Harnessing Big Data and Precision Medicine – Intelligent & Integrative Data Analysis for Health Impact

Presented by: **Zeeshan Ahmed, Ph.D.**

CDC

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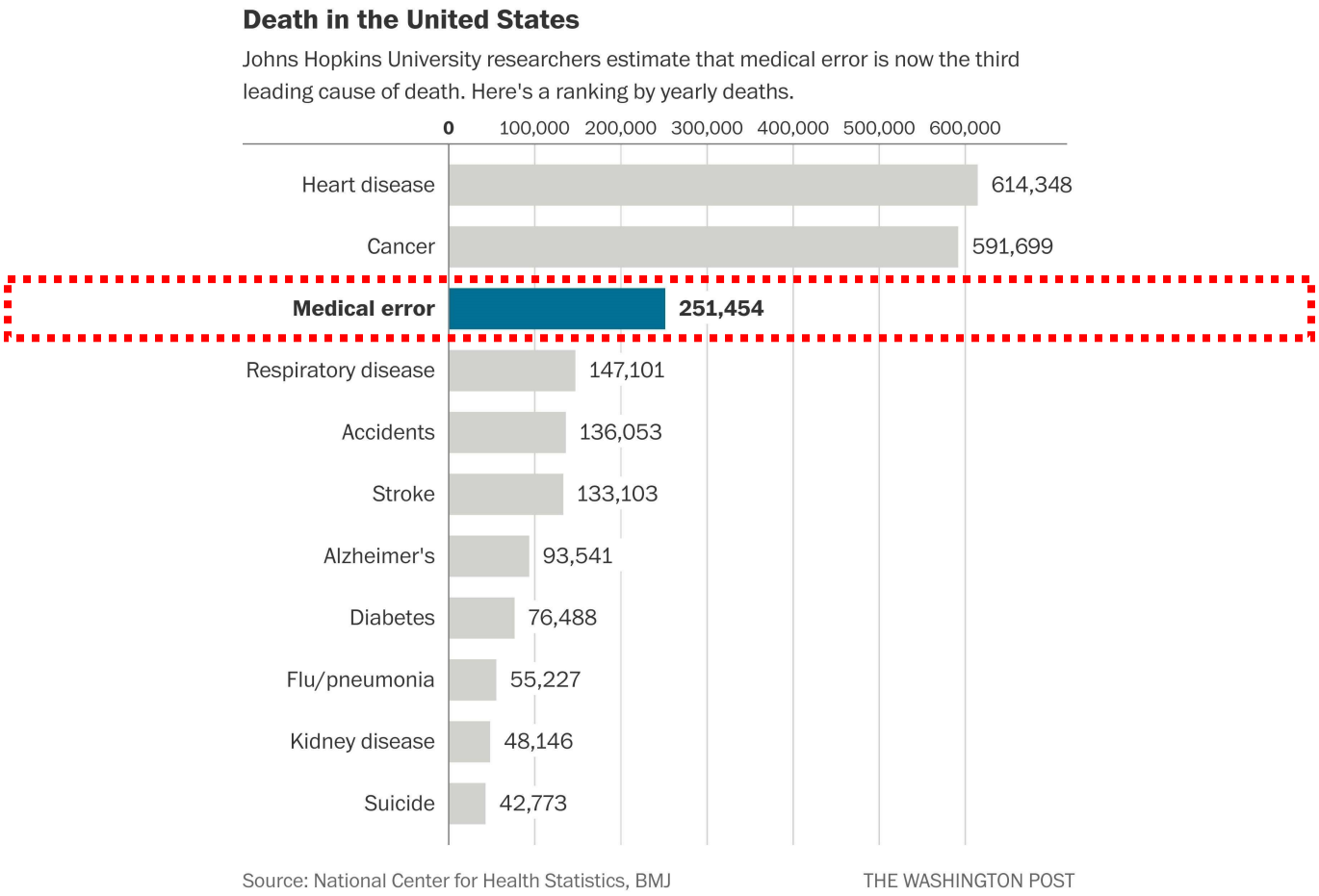
One of three leading causes of deaths



Articles in PMC - NCBI

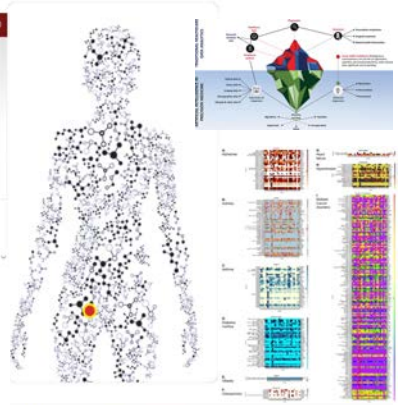
Medication error: Over 200,000

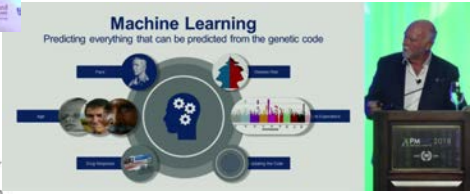
Delayed treatment: Over 600,000

URL: https://www.ncbi.nlm.nih.gov/pmc/

Precision Medicine

Trending … … …





PMWC® SILICON VALLEY JAN. 20-23
PRECISION MEDICINE WORLD CONFERENCE 2019

"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"

President Obama, January 30, 2015

https://obamawhitehouse.archives.gov/precision-medicine

Precision Medicine Initiative

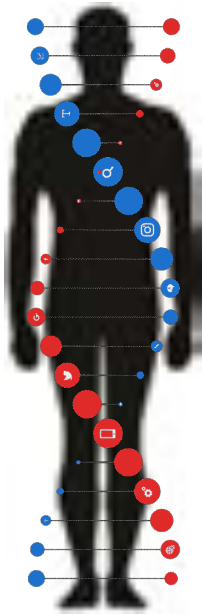
Institute for Health, Health Care Policy and Aging Research
Rutgers University-New Brunswick

Robert Wood Johnson Medical School
Rutgers Biomedical and Health Sciences

Precision Medicine?

Lifestyle

Genomics



Clinics

Phenotype

Metabolomics

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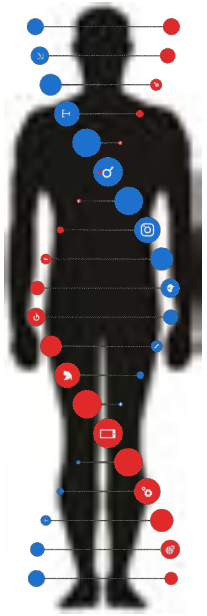
Lifestyle

Genomics



Clinics

Phenotype

Metabolomics

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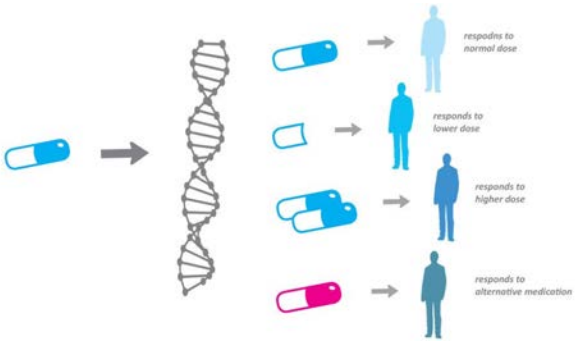
Healthcare Data and Precision Medicine

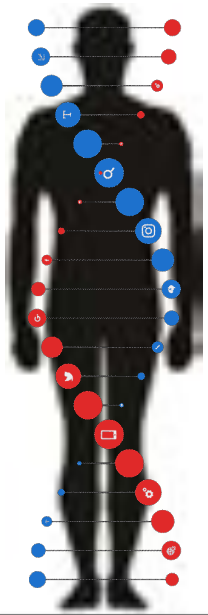
Personalized Treatment

Predictive Diagnostic

Lab tests

Diagnoses





Clinics

Medications

Procedures

Providers

Practices

Enterprises

CDC

Oak Ridge Institute For Science and Education

Integrating Sequence Data and Precision Medicine

Personalized Treatment

Predictive Diagnostic

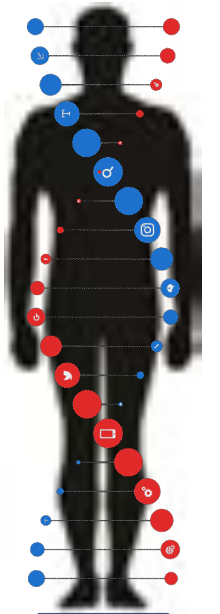
Genomics

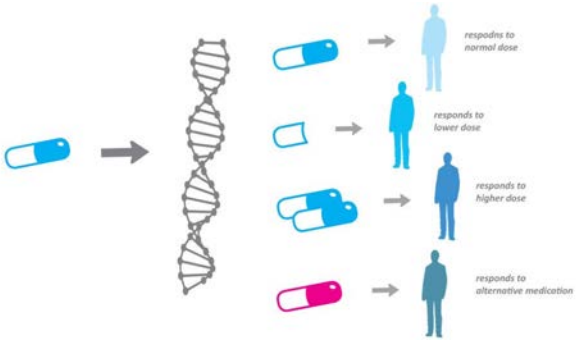
A portion of DNA molecule that serves as the basic unit of heredity.

Genes

Permanent alteration of the nucleotide sequence of the genome.

Mutations





SNPs

DNA sequence variation occurring in a single nucleotide – A (Adenine), C (Cytosine), G (Guanine), T (Thymine).

Transcripts

Protein sequence transcribed from DNA that forms different types of RNA and protein.

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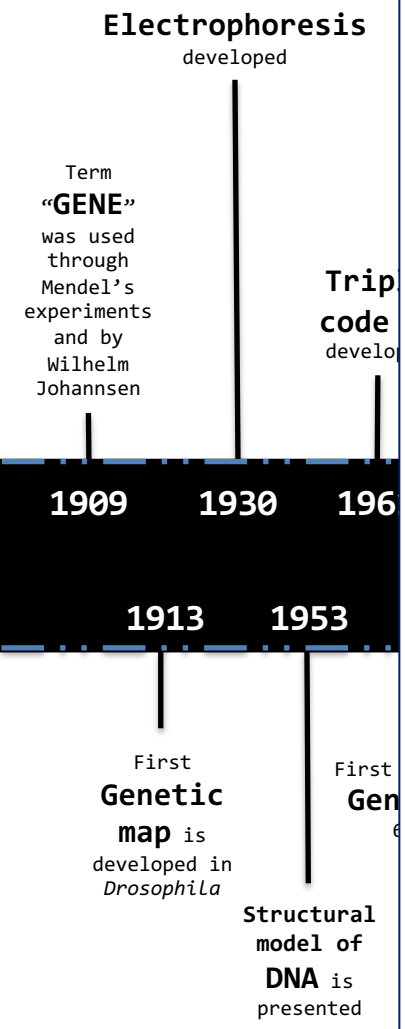

OXFORD

Briefings in Bioinformatics, 21(3), 2020, 885–905

doi: 10.1093/bib/bbz038
Advance Access Publication Date: 11 April 2019
Review article

100 Years of evolving gene–disease complexities and scientific debutants

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*These authors are equally contributing first authors.

Abstract

It's been over 100 years since the word 'gene' is around and progressively evolving in several scientific directions. Time-to-time technological advancements have heavily revolutionized the field of genomics, especially when it's about, e.g. triple code development, gene number proposition, genetic mapping, data banks, gene–disease maps, catalogs of human genes and genetic disorders, CRISPR/Cas9, big data and next generation sequencing, etc. In this manuscript, we present the progress of genomics from pea plant genetics to the human genome project and highlight the molecular, technical and computational developments. Studying genome and epigenome led to the fundamentals of development and progression of human diseases, which includes chromosomal, monogenic, multifactorial and mitochondrial diseases. World Health Organization has classified, standardized and maintained all human diseases, when many academic and commercial online systems are sharing information about genes and linking to associated diseases. To efficiently fathom the wealth of this biological data, there is a crucial need to generate appropriate gene annotation repositories and resources. Our focus has been how many gene–disease databases are available worldwide and which sources are authentic, timely updated and recommended for research and clinical purposes. In this manuscript, we have discussed and compared 43 such databases and bioinformatics applications, which enable users to connect, explore and, if possible, download gene–disease data.

Key words: gene; disease; databases; bioinformatics; precision medicine

Introduction

Despite all of the scientific knowledge, much of medicine is still based on the treatment of symptoms and performing learned trials based on treatments, which works for most patients. Genetic research is assisting in producing tailored solutions to each individual, rather than what works for the average population, and understanding who is at risk for critical diseases like diabetes, high blood pressure or cancer. The variability in human genome sequence is a result of the biological code responsible for the development and functioning of a human being [1–6]. The complexity of human deoxyribonucleic acid (DNA) is a measure of the information contained within the DNA, and the maximal information possible in a solution of genomic DNA purified from a tissue or cell is equivalent to the total number of base pairs (bps) present in the haploid genome [7–12]. The majority (~62%) of the human genome comprises of intergenic regions, the non-protein coding parts of the genome that lie between genes, used to be called 'junk DNA', but now genome research over the past few years has revealed functions associated with these regions, suggesting that every part of the genome may have some importance [13–23]. Intergenic DNA may also include gene regulatory sequences [24–31], such as promoters [32–37], enhancers [38–43] and silencers [44–46] that have yet to be characterized. Ribonucleic acid (RNA) [47–54] is the transcribed form of DNA and messenger RNA (mRNA) is the protein-coding form of RNA [55,56]. Non-coding RNAs, such as transfer RNA (tRNA) [57–59], micro RNA (miRNA) [60–62], ribosomal RNA (rRNA) [63–67] and long non-coding RNA (lncRNA) [68–71], play various roles in the cell, from protein translation to gene regulation.

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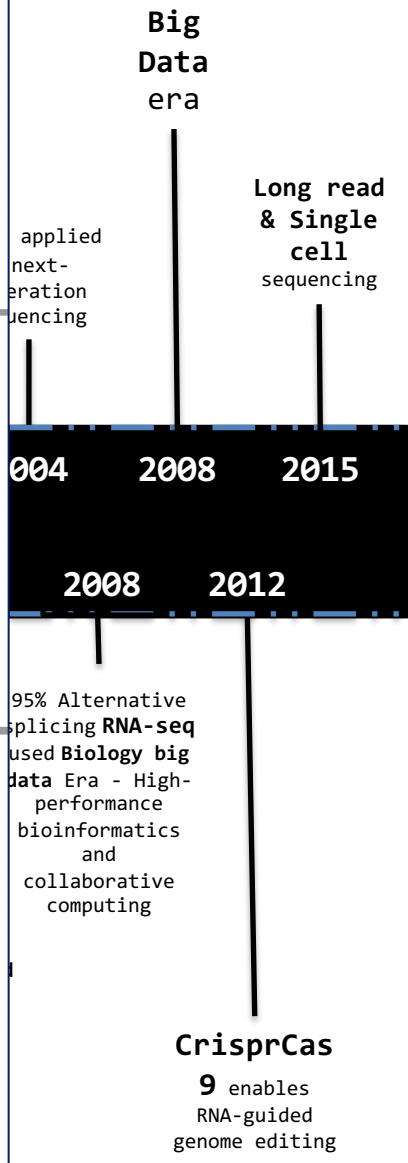
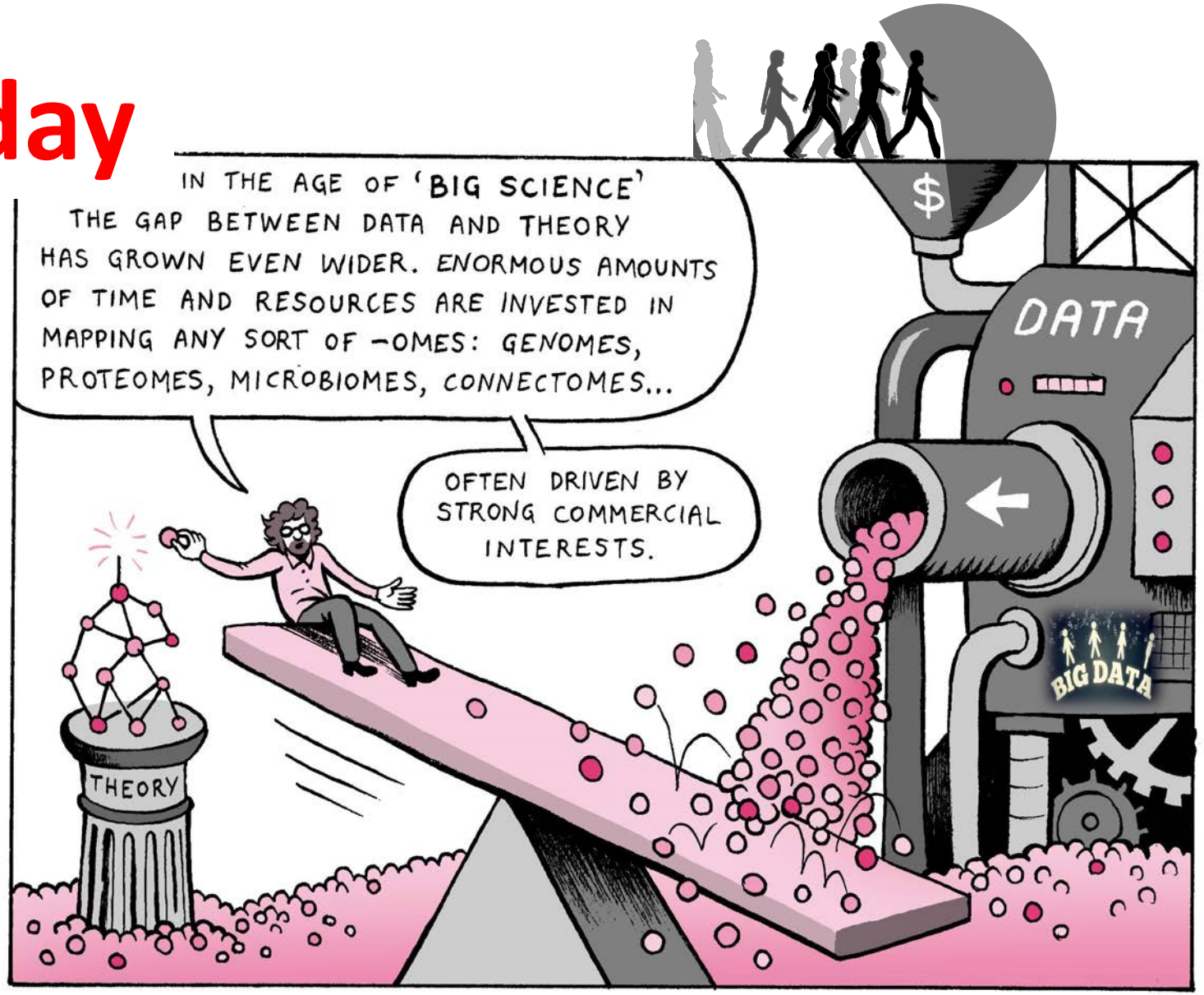


Today


IN THE AGE OF 'BIG SCIENCE' THE GAP BETWEEN DATA AND THEORY HAS GROWN EVEN WIDER. ENORMOUS AMOUNTS OF TIME AND RESOURCES ARE INVESTED IN MAPPING ANY SORT OF -OMES: GENOMES, PROTEOMES, MICROBIOMES, CONNECTOMES...
OFTEN DRIVEN BY STRONG COMMERCIAL INTERESTS.
$
DATA
BIG DATA
THEORY

Research Investigators

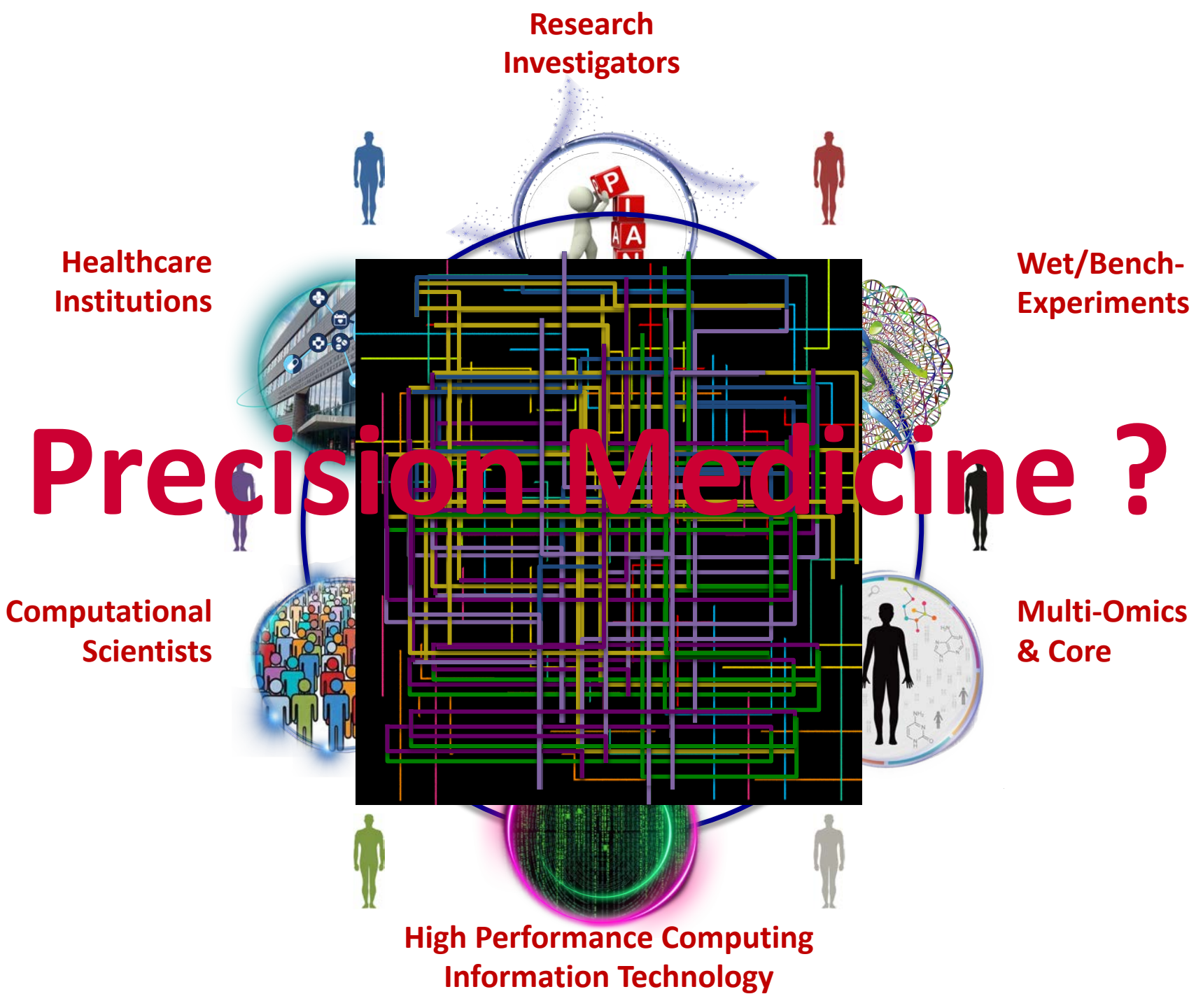
Healthcare Institutions

Wet/Bench-Experiments

Computational Scientists

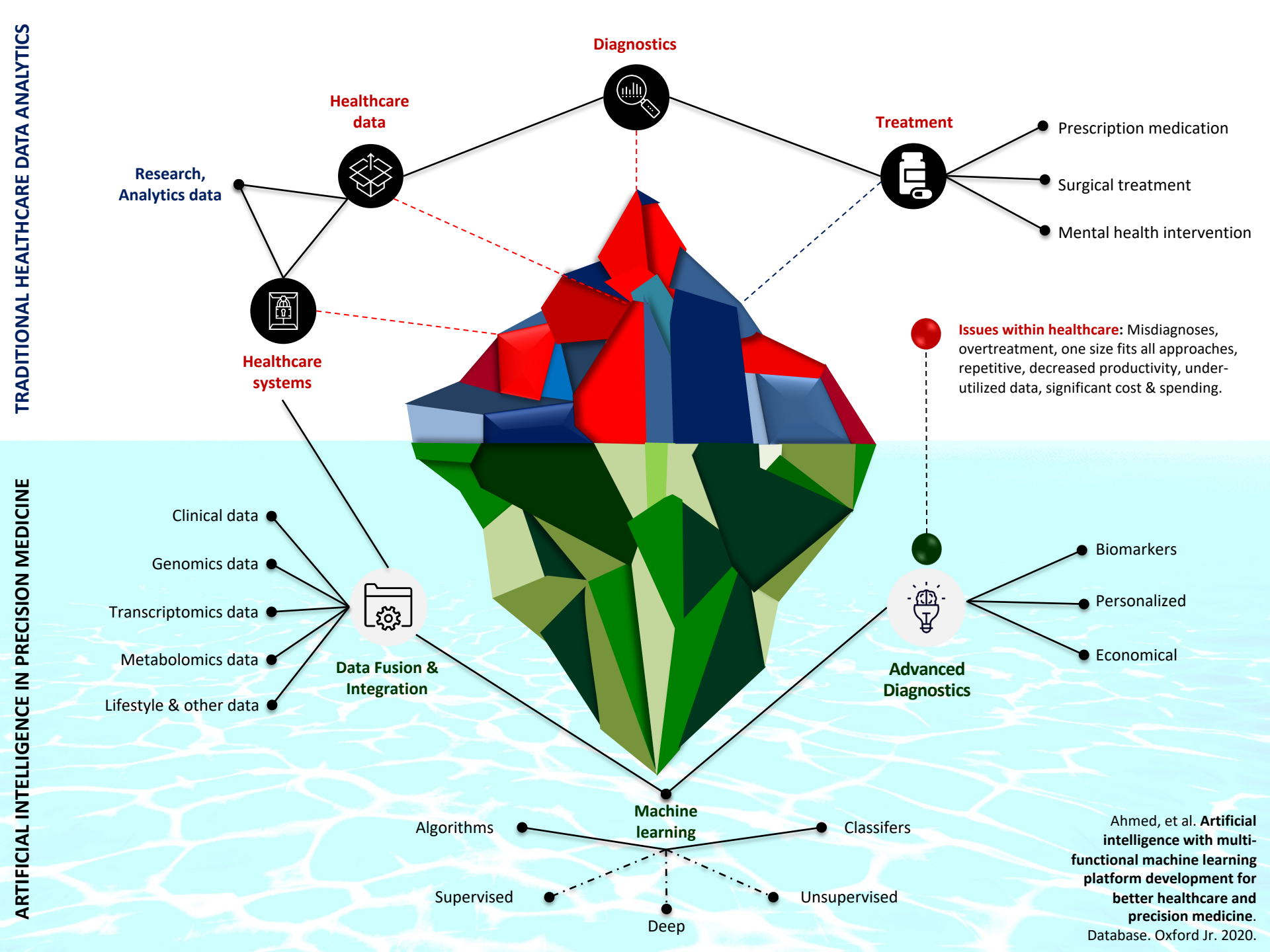
Multi-Omics & Core

High Performance Computing
Information Technology


Research
Investigators
Healthcare
Institutions
Wet/Bench-
Experiments
Precision Medicine ?
Computational
Scientists
Multi-Omics
& Core
High Performance Computing
Information Technology

Precision Medicine ?

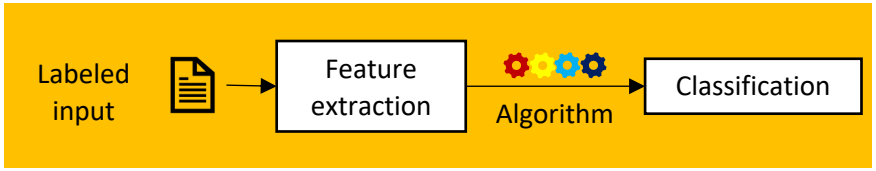
How such heterogenous data can be integrated, analyzed, and interpreted to support precision medicine and translational research in clinical settings and variable research environments?



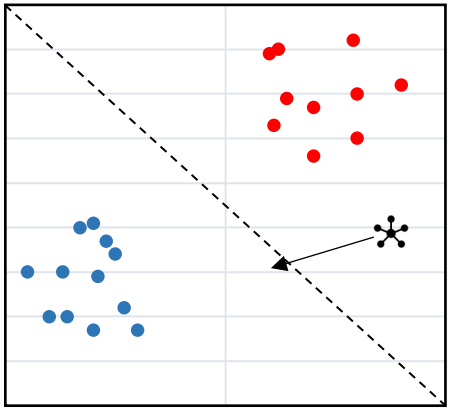
Ahmed, et al. **Artificial intelligence with multi-functional machine learning platform development for better healthcare and precision medicine**. Database. Oxford Jr. 2020.

Artificial Intelligence (AI) & Machine Learning (ML) Application

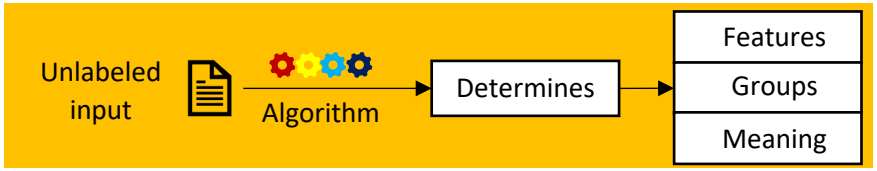
1. Data Classification.



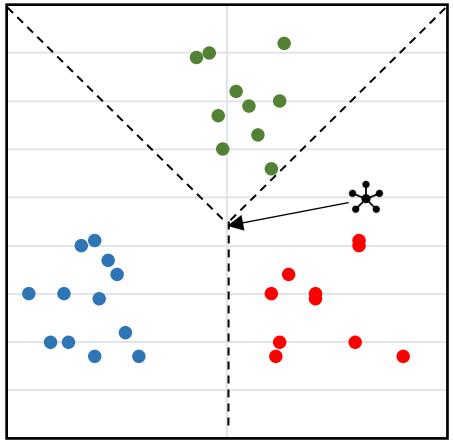
A training a model utilizing a set of labeled data to distinguish between positive and negative results e.g., determining if a biopsy sample is cancerous or not.



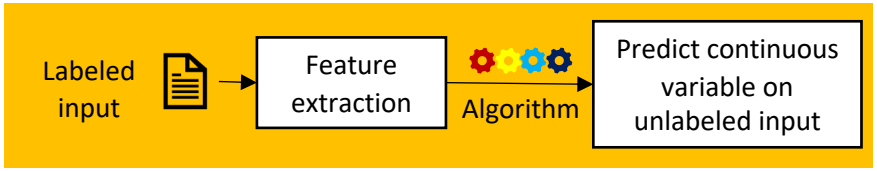
2. Data Cluster.



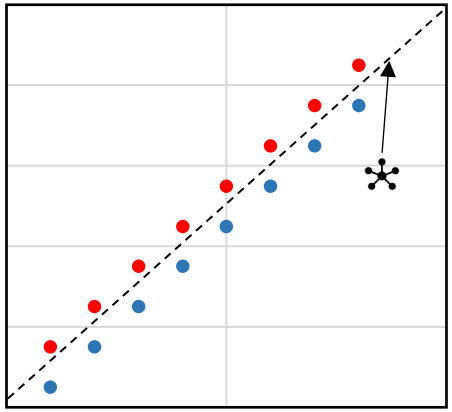
A model utilized to determine if any distinctive patterns are present without any determined outcome e.g., what is the prevalence of disease recurrence in a certain population due to pollution or chemical spill.

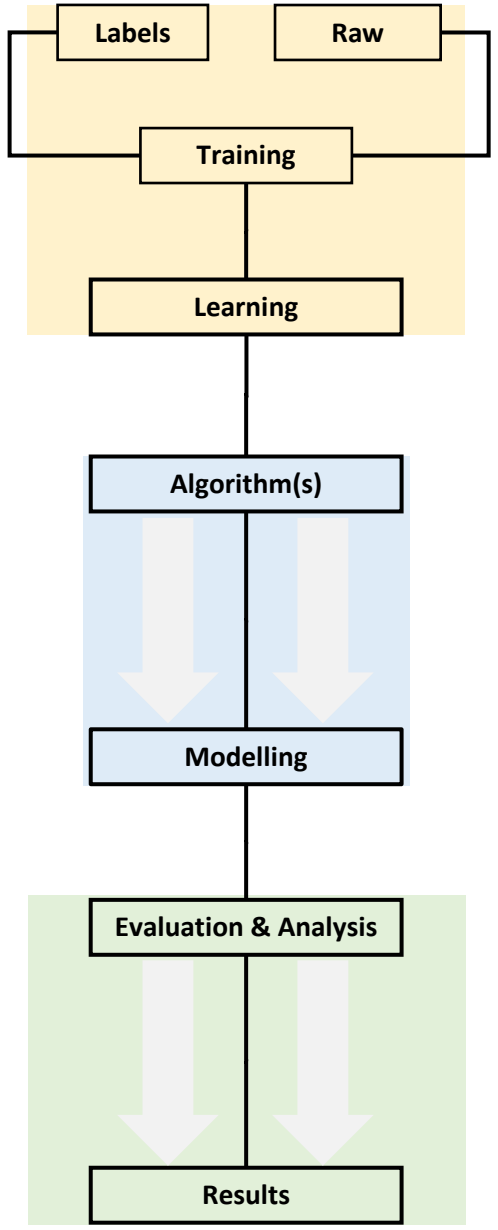


3. Data Regression.



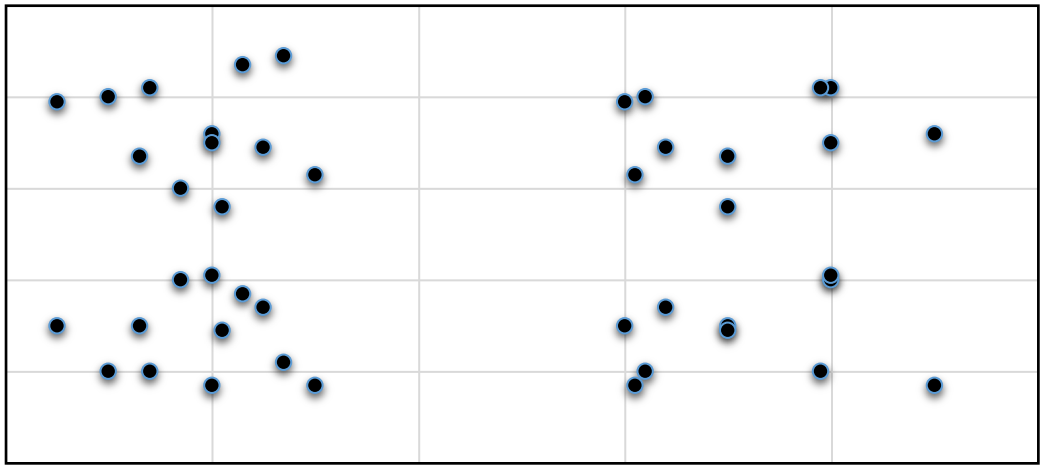
A predictive model used to examine and apply similar features obtained from a labeled data set to another data to make an accurate prediction e.g., how long before a patient is readmitted to the hospital following his/her discharge.



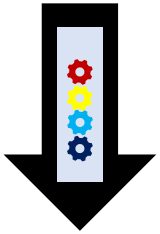


Positive result Negative result Common relationship between dataset Rules determined by algorithms

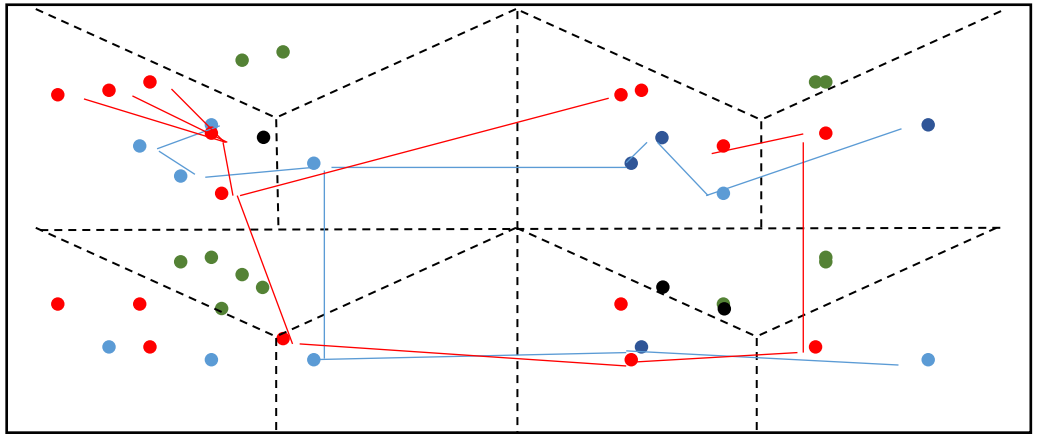
Artificial Intelligence (AI) & Machine Learning (ML) Application

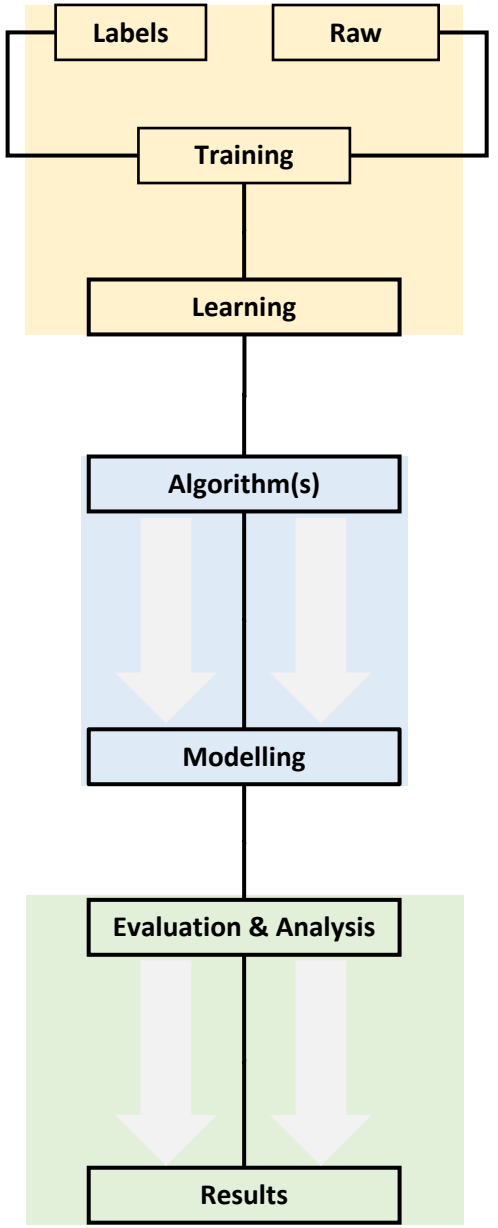


Raw inputs reflecting non associated illness and symptoms expressed by one individual or distinct population.



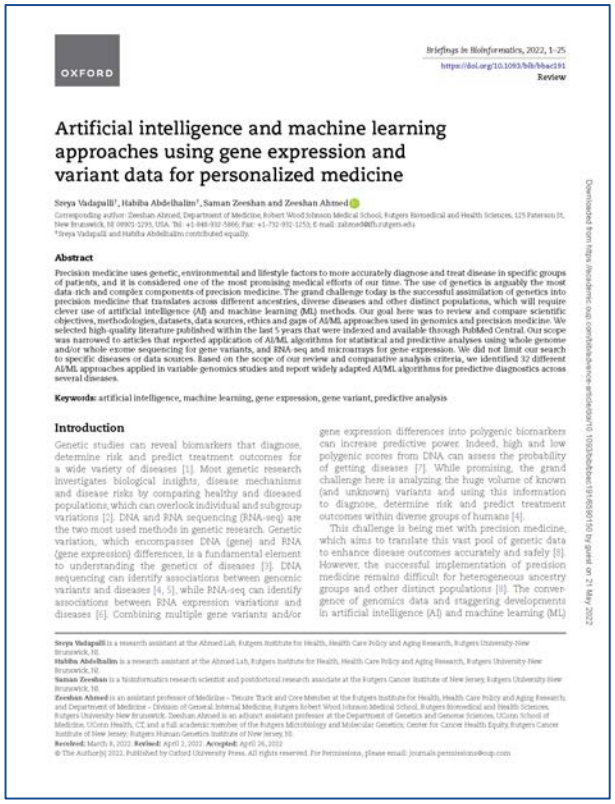
Following the application of machine learning algorithms to multiple layers of data, we are able to generate meaningful connection between previously unrelated inputs





Positive result Negative result Common relationship between dataset Rules determined by algorithms

Which AI/ML approach/algorithm is appropriate?



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Briefings in Bioinformatics, 2022, 1–25
https://doi.org/10.1093/bib/bbac191
Review

Artificial intelligence and machine learning approaches using gene expression and variant data for personalized medicine

Sreya Vadapalli[†], Habiba Abdelhalim[†], Saman Zeeshan and Zeeshan Ahmed
Corresponding author: Zeeshan Ahmed, Department of Medicine, Robert Wood Johnson Medical School, Rutgers Biomedical and Health Sciences, 125 Paterson St, New Brunswick, NJ 08901-2293, USA. Tel: +1-848-932-5866; Fax: +1-732-932-1253; E-mail: zahmed@rbhs.rutgers.edu
[†]Sreya Vadapalli and Habiba Abdelhalim contributed equally.

Abstract

Precision medicine uses genetic, environmental and lifestyle factors to more accurately diagnose and treat disease in specific groups of patients, and it is considered one of the most promising medical efforts of our time. The use of genetics is arguably the most data-rich and complex components of precision medicine. The grand challenge today is the successful assimilation of genetics into precision medicine that translates across different ancestries, diverse diseases and other distinct populations, which will require clever use of artificial intelligence (AI) and machine learning (ML) methods. Our goal here was to review and compare scientific objectives, methodologies, datasets, data sources, ethics and gaps of AI/ML approaches used in genomics and precision medicine. We selected high-quality literature published within the last 5 years that were indexed and available through PubMed Central. Our scope was narrowed to articles that reported application of AI/ML algorithms for statistical and predictive analyses using whole-genome and/or whole-exome sequencing for gene variants, and RNA-seq and microarrays for gene expression. We did not limit our search to specific diseases or data sources. Based on the scope of our review and comparative analysis criteria, we identified 32 different AI/ML approaches applied in variable genomics studies and report widely adapted AI/ML algorithms for predictive diagnostics across several diseases.

Keywords: artificial intelligence, machine learning, gene expression, gene variant, predictive analysis

Introduction

Genetic studies can reveal biomarkers that diagnose, determine risk and predict treatment outcomes for a wide variety of diseases [1]. Most genetic research investigates biological insights, disease mechanisms and disease risks by comparing healthy and diseased populations, which can overlook individual and subgroup variations [2]. DNA and RNA sequencing (RNA-seq) are the two most used methods in genetic research. Genetic variation, which encompasses DNA (gene) and RNA (gene expression) differences, is a fundamental element to understanding the genetics of diseases [3]. DNA sequencing can identify associations between genomic variants and diseases [4, 5], while RNA-seq can identify associations between RNA expression variations and diseases [6]. Combining multiple gene variants and/or gene expression differences into polygenic biomarkers can increase predictive power. Indeed, high and low polygenic scores from DNA can assess the probability of getting diseases [7]. While promising, the grand challenge here is analyzing the huge volume of known (and unknown) variants and using this information to diagnose, determine risk and predict treatment outcomes within diverse groups of humans [4].

This challenge is being met with precision medicine, which aims to translate this vast pool of genetic data to enhance disease outcomes accurately and safely [8]. However, the successful implementation of precision medicine remains difficult for heterogeneous ancestry groups and other distinct populations [9]. The convergence of genomics data and staggering developments in artificial intelligence (AI) and machine learning (ML)

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Habiba Abdelhalim is a research assistant at the Ahmed Lab, Rutgers Institute for Health, Health Care Policy and Aging Research, Rutgers University-New Brunswick, NJ.
Saman Zeeshan is a bioinformatics research scientist and postdoctoral research associate at the Rutgers Cancer Institute of New Jersey, Rutgers University-New Brunswick, NJ.
Zeeshan Ahmed is an assistant professor of Medicine – Tenure Track and Core Member at the Rutgers Institute for Health, Health Care Policy and Aging Research, and Department of Medicine – Division of General Internal Medicine, Rutgers Robert Wood Johnson Medical School, Rutgers Biomedical and Health Sciences, Rutgers University-New Brunswick. Zeeshan Ahmed is an adjunct assistant professor at the Department of Genetics and Genome Sciences, UConn School of Medicine, UConn Health, CT and a full academic member of the Rutgers Microbiology and Molecular Genetics, Center for Cancer Health Equity, Rutgers Cancer Institute of New Jersey, Rutgers Human Genetics Institute of New Jersey, NJ.
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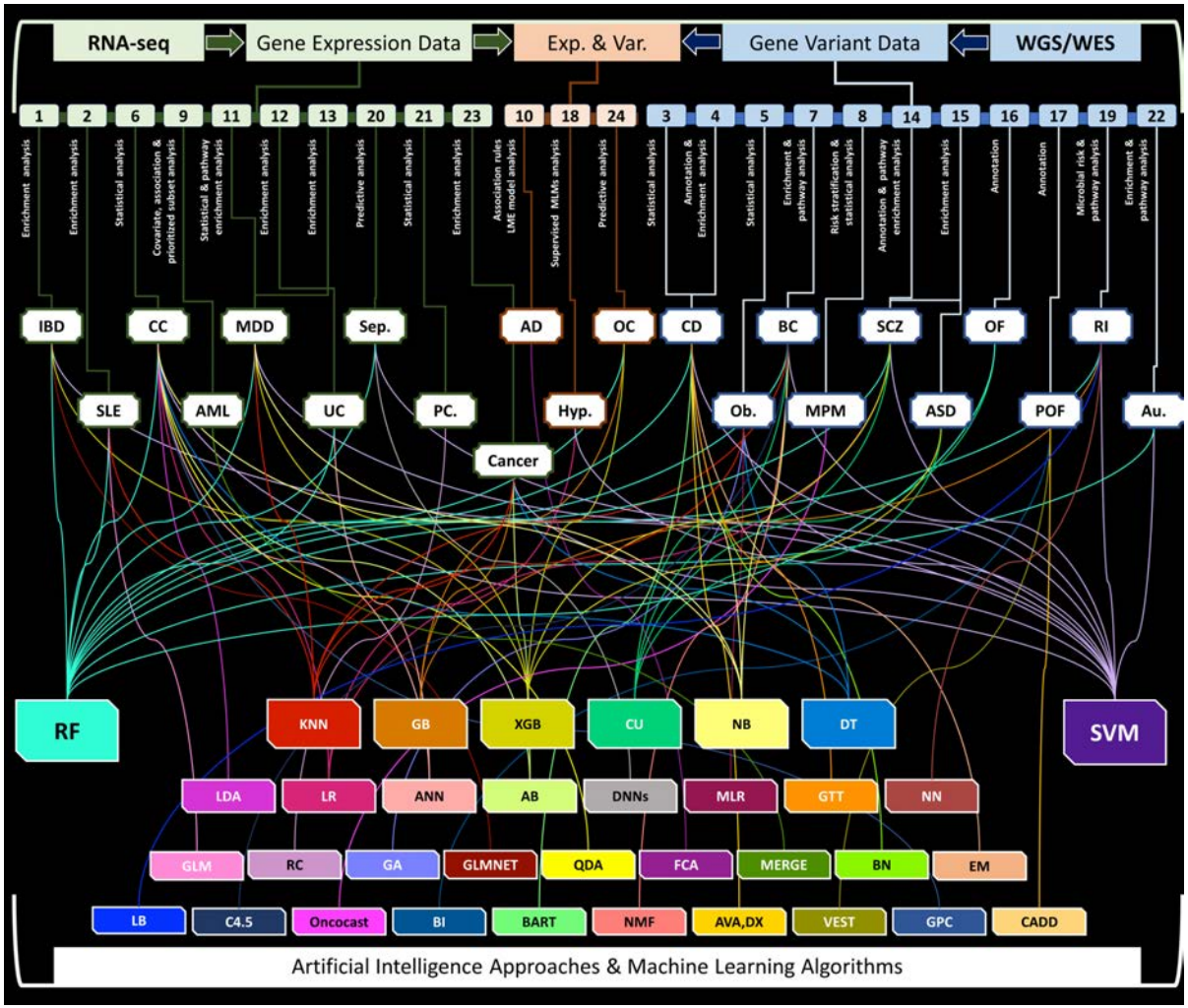

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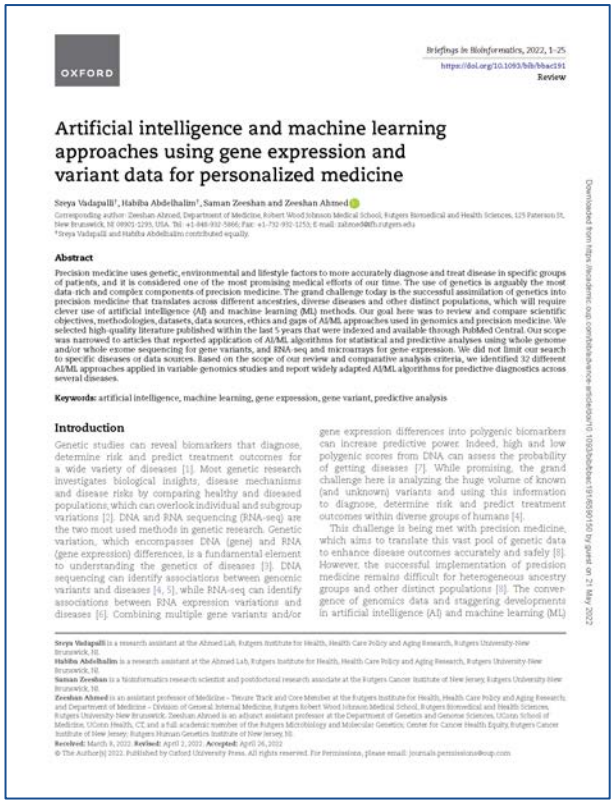

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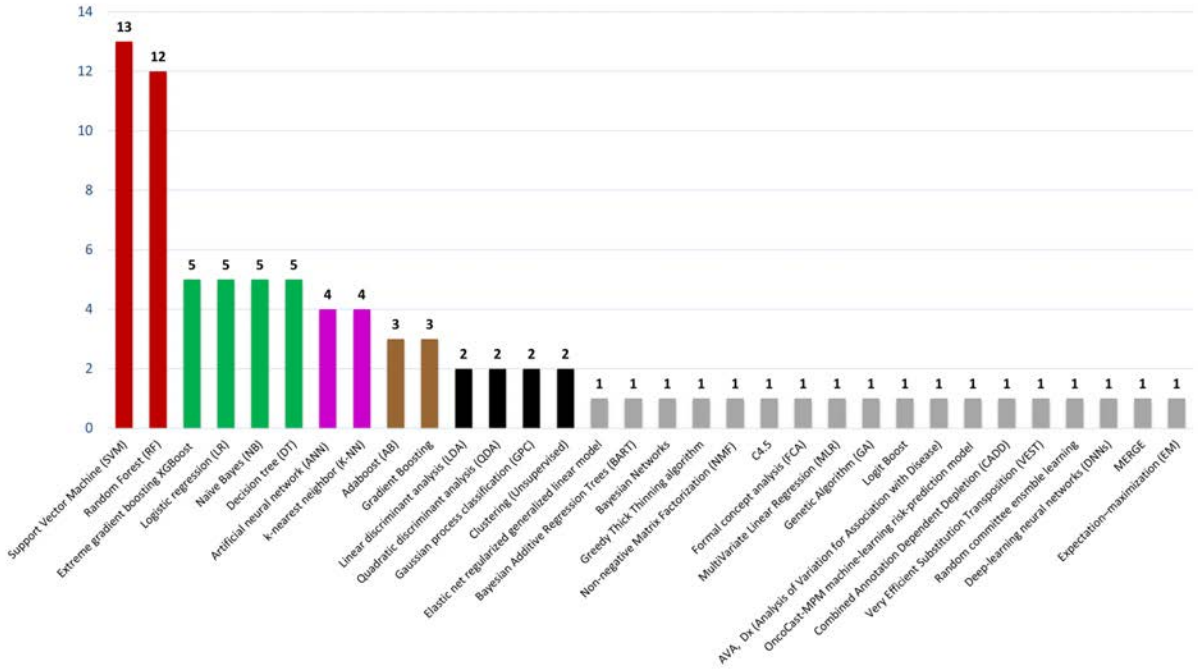

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Precision Medicine Project @ Ahmed Lab

1. Technology Development

2. Multi/Disease Research

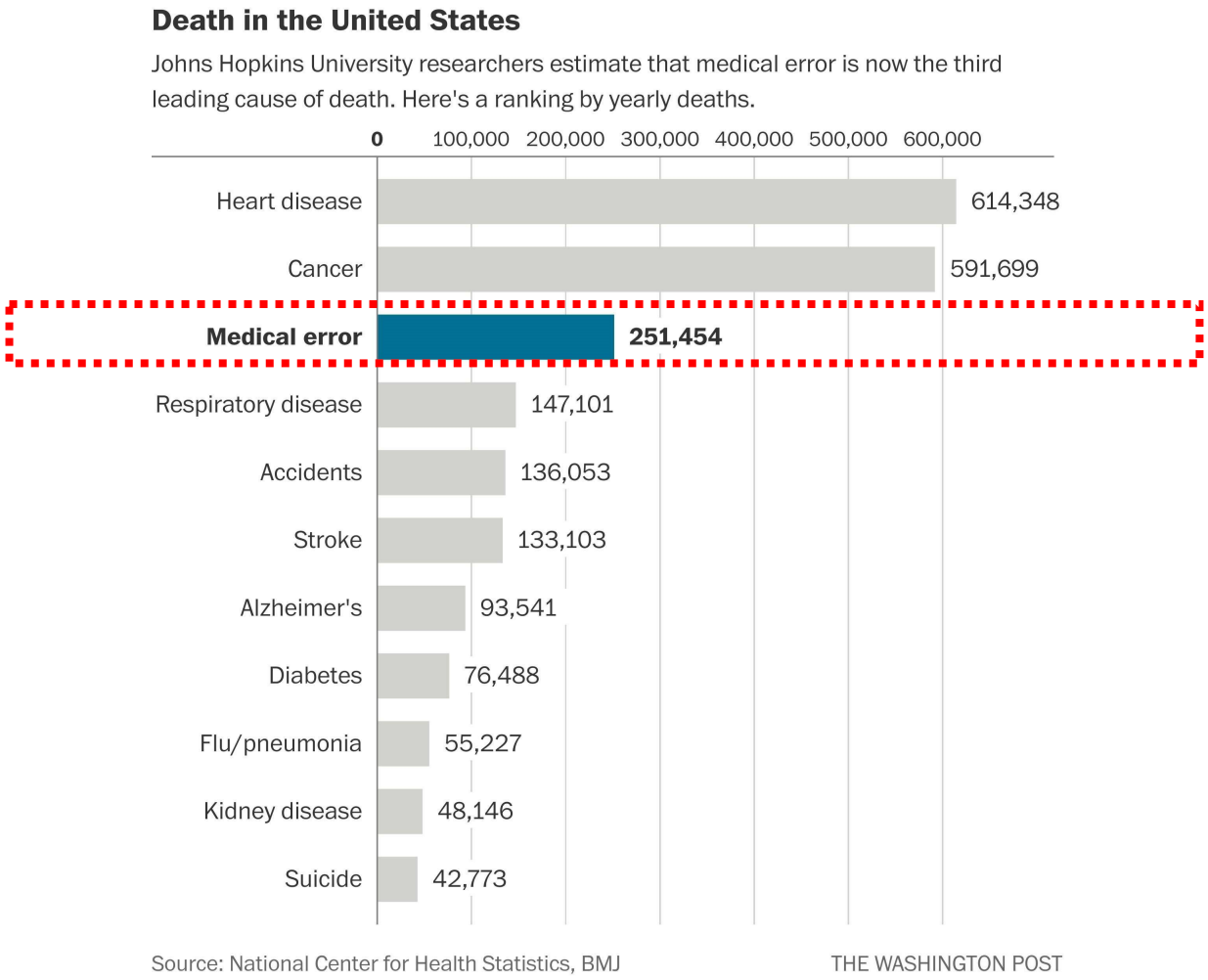
I. High Performance & Secure Computing Frameworks
for secure clinical and multi-omics/genomics data acquisition, processing, modelling, integration, sharing, and management.

II. Biomedical Informatics Applications
for electronic healthcare records (EHR) extraction, transfer, loading (ETL), and analysis. Patient recruitment, consenting, sample collection and management.

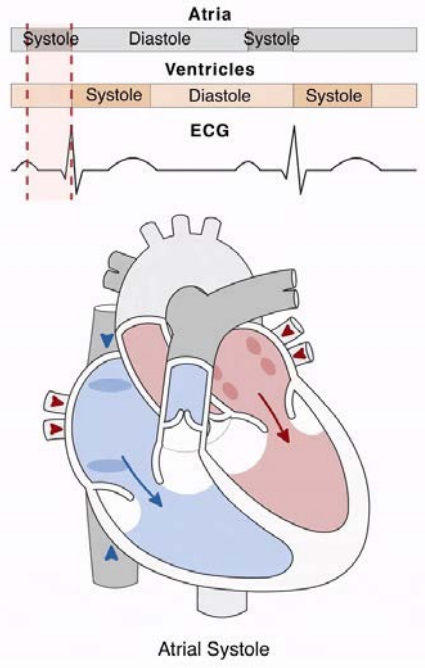
III. Bioinformatics Tool, Scripts, and Pipelines
for standard multi-omics/genomics (e.g., expression, variant, enrichment, pathway, metabolic flux etc.) data analysis and deep phenotyping.

IV. Artificial Intelligence (AI) and Machine Learning (ML) Approaches
for the identification of patterns revealing predictive and modifiable risk factors to support earlier diagnosis of targeted disorders and sequela.

Multi/Disease Research @ Ahmed Lab



Cardiovascular disease (CVD)



- **Heart Failure (HF)** and **Atrial Fibrillation (AF)** are among the most common manifestations of CVD and contribute to about 45% of all CVD deaths. *(Dickinson et al., 2014)*
  - **AF is an arrhythmic disorder** in the atrium of the heart, which can cause irregular heart rhythms. *(Staerk et al., 2017)*
  - **HF is a chronic disorder**, which weakens heart muscle and affects the regular function of the heart impairing its ability to pump enough oxygen-rich blood. *(Kalogirou et al., 2020)*

- Due to the **complex nature, progression, inherent genetic makeup, and heterogeneity in CVDs**, personalized treatments are critical for CVD patients.
- To improve the **deciphering of CVD mechanisms**, it will be necessary to systematically investigate known and identify novel genes that are responsible for the CVD development.
- Studying genetic insight with the application of **Artificial Intelligence (AI), Machine Learning (ML),** and state-of-the-art bioinformatics approaches can accelerate the processes of discovering disease causing variants and decode genetics of complex phenotypes to predict, prevent, and treat CVD.

Bioinformatics & CVD

Patel et al. Human Genomics (2023) 17:47
https://doi.org/10.1186/s40246-023-00498-0

Human Genomics

REVIEW Open Access

Genomic approaches to identify and investigate genes associated with atrial fibrillation and heart failure susceptibility

Kush Ketan Patel[1†], Cynthia Venkatesan[1†], Habiba Abdelhalim[1], Saman Zeeshan[2], Yuichiro Arima[3], Suvi Linna-Kuosmanen[4,5,6] and Zeeshan Ahmed[7,8*]

Abstract

Atrial fibrillation (AF) and heart failure (HF) contribute to about 45% of all cardiovascular disease (CVD) deaths in the USA and around the globe. Due to the complex nature, progression, inherent genetic makeup, and heterogeneity of CVDs, personalized treatments are believed to be critical. To improve the deciphering of CVD mechanisms, we need to deeply investigate well-known and identify novel genes that are responsible for CVD development. With the advancements in sequencing technologies, genomic data have been generated at an unprecedented pace to foster translational research. Correct application of bioinformatics using genomic data holds the potential to reveal the genetic underpinnings of various health conditions. It can help in the identification of causal variants for AF, HF, and other CVDs by moving beyond the one-gene one-disease model through the integration of common and rare variant association, the expressed genome, and characterization of comorbidities and phenotypic traits derived from the clinical information. In this study, we examined and discussed variable genomic approaches investigating genes associated with AF, HF, and other CVDs. We collected, reviewed, and compared high-quality scientific literature published between 2009 and 2022 and accessible through PubMed/NCBI. While selecting relevant literature, we mainly focused on identifying genomic approaches involving the integration of genomic data; analysis of common and rare genetic variants; metadata and phenotypic details; and multi-ethnic studies including individuals from ethnic minorities, and European, Asian, and American ancestries. We found 190 genes associated with AF and 26 genes linked to HF. Seven genes had implications in both AF and HF, which are *SYNPO2L*, *TTN*, *MTSS1*, *SCN5A*, *PITX2*, *KLHL3*, and *AGAP5*. We listed our conclusion, which include detailed information about genes and SNPs associated with AF and HF.

Keywords Genes, Genetic loci, Heart failure, Atrial fibrillation, Cardiovascular diseases, Genomics, Multi-OMICS

†Kush Ketan Patel and Cynthia Venkatesan are equally contributing first authors.

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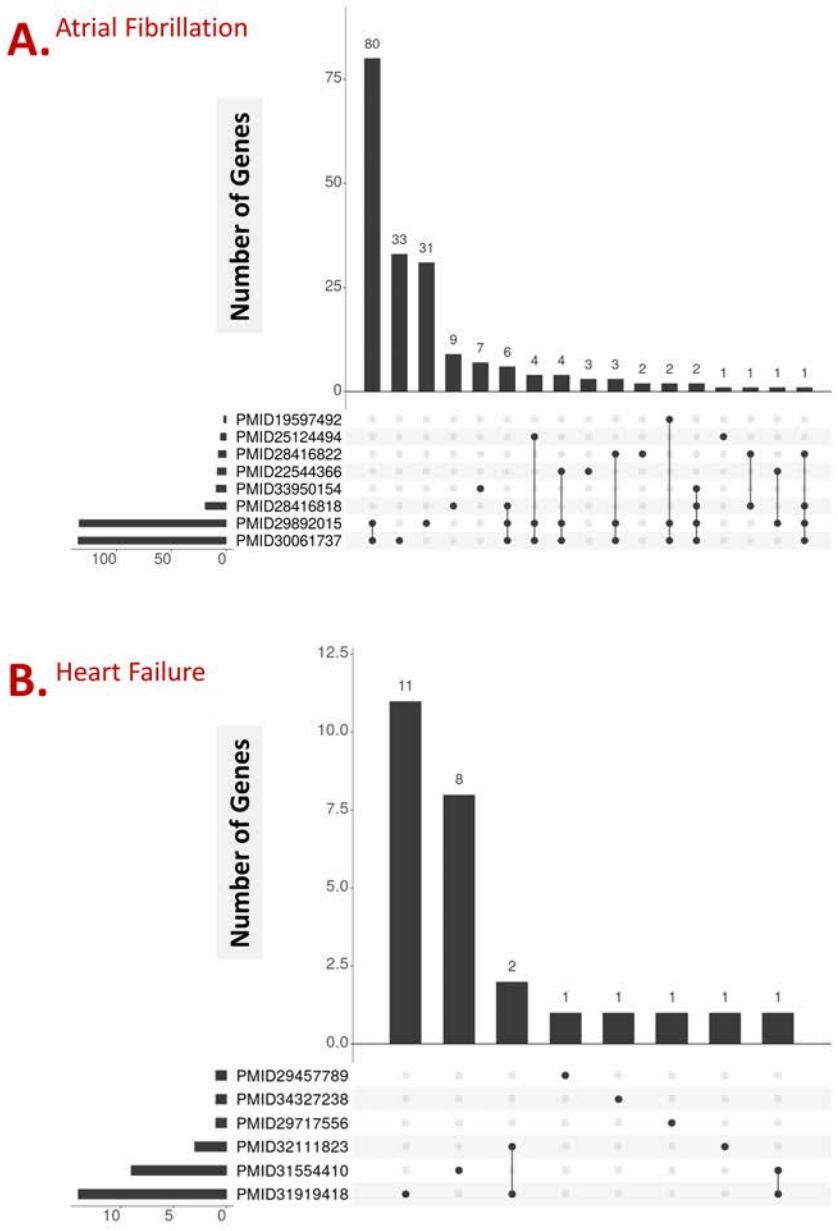
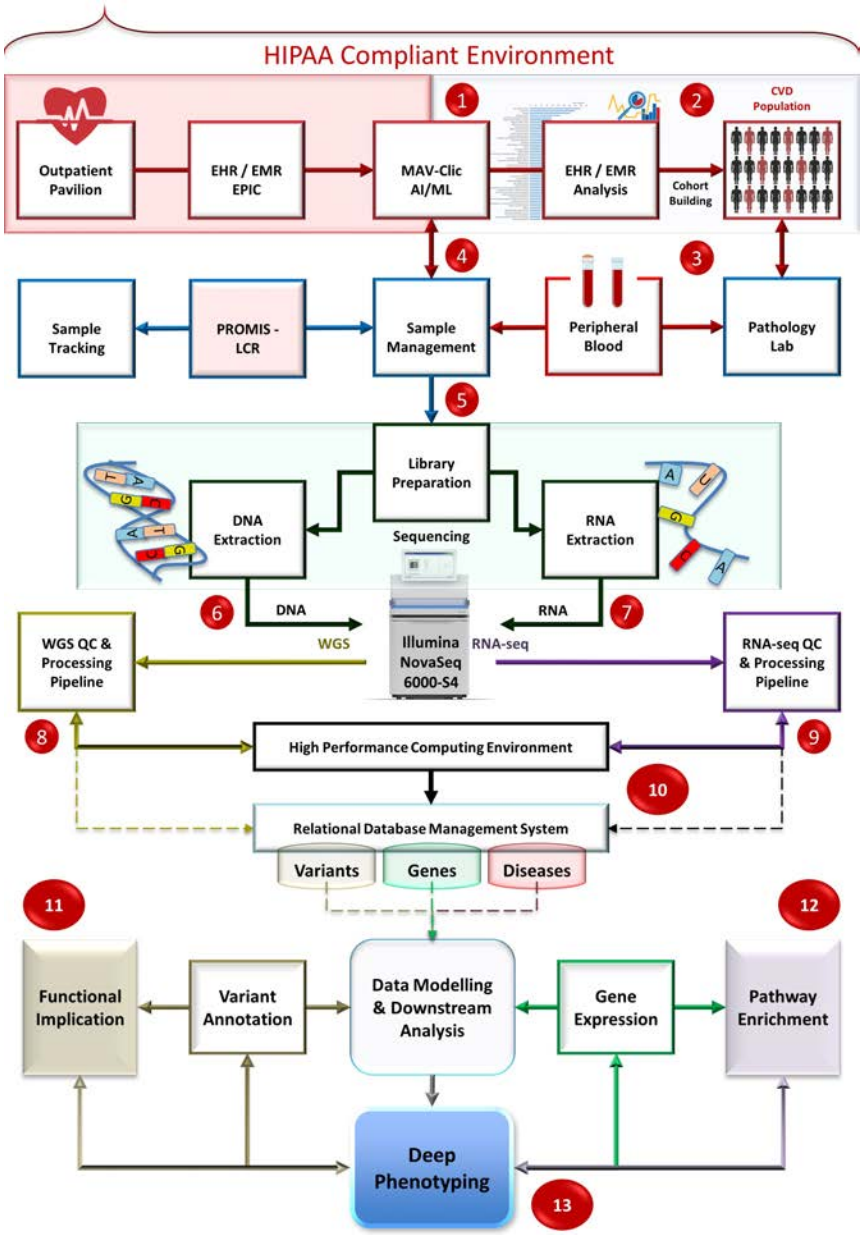


CDC

OAK RIDGE INSTITUTE FOR SCIENCE AND EDUCATION

CVD Study Design

1. EHR extraction from EPIC
2. CVD cohort building
3. Consenting patients
4. Sample collection & management
5. Sequence data generation
6. Gene expression analysis (RNA-seq)
7. Gene-disease annotation
8. Variant analysis & validation (WGS)
9. AI/ML ready data generation (CIGT)
10. Predict disease with high accuracy



Cohort Building & MAV-clic

JAMIA Open, 2(1), 2019, 23–28
doi: 10.1093/jamiaopen/ooy052
Advance Access Publication Date: 29 December 2018
Database Notes

Database Notes

MAV-clic: management, analysis, and visualization of clinical data

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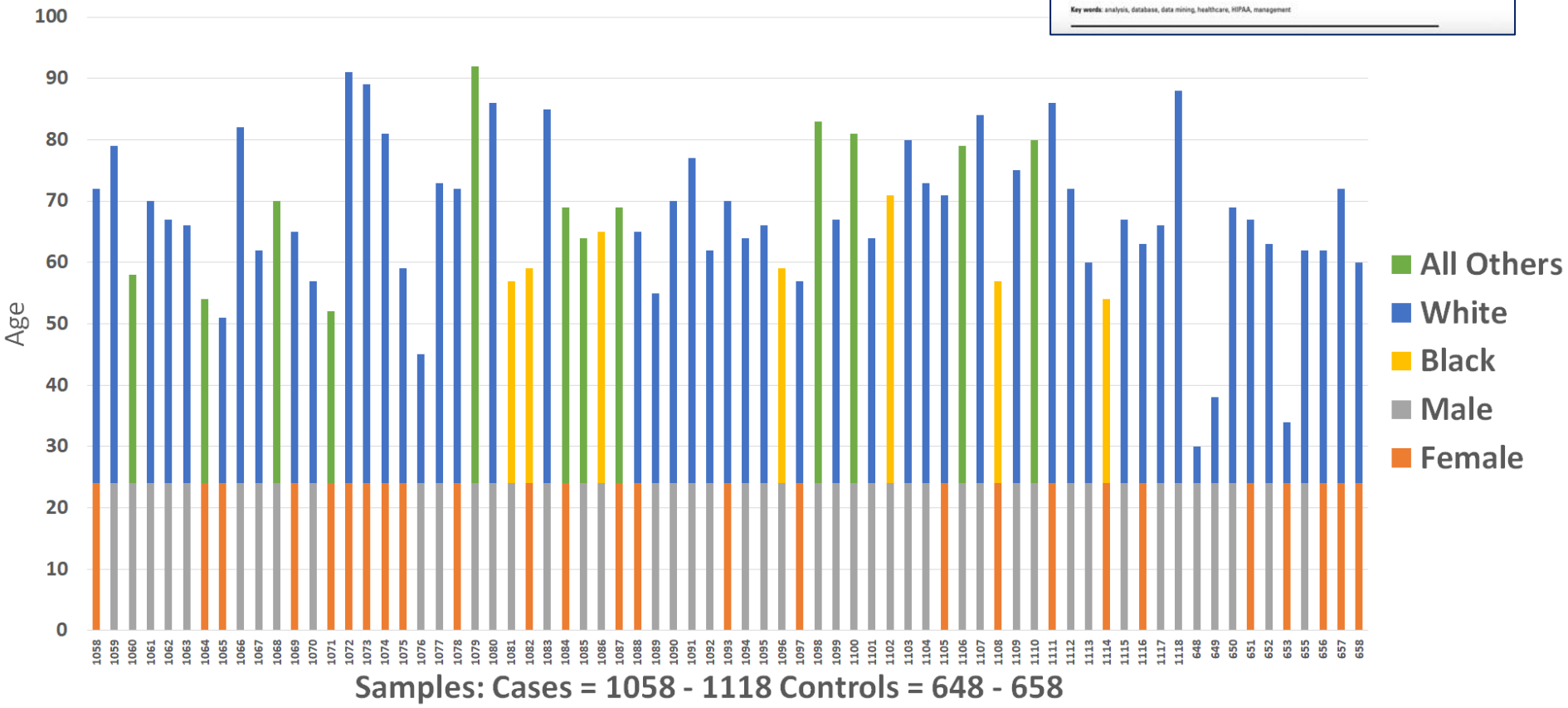
Received 30 January 2018; Revised 18 July 2018; Editorial Decision 3 November 2018; Accepted 22 November 2018

ABSTRACT

Objectives: Develop a multifunctional analytics platform for efficient management and analysis of healthcare data.
Materials and Methods: Management, Analysis, and Visualization of Clinical Data (MAV-clic) is a Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant framework based on the Butterfly Model. MAV-clic extracts, cleanses, and encrypts data then restructures and aggregates data in a deidentified format. A graphical user interface allows query, analysis, and visualization of clinical data.
Results: MAV-clic manages healthcare data for over 800 000 subjects at UConn Health. Three analytic capabilities of MAV-clic include: creating cohorts based on specific criteria; performing measurement analysis of subjects with a specific diagnosis and medication; and calculating measure outcomes of subjects over time.
Discussion: MAV-clic supports clinicians and healthcare analysts by efficiently stratifying subjects to understand specific scenarios and optimize decision making.
Conclusion: MAV-clic is founded on the scientific premise that to improve the quality and transition of healthcare, integrative platforms are necessary to analyze heterogeneous clinical, epidemiological, metabolomics, proteomics, and genomics data for precision medicine.

Key words: analysis, database, data mining, healthcare, HIPAA, management

The CVD cohort include **40 male and 21 female individuals (n=61)**, aged between 45 to 92, with self-described race (42 Whites, 7 Blacks or African Americans, 1 Asian, and 11 of unknown race). In addition, the PI has built a control set, which included healthy individuals (n=10); 5 males and 5 females; out of which 9 were White race and 1 unknown race; aged between 28 to 78.



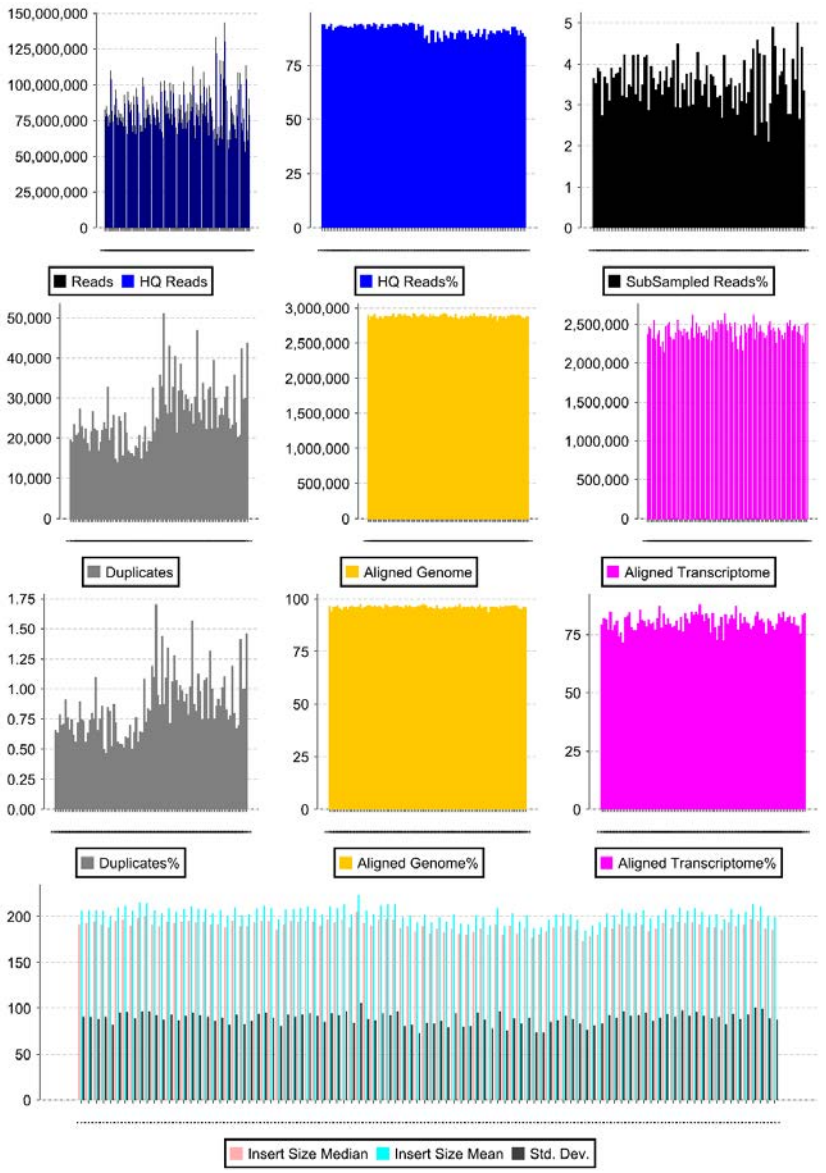
Sequence Data Generation

Illumina NovaSeq 6000-S4

RNA-seq → Expression Analysis

WGS → Variant Analysis

QC Report using PROMS-MED



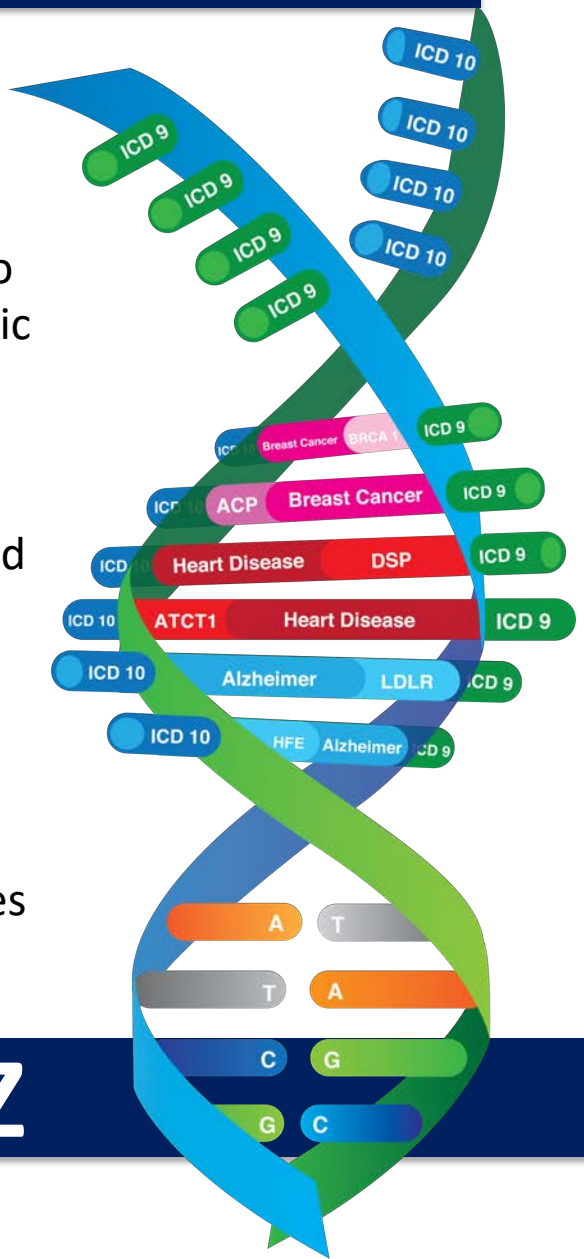
RNA-seq Driven Gene Expression and Gene-Disease Annotation

- **RNA-seq** has become the most used method for gene expression analysis

- **Gene expression** analysis is a widely adopted method to identify abnormalities in normal function and physiologic regulation.

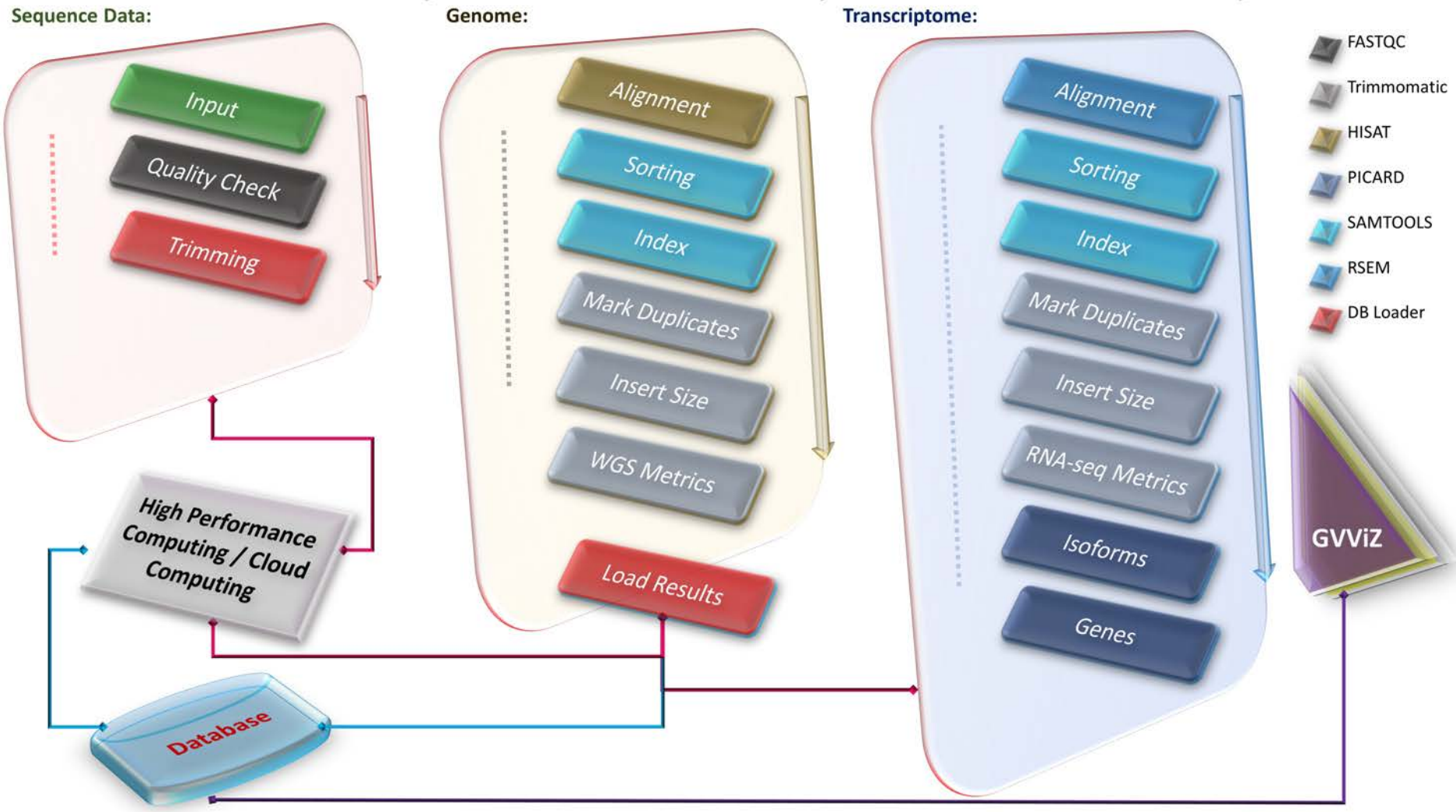
- Findable, accessible, interactive, and reusable (FAIR) bioinformatics platform for **RNA-seq**-driven variable and complex **gene-disease data annotation and expression analysis** with a dynamic heat map visualization.

- It supports **transcriptomic profiling and expression analyses** to identify measure and compare genes and transcripts in multiple conditions, and in different tissues and individuals.



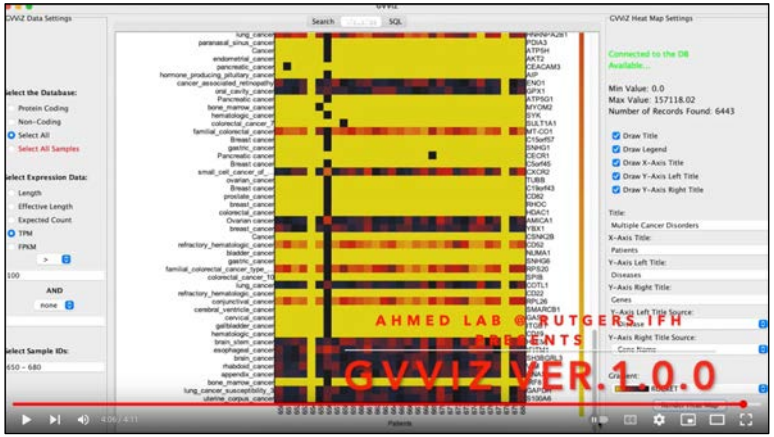
GVViZ

GVViZ – RNA-seq Data Analysis

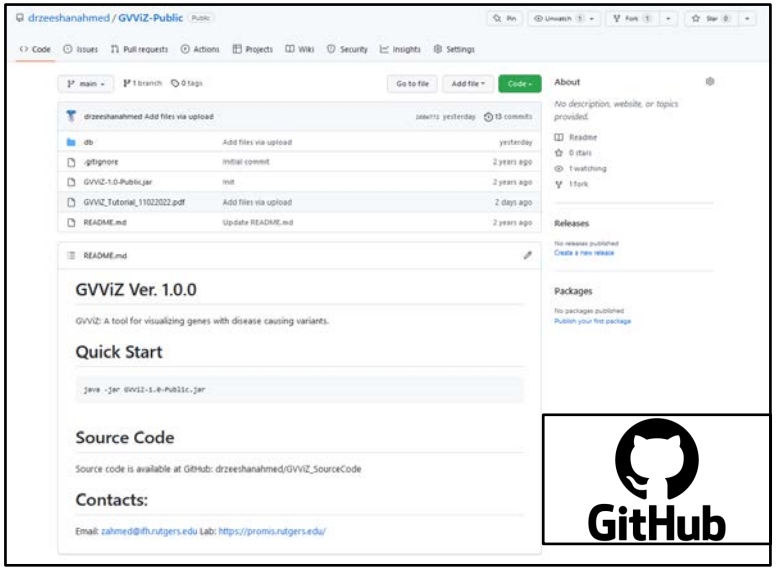


Ahmed, Z., et al. (2021). **Advancing clinical genomics and precision medicine with GVViZ: FAIR bioinformatics platform for variable gene-disease annotation, visualization, and expression analysis.** Human Genomics. 15(1), 37. PMID: 34174938.

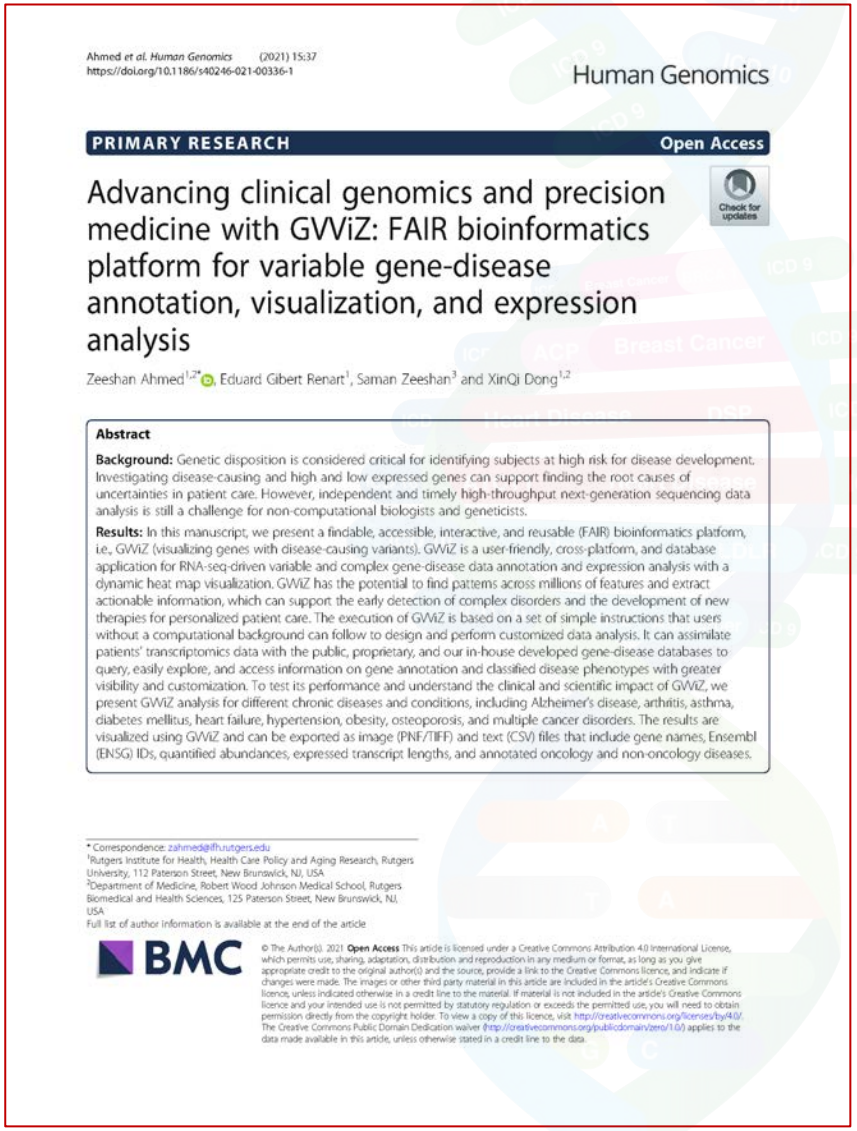
GVViZ – Demo and Download Information



URL: https://www.youtube.com/watch?v=x0RroYpk8Nw



URL: https://github.com/drzeeshanahmed/GVViZ-Public



Ahmed *et al. Human Genomics* (2021) 15:37
https://doi.org/10.1186/s40246-021-00336-1

Human Genomics

PRIMARY RESEARCH Open Access

Advancing clinical genomics and precision medicine with GVViZ: FAIR bioinformatics platform for variable gene-disease annotation, visualization, and expression analysis

Zeeshan Ahmed[1,2*], Eduard Gibert Renart[1], Saman Zeeshan[3] and XinQi Dong[1,2]

Abstract

Background: Genetic disposition is considered critical for identifying subjects at high risk for disease development. Investigating disease-causing and high and low expressed genes can support finding the root causes of uncertainties in patient care. However, independent and timely high-throughput next-generation sequencing data analysis is still a challenge for non-computational biologists and geneticists.

Results: In this manuscript, we present a findable, accessible, interactive, and reusable (FAIR) bioinformatics platform, i.e., GViZ (visualizing genes with disease-causing variants). GViZ is a user-friendly, cross-platform, and database application for RNA-seq-driven variable and complex gene-disease data annotation and expression analysis with a dynamic heat map visualization. GViZ has the potential to find patterns across millions of features and extract actionable information, which can support the early detection of complex disorders and the development of new therapies for personalized patient care. The execution of GViZ is based on a set of simple instructions that users without a computational background can follow to design and perform customized data analysis. It can assimilate patients' transcriptomics data with the public, proprietary, and our in-house developed gene-disease databases to query, easily explore, and access information on gene annotation and classified disease phenotypes with greater visibility and customization. To test its performance and understand the clinical and scientific impact of GViZ, we present GViZ analysis for different chronic diseases and conditions, including Alzheimer's disease, arthritis, asthma, diabetes mellitus, heart failure, hypertension, obesity, osteoporosis, and multiple cancer disorders. The results are visualized using GViZ and can be exported as image (PNF/TIFF) and text (CSV) files that include gene names, Ensembl (ENSG) IDs, quantified abundances, expressed transcript lengths, and annotated oncology and non-oncology diseases.

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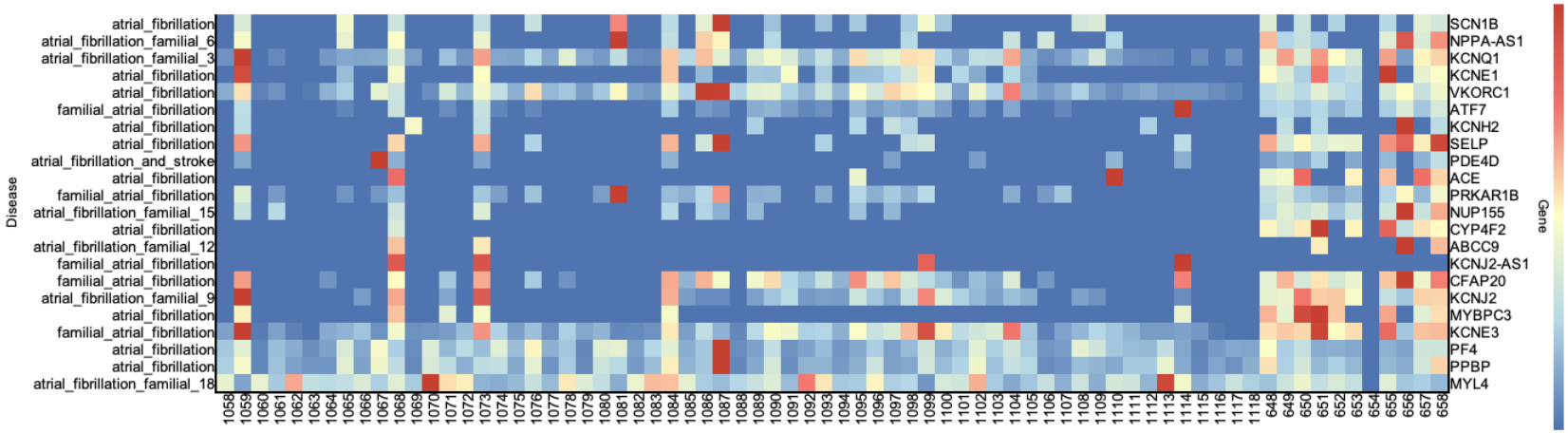
Full list of author information is available at the end of the article

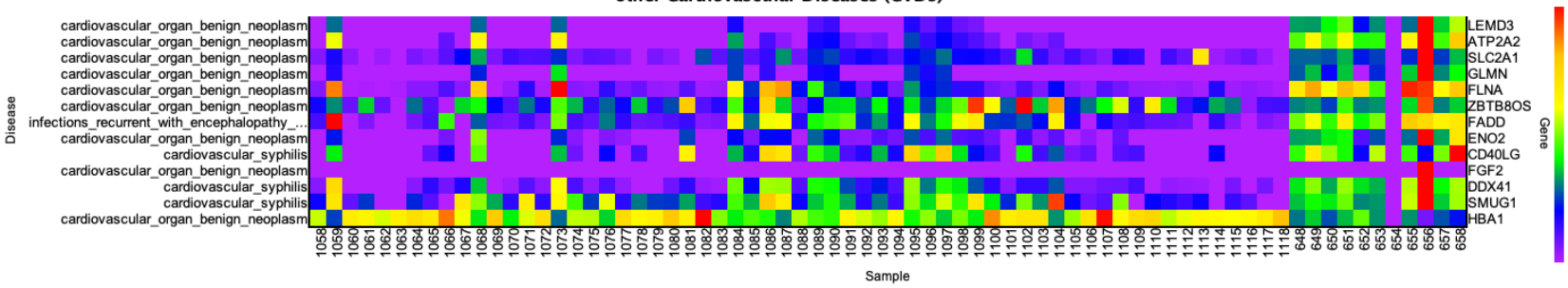
GVViZ & Gene-disease annotation

A.

B.



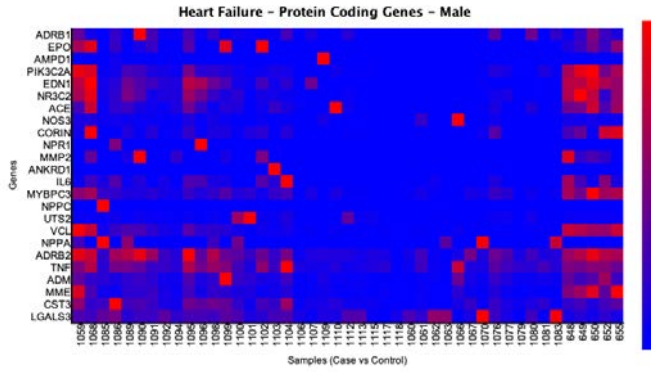
C.

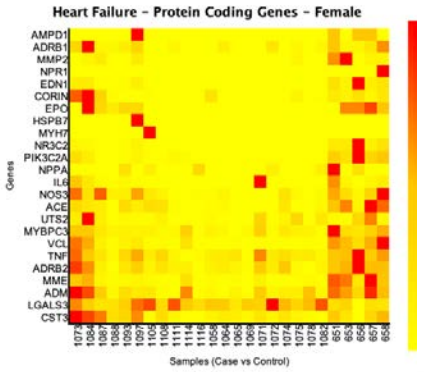


Gender-based gene expression analysis

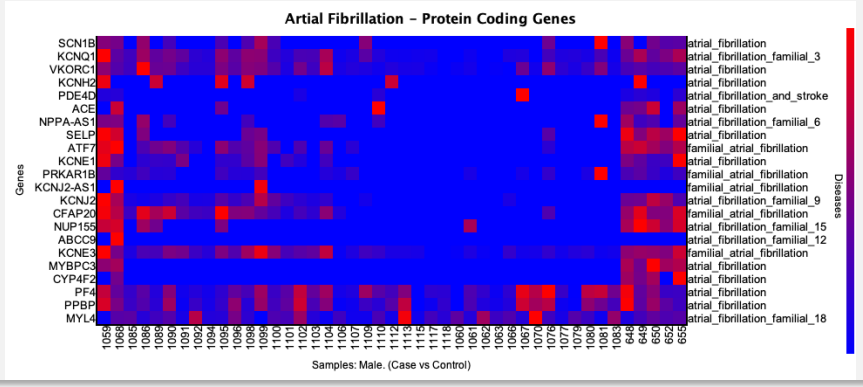
MALE **FEMALE**

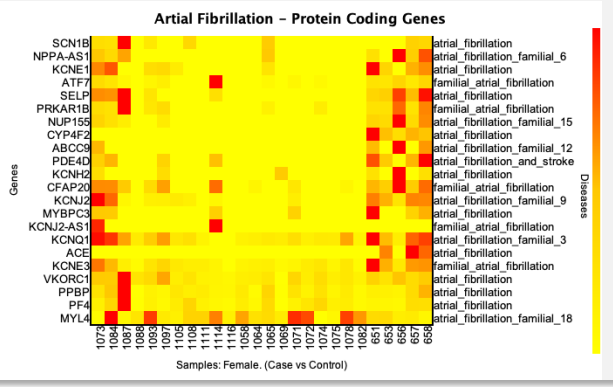
A. HF



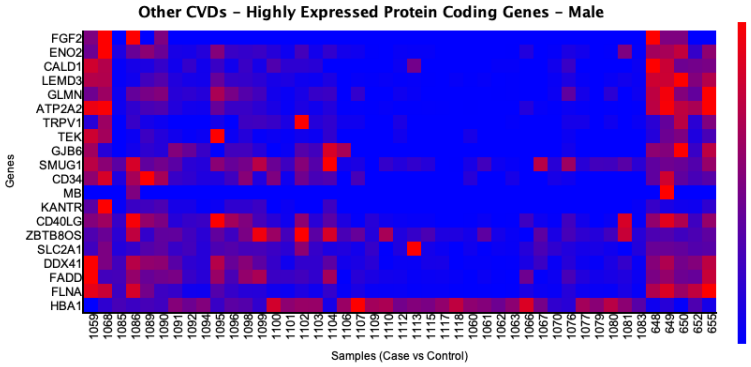


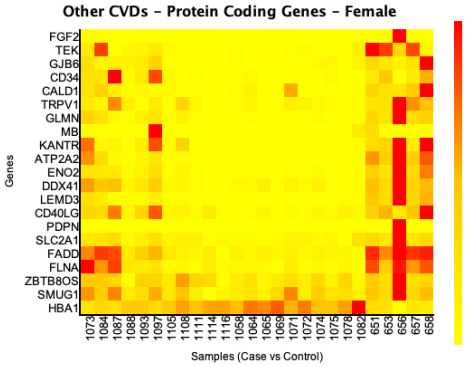
B. AF



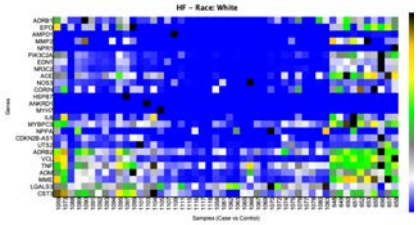
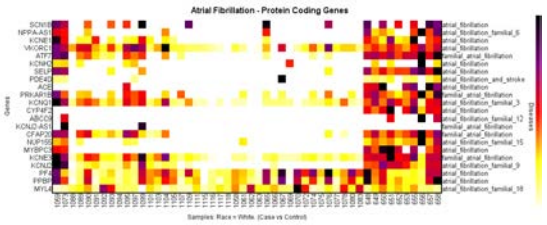
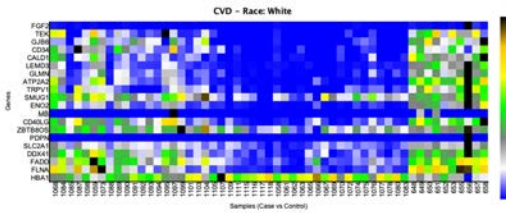
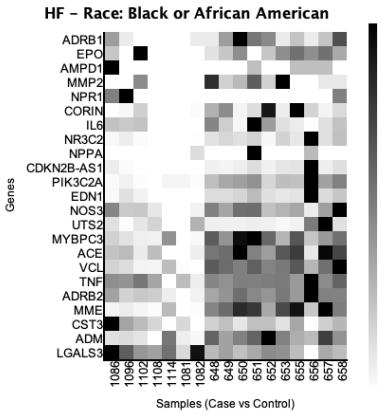
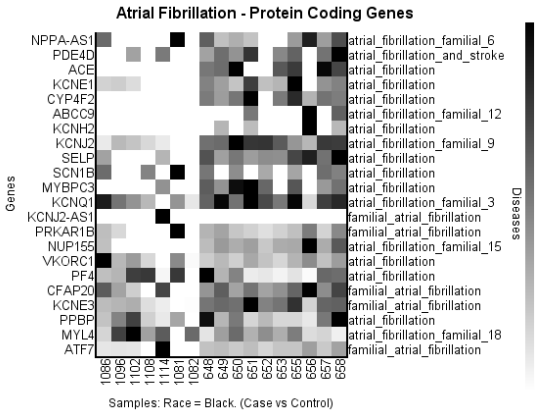
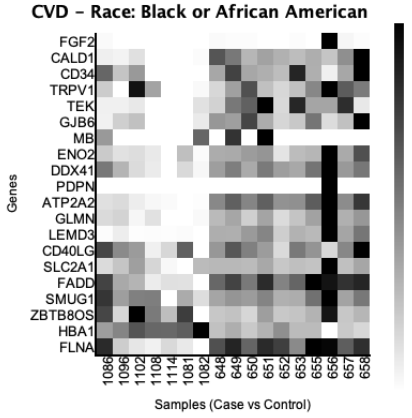
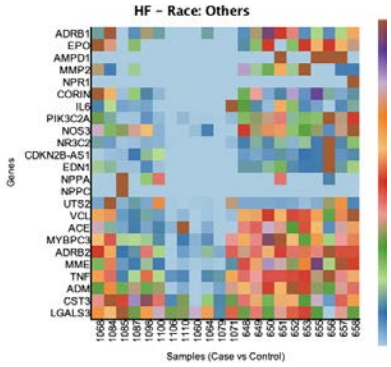
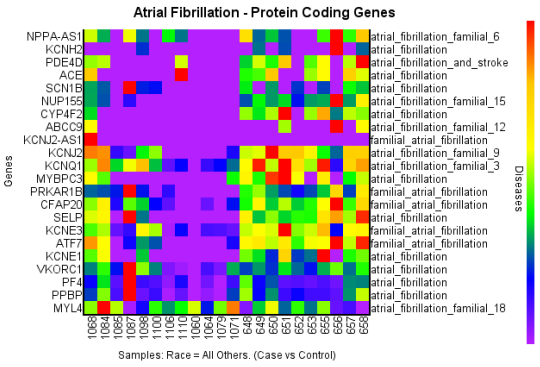
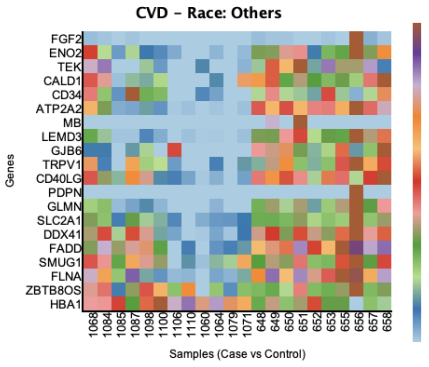


C. other CVDs

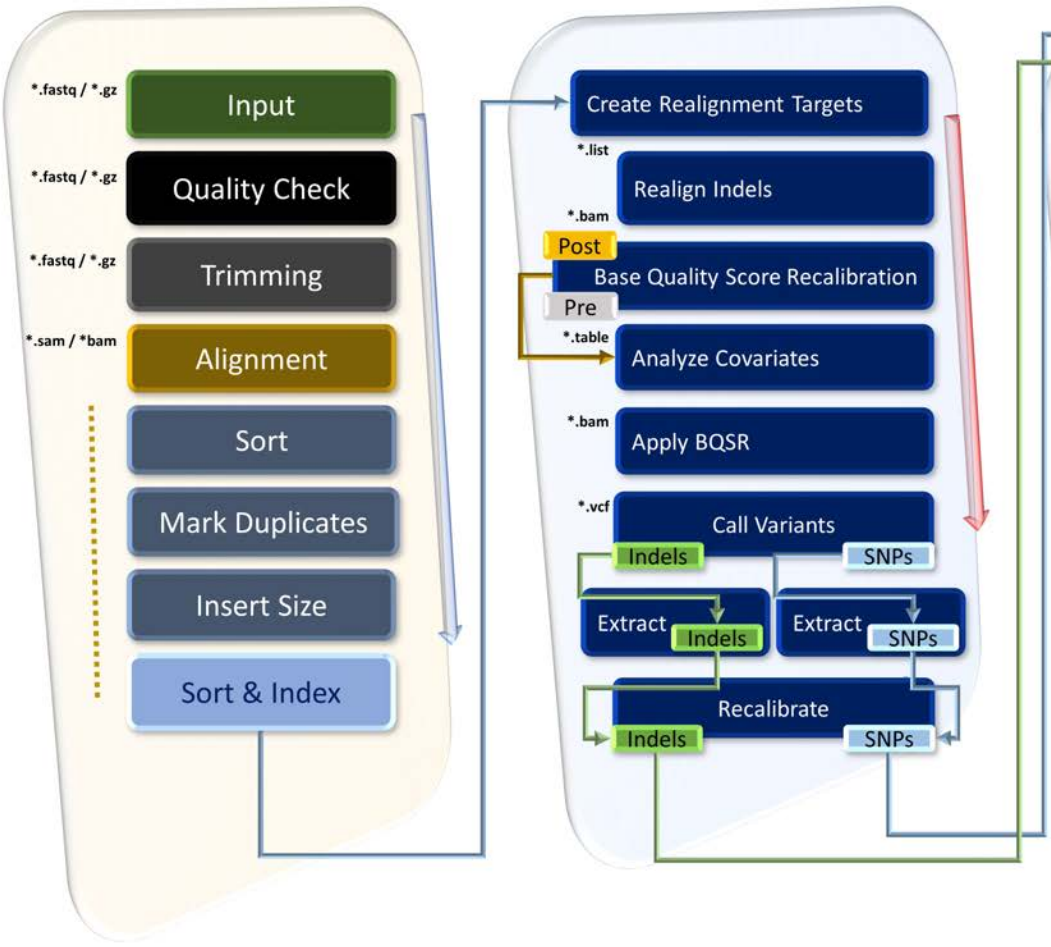




Race-based gene expression analysis

	HF	AF	Other CVDs
A. White			
B. Black			
C. All others			

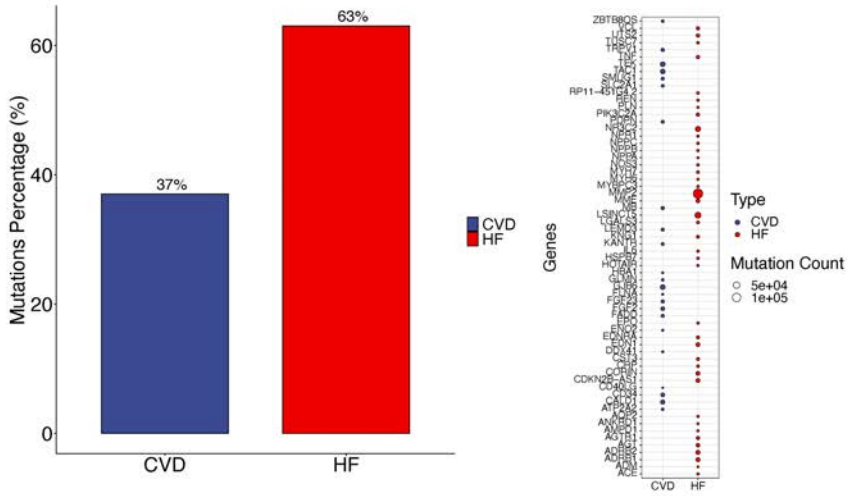
JWES: Variant Analysis



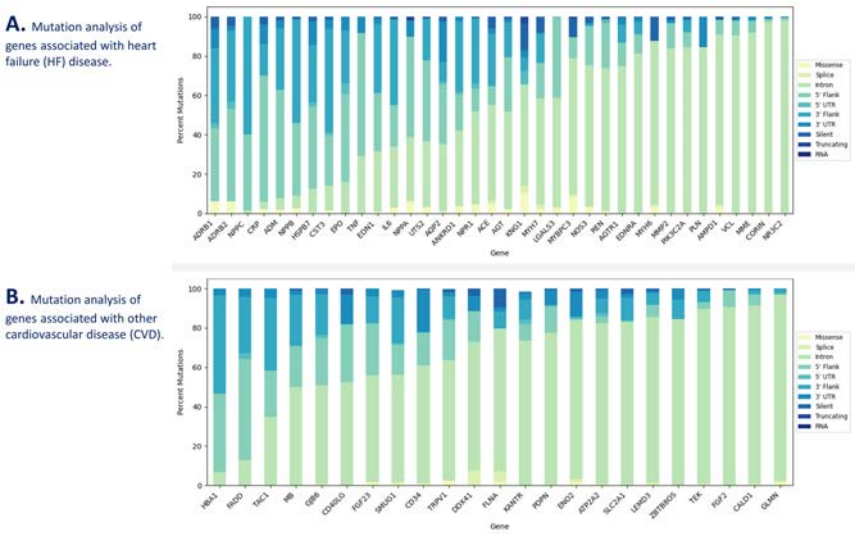

FEBS Open Bio
FEBS PRESS
METHOD
JWES: a new pipeline for whole genome/exome sequence data processing, management, and gene-variant discovery, annotation, prediction, and genotyping

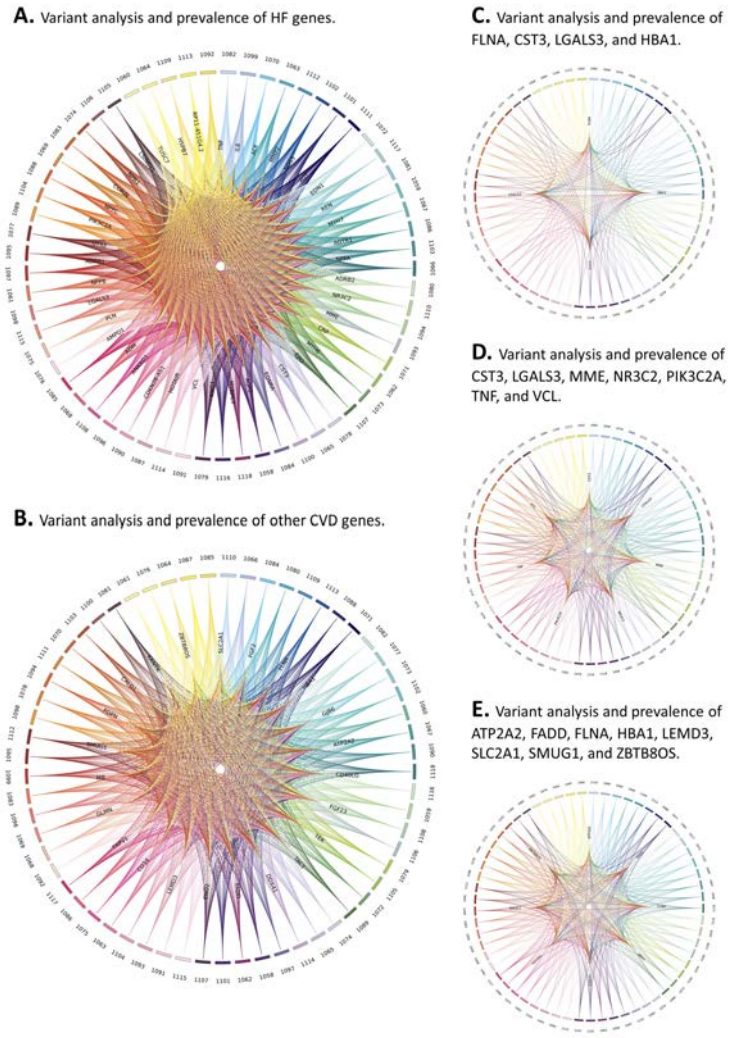
Download URL: https://github.com/drzeeshanahmed/JWES-DB

Variant, Prevalence, and Splice Mutation Analysis



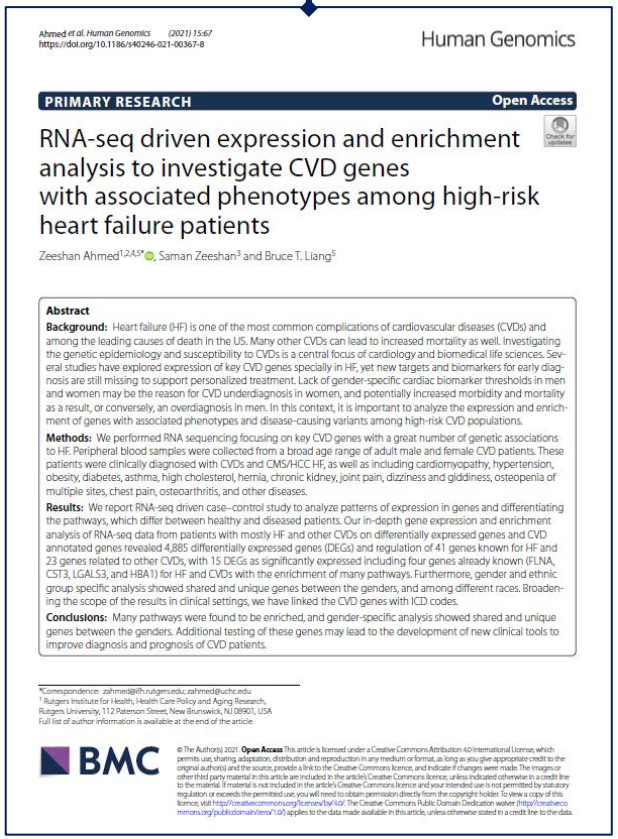
Mutation-percentage of HF (63%) and other CVD (37%) genes.





A) Variant analysis and prevalence of HF genes. **B)** Variant analysis and prevalence of other CVD genes. **C)** Variant analysis and prevalence of *FLNA, CST3, LGALS3*, and *HBA1*. **D)** Variant analysis and prevalence of *CST3, LGALS3, MME, NR3C2, PIK3C2A, TNF,* and *VCL*. **E)** Variant analysis and prevalence of *ATP2A2, FADD, FLNA, HBA1, LEMD3, SLC2A1, SMUG1,* and *ZBTB8OS*.

Publications at CVD Gene Expression, Annotation, and Variant Analysis



Ahmed et al. Human Genomics (2021) 15:67
https://doi.org/10.1186/s40246-021-00367-8

Human Genomics

PRIMARY RESEARCH — Open Access

RNA-seq driven expression and enrichment analysis to investigate CVD genes with associated phenotypes among high-risk heart failure patients

Zeeshan Ahmed[1,2,4,5*], Saman Zeeshan[3] and Bruce T. Liang[5]

Abstract

Background: Heart failure (HF) is one of the most common complications of cardiovascular diseases (CVDs) and among the leading causes of death in the US. Many other CVDs can lead to increased mortality as well. Investigating the genetic epidemiology and susceptibility to CVDs is a central focus of cardiology and biomedical life sciences. Several studies have explored expression of key CVD genes specially in HF, yet new targets and biomarkers for early diagnosis are still missing to support personalized treatment. Lack of gender-specific cardiac biomarker thresholds in men and women may be the reason for CVD underdiagnosis in women, and potentially increased morbidity and mortality as a result, or conversely, an overdiagnosis in men. In this context, it is important to analyze the expression and enrichment of genes with associated phenotypes and disease-causing variants among high-risk CVD populations.

Methods: We performed RNA sequencing focusing on key CVD genes with a great number of genetic associations to HF. Peripheral blood samples were collected from a broad age range of adult male and female CVD patients. These patients were clinically diagnosed with CVDs and CMS/HCC HF, as well as including cardiomyopathy, hypertension, obesity, diabetes, asthma, high cholesterol, hernia, chronic kidney, joint pain, dizziness and giddiness, osteopenia of multiple sites, chest pain, osteoarthritis, and other diseases.

Results: We report RNA-seq driven case–control study to analyze patterns of expression in genes and differentiating the pathways, which differ between healthy and diseased patients. Our in-depth gene expression and enrichment analysis of RNA-seq data from patients with mostly HF and other CVDs on differentially expressed genes and CVD annotated genes revealed 4,885 differentially expressed genes (DEGs) and regulation of 41 genes known for HF and 23 genes related to other CVDs, with 15 DEGs as significantly expressed including four genes already known (FLNA, CST3, LGALS3, and HBA1) for HF and CVDs with the enrichment of many pathways. Furthermore, gender and ethnic group specific analysis showed shared and unique genes between the genders, and among different races. Broadening the scope of the results in clinical settings, we have linked the CVD genes with ICD codes.

Conclusions: Many pathways were found to be enriched, and gender-specific analysis showed shared and unique genes between the genders. Additional testing of these genes may lead to the development of new clinical tools to improve diagnosis and prognosis of CVD patients.

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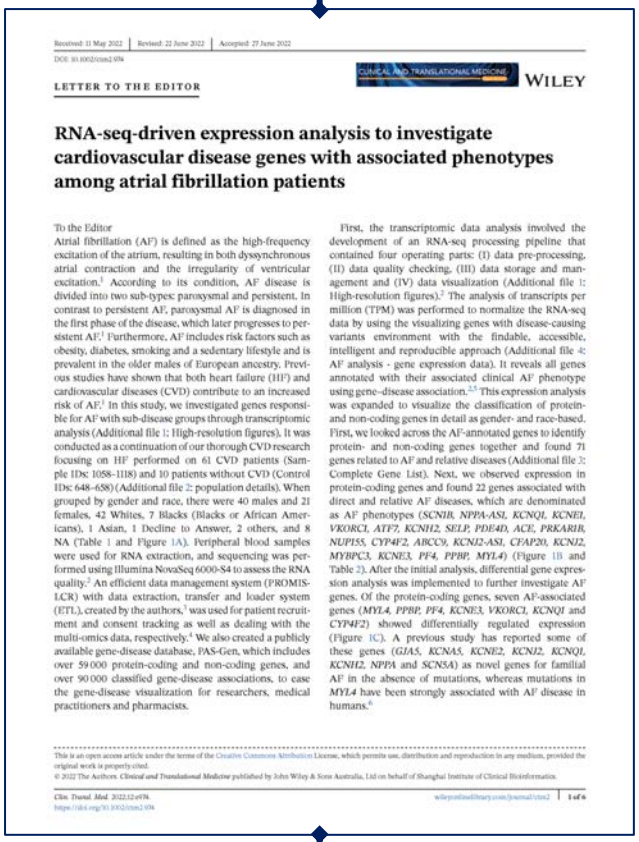

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DOI: 10.1002/ctm2.976

LETTER TO THE EDITOR — CLINICAL AND TRANSLATIONAL MEDICINE — WILEY

RNA-seq-driven expression analysis to investigate cardiovascular disease genes with associated phenotypes among atrial fibrillation patients

To the Editor

Atrial fibrillation (AF) is defined as the high-frequency excitation of the atrium, resulting in both dyssynchronous atrial contraction and the irregularity of ventricular excitation.[1] According to its condition, AF disease is divided into two sub-types: paroxysmal and persistent. In contrast to persistent AF, paroxysmal AF is diagnosed in the first phase of the disease, which later progresses to persistent AF.[1] Furthermore, AF includes risk factors such as obesity, diabetes, smoking and a sedentary lifestyle and is prevalent in the older males of European ancestry. Previous studies have shown that both heart failure (HF) and cardiovascular diseases (CVD) contribute to an increased risk of AF.[1] In this study, we investigated genes responsible for AF with sub-disease groups through transcriptomic analysis (Additional file 1: High-resolution figures). It was conducted as a continuation of our thorough CVD research focusing on HF performed on 61 CVD patients (Sample IDs: 1058–1118) and 10 patients without CVD (Control IDs: 648–658) (Additional file 2: population details). When grouped by gender and race, there were 40 males and 21 females, 42 Whites, 7 Blacks (Blacks or African Americans), 1 Asian, 1 Decline to Answer, 2 others, and 8 NA (Table 1 and Figure 1A). Peripheral blood samples were used for RNA extraction, and sequencing was performed using Illumina NovaSeq 6000-S4 to assess the RNA quality.[2] An efficient data management system (PROMIS-LCR) with data extraction, transfer and loader system (ETL), created by the authors,[3] was used for patient recruitment and consent tracking as well as dealing with the multi-omics data, respectively.[4] We also created a publicly available gene-disease database, PAS-Gen, which includes over 59 000 protein-coding and non-coding genes, and over 90 000 classified gene-disease associations, to ease the gene-disease visualization for researchers, medical practitioners and pharmacists.

First, the transcriptomic data analysis involved the development of an RNA-seq processing pipeline that contained four operating parts: (I) data pre-processing, (II) data quality checking, (III) data storage and management and (IV) data visualization (Additional file 1: High-resolution figures).[2] The analysis of transcripts per million (TPM) was performed to normalize the RNA-seq data by using the visualizing genes with disease-causing variants environment with the findable, accessible, intelligent and reproducible approach (Additional file 4: AF analysis - gene expression data). It reveals all genes annotated with their associated clinical AF phenotype using gene–disease association.[2,5] This expression analysis was expanded to visualize the classification of protein- and non-coding genes in detail as gender- and race-based. First, we looked across the AF-annotated genes to identify protein- and non-coding genes together and found 71 genes related to AF and relative diseases (Additional file 3: Complete Gene List). Next, we observed expression in protein-coding genes and found 22 genes associated with direct and relative AF diseases, which are denominated as AF phenotypes (*SCN1B, NPPA-AS1, KCNQ1, KCNE1, VKORC1, ATF7, KCNH2, SELP, PDE4D, ACE, PRKAR1B, NUP155, CYP4F2, ABCC9, KCNJ2-AS1, CFAP20, KCNJ2, MYBPC3, KCNE3, PF4, PPBP, MYL4*) (Figure 1B and Table 2). After the initial analysis, differential gene expression analysis was implemented to further investigate AF genes. Of the protein-coding genes, seven AF-associated genes (*MYL4, PPBP, PF4, KCNE3, VKORC1, KCNQ1* and *CYP4F2*) showed differentially regulated expression (Figure 1C). A previous study has reported some of these genes (*GJA5, KCNA5, KCNE2, KCNJ2, KCNQ1, KCNH2, NPPA* and *SCN5A*) as novel genes for familial AF in the absence of mutations, whereas mutations in *MYL4* have been strongly associated with AF disease in humans.[6]

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RESEARCH ARTICLE — CLINICAL AND TRANSLATIONAL DISCOVERY — WILEY

Investigating genes associated with cardiovascular disease among heart failure patients for translational research and precision medicine

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Abstract

Background: Cardiovascular disease (CVD) is a leading cause of premature mortality in the United States and the world. CVD comprises several complex and mostly heritable conditions, which range from myocardial infarction to congenital heart disease. The risk factors contributing to the development of CVD and response to therapy in an individual patient are highly variable. Here, we report our findings from an integrative analysis of gene expression, disease-causing gene variants and associated phenotypes among CVD populations, with a focus on high-risk heart failure (HF) patients.

Methods: We built a cohort using electronic health records of consented patients with available samples and then performed high-throughput whole genome and RNA sequencing of key genes responsible for HF and other CVD pathologies. Our in-depth gene expression analysis revealed differentially expressed genes associated with HF and other CVDs. We performed a variant analysis of whole genome sequence data of CVD patients and identified genes with altered gene expression with functional and non-functional mutations in these genes.

Results: Our results highlight the importance of investigating the mechanisms of CVD progression through multi-omics datasets. Next, we performed splice mutation and variant distribution analysis of genes associated with HF and other CVD. We implemented Jensen–Shannon divergence (JSD)-based method and identified *HBA1, FADD, ADRB2, NPPB, ADRB1, ADB* and *NPPC* genes with the greatest variance based on their JSD scores. Our study provided evidence that applying integrative data analysis approach involving genomics and transcriptomics data will not only help understand the pathophysiology of CVD diseases but also reduce heterogeneity in disease subtypes.

KEYWORDS
cardiovascular disease, expression, gene, genome, heart failure, RNA-seq, variant

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Implementing Artificial Intelligence (AI) & Machine Learning (ML)

1. **Generate AI/ML ready data** with the integration of existing bioinformatics tools and development of new pipelines for the multi-omics and clinical data management, integration, annotation, and sharing.

2. **Predict CVD with high accuracy** with knowledge-driven approach based on known genetic evidence establishing association by implementing best fitting AI/ML algorithms for deep phenotyping and predictive analytics.

Software Impacts 16 (2023) 100493

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Original software publication

Hygieia: AI/ML pipeline integrating healthcare and genomics data to investigate genes associated with targeted disorders and predict disease

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Keywords:
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Machine learning
Genomics
Healthcare
Predictive analysis

ABSTRACT

Due to the advancements in sequencing technologies, genomics data is developing at an unmatched pace and levels to foster translational research. Over ten million genomics datasets have been produced and publicly shared in the year 2022. Genome-wide association studies (GWAS) have remarkably assisted in understanding the genetic basis of human disease by uncovering millions of loci associated with various complex phenotypes. However, GWAS are unable to predict disease and detect all the heritability explained by single nucleotide polymorphisms (SNPs) and can only target specific variants. The rightful use of the artificial intelligence (AI) and machine learning (ML) techniques can accelerate our ability to leverage and extend the information contained within the original data, and model patient-specific genomics data against publicly available annotation repositories for understanding how coding and non-coding genomic variations are connected to disease mechanisms. The grand challenge here is assimilation of genetics into precision medicine that translates across different ancestries, diverse diseases, and other distinct populations with the implementation of effective AI/ML methods. We present first AI/ML ready pipeline i.e., *Hygieia*., integrating genomics and clinical data to investigate genes associated with the targeted disorders and predict disease with high accuracy. *Hygieia* can utilize broad dataset sizes with heterogeneous levels of granularity and offer a supervised approach to analyze integrated gene expression and multivariate clinical data. It includes the Random Forest based model for regression analysis and predict without hyperparameter tuning. We trained and tested our model across variable disorders and using diverse datasets. *Hygieia* is an open-source and simple to use pipeline, which does not strong require computational background to execute.

Code metadata

Current Code Version	*Hygieia v1.0.2*
Permanent Link to Repository	https://github.com/SoftwareImpacts/SIMPAC-2023-36
Reproducible Capsule	https://codeocean.com/capsule/7964745/tree/v1
Legal License	*GNU General Public License (GPL)*
Code Versioning System	*Git*
Software Code Languages	*Python 3.10.9*
Compilation Requirements, Dependencies	*pandas, scikit-learn, matplotlib, seaborn*
Support email for questions	zahmed@ifh.rutgers.edu

1. Introduction

Precision and genomics medicine is driven by the paradigm shift of empowering clinicians to predict the most appropriate course of action

The code (and data) in this article has been certified as Reproducible by Code Ocean: (https://codeocean.com/). More information on the Reproducibility Badge Initiative is available at https://www.elsevier.com/physical-sciences-and-engineering/computer-science/journals.

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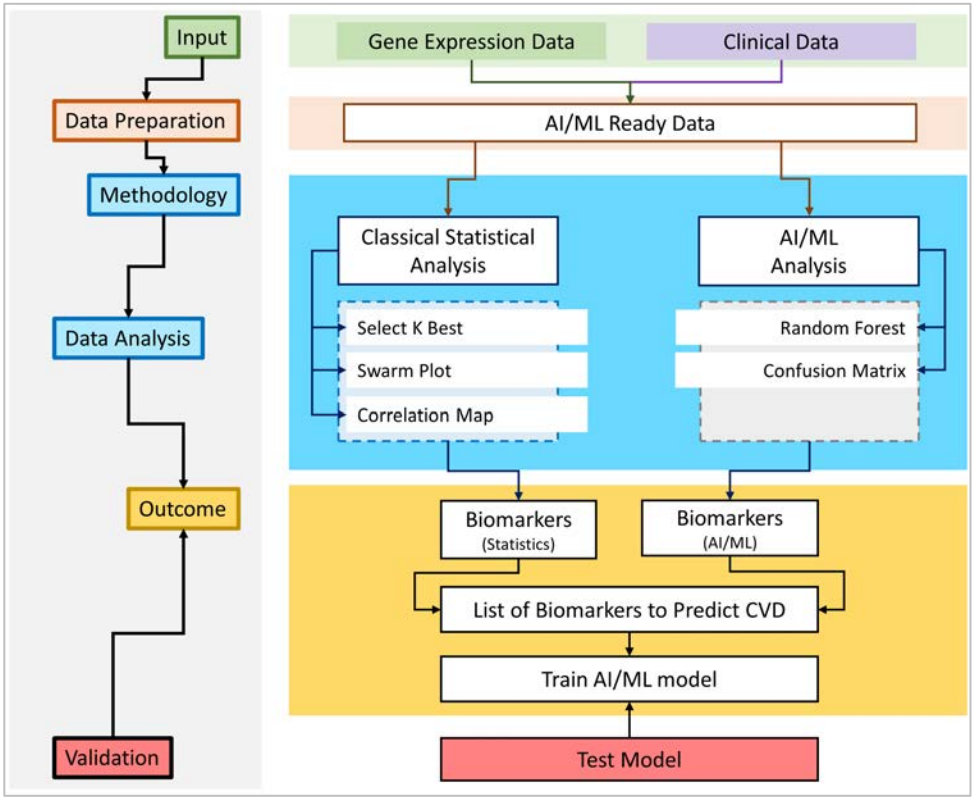
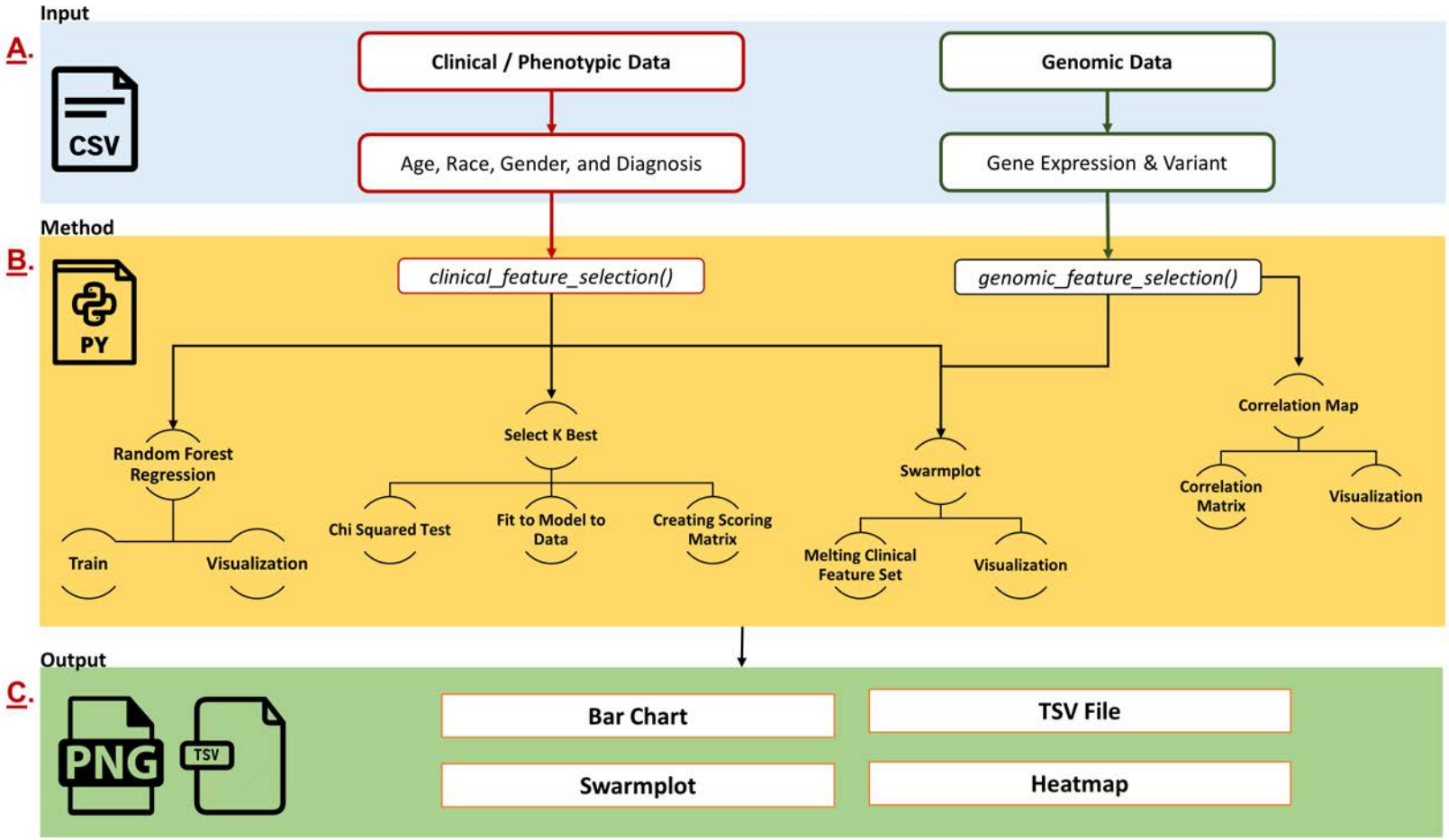
Implementing Artificial Intelligence (AI) & Machine Learning (ML)

1. **Generate AI/ML ready data** with the integration of existing bioinformatics tools and development of new pipelines for the multi-omics and clinical data management, integration, annotation, and sharing.

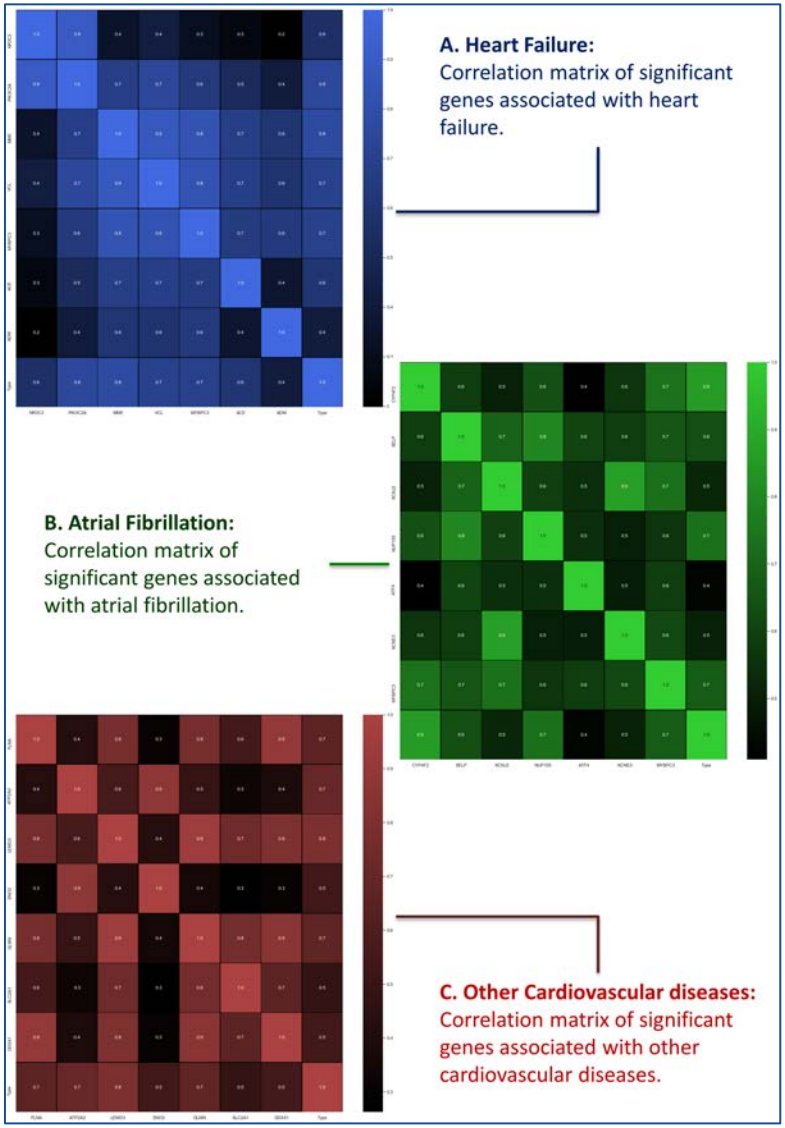
2. **Predict CVD with high accuracy** with knowledge-driven approach based on known genetic evidence establishing association by implementing best fitting AI/ML algorithms for deep phenotyping and predictive analytics.



Hygieia Design



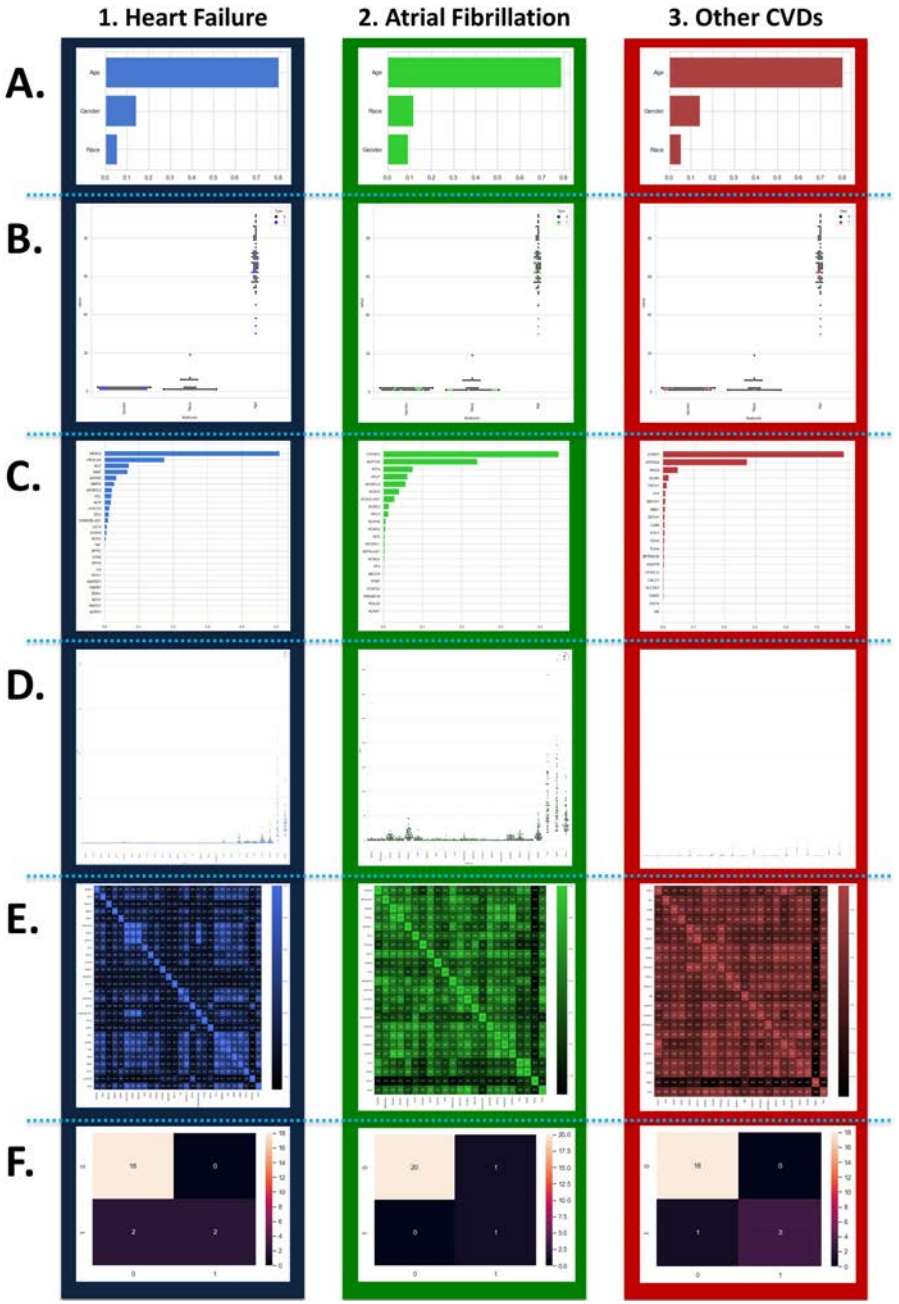
AI/ML Analysis



A. Heart Failure:
Correlation matrix of significant genes associated with heart failure.

B. Atrial Fibrillation:
Correlation matrix of significant genes associated with atrial fibrillation.

C. Other Cardiovascular diseases:
Correlation matrix of significant genes associated with other cardiovascular diseases.



(A) Population distribution based on clinical features; (B) Correlation matrix; (C) Gene ranking; (D) Feature Swarm Plot; (E) Correlation matrix of genes; (F) Confusion matrix of genes.

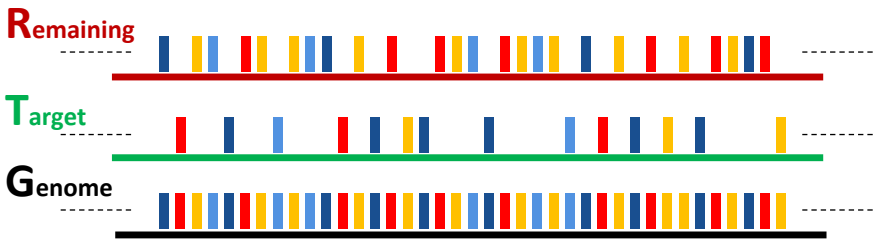
AI/ML Analysis

- We used our **open-source AI/ML ready pipeline i.e., *Hygieia***, which is based on the Random Forest (RF) for regression analysis and predicting disease without requiring hyperparameter tuning.
- We **trained our model on different cross-sections** of the three different matrices based on HF, AF, and other CVDs.
- We uncovered an interesting correlation between age, gender, race, and diagnosis. During our analysis, it was observed that **age and gender appeared to have a high correlation in HF and other CVDs while age, and race were highly correlated in AF**.
- We observed the most significant genes associated with HF, AF, and other CVDs based on the RF feature importance global variable. **A score was assigned to each gene, which represents the feature importance for the model in stratifying CVD patients**.
- Visible data clusters were observed for the genes highly correlated, downregulated and with altered expression in CVD patients compared to healthy individuals. Our model was able to correctly classify individuals as CVD patients and predict CVD with **95% accuracy**.
- We observed and reported overlapping in **significant results produced in gene expression, variant, phenotypic, and predictive analyses**, which include genes associated with HF, AF, and other CVDs.

AI/ML Analysis

Identify new predictive biomarkers

using data-driven approach with a novel nexus of AI/ML algorithms to reveal biological patterns explaining the causal relationship based on genomic, transcriptomic, and phenotypic data of patients with CVD.



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Investigating genes associated with heart failure, atrial fibrillation, and other cardiovascular diseases, and predicting disease using machine learning techniques for translational research and precision medicine

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ARTICLE INFO

Keywords:
Artificial intelligence
Atrial fibrillation
Cardiovascular diseases
Gene expression
Heart failure
Machine learning
Predictive analysis

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of mortality and loss of disability adjusted life years (DALYs) globally. CVDs like Heart Failure (HF) and Atrial Fibrillation (AF) are associated with physical effects on the heart muscles. As a result of the complex nature, progression, inherent genetic makeup, and heterogeneity of CVDs, personalized treatments are believed to be critical. Rightful application of artificial intelligence (AI) and machine learning (ML) approaches can lead to new insights into CVDs for providing better personalized treatments with predictive analysis and deep phenotyping. In this study we focused on implementing AI/ML techniques on RNA-seq driven gene-expression data to investigate genes associated with HF, AF, and other CVDs, and predict disease with high accuracy. The study involved generating RNA-seq data derived from the serum of consented CVD patients. Next, we processed the sequenced data using our RNA-seq pipeline and applied GVViZ for gene-disease data annotation and expression analysis. To achieve our research objectives, we developed a new Findable, Accessible, Intelligent, and Reproducible (FAIR) approach that includes a five-level biostatistical evaluation, primarily based on the Random Forest (RF) algorithm. During our AI/ML analysis, we have fitted, trained, and implemented our model to classify and distinguish high-risk CVD patients based on their age, gender, and race. With the successful execution of our model, we predicted the association of highly significant HF, AF, and other CVDs genes with demographic variables.

1. Introduction

Cardiovascular disease (CVD) is the leading causes of mortality and loss of disability adjusted life years (DALYs) globally [1–3]. The World Health Organization (WHO) states that over 75% of premature CVDs are preventable with a better understanding of risk factors and gene-disease associations [2]. CVDs like Heart Failure (HF) and Atrial Fibrillation (AF) are associated with physical impacts on the heart muscles [1,3]. HF occurs due to weak heart muscles that impact the efficiency of pumping blood to the body's cells [1]. While AF occurs due to the high-frequency excitation of the atrium, resulting in both dyssynchronous atrial contraction and the irregularity of ventricular excitation [3,4]. Genomics studies done using genome-wide association studies (GWAS) have aided in disease prediction [5,6], discovery of genetic loci and alleles

Abbreviations: Artificial intelligence, (AI); Atrial fibrillation, (AF); Cardiovascular diseases, (CVDs); Computerized tomography, (CT); Differentially expressed genes, (DEGs); Electronic health records, (EHR); Extract, transfer, and load, (ETL); Fragments per kilobase million, (FPKM); Genome-wide association studies, (GWAS); Heart failure, (HF); Institutional review board, (IRB); Machine learning, (ML); Mean expressed transcript lengths, (METL); Next generation sequencing, (NGS); Normalized enrichment score, (NES); Random forest, (RF); Reads per kilobase of transcript per million mapped reads, (RPKM); RNA-sequencing, (RNA-seq); Sci-kit learn, (Sklearn); Support vector machine, (SVM); Transcripts per million, (TPM); Visualizing genes with disease-causing variants, (GVViZ); World Health Organization, (WHO); Whole genome sequencing, (WGS); Whole exome sequencing, (WES).

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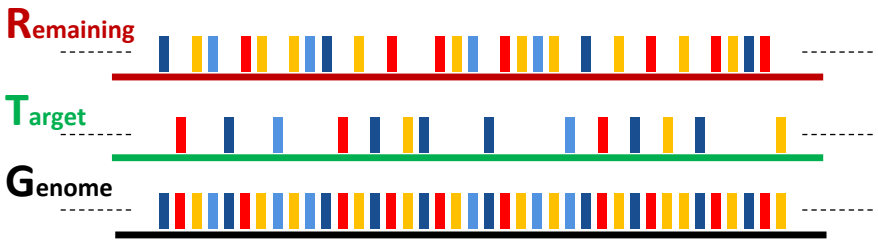
AI/ML Analysis

Identify new predictive biomarkers

using data-driven approach with a novel nexus of AI/ML algorithms to reveal biological patterns explaining the causal relationship based on genomic, transcriptomic, and phenotypic data of patients with CVD.



1 **Title**

2 Discovering biomarkers associated and predicting cardiovascular disease with high
3 accuracy using a novel nexus of machine learning techniques for precision medicine

4 **Running Head**

5 Discovering biomarkers and predicting CVD using AI/ML

6 **Authors**

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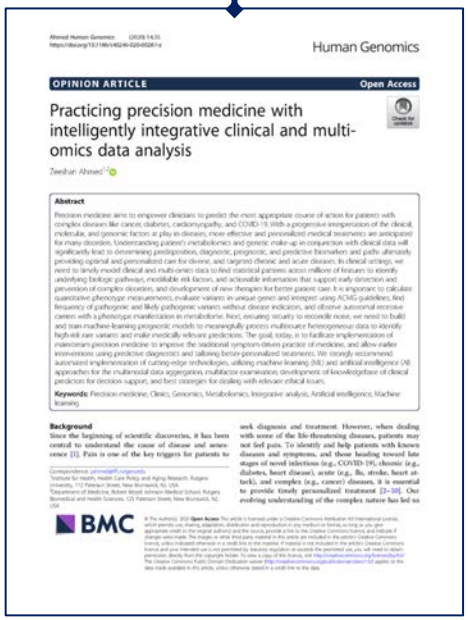
20

Traditional Bioinformatics and AI/ML

- **Gene Expression Analysis (GEA)** and **Genome-wide association studies (GWAS)** have been useful in providing deeper understanding of the genetic basis of human diseases by uncovering millions of loci associated with various complex phenotypes.
- **These are unable to predict disease and detect all the heritability** explained by SNPs, as they can only target specific variants of disease.
- These limitations are not exclusive to GEA and GWAS, as **no method to date can identify all the genetic components of complex diseases.**
- In addition, a persistent challenge in multi-genomic data analysis lies in the handling, **integration, and standardization of large volumes of sequencing data.**
- **The proficient and synergistic implementation of AI/ML techniques holds the promise of fostering an augmented comprehension of CVD at the systemic level, unveiling the intricacies of genomic regulatory networks.**

Global impact of precision medicine

The appropriate utilization of artificial intelligence (AI) and machine learning (ML) methodologies can yield novel understandings of complex traits, enabling improved personalized treatments through predictive analysis and deep phenotyping.


Human Genomics

OPINION ARTICLE Open Access

Practicing precision medicine with intelligently integrative clinical and multi-omics data analysis

Zeeshan Ahmed

Abstract


Progress in Molecular Biology and Translational Science

Volume 190, Issue 1, 2022, Pages 101-125

Precision medicine with multi-omics strategies, deep phenotyping, and predictive analysis

Zeeshan Ahmed

Contents


DATABASE

Review

Artificial intelligence with multi-functional machine learning platform development for better healthcare and precision medicine

Zeeshan Ahmed, Khalid Mohamed, Saman Zeeshan and XinQi Dong

Abstract


frontiers | Frontiers in Genetics

Artificial Intelligence, Healthcare, Clinical Genomics, and Pharmacogenomics Approaches in Precision Medicine

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INTRODUCTION

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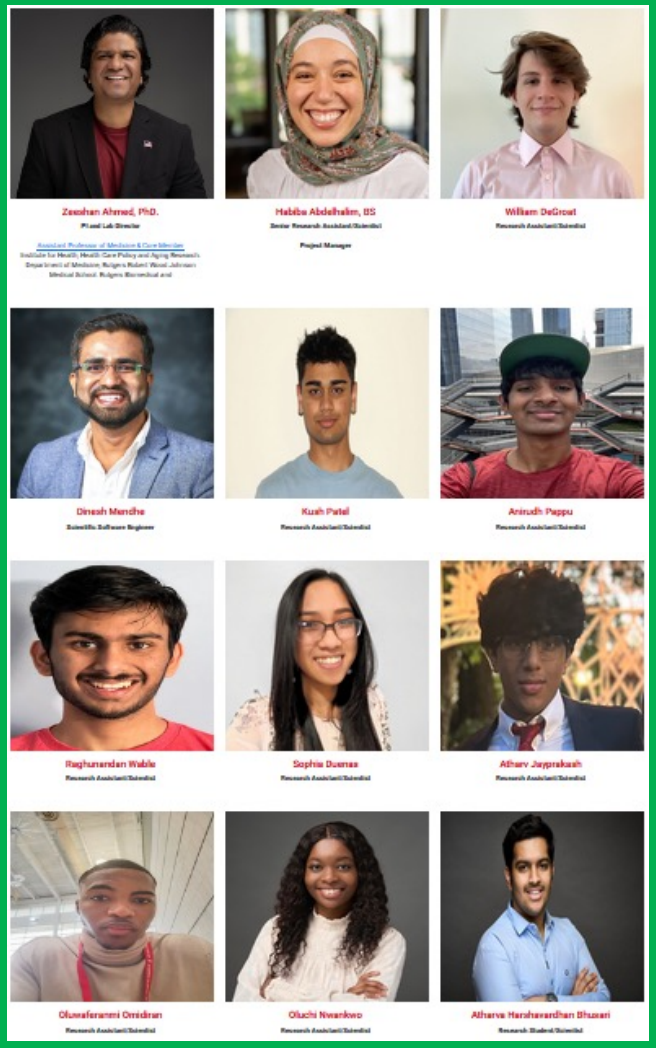
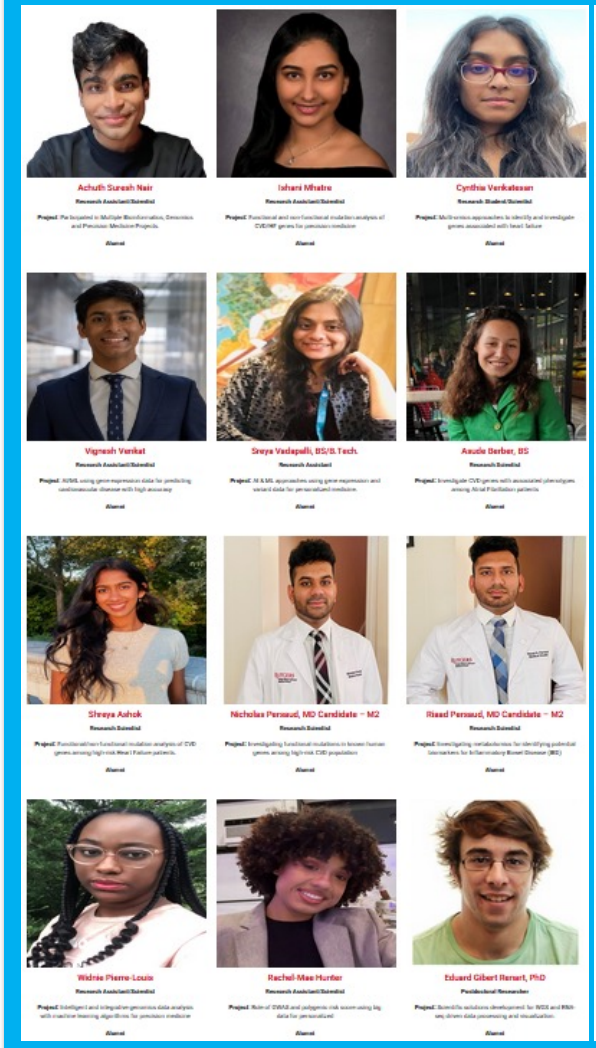
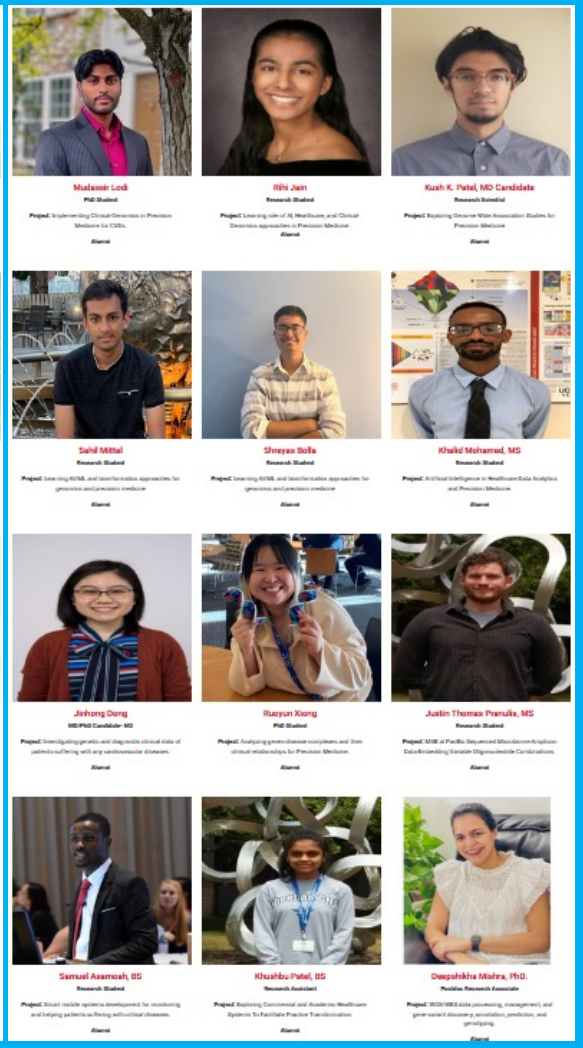


Alumni





Collaborations

UCONN HEALTH

Kumamoto University

IRCMS International Research Center for Medical Sciences

UNIVERSITY OF EASTERN FINLAND

A.I.VIRTANEN INSTITUTE

BROAD INSTITUTE

MIT

MIT CSAIL

RUTGERS Addiction Research Center

RUTGERS School of Dental Medicine

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Kumamoto University, Japan.

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Institute for Health, Health Care Policy and Aging Research
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Rutgers Biomedical and Health Sciences

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The New York Academy of Sciences

AMED 国立研究開発法人 日本医療研究開発機構 Japan Agency for Medical Research and Development

NIH National Institute on Aging

RUTGERS Brain Health Institute

RUTGERS BIOMEDICAL AND HEALTH SCIENCES

UCONN SCHOOL OF MEDICINE

Google Research

CMS TCPi Transforming Clinical Practice Initiative
CENTERS FOR MEDICARE & MEDICAID SERVICES

RUTGERS
THE STATE UNIVERSITY OF NEW JERSEY

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Precision Medicine Project: < https://sites.rutgers.edu/precision-medicine/ **>**

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