that were delivered "fresh" the day of donation (eg, for organoid development) and 98 (4%) from a frozen collection. A total of 8.2% (174/2113) were "on hold"

for a designated study, and 83.15% (1757/2113) were "available." App users' specimens were distributed to 22 different investigators under 42 research protocols. Between February 15, 2023, and May 4, 2023, users donated 39 new specimens, which appeared on the app, 2 (5%) of which were distributed fresh. In addition, 18% (7/39) were distributed from frozen storage, and 54% (21/39) were placed "on hold" during the pilot.

**Figure 9.** Biowallet sample tracking journey. This figure illustrates the participant experience learning about their personal specimen donations via an interactive biowallet landing page. Pop-up and accordion features enabled participants to learn about their specimens, including the type, collection date, distribution to a research protocol versus availability for future use, and explore further details about similar donations and distributions.



## Participant Feedback During the Pilot

During the pilot, cognitive walk-throughs with participants illuminated areas of interest along with potential opportunities for design improvement. Key areas of excitement included seeing how their samples were used. One participant stated the following:

## I will [otherwise] never know anything about my cells.

Areas for improvement included improving technological accessibility (eg, making it iPad compatible) and clarifying the information presented (eg, "Will there be a way to learn more about each study?"). Table 4 provides a detailed thematic overview and representative quotes.



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Table 4. A thematic overview of participant feedback gathered through cognitive walk-throughs conducted during the pilot.

Theme	Pilot participant feedback
Things they liked	
Big picture	<ul> <li>"This is cool on so many levels."</li> <li>"Incredible concept to learn about."</li> <li>"There are endless possibilities and uses for this."</li> <li>"There is hope for others by giving my cells."</li> </ul>
Personalized feedback	<ul> <li>"I can't wait to see what's being done with my samples!"</li> <li>"Loved the idea of having access to my tissue info+how the two cancers are connected."</li> <li>"I will [otherwise] never know anything about my cells."</li> <li>"I'll get to see the process."</li> </ul>
Empowerment	<ul> <li>"Information I could never access before."</li> <li>"Give patients more control and information."</li> <li>"Profile preferences—great idea."</li> <li>"Private ID+Ability to connect w/ others in similar diagnosis."</li> </ul>
User interfaces and user experience	<ul> <li>"Menus under biowallet are clear+concise."</li> <li>"Look of the app."</li> <li>"Easy to navigate."</li> <li>"Easy to use/menus good."</li> <li>"Love the status of 'in use' and 'available."</li> </ul>
Things they did not like or that did not	meet their expectations
Information provided	<ul> <li>"Where are investigators that have my tissue or samples."</li> <li>"Unclear when no samples (needs explanation)."</li> <li>"Will there be a way to learn more about each study?"</li> <li>"I need a little more background before fooling around with the app."</li> </ul>
Accessibility	<ul> <li>"Needed tutorial."</li> <li>"Are there options for people who do not have email on their phone."</li> <li>"Under personal history, other than TNBC (triple negative breast cancer) other breast cancers should be identified."</li> <li>"Need to be able to use on an iPAD for larger screen."</li> <li>"Possible to put app on android tablet?"</li> <li>"Being older I'm not a techie and it takes a while."</li> </ul>
Functionality and user navigation	<ul> <li>"Biowallet should be first icon."</li> <li>"Make biobank/wallet first tab."</li> <li>"Add search bar in connect."</li> <li>"Some functions are more intuitive than others—more prompts are needed."</li> <li>"What was the purpose behind 'home' icon community samples."</li> </ul>

## Discussion

## **Principal Findings**

The decentralized biobanking pilot demonstrated the technical feasibility of design, development, and implementation of a user-friendly app to deliver transparency and engagement for donors to a well-established biospecimen collection protocol at a US academic medical center. Over 400 participants downloaded and tested the decentralized biobanking app during the pilot, asserting interest in tracking their biospecimens, demonstrating the usability of a patient interface for institutional biobanking data. "Biowallet" tokens (ERC-721) were minted for app users with confirmed specimens, and 89.3% (125/140) successfully claimed their NFTs on the app, with over half (72/125, 57.6%) of the population achieving the task within 1 day of token minting.

Pilot participants' biowallet token claiming process symbolically asserted their right to know what happens to their inherently unique biospecimens, to which they are immutably linked via a nontransferable, one-of-a-kind relationship. The user experience simulated an NFT-gated process, functionally reconnecting app users to >1800 deidentified specimens, providing visibility of affiliated community members and related research activities all while preserving confidentiality. Critically, this was achievable with data architecture, interfaces, and workflows that maintained compliance with preexisting deidentification standards and specimen collection and distribution protocols.

Similarly, we showed how integration with institutional biobank infrastructure can passively provide transparency for donors without imposing undue burdens on investigators or relying on individual research programs to sustain community engagement. Transparency in biobanking has the potential to rebuild donor

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trust in biobanks and improve accountability in biomedical research [27-29]. Consequently, transparency may be a driver to improve biobank donations, particularly among communities with historically rooted distrust of biomedical research [30,31]. The decentralized biobanking framework also allowed for the retrospective and prospective onboarding of donors, demonstrating the potential to convert existing biobanks to a progressively decentralized, patient-centered model.

Minting biowallet NFTs averaged US \$4.51 (SD US \$2.54; range US \$1.84-\$11.23) per token, with a projected total cost of US \$17,769.40 (SD US \$159.52) for all biobank members with specimens. Importantly, a 1-time minting expense of <US \$5 per patient may be considered marginal, especially in view of the cost of specimen procurement, storage, and distribution. A workshop on biospecimen economics found the cost of operating a large biobank to be US \$861 per patient [32]. The value of the specimens themselves is also substantial relative to minting expenses; academic researchers may pay up to US \$200 per sample, whereas commercial entities may pay up to US \$20,000 per sample [32]. When biospecimens are converted into living models (eg, organoids), the expenses of both processing and development increase, but the value is multiplied several-fold as 1-mL aliquots of the model may cost upward of several thousand dollars per copy for academic and commercial users alike [33,34].

Importantly, we also demonstrated how empowering patients may in turn help scientists by allowing them to annotate their biospecimens with relevant data that may not be represented in the institutional biobank database or may be otherwise not directly available to prospective or current specimen users. Over 37% (150/405) of the participants demonstrated how longitudinal donor involvement might be leveraged to improve biosample curation and discoverability, creating opportunities to enrich research; link siloed datasets; and drive more efficient, community-driven use of biobank resources. Enhanced annotation of biospecimens with clinical data reflects increasing demand among the biobanking community to gain more contextual biospecimen data [35]. Project LUNGBANK is an example of ongoing efforts to provide more comprehensive clinical data to enrich biospecimens [36]. In LUNGBANK, clinically relevant findings collected through manual chart review of patient medical records were used to annotate biospecimens [36]. For the decentralized biobanking app, more intuitive, strategic placement of the profile feature and improved framing of its functionality and benefits for donors and scientists will be essential to optimize the utility of this feature.

Although relatively limited in functionality compared to the NFT framework advanced in our preclinical prototypes, the blockchain aspect of the piloted app was significant for several reasons. First, it represents the first time that most of our participants, including several octogenarians, had ever interacted with blockchain technologies. Second, persistence in overcoming the friction of onboarding related to the blockchain elements served as further evidence of the high value that patients place on tracking their specimens, to the point that they were willing to participate in a cumbersome, multistage process that, in some cases, took weeks. Third, the blockchain aspect of the piloted app remains a permanent, institution-agnostic

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record of the relationship between specific donors and their respective biospecimens, highlighting the potential to reunite individuals with these deeply personal assets, with yet unmet potential for assurances of trust and shared rewards of research. Finally, the biowallet NFT represents a foundational gateway to a composable and progressively decentralized biobanking ecosystem. That which starts with 1 biowallet token per participant who contributes specimens may be built upon in a stepwise manner, forging an interconnected overlay network that recognizes and unlocks value across today's siloed biobank landscape.

#### Limitations

The pilot relied on manual data workflows to enable demonstration of a functional decentralized biobanking platform without requiring full integration of the patient-facing apps with the enterprise system. Such manual workflows are impractical for sustainability and scalability. The exponential growth of health information and advanced computing makes workflow automation increasingly fundamental [37]. Thus, application programming interface (API) integration and automated processes will be necessary for future apps. In view of the volume of requests received during the pilot as well as interest in expanding the program to other institutional biobanks, hospital leadership approved API development to facilitate such integrations for the next stages of the pilot program. In addition to being essential for technical feasibility, this approval was critical as it demonstrated that the manual aspects of our workflows were not material for the acceptability of our strategy for reconnecting donors with their deidentified specimens within institutional biobanks.

Notifications based on in-app activity event triggers were not fully implemented during the pilot, and a number of manual steps were required, including substantial coordination across study team members and email-based messaging to notify participants about critical changes such as token availability and biosample status updates. Automated communications must be incorporated into future pilots with accommodation for a range of patient preferences and values. Subsequent development will also make a web-based version to avoid exclusion of participants for whom smartphone apps may not be preferred or accessible, particularly with respect to age and household income [38].

Furthermore, the piloted app interfaces and user journeys were designed for patient users, whereas engagement with physicians, biobankers, and scientists occurred via alternative channels (eg, email and institutional platforms). This limited the functionality and value within the app as research content was high level, limited to the scope of the biobank database. Ongoing work is advancing real-world applications of decentralized biobanking for scientists and other stakeholders within the NFT digital twin ecosystem. Inclusion of professional users directly within the decentralized biobanking platform will be key for unlocking the ongoing value and network effects of our framework.

Regarding the blockchain elements, the high and highly variable costs of token mints on Ethereum illustrate the importance of more cost-efficient strategies, such as layer-2 solutions, for full-scale implementation. Importantly, our focus on the primary

NFT digital twin framework centers the stakeholders and their relational mappings within the ecosystem. This allowed us to focus on tokenizing the individual participants, in this case, 1 token per biospecimen donor rather than 1 per biospecimen, which would have increased costs 10- to 20-fold. This was sensible, especially considering limitations on functionality of a specimen-representing NFT in the setting of our pilot app; that is, it was not necessary to tokenize specimens for implementing transparency and our study did not provide additional permissions relevant to potential tokenized specimen utility for shared governance or profit sharing regarding the underlying biobank assets. Moreover, ensuring the long-term economic sustainability of biobanks is already a salient concern, with high costs driven by human resources, equipment, and sample handling [39-41]. Cost-effectiveness will be essential for broader adoption of decentralized biobanking technology, and blockchain solutions in themselves must be complemented with social, cultural, and legal innovations to enact meaningful progress [40,42,43].

In addition, NFTs were minted for individual participants, and personal NFTs were rendered via an in-app Etherscan display, although the token-gated aspect of the app leveraged Firebase Unique Identifiers rather than NFTs to minimize complexity and potential points of failure. Simulation of the user interface and user experience of blockchain interactions was necessary to overcome barriers to onboarding inherent to contemporary avoidances and constraints of decentralized apps, particularly as our patient population was older and almost exclusively from non-digital native generations and many were actively grappling with cancer. This was especially critical given concurrent educational barriers surrounding the simultaneous introduction of patients to both biobanking and blockchain for the first time. For example, a knowledge assessment on biobanking administered to biospecimen donors found that approximately half of all questions were answered either incorrectly or with "I don't know." Similarly, most patients we engaged with during app design, development, and pilot-testing were not familiar with the term "biobank," illustrating the fundamental challenge of delivering a patient-friendly biobanking app. These findings underscore the gap between providing information during the prospective informed consent process and achieving true comprehension via enduring transparency and ongoing feedback [44,45]. To this end, we prioritized orientation to biobanking and developed lexicon and app design features that make data within biobank databases accessible to donors via a decentralized biobanking platform that coheres with the ethos of decentralization at its core.

implementations, For future we aim to advance blockchain-backed solutions with seamless onboarding experiences through the exploration of newer standards such as ERC-4337 for account abstraction, which awards the programmable flexibility to remove complex barriers to entry such as the current requirement for users to create their own third-party wallets to interact with the decentralized app. Advancement of these technologies may provide seamless integration of decentralized biobanking platforms with both institutional databases and blockchain overlay networks, with future potential to unite participants, specimens, and scientists

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across various institutions. Transparency and engagement in biospecimen management is a necessary step toward institutional transformation to achieve community partnership, shared decisions, and progressive democratization. More research is needed to test our hypotheses about the role of blockchain technology in a comprehensive and universal decentralized biobanking solution [46].

The success of our pilot inspired potential to revolutionize biobanking via a decentralized platform but also revealed challenges and limitations for current biospecimen collection workflows, standard operating procedures, and data management strategies [47]. Implementation of transparency for past, present, and future biospecimen collection and distribution will require innovative system designs that overcome idiosyncrasies of individual biobank databases coupled with incentive structures and governance models that promote trust and ensure that biobanking practice optimizes individual and collective interests for patients, scientists, and society [48-50]. While the principles and techniques demonstrated in this study theoretically translate to any other research biobanking context, our technical approach must be validated across a variety of clinical and socioeconomic settings, institutional and regional cultures, and biomedical research contexts.

Critically, this pilot addressed a single, disease-focused university biobank with a largely White, female, and geographically localized population. Technology acceptance must be confirmed for diverse patients, diseases, and contexts [51]. Both iOS and Android users were included, yet some did not use smartphones, and others preferred not to download apps. We have since developed a web-based platform, expanding availability to anyone with internet access, although disparities persist. Ongoing research is exploring the impact of age, race, time elapsed since surgery, and stage of disease on technology acceptability, as well as how to optimize recruitment and trustworthiness for underserved populations [51,52]. Current work is also addressing populations such as those with prostate and lung cancer in which male individuals are more heavily represented, and we have incorporated socioeconomic assessments into our data collection to ensure that we advance solutions that are broadly accessible and applicable, especially for economically and educationally marginalized groups.

Looking ahead beyond feasibility, the practical implementation of scalable, decentralized biobanking solutions requires technical enhancements to overcome the discussed challenges and limitations of this pilot. User interfaces must prioritize usability, comprehensibility, and accessibility by leveraging new standards for account abstraction to reduce the complexity of interacting with blockchain components in our solution. Similarly, ongoing research should inform iterative refinement of different strategies for effective presentation of research-related information curated for diverse patient populations. Efforts toward long-term sustainability should include app cost optimization techniques such as deployment on layer-2 networks for major reductions in blockchain transaction costs and the automation of key workflows and processes through proper integration with institutional software and databases. Because each new environment can be quite nuanced, the application of our technology to new use cases will still require custom

configurations when onboarding, but some of these efforts may be streamlined by standardizing integration patterns with widely used laboratory information management systems and research tools.

Finally, our privacy-by-design approach requires due diligence in execution to mitigate risks to users. Abiding by security best practices in development and thorough vulnerability testing are essential measures in protecting against critical security risks. Intentional disaster recovery plans with detailed incident response protocols for specific events are important for prompt threat containment, recovery of system resources with minimal downtime, and communication to affected users and stakeholders. Proactive preparation to set up comprehensive monitoring, automated backups with manual snapshots across system resources and environments, and pre-emptively programmed functionality for pausing and redeploying compromised system components or deployed smart contracts are crucial for the effective execution of incident response plans.

## Conclusions

This pilot demonstrates the technical capacity and resources for a functional decentralized biobanking software app that empowers patients to track specimens donated to a real-world breast cancer research biobank with a novel implementation of blockchain technology. The patient-friendly mobile app renders institutional biobank inventory and transactions in a meaningful, personalized biowallet context, providing a rewarding user experience. We demonstrated the app's readiness for API integrations, which would allow for sustainable and scalable implementation across multiple biobank protocols by seamlessly and dynamically displaying biobanking activities to donors. Pilot participants successfully claimed NFTs within the app, restoring provenance for personal biospecimens and related data. This advancement introduces a new paradigm for ethical biobanking, fostering donor engagement and inclusion in personalized research networks appropriate to contemporary learning health systems and mobile computing capabilities while maintaining deidentification and compliance with established protocols.

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## **Data Availability**

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

## **Conflicts of Interest**

WS, RCM, JK, MM, and MG are shareholders in de-bi, co, a company created to advance decentralized biobanking technology to empower patients, accelerate science, and realize precision medicine, and ME is a consultant thereof. The pilot study described in this paper was not sponsored by de-bi, co; however, detailed conflict of interest disclosures were incorporated into all informed consent forms and quality improvement procedures, and verbal disclosures were made throughout pilot engagement. Conflicts of interest were disclosed in accordance with the pilot protocol under Conflict Management Plans, and the principal investigator on the decentralized biobanking app pilot protocol was nonconflicted.

### Multimedia Appendix 1

Architecture details of the deployed cloud infrastructure, encompassing networking setup, front-end and back-end deployment configurations, database architecture, continuous integration and continuous delivery processes, domain management, and monitoring systems.

[DOCX File, 17 KB - bioinform\_v6i1e70463\_app1.docx]

Multimedia Appendix 2



Workflow for the de-bi pilot, including consent for the pilot, downloading the app, and minting biowallet tokens to link personal biospecimen data to their biowallet.

[DOCX File, 179 KB - bioinform\_v6i1e70463\_app2.docx]

## Multimedia Appendix 3

Decentralized biobanking pilot study participation rates among eligible biobank members by age, race, and time from initial biobank consent.

[DOCX File, 31 KB - bioinform\_v6i1e70463\_app3.docx ]

## Multimedia Appendix 4

Decentralized biobanking pilot study and breast cancer biobank age distributions, and comparison of pilot enrollment rates by time from initial biobank consent.

[DOCX File, 136 KB - bioinform\_v6i1e70463\_app4.docx]

Multimedia Appendix 5

Demographics of the breast cancer biobank and decentralized biobanking pilot populations. [DOCX File , 35 KB - bioinform v6i1e70463 app5.docx ]

## Multimedia Appendix 6

Decentralized biobanking pilot participant age ranges and engagement metrics among app onboarded participants by sample collection status, including age, biobank membership, years since initial biobank consent, and research profile completion rates. [DOCX File, 2726 KB - bioinform\_v6i1e70463\_app6.docx]

Multimedia Appendix 7

Characteristics of pilot participants who did versus did not complete research profiles and claim biowallet tokens on decentralized biobanking app.

[DOCX File, 15 KB - bioinform\_v6i1e70463\_app7.docx]

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## Abbreviations

**API:** application programming interface **BDRR:** Breast Disease Research Repository **IRB:** institutional review board **NFT:** nonfungible token

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# Designing a Finite Element Model to Determine the Different Fixation Positions of Tracheal Catheters in the Oral Cavity for Minimizing the Risk of Oral Mucosal Pressure Injury: Comparison Study

Zhiwei Wang<sup>1,2</sup>, MSc; Zhenghui Dong<sup>1</sup>, MSc; Xiaoyan He<sup>2</sup>, BSc; ZhenZhen Tao<sup>3</sup>, MSc; Jinfang QI<sup>1</sup>, MSc; Yatian Zhang<sup>4</sup>, MSc; Xian Ma<sup>4</sup>, MSc

<sup>1</sup>The Sixth Affiliated Hospital of Xinjiang Medical University, No. 39 Wuxing South Road, Tianshan District, Urumqi, Xinjiang, China

<sup>2</sup>Department of Critical Care Medicine, Qinghai Fifth People's Hospital, Xining, China

<sup>3</sup>Emergency Department, The Fourth Affiliated Hospital of Xinjiang Medical University, Xin Jiang, China

<sup>4</sup>School of Nursing, Xinjiang Medical University, Xin Jiang, China

## **Corresponding Author:**

Zhenghui Dong, MSc

The Sixth Affiliated Hospital of Xinjiang Medical University, No. 39 Wuxing South Road, Tianshan District, Urumqi, Xinjiang, China

# Abstract

**Background:** Despite being an important life-saving medical device to ensure smooth breathing in critically ill patients, the tracheal tube causes damage to the oral mucosa of patients during use, which increases not only the pain but also the risk of infection.

**Objective:** This study aimed to establish finite element models for different fixation positions of tracheal catheters in the oral cavity to identify the optimal fixation position that minimizes the risk of oral mucosal pressure injury.

**Methods:** Computed tomography data of the head and face from healthy male subjects were selected, and a 3D finite element model was created using Mimics 21 and Geomagic Wrap 2021 software. A pressure sensor was used to measure the actual pressure exerted by the oral soft tissue on the upper and lower lips, as well as the left and right mouth corners of the tracheal catheter. The generated model was imported into Ansys Workbench 22.0 software, where all materials were assigned appropriate values, and boundary conditions were established. Vertical loads of 2.6 N and 3.43 N were applied to the upper and lower lips, while horizontal loads of 1.76 N and 1.82 N were applied to the left and right corners of the mouth, respectively, to observe the stress distribution characteristics of the skin, mucosa, and muscle tissue in four fixation areas.

**Results:** The mean (SD) equivalent stress and shear stress of the skin and mucosal tissues were the lowest in the left mouth corner (28.42 [0.65] kPa and 6.58 [0.16] kPa, respectively) and progressively increased in the right mouth corner (30.72 [0.98] kPa and 7.05 [0.32] kPa, respectively), upper lip (35.20 [0.99] kPa and 7.70 [0.17] kPa, respectively), and lower lip (41.79 [0.48] kPa and 10.02 [0.44] kPa, respectively; P<.001 for both stresses). The equivalent stress and shear stress of the muscle tissue were the lowest in the right mouth angle (34.35 [0.52] kPa and 5.69 [0.29] kPa, respectively) and progressively increased in the left mouth corner (35.64 [1.18] kPa and 5.74 [0.30] kPa, respectively), upper lip (43.17 [0.58] kPa and 8.91 [0.55] kPa, respectively), and lower lip (43.17 [0.58] kPa and 11.96 [0.50] kPa, respectively; P<.001 for both stresses). The equivalent stresses). The equivalent stress and shear stress and shear stress of the muscle tissue were the lowest lip (43.17 [0.58] kPa and 5.74 [0.30] kPa, respectively), upper lip (43.17 [0.58] kPa and 8.91 [0.55] kPa, respectively), and lower lip (43.17 [0.58] kPa and 11.96 [0.50] kPa, respectively; P<.001 for both stresses). The equivalent stress and shear stress of muscle tissues were significantly greater than those of skin and mucosal tissues in the four fixed positions, and the difference was statistically significant (P<.05).

**Conclusions:** Fixation of the tracheal catheter at the left and right oral corners results in the lowest equivalent and shear stresses, while the lower lip exhibited the highest stresses. We recommend minimizing the contact time and area of the lower lip during tracheal catheter fixation, and to alternately replace the contact area at the left and right oral corners to prevent oral mucosal pressure injuries.

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## **KEYWORDS**

tracheal catheter; fixed position; oral mucosal pressure injury; finite element; biomechanical analysis

# Introduction

The primary method of respiratory support for critically ill patients in the intensive care unit (ICU) is oral tube intubation, which ensures airway patency, increases ventilation volume, and enhances lung function. However, the use of oral tube intubation may lead to oral mucosal pressure injury (OMPI) due to excessive or prolonged pressure, friction, and shear forces [1]. OMPI can increase patient pain, elevate the risk of infection, impose a financial burden on health care, increase staff workload, and even result in medical disputes. The incidence of OMPI in patients in the ICU ranges from 2.95% to 49.2%, with different fixation positions and methods of tracheal catheterization influencing its occurrence [2]. While numerous factors contribute to OMPI, including patient-related factors, physiological conditions, the use of specific medications, and nursing-related aspects, there are limited reports addressing the mechanical factors that cause OMPI [3-5]. The International Guidelines for the Clinical Prevention and Treatment of Stress Injuries suggest that finite element models can be employed to evaluate mechanical factors by assessing stress distribution characteristics within tissue structures and predicting the risk of cellular and tissue damage [6].

The purposes of this study were to use the finite element theory contact algorithm to simulate and analyze the compression process of the oral soft tissue when the endotracheal tube is fixed in different fixed positions in the oral cavity, and to explore the stress distribution characteristics of the oral soft tissue under the force of the endotracheal tube. This would help to more realistically and accurately evaluate the actual force on the oral soft tissue structure and to clarify the reasonable fixed position of the endotracheal tube when it is fixed in the oral cavity, so as to prevent the occurrence of OMPI.

# Methods

## **Finite Element Model**

A finite element model of the tracheal catheter positioned at various locations within the mouth was established. The selected participant for the head and facial computed tomography scan was a 28-year-old male volunteer with a normal BMI, measuring 175 cm in height and weighing 72 kg. A total of 512 images, each with a thickness of 0.625 mm, were obtained. The DICOM format data were imported into the 3D reconstruction software Mimics (version 21.0; Materialise) and Geomagic Wrap (version 2021; Raindrop) for model fitting and structural segmentation, respectively. A resistive film pressure sensor was employed to measure the actual pressure exerted by the tracheal catheter in different areas of the patient's mouth, with each measurement being repeated 100 times to calculate an average value using the gravitational formula. Subsequently, using the measured pressures from solid models as the input data, the Ansys software (version 22.0; ANSYS) was used to import the optimized model, define material properties, remesh the model, and generate an accurate finite element model to conduct finite element analysis based on the defined elastic modulus, Poisson ratio, boundary conditions, and simulated loads for various tissues (skin mucosa and muscle tissue), as well as the tracheal catheter and bone [7,8]. The properties of each material are shown in Table 1; the skin and mucosa are set as nonlinear materials, and the bones are set as isotropic materials

Material	Modulus of elasticity (Mpa)	Young modulus (Mpa)	Shear modulus (Mpa)	Poisson ratio (%)
Tracheal catheter	3	a	1500	0.38
Skeleton	13,400	18,000	—	0.25
Muscle	0.045	0.25	—	0.49
Cutaneous mucosa	_	3	2	0.49

Table . Material properties of the finite element model.

<sup>a</sup>not available.

## **Ethical Considerations**

This study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Xinjiang Medical University (approval number: LFYLLSC20220905-01). All procedures in this study are in line with the ethical standards of the Human Experiments Responsible Committee (Institution and State) and the Declaration of Helsinki.

## **Setting of Boundary Conditions**

In this study, four models representing the upper lip, lower lip, left mouth corner, and right mouth corner were established. The fixed support areas of the models were designated as the top and bottom, allowing for rigid support to be simulated through fixed constraints. A sliding friction contact was implemented between the lip and the tracheal tube, with a friction coefficient set at 1 [9]. A bonded connection was established among the

skin, mucous membrane, and muscle tissue. The model accounted for the effects of gravity in a vertical downward direction, with a gravitational acceleration of 9.8 m/s<sup>2</sup>.

### **Measurement Indicators**

The equivalent stress and shear stress of the skin mucosa and muscle tissue were measured under different fixed positions of the tracheal catheter within the mouth. The stress distribution characteristics of the pressure injury model were analyzed for the fixed positions of the upper lip, lower lip, left mouth corner, and right mouth corner. The stress measurement for each part was conducted 10 times to obtain an average value.

## **Statistical Analysis**

Statistical analysis was performed using SPSS (version 25.0; IBM Corp). Measurement data were expressed as mean (SD). One-way ANOVA was employed for comparisons between

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groups, while the t test was used for intragroup comparisons. A P value of less than .05 was considered statistically significant.

# Results

### **Model Verification**

A finite element model of the tracheal catheter was established with a total of 14,635 nodes and 8267 elements at various fixed positions within the oral cavity. This model included the ilium of the upper and lower jaws, as well as the skin, mucosa, and muscle tissues of the oral cavity. The extreme values and distribution trends of stress at the mouth angle and lower lip were consistent with the findings of Amrani et al [9], indicating the effectiveness of the modeling approach employed in this study.

#### **Equivalent Stress**

The equivalent stress of the skin mucosa was the lowest in the left mouth corner, and then progressively increased in the right mouth corner, upper lip, and lower lip. In contrast, the equivalent stress of muscle tissue was the highest in the right mouth corner, followed by the left mouth corner, upper lip, and lower lip. Notably, the equivalent stress of muscle tissue was significantly greater than that of the skin mucosal tissue (P<.001; Table 2).

Table . Comparison of equivalent stress results between skin mucosa and muscle tissue (kPa, n=10).

Position	Cutaneous mucosa, mean (SD)	Muscle tissue, mean (SD)	$t  ext{ test } (df)$	<i>P</i> value	95% CI
Upper lip	35.20 (0.99)	43.59 (0.84)	-20.371 (9)	<.001	-9.252 to -7.522
Lower lip	41.82 (0.92)	48.35 (0.92)	-15.927 (9)	<.001	-7.389 to -5.667
Left mouth corner	28.42 (0.65)	35.64 (1.18)	-16.924 (9)	<.001	-8.118 to -6.325
Right mouth corner	30.72 (0.99)	34.34 (0.38)	-10.789 (9)	<.001	-3.420 to -2.912
<i>F</i> <sub>1</sub> -score	430.942	573.406	N/A <sup>a</sup>	N/A	N/A
<i>P</i> value	<.001	<.001	N/A	N/A	N/A

<sup>a</sup>not available.

### **Shear Stress**

The shear stress of the skin mucosal tissue was the lowest in the left mouth corner, and progressively increased in the right mouth corner, upper lip, and lower lip. In contrast, the shear stress of the muscle tissue was the lowest in the right mouth corner, and progressively increased in the left mouth corner, upper lip, and lower lip. At the four fixed positions, the shear stress of the left and right oral muscle tissue was lower than that of the skin mucosa, while the shear stress of the upper and lower lip muscle tissue was higher than that of the skin mucosal tissue (P<.005; Table 3)

Table . Comparison of shear stress results between the skin mucosa and muscle tissue (kPa, n=10)

Position	Cutaneous mucosa, mean (SD)	Muscle tissue, mean (SD)	$t  ext{ test } (df)$	<i>P</i> value	95% CI
Upper lip	7.60 (0.21)	8.91 (0.39)	-8.959 (9)	<.001	-1.613 to -0.998
Lower lip	10.17 (0.16)	11.69 (0.78)	-5.057 (9)	<.001	-2.145 to -0.882
Left mouth corner	6.58 (0.17)	5.79 (0.33)	6.799 (9)	.001	0.543 to 1.030
Right mouth corner	7.45 (0.36)	5.69 (0.29)	11.972 (9)	<.001	1.450 to 2.068
<i>F</i> <sub>1</sub> -score	244.363	126.411	N/A <sup>a</sup>	N/A	N/A
P value	<.001	<.001	N/A	N/A	N/A

<sup>a</sup>not available.

## Comparison of Equivalent Stress and Shear Stress in the Mucosal Tissue of the Upper and Lower Lips and the Left and Right Mouth Corners

Equivalent stress was found to be lower in the upper lip compared to the lower lip, and the left mouth corner exhibited

lower stress than the right mouth corner (P<.001; Table 4-5). In terms of shear stress, the upper lip also showed significantly lower values than the lower lip (P<.001;Table5), while the left mouth corner had lower shear stress than the right mouth corner (P<.001; Table 5).



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Table . Comparison of the results of equivalent stress and shear force in the left and right mouth corners (kPa, n=10).

Position	Left side mouth corner, mean (SD)	Right side mouth cor- ner, mean (SD)	t test (df)	<i>P</i> value	95% CI
Equivalent stress	28.42 (0.65)	30.72 (0.99)	-6.160 (9)	<.001	-3.094 to -1.520
Shear stress	6.58 (0.17)	7.45 (0.36)	-6.984 (9)	<.001	-1.125 to -0.605

Table . Comparison of the results of equivalent stress and shear force in the skin mucosal tissue of the upper and lower lip (kPa, n=10).

Position	Upper lip, mean (SD)	Lower lip, mean (SD)	t test (df)	P value	95% CI
Equivalent stress	35.20 (0.99)	41.82 (0.92)	-15.472 (9)	<.001	-7.519 to 5.721
Shear stress	7.60 (0.21)	10.17 (0.16)	-16.769 (9)	<.001	-2.931 to -2.279

## Comparison of Equivalent Stress and Shear Stress in the Muscle Tissue of the Upper and Lower Lips and Left and Right Mouth Corners

the right mouth corner (P=.004; Table 6). The shear stress was lower in the upper lip than in the lower lip (P<.001), and lower in the left mouth angle than in the right mouth angle (P=.298; Table 7)

The equivalent stress was the lower in the upper lip than in the lower lip (P<.001), and higher in the left mouth corner than in

 $\label{eq:comparison} \textbf{Table} \ . \ Comparison of equivalent stress and shear force results in the left and right mouth corners (kPa, n=10).$ 

Position	Left side mouth corner, mean (SD)	Right side mouth cor- ner, mean (SD)	t test ( $df$ )	<i>P</i> value	95% CI
Equivalent stress	35.64 (1.18)	34.34 (0.38)	3.308 (9)	.004	0.474 to 2.124
Shear stress	5.74 (0.30)	5.69 (0.29)	1.071 (9)	.50	-0.221 to 0.435

Table . Comparison of equivalent stress and shear force results in the muscle tissue of the upper and lower lips (kPa, n=10).

Position	Upper lip, mean (SD)	Lower lip, mean (SD)	t test (df)	P value	95% CI
Equivalent stress	43.59 (0.84)	48.35 (0.92)	-12.115 (9)	<.001	-5.587 to -3.935
Shear stress	8.91 (0.39)	11.69 (0.78)	-12.477 (9)	<.001	-3.561 to -2.545

## Stress Distribution Rules of the Four Groups of Models

The equivalent stress range of the skin mucosa and muscle tissue gradually extends from the stress center to the periphery. In this study, the application direction of the forces on the upper and lower lips is vertical, with the maximum peak values of both equivalent stress and shear stress occurring at the stress point and subsequently radiating outward in the vertical direction. Conversely, the forces applied at the left and right mouth corners are horizontal, causing the stress range to spread horizontally, with the highest stress values appearing at the direct contact point between the tracheal catheter and the mucosal tissue. The distribution of shear stress is centered on the soft tissue stress point and encompasses the entire lip, mandibular region, and both sides of the face, resulting in a broader range of stress. The equivalent stress and shear stress at the mouth corners are significantly lower than those at the upper and lower lips.

To explore the underlying reasons, when the tracheal catheter is fixed at the corner of the mouth, it makes contact with the corner, the upper lip, and the lower lip. The pressure, shear force, and friction generated by this contact are dispersed across the three contact surfaces of the mouth and the upper and lower lips. The contact surface between the tracheal tube and the upper and lower lips serves as the primary stress point, leading to greater stress values at the upper and lower lips compared to the corners of the mouth, with the lower lip experiencing the highest stress. The results of the finite element analysis indicate that the stress at the corners of the mouth is lower, followed by that at the upper lip (Figures 1-4).



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Figure 1. Mimics21.0 software was used to reconstruct the patient's head, face and oral tissues in 3D with an interval of 0.25 mm, and the contour range of the skin mucosa and muscle tissue was constructed through the thresholds of different tissues.



**Figure 2.** The probe contour line is used to redraw the contour line of the model, so that the surface pieces are more extensible and the concave and convex surfaces are reduced. The structural patch trims the model patch again to make the patch smoother and smoother, which is consistent with the characteristics of the skin tissue. Construct grids, and optimize and adjust all patch nodes and elements. Finally, the fitting surface constructs a model that is similar to the actual oral and facial features of the human body.





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**Figure 3.** (1a-1d) Equivalent stress nephogram of two tissues at 4 fixed locations: upper lip, lower lip, left mouth corner, and right mouth corner. (2a-2d) Equivalent stress nephogram of the muscle tissue of the upper lip, lower lip, left mouth corner, and right mouth corner.



Figure 4. Shear stress nephogram of two tissues at 4 fixed locations. (1a-1d) Shear stress nephogram of the mucosa tissue of the upper lip, lower lip, left mouth corner, and right mouth corner. (2a-2d) Shear stress nephogram of the muscle tissue of the upper lip, lower lip, left mouth corner, and right mouth corner.



# Discussion

The results of this study showed that when the tracheal tube was in contact with the lower lip, the equivalent stress and shear stress values of muscle tissue and mucosal tissue were the largest, followed by the upper lip, and the left and right mouth angles were lower than those of the upper and lower lip. Finite element analysis modeling is a powerful bioengineering technique employed to assess tissue loading, encompassing the interactions between tissues, objects, and medical devices. This numerical method effectively addresses mechanical problems [10]. It enables rapid and accurate stress-strain analysis of the structure, shape, load, and mechanical properties of materials in any given model [11]. Moreover, finite element analysis objectively and accurately reflects the distribution of stress, strain, and deformation, and has gained widespread application in oral biomechanics research in recent years [12].

The tracheal catheter is a critical instrument for mechanical ventilator-assisted therapy in patients in the ICU; however, the

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catheter itself and improper fixation methods may lead to OMPI [6]. From a biomechanical perspective, the OMPI associated with tracheal catheters primarily results from vertical pressure, shear forces, and friction [13]. Continuous mechanical loading on soft tissues is the main contributor to stress injuries, typically occurring at bony prominences or in areas contacting medical devices. When skin or deep tissue deformation persists for a certain duration owing to the pressure from medical devices, pressure injuries may develop [14]. In this study, the mechanical load originated from the force exerted by the tracheal catheter on the oral soft tissue. Contact between the tracheal catheter and the oral mucosal tissue resulted in continuous pressure, leading to tissue deformation in the mucosa. Research indicates that tracheal catheters and their fixation devices are stiffer than oral soft tissues. When the mechanical properties of these instruments do not align with those of the soft tissues, deformation occurs in the latter, concentrating mechanical stress and strain at the points of direct contact, which then gradually extends to the surrounding areas [15, 16].

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Continuous vertical pressure on soft tissues is a significant factor in the occurrence of stress injuries. The incidence of OMPI correlates with the intensity and duration of pressure; the greater the pressure and the longer its application, the higher the risk of developing OMPI is [17]. Furthermore, when the tracheal tube is improperly fitted and fixed too tightly, the pressure and shear force exerted will increase [14]. Shear forces applied to deep skin tissues can obstruct capillaries, leading to localized ischemia and hypoxia, which may result in deep tissue necrosis. Consequently, damage from shear forces is often undetected in the early stages and is more challenging to heal than damage from typical wounds [13]. Friction arises from the movement between the oral mucosal tissue and the surface of the tracheal tube; while it does not directly cause OMPI, it can compromise the epidermal cuticle, leading to the shedding of the mucosal surface layer and heightened sensitivity to pressure injuries. Once the compromised oral mucosal tissue is subjected to stimuli from saliva and other secretions, the risk of pressure injury escalates. Additionally, friction raises the temperature of the local mucosal tissue, disrupts the local microenvironment, alters pH levels, and increases tissue oxygen consumption, further exacerbating tissue ischemia and heightening the risk of OMPI [16].

The magnitude of the internal mechanical load required to cause tissue damage depends on the duration of the applied force and the specific biomechanical tolerance of the stressed tissue, which is influenced by factors such as age, shape, health status, and the functional capacity of the body systems, including tissue repair ability [18]. Both high loads applied for short durations and low loads sustained over extended periods can lead to tissue damage [18-20]. Continuous loading is one of the primary contributors to this damage; it refers to loads applied over prolonged periods (ranging from a few minutes to several hours or even days), also known as quasi-static mechanical loading. Research indicates that when soft tissues come into contact with the support surfaces of medical devices, pressure and shear forces are generated between the soft tissues and these surfaces [21]. This interaction results in distortion and deformation of the soft tissues under pressure, affecting both the skin and deeper tissues (including fat, connective tissue, and muscle), leading to stress and strain within the tissues [21]. Excessive internal

stress in the tissues can disrupt intracellular material transport by damaging cellular structures (such as the cytoskeleton or plasma membrane) or by hindering the transport process itself (for example, by reducing blood perfusion, impairing lymphatic function, and affecting material transport in the interstitial space), which can ultimately result in cell death and trigger an inflammatory response. Concurrently, the emergence of endothelial cell spacing increases vascular permeability, leading to inflammatory edema, which further exacerbates the mechanical load on cells and tissues due to elevated tissue pressure, thus contributing to the development of pressure injuries [22-24].

According to the results of finite element analysis, the stress experienced by the lower lip is the highest, followed by the upper lip, with levels significantly exceeding those at the corners of the mouth. Therefore, in clinical practice, when fixing a tracheal catheter, it is advisable to select the mouth corner to maximize the contact surface area between the catheter and this region. Placing the tracheal catheter in the middle of the mouth minimizes the contact time between the catheter and the oral mucosa. Additionally, regular changes in the fixation position can help redistribute pressure, thereby reducing pressure, shear forces, and friction on the oral mucosa, ultimately lowering the risk of OMPI.

This study analyzed alterations in the stress experienced by oral soft tissue under pressure at various fixation positions of the tracheal catheter within the mouth, from a biomechanical perspective. It provides a theoretical foundation for preventing OMPI in patients with tracheal catheters in the ICU. While this study effectively simulates the biomechanical effects of contact between oral soft tissue and the tracheal catheter, it does not fully replicate the actual forces experienced by oral soft tissue in real-life situations, as the area of contact between the tracheal catheter and the oral soft tissue cannot be completely simulated. Additionally, the study included only one young adult male, which limits the generalizability of the findings. Therefore, it is essential to include participants of varying genders and ages to enhance the scientific validity of the research. Furthermore, improvements in the identification rate and curvature of the 3D grid of the model should be pursued to generate higher-quality 3D models, thereby enhancing data accuracy.

## Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

### **Conflicts of Interest**

None declared.

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## Abbreviations

**ICU:** intensivec are unit **OMPI:** oral mucosal pressure injury



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# Framework for Race-Specific Prostate Cancer Detection Using Machine Learning Through Gene Expression Data: Feature Selection Optimization Approach

David Agustriawan<sup>1\*</sup>, PhD; Adithama Mulia<sup>1\*</sup>; Marlinda Vasty Overbeek<sup>1</sup>, MSc; Vincent Kurniawan<sup>1\*</sup>; Jheno Syechlo<sup>1\*</sup>; Moeljono Widjaja<sup>1\*</sup>, PhD; Muhammad Imran Ahmad<sup>2\*</sup>, PhD

<sup>1</sup>Faculty of Engineering and Informatics, Universitas Multimedia Nusantara, Scientia Garden Jalan Boulevard Gading Serpong, Tangerang, Indonesia <sup>2</sup>Faculty of Electronic Engineering and Technology, Universiti Malaysia Perlis, Perlis, Malaysia

\*these authors contributed equally

### **Corresponding Author:**

David Agustriawan, PhD Faculty of Engineering and Informatics, Universitas Multimedia Nusantara, Scientia Garden Jalan Boulevard Gading Serpong, Tangerang, Indonesia

# Abstract

**Background:** Previous machine learning approaches for prostate cancer detection using gene expression data have shown remarkable classification accuracies. However, prior studies overlook the influence of racial diversity within the population and the importance of selecting outlier genes based on expression profiles.

**Objective:** We aim to develop a classification method for diagnosing prostate cancer using gene expression in specific populations.

**Methods:** This research uses differentially expressed gene analysis, receiver operating characteristic analysis, and MSigDB (Molecular Signature Database) verification as a feature selection framework to identify genes for constructing support vector machine models.

**Results:** Among the models evaluated, the highest observed accuracy was achieved using 139 gene features without oversampling, resulting in 98% accuracy for White patients and 97% for African American patients, based on 388 training samples and 92 testing samples. Notably, another model achieved a similarly strong performance, with 97% accuracy for White patients and 95% for African American patients, using only 9 gene features. It was trained on 374 samples and tested on 138 samples.

**Conclusions:** The findings identify a race-specific diagnosis method for prostate cancer detection using enhanced feature selection and machine learning. This approach emphasizes the potential for developing unbiased diagnostic tools in specific populations.

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## **KEYWORDS**

prostate cancer; feature selection; gene expression; race specific; classification; support vector machine; machine learning

## Introduction

## **Prostate Cancer Statistics**

Prostate cancer is the most common type of organ cancer and the second leading cause of death in the United States among men [1,2]. In 2019, over 893,660 cancer cases were recorded in the United States, with prostate cancer being over 191,930 of them, along with the 2020 estimated number of deaths caused by cancer being 321,160, of which 33,310 were prostate cancer [3-5]. This is likely caused by risk factors found in prostate cancer that include age, family history, and lifestyle. Studies have shown that Asians tend to have a lower risk of prostate cancer than Europeans and Africans due to their genetics and environmental differences [6]. This indicates racial disparity in prostate cancer, which has been extensively documented by numerous studies, with African American men having a higher risk of developing prostate cancer and facing a 2.5-fold higher mortality rate compared to European American men [7,8]. This disparity is attributed to socioeconomic and biological differences, including aggressive tumor phenotypes documented at the molecular level in African American men [9].

### **Prostate Cancer Detection Methods**

In the early 1990s, digital rectal examination was used for screening prostate cancer, which had a significant impact on prostate cancer diagnosis at the time. Digital rectal examination remains beneficial for distinguishing between benign and malignant conditions in the prostate, but it is limited by its low sensitivity and inability to detect cancer at an early stage [3,10,11]. Another screening method is the prostate-specific antigen (PSA) test. While widely used, PSA testing is

controversial due to its susceptibility to false positives, as PSA is a gland-specific biomarker rather than cancer-specific biomarker [10,12]. The lack of a reliable and robust detection method gives rise to the need for a race-based approach to detect prostate cancer.

#### Machine Learning and Support Vector Machine

In recent years, machine learning applications in health care and biotechnology have grown rapidly, driving advancements diagnostics, personalized medicine, in disease and bioinformatics [13]. In this research, support vector machines (SVMs) were selected for their remarkable performance in classification tasks in the medical field using gene expression data [14-18]. Being a supervised machine learning algorithm that is proficient at distinguishing between 2 sample classes, SVM works by creating a hyperplane that optimally separates sample classes. SVM transforms class data into a higher-dimensional space to effectively identify complex, nonlinear relationships. This makes SVM especially powerful in cases with small sample sizes and high-dimensional data, such as gene expression profiles or genomic datasets. These characteristics made SVM an invaluable algorithm in bioinformatics, where the classification of diseases such as cancer requires robust, data-driven methods to handle variability and heterogeneity [10,15].

#### **Gene Expression Data**

Gene expression is a process where information in DNA becomes instructions to make proteins or other molecules [16,19]. The process starts when DNA is copied into mRNA and changed into proteins. Gene expression analysis is typically used for monitoring genetic changes in tissues or single cells under certain conditions. It checks how many DNA transcripts are in a sample to know which genes are active and by how much, including comparing the sequenced reads with the number of base pairs from a DNA piece to a known genome or transcriptome. The process' accuracy depends on the clarity of information obtained, which allows bioinformatics tools to match them to the right genes. However, the gene expression dataset poses an additional challenge due to their high dimensionality, where the ratio of features to samples is high, hindering the performance of classification models. To address this, researchers have used feature selection methods to filter out irrelevant or redundant genes [20,21]. Feature selection has a critical role in improving machine learning models' classification outcomes in high-dimensional datasets, making it a basis for an efficient classification model for cancer detection [22,23].

## **Racial Dataset Influence in Artificial Intelligence**

Racial-based genomic datasets present challenges for machine learning applications. Studies have shown that using race-based genomics data for artificial intelligence algorithms may exhibit biases where trained models favor the majority race in training data, lowering the accuracy on the minority races [8,24]. Racial class imbalance in the dataset, where certain races have more samples, can influence the accuracy of algorithms. However, when the class imbalance is less severe, the algorithms tend to achieve higher balanced accuracy across all racial groups [25]. To mitigate this, an approach that reweighs the minority classes is performed, yet this approach was unreliable when the class imbalance is severe [24,26]. This research uses race-based genomics data instead of a combined race dataset to address the biases that may appear when using a combined dataset.

#### **Prior Research and Objective**

Despite significant advancements in machine learning and prostate cancer diagnosis, a gap remains in addressing racial disparities in prostate cancer. A recent study by Alshareef et al [27] introduces artificial intelligence-based feature selection with deep learning model for prostate cancer detection, a newly developed method of prostate cancer detection using deep learning approach using microarray gene expression data with 52 prostate samples and 50 normal samples on 2135 genes [28]. It focuses on feature selection using Chaotic Invasive Weed Optimization and hyperparameter tuning over multiple iterations of the proposed artificial intelligence-based feature selection with deep learning model for prostate cancer detection model which leads to an average accuracy of 97.19%, precision of 97.14%, and  $F_1$ -score of 97.28%. Similarly, Ravindran et al [29] proposed a prediction deep learning model for prostate cancer which focuses on data augmentation using the Wasserstein Tabular Generative Adversarial Network technique, which enables powerful discriminators that supply reliable gradient information to the sample generator even with poor sample qualities, allowing for a more stable training process [27]. The research uses a Micro Gene Expression Cancer Dataset (MGECD), of which the prostate cancer MGECD consists of 102 samples and 6033 features, and feature selection based on correlation coefficients with the goal of reducing the features to 1/3 of the initial MGECD by applying a threshold of 0.7. This results in 1833 features being used for the final model that has a 97% accuracy, 98% precision, and 97% recall values, a total of 3.4% accuracy improvement on prostate cancer classification using Wasserstein Tabular Generative Adversarial Network SVM compared to only using SVM. Previous research has demonstrated admirable results with limited amounts of samples, yet the proposed methods do not account for the racial biases that may be present in gene expression data and the number of genes needed to efficiently train machine learning models. To bridge this gap, we use feature selection methods such as differentially expressed gene (DEG) analysis, receiver operating characteristic (ROC) analysis, and MSigDB (Molecular Signature Database) verification. Our goal is to develop a race-based SVM model that improves prostate cancer detection for White populations and provides a novel genomics-based approach for health care professionals.

## Methods

## **Study Design**

This study implements data collection, preprocessing, feature selection, and SVM modeling and evaluation as seen in Figure 1. These methods are conducted using Python (version 3.12.3; Python Software Foundation) programming language and the necessary libraries using Visual Studio Code editor (version 1.95.3; Microsoft Corp) [30].

Figure 1. Race-specific prostate cancer detection modeling framework. DEG: differentially expressed gene; GDC: Genomic Data Commons; MSigDB: Molecular Signature Database; ROC: receiver operating characteristic; STAR: Spliced Transcripts Alignment to a Reference; SVM: support vector machine; TCGA: The Cancer Genome Atlas; UCSC: University of California, Santa Cruz.



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#### **Ethical Considerations**

This study used publicly available datasets from the University of California, Santa Cruz Xena [31]. University of California, Santa Cruz Xena allows users to explore functional genomic data sets for correlations between genomic or phenotypic variables. Thus, no ethics approval was required.

## **Data Collection**

This study implements a structured methodology to identify and model significant genes for prostate cancer using gene expression data. There are 2 datasets used and obtained in August 2024 from Xenabrowser's GDC (Genomic Data Commons) TCGA-PRAD (The Cancer Genome Atlas Prostate Adenocarcinoma) cohort, of which 1 contains gene expression counts data, and the other contains the clinical information of the samples [29]. Gene expression dataset has been prenormalized by Xenabrowser using log2(count+1).

## **Data Preprocessing**

Data preprocessing involved separating the counts dataset racially by mapping the samples to their race in the phenotype dataset, filtering samples with missing gene expression values, and labeling samples as normal or cancer via the TCGA (The Cancer Genome Atlas) barcode. These steps were conducted using the Pandas (version 2.2.2; NumFOCUS, Inc) and NumPy (version 1.26.4; NumPy Developers) libraries in a Jupyter Notebook (LF Charities) environment [32-34].

### **Feature Selection**

Feature selection to train the machine learning model was achieved through refining the filtered genes from DEG analysis, performed using the PyDESeq2 package (version 0.4.10; OWKIN) [35-37]. After creating metadata and the appropriate data frame, we used the DESeqDataSet function to create a suitable dataset for the DESeq2 process. There are 3 parameters used in creating the DESeqDataSet. First is counts, which is where the data frame of gene expression values of each gene ID and sample ID is used. To create metadata for the DeseqDataSet function, we specify the design of the DEG experiment and the factors to be analyzed. The factors in this research are labeled sample IDs with their condition that has been converted to a data frame by using the DeseqStats function. Lastly, we defined the design factor to guide the DEG analysis to focus on the important variables, in this case, the sample conditions. Identifying significant genes is based on the set threshold of baseMean  $\geq 10$  and *p*-adj <.05. The filtered genes were used to create 5 experimental scenarios, with the first scenario focusing on the outlier genes identified through PyDESeq2 that met the specified thresholds.

The second and third scenarios were developed by introducing additional thresholds to the DEG results. The additional scenarios further narrowed down the outlier genes by applying log2FoldChange>0.35 and >0.4, respectively.

For the fourth scenario, ROC analysis was performed using the scikit-learn metrics library (version 1.5.1; scikit-learn developers) to isolate genes with high predictive impact [38,39]. Genes were filtered based on a cutoff threshold of area under the curve value above 0.90, and the results were visualized using

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the matplotlib library (version 3.9.1; The Matplotlib development team) [40]. These genes were then used to create the fourth scenario.

The final scenario involves converting the isolated genes' Ensembl IDs into gene symbols using BioTools.fr for the human species Ensembl format [41] and verifying using gene set enrichment analysis (GSEA). Gene symbols were queried to MSigDB from GSEA to compute overlaps on curated gene sets which enables identification of well-established biological pathways and is widely used in cancer immunology and metabolic research, computational gene sets to complement the curated gene sets by providing unbiased large-scale insights and specific gene expression patterns, oncogenic gene sets that are directly relevant to cancer research and linked to gene expression changes on specific oncogenic events, and False Discovery Rate q-value less than 0.05 to reduce the likelihood of false positives in enrichment results [22,42-46]. Overlaps between the queried genes and the gene sets in MSigDB were analyzed to validate their relevance to prostate cancer. Genes with confirmed prostate cancer relevance were selected for use in the final scenario.

## **SVM Modeling**

The dataset initially shows a strong class imbalance, with a cancer-to-normal ratio of 1:9. To address this class imbalance, the data were split into training and testing sets using various stratified splits: 60%/40%, 70%/30%, and 80%/20%. Stratification ensures that the class distribution among the training data class imbalance was then addressed on all the training data scenarios using oversampling methods, including RandomOverSampler, SVMSMOTE, SMOTEENN, SMOTETomek, ADASYN, BorderlineSMOTE, and KMeansSMOTE from sci-kit libraries with a sampling strategy of 0.3, meaning the training data consists of 66.66% cancer samples and 33.33% normal samples, creating a balanced dataset for model training and preserving the authenticity of the testing data, making a realistic environment for the model to perform in.

Multimedia Appendix 1 (Table S1) and Table 1 show multiple experimental scenarios that were designed to test different parameter combinations and datasets. Two modeling scenarios were used; first, using the default SVC function with linear kernel. Second, conducting hyperparameter tuning to optimize model performance. Hyperparameter tuning was performed using GridSearchCV with a linear kernel SVC classifier and 5-fold cross-validation. The hyperparameters and their ranges were as follows: multiple kernels of the SVC function were used, linear, polynomial, and radial basis function. C values were ranging from 0.01, 0.1, 1, and 10, with gamma values of 0.01, 0.1, and 1, coef0 values of 0 and 1, and lastly class weights of none and balanced.

Evaluation of the model was obtained and inspected using the *classification\_report* function, by focusing on harmonization between  $F_1$ -score, recall, accuracy, precision, and macro-avg values, we evaluated the models' performance on training and test sets to ensure reliability of the model with no over- or underfitting present. To further validate the results of the obtained machine learning model, we tested the model on a

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black dataset with corresponding gene amounts to further investigate the racial differences in prostate cancer. This approach aligns with the goal of improving the identification of prostate cancer within a specific population.

Table . Top 5 models for 4-gene scenario.

Balancing method	Data split- ting ratio	Hyper-pa- rameter	White					Black			
			Train accu- racy (%)	Test accu- racy (%)	<i>F</i> <sub>1</sub> -score (%)	Precision (%)	Recall (%)	Test accu- racy (%)	<i>F</i> <sub>1</sub> -score (%)	Precision (%)	Recall (%)
KMeansS- MOTE	80:20	Yes	94.2	94.6	97	94.3	100	93.7	96.5	94.9	98.2
KMeansS- MOTE	70:30	No	92.8	93.5	96.5	94.6	98.4	93.7	96.5	94.9	98.2
KMeansS- MOTE	80:20	No	92.8	93.5	96.4	95.3	97.6	92.2	95.6	94.8	96.5
SVMSMOIE	80:20	Yes	94.9	92.4	95.8	95.2	96.4	92.2	95.6	96.4	94.7
KMeansS- MOTE	70:30	Yes	93.6	92	95.7	92.5	99.2	90.6	94.9	91.8	98.2

## Results

#### Datasets

Data for this research consists of 2 correlated secondary datasets, obtained through an open-source prostate cancer gene expression database, Xenabrowser GDC TCGA gene expression RNAseq Spliced Transcripts Alignment to a Reference-counts, and Xenabrowser GDC TCGA phenotypes. Gene expression RNAseq Spliced Transcripts Alignment to a Reference-counts contains 550 samples and 60,480 gene IDs in Ensembl format. On the other hand, the phenotype dataset contains 623 rows and 127 samples of clinical information on the samples included, from which sample types and race demographics columns are used to create a dataset based on race demographics. Out of the 550 samples present in the phenotype dataset, 458 were White, 12 were Asian, 1 was American Indian, 64 were African Americans, and 15 were not reported. The filtered-out White race count data that contains 57,429 gene IDs and 458 samples with their respective classes are presented in Multimedia Appendix 1 (Table S2).

## **Feature Selection**

To create a more enhanced feature selection method, several scenarios were made combining multiple methods based on DEG analysis thresholds. These scenarios reveal the most optimal combination of methods to identify genes relevant to prostate cancer.

From DEG analysis, various genes are extracted with several thresholds (Table S3 in Multimedia Appendix 1), the most being 139 genes. This result is further refined with ROC analysis and MSigDB investigation, which reveals 9 of 139 genes to have a direct correlation to prostate cancer.

Of the 139 genes identified through DEG analysis, PCA3 showed the strongest up-regulated correlation with prostate cancer (Table S4 in Multimedia Appendix 1). PCA3 had a baseMean of 12.33, indicating high expression across samples, a log2FoldChange of 0.6198, reflecting increased expression in cancerous tissue, and a *p*-adj value of <.001, confirming statistical significance.

Among the 139 genes identified from DEG analysis, WFDC2 has the strongest down-regulated correlation with prostate cancer (Table S5 in Multimedia Appendix 1). This is evident with a baseMean of 10.17 indicating a moderate expression level across samples, a log2FoldChange of -0.3069 which shows a decrease in expression levels in cancerous tissue compared to normal tissue, and a *p*-adj<.001 indicating high statistical significance after adjustment for multiple testing.

ROC analysis was performed on 139 genes obtained using the White race DEG analysis, applying an area under the curve score threshold above 0.9. This process identified 13 genes as outliers, as shown in Figure 2, significantly narrowing down the initial gene set.



Figure 2. A total of 13 genes were identified to have a strong correlation (AUC>0.9) with prostate cancer obtained through ROC analysis of 139 genes. AUC: area under the curve; ROC: receiver operating characteristic.



Genes that were identified from ROC analysis were converted from Ensembl format to gene symbol using BioTools.fr (Table S1 in Multimedia Appendix 1) to be verified through MSigDB. GSEA MSigDB investigation results reveal that the genes' correlation varies between gene sets. We found that out of 13 genes, 9 were found to have a correlation to MSigDBs' LIU\_PROSTATE\_CANCER\_DN gene set with a P<.001 and False Discovery Rate q-value of 2.05 e<sup>-11</sup> as seen in Figure 3.



**Figure 3.** GSEA MSigDB investigation results of 139 genes selected from DEG analysis reveal 9 genes that are down-regulated in prostate cancer. 3CA / PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; AILT: Angioimmunoblastic T-cell lymphoma; CNS: Central Nervous System; DEG: differentially expressed gene; FDR q: False Discovery Rate q-value; GSEA: gene set enrichment analysis; HDAC:Histone Deacetylase; k/K: is a ratio of number of genes in GSEA MSigDB data set (k) divided by the number of genes in the indicated dataset (K); LIU: protein LIU; MSigDB: Molecular Signature Database; PDGFB: Platelet-Derived Growth Factor Subunit B; PTC: papillary thyroid carcinoma; RNAi: RNA interference; U2OS: a human osteosarcoma cell line;

Gene Set Name [# Genes (K)]	Description	in Overlap (k)	k/K	p-value <mark>?</mark>	FDRq-value ?	
LIU_PROSTATE_CANCER_DN [493]	Genes down-regulated in prostate cancer samples.	9		2.39 e <sup>-15</sup>	2.05 e <sup>-11</sup>	
PICCALUGA_ANGIOIMMUNOBLASTIC_LYMPHOMA_ MA_UP [211]	Up-regulated genes in angioimmunoblastic lymphoma (AILT) compared to normal T lymphocytes.	5		3.55 e <sup>-9</sup>	1.53 e <sup>-5</sup>	
JOHANSSON_BRAIN_CANCER_EARLY_VS_LATE_D E_DN [43]	Genes down-regulated in early vs late brain tumors induced by retroviral delivery of PDGFB [GeneID=5155].	3		2.72 e <sup>-7</sup>	4.65 e <sup>-4</sup>	
MODULE_11 [540]	Genes in the cancer module 11.	5	1	3.81 e <sup>-7</sup>	4.65 e <sup>-4</sup>	
MODULE_100 [544]	Genes in the cancer module 100.	5	l l	3.95 e <sup>-7</sup>	4.65 e <sup>-4</sup>	
MODULE_137 [546]	CNS genes.	5	I	4.03 e <sup>-7</sup>	4.65 e <sup>-4</sup>	
MODULE_66 [552]	Genes in the cancer module 66.	5	1	4.25 e <sup>-7</sup>	4.65 e <sup>-4</sup>	
GAVISH_3CA_MALIGNANT_METAPROGRAM_25_AS _ASTROCYTES [50]	Genes upregulated in subsets of cells of a given type within various tumors	3		4.32 e <sup>-7</sup>	4.65 e <sup>-4</sup>	
DELYS_THYROID_CANCER_DN [233]	Genes down-regulated in papillary thyroid carcinoma (PTC) compared to normal tissue.	4	•	6.01 e <sup>-7</sup>	5.63 e <sup>-4</sup>	
SENESE_HDAC1_AND_HDAC2_TARGETS_DN [238]	Genes down-regulated in U2OS cells (osteosarcoma) upon knockdown of both HDAC1 and HDAC2 [GeneID=3065;3066] by RNAi.	4		6.54 e <sup>-7</sup>	5.63 e <sup>-4</sup>	

## **SVM Classifier**

Various scenarios with different balancing methods and splitting percentages were implemented for constructing the ideal SVM model, creating minimal but important differences in class counts as seen in Multimedia Appendix 1 (Table S7).

From the various scenarios, we identified the top 5 best-performing models across different feature categories. The model using 139 genes from DEG analysis combined with the SMOTEENN balancing technique achieved the most consistent results, with a training accuracy of 100% and test accuracies of 97% for the White race and 96% for the Black race, alongside strong harmonization across  $F_1$ -score, precision, and recall.

Compared to models using 4 and 7 genes, obtained through DEG analysis thresholds of log2FoldChange>0.35 and 0.4, achieved accuracies of 95% or below with unfavorable harmonization, thus the need for more advanced feature selection methods, such as ROC analysis combined with online GSEA. Models with 13 and 9 selected genes obtained through ROC analysis and GSEA demonstrated competitive performance, achieving 97% accuracy for the White race and 95% for the Black race, though slight deviations in precision and recall for the Black race were observed. Detailed metrics for all scenario models can be found from Tables 1-5.



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#### Table . Top 5 models for 7-genes scenario.

Balancing method	Data split- ting ratio	Hyper-pa- rameter	White					Black			
			Train accu- racy (%)	Test accu- racy (%)	<i>F</i> <sub>1</sub> -score (%)	Precision (%)	Recall (%)	Test accu- racy (%)	<i>F</i> <sub>1</sub> -score (%)	Precision (%)	Recall (%)
KMeansS- MOTE	80:20	Yes	94.9	95.6	97.6	95.4	100	95.3	97.4	96.5	98.2
SVMSMOIE	80:20	Yes	97.9	94.6	97	96.4	97.6	90.6	94.6	96.4	93
KMeansS- MOTE	80:20	No	94.4	94.6	97	95.3	98.8	93.7	96.5	94.9	98.2
KMeansS- MOTE	60:40	No	96	92.9	96.1	94.7	97.6	95.3	97.4	96.5	98.2
SVMSMOIE	70:30	Yes	98.7	92.7	96.1	93.9	98.4	95.3	97.4	96.5	98.2

## Table . Top 5 models for 9-genes scenario.

Balancing method	Data split- ting ratio	Hyper-pa- rameter	White					Black			
			Train accu- racy (%)	Test accu- racy (%)	<i>F</i> <sub>1</sub> -score (%)	Precision (%)	Recall (%)	Test accu- racy (%)	<i>F</i> <sub>1</sub> -score (%)	Precision (%)	Recall (%)
SVMSMOIE	70:30	Yes	98.4	97.1	98.4	98.4	98.4	95.3	97.3	98.2	96.5
KMeansS- MOTE	80:20	No	96.5	96.7	98.2	98.8	97.6	93.7	96.4	100	93
KMeansS- MOTE	80:20	Yes	95.6	96.7	98.2	98.8	97.6	96.9	98.2	98.2	98.2
SMOTE- Tomek	70:30	Yes	98.7	96.4	98	98.4	97.6	95.3	97.3	98.2	96.5
KMeansS- MOTE	70:30	No	95.7	96.4	98	99.2	96.8	95.3	97.3	98.2	96.5

#### Table . Top 5 models for 13-genes scenario.

Balancing method	Data split- ting ratio	Hyper-pa- rameter	White					Black				
			Train accu- racy (%)	Test accu- racy (%)	<i>F</i> <sub>1</sub> -score (%)	Precision (%)	Recall (%)	Test accu- racy (%)	<i>F</i> <sub>1</sub> -score (%)	Precision (%)	Recall (%)	
KMeansS- MOTE	70:30	No	95.2	97.1	98.4	99.2	97.6	95.3	97.3	98.2	96.5	
SMOTE- Tomek	80:20	Yes	98.1	96.7	98.2	97.6	98.8	95.3	97.3	100	94.7	
Borderli- neS- MOTE	70:30	No	90.4	96.4	97.9	99.2	96.8	95.3	97.3	100	94.7	
KMeansS- MOTE	60:40	No	96.9	96.2	97.9	98.2	97.6	92.2	95.5	98.1	93	
KMeansS- MOTE	70:30	Yes	95.2	95.6	97.6	98.4	96.8	95.3	97.3	98.2	96.5	



Table . Top 5 models for the 139 genes scenario.

Balancing method	Data split- ting ratio	Hyper-pa- rameter	White					Black			
			Train accu- racy (%)	Test accu- racy (%)	<i>F</i> <sub>1</sub> -score (%)	Precision (%)	Recall (%)	Test accu- racy (%)	<i>F</i> <sub>1</sub> -score (%)	Precision (%)	Recall (%)
SMO- TEENN	80:20	No	100	97.8	98.8	98.8	98.8	96.9	98.2	100	96.5
Borderli- neS- MOTE	60:40	Yes	98.8	97.3	98.5	99.4	97.6	96.9	98.2	100	96.5
SMO- TEENN	70:30	Yes	100	97.1	98.4	99.2	97.6	96.9	98.2	100	96.5
SMO- TEENN	70:30	No	100	97.1	98.4	99.2	97.6	96.9	98.2	100	96.5
SMO- TEENN	80:20	Yes	100	96.7	98.2	98.8	97.6	96.9	98.2	100	96.5

## Discussion

## **Principal Results**

In this study, we explored multiple feature selection scenarios for race-based SVM classification models aimed at prostate cancer detection using gene expression data. Our findings demonstrate that race-based models with significantly reduced features are capable of achieving competitive performance comparable to models using thousands of genes. The best-performing model, achieved without hyperparameter tuning or cross-validation, demonstrated outstanding results with a training accuracy of 100% and test accuracies of 98% on the White race and 97% on the Black race. Additionally, the model showed strong harmonization across  $F_1$ -score, precision, and recall values, which indicates consistent model classification performance. However, models in scenarios with 4 and 7 genes, selected DEG analysis with thresholds using of log2FoldChange>0.35 and 0.4, respectively, showed lower accuracies of 95% or lower, despite noteworthy harmonization between  $F_1$ -score, precision, and recall values. This shows the limitations of feature selection solely using DEG analysis thresholds, as it failed to capture the critical biomarkers necessary for reliable classification.

Moreover, models with 9 and 13 selected genes through ROC analysis and GSEA present matched performance, achieving accuracies of 97% on the White race and 95% on the Black race. These models also demonstrated good stability, consistently performing well over different train-test dataset splits. While these reduced-feature models showed strong metrics for the White race, the slight drop in accuracy for the Black race indicates the presence of racial disparities in feature selection. This highlights the need for further research to improve model generalizability across more diverse populations.

### Strengths

This study addresses racial disparities in prostate cancer gene expression datasets to create a race-specific SVM classification model with multiple scenarios. Our testing demonstrated greater accuracies on scenarios using 139 genes; however, models with

13 and 9 selected genes also yielded 97% accuracy, highlighting the effectiveness of an optimized feature selection strategy. This feature reduction implies the significance of feature selection along with model construction parameters such as balancing methods, data splitting ratios, and hyperparameter optimization in achieving a robust classification model.

From a clinical standpoint, these results imply significant cost reduction and practical applicability. Reducing the number of genes required for sequencing substantially lowers the financial and computational cost of diagnostic workflows, making this approach more accessible and scalable for routine prostate cancer screening and early detection [47-49].

### **Comparison With Prior Works**

While prior works used feature selection methods with correlation-based and evolutionary algorithm approaches without further validations, our approach used tools such as *PyDESeq2* and MSigDB investigation to further validate the biological relevance of our selected genes to prostate cancer to improve the diagnostic accuracy and provide insights into race-specific prostate cancer biology, an area often neglected by other studies.

Our study achieved comparable accuracies to prior works while significantly reducing the number of features used. For example, Ravindran et al [29] reported a 97% accuracy while using 1833 features selected from the initial 6033 genes through a correlation-based approach [27]. Conversely, our models achieved similar accuracy using only 13 or 9 features, validating the performance of our feature selection method. Additionally, our study integrates racially based datasets to account for racial disparities while achieving robust performance for both the White (98% accuracy) and Black populations (97% accuracy). This further addresses the gap between prior works such as the model by Alshareef et al [27], with 52 prostate cancer samples and 1833 features, which overlook racial disparities [28]. To further appraise our model, we also compared it to a recent study by Xie and Xie [50] using an artificial neural network model on a DEG panel of 220 genes and reporting an accuracy of 78%, our optimized racial-based SVM model outperformed it with higher accuracy and fewer features, while maintaining consistent results across multiple dataset splits. These comparisons

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highlight the competitiveness and reliability of our SVM-based framework in prostate cancer detection.

## Limitations

However, this study has the following limitations. The datasets used are heavily imbalanced, with an overrepresentation of White individuals and cancer samples compared to normal samples. Only a single dataset source was used due to restricted access to other publicly available datasets, which limits the diversity and variability of the data. Future work should prioritize the inclusion of larger, more diverse populations to enhance the model's generalizability and consider an external independent dataset to validate the model's performance. Additionally, exploring other genomic and epigenomic features, such as DNA methylation patterns, may yield further insights into race-specific prostate cancer biology.

## Conclusions

This research used enhanced feature selection methods such as DESeq2 DEG analysis and ROC analysis to reduce feature quantity in machine learning models for prostate cancer detection in specific racial groups. Our findings show that while testing on White race reducing features-maintained model, performance was comparable to studies with larger feature sets. To examine racial disparities, we tested the model on African American data, revealing minimal (~1%) accuracy differences between racial groups. These findings indicate a low influence of racial features on classification while emphasizing the importance of feature selection in developing race-based SVM models for prostate cancer using gene expression data.

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## **Authors' Contributions**

Conceptualization: DA (lead), MVO (equal), MW (equal) Data curation: AM (lead), VK (sopporting), JS (supporting) Formal analysis: AM Funding acquisition: DA Investigation: AM Methodology: DA (lead), MVO (equal), MW (equal), MIA (equal) Project administration: AM (lead), VK (sopporting), JS (supporting) Resources: AM (lead), VK (sopporting), JS (supporting) Supervision: DA (lead), MVO (equal), MW (equal), MIA (equal) Validation: DA (lead), MVO (equal), MW (equal), MIA (equal) Visualization: AM (lead), VK (sopporting), JS (supporting) Writing – original draft: AM (lead), VK (sopporting), JS (supporting) Writing – review & editing: AM (lead), VK (sopporting), JS (supporting)

## **Conflicts of Interest**

None declared.

### Multimedia Appendix 1

Tables on modeling scenarios, dataset, genes, and the machine learning training model. [DOC File, 88 KB - bioinform v6i1e72423 app1.doc]

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#### Abbreviations

DEG: differentially expressed gene
GDC: Genomic Data Commons
GSEA: gene set enrichment analysis
MGECD: Micro Gene Expression Cancer Dataset
MSigDB: Molecular Signature Database
PSA: prostate-specific antigen
ROC: receiver operating characteristic
SVM: support vector machine
TCGA: The Cancer Genome Atlas
TCGA-PRAD: The Cancer Genome Atlas Prostate Adenocarcinoma



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# Stacked Deep Learning Ensemble for Multiomics Cancer Type Classification: Development and Validation Study

Amani Ameen<sup>1</sup>, BSc; Nofe Alganmi<sup>1,2</sup>, PhD; Nada Bajnaid<sup>1</sup>, PhD

<sup>1</sup>Faculty of Computing and Information Technology, King Abdulaziz University, P.O.Box 80200, Jeddah, Saudi Arabia <sup>2</sup>Institute of Genomic Medicine Sciences (IGMS), King Abdulaziz University, Jeddah, Saudi Arabia

#### **Corresponding Author:**

#### Nofe Alganmi, PhD

Faculty of Computing and Information Technology, King Abdulaziz University, P.O.Box 80200, Jeddah, Saudi Arabia

## Abstract

**Background:** Cancer is one of the leading causes of disease burden globally, and early and accurate diagnosis is crucial for effective treatment. This study presents a deep learning–based model designed to classify 5 common types of cancer in Saudi Arabia: breast, colorectal, thyroid, non-Hodgkin lymphoma, and corpus uteri.

**Objective:** This study aimed to evaluate whether integrating RNA sequencing, somatic mutation, and DNA methylation profiles within a stacking deep learning ensemble improves cancer type classification accuracy relative to the current state-of-the-art multiomics models.

**Methods:** Using a stacking ensemble learning approach, our model integrates 5 well-established methods: support vector machine, k-nearest neighbors, artificial neural network, convolutional neural network, and random forest. The methodology involves 2 main stages: data preprocessing (including normalization and feature extraction) and ensemble stacking classification. We prepared the data before applying the stacking model.

**Results:** The stacking ensemble model achieved 98% accuracy with multiomics versus 96% using RNA sequencing and methylation individually, 81% using somatic mutation data, suggesting that multiomics data can be used for diagnosis in primary care settings. The models used in ensemble learning are among the most widely used in cancer classification research. Their prevalent use in previous studies underscores their effectiveness and flexibility, enhancing the performance of multiomics data integration.

**Conclusions:** This study highlights the importance of advanced machine learning techniques in improving cancer detection and prognosis, contributing valuable insights by applying ensemble learning to integrate multiomics data for more effective cancer classification.

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#### **KEYWORDS**

deep learning; ensemble learning; cancer classification; omics data; stacking ensemble

## Introduction

Cancer is a complex worldwide health problem associated with high mortality [1]. Recent years have seen the use of a variety of machine learning techniques applied to high-throughput sequencing technology, which has advanced the classification of cancers based on omics data and offered a promising future for precise treatment choices.

Omics data provide a thorough understanding of biological systems, facilitating research into disease pathways, molecular causes, and ecological dynamics. Omics comprises the following fields: metagenomics (eg, microbial genomes), proteomics (eg, protein abundances), metabolomics (eg, small molecule concentrations), epigenomics (eg, DNA methylation patterns), and genomics (eg, DNA sequences and mutations) [2]. RNA sequencing is one type of omics data and is a powerful

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sequencing-based method that enables researchers to discover, characterize, and quantify RNA transcripts across the entire transcriptome [3]. RNA sequencing can tell us which genes are turned on in the cell, their expression levels, and at what time they are turned on or off [4]. This allows scientists to better understand cell biology and evaluate changes that might indicate disease. These data are characterized as high-throughput and high-dimensional [5]. Methylation, an epigenetic process involving the addition of methyl groups to DNA, plays a vital role in gene expression regulation [6]. Aberrant methylation patterns are pervasive in human cancers, impacting carcinogenesis stages and serving as potential biomarkers for cancer diagnosis and prognosis [7,8]. A somatic mutation is a permanent change that can arise naturally or be brought about by environmental influences in the DNA sequence of a gene or chromosome. It may have an impact on the structure or function of proteins. In cancer research, they are essential markers that

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shed light on the genetic causes of carcinogenesis and inform the creation of patient-specific targeted therapy [9].

Studies have shown that while single-genome research has yielded significant results, integrating multiple omics can enhance our understanding of diseases and provide patients with better treatment options. Therefore, integrating data from multiple omics, rather than using single-omic techniques, may provide a better understanding of biological systems and the causes of diseases. This integration improves prediction accuracy and facilitates more efficient identification of therapeutic targets [10,11].

Dealing with omics data poses several challenges, one of which is that sequencing data are high-dimensional. Second, class imbalance in patient data will reduce the model's performance. The third challenge is that the number of patients in the study is still relatively small, which may cause overfitting problems [12]. Based on these challenges, there is a need for development and contribution in this field, including the development of models that can successfully distinguish between types of cancer while considering the 3 challenges.

Recent studies on the analysis of critical data for cancer disorders have used a variety of machine learning strategies, including the multilayer perceptron [13-16]. The multilayer perceptron is a 3-layer system that consists of an input layer, an output layer, and a hidden layer positioned in the middle. A convolutional neural network (CNN) [17,18] is another kind of neural network that is used. It functions similarly to a feed-forward neural network and consists of a convolutional layer that processes the input and outputs the result to the next layer. They also used random forest (RF) [13,19], which is a technique that involves training a large number of decision trees. The final output of the RF is the class that the majority of the trees select. Deep neural architectures for classification have also been used in [18,20,21]. In addition, the support vector machine (SVM) and k-nearest neighbors (KNN), which are typically used for regression and classification, are commonly applied in this field.

Working with omics data presents several challenges, such as overfitting and class imbalance, which we outline below, along with an overview of how previous work has addressed them. Overfitting is common due to the limited amount of data, often resulting in lower model performance. The model's accuracy is directly influenced by the amount of data used. This issue has been noted in several studies where models are excessively trained to fit the training examples. Upon review, some papers overlooked this issue, while others addressed it through approaches such as regularization, cross-validation, and dropout techniques. Class imbalance is another significant issue in this type of data, affecting model training by biasing it toward the class with more data. Summarizing the methods for dealing with this problem involves 2 main approaches. First, oversampling techniques such as SMOTE (Synthetic Minority Oversampling Technique) and undersampling methods such as downsampling are used to balance class distribution in the dataset. Second, another effective strategy is to use ensemble learning, where different models are trained on either different subsets of data or using various algorithms, pooling their predictions for improved overall performance. These methods collectively aim to address the challenges posed by class imbalance in data-driven tasks such as cancer classification using omics data.

The model proposed in this paper uses ensemble learning of 5 common models to classify the 5 most common types of cancer in the Kingdom of Saudi Arabia using 3 types of omics data. The objective is to investigate whether the model's classification accuracy improves upon integrating multiomics data into our stacking model, which combines 5 of the most popular methods in this field.

### Methods

#### Overview

Our proposed model presents a classification of the 5 most common types in the Kingdom of Saudi Arabia, which are breast, colorectal, thyroid, non-Hodgkin lymphoma, and corpus uteri [22], by using deep learning, which in turn extracts features that are believed to have an important role. The model was designed using stacking ensemble learning as shown in Figure 1, which goes through 2 phases: a preprocessing phase that includes normalization and feature extraction (FE), and a classification phase using an ensemble stacking model. Data entered the preprocessing phase, and the output was then directed to the stacking model. We have performed our experiments in Python 3.10 (Python Software Foundation) on the Aziz Supercomputer of King Abdulaziz University, which is the second fastest supercomputer in the Middle East and North Africa region. The following sections explain how the proposed model works, starting with data collection, followed by preprocessing, and ending with the stacking model.



**Figure 1.** Methodology of the proposed model. ANN: artificial neural network; CNN: convolutional neural network; FE: feature extraction; KNN: k-nearest neighbors; RF: random forest; SVM: support vector machine; TPM: transcripts per million.





#### **Data Collection and Preprocessing**

For RNA sequencing data in this investigation, we used The Cancer Genome Atlas (TCGA) dataset, which is openly accessible to researchers. TCGA comprises approximately 20,000 primary cancer and matched normal samples across 33 cancer types, including the 5 cancer types addressed in our work. Its main goal is to provide scientists with information to improve cancer detection, treatment, and prevention [23]. Furthermore, somatic mutation and methylation data were obtained from the publicly accessible LinkedOmics dataset, which includes

multiomics data from all 32 TCGA cancer types and 10 Clinical Proteomic Tumor Analysis Consortium (CPTAC) cohorts [24].

Figure 2 shows a screenshot of the data types. These are tabular data, with columns representing genes and rows representing cases that are infected by cancer. In Figure 2A, RNA sequencing data capture gene expression levels as continuous values. In Figure 2B, somatic mutation data are sparse and binary (0 or 1), indicating the presence of genomic alterations. In Figure 2C, methylation data provide continuous epigenetic information reflecting gene regulation patterns, with values ranging from -1 to 1.

Figure 2. Show screenshots of the data types: (A) RNA sequencing, (B) somatic mutations, and (C) methylation.

	ENSG0000000003	ENSG000	00000005	ENSG00000004	19		ENSG00000121410	ENSO	500000148584	ENSG0000078328
0	24.175732	2.263355		43.973230		0	0	0		0
1	15.584672	0.094068		136.057880		1	0	0		1
2	24.305586	0.274953		32.396744		2	0	0		0
3	20.707151	3.097024		79.695340		3	0	0		0
		(A)							(B)	
			E	NSG00000121410	ENSG000001	48584	ENSG0000078328			
			0 -0	0.3168	0.2011		-0.3811			
			1 -0	0.4456	0.2215		-0.4121			
			2 0.	1558	-0.1861		0.1697			
			3 –0	0.4865	0.3416		0.3925			

(C)

Initially, the data underwent extensive cleaning to ensure the integrity of the model by identifying and removing 7% of cases with missing or duplicate values. Table 1 describes the number of cases of the 5 types of cancer after preprocessing. Regarding

RNA sequencing data, preparation is required before use to provide a precise model evaluation. Thus, 2 processes were carried out in order to preprocess the data: normalization and Feature Extraction (FE).



Cancer type	Abbreviation	RNA sequencing	Somatic mutation	Methylation
Breast	BRCA <sup>a</sup>	1223	976	784
Colorectal	COAD <sup>b</sup>	521	490	394
Thyroid	THCA <sup>c</sup>	568	496	504
Non-Hodgkin lymphoma	NHL <sup>d</sup>	481	240	288
Corpus uteri	UCEC <sup>e</sup>	587	249	432

Table . Show the number of samples in each cancer type after preprocessing.

<sup>a</sup>BRCA: breast invasive carcinoma.

<sup>b</sup>COAD: colon adenocarcinoma.

<sup>c</sup>THCA: thyroid carcinoma.

<sup>d</sup>NHL: non-Hodgkin lymphoma.

<sup>e</sup>UCEC: uterine corpus endometrial carcinoma.

Next, for the normalization step, we used the transcripts per million method to eliminate systematic experimental bias and technical variation while maintaining biodiversity. In addition, it can reduce the bias resulting from the choice of technique used and the conditions tested, or from the experimental procedure, and it can reduce the variance resulting from natural variation and measurement precision [25]. Transcripts per million can be calculated by equation 1 and should be read as "for every 1,000,000 RNA molecules in the RNA-seq sample, x came from this gene/transcript" [26].

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#### **Feature Extraction**

RNA sequencing data are high-dimensional. Therefore, to reduce the dimensionality, we use an autoencoder technique based on the results of a study [27] that concluded that autoencoders perform effectively while preserving essential biological properties, allowing for better visualization and interpretation of complex data structures. The architecture of the autoencoder model is composed of an encoder, a code, and a decoder. The encoder compresses the input (features), and the decoder attempts to recreate the input (features) from the compressed version provided by the encoder. The autoencoder model has 5 dense layers, each with 500 nodes and a rectified linear unit (ReLU) activation function. A dropout of 0.3 was applied to handle the overfitting.

#### Methods for Handling Class Imbalances

In particular, for classes with tiny sample sizes, imbalanced class sizes in the dataset may result in subpar prediction accuracy. Downsampling and SMOTE are 2 methods used to address class imbalances and enhance model performance [28]. In the study by Dittman et al [29], researchers tried class oversampling and class undersampling; then, after evaluating the data, they concluded that undersampling has better results than the oversampling method. Therefore, we decided to apply the downsampling method for the data used in this paper and verified that the data were free of duplicates and then divided into 80% training and 20% test data (Figure 3).



**Figure 3.** Downsampling for data. NHL had 481 cases in RNA-seq data; 80% (385 cases) were allocated for training and 20% (96 cases) for testing. Somatic mutation types were downsampled to 80% (192 cases) for training and 20% (48 cases) for testing. Methylation data followed suit, with 80% (230 cases) and 20% (58 cases) for training and testing, respectively. BRCA: breast invasive carcinoma; COAD: colon adenocarcinoma; NHL: non-Hodgkin lymphoma; RNA-seq: RNA sequencing; THCA: thyroid carcinoma; UCEC: uterine corpus endometrial carcinoma.



In this dataset, the smallest class (ie, non-Hodgkin lymphoma) included 481 cases in the RNA sequencing data. To balance the dataset, 481 cases were randomly selected from each of the other classes. This resulted in 80% (385 cases) used for training and 20% (96 cases) for testing. For somatic mutations data, each of the 5 types was downsampled to 80% (192 cases) for training and 20% (48 cases) for testing. Similarly, for methylation data, 80% (230 cases) were assigned for training and 20% (58 cases) for testing.

#### **Stacking Ensemble Model**

Stacking builds a model with improved performance by training multiple models to come up with the best combination of predictions from these models. The model structure consists of 5 base models and a meta-model that collects the predictions of the base models.

The hyperparameters of each model were described using GridSearchCV (scikit-learn developers), providing a comprehensive configuration for testing and optimization. For the nearest neighbor classifier (BM1), GridSearchCV was used to discover the optimal number of neighbors from values of (1, 3, 5, 10, 5, and 0) and found that the optimal number of neighbors was 10. For the RF classifier (BM2), GridSearchCV was used to explore combinations of "n\_estimators" and "min\_samples\_leaf," achieving the best performance using 500

trees and a minimum of 2 samples per leaf. For the support vector classifier (BM3), the regularization parameter "C" was tuned across a range of values (0.1, 1, 5, 7, and 10), with C=10 achieving the highest accuracy. For CNN (BM4) and artificial neural network (ANN; BM5), GridSearchCV was used to find the optimal activation function from ReLU and softmax, choose dropout rates from 0.1 to 0.6, and finally find the filter value in CNN. Table 2 shows the hyperparameters that we used in each model. Next, the stacking ensemble uses an ANN as the meta-model to combine predictions from BM1 to BM5. The meta-model architecture consists of a neural network with multiple layers. The first dense layer has 32 units and uses a ReLU activation function, followed by a dropout layer with a 50% rate to reduce overfitting. The second dense layer has 16 units and a ReLU activation function, followed by a dropout layer with a 50% rate. The model ends with an output layer that has 5 units and a softmax activation function, suitable for multiclass classification. The model is trained using an Adam optimizer with a learning rate of 0.001 and sparse categorical cross-entropy loss. The integration of the 5 models (SVM, KNN, ANN, CNN, and RF) follows a stacking ensemble approach, where the predictions from each model serve as input features for the meta-model. These base models are trained independently, and their outputs are concatenated to form the input layer of the meta-model.



Model	Classifier	Hyperparameter
BM1	KNN <sup>a</sup>	Neighbors=10
BM2	RF <sup>b</sup>	n_estimators=500 and min_samples_leaf=2
BM3	SVM <sup>c</sup>	C=10
BM4	CNN <sup>d</sup>	Conv1D with filters= 64, activation="ReLU," optimizer= "adam," loss= "sparse_categori- cal_crossentropy," and dropout=0.3
BM5	ANN <sup>f</sup>	3 dense layers, activation="ReLU," "softmax," optimizer="adam," loss="sparse categorical crossentropy." and dropout=0.4

<sup>a</sup>KNN: k-nearest neighbor.

<sup>b</sup>RF: random forest.

<sup>c</sup>SVM: support vector machine.

<sup>d</sup>CNN: convolutional neural network.

<sup>e</sup>ReLU: rectified linear unit.

<sup>f</sup>ANN: artificial neural network.

#### **Ethical Considerations**

This study exclusively used publicly available datasets obtained from TCGA and LinkedOmics with project names "TCGA-BRCA," "TCGA-COAD," "TCGA-THCA," "TCGA-DLBC," and "TCGA-UCEC". All datasets were fully anonymized and complied with the respective repository's data usage policies.

#### Results

#### Overview

In this section, we present the results of our study. First, in the "Performance Evaluation Metrics" section, we analyze critical metrics including the classification report, the confusion matrix, and the receiver operating characteristic (ROC) curve. Second, we present the results of the 5 models individually to compare with our results.

#### **Performance Evaluation Metrics**

To assess the effectiveness of the multiclass classification model, various performance metrics were calculated and are shown in Figure 4. The graph shows the performance metrics for a multiclass classification model, including precision, recall, and  $F_1$ -score for each class. Precision indicates the accuracy of positive predictions, while recall measures how many actual positives were correctly identified. The  $F_1$ -score balances precision and recall. The model achieved an overall accuracy of 98%. Both the macro and weighted averages of the metrics are very similar, reflecting consistent performance across all classes. Subsequently, in Figure 5, we examined the confusion matrix to assess the model's classification performance across the 5 classes. The matrix percentages indicated that the correct classification rates (the diagonal values) were between 91.67% and 100%, showing accurate classification results with error rates (the off-diagonal values) of roughly 8% or less for each class.



Figure 4. Classification report visualizing precision, recall,  $F_1$ -score, and support for each class in the stacking ensemble model. BRCA: breast invasive carcinoma; COAD: colon adenocarcinoma; NHL: non-Hodgkin lymphoma; THCA: thyroid carcinoma; UCEC: uterine corpus endometrial carcinoma.





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Figure 5. Confusion matrix illustrating the true versus predicted classifications generated by the stacking ensemble model.



Furthermore, we analyzed the ROC curve, which is a tool for assessing the model's discriminative abilities across multiple classifications. The ROC curve, which provides information about model performance, was modified for our multiclass scenario even though it is usually used in binary classification. In our experiment, we observed compromises between true and false positive rates, which validates the discriminative power of the model. The results, shown in Figure 6, indicate that all classes had consistent performance, as indicated by the area under the curve ranging from 0.90 to 1. These results demonstrate how well the model can classify cases in various classes.



Figure 6. Receiver operating characteristic curve demonstrating the performance of the stacking ensemble model.



To evaluate the performance of different machine learning approaches on individual omics datasets, we evaluated 5 commonly used classifiers-KNN, RF, SVM, CNN, and ANN-as well as a stacking model composed of all 5 models for each omics type. As shown in Table 3, the RF achieved the highest accuracy on the RNA sequencing dataset (0.98), while the CNN outperformed all other models on the somatic mutations dataset with an accuracy of 0.87. On the methylation dataset, the ANN slightly outperformed the other models with an accuracy of 0.97. The proposed stacking model demonstrated balanced performance across all 3 genome types, achieving accuracies of 0.96 (RNA sequencing), 0.81 (somatic mutations), and 0.96 (methylation). To detail the stacking results, we present Table 4, which shows the performance metrics-precision,  $F_1$ -score, recall, and accuracy—for different inputs: RNA sequencing, somatic mutations, methylation separately, and the multiomics approach. For the RNA sequencing input, the model consistently performs well across all 3 folds, with an average

precision,  $F_1$ -score, recall, and accuracy of 0.96. For the somatic mutations data, the model's accuracy,  $F_1$ -score, and recall were relatively low at 0.60, with a slightly higher precision of 0.70. With a mean of 0.97, the accuracy of the model tested on the methylation dataset varied between 0.95 and 0.99 across folds. Similarly,  $F_1$ -score and recall averaged 0.96 and 0.97, respectively, while accuracy averaged 0.96. In the multiomics approach, the model achieved an average score of 0.98 across all metrics. Specifically, the model demonstrates near-perfect performance in folds 2 and 3, achieving a precision, recall, and  $F_1$ -score of 0.99, reflecting the added value of incorporating multiple data modalities. Overall, the multiomics approach outperforms using each omics type separately, offering a more robust and accurate model across all evaluation metrics. Our analysis showed that some models performed better in terms of recall and precision for certain cancer types when using multiomics, highlighting the importance of combining data to get the most out of the analysis.



Table . Classification accuracy of individual models and the stacking model across RNA sequencing, somatic mutations, and methylation datasets.

Classification model	RNA sequencing	Somatic mutation	Methylation
K-nearest neighbors	0.91	0.72	0.95
Random forest	0.98	0.73	0.96
Support vector machine	0.95	0.79	0.96
Convolutional neural network	0.96	0.87	0.96
Artificial neural network	0.96	0.80	0.97
Stacking with the five model	0.96	0.81	0.96

Table . Performance of the stacking model using RNA sequencing, somatic mutations, methylation, and multiomics data.

Input type and k-fold	Precision	F <sub>1</sub> -score	Recall	Accuracy		
RNA sequencing	RNA sequencing					
1	0.95	0.94	0.94	0.94		
2	0.97	0.96	0.96	0.96		
3	0.98	0.98	0.98	0.98		
Avg <sup>a</sup>	0.96	0.96	0.96	0.96		
Somatic mutations						
1	0.6	0.6	0.6	0.7		
2	0.86	0.85	0.86	0.86		
3	0.92	0.91	0.91	0.91		
Avg	0.79	0.79	0.79	0.81		
Methylation						
1	0.95	0.94	0.94	0.94		
2	0.97	0.96	0.97	0.96		
3	0.99	0.98	0.99	0.99		
Avg	0.97	0.96	0.97	0.96		
Multiomics (RNA sequencing, somatic mutations, and methylation)						
1	0.96	0.95	0.95	0.95		
2	0.99	0.99	0.99	0.99		
3	0.99	0.99	0.99	0.99		
Avg	0.98	0.98	0.98	0.98		

<sup>a</sup>Avg: average.

#### Discussion

#### **Principal Findings**

The results of this study provide insights into ensemble learning for cancer classification and diagnosis, using 5 different machine learning models. These models were selected based on their proven effectiveness in previous studies and their popularity in the literature, offering a balanced approach to handling the complex nature of multiomics data.

#### **Comparison With Prior Work**

Table 5 summarizes several studies that used multiomics data and machine learning techniques to classify and predict various types of cancer. It is worth noting that these studies are not based on the same data but have been reviewed to support our

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XSL•FO RenderX findings that using multiomics data enhance accuracy. As seen, models from recent studies such as Koh et al [30] and Mohamed and Ezugwu [31] show high area under the curve scores (0.96) and accuracy (97%). Other models, such as Cappelli et al [32] and Jagadeeswara Rao and Sivaprasad [33], also report strong results, typically in the range of 91% - 95%. Overall, these studies highlight the power of integrating multiomics data with advanced machine learning techniques, which consistently led to high accuracy, with models achieving between 91% and 98% accuracy across different cancer types [34]. Although, when comparing the performance of our model with theirs, our approach shows the highest overall accuracy (98%) across a range of cancer types and data modalities. We addressed common challenges in omics data analysis, such as overfitting, class imbalance, and high dimensionality, through the

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application of techniques such as dropout, downsampling, and FE. These methods significantly contributed to the robustness

of our models, though their effectiveness varied depending on the model and data type.

Table . Comparison of cancer classification performance across multiomics research.

Paper	Year	Data type	Cancer types	Classification model	Overfitting han- dling	Class imbalance handling	Results (accura- cy)
Cappelli et al [32]	2018	RNA sequencing and methylation	BRCA <sup>a</sup> , THCA <sup>b</sup> , and KIRP <sup>c</sup>	C4.5, RF <sup>d</sup> , RIPPER <sup>e</sup> , and CAMUR <sup>f</sup>	Feature regular- ization methods	N/A <sup>g</sup>	95%
Kwon et al [34]	2023	cfDNA <sup>h</sup> and CNVs <sup>i</sup>	LUAD <sup>j</sup>	AdaBoost, MLP <sup>k</sup> , and LR <sup>1</sup>	Cross-validation	N/A	91%-98%
Koh et al [30]	2024	Proteomics, RNA sequenc- ing, metabolomics, and targeted im- munoassays	Lung	Machine learn- ing	Regularization and QC <sup>m</sup>	Balanced datasets	AUC <sup>n</sup> 0.96
Jagadeeswara Rao and Sivaprasad [33]	2024	RNA sequencing and methylation	PAAD <sup>o</sup>	Ensemble learn- ing	Ensemble tech- niques	SMOTE <sup>p</sup>	95%
Mohamed and Ezugwu [31]	2024	RNA sequenc- ing, miRNA <sup>q</sup> , and DNA methylation	LUAD	CNN <sup>r</sup>	Dropout	SMOTE	97%
Our model	2024	RNA sequenc- ing, methylation, and somatic mu- tations	BRCA, THCA, NHL <sup>s</sup> , UCEC <sup>t</sup> , and COAD <sup>u</sup>	Ensemble learn- ing	Cross-validation and dropout	Downsampling	98%

<sup>a</sup>BRCA: breast carcinoma.

<sup>b</sup>THCA: thyroid carcinoma.

<sup>c</sup>KIRP: kidney renal papillary cell carcinoma.

<sup>d</sup>RF: random forest.

<sup>e</sup>RIPPER: Repeated Incremental Pruning to Produce Error Reduction.

<sup>f</sup>CAMUR: Computer Assisted Molecular Unified Receptor.

<sup>g</sup>N/A: not available.

<sup>h</sup>cfDNA: cell-free DNA.

<sup>i</sup>CNV: copy number variation.

<sup>j</sup>LUAD: lung adenocarcinoma.

<sup>k</sup>MLP: multilayer perceptron.

<sup>1</sup>LR: logistic regression.

<sup>m</sup>QC: quality control.

<sup>n</sup>AUC: area under the curve.

<sup>o</sup>PAAD: pancreatic adenocarcinoma.

<sup>p</sup>SMOTE: Synthetic Minority Oversampling Technique.

<sup>q</sup>miRNA: microRNA.

<sup>r</sup>CNN: convolutional neural network.

<sup>s</sup>NHL: non-Hodgkin lymphoma.

<sup>t</sup>UCEC: uterine corpus endometrial carcinoma.

<sup>u</sup>COAD: colon adenocarcinoma.

Typically, deep learning components benefit from graphics processing unit acceleration and need a large amount of computational power, particularly when trained on high-dimensional clinical data. Nevertheless, after training, the model inference time is rather short, allowing for quick predictions that can assist with clinical decisions made in real

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time. Even while low-resource systems might not be able to support model training, these pretrained models could be used for clinical deployment, particularly in settings with recent computer technology.

#### **Strengths and Limitations**

Typically, deep learning components benefit from graphics processing unit acceleration and need a large amount of computational power, particularly when trained on high-dimensional clinical data. Nevertheless, the model inference time is rather short after the ensemble has been trained, allowing for quick predictions that can assist with clinical decisions made in real time. Even while low-resource systems might not be able to support model training, pretrained models can be used for clinical deployment, particularly in settings with recent computer technology.

However, the study has several limitations that must be acknowledged. Data availability constraints limited the scope of our analysis, and the absence of clinical data meant that our findings are based solely on omics data. This restricts the generalizability of our results to real-world clinical settings, where the integration of clinical and omics data is crucial for accurate cancer diagnosis and prognosis. Furthermore, the common limitation in omics data is dataset size, which may result in overfitting. Another restriction is the absence of external validation.

#### **Future Directions**

Future research should focus on expanding the types of data used in cancer classification, particularly by incorporating patient clinical data and exploring additional omics layers such as metabolomics and proteomics. Furthermore, the integration of multiomics data with advanced machine learning methods holds promise for deepening our understanding of the molecular mechanisms underlying cancer development. This could lead to more precise cancer staging and prognosis, ultimately improving patient outcomes.

#### Conclusions

In conclusion, while our study advances the accuracy of cancer classification algorithms, it underscores the need for continuous improvement and validation in diverse and clinically relevant datasets. By addressing these challenges, future research can enhance the applicability of these models in clinical practice, contributing to more effective cancer detection and treatment strategies.

The study aimed to investigate whether incorporating multiomics data into a stacking model that integrates 5 key methods, namely SVM, KNN, ANN, CNN, and RF, enhances the model's ability to classify cancer. With multiomics, the stacking ensemble model obtained 98% accuracy, compared to 96% with RNA sequencing and methylation separately and 81% with somatic mutation data. It emphasizes the importance of integrating advanced machine learning techniques into health care for more effective cancer detection and prognosis. This highlights the need for continuous improvement and validation of classification models in real-world clinical settings to maximize their impact on cancer care. Future research should focus on incorporating clinical metadata and multiomics data to enhance cancer classification, which would improve patient outcomes and clinical applicability.

#### **Conflicts of Interest**

None declared.

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#### Abbreviations

ANN: artificial neural network CNN: convolutional neural network FE: feature extraction KNN: k-nearest neighbors ReLU: rectified linear unit RF: random forest ROC: receiver operating characteristic SMOTE: Synthetic Minority Oversampling Technique SVM: support vector machine TCGA: The Cancer Genome Atlas

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# Extracting Knowledge From Scientific Texts on Patient-Derived Cancer Models Using Large Language Models: Algorithm Development and Validation Study

Jiarui Yao<sup>1,2\*</sup>, PhD; Zinaida Perova<sup>3\*</sup>, PhD; Tushar Mandloi<sup>3</sup>, MSc; Elizabeth Lewis<sup>3</sup>, MSc; Helen Parkinson<sup>3</sup>, PhD; Guergana Savova<sup>1,2</sup>, PhD

<sup>1</sup>Computational Health Informatics Program, Boston Children's Hospital, 401 Park Drive, Boston, MA, United States

<sup>2</sup>Harvard Medical School, Boston, MA, United States

<sup>3</sup>European Molecular Biology Laboratory, European Bioinformatics Institute, Hinxton, United Kingdom <sup>\*</sup>these authors contributed equally

#### **Corresponding Author:**

Jiarui Yao, PhD Computational Health Informatics Program, Boston Children's Hospital, 401 Park Drive, Boston, MA, United States

## Abstract

**Background:** Patient-derived cancer models (PDCMs) have become essential tools in cancer research and preclinical studies. Consequently, the number of publications on PDCMs has increased significantly over the past decade. Advances in artificial intelligence, particularly in large language models (LLMs), offer promising solutions for extracting knowledge from scientific literature at scale.

**Objective:** This study aims to investigate LLM-based systems, focusing specifically on prompting techniques for the automated extraction of PDCM-related entities from scientific texts.

**Methods:** We explore 2 LLM-prompting approaches. The classic method, direct prompting, involves manually designing a prompt. Our direct prompt consists of an instruction, entity-type definitions, gold examples, and a query. In addition, we experiment with a novel and underexplored prompting strategy—soft prompting. Unlike direct prompting, soft prompts are trainable continuous vectors that learn from provided data. We evaluate both prompting approaches across state-of-the-art proprietary and open LLMs.

**Results:** We manually annotated 100 abstracts of PDCM-relevant papers, focusing on PDCM papers with data deposited in the CancerModels.Org platform. The resulting gold annotations span 15 entity types for a total 3313 entity mentions, which we split across training (2089 entities), development (542 entities) and held-out, eye-off test (682 entities) sets. Evaluation includes the standard metrics of precision or positive predictive value, recall or sensitivity, and  $F_1$ -score (harmonic mean of precision and recall) in 2 settings: an exact match setting, where spans of gold and predicted annotations have to match exactly, and an overlapping match setting, where the spans of gold and predicted annotations have to overlap. GPT4-o with direct prompting achieved  $F_1$ -scores of 50.48 and 71.36 for exact and overlapping match settings, respectively. In both evaluation setting; and 12.0 to 71.80 in the overlapping evaluation setting). Results with LLaMA3 soft prompting are slightly higher than GPT4-o direct prompting in the overlapping match evaluation setting.

**Conclusions:** We investigated LLM-prompting techniques for the automatic extraction of PDCM-relevant entities from scientific texts, comparing the traditional direct prompting approach with the emerging soft prompting method. In our experiments, GPT4-o demonstrated strong performance with direct prompting, maintaining competitive results. Meanwhile, soft prompting significantly enhanced the performance of smaller open LLMs. Our findings suggest that training soft prompts on smaller open models can achieve performance levels comparable to those of proprietary very large language models.

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#### **KEYWORDS**

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patient-derived cancer models; large language models; knowledge extraction; in-context learning; soft prompting; prompt tuning; information extraction

## Introduction

Patient-derived cancer models (PDCMs) are created from a patient's own tumor sample and capture the complexity of human tumors to enable more accurate, personalized drug development and treatment selection. These models, including patient-derived xenografts (PDXs), organoids, and cell lines, allow researchers to test treatments and identify the most effective therapies, and have emerged as indispensable tools in both cancer research and precision medicine. The US National Institutes of Health (NIH) have made significant investments in the generation and characterization of these models, with more than US \$3 billion dedicated to active grants referencing PDCMs with a component of their research based on data extracted from the NIH RePORTER [1] for fiscal year 2024 alone. The number of publications using PDCMs continues to increase generating substantial and rich metadata and data that require standardization, harmonization, and integration to maximize the impact of these models and their associated data within the research and clinical communities. CancerModels.Org platform [2] serves as a unified gateway to the largest collection of PDCMs and related data. It empowers researchers and clinicians to discover suitable models for testing research hypotheses, conducting large-scale drug screenings, and advancing precision medicine initiatives. Extraction of PDCM-relevant knowledge and its harmonization within CancerModels.Org is essential to ensure that basic and translational researchers, bioinformaticians, and tool developers have access to PDCM knowledge. While manual curation of publications ensures high accuracy when performed by domain experts, it is time-consuming and labor-intensive. Thus, a more streamlined and efficient knowledge acquisition method is needed to address the growing demand within the scientific community for the timely availability of the PDCM metadata and its associated data.

In parallel, large language models (LLMs) [3-5] often referred to as generative artificial intelligence (AI) systems are trained on vast amounts of data and have demonstrated impressive capabilities in the health care domain [6-8]. Researchers have studied the use of LLMs in addressing various tasks related to health care such as diagnosing conditions [9,10], clinical decision support [11], answering patient questions [12], and medical education [13,14]. It has been shown that LLMs can extract meaningful information from texts [15-17]. In this work, we explore LLM-prompting techniques with the goal of extracting knowledge from PDCM-relevant scholarly publications. We focus on the classic direct prompting [4] and the underexplored soft prompting [18] with state-of-the-art (SOTA) proprietary and open LLMs. Our experimental results provide insights into selecting the optimal prompting methods for specific tasks. The contributions of this paper are:

- 1. Studying the feasibility of SOTA LLMs as oncology knowledge extractors for PDCM-relevant information from scholarly scientific literature.
- 2. Creating a manually curated gold dataset spanning 15 entity types for a total 3313 entity mentions from 100 abstracts of PDCM-relevant papers.
- Researching and comparing, to our knowledge for the first time, direct versus soft prompting techniques for oncology knowledge extraction, specifically PDCM-relevant information from scholarly scientific literature.

## Methods

#### Concepts

We define "knowledge" as entities of interest to researchers working with PDCMs in the cancer research field. For example, the patient's diagnosis provides a reference point to confirm that a PDCM faithfully recapitulates the biology of the original tumor and is essential for ensuring the model's relevance and reliability in studies of cancer progression or treatment response. Thus, "diagnosis" is important to understand the model's characteristics in the context of patient's disease. The patient's age can significantly affect the molecular and genetic characteristics of the tumor. For example, pediatric cancers often have distinct genetic drivers and tumor microenvironments compared to cancers in older adults. In addition, age-related biological factors, such as immune system, metabolism, and hormone levels, influence how a tumor responds to treatments. Thus, knowing the patient's age is imperative for predictive accuracy of the model in preclinical testing and relevance of research findings. Therefore, we selected 15 most commonly used CancerModels.Org data model attributes (Table 1), which include the attributes defined in the minimal information standard for patient-derived xenograft models [19] and the draft minimal information standard for in vitro models [20].



Table .	Entity definitions based on the	CancerModels.Org data mod	lel with examples and	interannotator agreem	ent $F_1$ -scores in the	e exact match se	etting
that req	uires the spans of the annotator	s to match exactly.					

Entity type	Definition	Example	IAA <sup>a</sup>
diagnosis	Diagnosis at the time of collection of the patient tumor used in the cancer model	TNBC <sup>b</sup>	61.67
age_category	Age category of the patient at the time of tissue sampling	Adult, pediatric	60
genetic_effect	Any form of chromosomal rearrange- ment or gene-level changes	Missense, amplification	57.67
model_type	Type of patient-derived model	PDX <sup>c</sup> , organoid	53.33
molecular_char	Data or assay generated from or performed on the model in this study	RNA sequencing, whole-exome sequencing	54.33
biomarker	Gene, protein or biological molecule identified in or associated with pa- tient's/model's tumor	BRCA1 <sup>d</sup> , IDH <sup>e</sup> , epidermal growth factor receptor 2	61.33
treatment	Treatment received by the patient or tested on the model	Surgery, chemotherapy, PARP-in- hibitor	55.67
response_to_treatment	Effect of the treatment on the pa- tient's tumor or model	Progression-free survival, reduced tumor growth	55
sample_type	The type of material used to gener- ate the model or how this material was obtained	Tissue fragment, autopsy	49
tumor_type	Collected tumor type used for gener- ating the model	Primary, recurrent	49.67
cancer_grade	Quantitative or qualitative grade re- flecting how quickly the cancer is likely to grow	Grade 1, low-grade	42
cancer_stage	Information about the cancer's ex- tent in the body according to specif- ic type of cancer staging system	TNM <sup>f</sup> system, T0, stage I	59.33
clinical_trial	The type of clinical trial or Clinical- trials.org identifier	Phase II, prospective randomized clinical trials	60.67
host_strain	The name of the mouse host strain where the tissue sample was engraft- ed for generating the PDX model	NOD-SCID <sup>g</sup>	61.67
model_id	ID of the patient-derived cancer model generated in this study	PHLC402	100

<sup>a</sup>IAA: interannotator agreement.

<sup>b</sup>TNBC: triple-negative breast cancer.

<sup>c</sup>PDX: patient-derived xenograft.

<sup>d</sup>BRCA1: breast cancer gene 1.

<sup>e</sup>IDH: isocitrate dehydrogenase.

<sup>f</sup>TNM: tumor node metastasis.

<sup>g</sup>NOD-SCID: nonobese diabetic severe combined immunodeficiency.

#### Corpus

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We used 100 abstracts to develop the gold-standard corpus annotated for the 15 entities (Table 1). The abstracts were chosen from publications linked to the PDCMs submitted to CancerModels.Org platform. They were selected to cover all 3 types of models in the resource-PDXs, organoids, and cell lines. The final corpus is available on GitHub (see Data and Code Availability section).

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Three annotators (ZP, TM, and EL) independently labeled entities in all 100 abstracts for a total of 40 hours. The annotation quality was tracked through interannotator agreement (IAA), a measure of agreement between each annotation produced by different annotators working on the same dataset. The IAA is an indication of how difficult the task is for humans and it becomes the target for system development. We used pairwise  $F_1$ -score as the IAA metric [21] in the exact match setting that

requires the spans of the annotators to match exactly. We computed the agreement between each pair of annotators and averaged across the 3 sets of scores. The final IAA for each entity type is reported in Table 1. The IAA range is 42 - 100 indicating moderate agreement. Note that the lowest agreement is for low occurrence entity types, for example, cancer\_grade has only 8 instances with 42 IAA. These low-frequency entity types are more likely to be overlooked by the human experts as annotation is a cognitively demanding task. Thus, to ensure a high-quality gold-standard dataset, we overlayed the single

annotations with an adjudication step, where the annotators discussed annotation disagreements and potential missed annotations to come to final joint decisions. The resulting gold dataset spans 15 entity types for a total 3313 entity mentions (refer Table 2 for distributions) was split into training, development, and test sets in the standard 60:20:20 ratio. The train set was used for creating entity extraction algorithms, the development set for refining the algorithms, and the test set for the final evaluation.

Entity type	Training, n	Development, n	Test, n	Total, n
diagnosis	362	122	114	598
age_category	19	0	0	19
genetic_effect	69	20	33	122
model_type	326	114	110	550
molecular_char	128	37	46	211
biomarker	503	118	163	784
treatment	426	77	130	633
response_to _treatment	99	21	28	148
sample_type	22	8	7	37
tumor_type	61	19	28	108
cancer_grade	6	1	1	8
cancer_stage	7	1	4	12
clinical_trial	35	2	4	41
host_strain	9	0	7	16
model_id	17	2	7	26
Total	2089	542	682	3313

Table . Distribution of entity type annotations across training, development, and test sets.

#### **Prompting Methods**

Various prompting techniques have been proposed since the emergence of LLMs [22-25]. At a high level, these prompting techniques can be divided into 2 categories, direct prompting [4] and soft prompting [18,24,26]. The main difference between the two methods is the prompt representation, that is whether the prompt consists of human language words or vectors (Figure 1). Direct prompting (or discrete prompting) is the most intuitive and now classic prompting method where users directly interact with LLMs using natural language. For example, a user may ask ChatGPT to "Write a thank you note to an old friend of my parents"; in this case, the text within the quotation marks is a discrete prompt. Soft prompting (or continuous prompting) uses

a machine learning approach to train a sequence of continuous vectors, which are the "virtual tokens" of the prompt. It is worth noting that soft prompting differs from fine tuning. With soft prompting, the LLM parameters are not updated, only the soft prompt parameters are adjusted. In contrast, finetuning requires to update the parameters of the entire LLM, and therefore needs more computation resources. Both prompting techniques have their advantages and disadvantages. Compared to direct prompting, soft prompting does not require the tedious process of manually creating prompts; however, it requires some labeled data to train the prompt. In this work, we explore both direct and soft prompting as we aim to explore the latest developments in LLMs and prompting techniques for the task of extracting PDCM entities from abstracts of academic papers.



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Figure 1. Illustration of the 2 prompting methods. In direct prompting, a prompt contains a sequence of words. In soft prompting, a prompt consists of a list of vectors. LLM: large language model.



#### **Direct Prompting**

When asking LLMs to extract entities such as diagnoses or biomarkers, the most intuitive way is to ask LLMs to output the entities directly. In example 1 below, "ALK" is a biomarker entity. One may expect the model to output *["biomarker" [ALK]]*. However, we note that the string "ALK" is mentioned multiple times in this example text, therefore it is not clear which "ALK" the model refers to. To get the most precise extraction to facilitate a more fine-grained analysis, we instruct the model to output the offsets of the specific mentions in the text (ie, the spans). For instance, if the model gives us *[(48, 51, "ALK," biomarker), (323, 326, "ALK," biomarker), ...]*, we know that from character 48 to character 51, there is a biomarker entity, "ALK." Similarly, we can find another biomarker entity "ALK" at position 323 - 326.

#### Example 1:

Oncogenic fusion of anaplastic lymphoma kinase (ALK) with echinoderm microtubule associated protein like 4 protein or other partner genes occurs in 3 to 6% of lung adenocarcinomas. Although fluorescence in situ hybridization (FISH) is the accepted standard for detecting anaplastic lymphoma receptor tyrosine kinase gene (ALK) gene rearrangement that gives rise to new fusion genes, not all ALK FISH-positive patients respond to ALK inhibitor therapies.

We started our exploration by designing prompts with an explicit instruction to specify the character offsets of each entity along with the entity text and type (eg, 48, 51, "ALK", biomarker). However, our experiments show that it was challenging for the LLM to output the correct character offsets, a seemingly straightforward task (all the model needs to do is to count the number of characters); however, the complexity of this seemingly straightforward task is likely due to the LLM's way of breaking words outside its vocabulary into so-called word pieces, for example, "organoid" is broken down into 2 word pieces "organ" and "-oid." Considering that LLMs were trained as generative models [3,4], we subsequently cast the entity extraction task as a generation task, where we instructed the model to mark the entities with XML tags. For instance, if the model outputs "Oncogenic fusion of anaplastic lymphoma kinase (<biomarker>ALK</biomarker>) with echinoderm microtubule ...," then postprocessing the output with regular expressions would find the exact position of "ALK" in the text. Specifically,

we asked the LLMs to mark the start and end of an entity with <entity\_type> and </entity\_type> tags, where entity\_type is a placeholder for the specific entity type, such as biomarker or treatment (refer Table 1 for the full list).

#### Soft Prompting

Designing the direct prompts manually could be time-consuming and minor changes in the prompt language could lead to drastic changes in the model performance [24,27]. On the other hand, soft prompting requires some amount of gold data for its training and annotating gold data by domain experts could also be time-consuming. Fortunately, only a small set of labeled data are needed to train soft prompts. As described above, we created a gold dataset, which we used for training and evaluating our soft prompting approach.

There are a few soft prompting methods, the difference usually lies in how the prompt vectors are initialized and learned. Prompt-tuning [18] is a technique that learns the prompt by adding a list of virtual tokens (ie, vectors) in front of the input, where the virtual tokens can be randomly initialized, or drawn from a pretrained word embedding [28] set. Another method is P-tuning [24], which uses small neural networks such as feedforward neural networks [29] (multilayer perceptron) or recurrent neural networks [30] (eg, long-short term memory) as the prompt encoder to learn the prompt. Only the parameters in the prompt encoder are updated during training, while the weights in the LLMs remain frozen. In our experiments, we found P-tuning did not always converge to an optimal solution for our task perhaps due to the random initialization of the vectors rather than using carefully pretrained word embeddings. Therefore, we focused on prompt-tuning in this work. Following Lester et al [18], we initialized the vectors in the prompt with the embeddings of the label words in the entity type set (Table 1).

The standard approach for entity extraction in natural language processing is via token classification [31]. Concretely, a classifier is trained to predict the label for each token in a sentence according to a predefined label set. Additionally, each label is prepended with a B or I prefix to indicate the entity's Beginning or Inside mention, respectively. An example is provided in Figure 2. "Ewing sarcoma" is an entity mention of the diagnosis type. Thus "Ewing" and "sarcoma" are labeled as "Diagnosis," while all other tokens are labeled as "O," meaning they are Outside of an entity. To be more precise, "Ewing" is at the beginning of the diagnosis entity, and "sarcoma" is inside

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of the entity, so they are labeled as "B-Diagnosis" and "I-Diagnosis," respectively.

To summarize, we trained a multiclass classifier for the soft-prompting training step. There are 15 entity types in our dataset, therefore there are  $15 \times 2+1=31$  labels for token classification, with one extra label for "O."





#### **Experimental Set-Up**

For efficiency purposes, we used Apache cTAKES [32] to split an abstract into sentences which were then passed to the LLMs to extract entities one sentence at a time. Our direct prompt included the instruction, the definition of each entity type, 5 examples (few-shot in-context learning) and the query (the sentence). The in-context learning [4] is a common practice in LLM prompting and has consistently shown improved results as the examples guide the LLM onto an optimal path [33,34]. Figure 3 presents our prompt template, and examples are in Multimedia Appendix 1.



When choosing the LLMs, we used GPT-40 [35], one of the most powerful proprietary LLMs at the time of this study, and SOTA open LLMs from the LLaMA3 family [36], including LLaMA3.1 70B, LLaMA3.1 8B, LLaMA3.2 1B, and LLaMA3.2

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prompts due to computational resource limitations; thus, our

work here is representative of the computational environment

in the vast majority of academic medical centers and research

labs. We set the soft prompt length to 30. We trained the soft prompt on the training set for 50 epochs with a learning rate of 0.001. Hyperparameters were tuned on the development set using the LLaMA3.1 8B model.

We report the evaluation results on the test set in the next section. In addition, we apply 5-fold cross-validation and report the average scores with SDs. For the 5-fold cross-validation, we excluded the 3 abstracts used to sample the gold examples for direct prompting and split the remaining 97 abstracts into 5 folds with a 20:20:20:20:17 ratio. For direct prompting, we ran the model on each fold and reported the average scores. For soft prompting, we set aside one fold as the test set and trained the soft prompts on the remaining 4 folds.

## Results

We used the standard evaluation metrics of precision or positive predictive value, recall or sensitivity, and  $F_1$ -score (the harmonic mean of precision and recall) with 2 evaluation settings: "exact match" setting requires the span output from the model to exactly match the span of the gold annotation, and "overlapping

match" setting allows the model to get partial credit if its extraction overlaps the spans in the gold annotation. For example, the model may extract "patient-derived tumor xenograft (PDX)" as a model\_type entity, while the gold annotation is "patient-derived tumor xenograft (PDX) models." Under the "exact match" setting, "patient-derived tumor xenograft (PDX)" is NOT a match to "patient-derived tumor xenograft (PDX) models;" while under the "overlapping match" setting, it is a match since the spans overlap.

Tables 3 and 4 show the evaluation results on the test set. In Table 3, we can see that under the "exact match" setting, GPT-40 direct prompting achieves the highest  $F_1$ -score of 50.48. The performances of the LLaMA3 family models drop as the model size decreases, with  $F_1$ -score from 38.40 for the 70B model to 6.78 for the 1B model. However, there is a consistent improvement in  $F_1$ -scores with soft prompting over direct prompting. For the LLaMA3.2 models, the performance of the 3B model improves significantly, with  $F_1$ -score rising from 7.06 to 46.68  $F_1$ -score—more than 8 points higher than the LLaMA3.1-70B model with direct prompting ( $F_1$ -score=38.40), despite the substantial difference in model size.

**Table**. Evaluation results on the test set (exact match) as precision or positive predictive value, recall or sensitivity, and  $F_1$ -score (harmonic mean of precision and recall).

Exact match	Precision	Recall	F <sub>1</sub> -score
Direct prompting			
GPT-40	56.09	45.89 <sup>a</sup>	50.48 <sup>a</sup>
LLaMA3.1-70B	57.27 <sup>a</sup>	28.89	38.40
LLaMA3.1-8B	35.80	18.48	24.37
LLaMA3.2-3B	25.23	4.10	7.06
LLaMA3.2-1B	23.48	3.96	6.78
Soft prompting			
LLaMA3.1-8B	47.17	45.75	46.44
LLaMA3.2-3B	47.30 <sup>a</sup>	46.09 <sup>a</sup>	46.68 <sup>a</sup>
LLaMA3.2-1B	46.19	45.01	45.59

<sup>a</sup>These are the best results.



**Table**. Evaluation results on the test set (overlapping match) as precision or positive predictive value, recall or sensitivity, and  $F_1$ -score (harmonic mean of precision and recall).

Overlapping match	Precision	Recall	F <sub>1</sub> -score
Direct prompting			
GPT-40	76.96	66.52 <sup>a</sup>	71.36 <sup>a</sup>
LLaMA3.1-70B	77.95 <sup>a</sup>	43.99	56.24
LLaMA3.1-8B	50.54	27.49	35.61
LLaMA3.2-3B	41.03	7.03	12.00
LLaMA3.2-1B	35.34	6.01	10.28
Soft prompting			
LLaMA3.1-8B	71.19	70.53	70.86
LLaMA3.2-3B	72.05 <sup>a</sup>	71.55 <sup>a</sup>	71.80 <sup>a</sup>
LLaMA3.2-1B	70.38	70.48	70.42

<sup>a</sup>These are the best results.

Similar trends are observed in Table 4 under the "overlapping match" evaluation. GPT4-o shows an  $F_1$ -score performance of 71.36, maintaining its position as the top performer for direct prompting. The 3 smaller LLaMA3 models continue to benefit from soft prompting, with the LLaMA3.2 3B model achieving slightly higher score than GPT4-o with direct prompting ( $F_1$ -scores of 71.80 vs 71.36).

Tables 5 and 6 present the results with 5-fold cross-validation under "exact match" and "overlapping" match respectively. Once again, our observations indicate that with soft prompting, the smaller LLaMA models attain performance levels comparable to GPT-40.

Table . Five-fold cross-validation results (exact match) as precision or positive predictive value, recall or sensitivity, and  $F_1$ -score (harmonic mean of precision and recall).

Exact match	Precision	Recall	F <sub>1</sub> -score			
Direct prompting, mean (SD)						
GPT-40	60.73 (2.69)	49.92 (3.46)	54.75 (2.84)			
LLaMA3.1-70B	57.56 (1.53)	31.70 (1.24)	40.87 (1.25)			
LLaMA3.1-8B	38.29 (3.29)	20.57 (2.18)	26.75 (2.61)			
LLaMA3.2-3B	27.01 (3.20)	5.25 (0.80)	8.80 (1.29)			
LLaMA3.2-1B	9.84 (5.98)	0.74 (0.47)	1.38 (0.87)			
Soft prompting, mean (SD)						
LLaMA3.1-8B	51.76 (3.09)	50.21 (2.24)	50.94 (2.55)			
LLaMA3.2-3B	50.99 (2.43)	49.54 (2.98)	50.24 (2.53)			
LLaMA3.2-1B	49.34 (3.47)	49.98 (3.19)	49.13 (3.10)			



**Table**. Five-fold cross-validation results (overlapping match) as precision or positive predictive value, recall or sensitivity, and  $F_1$ -score (harmonic mean of precision and recall).

Overlapping match	Precision	Recall	F <sub>1</sub> -score				
Direct prompting, mean (SD)							
GPT-40	77.82 (2.54)	67.52 (2.17)	72.28 (1.88)				
LLaMA3.1-70B	78.01 (1.14)	47.77 (0.71)	59.25 (0.81)				
LLaMA3.1-8B	52.75 (3.02)	29.78 (2.60)	38.04 (2.84)				
LLaMA3.2-3B	42.42 (2.89)	8.64 (1.09)	14.34 (1.64)				
LLaMA3.2-1B	22.09 (5.74)	1.67 (0.54)	3.10 (0.99)				
Soft prompting, mean (SD)							
LLaMA3.1-8B	73.78 (3.09)	73.77 (1.25)	73.75 (2.06)				
LLaMA3.2-3B	73.48 (1.97)	73.51 (1.11)	73.48 (1.31)				
LLaMA3.2-1B	71.51 (3.43)	73.25 (2.46)	72.34 (2.63)				

## Discussion

#### **Principal Findings**

Our experiments demonstrate that soft prompting, a relatively underexplored aspect of LLM prompting, can significantly enhance the performance of smaller LLMs. The 3 LLaMA models exhibit comparable performance under soft prompting (an  $F_1$ -score of 46 in the exact match setting, and 70 in the overlapping match setting). These results are particularly promising results given the limited training data, consisting of 60 abstracts with 2089 entity mentions. Please note that all  $F_1$ -scores mentioned in this section refer to the  $F_1$ -scores on the test set.

How much data is needed to train the soft prompt? To answer this question, we trained LLaMA3.2 1B model, the smallest model used in this work, with different amounts of training data. Figure 4 shows the relation between the proportion of training data and the  $F_1$ -scores on the test set (overlapping match). Solid performance was achieved with only 5% of the training data (26 sentences from 3 abstracts). With 25% of the training data (129 sentences from 15 abstracts), the model achieved an  $F_1$ -score of 68.21, only 2 points lower than using the entire training set, and only 3 points lower than GPT4-o with direct prompting. Despite the impressive performance of GPT4-o direct prompting, one potential issue is that not all data used in biomedical research can be sent to proprietary models such as GPT or the Gemini family models [8] via public application programming interfaces. That is, for applications using real patient data that require Health Insurance Portability and Accountability Act-compliant platforms, our findings demonstrate that achieving performance comparable to proprietary LLMs such as GPT4-o remains feasible through soft prompting. However, this approach necessitates a tradeoff, requiring a small set of labeled data for optimal effectiveness.



Figure 4. Performance curve of the LLaMA3.2 1B model as the size of training data increases.



Some entities appear more frequently than other entities in our dataset. For example, diagnosis and treatment mentions are more frequent than mentions of cancer\_grade. In Table 7, we present the number of instances of each entity type in our dataset and the corresponding performance of GPT4-o direct prompting. We can see that GPT4-o performs the best for the entity types that have the most instances—diagnosis, model type, and treatment entities. Of these frequent entity types, biomarker is the one with the lowest performance. Our error analysis points to several factors that could have contributed to these results, including ambiguous and inconsistent mentions and contextual dependencies. In this task, we defined a biomarker as "gene, protein or biological molecule identified in or associated with patient's/model's tumor." Thus, biomarker entities can be mentioned using their full names (eg, epidermal growth factor

receptor, Inc-RP11-536 K7.3, echinoderm microtubule-associated protein-like 4), standardized gene or protein symbols (NPM1, KRAS, PTEN) or abbreviations of metabolites (NADPH, D2HG). Moreover, a biomarker entity (eg, "MEK") often overlaps with a treatment entity (eg, "MEK inhibitor"). The ambiguity in biomarker entity mentions might interfere with the model's ability to recognize them consistently. In addition, biomarker entities are often mentioned as lists (see Example 2) resulting in a different frequency within and across the abstracts and patterns of entity mentions, in comparison with other entities. Overall, ambiguity emerges as the primary source of error. More precise definitions, accompanied by examples illustrating the distinct meanings, might present a solution. Table S2 in Multimedia Appendix 1 provides the breakdown of errors per entity type along with examples.



**Table**. Evaluation results of GPT4-o with direct prompts for each entity type as precision or positive predictive value, recall or sensitivity, and  $F_1$ -score (harmonic mean of precision and recall). Results are overlapping match setting on the test set.

Entity type	Training in- stances, n	Development in- stances, n	Test instances, n	Precision	Recall	<i>F</i> <sub>1</sub> -score	IAA <sup>a</sup>
diagnosis	362	122	114	92.47	75.44	83.09 <sup>b</sup>	61.67
age_category	19	0	0	0.0	0.0	0.0	60
genetic_effect	69	20	33	45.71	47.06	46.38	57.67
model_type	326	114	110	88.07	84.21	86.10 <sup>b</sup>	53.33
molecular_char	128	37	46	65.22	63.83	64.52 <sup>b</sup>	54.33
biomarker	503	118	163	85.05	55.49	67.16 <sup>b</sup>	61.33
treatment	426	77	130	81.74	70.15	75.50 <sup>b</sup>	55.67
response_to _treatment	99	21	28	38.64	60.71	47.22	55
sample_type	22	8	7	45.45	71.43	55.56 <sup>b</sup>	49
tumor_type	61	19	28	66.67	57.14	61.54 <sup>b</sup>	49.67
cancer_grade	6	1	1	50.0	100	66.67 <sup>b</sup>	42
cancer_stage	7	1	4	33.33	25.0	28.57	59.33
clinical_trial	35	2	4	80.0	100	88.89 <sup>b</sup>	60.67
host_strain	9	0	7	100	28.57	44.44	61.67
model_id	17	2	7	66.67	28.57	40.0	100

<sup>a</sup>IAA: interannotator agreement.

 ${}^{b}F_{1}$ -scores exceeding interannotator agreement.

#### Example 2:

Genomic alterations involved RB1 (55%), TP53 (46%), PTEN (29%), BRCA2 (29%), and AR (27%), and there was a range of androgen receptor signaling and NEPC marker expression.

The moderate performance of entity types such as genetic\_effect, molecular\_char, and response\_to\_treatment, and tumour\_type is due to the number of training instances ranging from 61 to 128 as well as the IAA ranging from 49.67 to 57.67. The moderate IAA scores of those entity types underscore the need for refined annotation protocols and modeling strategies that better capture domain-specific knowledge. Furthermore, the lower performance observed for entity types with smaller sample sizes (eg, model\_id) highlights the need for enhancing model performance on low-frequency labels. Future research could explore strategies such as data augmentation to improve the model's generalizability for underrepresented entities.

The extraction of PDCM-relevant knowledge is not an easy task for the domain experts as indicated by the IAA ( $F_1$ -score below 65 for all entity types except for model\_id). In 9 out of 15 entity types, the system performance in an overlapping match setting exceeds the IAA (last two columns of Table 7). This is the case for categories with plentiful training instances (eg, diagnosis, model\_type) as well as for categories with fewer training instances (eg, sample\_type, cancer\_grade). For the exact match setting, in 6 out of 15 entity types, the system performance exceeds the IAA (last two columns in Table 8). Therefore, the LLM could be a viable assistant, with its outputs reviewed by a domain expert to ensure the accuracy of the finalextraction. We believe such human-in-the-loop approaches present a promising direction for future research and application.

**Table**. Evaluation results of GPT4-0 with direct prompts for each entity type as precision or positive predictive value, recall or sensitivity, and  $F_1$ -score (harmonic mean of precision and recall). Results are exact match setting on the test set.

Entity type	Training in- stances, n	Development in- stances, n	Test instances, n	Precision	Recall	<i>F</i> <sub>1</sub> -score	IAA <sup>a</sup>
diagnosis	362	122	114	77.17	62.28	68.93 <sup>b</sup>	61.67
age_category	19	0	0	0.0	0.0	0.0	60.0
genetic_effect	69	20	33	25.71	27.27	26.47	57.67
model_type	326	114	110	56.88	56.36	56.62 <sup>b</sup>	53.33
molecular_char	128	37	46	54.35	54.35	54.35 <sup>b</sup>	54.33
biomarker	503	118	163	46.74	26.38	33.73	61.33
treatment	426	77	130	72.34	52.31	60.71 <sup>b</sup>	55.67
response_to _treatment	99	21	28	27.91	42.86	33.80	55
sample_type	22	8	7	45.45	71.43	55.56 <sup>b</sup>	49
tumor_type	61	19	28	50.0	39.29	44.0	49.67
cancer_grade	6	1	1	50.0	100	66.67 <sup>b</sup>	42
cancer_stage	7	1	4	33.33	25.0	28.57	59.33
clinical_trial	35	2	4	40.0	50.0	44.44	60.67
host_strain	9	0	7	100	14.29	25.0	61.67
model_id	17	2	7	66.67	28.27	40.0	100

<sup>a</sup>IAA: interannotator agreement.

 ${}^{b}F_{1}$ -scores exceeding the interannotator agreement.

We would like to note that the work presented in the paper was done in a computational environment representative of the vast majority of academic medical centers and nonindustry research labs. Although we have access to SOTA Graphics Processing Units, we still found ourselves constrained as to the extent to which we could use very large language models. The larger community needs to address the growing gap in computational resources between big tech and the rest of the research community.

#### Limitations

As this is a feasibility study, we limited ourselves to the extraction of entity mentions of 15 entity types chosen from attributes in the descriptive standards for PDCMs. While these are recognized by the PDCM and oncology community, they do not cover all knowledge in the PDCM-relevant texts. Some refinement of the entity types will be beneficial to improve prompting results.

We limited our corpus to 100 abstracts from papers associated with PDCMs deposited in CancerModels.Org. We did not assess the abstracts for the presence and equal distribution of all the entities. Thus, there were very few mentions of some entities in the corpus (eg, cancer\_stage), negatively affecting our overall  $F_1$ -score. We decided not to exclude those entities as these results could guide refinements of future studies. The computational methods discussed here are applicable to other studies requiring the extraction of textual information from scientific papers. Future work could involve extending this method to extract knowledge from the main body of the papers.

#### Conclusions

This study investigates the potential of LLMs as powerful tools for extracting PDCM-relevant knowledge from scientific literature—an essential task for advancing cancer research and precision medicine. By comparing direct and soft prompting across both proprietary and open LLMs, we provide valuable insights into the most effective strategies for PDCM-relevant knowledge extraction. Our findings indicate that GPT-40, when used with direct prompting, maintains competitive performance, while soft prompting significantly enhances the effectiveness of smaller LLMs. In conclusion, our results demonstrate that training soft prompts on smaller open models can achieve performance levels comparable to those of proprietary LLMs.

To our knowledge, this is the first study to implement SOTA LLMs prompting for knowledge extraction in the PDCM domain and the first to explore the emerging topic of soft prompting in this context. Our findings demonstrate that LLMs can effectively streamline the extraction of complex cancer model metadata, potentially reducing the burden of manual curation and accelerating the integration of PDCMs into research and clinical workflows. Additionally, this study lays the foundation for future research aimed at optimizing LLMs for large-scale knowledge extraction tasks. Efficiently extracting and harmonizing PDCM-relevant knowledge will ultimately drive progress in cancer research and precision oncology, equipping researchers and clinicians with better tools to improve patient

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outcomes. More broadly, our study contributes to the ongoing discourse on the applicability of LLMs, acknowledging that

while they offer transformative potential, they are not a universal solution for all tasks.

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#### Data Availability

The data and code will be available upon publication in the CancerModels.Org Github repository [37].

#### **Conflicts of Interest**

None declared.

#### Multimedia Appendix 1

Prompts used in direct prompting experiments and detailed error analysis. [DOCX File, 20 KB - bioinform\_v6i1e70706\_app1.docx ]

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#### Abbreviations

IAA: interannotator agreement LLM: large language model PDCM: patient-derived cancer model PDX: patient-derived xenografts SOTA: state-of-the-art



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## Using Natural Language Processing to Identify Symptomatic Adverse Events in Pediatric Oncology: Tutorial for Clinician Researchers

Clifton P Thornton<sup>1,2\*</sup>, PhD; Maryam Daniali<sup>3\*</sup>, PhD; Lei Wang<sup>3,4\*</sup>, PhD; Spandana Makeneni<sup>3\*</sup>, PhD; Allison Barz Leahy<sup>5,6\*</sup>, MD

<sup>1</sup>Center for Pediatric Nursing Research & Evidence-Based Practice, Children's Hospital of Philadelphia, 734 Schuylkill Avenue, Philadelphia, PA, United States

<sup>4</sup>College of Computing and Informatics, Drexel University, Philadelphia, PA, United States

<sup>5</sup>Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

<sup>6</sup>Cancer Center, Children's Hospital of Philadelphia, Philadelphia, PA, United States

\*all authors contributed equally

#### **Corresponding Author:**

Clifton P Thornton, PhD

Center for Pediatric Nursing Research & Evidence-Based Practice, Children's Hospital of Philadelphia, 734 Schuylkill Avenue, Philadelphia, PA, United States

## Abstract

Artificial intelligence (AI) is poised to become an integral component in health care research and delivery, promising to address complex challenges with unprecedented efficiency and precision. However, many clinicians lack training and experience with AI, and for those who wish to incorporate AI into research and practice, the path forward remains unclear. Technical barriers, institutional constraints, and lack of familiarity with computer and data science frequently stall progress. In this tutorial, we present a transparent account of our experiences as a newly established interdisciplinary team of clinical oncology researchers and data scientists working to develop a natural language processing model to identify symptomatic adverse events during pediatric cancer therapy. We outline the key steps for clinicians to consider as they explore the utility of AI in their inquiry and practice, including building a digital laboratory, curating a large clinical dataset, and developing early-stage AI models. We emphasize the invaluable role of institutional support, including financial and logistical resources, and barriers encountered spanning financial support, learning curves inherent with interdisciplinary collaboration, and constraints of time and personnel. Through this narrative tutorial, we intend to demystify the process of AI research and equip clinicians with actionable steps to initiate new ventures in oncology research. As AI continues to reshape the research and practice landscapes, sharing insights from past successes and challenges will be essential to informing a clear path forward.

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#### **KEYWORDS**

neoplasms; artificial intelligence; natural language processing; interdisciplinary research; oncology

## Introduction

The development of sophisticated machine learning, deep learning, natural language processing (NLP), and large language models has showcased artificial intelligence's (AI's) potential to accelerate advances in health care research and clinical practice [1-3]. However, growing clinician interest in employing AI as a research tool is often met with challenges in understanding its nuances and applications. The proper and safe use of AI requires in-depth knowledge of computer science, big data analytics, and specialized data science and biostatistical

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approaches – skills that clinicians typically do not possess. Conversely, computer and data scientists with expertise in AI who wish to contribute to clinical advances must develop familiarity with a clinical specialty and acquire a deep understanding of the intricacies of care delivery, research, and biomedical needs. As a result, the effective use of AI in health care environments necessitates collaborative integration between computer science and health care disciplines, bringing together expertise from these disparate fields [4-6].

Although clinicians are increasingly eager to incorporate AI into their research efforts, many face uncertainty on how to

<sup>&</sup>lt;sup>2</sup>School of Nursing, University of Pennsylvania, Philadelphia, PA, United States

<sup>&</sup>lt;sup>3</sup>Department of Biomedical and Health Informatics, Children's Hospital of Philadelphia, Philadelphia, PA, United States

begin or establish effective collaborations with computer and data scientists. Using the initial phase of our pilot AI work as an exemplar, we outline strategies for leveraging AI and NLP in pediatric cancer inquiry, focusing on the process of building a team blending AI and clinical oncology research. Our transparent account details the formation of an interdisciplinary team bridging clinical oncology and data science, highlights challenges encountered, and shares lessons learned. The purpose of this descriptive tutorial is to make AI approachable for clinical researchers who are motivated to address complex clinical questions but may lack technical expertise. Key challenges for teams to consider are explicitly identified within this study. We aim to equip clinician readers with an introductory framework for initiating AI-driven research projects, while emphasizing the logistic, financial, and personnel resources essential for success.

## The Clinical Problem and Need for an AI-Based Solution

Cancer-directed therapy is inherently toxic, causing a host of adverse events that are burdensome, costly, dangerous, and sometimes life-threatening [7-9]. When toxicities become severe, future therapy doses are reduced, delayed, or omitted, which potentially compromises long-term survival [10]. Because of these deleterious effects, research focused on early detection has been prioritized, so that prompt and effective interventions can be designed to mitigate toxicity and improve clinical outcomes [11-13].

Therapy-related toxicities are broadly categorized into nonsymptomatic and symptomatic adverse events. Nonsymptomatic adverse events are objective and easy to identify, quantify, and analyze because they are readily detectable through structured data like laboratory values or diagnostic imaging. These clean and structured data allow researchers to stratify patient cohorts, correlate symptoms with biomarkers and treatment factors, and derive actionable insights.

In contrast, symptomatic adverse events are subjective and must be elicited, interpreted, or individually assessed by clinicians [14,15]. Furthermore, these events are typically captured in unstructured, free-text clinical notes which constrains systematic identification and analysis, making data extraction labor-intensive, time-consuming, and prone to inconsistencies [7-9,16,17]. Not surprisingly, the data are often unreliable [18,19], with significant negative repercussions on subsequent analyses. The inability to reliably study symptomatic adverse events is particularly concerning because they are among the most common therapy-related toxicities and frequently lead to treatment interruptions.

AI is a promising method for the reliable extraction and analysis of symptomatic adverse events from electronic medical records (EMRs). In fact, NLP technology has already had preliminary success in identifying their presence within unstructured, free-text clinical notes [20-24].

In pediatric oncology, 5 symptomatic adverse events associated with chemotherapy stand out due to their prevalence and serious sequelae—nausea, vomiting, constipation, neuropathy, and

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mucositis. Herein, we describe our interdisciplinary approach for assessing the ability of an NLP algorithm to identify these adverse events in pediatric oncology patient records. The initial phase of this work, serving as the exemplar for this tutorial, is to evaluate the degree to which existing NLP models can identify symptomatic adverse events in pediatric cancer therapy.

## Infrastructure, Personnel, and Funding

AI-based health care research necessitates substantial data and computer science support. Optimally, this support is institutional, with health care enterprises investing in employing, contracting, or collaborating with skilled data scientists dedicated to advancing clinical inquiry. Collaboration between these technology experts and clinical researchers, along with departmental backing to support clinical inquiry and innovation, as well as the necessary data infrastructure, is essential to cultivating advancements in this emerging domain [25].

Our institution houses a Data Science and Biostatistics Unit (DSBU), a centralized service unit that comprises a robust mix of 30 PhD- and master-level biostatisticians and data scientists who work with principal investigators to address research questions via data consultation, study design, methodology expertise, data preparation, data analyses, and manuscripts development. The DSBU is housed within the Department of Biomedical and Health Informatics, which provides an academic home and service base for all research informatics activities at the institution, including the development and deployment of intellectual, technical, and educational resources in biomedical computing.

Through an enterprise-level strategic initiative, our institute developed a next-generation suite of tools and services, Arcus, that provides a digital laboratory environment for investigators and project staff to securely store, access, and process electronic patient data. The Arcus program is staffed by archivists, librarians, information analysts, cloud computing engineers, programmers, statisticians, and privacy experts. Data are managed through the oversight of the Institutional Review Board (IRB), and access is governed by multiple institutional policies. Arcus security configuration and controls are based on the HIPAA (Health Insurance Portability and Accountability Act) Security Rule.

For this work, project team members from DSBU and Arcus included 3 PhD-prepared data scientists and a data integration manager. Initial services to set up the project were provided at no cost through the internal consultation mechanisms. As the project developed and expanded, pilot funding was secured through internal grant mechanisms and preliminary data were used to secure external grant funding. A data science supervisor available through the center provided guidance in approaching an AI-based research project.

The project team's clinical experts were 2 oncology clinicians and researchers who served as coprincipal investigators—a PhD-prepared scientist and nurse practitioner under the Center for Pediatric Nursing Research and Evidence-Based Practice and Cancer Center and an attending pediatric oncologist in the Division of Pediatric Oncology and School of Medicine.

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## Building the Digital Laboratory

The clinician researchers consulted with the data science team extensively to determine necessary data elements and ensure feasibility. An IRB application was submitted, the research was determined to meet exemption criteria, and a HIPAA waiver was authorized (IRB 24 - 021922).

Activities relating to building the digital laboratory, including data flow and processing, are outlined in Figure 1. Inclusion criteria were set to any patient aged younger than 25 years who received treatment for cancer at our institution within the previous 10 years. We used *International Classification of Diseases, Ninth Revision (ICD-9)* or *International Classification* 

of Diseases, Tenth Revision (ICD-10) diagnosis codes, Current Procedural Terminology codes for cancer-directed therapies in conjunction with institutional cancer registry data to identify those who received cancer treatment ("Clinical Encounter" in Figure 1). Eligible patients were assigned a unique identifier and added to the digital laboratory. Importantly, each unique identifier retained a link to the patient's electronic health record (EHR) medical record number to ensure reliable linking of patients with relevant clinical data. Necessary EHR data elements (eg, chemotherapy administration records, clinical notes, and laboratory values) were identified via joint clinical and data science team meetings and were then imported from the data warehouse into the digital environment ("Data Warehouse" in Figure 1).

Figure 1. Research project progression and data flow from clinical encounters to the data warehouse, and manipulation within the digital laboratory environment. NLP: natural language processing.



Although careful planning to meet aims is necessary for all research projects, big data and AI-based research involves the additional step of evaluating the accessibility and reliability of data. A key challenge in building a digital lab is the extensive refinement of data that is required because digital storage of medical data differs from digital data display (the way data appears to the clinician in the EHR). Within the data warehouse, clinical notes are sorted and stored based on their version status as templated, signed, addended, or modified - with each note potentially possessing multiple versions. But in the clinical setting, the only note displayed for staff is the most recent version. Therefore, to ensure data matched the clinical documentation, the data science team wrote complex code that selected the most recent version, irrespective of its assigned status. This was essential because there are millions of source notes for this work and importing multiple versions of each is not feasible due to time, data storage, and computational processing limitations.

Chemotherapy agents were identified using medication classification codes created for the purpose of this work and then integrated with patient medication administration records to identify the specific administration time and dose. This vital step underscores the need for a skilled data scientist or analyst to be an integral member of the research team. Laboratory values, easily extracted from the source EHR data warehouse, also were imported to assist clinical researchers with interpretation of data, as needed.

After 14 months of collaborative effort, all data were imported to the laboratory ("Digital laboratory environment" in Figure 1) which included data on 18,408 patients, encompassing 4.8 million clinical notes and over 450 million medication dose administrations. From this point forward, all research activities were performed in the digital laboratory environment. It should be noted that due to the massive size of EHR data files and the sheer number of individual variables, discrete data elements are imported to the digital laboratory in the form of tables in a relational database. For example, the medication administration table comprised dozens of datapoints for each of the hundreds of millions of doses administered within our patient cohort. Similarly, the demographic information table contained dozens of variables and associated metadata for each patient. The clinical notes table not only included the full note text, but also other metadata that provided information about the notes themselves (eg, timestamps, subtype, and author type).

Identifying the relevant and necessary data elements from these tables and joining them in relational databases required the expertise of a PhD-level data scientist with fluency in programming and querying in SQL and R languages. The

clinician scientists provided direction for selecting elements but did not have the skill to perform the tasks. Once relational tables and databases were created, the team could jointly verify data integrity through face validity of items (eg, chemotherapy agents matched oncologic diagnoses for patients). The team also reviewed randomly selected medical records of patients in the database to ensure correct elements and values were identified and joined appropriately in the newly created data tables.

During the process of building the digital laboratory, unexpected challenges arose from the complexity of the structures of EHR data and the differences between digital data storage and display that complicated data pulling and importing approaches. The complexity of identifying and pulling these data was also underestimated by the data science team, and the process took much longer than expected, by a scale of about a year. Clinician researchers taking initial steps to AI-based methods should account for time required to learn new skills and take additional time to clean and validate data. However, the accessibility to data scientist and technology expert knowledge, skills, and time coupled with the infrastructure provided by institutional investments and external grant funding made the project both feasible and possible.

## Identifying Notes of Interest

Training and evaluation of the NLP model is an iterative process requiring labeled data. For this project, the labeled data are annotations of text, wherein a clinician reads through clinical notes and tags sections that indicate the absence, presence, and severity of the adverse event of interest. A typical allocation of 80% of annotated notes for model training and 20% for validation was used. The necessary number of labeled notes varies considerably depending on the complexity of the task (ie, difficulty of being able to identify the adverse event of interest) and the selected NLP methodology. For these reasons, it is not possible to a priori estimate the minimum number of notes required to adequately train and validate the model. Thus, we used an incremental annotation process starting with a minimum sample size for a limited population similar to previous work [26]. For clinician researchers accustomed to a priori-determined sample sizes, this was difficult to conceptualize and resulted in downstream challenges in time management and resource allocation for the project. Adopting a qualitative research mindset - where recruitment is ongoing until data saturation is achieved - is helpful when conceptualizing sample size for a project like this, despite being a technique not used frequently in quantitative methodologies.

The process of identifying notes for annotation required several months and the expertise of a PhD-prepared data scientist skilled in coding and data analysis. Our goal was to identify notes with a high likelihood of containing documentation related to the adverse events of interest to facilitate faster model training. As such, clinical researchers identified key scenarios and exposures associated with nausea, vomiting, constipation, neuropathy, and mucositis. This process involved specifying chemotherapy agents, dosages, and the typical time frames within which these toxicities manifest following administration. The schema used for identifying notes meeting these criteria is outlined in Figure 2.

Figure 2. Schema for identifying clinical notes to annotate for natural language processing training. BSA: body surface area; *ICD-10: International Classification of Diseases, Tenth Revision.* 



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To identify clinical notes most likely to document constipation or neuropathy, we identified instances of vincristine administration. For nausea and vomiting, highly emetogenic chemotherapy agents were identified [27]. Given that emetogenicity depends on dosage, body surface area was calculated using the most recent height and weight measurements, and doses below the emetogenic threshold were excluded. Patients undergoing conditioning chemotherapy for stem cell transplantation, which is universally highly emetogenic, were included based on an institutional transplant registry. To identify documentation of mucositis, we focused on intravenous methotrexate administrations as well as stem cell transplantation.

Chemotherapy doses were identified from the medication table, and a frequency table of administration events, including action and date and time, was reviewed to ensure proper documentation (eg, marked as "given" in the medical records). Determination of how administered medications are recorded in the data warehouse required consultation with an informaticist, since "late," multiple actions (eg "missed," "withheld," "administered," and "given") are assigned to medications in the dataset with ambiguous meanings. Cross-referencing with data visible in the EHR was required to ensure that the devised algorithm and decisions were made. As before, the clinical researchers learned that data stored in the data warehouse is far more complex than that which is displayed in the EHR. Identifying administered medications within the medication administration record in the "visible" EHR, for example, is far more straightforward, but incredibly labor-intensive.

Patient identifiers were cross-referenced with demographic and diagnosis tables, followed by the generation of a frequency table of oncologic diagnoses and associated *ICD-9* and *ICD-10* codes for each target symptom. Clinical researchers reviewed these tables for errors or incongruences to establish face validity, ensuring that chemotherapy agents matched the diagnoses. After validating these data, we cross-referenced the clinical notes table using patient identifiers to extract notes written within 14 days of chemotherapy administration for neuropathy, constipation, and mucositis; and 7 days for nausea or vomiting, in accordance with expected clinical timelines.

Initial review suggested that certain note types—such as history and physicals, progress notes, nursing notes, and discharge summaries—were most likely to contain relevant data. However, inconsistencies in data labeling posed challenges; for instance, "progress notes" were used for documentation by multiple specialties, adding noise to the dataset. After careful review, notes authored by clinical nutritionists, pharmacists, social workers, case managers, speech and language pathologists, occupational therapists, and physical therapists were excluded. Only the most recent version of each note (signed, addended, or modified) as determined by date of note initiation and note status was retained.

Key challenges to identifying relevant note types, versions, and authors arose from the time-intensive nature of extensive data extraction and manual review required. Clinical staff encountered challenges in understanding how medical record data were stored within the data warehouse, particularly

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regarding labeling of note versions and determining when patients received medications. Overcoming this challenge highlights the importance of properly understanding the metadata that accompanies variables of interest, and the parallel importance of including all metadata in the digital laboratory. As before, the team learned that the vocabulary typically used in the clinical environment does not match that used in informatics. For example, in clinical practice, "administered" or "given" are used synonymously to indicate that a patient has received a medication. However, these had different meanings in the data warehouse, so understanding how data are labeled and not making assumptions is vital. Validating the data by reviewing constructed tables and comparing them to patient medical records is necessary to ensure the integrity of the data. These are both nuanced and time-consuming steps that should be considered as expected components of all big data or AI-based research projects.

Real-time collaboration with a dedicated data scientist enabled efficient extraction and validation of large datasets. The integration of this expertise allowed for immediate adjustments based on clinical input, ensuring that the final dataset was both comprehensive and focused and underscored the importance of interdisciplinary collaboration and iterative problem-solving.

## Annotation and Validation

An annotation guide was created by the clinician researchers to standardize the annotation process and ensure consistency in identifying and grading adverse events. The guide aimed to provide clear instructions for clinical abstractors and facilitate uniform application of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) [28] to patient records.

The guide was created iteratively, beginning with an initial draft used by clinician researchers during joint annotation sessions. Common challenges encountered during annotation were documented, and adjudication decisions were included to ensure consistency. Common data extraction elements that required discussion among clinicians were included in the guide to define consensus between researchers and to provide consistency to annotators. The guide accounts for nuances of clinical documentation such as shorthand abbreviations, terminology variations, and physical exam findings. To initiate the annotation process, 100 notes, representing an intersection of chemotherapy exposures associated with all the target adverse events, were uploaded to the annotation tool. Clinicians independently annotated 30 notes, comparing results to assess alignment that facilitated refinement of the annotation guide before independently completing the remaining 70 notes. Annotation overlap and agreement were systematically evaluated, with areas of disagreement manually adjudicated and further revisions made to the guide.

A second and third batch of 100 notes was then annotated independently and annotator agreement calculated after each round. Annotator agreement was evaluated by interrater reliability calculated by tag agreement at the symptom level (constipation, mucositis, nausea, neuropathy, and vomiting) and at the symptom degree level (eg, CTCAE severity level).

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Weighted Cohen kappa quantified the level of agreement to provide a measure of agreement accounting for the likelihood of agreement occurring by chance. Manual adjudication after each round was then undertaken, followed by revision of the annotation guide. Discrepancies were explored to identify opportunities for improvement and additional nuances in clinical documentation.

Unexpectedly, initial low agreement between abstractors highlighted challenges in applying CTCAE criteria to retrospective medical records. This partially stemmed from the format of notes in the annotator tool. Because they were removed from the EMR system, there was an inability to incorporate contextual data typically used by clinicians to make severity assessments. Administration of as-needed medication, for example, was not always apparent in free-text clinical notes. Such ambiguities are inherent to retrospective reviews and reflect broader limitations in applying clinical grading systems to medical record data, but the iterative approach facilitated the creation of a detailed annotation guide and established a reliable methodology for future annotation efforts. The complexity of these clinical scenarios underscores the need for expert clinicians to remain closely involved with annotations when training AI models.

This study used a modified version of an open-source NLP pipeline, clinical text analysis and knowledge extraction system (cTAKES) [29], as a baseline for comparison against clinician annotations and our novel AI-based model in phenotyping constipation, mucositis, nausea, neuropathy, and vomiting. While cTAKES offers a valuable NLP solution for clinical text, its default configuration is computationally intensive and unsuitable for large-scale datasets. Our existing pipeline

addressed this limitation by implementing a distributed processing pipeline capable of handling millions of clinical notes. It also further enhanced cTAKES by incorporating the human phenotype ontology to improve entity recognition and improving the negation annotator to refine accuracy in identifying negated findings [30,31]. This modified cTAKES pipeline served as a baseline for evaluating the performance of our novel transformer models.

With the revised annotation guide and further adjudication between annotators,  $F_1$ -scores could be assessed between our baseline NLP model and the clinician annotators. The  $F_1$ -score accounts for both sensitivity and recall of an NLP model. The existing off-the-shelf NLP model (cTAKES) was unable to reliably identify symptomatic adverse events of interest for pediatric oncology patients based on interrater reliability, Cohen kappa, and  $F_1$ -score analyses. This is clinically problematic, as reliable identification would be necessary for clinical work and to use this model for research purposes. Furthermore, the model is unable to identify symptom severity, further highlighting a need for the development of a fit-for-purpose novel NLP model which is proposed as stage 2 of this study.

## Barriers and Lessons Learned

The first phase of this work provides valuable findings that justify continued research in this area. Our experiences as a newly developed transdisciplinary research team offer insights relevant to other teams that are beginning to integrate AI technologies into clinical research. Table 1 provides a review of our key challenges and the associated implications specific to this work.



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Table . Key challenges, impact specific to this project, and facilitators for success in overcoming challenges.

Key challenge and implications	Facilitator					
Require substantial data and computer science support						
Clinician scientists and researchers with limited knowledge in computer science and big data methodology	In-house Data Science and Biostatistical Unit with PhD- and master-level biostatisticians and data scientists					
Cost associated with collaborative efforts and time of external experts	Free data science consultation for clinical investigators and internal pilot funding that allowed securement of external grants					
Platform to manage very large data files and analyze millions of data- points in analyses	Enterprise-level strategic initiative developed a suite of tools and services for large-scale data analyses					
Complexity of data structures between electronic health records and data warehouse						
Multiple versions of millions of clinical notes needed to be reviewed to select the correct version	Collaborative effort between PhD-prepared data scientist who coded and executed the tasks and clinicians who validated the output					
Chemotherapy agents need to be identified and incorporated to patient selection as part of inclusion criteria	Senior data integration analysts created bespoke labeling system to identify all chemotherapy agents					
Clinical data and associated metadata are stored in massive, discrete data tables	PhD-level data scientists with skills in variable identification, database management, and creation of relational databases					
Extensive time for database creation and importing of large files to create a workable data model	Flexible timelines and expectations, mutual goals and understanding, and a data model that supports ongoing addition of new data elements					
Inconsistent or misunderstood data labeling in the warehouse						
Validate research data to ensure consistency with clinical entry formats	Data extraction from the data warehouse and then validated against medical records by clinician staff					
Extensive filtering of data elements to ensure integrity of data used for research purposes	Real-time collaboration between data scientists and clinician team members to refine and validate data filtering					
Subjective nature of clinical interpretation of patient scenarios						
Lack of contextual data available for clinical symptom evaluation	Expert clinicians are required to annotate text for model training					
Consistent method is needed to identify outcomes of interest to train $AI^{a}$ models	Creation of an annotation guide and consistent ontology					
Multiple targets for annotation, creating a complicated validation process	Annotation tools and software as standard components of the digital lab environment					
Transparent assessment of agreement for decision making between clinicians	Annotation review by expert clinicians to assess performance before model training and evaluation					
Bridging distinct scientific domains to enable unified project execution						
Mutual understanding of priorities, feasibility, and methodology between data science and clinical research team members	Open, clear, and respectful communication; time to understand terminol- ogy and needs; flexible timelines and ongoing dedication from all research team members					

#### <sup>a</sup>AI: artificial intelligence.

Barriers that slowed progress were primarily related to the inevitable learning curves encountered when embarking on a novel line of inquiry or acquiring a new skill set. The clinical researchers underestimated the time required to develop proficiency in these new methods and the time-intensive nature of interdisciplinary communication. Considerable effort was needed to understand how raw data are stored, transformed, and imported into a digital laboratory. This is noteworthy, not just for planning purposes for other teams, but also in understanding that data labeling and storage is unique to both the individual EMR platforms and the health institutions that use them. This makes the algorithm we have developed for identifying clinical notes specific to our institution and not likely directly transferrable to other sites. However, our methodology and approach can be replicated using institution-specific data elements and metadata, but this will require ongoing time investment.

XSL•FO RenderX Key challenges relating to the building of the digital laboratory related to the need for complex coding to identify appropriate clinical notes, the development of novel codes to identify chemotherapy agents, extensive data cleaning and refinement, and time-intensive data validation activities. Variations between how data are presented in the live, front-end version of EMR systems and how they are transformed and stored in the data warehouse created difficulty in translating between these views and ensuring the data accessed were accurate and correct. Logistic challenges related to data acquisition and organization arose from the size of datasets and tables because they included vast amounts of metadata in their raw form and extensive time for the data team to identify appropriate sources for importing. These challenges were overcome by continual partnership between clinical and data science team members and ensuring mutual understanding of needs before each phase of work.

Unfortunately, these unanticipated difficulties extended the project's timeline beyond what was initially anticipated.

Similarly, substantial time was dedicated to ensuring that the data science team comprehended the clinical scenarios underpinning this work. This reflexive exchange was critical for troubleshooting, planning data extraction, and conducting validation activities for model training. As a result, establishing the digital laboratory took significantly longer than anticipated, requiring adjustments to project timelines. Working meetings often focused on aligning terminology and achieving a mutual understanding of project milestones, underscoring the importance of interdisciplinary fluency. Finally, as with many research projects, cost considerations posed challenges. Incentives for clinicians to annotate notes could facilitate a larger group of trained annotators or dedicated research assistants, accelerating the process of achieving an adequate sample size for model training.

As AI becomes increasingly embedded in clinical practice, these models may become core components of clinical and research training programs, underscoring the need for ongoing interdisciplinary collaboration between data scientists and clinicians. These advancements signal an exciting future for AI-driven methodologies in improving patient care and advancing clinical research.

## Facilitators and Necessary Infrastructure

Key facilitators to successfully completing the initial phase of our pilot work are also summarized in Table 1, matched to the implications of this project. They mainly included robust data science infrastructure and support in addition to flexibility of time and working toward mutual understandings. The DSBU and Arcus teams supplied critical expertise, technology, and financial resources, which were leveraged to scaffold this research project and are noted essential components of this type of collaborative work [25]. The clinical researchers defined a research question amenable to AI solutions, fostering a synergistic collaboration between the teams. A balance of funding and accessible resources is needed such that a researcher can either have access to the data science personnel or be able to contract with them for research purposes. These resources enabled our team to establish relationships, evaluate feasibility, and begin data harvesting to generate preliminary data that ultimately secured external funding. Once established, ongoing collaboration, shared priorities, and mutual commitment among team members facilitated a unified direction forward and long-term engagement in the project.

Clinician investigators who desire to engage with AI research need to have affiliation with an organization that has embraced and built an environment to support this work. Doing so requires the organization to make significant financial and personnel investments and overcome several hurdles and barriers to build a team that can orchestrate a large AI platform. Organizations must first determine that the clinical or financial benefits from an AI platform outweigh the upfront costs and long-term risks, requiring a long-term investment mindset [32]. Typical approaches involve identifying AI as a potential useful tool for improving the execution of daily operations and, once instituted,

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can be used as a research platform. It is therefore primarily integrated to an organization as part of reengineering business processes [33], although there are cases of initiating AI platforms for research purposes as a primary objective. In either case, primary concerns and challenges are typically related to cost, confidentiality and security, data integration and system compatibility, and trustworthiness.

Upfront costs for AI infrastructure are high. Computational resources and power for initial training of algorithms are much higher than later simple execution of the models [34]. Lengthy time to production or to see benefit can deincentivize companies from investments [32], especially when considering that benefits and success are subject to time and other costly factors like computational power [35]. Computational resources, staff, personnel, training, and ongoing maintenance - including data audits, revised learning algorithms, ongoing data management, and updates – further add cost to AI adoption across a multitude of industries [32,34,35]. For these reasons, some smaller pharmaceutical companies, for example, have declined integration because the upfront costs are too high, unlike their larger counterparts, who see significant financial gain from even a small amount of process improvement [33]. However, taking strategic recommendations from end users, ensuring that there are well-defined problems amenable to AI-based solutions, and ensuring clear objectives for its use ensure valued return on investment [32,36].

Beyond cost, confidentiality and data security are of paramount concern, especially in health systems that are subject to stringent privacy laws and ethical considerations [6,34-36]. Safeguarding patient information requires legal counsel, information security personnel, and computer scientists. Similarly, these resources assist with concerns of data integration and system compatibility, ensuring that the AI platform can accept, synthesize, and augment existent data and work synergistically with programs already in use. For health care, this includes the EHR system, radiology software, mobile apps, pharmacy programs, billing systems, and scheduling programs.

Finally, uptake and integration of AI are halted if there is concern about the trustworthiness of the programs or if users inclusive of clinicians, staff, and patients - have unfavorable views [33]. Known trust issues, algorithmic biases, lack of transparency, and unfairness have deincentivized health systems from adopting AI because it is viewed as an unreliable technology [32,33,37]. Further, health care providers often feel threatened by AI, worried that it will replace their positions. Concern for having AI handle the large, complex tasks of care, they will only perform simple tasks and lose skill over time or have to continuously learn about emerging technologies. Past successes of using AI in health care, however, indicate that it can augment, not replace, care practices. By reconsidering AI as an enabler, health care practices have seen improvements in diagnostics, radiology, analyzing data from wearable technologies, EHR monitoring, use of digital assistants, decision support systems, and breakthroughs in drug discovery, care models, streamlining workflow, and minimizing administrative burdens [32].

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## Conclusion

Despite these barriers and unexpected challenges, the results of this pilot study emphasize the transformative potential of AI in clinical research. The successful incorporation of AI into clinical workflows can replace the labor-intensive, time-consuming, and often imprecise process of manual data extraction. The model is being trained on clinical notes from a single institution, and since institutions use individualized note templates with templated free text, the NLP model may not be transferrable to other sites. However, future phases of this project can include data imported from diverse clinical sites to refine the model and expand its capability.

NLP, in particular, holds significant promise as a methodological innovation to address the limitations of extracting symptomatic adverse events from medical records. Future use of more lightweight models or integration of a large language model into the health system may further improve research efficiency. The development of a custom workflow that allowed for parallel processing of thousands of clinical notes simultaneously by a relatively small and inexpensive model. By improving research efficiency across health system networks, AI enables the rapid and consistent identification of symptomatic adverse events among patients treated for cancer. Leveraging these large patient cohorts, researchers can better explore the etiology, management, and mitigation of therapy-related toxicities.

Progress in harnessing the potential of AI in clinical research hinges on successful partnerships between clinical and data science researchers. This transparent account of our journey as a newly formed interdisciplinary team integrating AI into oncology research provides a framework, key lessons, and actionable recommendations for clinicians aiming to explore AI applications. Success is contingent on institutional support-both financial and logistical-and the assembly of a team of data and computer scientists with aligned priorities. Regardless of previous research experience, sufficient time must also be allocated to achieve mutual understanding, acquire new skills, build trust, and foster effective working relationships. By sharing our experience, we are hopeful that readers are empowered to take their first steps with greater confidence, mitigate delays we encountered, and chart a more efficient path toward advancing their own AI-driven research endeavors.

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## **Conflicts of Interest**

None declared.

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## Abbreviations

AI: artificial intelligence cTAKES: clinical text analysis and knowledge extraction system CTCAE: Common Terminology Criteria for Adverse Events DSBU: Data Science and Biostatistics Unit EHR: electronic health record EMR: electronic medical record HIPAA: Health Insurance Portability and Accountability Act ICD-10: International Classification of Diseases, Tenth Revision ICD-9: International Classification of Diseases, Ninth Revision IRB: Institutional Review Board NLP: natural language processing

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## **Original Paper**

# A Hybrid Deep Learning–Based Feature Selection Approach for Supporting Early Detection of Long-Term Behavioral Outcomes in Survivors of Cancer: Cross-Sectional Study

Tracy Huang<sup>1\*</sup>, BA; Chun-Kit Ngan<sup>2\*</sup>, BA, PhD; Yin Ting Cheung<sup>3</sup>, PhD; Madelyn Marcotte<sup>2</sup>, BSc; Benjamin Cabrera<sup>4</sup>, BSc

<sup>1</sup>Emory University, Atlanta, GA, United States

<sup>2</sup>Worcester Polytechnic Institute, Worcester, MA, United States

<sup>3</sup>Chinese University of Hong Kong, Hong Kong, China (Hong Kong)

<sup>4</sup>Arizona State University, Tempe, AZ, United States

\*these authors contributed equally

## **Corresponding Author:**

Chun-Kit Ngan, BA, PhD Worcester Polytechnic Institute 100 Institute Rd Worcester, MA, 01609 United States Phone: 1 (508) 831 5000 Email: <u>cngan@wpi.edu</u>

## Abstract

**Background:** The number of survivors of cancer is growing, and they often experience negative long-term behavioral outcomes due to cancer treatments. There is a need for better computational methods to handle and predict these outcomes so that physicians and health care providers can implement preventive treatments.

**Objective:** This study aimed to create a new feature selection algorithm to improve the performance of machine learning classifiers to predict negative long-term behavioral outcomes in survivors of cancer.

**Methods:** We devised a hybrid deep learning–based feature selection approach to support early detection of negative long-term behavioral outcomes in survivors of cancer. Within a data-driven, clinical domain–guided framework to select the best set of features among cancer treatments, chronic health conditions, and socioenvironmental factors, we developed a 2-stage feature selection algorithm, that is, a multimetric, majority-voting filter and a deep dropout neural network, to dynamically and automatically select the best set of features for each behavioral outcome. We also conducted an experimental case study on existing study data with 102 survivors of acute lymphoblastic leukemia (aged 15-39 years at evaluation and >5 years postcancer diagnosis) who were treated in a public hospital in Hong Kong. Finally, we designed and implemented radial charts to illustrate the significance of the selected features on each behavioral outcome to support clinical professionals' future treatment and diagnoses.

**Results:** In this pilot study, we demonstrated that our approach outperforms the traditional statistical and computation methods, including linear and nonlinear feature selectors, for the addressed top-priority behavioral outcomes. Our approach holistically has higher  $F_1$ , precision, and recall scores compared to existing feature selection methods. The models in this study select several significant clinical and socioenvironmental variables as risk factors associated with the development of behavioral problems in young survivors of acute lymphoblastic leukemia.

**Conclusions:** Our novel feature selection algorithm has the potential to improve machine learning classifiers' capability to predict adverse long-term behavioral outcomes in survivors of cancer.

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## **KEYWORDS**

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machine learning; data driven; clinical domain–guided framework; survivors of cancer; cancer; oncology; behavioral outcome predictions; behavioral study; behavioral outcomes; feature selection; deep learning; neural network; hybrid; prediction; predictive modeling; patients with cancer; deep learning models; leukemia; computational study; computational biology

## Introduction

### Background

The number of survivors of cancer is increasing globally. The American Cancer Society recently reported that in 2023, a total of 1,958,310 new cancer cases were projected to occur in the United States [1]. Treatment advances have resulted in a dramatic improvement in the survival rates of most cancers, especially in resource-limited countries and regions. However, this growing population of survivors of cancer may develop a myriad of treatment-related adverse effects that lead to a compromised health status. Studies have also shown that survivors of cancer are more likely than the general population to experience negative long-term behavioral outcomes, such as anxiety, depression, attention problems, and sluggish cognitive tempo, after cancer treatments [2]. Contemporary treatment strategies have led to improved life expectancy after treatment for pediatric cancer, especially in survivors of acute lymphocytic leukemia (ALL) [3]. Given that studies have shown that the promotion of a healthy lifestyle and interventions that reduce physical and mental health burdens can lead to reduction in all-cause and cause-specific mortality, addressing the risk factors of adverse functional outcomes early on is critical [4-6]. Thus, developing an effective approach to identify crucial factors and then detect these negative outcomes in advance is needed so that medical therapists can intervene early and take the appropriate actions and treatments promptly to mitigate adverse effects in survivors of cancer.

## **Current Approaches for Detecting Adverse Behavioral Outcomes in Survivors of Cancer**

Currently, to support the identification of relevant factors and the early detection of adverse behavioral outcomes for survivors of cancer, clinical scientists use various statistical analyses to understand the relationship among those behavioral outcomes, health cancer treatments, chronic conditions, and socioenvironmental factors [7-9]. Specifically, traditional statistical methods (ie, linear regression analysis) are used to extract predictor variables and then model the relationship between the extracted predictor variables and the behavioral outcomes. This analysis assumes that the behavioral outcomes are, for the most part, linearly correlated with those predictor variables. However, this assumption may not always hold in this complex and dynamic problem. Furthermore, the predictors for those behavioral outcomes extracted by statistical methods may have weak prediction accuracy, as modeling human behavioral outcomes is challenging due to its multifactorial nature (ie, many predictors as well as interactions among the predictors affecting the outcome), heterogeneity (ie, differences across individuals), nonlinearity of data, multicollinearity (ie, highly correlated variables), class imbalance (ie, few observations of the outcome of interest), and missing data [10,11]. As a result, this class of linear regressors can only account for a small proportion of variance, with limited usability in a clinical setting. Thus, developing an effective computational methodology that can maximize the use of those data for prognostic and predictive behavioral outcomes is highly desirable.

To address the abovementioned problems, feature selection techniques in machine learning (ML) play an important role. Feature selection techniques can be broadly divided into 4 categories: filter, wrapper, embedded, and hybrid. Filter methods select features based on their statistical significance to the outcome of interest. Unlike other feature selection methods, such as wrapper and embedded methods, filter methods function independent of any ML classifiers. However, filter methods are less accurate than other methods of feature selection, such as wrapper methods. In addition, there is a risk of selecting redundant features when using filter methods that do not consider the correlation between features. Wrapper methods use a greedy search algorithm (ie, an iterative algorithm that makes the locally optimal choice at each step) with a classifier to sequentially add and remove features from the classifier to maximize the specified scoring metrics, that is, precision, recall, and  $F_1$ -score. The output is the best subset of features that the algorithm found. While wrapper methods are proficient in achieving high classification accuracy, they are not efficient in computation time or complexity. In addition, there is also a risk of overfitting with wrapper methods, where the classifier is highly trained to generate accurate predictions for the training data only and cannot correctly create generalized predictions for testing data or any novel datasets. Embedded methods use qualities from both filter and wrapper methods to perform feature selection during the construction of the ML classifiers. The baseline embedded methods that are commonly used are least absolute shrinkage and selection operator (Lasso), Ridge, and ElasticNet. However, to effectively use embedded methods, prior knowledge of the feature sets is required. In addition, embedded methods could pose problems when identifying small feature sets. Hybrid methods combine filter and wrapper methods to take advantage of the benefits each method provides, while minimizing their limitations [12]. A filter method first selects a subset of features, which are then input into a wrapper method to further select the best subset of features. As hybrid methods are a combination of filter and wrapper methods, they inherit problems from both-filter methods may exclude important features and wrapper methods are inefficient in computation time.

### **Goal of This Study**

To bridge the abovementioned gaps, we propose a hybrid deep learning-based feature selection approach to support early detection of long-term adverse behavioral outcomes in survivors of cancer. Specifically, our goals are four-fold: (1) devise a data-driven, clinical domain-guided framework to select the best set of features among cancer treatments, chronic health conditions, socioenvironmental factors, and others; (2) develop a 2-stage feature selection algorithm, that is, a multimetric, majority-voting filter and a deep dropout neural network (DDN), to dynamically and automatically select the best set of features for each behavioral outcome; (3) conduct an experimental case study on our existing study data with 102 survivors of ALL (aged 15-39 years at evaluation and >5 years postcancer diagnosis) who were treated in a public hospital in Hong Kong; and (4) design and implement radial charts to illustrate the significance of the selected features on each behavioral outcome to support clinical professionals' future treatment and diagnoses.

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In this pilot study, we demonstrate that our approach outperforms the traditional statistical and computation methods, including linear and nonlinear feature selectors, for the addressed top-priority behavioral outcomes.

## Methods

## **Review of Baseline Feature Selection Methods**

### Overview

Four baseline feature selection methods were used in the experimental studies as a comparison for our novel feature selection algorithm (Textbox 1).

Textbox 1. Summary of the baseline feature selection methods.

- Correlation-based feature selection (CFS)
- Information gain (IG)
- Maximum relevance minimum redundancy (MRMR)

#### Wrapper

- Sequential forward selection (SFS)
- Sequential backwards selection (SBS)
- Stepwise selection (SS)

#### Embedded

- Least absolute shrinkage and selection operator (Lasso)
- Ridge
- ElasticNet

#### Hybrid

- CFS→SFS
- IG→SFS
- MRMR→SFS
- CFS→SFS
- IG→SFS
- MRMR→SFS
- CFS→SBS
- IG→SBS
- MRMR→SBS
- CFS→SS
- IG→SS
- MRMR→SS

## Filter Methods

Filter methods select features based on their statistical significance to the outcome of interest, independent of any ML classifiers. To evaluate the performance of existing filter methods, we use information gain (IG), maximum relevance minimum redundancy (MRMR), and correlation-based feature selection (CFS) [13]. IG is calculated by comparing the entropy of the dataset before and after a transformation. When IG is used for feature selection, it is called mutual information and works by evaluating the IG of each variable in the context of the target. The MRMR algorithm selects the best K features at

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each iteration that have maximum relevance with respect to the target variable and minimum redundancy with respect to the other features. The CFS algorithm involves splitting the features into subsets based on whether their values are continuous or discrete and can be used to measure the correlation between features and the target outcomes. For continuous data, Pearson correlation can be used, and for discrete data, symmetrical uncertainty can be used. Symmetrical uncertainty is a measure of relevance between features and targets that uses mutual information [14]. When evaluating the performance of the existing filter methods, we selected the top 15 features that had the highest scores for each of the 3 approaches.

#### Wrapper Methods

For binary classification, wrapper methods use a greedy search algorithm with a classifier to sequentially add and remove features from the classifier to maximize the specified scoring metric, that is, precision, recall, and  $F_1$ -score. The output is the best subset of features that the algorithm found. To evaluate existing wrapper methods' performances, we selected 3 commonly implemented wrapper methods: sequential forward selection (SFS), sequential backward selection (SBS), and stepwise selection (SS). SFS starts with an empty subset of features and iteratively adds features if adding them improves the specified score, according to the ML classifier. The selection terminates when a feature subset of the desired size k, where k refers to the number of features expected by the domain experts, is reached. In contrast, SBS starts with a full subset of all the features and iteratively removes features if removing them increases the specified score, according to the classifier. The selection also terminates when a feature subset of the desired size k is reached. SS, also known as bidirectional selection, alternates between forward and backward selection to select the best subset of features. To implement the wrapper selection approaches, we used the support vector machine classifier and used accuracy as the default scoring metric [15]. We also specified that the selection process should terminate when a feature subset of size 15 is reached. For the purpose of the study, we decided a priori that the feature subset should be limited to 15 because if there are too many exploratory factors in the model, the contribution of each factor to the variance may be too small and its clinical significance may be questionable.

## **Embedded Methods**

Embedded methods use qualities from both filter and wrapper methods to perform feature selection during the construction of the ML classifier. The embedded classifiers we used were Lasso, Ridge, and ElasticNet. Lasso regression is a form of

Figure 1. Data-driven, clinical domain-guided framework.

linear regression that imposes an L1 regularization penalty to identify the features that minimize the prediction error [16]. Similar to Lasso, Ridge regression is another form of linear regression that uses an L2 penalty instead [17]. ElasticNet regression merges Lasso and Ridge regression using the L1 and L2 regularization penalties [18]. ElasticNet regression can shrink some features to zero, similar to Lasso, while reducing the magnitude of other features, like Ridge. For each evaluated embedded method, we selected the top 15 most relevant features for each behavioral outcome.

## Hybrid Methods

Hybrid methods combine filter and wrapper methods to take advantage of the benefits each method provides, while minimizing their limitations [12]. We implemented 9 different hybrid methods using the top 30 features selected from the 3 filter methods (ie, CFS, IG, and MRMR) and inputting them each into the 3 wrapper methods, including SFS, SBS, and SS, to subsequently select the top 15 features.

## Data-Driven, Clinical Domain–Guided Framework

In this section, we describe and explain our framework that consisted of 6 main modules (Figure 1). The cancer survivor medical records, including the features, such as biomarkers, chronic health conditions, and socioeconomic factors, were first passed into the data cleaner that "sanitizes" the records with the clinical domain knowledge from our investigators. Note that throughout the framework, our clinical domain experts assisted us with certain processes. In this case study, for example, it consisted of replacing missing values in a patient's record by averaging the existing values of the corresponding feature among all the other patients' records grouped by a specific cancer type, age range, and biological sex. Clinical domain experts also helped us interpret and explain what different variable values mean for us to properly transform them into the correct variables.



Afterward, the records were passed into the feature transformer, where the one-hot encoding technique was used to transform categorical variables into binary ones [19]. For instance, we transformed the "gender" variable from categorical to binary by replacing "M" and "F" with 1 and 0.

Following feature transformation, the records were normalized by the feature normalizer. The Shapiro-Wilk test, the Kolmogorov-Smirnov test, and the D'Agostino-Pearson test

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were used to check whether features follow a normal distribution. If 2 out of the 3 tests conclude that a feature follows a normal distribution, it is standardized by removing the mean and scaling to unit variance [20-22]. Otherwise, features are normalized using the minimum-maximum normalization technique so that all features have values between "0" and "1." This eliminates any feature bias, where features with high values are given more importance than features with low values [23].

Once the records are cleaned, transformed, and normalized, they are then passed into the data balancer. At this point, the results differ depending on the behavioral outcome being predicted. The synthetic minority oversampling technique for nominal and continuous (SMOTE-NC) is used to artificially balance the instances where the number of patients having a behavioral outcome of "1" is the minority, which is most often the case as cancer survivor datasets are often imbalanced. The SMOTE-NC technique oversamples the minority class in unbalanced datasets by creating synthetic examples instead of oversampling using replacement. The algorithm involves computing the median of the SD of continuous variables for the minority class and using the median to penalize nominal features that differ between the considered feature vector and its potential nearest neighbors, conducting nearest neighbors computation, and populating the synthetic class [24]. The SMOTE-NC technique is also used to artificially oversample the minority gender so the final datasets can have equal instances of "0" and "1" for the behavioral outcome. We specifically chose the SMOTE-NC technique over the regular synthetic minority oversampling technique because our dataset had a mixture of nominal and continuous features. synthetic minority oversampling technique can only handle datasets with continuous features. The data were then split into 69.6% (71/102) training and 30.4% (31/102) testing data.

Once the survivors of cancer' clinical records passed through all the steps of data preprocessing, they were passed into our hybrid deep learning-based feature selection that was a 2-stage feature selection algorithm, that is, a multimetric, majority-voting filter and a DDN, to dynamically and automatically select the best set of features for each behavioral outcome. Specifically, the first stage was a novel filter method that uses 4 metrics to select the most relevant features for a behavioral outcome and removes any redundant features. The second stage was a DDN that replaces a wrapper method, where it further selects features from the ones selected by the multimetric, majority-voting filter to maximize prediction performance in ML classifiers. Note that our clinical domain experts used their clinical expertise to recommend certain features that should be kept in all the final feature lists due to their clinical importance (ie, gender, current age, and age at diagnosis in our case), if they were not already selected to be in the final feature list by our feature selection approach. Finally, the training data with the final feature list selected from the feature selector with the clinical domain expertise were passed into 3 ML classifiers, including logistic regression, naive Bayes, and k-nearest neighbors, to calculate the precision, recall, and  $F_1$ -score for the performance evaluation on the testing data.

## 2-Stage Feature Selection Algorithm

Our proposed 2-stage feature selection algorithm consisted of 2 sequential stages, including a multimetric, majority-voting filter, and a DDN (Figure 2).



## Stage 1: A Multimetric, Majority-Voting Filter

### Overview

Our hybrid deep learning-based feature selection methodology specifically addressed the limitations of existing feature selection methods. In the first stage, it removed redundant features, which some existing filter methods do not consider. Specifically, our 3 majority-voting (MV) filter had 2 processing steps in stage 1.

In stage 1A, we used 4 different metrics to select the features that are the most relevant to predict a behavioral outcome. Those metrics include maximal information coefficient (MIC), Gini

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index (GI), IG, and correlation score (CS) that we calculated between each candidate feature in our preprocessed dataset and the corresponding behavioral outcome of interest. The MIC is a measure of the strength of the linear or nonlinear association between 2 variables X and Y, where  $X \in R$  is the input feature and  $Y \in R$  is the corresponding behavioral outcome.

The GI represents the amount of probability of a specific feature that is classified incorrectly when selected randomly. Unlike the other 3 metrics, a higher GI score represents lower associations with the behavioral outcome of interest. To make the scale of the correlation strength between *X* and *Y* consistent among all the metrics, the metric that we used was 1–GI instead.

That is, for all the 4 metrics, a higher value indicated a higher association with the behavioral outcome of interest.

The IG is a measure of the expected reduction in entropy caused by partitioning the samples according to a specific attribute *X*.

The CS between X and Y is calculated using the Pearson correlation coefficient, point-biserial correlation, and the  $\phi$  coefficient, based upon the data type of X and Y [25]. When both X and Y are the continuous variables, the Pearson correlation coefficient should be used. When comparing 1 continuous and 1 binary variable, the point-biserial correlation is used [26]. Finally, when comparing 2 binary variables, the  $\phi$  is used. All these measures are values between -1 and 1, with -1 being a perfect negative correlation and 1 being a perfect positive correlation. We take the absolute value of each measure so that the CS is always between 0 and 1.

After we calculated the values of all 4 abovementioned metrics between each candidate feature and the behavioral outcome of interest, we ranked the top N features (ie, the number of features expected by the domain experts) for each of the metrics in descending order and stored them in a master list, without repetition. From this master list, we constructed 3 feature lists. The first list contained the features selected by at least 3 metrics, as they are highly likely relevant to predict the behavioral outcome and are then included in the final feature list. The second one contained the features selected by exactly 2 metrics, as they might have been relevant to predict the behavioral outcome and were then needed for further analysis in stage 1B. The third one combined all the features from the previous 2 lists so that we could evaluate the redundancy between any 2 features from this list.

In stage 1B, we removed any redundant features from the third combined list generated from stage 1A. We used the *MIC* and the *CS* and then calculated these 2 values for all the feature-to-feature combinations in the combined feature list output from stage 1A. We subtracted the *MIC* and the *CS* values from 1 and then used the 1-MIC and 1-CS values to determine if any feature was redundant by other features. The threshold

we set was 0.05, based upon our preliminary experimental analysis, so that any combination of 2 features that resulted in both scores being <0.05 was determined to be redundant. Once it was determined that 2 features were redundant, we looked at the number of metrics that selected the features. If one of the features was selected by fewer metrics, that feature was removed from the third combined list. If both features were selected by the same number of metrics and they were redundant, we then looked at the average rank of each feature across the 4 ranked lists by MIC, GI, IG, and CS. The feature with the lower rank was removed from the third combined list. The pseudocode algorithm is detailed for the multimetric, majority-voting filter in Multimedia Appendix 1.

For illustration, we used our dataset as an example to explain our multimetric, majority-voting filter.

#### Stage 1A: Select the Top N Features Per Metric

#### Overview

Suppose we want to select the best features for predicting the behavioral outcome, thought problems. This is our *B\_Outcome*. *F* is the set of all input candidate features  $F_i$  in the preprocessed clinical records. We then calculate the MIC, 1–GI, IG, and CS scores for all the candidate features in the preprocessed clinical records and our *B\_Outcome*, thought problems. We store these results in 4 sets, *MIC*, 1–GI, *IG*, and *CS*. In this example, our domain experts expected 15 nonredundant input candidate features to be selected; thus, *N* was set to 15.

#### Step 1

We first sorted the input features (ie,  $F_{i}$ s) according to their MIC, 1–GI, CS, and IG scores. Since *N* was 15, we then took the top 15 features with the highest values from the MIC set and placed them into a separate set, that is,  $F_{MIC}$ . We repeated this with (1–GI), IG, and CS scores and placed the top 15 features into the corresponding sets, that is,  $F_{1-GI}$ ,  $F_{CS}$ , and  $F_{IG}$ . At this point, we had the following features in these sets:  $F_{MIC}$ ,  $F_{1-GI}$ ,  $F_{CS}$ , and  $F_{IG}$ . As there were 15 features in each set, we had 60 features across all the 4 sets (Textbox 2).



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Textbox 2. Total input features sorted by maximal information coefficient (MIC), 1- Gini index (GI), correlation score (CS), and information gain (IG) scores in descending order.

## F<sub>MIC</sub>

Physical fatigue>overall fatigue>cognitive fatigue>family communication>family concern>IV high-dose methotrexate (MTX)>sleep fatigue>physical activity>family conflict>parental control>family mutuality>age at cancer diagnosis>intrathecal MTX dose>noncranial radiation>cranial radiation therapy

## F<sub>1-GI</sub>

Years of education>intrathecal chemotherapy>leukemia risk group>intrathecal MTX dose>living space>physical activity>cognitive fatigue>family communication>physical fatigue>family mutuality>IV high-dose MTX>sleep fatigue>family conflict>age at cancer diagnosis>age at evaluation

#### F<sub>CS</sub>

Physical fatigue>cognitive fatigue>family communication>IV high-dose MTX>family concern>sleep fatigue>family conflict>parental control>physical activity>cranial radiation therapy>noncranial radiation>intrathecal MTX dose>years of education>family mutuality

## F<sub>IG</sub>

Impulsivity (on continuous performance test [CPT; Conner continuous performance test to measure a person's performance in attention, particularly in areas of inattentiveness, impulsivity, variation in response speed, sustained attention, and information processing efficiency] attention test)>inattentiveness (on CPT Attention test)>information processing efficiency (on CPT attention test)>hematopoietic stem cell transplant>response speed variability (on CPT Attention Test)>surgery>sustained attention (on CPT attention test)>physical fatigue>neurological complications>leukemia risk group >living space>inattentiveness (on CPT attention test)>inflammatory interleukin-7

### Step 2

We then created a new set  $F_{UNION}$ , the union of sets  $F_{MIC}$ ,  $F_{I-GI}$ ,  $F_{CS}$ , and  $F_{IG}$  in step 1, allowing duplicate values. This set  $F_{UNION}$  represents all the features that have the top 15 MIC, 1–GI, IG, and CS scores. At this point, the set  $F_{UNION}$  contained 60 total features.

## Step 3

From the set  $F_{UNION}$ , we created the subset *3Metrics*+ from the features that were stored in at least 3 of these 4 sets,  $F_{MIC}$ ,  $F_{I-GI}$ ,  $F_{CS}$ , and  $F_{IG}$ . These features were then selected as 1 of the top 15 by at least 3 out of the 4 metrics, so these are likely to be highly relevant to predict our *B\_Outcome*, thought problems, and were included in the final feature list. By applying this concept, the subset *3Metrics*+ contained 10 features.

#### Step 4

From the set  $F_{UNION}$ , we also created a subset 2Metrics from features that were stored in exactly 2 out of these 4 sets,  $F_{MIC}$ ,  $F_{1-GI}$ ,  $F_{CS}$ , and  $F_{IG}$ . These features were selected as the top 15 by 2 out of the 4 metrics only. Thus, they may be relevant to predict the *B\_Outcome*, thought problems, but needed to be further analyzed in stage 2 to determine if they should be kept in the final feature list. By applying this concept, the subset 2Metrics contained 8 features only.

#### Step 5

We created another set 3+2Metrics, that is, the union of the sets 3Metrics+ and 2Metrics, without the duplicate values. At this point, the set 3+2Metrics contained 18 features, including 10 in the 3Metrics+ set and 8 in the 2Metrics set (Textbox 3).



Textbox 3. Features in the 3Metrics+ and 2Metrics sets.

#### 3Metrics+

- Physical fatigue
- Overall fatigue
- Cognitive fatigue
- Family communication
- Sleep fatigue
- Family conflict
- Family mutuality
- Physical activity
- IV high-dose methotrexate (MTX)
- Intrathecal MTX dose

#### 2Metrics

- Leukemia risk group
- Living space
- Family concern
- Cranial radiation therapy
- Years of education
- Family control
- Age at cancer diagnosis
- Noncranial radiation

### Step 6

We also created a 1D matrix, *Rank*, which stored the average rank position of each feature in 3+2Metrics from the sets  $F_{MIC}$ ,  $F_{I-GI}$ ,  $F_{CS}$ , and  $F_{IG}$ . For instance, if we consider the feature "physical fatigue," as its position was 1, 9, 1, and 9 in the sets  $F_{MIC}$ ,  $F_{I-GI}$ ,  $F_{CS}$ , and  $F_{IG}$ , respectively, its average position value in *Rank* was equal to 5.

#### Step 7

Finally, we evaluated whether there were too many or too few features at this stage. We first evaluated the number of features in *3Metrics*+. As *3Metrics*+ had 10 features, which was less than N, there was no need to remove any extra features. We then evaluated the number of features in 3+2Metrics. As there were 18 features in 3+2Metrics, which was greater than N, there was no need to go back to step 1 to find at least 15 features. We now had 3 sets as the outputs: *3Metrics*+ with 10 features that were selected by at least 3 metrics; *2Metrics* with 8 features that were selected by exactly 2 metrics; and 3+2Metrics, with 18 features that included the features from both *3Metrics*+ and *2Metrics*.

#### **Stage 1B: Remove Redundant Input Features**

At this step, we wanted to remove any redundant features from the features that we selected in stage 1A.

#### Step 1

We computed  $1-MIC(f_i, f_j)$  values and  $1-CS(f_i, f_j)$  values by the developed *compute\_MIC* and *compute\_CS* functions between any pair of 2 features  $f_1$  and  $f_2$  in 3+2Metrics. We stored the  $1-MIC(f_i, f_j)$  values and  $1-CS(f_i, f_j)$  values in the sets *MIC\_Feature\_Score* and *CS\_Feature\_Score*, respectively.

## Step 2

We iterated each value in MIC\_Feature\_Score and CS\_Feature\_Score between any pair of 2 features  $f_1$  and  $f_2$  in 3+2Metrics and checked if any values were <0.05. We then checked if there was any feature pair that had values <0.05 in both MIC\_Feature\_Score and CS\_Feature\_Score. Suppose we found that the values in MIC\_Feature\_Score and CS\_Feature\_Score that corresponded to the feature pair, "cranial radiation therapy" and "noncranial radiation," were indeed both <0.05, then we select those 2 features as the feature pair that we need to further analyze, as they were categorized as the redundant features at this step. Suppose that "cranial radiation therapy" and "noncranial radiation" were both in the set 2Metrics, meaning that they were both selected by 2 metrics, then according to the algorithm, they were selected by an equal number of metrics and we must compare their rankings in Rank to decide which one must be removed. Suppose that "noncranial radiation" had a lower rank, or a higher score, compared to "cranial radiation therapy," then we remove "noncranial radiation" from the set 3+2Metrics.

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#### Step 3

After we removed the redundant features from the set 3+2Metrics, we then split the set 3+2Metrics into 2 new sets:  $F_{3M+}$ , such that its nonredundant features were selected by at least 3 metrics in the set  $F_{UNION}$  and  $F_{2M}$ , such that its

Textbox 4. Nonredundant features in the set F3M+ and set F2M.

#### $F_{3M^+}$

- Physical fatigue
- Overall fatigue
- Cognitive fatigue
- Family communication
- Sleep fatigue
- Family conflict
- Family mutuality
- Physical activity
- IV high-dose methotrexate (MTX)
- Intrathecal MTX dose

#### $F_{2M}$

- Leukemia risk group
- Living space
- Family concern
- Cranial radiation therapy
- Years of education
- Parental control
- Age at cancer diagnosis

At this step, we checked if the sum of features from  $F_{3M+}$  and  $F_{2M}$  was<25. After removing redundant features, we still had 17 features, which was greater than N=15; thus, we do not need to go back to step 1 in stage 1A to find at least 15 features. We can then proceed to stage 2.

#### Stage 2: A DDN

#### Overview

In the second stage, the deep neural network had a dropout parameter, where neurons are randomly ignored during construction of the neural network, to avoid model overfitting, which is a problem that the existing wrapper methods have. Thus, our methodology is better suited for finding the best features from the high-dimension, low-sample size dataset. More specifically, after the features were processed by our multimetric majority-voting filter, we passed all the nonredundant features to the deep dropout neural (DDN) network that was designed to determine whether adding any of those features selected by the only 2 metrics to the list of the features selected by at least 3 metrics resulted in a higher  $F_1$ -score. Note that this step was not conducted if the number

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nonredundant features were selected by exactly 2 metrics in the set  $F_{UNION}$ .

## Step 4

We now had 2 sets:  $F_{3M+}$  and  $F_{2M}$ . The set  $F_{3M+}$  had 10 features and the set  $F_{2M}$  had 7 features after we removed "noncranial radiation" (Textbox 4).

of the nonredundant features, that is, those features that were already selected by at least 3 metrics in stage 1, had met the domain experts' expectation. Our designed DDN network was a 2-hidden– and 1-output–layer architecture. Due to the limited number of patients' medical records with many input features, our DDN network was likely to quickly overfit a training dataset. To address this issue, we used the grid search algorithm with the *K*-fold cross-validation (CV) to find the best dropout rate for our network. We also dynamically set the network's hidden

layer size using the formula  $[\square]$ , where *I* is the number of selected input subset features and *O* is the number of labels per behavioral outcome [27]. For the remaining network's initialization parameters, default values were used [28]. The goal was to perform the hyperparameter tuning using the grid search algorithm with the *K*-fold CV to obtain the optimal parameters, and the size of each hidden layer [29].

Specifically, the subset of features selected by  $\geq 3$  metrics in stage 1 was used in building the initial network architecture to produce the baseline  $F_1$ -score. This baseline  $F_1$ -score tells us how well the network predicts that a cancer survivor will

develop the behavioral outcome of interest, using only the features selected by at least 3 metrics. Afterward, we wanted to see whether adding any subset of features selected by 2 metrics would improve the baseline  $F_1$ -score. To achieve this, we tried different combinations among the features selected by 2 metrics; added them on top of the features selected by at least 3 metrics; used all those features to build, train, and optimize our network using the grid search algorithm with the K-fold CV to obtain the optimal parameters' values; and then recorded each new  $F_1$ -score. This allowed us to compare  $F_1$ -scores between the baseline and the baseline plus additional subsets of features. If any of the new  $F_1$ -scores were higher than the baseline, then our final feature list was the one that produced the highest  $F_1$ -score. If none of the new  $F_1$ -scores were higher than the baseline, then our final feature list was simply the baseline features, that is, the features selected by at least 3 metrics. A step-by-step pseudocode algorithm for our DDN network is detailed in Multimedia Appendix 2).

Let us use our dataset as an example to explain our DDN network. At this stage, we wanted to determine whether any features selected by 2 metrics should be kept in the final feature list on top of the features selected by at least 3 metrics. Our input included the following:

- 1.  $F_{3M+}$  and  $F_{2M}$ , which were our outputs from stage 1B.
- 2. *Drop\_Out\_Rate*, a set of fine-tuning dropout rates for building a DDN network.
- 3. *D\_Train*, which was the training dataset that only included features in  $F_{3M+}$
- 4. Z, the set that included all possible subsets from  $F_{2M}$ , excluding the null set, where the size of subsets was less than or equal to N minus the size of  $F_{3M+}$  so that the total number of features does not exceed N. In our example, the set Z only included all the possible subsets of size  $\leq 5$ already had 10 because we features in non\_redundant\_three\_more and N minus 10 was 5. Given that there were 7 features in non\_redundant\_two, there were 128 possible subsets. However, because we only needed the subsets with size  $\leq 5$  and we also excluded the null set, we ended up with a total of 119 different subsets in the set Z.
- 5. M, a set of lists that add all the possible subsets in the set Z to the set  $F_{3M+}$ ; thus, there were 119 different lists.
- 6. *E\_Train*, which is the set of training datasets that includes features in each list in M.
- 7. *K*, the number of training partitions on *D\_Train* and *E\_Train* for performing CV.

#### Step 1

We wanted to find the best dropout rate for the neural network, using the *grid-search* technique,  $F_1$ -score, and *K*-fold CV, on  $D_Train$ ,  $F_{3M+}$ ,  $B_Outcome$ , and  $Drop_Out_Rate$  of a DDN network. *K* was set to 5. We thus first constructed a neural network using the *create\_DDN* function to perform the *grid-search* technique. The neural network was initialized to have a learning rate of 0.001, 500 epochs, used the "Adam" optimizer, used the "Binary Cross Entropy" loss function, had 2 hidden layers with  $\square$  number of neurons and the "Relu" activation function, and 1 output layer with 1 neuron and the activation function "Sigmoid." Suppose using the *grid-search* technique with the *D\_Train* training dataset, the  $F_{3M+}$  feature set, the *B\_Outcome* thought problems, the set of fine-tuning dropout rates *Drop\_Out\_Rate*, and using 5-fold CV, we found that the best dropout rate was 0.1 (*bestDropOutRate* was set to 0.1).

#### Step 2

We constructed a deep neural network with the initialized attributes in the *create\_DDN* function, *bestDropOutRate*,  $D_Train$ ,  $F_{3M+}$ , and  $B_Outcome$ , and then performed 5-fold CV to obtain the baseline  $F_1$ -score, F1<sub>Baseline</sub>.

#### Step 3

We then iterated through each feature set (ie,  $F_{3M+}+Z_r$ ) in Mand constructed a deep neural network with the same initialized attributes in the *create\_DDN* function, *bestDropOutRate*,  $E_Train, F_{3M+}+Z_r$ , and  $B_Outcome$ , and then performed 5-fold CV to obtain the  $F_1$ -score, F1, for each training dataset in  $E_Train$ . The hidden layer size of each neural network was calculated using the number of features in M+1, divided by 2. If any  $F_1$ -score was greater than F1<sub>Baseline</sub>, the final feature list (ie, *Final\_Features*) was set to the feature set (ie,  $F_{3M+}+Z_r$ ) in M in which the  $F_1$ -score was obtained.

#### Step 4

We had the feature list with the best  $F_1$ -score (ie, *Final\_Features*), which was passed into 3 ML classifiers: logistic regression, naive Bayes, and k-nearest neighbors.

#### Pilot Experimental Study

In our experimental study, we used a 2018 to 2020 dataset that contained 102 ALL survivors' clinical records collected from a public hospital in Hong Kong. The survivors were aged between 15 and 39 years, had completed treatment, and were >5 years postcancer diagnosis at the time of recruitment. In each patient record, there were >50 features, including demographic factors (eg, age, gender, and education level), cancer treatments received (eg, radiation, chemoradiotherapy, and surgery), inflammatory biomarkers (eg, interleukin-7, monocyte chemoattractant protein-1, and tumor necrosis factor alpha- $\alpha$ ), physical health conditions (eg, BMI, sleep fatigue, and cognitive fatigue), family life and socioeconomic descriptors (eg, family conflict, family communication and living space), attention-related outcomes (eg, measures of inattentiveness, impulsivity, and sustained attention), and lifestyle habits (eg, drinking, smoking, and physical activity). The features were obtained from a behavioral assessment that included the traditional Chinese version of the Achenbach System of Empirically Based Assessment youth self-report checklist. It consisted of syndrome scales measuring attention problems, thought problems, internalizing problems (eg, somatic complaints, anxiety and depressive symptoms, and withdrawn behavior), externalizing problems (eg, aggressive behavior, intrusive behavior, and rule-breaking behavior), and sluggish cognitive tempo. The Achenbach System of Empirically Based

Assessment measures were previously validated and used in the local young adult cancer population [9,30]. The inclusion of these features specifically in patient records was based on existing evidence in the literature and data from the local study cohort. The features predicting behavioral outcomes included clinical factors (eg, leukemia risk group, age at cancer diagnosis, and neurological complications), treatment factors (eg, cranial radiation therapy, intrathecal methotrexate dose, intravenous high-dose methotrexate, and hematopoietic stem cell transplant), socioenvironmental factors (eg, living space and family functioning), and lifestyle factors (eg, physical activity and sleep fatigue) [9,30-34].

After preprocessing the data and using our 2-stage feature selection algorithm, we selected 15 input features, expected by our medical investigators, to train and test our 3 ML classifiers, that is, logistic regression, naive Bayes, and k-nearest neighbors, to predict 6 behavioral outcomes (ie, anxiety and depression, thought problems, attention problems, internalizing problems, externalizing problems, and sluggish cognitive tempo) that our medical investigators would like to focus on. Due to their

clinical importance recommended by our medical investigators, we also added 3 more clinically relevant features (ie, gender, current age, and age at diagnosis) to the final feature list if those features had not been already selected by our 2-stage feature selection approach.

#### Ethical Considerations

Approval of this study was obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (2017.701). Written informed consent was obtained from all participants.

## Results

#### Overview

The experimental results included the  $F_1$ -score, precision, and recall on the testing data (Table 1). Note that for each feature selection method category, those scores are the average values of prediction performance among all the 3 ML classifiers for every behavioral outcome.

 Table 1.
 Average F1-scores.

Behavioral outcome	Filter	Wrapper	Embedded	Hybrid	Our method	Percentage change (our method vs highest baseline)
Anxiety and depression						
$F_1$ -score	0.624	0.437	0.585	0.449	0.738 <sup>a</sup>	+18.27
Precision score	0.562	0.407	0.563	0.424	0.708	+25.75
Recall score	0.813	0.519	0.630	0.580	0.778	-4.31
Thought problems						
F <sub>1</sub> -score	0.490	0.438	0.477	0.394	0.511	+4.29
Precision score	0.522	0.385	0.590	0.496	0.448	-24.07
Recall score	0.537	0.556	0.463	0.383	0.611	+9.89
Attention problems						
F <sub>1</sub> -score	0.348	0.417	0.440	0.350	0.568	+29.10
Precision score	0.290	0.360	0.350	0.329	0.515	+43.10
Recall score	0.463	0.519	0.630	0.424	0.667	+5.87
Internalizing problems						
F <sub>1</sub> -score	0.533	0.706	0.619	0.637	0.700	-0.85
Precision score	0.583	0.665	0.665	0.668	0.618	-7.49
Recall score	0.587	0.762	0.651	0.651	0.857	+12.47
Externalizing problems						
F <sub>1</sub> -score	0.219	0.459	0.267	0.265	0.278	-39.43
Precision score	0.230	0.417	0.278	0.297	0.444	+6.47
Recall score	0.222	0.556	0.259	0.259	0.222	-60.07
Sluggish cognitive tempo						
F <sub>1</sub> -score	0.560	0.463	0.582	0.489	0.639	+9.79
Precision score	0.542	0.409	0.577	0.494	0.570	-1.21
Recall score	0.654	0.568	0.617	0.568	0.741	+13.30

<sup>a</sup>Italicized values indicate that our score was higher than the other 4 methods.

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Our 2-stage feature selection approach outperformed or leveled the existing feature selection methods to support the prediction of 5 out of 6 behavioral outcomes (ie, anxiety and depression, thought problems, attention problems, internalizing problems, and sluggish cognitive tempo) in terms of the average  $F_1$ -scores (Table 1). Although the wrapper method outperformed our feature selection approach to support the prediction of externalizing problems, our approach's performance was more stable, as the  $F_1$ -score variance was smaller. Thus, our feature selection approach still outperforms the other 3 existing feature selection methods.

In addition, our feature selection approach outperformed or leveled the existing feature selection methods to support the prediction of 5 out of 6 behavioral outcomes (ie, anxiety and depression, attention problems, internalizing problems, externalizing problems, and sluggish cognitive tempo) in terms of precision scores (Table 1). Although the embedded method outperformed our feature selection approach to support the prediction of thought problems, our approach's performance variance was much smaller, which implies our approach was more stable.

Finally, our feature selection approach outperformed the existing feature selection methods to support the prediction of 4 out of 6 behavioral outcomes (ie, thought problems, attention problems, internalizing problems, and sluggish cognitive tempo) in terms of recall scores (Table 1). Although the filter and wrapper method outperformed our feature selection approach to support the prediction of anxiety and depression and externalizing problems, our approach's performance variance was much smaller as well.

As the  $F_1$ -scores were calculated from both precision and recall scores, we can infer that our feature selection approach improves the  $F_1$ -scores largely because it increases the recall scores as opposed to the precision scores (Table 1). Overall, the experimental results show promising evidence that our method improves the ML classifiers' prediction performance to support better early detection of long-term behavioral outcomes in survivors of cancer.

## **Radial Feature Charts**

Radial feature charts were generated for each of the 6 behavioral outcomes analyzed, including anxiety and depression, thought problems, attention problems, internalizing problems, externalizing problems, and sluggish cognitive tempo (Figure 3). Each chart includes the top 15-plus features selected by our proposed methodology. The size and the color of each red slice is measured by the unified metric value of each feature, which is calculated by averaging the scores of the metrics that select each feature during stage 1A of our proposed method.

The variables represent the documented risk factors associated with the development of behavioral problems in the literature. They include (1) sociodemographic variables (ie, age at evaluation and gender), (2) clinical variables (ie, age at cancer diagnosis, intrathecal chemotherapy, intrathecal methotrexate dose, IV high-dose methotrexate, and inflammatory interleukin-8 levels), and (3) socioenvironmental and lifestyle variables (ie, sleep, fatigue, physical activity, and family functioning). Physicians can interpret the charts by seeing which features have the darkest color and largest size, indicating higher unified metric values and thus greater associations with the behavioral problem of interest. Those features can then be further used to devise customized prevention plans and advice.



Figure 3. Radial feature charts.



## Discussion

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### **Principal Findings**

In this work, we sought to develop a prognostic ML framework and feature selection approach to predict the trajectory of functional outcomes in a specific population: survivors of ALL. Our hybrid deep learning-based feature selection approach outperforms or equals the existing feature selection methods

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assessed (ie, filter, wrapper, embedded, and hybrid) for 5 out of 6 long-term behavioral outcomes. Even in cases where our feature selection method did not outperform existing methods, our approach's performance variance was much smaller and thus more stable. We observed that the performance of the model was significantly weaker in predicting externalizing problems than internalizing problems. This may be attributed to the complex phenotypic nature of externalizing behaviors, such as antisocial or aggressive behaviors and conduct problems. In

addition, there are other factors that may predict externalizing problems that were not considered in this study. For example, our previous work showed that increased screen time during the COVID-19 pandemic was associated with inattentiveness and impulsivity in pediatric survivors of cancer in China, but screen time was not included in the data [35]. Social support and rehabilitation, which are important interventions addressing behavioral functioning and mental health in young Chinese survivors of cancer, were also not assessed in this study [36]. From the data, we infer that our feature selection approach improves  $F_1$ -scores from ML classifiers compared to existing feature selection methods largely because it increases the recall scores as opposed to the precision scores. We also developed radial feature charts that can quickly and effectively help clinicians understand which predictor variables were most important in predicting long-term behavioral outcomes. Overall, the experimental results show promising evidence that our method improves ML classifiers' prediction performance on high-dimension low-sample size data, which can support better early detection of long-term behavioral outcomes in survivors of cancer.

### Limitations

Our study was limited to a pilot study with young Chinese survivors of leukemia. As one's neurodevelopment and social skills are often dependent on cultural norms, our findings may not be extrapolated or applicable to other populations. However, the contemporary treatment for childhood ALL is similar in most countries or regions, consisting of high-dose methotrexate, intrathecal chemotherapy, and a standard set of intravenous and oral chemotherapy drugs as the backbone. Therefore, we reasoned that our findings may still be generalizable to the existing population of individuals in the health care system of Hong Kong who have survived leukemia over the past decade. In addition, although clinical domain experts assisted with additional input for the features that were kept in ML classifiers, there remains room for human error, and domain experts' opinions may occasionally differ from what features would optimize ML classifiers' performance. Furthermore, as this is a cross-sectional study, it was not possible to delineate the causal relationship between the risk factors and behavioral outcomes. The model developed through this study should be validated in a larger cohort with prospective collection of outcome data to better reflect the trajectories of functional outcomes in these young survivors as they advance from young to middle adulthood. Finally, additional biases may have influenced the data, such as those related to patients who had access to hospital care and were willing to share their data with our clinical investigators.

#### **Comparison With Prior Work**

Our findings reinforce existing evidence that adverse behavioral outcomes in survivors of cancer are a complex and multifactorial phenotype. Most preexisting research is focused on either disease- or treatment-related factors as predictors of cognitive dysfunction. However, socioenvironmental factors play an important role in the neurodevelopment of these young survivors. Our findings showed the interaction and unique contribution of the socioenvironmental factors, such as family

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dynamics and lifestyle factors, on anxiety, depression, and sluggish cognitive symptoms in survivors. Studies have found associations of parents' psychological distress on the child's cognitive and behavioral outcomes [8,37]. Environmental events can elicit a biological stress response that results in neurological reactions to that stress. This is especially relevant in the context of Hong Kong and Mainland China, where much emphasis is now placed on ameliorating the adverse health effects of the urban environment in children and adolescents. The findings provide directions for the development of multidisciplinary services and interventions. For example, social workers can pay more attention to the occupational or employment challenges of young survivors who experience fatigue symptoms from treatment and manifest adverse behavioral outcomes. The study findings can help us identify high-risk subgroups from dysfunctional families or households struggling with financial problems and conflicts. Interventions that promote self-confidence and positive peer interaction can be implemented during the early survivorship phase when young survivors transit back to their full-time school or work.

Our results also build upon existing computational methods and feature selection approaches for predicting behavioral outcomes in survivors of cancer. Traditional computational methods in the clinical and social sciences typically use regression analysis to model the relationship between  $\geq 2$  variables for prediction. However, modeling human behavioral data is challenging due to its multifactorial nature, heterogeneity, nonlinearity of data, and class imbalance [10,11]. As a result, the model can only account for a small proportion of variance, with limited utility in clinical settings. For example, we have reported that cranial radiation, chronic health conditions, and poor physical activity are associated with worse cognitive and behavioral outcomes in Chinese survivors of childhood leukemia [9]. However, these factors only accounted for 22.9% to 35.8% of the variance in the traditional regression models. Identifying an effective computational method that minimizes algorithmic bias, such as the 2-stage feature selection algorithm within the clinical domain-guided framework outlined in this study, can maximize the use of clinical and behavioral data for predictive purposes. Such prognostic models will aid in informing strategies aimed at changing behavior and designing social and clinical interventions.

## Conclusions

Future studies can validate our prediction model in other Chinese populations of survivors of cancer sharing similar cultural norms in mainland China and Taiwan, as well as validate the model in larger samples with a longitudinal prospective cohort study design. In addition, studies can further investigate the real-world feasibility of incorporating such algorithms into health care systems as risk stratification tools to assist clinicians and psychologists in identifying patients at risk of adverse behavioral outcomes. Incorporation of diverse populations, larger sample sizes, and similar prediction models in future studies may provide deeper insights into the interaction among clinical, treatment, socioeconomic, and lifestyle factors and their impact on functional outcomes, ultimately enabling the incorporation of such multifactorial insights to improve strategies for the personalized care of patients with cancer.

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Given that we are working with such small cancer survivor datasets, even a slight improvement in prediction performance from ML classifiers can make a substantial difference in helping survivors of cancer. Our data-driven, clinical domain–guided approach can potentially address the problem of "high dimension low sample size." The pilot analysis shows that this approach has allowed us to identify a set of interacting clinical and socioenvironmental characteristics that predicted behavioral outcomes in survivors.

In late 2019, the American Cancer Society had a special call for attention to financial, social, and emotional concerns that uniquely affect young survivors of cancer [38]. Currently, in Hong Kong, there are no centralized cancer programs for adolescent and young adult patients. From a clinical perspective, identifying the unique factors associated with interindividual differences in functional outcomes will help clinicians to identify individualized modifiable risk factors. This will contribute to the development of a personalized, patient-centered cancer care program for local patients with cancer. From a research perspective, this project serves as a pilot study to apply ML-based prognostic technology, guided by clinical knowledge, on a combination of objective data (ie, clinical and demographics variables) and subjective data (ie, behavioral and patient-reported variables). The framework and algorithms developed through this analysis can be applied to address clinically relevant research questions in patients with other chronic diseases. The aim of this application is in line with the recent call by the government of the Hong Kong Special Administrative Region to harness data-driven analytics to formulate health care policies [39].

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## **Conflicts of Interest**

None declared.

### Multimedia Appendix 1

Step-by-step pseudocode algorithm for the multimetric, majority-voting filter. [DOCX File , 22 KB - bioinform\_v6i1e65001\_app1.docx ]

## Multimedia Appendix 2

Step-by-step pseudocode algorithm for the DDN network. [DOCX File, 18 KB - bioinform\_v6i1e65001\_app2.docx]

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## Abbreviations

ALL: acute lymphocytic leukemia CFS: correlation-based feature selection CS: correlation score CV: cross-validation DDN: deep dropout neural network GI: Gini index IG: information gain Lasso: least absolute shrinkage and selection operator MIC: maximal information coefficient ML: machine learning MRMR: maximum relevance minimum redundancy SBS: sequential backwards selection SFS: sequential forward selection SMOTE-NC: synthetic minority oversampling technique for nominal and continuous SS: stepwise selection

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