

DISEASE PREDICTION USING DEEP LEARNING TECHNIQUES

Submitted in partial fulfillment of the requirements for the award of
Bachelor of Science in Bioinformatics and Data Science

By

Kollipara Tejasree (41738019)



**DEPARTMENT OF BIOINFORMATICS
SCHOOL OF BIO AND CHEMICAL ENGINEERING**

SATHYABAMA

INSTITUTE OF SCIENCE AND TECHNOLOGY (DEEMED TO BE UNIVERSITY)
Accredited with Grade "A++" by NAAC I Category-1 University by UGC | Approved by
AICTE

Jeppiaar Nagar, Rajiv Gandhi Salai, Chennai - 600 119

APRIL - 2024



SATHYABAMA

INSTITUTE OF SCIENCE AND TECHNOLOGY

(DEEMED TO BE UNIVERSITY)

Accredited with Grade "A++" by NAAC I Category-1 University by UGC I Approved by AICTE

Jeppiaar Nagar, Rajiv Gandhi Salai, Chennai – 600 119

www.sathyabama.ac.in

DEPARTMENT OF BIOINFORMATICS

BONAFIDE CERTIFICATE

This is to certify that this Project Report is the bonafide work of **Kollipara Tejasree (41738019)**, who carried out the final year project entitled "**DISEASE PREDICTION USING DEEP LEARNING TECHNIQUES**" under my supervision from January 2024 to April 2024.

Dr. H. JEMMY CHRISTY

Internal Guide

Dr. H. JEMMY CHRISTY

Head of the Department

Submitted for Viva Voce Examination held on

27/04/24

Internal Examiner

External Examiner

DECLARATION

I, KOLLIPARA TEJASREE, hereby declare that the Project Report entitled **DISEASE PREDICTION USING DEEP LEARNING TECHNIQUES** done by me under the guidance of **Dr. H. JEMMY CHRISTY** at Sathyabama Institute of Science and Technology, Jeppiaar Nagar, Rajiv Gandhi Road, Chennai-600119, Tamil Nadu, India, is submitted in partial fulfillment of the requirements for the award of **Bachelor of Science in Bioinformatics and Data Science**.

DATE: 27.04.2024

PLACE: CHENNAI

K. Tejasree...

SIGNATURE OF THE CANDIDATE

ACKNOWLEDGEMENTS

I am delighted to express my heartfelt acknowledgement to the Board of Management of SATHYABAMA for their kind encouragement and support throughout the duration of my project. Their guidance has been invaluable in ensuring the successful completion of this project, and I am sincerely grateful for their contribution.

I convey my thanks to Dr. Rekha Chakravarthy, Dean, School of Science and Humanitites for providing me necessary support and details at the right time during the progressive reviews.

I sincerely thank Dr. H. Jemmy Christy, Head of the Department, Dept. of Bioinformatics, for her unwavering support and timely provision of necessary details during the progressive reviews. Her support has been instrumental in helping me to overcome obstacles and achieve success in this project.

I am deeply indebted to my Project Guide, Dr. H. Jemmy Christy, for her invaluable guidance, suggestions, and constant encouragement throughout the project. Her expertise and insights have been instrumental in shaping my work and ensuring its successful completion.

I also wish to extend my gratitude to my family for their support and assistance in various ways, which have contributed to the successful completion of this project.

Kollipara Tejasree



SATHYABAMA

INSTITUTE OF SCIENCE AND TECHNOLOGY

(DEEMED TO BE UNIVERSITY)

Accredited with Grade "A++" by NAAC I Category-1 University by UGC I Approved by AICTE

Jeppiaar Nagar, Rajiv Gandhi Salai, Chennai – 600 119

www.sathyabama.ac.in

CERTIFICATE

This is to certify that the dissertation entitled "**DISEASE PREDICTION USING DEEP LEARNING TECHNIQUES**" was carried out by **Ms. Kollipara Tejasree** (Reg. No. **41738019**), Department of Bioinformatics and Data Science, Sathyabama Institute of Science and Technology, Chennai in partial fulfillment of the requirements of the award of the **Degree of Bachelor of Science in Bioinformatics and Data Science** 2021- 2024, is a bonafide record of the project work done under my guidance and supervision.

This thesis or part, therefore, has not been submitted elsewhere for any other degree or diploma.

Date: 27/04/24

Place: Chennai

A handwritten signature in black ink, consisting of a stylized 'J' followed by a horizontal line and a small flourish.

Dr. H. JEMMY CHRISTY

CHAPTER NO.	TITLE	PAGE NO.
	ABSTRACT	i
	LIST OF ABBREVIATIONS	ii
	LIST OF FIGURES	iv
1	INTRODUCTION	1
	1.1 Background	1
	1.2 Stages	1
	1.2.1 Exposure and infection	2
	1.2.2 Latent tuberculosis infection	2
	1.2.3 Active tuberculosis disease	2
	1.3 Types	2
	1.3.1 Pulmonary tuberculosis	3
	1.3.2 Extra pulmonary tuberculosis	3
	1.3.3 Drug resistant tuberculosis	3
	1.3.4 Military tuberculosis	3
	1.3.5 Latent tuberculosis infection	3
	1.4 TREATMENTS	4
	1.4.1 Standard first-line drugs	4
	1.4.2 Combination therapy	4
	1.4.3 Directly observed therapy	5
	1.4.4 Short regimens	5
	1.4.5 Drug resistant tuberculosis	6
	1.4.6 Adjunctive therapies	6

CHAPTER NO.	TITLE	PAGE NO.
	1.5 Complications	6
	1.5.1 Improvement in symptoms	7
	1.6 Mortality rate	7
	1.7 Survival rate	8
2	REVIEW OF LITERATURE	12
3	AIM AND SCOPE	21
	3.1 AIM	21
	3.2 SCOPE	21
	3.3 FUTURE WORK	21
4	METHODOLOGY	22
	4.1 Gene Datasets	22
	4.2 Databases	22
	4.3 Filtering the genes	22
	4.4 Identification of rpoBgene	23
	4.5 Model development	23
	4.6 Personalized treatment recommendations	23
	4.7 Ethical considerations	23
5	RESULTS AND DISCUSSION	24
6	SUMMARY AND CONCLUSIONS	34
	6.1 Summary	35
	6.2 Conclusion	35
	REFERENCES	36

LIST OF FIGURES

FIGURE NO	TITLE	PAGE NO
1.1	Mortality rate of tuberculosis	07
1.2	Success rate of tuberculosis	09
1.3	Burden of tuberculosis	09
1.4	Death percentage of TB cases in united states	10
1.5	Estimated death rates of tb in India and globally	11
5.1	Packages required for the deep learning model	25
5.2	Analyzed percentages with rpoBgene in TB strains	26
5.3	AI-Predicted percentages for precaution optimization	27
5.4	Understanding Resistance: Exploring rpoB Gene Variants 1	27
5.5	Optimizing Precautionary Measures Based on AI-Predicted Resistance Percentages	28
5.6	Unveiling the Neural Network: Exploring Deep Learning Potential for seq 2	29
5.7	Optimizing Precautionary Measures Based on AI-Predicted Resistance Percentages	30

5.8	Resistance percentage for sequence 2	31
5.9	Precautions for sequence 2	31
5.10	Visualizing deep learning sequence 3	32
5.11	Resistance percentage for sequence 3	32
5.12	Optimizing precautionary measures based on ai model	33
5.13	Precautions for sequence 3	34

LIST OF ABBREVIATIONS

BCG	bacille Calmette-Guérin
LTBI	Latent tuberculosis infection
MDR -TB	Multidrug resistant tuberculosis
XDR-TB	Extensively drug- resistant
INH	Isoniazid
RIF	Rifampicin
PZA	Pyrazinamide
EMB	Ethambutol
DOT	Directly Observed Therapy
rpoB gene	RNA polymerase B subunit
CRyPTIC	Cryptic tuberculosis
ECG	Electrocardiogram
EEG	Electroencephalogram
cDST	Culture drug susceptibility
pDST	Phenotypic drug susceptibility
MTB	Mycobacterium tuberculosis
seqIO	Standard sequence input and output

ABSTRACT

This project introduces a pioneering methodology to predict the progression of tuberculosis (TB) and offer customized management strategies using sophisticated deep learning techniques through gene sequences. By leveraging the insights of gene sequences gleaned from resistance rates determined through analysis of the *rpoB* gene, further project aims to construct an advanced AI model capable of accurately determining TB stages. Moreover, this model will provide tailored recommendations for precautions and dietary plans, enhancing the precision and effectiveness of TB management. Through the integration of genetic data analysis and cutting-edge AI algorithms, the project aspires to empower healthcare professionals with the tools to deliver personalized interventions. This personalized approach not only optimizes patient outcomes but also contributes to broader public health initiatives aimed at combating TB. By revolutionizing TB management through early intervention strategies and personalized care, this innovative approach holds immense promise in improving the health and well-being of individuals affected by TB, ultimately leading to a significant reduction in the global burden of the disease.

CHAPTER 1

INTRODUCTION

1.1 Background :

Tuberculosis, a highly contagious disease caused by the bacterium *Mycobacterium tuberculosis*, has a rich and extensive history that can be traced back to ancient times. It has been a persistent and lethal ailment throughout the ages. In the late 19th century, the renowned scientist Robert Koch made a groundbreaking discovery by identifying the specific bacterium responsible for tuberculosis. This pivotal finding laid the foundation for comprehending the disease and paved the way for the development of effective treatments.(*Barberis et.al.,2017*)The 20th century witnessed remarkable advancements in the control of tuberculosis. In the 1920s, the BCG vaccine was introduced, providing a significant breakthrough in preventing the spread of the disease.(*Luca, et al.,2013.*) Additionally, the discovery of antibiotics like streptomycin in the 1940s revolutionized the treatment of tuberculosis, offering hope to countless individuals afflicted by this debilitating illness.(*Muteeb et al ., 2023*). Despite these significant achievements, tuberculosis continues to pose a grave threat to global health, particularly in impoverished regions where access to healthcare is limited.The challenges faced in combating tuberculosis have been further compounded by the emergence of drug-resistant strains and the devastating HIV/AIDS pandemic. Drug-resistant tuberculosis strains have proven to be more difficult to treat, requiring prolonged and complex treatment regimens. The co-infection of tuberculosis and HIV/AIDS has also presented a formidable obstacle, as individuals with compromised immune systems are more susceptible to developing active tuberculosis.(*Bloom, B. R.. et al.,2017*) This intersection of diseases has

created a complex web of challenges for healthcare systems worldwide. In the present day, tuberculosis remains a pressing global health concern. (Dheda et al., 2022) The World Health Organization has set ambitious goals for the elimination of tuberculosis by 2035, emphasizing the urgent need for concerted efforts to address this issue. (Birhanu Ayenew et al., 2024) Overcoming obstacles such as funding shortages and deficiencies in healthcare infrastructure is of paramount importance in the fight against tuberculosis. By allocating adequate resources, implementing effective prevention strategies, and strengthening healthcare systems, it is possible to make significant progress towards eliminating tuberculosis as a major public health threat. (Thakur et al., 2021).

1.2 STAGES:

1.2.1 Exposure and Infection : Inhaling *Mycobacterium tuberculosis* from an infected individual, who usually carries the bacteria, can lead to the development of a tuberculosis infection. Although the body's immune system may effectively control the bacteria, there is still a chance for the bacteria to become dormant and result in a latent tuberculosis infection (LTBI).

1.2.2 Latent tuberculosis infection (LTBI): It occurs when TB bacteria are in the body but are controlled by the immune system, causing no symptoms. While it is not dangerous, if the immune system weakens and the bacteria become active, it can progress to active tuberculosis. It can lead to the development of active tuberculosis. In cases of latent tuberculosis infection (LTBI), TB bacteria are present in the body but are suppressed by the immune system. While it is not transmissible, if the immune system weakens, it can progress to active tuberculosis.

1.2.3 Active tuberculosis disease: It occurs when the immune system fails to control the TB germs, leading to symptoms such as fever, night sweats, weight loss, fatigue, and coughing up blood. It can affect various parts of the body, including the lungs and other organs, known as extrapulmonary tuberculosis (Jagielski et al.,2016)

1.3 Types

1.3.1 .Pulmonary TB: The common form of tuberculosis (TB) attacks the lungs, resulting in fever, night sweats, exhaustion, weight loss, blood or sputum coughing, and a persistent cough.(Luies et al.,2020)

1.3.2 Extrapulmonary tuberculosis (TB): Extrapulmonary Tuberculosis refers to tuberculosis that affects parts of the body other than the lungs. Some common types of extrapulmonary TB include Tuberculous lymphadenitis, which is TB infection of the lymph nodes, Tuberculous meningitis, which is TB infection of the membranes surrounding the brain and spinal cord, Skeletal tuberculosis, which is TB infection of the bones and joints, Genitourinary tuberculosis, which is TB infection of the kidneys, bladder, and reproductive organs, and Gastrointestinal tuberculosis, which is TB infection of the gastrointestinal tract, including the intestines and abdomen.(Lee J. Y. (2015)

1.3.3 Drug resistant tuberculosis: There is a possibility for resistance to develop against one or more antibiotics that are commonly used to treat different types of infections. For instance, there is

- multidrug-resistant TB (MDR-TB) which is resistant to at least two of the most powerful first-line drugs.
- drug-resistant TB (XDR-TB) which is resistant to isoniazid and rifampicin, as well as fluoroquinolones and at least one of the injectable second-line drugs
- total drug-resistant TB (TDR-TB), which is extremely rare but refers to strains of tuberculosis that are resistant to all available drugs for tuberculosis.

1.3.4. Military tuberculosis (TB): Military Tuberculosis is a type of tuberculosis where the TB bacteria spread through the bloodstream and cause small lesions resembling millet seeds in various organs of the body, including the lungs and gastrointestinal tract.

1.3.5 Latent tuberculosis infection (LBTI) : In this kind of TB their immune system may deteriorate and they may acquire active tuberculosis even though they do not exhibit any outward signs of the disease.(Liebenberg, D et al.,2022).

1.4 TREATMENTS

1.4.1 Standard-first line drugs : TB treatment relies on the use of four crucial drugs:

Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol. Each drug plays a unique role in combating the disease.

- Isoniazid(INH) works by blocking the synthesis of mycolic acid, which is an essential component of the TB bacteria's cell wall.
- Rifampicin(RIF) on the other hand, hinders the replication of RNA, preventing the bacteria from multiplying.
- Pyrazinamide(PZA) destroys the metabolic processes of the bacteria, weakening its ability to survive and reproduce.
- Ethambutol(EMB) targets the cell wall components of the mycobacteria, inhibiting their growth. These drugs are commonly managed together as a combination therapy to effectively fight against TB.(Mayo Clinic. (2023)).

1.4.2 Combination Therapy

The standard therapy for drug-susceptible TB typically lasts between six to nine months and includes a combination of INH, RIF, PZA, and EMB. By using a combination of drugs, the therapy aims to prevent the development of resistant strains of tuberculosis by attacking the bacteria at different points in their growth cycle.

Isoniazid (INH) is a first-line medication that is highly effective in killing and actively dividing tuberculosis bacteria. It works by inhibiting the synthesis of mycolic acids, which are essential components of the bacteria's cell wall. By disrupting the cell wall formation, INH effectively kills the bacteria and prevents their replication.

Rifampin (RIF) is another key component of the tuberculosis treatment regimen. It targets the bacteria during both the active and dormant phases of their growth cycle. RIF works by inhibiting the synthesis of RNA, a crucial step in the bacteria's protein production. By disrupting this process, RIF effectively kills the bacteria and prevents them from multiplying.

Pyrazinamide (PZA) is a medication that specifically targets the dormant bacteria, which are often found in the body's immune cells. PZA is converted into pyrazinoic acid inside the bacteria, which then disrupts their energy production and kills them. This drug is particularly effective against the dormant bacteria, which are often more resistant to other medications.

Ethambutol (EMB) is the final component of the tuberculosis treatment regimen. It works by inhibiting the synthesis of arabinogalactan, a key component of the bacteria's cell wall. By disrupting the cell wall formation, EMB effectively kills the bacteria and prevents their replication.(Costa-Gouveia et al.,2017)

1.4.3 Directly Observed Therapy (DOT)

One of the most important strategies in the fight against tuberculosis (TB) is Directly Observed Therapy (DOT), which makes sure patients follow their treatment plans. In order to lower the chance of treatment failure, medical professionals or trained

observers watch patients when they take their medications. Additionally, DOT permits routine patient progress monitoring, which enables medical professionals to act quickly. Additionally, it gives patients information and support, enabling them to comprehend the end of their therapy and take charge of their health. By removing obstacles to adherence and providing flexibility, DOT promotes improved treatment results and slows the spread of tuberculosis in local communities. It is essential to the worldwide fight against tuberculosis because it lowers transmission rates and improves patient outcomes.(Karumbi et al.,2015)

1.4.4 Shorten Regimens

The duration of 4 to 6 months is necessary to ensure that all the bacteria are completely eradicated from the body. Tuberculosis is caused by a slow-growing bacteria, and it takes time for the medication to effectively kill off all the bacteria and prevent a relapse. Incorporating more recent medications such as rifampicin and moxifloxacin into the treatment regimens has been shown to improve treatment outcomes. These medications have a higher potency and are effective against drug-resistant strains of tuberculosis. By combining them with the traditional first-line drugs, the treatment protocols can effectively target a wider range of bacteria and increase the chances of successful treatment.(CDCTB et al 2022,).

1.4.5 Drug-resistant tuberculosis:

Comprehensive treatment plans are necessary, which often include the use of second-line medications that are more toxic and less effective compared to the initial drugs. The treatment duration can be quite long, ranging from 18 to 24 months, and typically involves the administration of injectable medications like kanamycin or capreomycin, in addition to oral drugs. It is crucial to adjust the treatment based on the results of drug susceptibility testing, as this helps determine the most suitable regimen for each patient. In some cases, newer medications such as bedaquiline and delamanid may be considered as potential additions to the treatment plan.

1.4.6 Adjunctive therapies

Effective treatment for tuberculosis should involve additional treatments like managing side effects of medication, treating other health conditions such as HIV, and offering nutritional support.

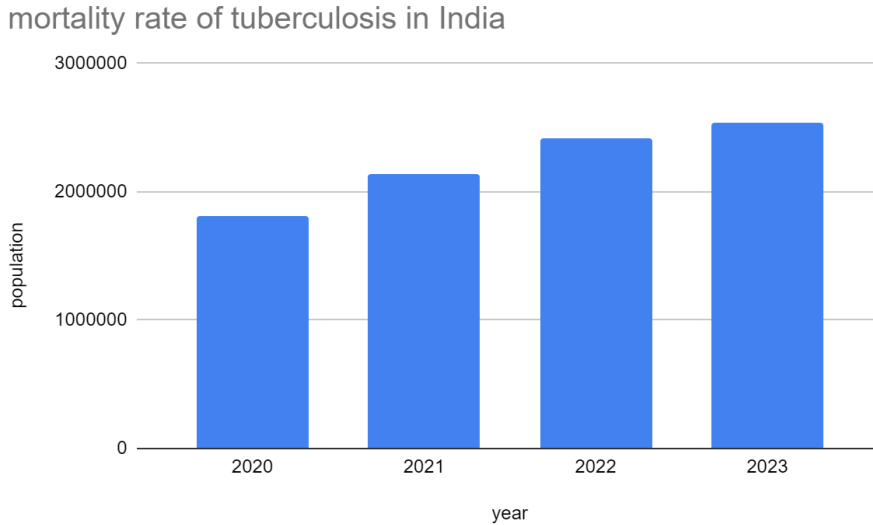
1.5 Complications

Side effects from TB treatment include skin rashes, nausea, upset stomach, itchy skin, yellow eyes or skin, and black urine. Talk about these with your healthcare professional because some of them can point to liver disease.(Mase, S. R., & Chorba, T. 2019).

1.5.1 Improvement in symptoms after the start of treatment for active tuberculosis

Increased energy and a reduction in symptoms may take weeks to manifest at first, but therapy will be more involved and medication will be needed for at least six to nine months.

1.6 Mortality rate



(Pathak et al.,2021)

Fig 1.1 mortality rate of tuberculosis

India had an estimated 2.95 million people infected with TB in 2021, in comparison to 2.59 million people in 2020. The incidence rate of TB in 2021 is estimated to be 210 per 100K people, up from 188 per 100K people in 2020. In 2021, 1.96 million incidences of new and relapsed cases were notified, 20.6% less than in 2020. Of the total new notifications in 2021, 57% were men and 37% were women. Children under 4.36 lakh TB accidental deaths in India in 2020 raised serious concerns about public health, but since 2023, there has been a significant fall to 3.31 lakh deaths, maybe as a result of better access to diagnosis and treatment. India's death rate from tuberculosis reduced from 36% in 2020 to 26% in 2023, which is a favorable change but yet shows the need for constant attention to the illness. Even though the number of drug-resistant TB infections has slightly decreased, it has remained consistent at 1.10 lakh cases in 2023, a serious concern prior to the epidemic. In 2020, India accounted for 27% of all drug-resistant tuberculosis cases worldwide, underscoring the importance of effective control strategies. The TB rate stays at 27%, underscoring

the ongoing difficulty of treating drug-resistant strains of the disease and the necessity of ongoing efforts.

1.7 Survival rate



Fig 1.2 Success rate of tuberculosis (*Reported TB in the US 2020 | Data & Statistics | TB | CDC. (2023)*

BURDEN OF TUBERCULOSIS										
	2019		2020		2021		2022		2023	
State	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases*	Deaths
Haryana	73,997	6,436	62,697	2,809	69,083	2,638	75,838	3,065	41,068	1,943
Punjab	58,204	2,355	46,198	2,824	50,142	2,667	55,150	2,619	28,605	1,570
Himachal	17,446	2,284	13,424	837	14,492	723	16,089	891	8,098	514

**Till June 30*

Fig 1.3 Burden of tuberculosis (Vinod kumar , 2023)

In India, survival rates for drug-sensitive tuberculosis are high, with over 90% of patients surviving with proper care. However, survival rates for drug-resistant tuberculosis are much lower, ranging from 50% to 60% or even lower, especially for multi-drug resistant and extensively drug-resistant cases. Factors such as patient health, access to healthcare, and treatment adherence influence survival rates. To obtain accurate statistics, consult recent studies and data from Indian authorities and healthcare organizations. These sources provide up-to-date information on the challenges of combating drug-resistant tuberculosis in India.

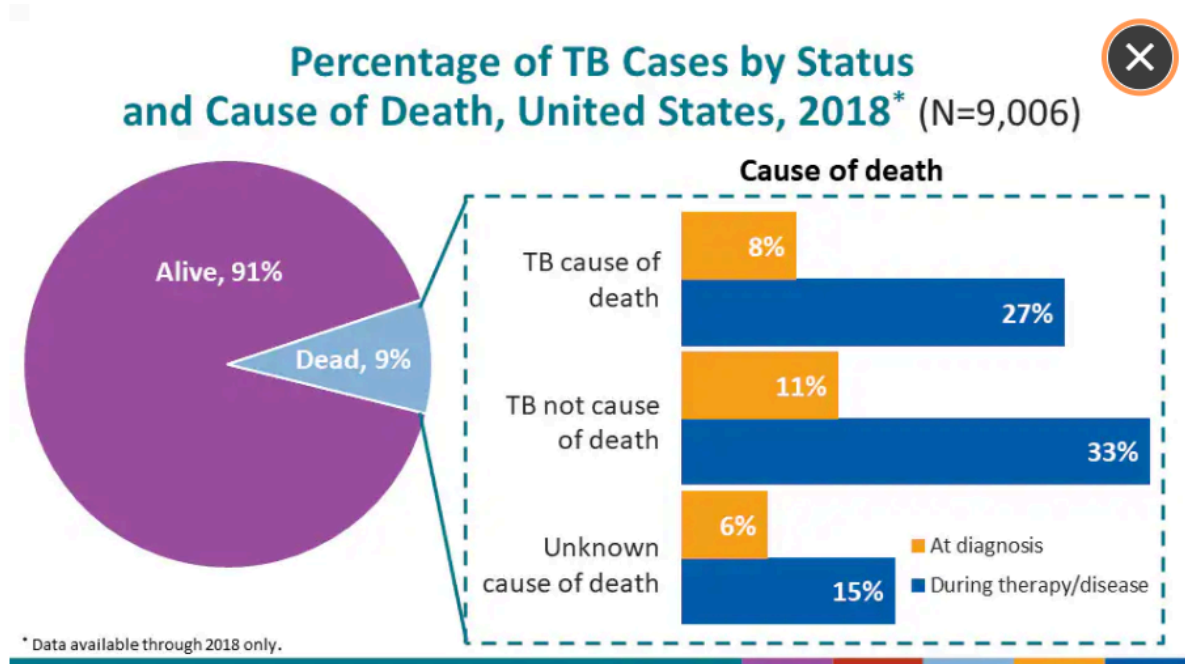


Fig 1.4 Death percentage of TB cases in US (center for disease control prediction .,2020)

In 2018, 801 fatalities from tuberculosis (TB) accounted for 8.9% of all deaths. Of these, TB illness was blamed for 35%. With 604 individuals passing away during therapy and 197 dying upon diagnosis, there were more deaths than in prior years. The death rate stays at the same percentage.

Estimated	Global	India
Incidence	99,00,000 (127/ lakh)	25,90,000 (188/ lakh)
Deaths (excluding HIV)	12,80,000 (17/ lakh)	4,93,000 (36/ lakh)
HIV TB cases	7,87,000 (10/ lakh)	53,000 (3.8/ lakh)
HIV TB deaths	2,14,000 (2.7/ lakh)	11,000 (0.78/ lakh)

(Ravichandra ,2022)

Fig 1.5 estimated death rates of TB IN INDIA and GLOBALLY

There is cause for concern over the incidence and death rate of tuberculosis (TB) worldwide, especially in India. India has an incidence rate of 188 cases per 100,000 people, or 2.59 million new cases, greater than the global average. India has more TB-related mortality than any other country in the world, with 493,000 deaths from the disease (apart from HIV) per 100,000 people. There are roughly 53,000 cases of HIV-TB co-infection, or 3.8 cases per 100,000 people, and 787,000 cases of TB plus HIV co-infection, or 10 cases per 100,000 people. An estimated 214,000 people with co-infections of HIV and TB passed away from the illness, or 2.7 fatalities per 100,000 people. An estimated 11,000 deaths in India were attributed to co-infection with HIV and tuberculosis, or 0.78 deaths per 100,000 people.

CHAPTER 2

REVIEW OF LITERATURE

The primary purpose of a literature review is to provide a comprehensive understanding of the existing knowledge on a particular topic or subject. It helps to identify gaps in the current knowledge, highlight areas for further research, and establish a theoretical framework for the study. A literature review typically involves a thorough search of relevant literature and research databases, followed by a careful analysis of the findings. The review may be conducted as part of a larger research project, or as a standalone piece of work, such as a dissertation or thesis.

The following are the various references reviewed for the purpose of the current study.

Carter JJ et al.(2024) In the year 2021, there were a staggering 10.6 million newly reported cases of *Mycobacterium tuberculosis*, which is considered to be the oldest known human pathogen. Unfortunately, this resulted in a devastating 1.6 million deaths. In light of this alarming situation, scientists have been diligently conducting research to combat this disease by studying genetic variations in specific genes such as *rpoB* and *katG/fabG1*. The aim of this research is to identify drug resistance patterns and develop effective treatment strategies. To further enhance their understanding, scientists have utilized a Train/Test dataset that encompasses a comprehensive range of genetic variations in the *pncA* gene. Interestingly, mutations have been observed in almost every codon of this gene, with only one exception. This dataset has proven to be invaluable in shedding light on the genetic makeup of the disease and its potential resistance to drugs. In addition to the Train/Test dataset, the CRYPTIC dataset has also played a crucial role in this research. Analysis of this dataset has revealed that approximately 14.7% of the samples exhibited resistance to pyrazinamide, a commonly used drug for tuberculosis treatment. This amounts to a

staggering 3351 samples. Furthermore, the dataset also identified 6851 samples with genetic variants in the *pncA* gene. It is worth noting that the majority of these samples displayed a single genetic variant, primarily in the form of substitutions. However, some samples exhibited more complex genetic alterations such as insertions, deletions, and frameshifts, which are associated with drug resistance. The information derived from these datasets has proven to be invaluable in the development of more effective treatment strategies for *Mycobacterium tuberculosis*. By understanding the genetic variations and drug resistance patterns, scientists can tailor treatment plans to target specific genetic mutations, ultimately improving patient outcomes and reducing the global burden of this ancient pathogen.

Jamal et al.(2020) , The current study anticipates the emergence of novel mutations that can either render tuberculosis-causing genes resistant or susceptible to the disease, through the utilization of artificial intelligence (AI) and machine learning (ML) techniques. This approach involves a thorough examination of the structural and sequential characteristics of these mutations within the genes. The models employed in this research exhibited an average accuracy rate of approximately 70%, with artificial neural networks (ANN) demonstrating the most optimal performance during cross-validation procedures. During the testing phase, the mutations were successfully categorized as either resistant or susceptible, achieving accuracy levels that ranged from 66.66% to a perfect score of 100%.

Singh et al.(2019). The research focuses on analyzing the occurrence and mortality rates of tuberculosis in India over the past three decades. The emergence of drug-resistant tuberculosis has become a significant challenge in the efforts to combat and control the disease. Specifically, in 2017, a staggering 82% of the 558,000 new cases of TB that were resistant to rifampicin developed multidrug-resistant TB (MDR-TB). This comprehensive overview encompasses the latest information on drug resistance mechanisms, newly developed or repurposed anti-TB medications, and global guidelines for effectively managing MDR-TB. The

aim is to enhance our understanding of drug resistance in order to improve the efficacy of TB treatment and clinical care, drawing upon contemporary literature and the guidance provided by the World Health Organization (WHO).

D L Williams et al.(1998) The *rpoB* gene of *M. tuberculosis* H37Rv experienced mutations that caused cross-resistance to all rifamycins examined, with the exception of KRM-1648 and rifabutin resistance. To gain a better understanding of how these mutations affect rifampin resistance, in vitro mutagenesis was employed. Through this process, it was discovered that specific mutations in *M. tuberculosis* clones exhibited a significant level of resistance to all tested rifamycins, except for a mutation at codon 516. Consequently, mutations in the *rpoB* gene of *M. tuberculosis* H37Rv resulted in cross-resistance to all rifamycins studied, except for KRM-1648 and rifabutin resistance. Further investigation through in vitro mutagenesis demonstrated that certain mutations in *M. tuberculosis* clones conferred a high level of resistance to all rifamycins, except for a mutation at codon 516.

Anastasia A Theodosiou et al(2023)¹. In the analysis of 1617 PubMed results focus primarily on research that utilizes real-world data and has clinical validation and translational potential. Specifically, we are interested in studies related to drug development and microbiome-based therapies. However, we have observed that the majority of research lacks measures of clinical usefulness or real-world validation, even though there is great potential for AI in laboratory diagnostics, imaging analysis, clinical decision support systems, and public health epidemic management. One of the challenges we have encountered is the lack of comparability due to variations in study design and reporting. Additionally, there are ethical and practical issues such as bias and algorithm transparency that need to be addressed in order to fully harness the benefits of these research findings.

Thi Binh et al.(2023) This is an investigation conducted to analyze the occurrence of rifampicin and/or isoniazid resistance among individuals suspected of having tuberculosis (TB). Among the 468 isolates examined, 22 (22.6%) showed resistance

to either one or both of the antibiotics. Interestingly, the majority of the resistant cases (69.8%) were resistant to isoniazid alone, with a small percentage (0.94%) being resistant to rifampicin exclusively. The mutations most commonly observed were located at codons 531, 526, and 516, indicating a pattern in resistance development. Various techniques were employed to efficiently identify drug-resistant TB strains, aiding in prompt diagnosis and treatment.

ArchanaSinghBhadauria et al.(2023) An investigation into the impact of isolation on the reduction of TB cases in India from 2015 to 2035 was conducted using a SIQR mathematical model to analyze the dynamics of TB. The main objective of the research was to assess whether the target of eradicating TB by 2025 is achievable with the current interventions in place and how isolation measures can contribute to reducing secondary transmission. It was observed that India lacks a specific policy for isolating highly contagious MDR-TB patients, possibly due to the fact that a significant portion of MDR-TB cases come from socially disadvantaged groups. To effectively combat the spread of the disease, it is crucial to implement measures that separate MDR-TB patients while still respecting their rights and minimizing any potential violations. The mathematical model suggests that isolating just half of the MDR-TB cases could lead to a significant decline in both TB and MDR-TB incidences by 2025, assuming that treatment success rates are maintained at a consistent level. This highlights the importance of implementing isolation measures as part of a comprehensive strategy to achieve the goal of TB eradication in India.

Vahid Lohrasbi et al.(2018)A major global health concern, tuberculosis (TB) accounts for about 10 million active cases and 1.5 million TB-related deaths annually. With most of their mechanisms of action understood, novel anti-TB medications are now undergoing preclinical and clinical testing. The FDA recently approved the use of BDQ to treat adult patients with MDR-MTB strains of pulmonary tuberculosis. MH, VL, and DDS started this study, and all of the authors revised and polished the final drafts.

Melanie Grobbelaar et al.(2019) In this article we study that the major medication used in multidrug TB therapy is rifampicin; due to cost and toxicity concerns, recommended doses have not changed in 40 years. High-dose rifampicin may decrease treatment duration and lower relapse rates, according to recent research. Regarding its effect on the metabolism of other common anti-TB and anti-HIV medications, there are still unanswered concerns.

Ahmed Aliyu Abulfathi et al(2019)This study examines the pharmacokinetics and pharmacodynamics of rifampicin in adults at different dosages, emphasizing factors that influence its efficacy. Rifampicin exposure can be impacted by a number of factors, including diabetes, hepatic cirrhosis, pharmacogenetic polymorphisms, malnourishment, HIV infection, dose size, and subpar medications. The pharmacokinetics of rifampicin at a dose of 600 mg are unaffected by renal impairment. Sterilizing activity is predicted by a rifampicin maximum concentration $> 8.2 \mu\text{g/mL}$, and therapeutic drug monitoring can assist in maximizing dosage to reach the advised concentration of $\geq 8 \mu\text{g/mL}$.

Xutao Wang et al.(2023)This study suggests that utilizing well-known TB gene signatures can be beneficial in predicting the likelihood of developing tuberculosis (TB) and evaluating the effectiveness of treatment. This is especially helpful in situations where existing models for predicting TB risk or treatment results are challenging to use. To accomplish this, researchers have applied gene set enrichment scoring to blood-based biomarker gene sets. This technique enables the accurate differentiation between individuals with active TB disease and those with latent TB infection. Gene set enrichment scoring entails examining the expression levels of specific genes within a set of blood-based biomarkers. By comparing the gene expression patterns in individuals with active TB disease and those with latent TB infection, researchers can identify unique gene signatures associated with each condition. These gene signatures can then be utilized to create predictive models that

can effectively determine the risk of developing TB or evaluate the success of treatment. By utilizing established TB gene signatures, researchers can overcome the complexities of initial models that may be challenging to use.

The use of blood-based biomarkers in this study is advantageous as it provides a non-invasive and easily accessible method for diagnosing and monitoring TB. By analyzing gene expression patterns in blood samples, healthcare professionals can promptly and accurately identify individuals at risk of developing active TB disease or monitor treatment progress in those already infected. Overall, the incorporation of established TB gene signatures and gene set enrichment scoring on blood-based biomarker gene sets has proven to be a valuable strategy in predicting TB risk and treatment outcomes. This research finding has the potential to significantly enhance the diagnosis, management, and prevention of TB, ultimately leading to improved health outcomes for individuals.

Thomas E Tavorara et al. (2021) In an experimentally infected cohort of Diversity Outbred mice, this study highlights the potential of machine learning in diagnostic and prognostic problems in computational histopathology by proposing a methodology using machine learning to predict gene expression values from haematoxylin and eosin whole-slide images to identify fulminant-like pulmonary tuberculosis.

Darya V Urusova et al. (2022) resistance to antibiotics A serious threat to public health, enterococcus bacteria are a major source of nosocomial infections. Alterations in the β subunit of RNA polymerase (rpoB) are associated with enterococci's resistance to the antibiotic rifampicin (RifR). These mutations in Mycobacterium tuberculosis change the production of lipids on the mycobacterial surface and the IL-1 cytokine response in macrophages. If RifR mutations affect how other bacteria respond to their hosts by producing cytokines, that is yet unknown. RifR mutations were found to cause strong pro- and anti-inflammatory reactions in addition to reducing the production of IL-1 β cytokine, according to a study conducted with Enterococcus

faecalis. The results imply that Rif^R bacteria share subversion of the IL-1R1 pathway and that immunomodulation by rpoB mutations may be conserved across several bacterial species.

Olifan Zewdie et al.(2020) The prevalence of tuberculosis detected with the GeneXpert assay was reported to be 21.3% in a research involving 2300 suspected patients. Of the confirmed patients, 25.9% had RIF-resistant tuberculosis (TB), a noteworthy proportion. Rifampicin-resistant tuberculosis was substantially correlated with patient category, age, sex, and MDR-TB contact. Compared to new patients, relapse patients had a 20-fold increased risk of developing MDR-TB. The study emphasizes how common rifampicin-resistant tuberculosis (TB) is across all age groups and how better treatment is needed to reduce the number of MDR-TB patients.

Raj N Yadav et al(2013)In a study comparing DST results utilizing LPA and LJ methods on 242 MDR-TB suspects, it was discovered that, in contrast to the traditional method, LPA detected MDR-TB in 66 of 68 cases, isoniazid (INH) resistance in 86 of 93 cases, and rifampicin (RIF) resistance in 70 of 71 cases. In terms of sensitivity and specificity for detecting RIF, INH, and MDR-TB, the LPA test showed a 96% agreement with the traditional DST. With a 48-hour turnaround time, the LPA test was extremely sensitive and specific for MDR-TB and offered an early identification of monoresistance to isoniazid and rifampicin. Based on this, it appears that in countries with large tuberculosis burdens, the LPA test may be helpful in the early detection of drug-resistant TB.

Hooman H Rashidi et al(2021)Clinical applications frequently use machine learning (ML), a potent technique for automated classification. Texts, photos, and quantitative factors are all included in the input data used in the healthcare industry. The outputs are either quantitative or class-based. For example, hematological digital morphology analyzers such as CellaVision are examples of how machine learning (ML) has been

applied to image classification jobs. When it comes to processing vast amounts of data more efficiently than manual human differential counting, machine learning (ML) algorithms are able to reliably assign IDs to distinct cell types based on previous training on big data sets. As a result, the hematology laboratory experiences significant efficiency gains because the majority of routine samples are not marked for manual inspection. But morphologic evaluation still uses ML algorithms in a conservative manner, serving as a prescreening tool for ML algorithms are used as pre screening tools for cases that need human involvement, but their application in morphologic evaluation is restricted. The first step in ML implementation can be to combine human confirmation with feature extraction from ML models. When it comes to categorization performance, trained machine learning algorithms might eventually outperform humans as stand-alone agents with quality assurance oversight. However, in practical clinical settings, obtaining strong performance and dependability continues to be difficult.

Dibyahash Bordoloi et al.(2022) The study analyzes the integration of deep learning (DL) and machine learning (ML) in healthcare systems for a range of applications, such as detecting respiratory illnesses, cancer, diabetes, tumors, and disease-discomfort detection, as well as averting pandemic breakouts. The ML/DL models have proven to be capable of making clinical decisions under supervision and have shown impressive performance in the Internet of Things (IoMT) network and services. In order to extract meaningful information from the complex health data produced by healthcare systems, such as medical imaging, wearable sensors and ECG and EEG recordings, electronic health records, and medical images, machine learning (ML) and deep learning (DL) are necessary. The study aims to generate ideas for future implementation of ML and DL in other healthcare system aspects, but does not cover the role of ML and DL in healthcare security

Mudassar Ali Khan et al(2022) The field of healthcare has witnessed a notable surge in interest in the Internet of Things (IoT) in the past few years. This paper investigates

IoMT authentication methods, examining strategies at various network layers, including cloud, fog as well, and edge. It also looks at the function of identity in an environment that uses IoMT. The results highlight the significance of IoT across a number of industries and exhort the research community to concentrate on delivering high-quality healthcare services using contemporary technologies.

Isabel Foster et al.(2023) According to surveys, at least one-third of people with tb and their carers face internal, external, and expected stigma, which has an impact on their participation throughout the care process. Participants from rural areas reported more internal, external, and expected stigma. Experiences with stigma, particularly HIV intersectional stigma, serve as roadblocks to care and serve as justification for withholding a TB diagnosis. Understanding that TB can affect anyone and does not reduce one's self-worth led to the emergence of stigma resilience. Stigma risks resulted in care disengagement and decreased mental health. Participants wanted community education and counseling.

Marty Chaplin et al .(2022) This study says that in two multicenter trials conducted in high-burden countries for tuberculosis, a total of 1228 patients who were resistant to multiple drugs or rifampicin were included. Additionally, one study focused on medication resistance and involved 1141 individuals. The prevalence of rifampicin resistance was found to be 47.9% and 80.9% among the subjects, respectively. Although both pDST and gDST are considered to be more precise, there was a significant risk of bias in the patient selection process for detecting ethionamide resistance and tuberculosis.

CHAPTER 3

AIM AND SCOPE OF THE STUDY

3.1 AIM

- Predicting tuberculosis disease by analyzing a gene sequence resistance percentage towards drug rifampicin by rpoB gene
- Through the AI model we get which stage of tuberculosis and also the precautions, diet plan should be taken by particular patient to overcome tuberculosis disease

3.2 SCOPE

Obtain gene sequence data from databases, preprocess it to remove irrelevant information and standardize the format, and extract relevant features for deep learning models. Create a deep learning-based model to predict drug resistance in tuberculosis using the rpoB gene sequence. Expand the model by incorporating additional genetic markers to predict infection. Enhance interpretability with explainable AI techniques. Use the model's predictions to generate personalized treatment recommendations based on resistance percentage, infection status, patient profiles, and tuberculosis stage. Provide comprehensive guidance on diet, medication, and management strategy

3.3 FUTURE WORK

As this project aims to model healthcare for medical professionals. We can also focus on creating a user-friendly experience, with streamlined input of gene sequences through web or mobile applications. Which can provide treatment suggestions and forecasts, aiding healthcare providers in making informed decisions for their patients. Compatibility with various devices, easy accessibility, and simple navigation are highlighted as essential aspects to ensure efficiency and effectiveness in healthcare

CHAPTER 4

METHODOLOGY

4.1 GENE DATASETS

Gene datasets were downloaded from National Center for Biotechnology Information (NCBI) and vast data was filtered in fasta format.

4.2 DATABASES

National Center for Biotechnology Information (NCBI)
<https://www.ncbi.nlm.nih.gov/gene>

We obtained a total of 11865 mycobacterium genes. Of these, 1595 were derived from adult patients while only 228 genes are associated with rifampicin drug resistance.

A wide range of analyses can be done within the database, such as the Expression of mycobacterium tuberculosis genes, their Interactions, their regulation, and mutations can be analyzed.

4.3 FILTERING THE GENES

A total of 228 genes were extracted from the database which are associated with rifampicin drug resistance <https://www.ncbi.nlm.nih.gov/gene>

4.4 IDENTIFICATION OF rpoB GENE

The goal of this study is to collect sequences which include the rpoB gene, which is an essential marker for treatment resistance and TB sickness. In this database we found a few gene sequences which are associated with rpoB gene and also extracted the gene sequences in fasta format. <https://www.ncbi.nlm.nih.gov/gene>

4.5 MODEL DEVELOPMENT

Developed a deep learning based model using framework PyTorch. Designed the model architecture to process gene sequence data and predict drug resistance and tuberculosis infection. Used unlabeled data to train the model. Use CNNs to capture sequence patterns and to effectively learn sequence patterns. Incorporate the similarity percentage as an additional feature in the model to capture sequence similarity to known drug-resistant sequences all these done in google colab. <https://colab.research.google.com/>

4.6 PERSONALIZED TREATMENT RECOMMENDATIONS

Develop an AI model that can accurately predict drug resistance and tuberculosis infection status, allowing for more personalized treatment recommendations. Design algorithms that consider the similarity percentage to determine the likelihood of medication resistance, enabling healthcare providers to make informed decisions about the most effective treatment options. Provide tailored treatment plans, dietary recommendations, and strategies for managing the illness based on the resistance percentage, ensuring that patients receive the most appropriate care for their specific needs. <https://colab.research.google.com/>

4.7 ETHICAL CONSIDERATIONS :

Regulations governing AI use must be followed by healthcare institutions to ensure ethical and responsible use. These rules address the use of AI in medical decision-making, patient consent, and patient data security. Healthcare professionals can lower risks, safeguard patient privacy, and deliver high-quality care by following these guidelines. By encouraging accountability and openness, this framework makes sure that the application of AI complies with moral and legal requirements.

CHAPTER 5

RESULTS AND DISCUSSION

RESULTS :

Genes from mycobacterium tuberculosis were given as input in FASTA format individually into the deep learning model .the model visualize and analyze the gene sequence with already incorporated rpoB gene and predict the drug resistance percentage

```
[ ] !pip install bio

[ ] !pip install openai==0.28

[ ] import openai
    openai.api_key = "sk-SBLNHc35QNZa7ZcuSvMoT3B1bkFJTBGsRJtKg6QUzW7xGwuG"
```

Fig 5.1 Packages required for deep learning model

The project's goal is to use Python and OpenAI's AI models to create a bioinformatics application inside of Google Colab. This platform offers a potent tool for bioinformatics analysis and AI-driven decision assistance for researchers and healthcare practitioners. It facilitates the effective analysis of genetic data and offers insights into disease pathways.

For computational biology and bioinformatics applications, the Python Bio package, sometimes referred to as Biopython, is a potent library. With its many modules and features, it can handle biological data, carry out sequence analysis, work with molecular structures, and much more. The Bio package's essential elements consist of {Seq}, {SeqIO}, {pairwise2}, and {sequence}. Sequences can be manipulated and analyzed because {Seq} represents biological sequences such as DNA, RNA, or proteins. The 'SeqIO' package makes it easier to read and write sequence data in a

variety of file formats, including FASTA, GenBank, and FASTQ. Sequence data can be imported from external databases or files by researchers, who can then use Biopython's capability to change the data and export the results for additional analysis or sharing. Tools for pairwise sequence alignments are provided by {pairwise2}. Sequence alignments are necessary when comparing two sequences to find similarities or differences. By aligning DNA, RNA, or protein sequences, researchers can determine conserved areas, sequence variations, and evolutionary links using pairwise2 tool

```
from Bio import SeqIO
from Bio import pairwise2
from Bio.Seq import Seq

# Read the rpoB gene sequence from a FASTA file
rpoB_record = SeqIO.read("/content/sequence (1).fasta", "fasta")
rpoB_sequence = str(rpoB_record.seq)

# Read the unlabelled gene sequences from a FASTA file
gene_sequences = []
with open("/content/sequence (2).fasta", "r") as file:
    for record in SeqIO.parse(file, "fasta"):
        gene_sequences.append(str(record.seq))

# Perform pairwise sequence alignment with the rpoB gene sequence
for seq in gene_sequences:
    alignment = pairwise2.align.globalxx(Seq(seq), Seq(rpoB_sequence), one_alignment_only=True)[0]
    aligned_seq, aligned_rpoB, score, start, end = alignment
    resistance = (score / max(len(seq), len(rpoB_sequence))) * 100

    print(f"Gene Sequence: {seq}")
    print(f"Alignment Score: {score}")
    print(f"resistance Percentage: {resistance:.2f}%")
    print()
```

Fig 5.2 "analyzing Percentages with rpoB Gene in Tuberculosis Strains"

Here in place of sequence 1 we incorporated rpoB gene where we can find the resistance percentage in labeled gene sequence

Type- Mycobacterium TB H37Rv; lineage - Bacteria, Actinobacteria, Corynebacteriales, Mycobacteriaceae, Mycobacterium; Mycobacterium tuberculosis

complex; gene symbol: rpoB; DNA-directed RNA polymerase subunit beta; locus tag: Rv0667.

In sequence 2 we incorporated another labeled gene where to find how much resistance percentage towards rpoB gene. Which is taken from NCBI mycobacterium tuberculosis with GENE ID NC_000962.3 with linear DNA containing 4411532 base pairs.

```
prompt = f""" give me the precautions should be taken in diet, and what medications should be taken according to the resistance percentage give me also Mention which stage of tuberculosis according to the resistance percentage {resistance} """

response = openai.ChatCompletion.create(

    model="gpt-3.5-turbo",

    messages=[{"role": "user", "content": prompt}],

    temperature=0)

#print(response)

result= response['choices'][0]['message']['content']

print(result)
```

Fig 5.3 "AI-Predicted Resistance Percentages for Precaution Optimization"

```
/usr/local/lib/python3.10/dist-packa
warnings.warn(
Gene Sequence: TTGGCAGATTCCCGCCAGAG
Alignment Score: 3519.0
resistance Percentage: 100.00%
```

Fig 5.4 resistance percentage of sequence 1

Precautions in diet:

- Eat a balanced diet rich in fruits, vegetables, and whole grains
- Avoid processed foods and sugary drinks
- Limit intake of alcohol and caffeine
- Stay hydrated by drinking plenty of water

Medications according to resistance percentage:

- First-line drugs: Isoniazid, Rifampin, Ethambutol, Pyrazinamide
- Second-line drugs: Levofloxacin, Kanamycin, Ethionamide, Cycloserine

Stage of *Mycobacterium tuberculosis* disease affected:

- The resistance percentage can affect any stage of tuberculosis, including latent infection, active infection, and drug-resistant strains.

Stage of tuberculosis according to resistance percentage:

- Drug resistance can occur at any stage of tuberculosis, but is more commonly seen in cases of active infection where the bacteria have had exposure

Fig 5.5 Optimizing Precautionary Measures Based on AI-Predicted Resistance Percentages

Through a comparative analysis, a previously unidentified gene sequence was found to be strongly associated with tuberculosis, as it exhibited 100% resistance in the patient. This groundbreaking discovery not only enhanced our understanding of the genetic factors behind tuberculosis but also opened up possibilities for targeted treatments for this infectious disease. By utilizing an advanced Artificial Intelligence model, we were able to extract crucial information regarding the necessary precautions and medications for the patient's recovery and overall well-being. This state-of-the-art AI model, equipped with sophisticated algorithms and extensive medical data, analyzed the patient's genetic profile, medical history, and other relevant factors to generate personalized treatment and care recommendations. Moreover, the AI model demonstrated an exceptional ability to predict the stage of tuberculosis that the patient was in. By analyzing various clinical indicators, such as specific biomarkers, radiological findings, and symptoms, the model accurately determined whether the patient was in the early, intermediate, or advanced stage of tuberculosis. This groundbreaking predictive capability not only allowed for timely

intervention and appropriate treatment strategies but also improved patient outcomes and optimized the allocation of healthcare resources.

In conclusion, the integration of genetic analysis and Artificial Intelligence has revolutionized our understanding and management of tuberculosis. By uncovering the genetic basis of resistance and utilizing AI models to provide personalized treatment recommendations, we have made significant strides in combating this infectious disease.

```
from Bio import SeqIO
from Bio import pairwise2
from Bio.Seq import Seq

# Read the rpoB gene sequence from a FASTA file
rpoB_record = SeqIO.read("/content/sequence (1).fasta", "fasta")
rpoB_sequence = str(rpoB_record.seq)

# Read the unlabelled gene sequences from a FASTA file
gene_sequences = []
with open("/content/sequence (4).fasta", "r") as file:
    for record in SeqIO.parse(file, "fasta"):
        gene_sequences.append(str(record.seq))

# Perform pairwise sequence alignment with the rpoB gene sequence
for seq in gene_sequences:
    alignment = pairwise2.align.globalxx(Seq(seq), Seq(rpoB_sequence), one_alignment_only=True)[0]
    aligned_seq, aligned_rpoB, score, start, end = alignment
    resistance = (score / max(len(seq), len(rpoB_sequence))) * 100

    print(f"Gene Sequence: {seq}")
    print(f"Alignment Score: {score}")
    print(f"resistance Percentage: {resistance:.2f}%")
    print()
```

Fig 5.6 Unveiling the Neural Network: Exploring Deep Learning Potential

The gene sequence of mycobacterium tuberculosis rpoB gene, which has a locus ID CP025606, is aligned with another strain's gene sequence. This particular strain contains a circular DNA with a total of 4,411,446 base pairs. The purpose of aligning these sequences is to calculate the resistance percentage between the standard rpoB gene sequence and the other strain's sequence.

```
) prompt = f""" give me the precautions should be taken in diet, and what medications should be taken according to the resistance percentage
also Mention which stage of tuberculosis according to the resistance percentage
{resistance} """

response = openai.ChatCompletion.create(

    model="gpt-3.5-turbo",

    messages=[{"role": "user", "content": prompt}],

    temperature=0)
#print(response)

result= response['choices'][0]['message']['content']
print(result)
```

Fig 5.7 Optimizing Precautionary Measures Based on AI-Predicted Resistance Percentages

Gene Sequence: GTGGCACGACGTGCCCCGCGTTGA
Alignment Score: 807.0
resistance Percentage: 22.93%

Fig 5.8 resistance percentage for sequence 2

Precautions in diet:

- Eat a balanced diet rich in fruits, vegetables, whole grains, and lean proteins
- Avoid processed foods, sugary drinks, and excessive alcohol consumption
- Stay hydrated by drinking plenty of water
- Avoid smoking and limit caffeine intake

Medications according to resistance percentage:

- First-line drugs for drug-sensitive TB: Isoniazid, Rifampin, Ethambutol, Pyrazinamide
- Second-line drugs for drug-resistant TB: Levofloxacin, Linezolid, Bedaquiline, Delamanid
- Treatment regimen will vary depending on the resistance percentage and may require a combination of different medications

Stage of tuberculosis according to resistance percentage:

- Drug-sensitive TB: Initial stage of TB infection where the bacteria are susceptible to first-line drugs
- Drug-resistant TB: Advanced stage of TB infection where the bacteria have developed resistance to one or more first-line drugs

Fig 5.9 precautions for sequence 2

A different gene sequence, without any label, has been aligned with a labeled gene sequence of mycobacterium tuberculosis that is linked to the rpoB gene. Through this alignment, we have determined that the unlabeled gene sequence exhibits a 22% resistance percentage. This indicates that the specific gene of the unidentified patient is associated with tuberculosis disease. By utilizing an Artificial Intelligence model, we have extracted valuable information regarding the precautions and medications that should be taken by the patient in order to recover and lead a normal, healthy life. Additionally, the model is capable of predicting the stage of tuberculosis that the patient is currently suffering from. This comprehensive analysis aids in providing personalized and effective treatment strategies for tuberculosis patients.

```

from Bio import SeqIO
from Bio import pairwise2
from Bio.Seq import Seq

# Read the rpoB gene sequence from a FASTA file
rpoB_record = SeqIO.read("/content/sequence (1).fasta", "fasta")
rpoB_sequence = str(rpoB_record.seq)

# Read the unlabelled gene sequences from a FASTA file
gene_sequences = []
with open("/content/sequence (5).fasta", "r") as file:
    for record in SeqIO.parse(file, "fasta"):
        gene_sequences.append(str(record.seq))

# Perform pairwise sequence alignment with the rpoB gene sequence
for seq in gene_sequences:
    alignment = pairwise2.align.globalxx(Seq(seq), Seq(rpoB_sequence), one_alignment_only=True)[0]
    aligned_seq, aligned_rpoB, score, start, end = alignment
    resistance = (score / max(len(seq), len(rpoB_sequence))) * 100

    print(f"Gene Sequence: {seq}")
    print(f"Alignment Score: {score}")
    print(f"resistance Percentage: {resistance:.2f}%")
    print()

```

fig 5.10 visualizing deep learning

In this study, I compared the complete sequence of the 16S ribosomal RNA of Mycobacterium tuberculosis H37Rv with a standard rpoB gene sequence in order to determine the level of resistance between the two sequences.

```

Gene Sequence: ATGACCCCCCGCACAACTACCTGGCCGTCATCAAGGTCGTGGC
Alignment Score: 1127.0
resistance Percentage: 32.03%

```

it can be curable, certain precautions to be taken

Fig 5.11 resistance percentage for sequence 3

After aligning the both the sequence I got percentage of 32 where we can conclude that tuberculosis is affected about 32% as this is early stage, by taking certain precautions it can be curable

```
▶ prompt = f""" give me the precautions should be taken in diet, and what medications should be taken according to the resistance percentage give me also Mention which stage of tuberculosis according to the resistance percentage {resistance} """

response = openai.ChatCompletion.create(

    model="gpt-3.5-turbo",

    messages=[{"role": "user", "content": prompt}],

    temperature=0)

#print(response)

result= response['choices'][0]['message']['content']

print(result)
```

Fig 5.12 Optimizing precautionary measures based on AI-model

Precautions in diet:

- Eat a balanced diet rich in fruits, vegetables, whole grains, and lean proteins
- Avoid processed foods, sugary drinks, and excessive alcohol consumption
- Stay hydrated by drinking plenty of water
- Avoid smoking and limit caffeine intake

Medications according to resistance percentage:

- First-line drugs for drug-sensitive TB: Isoniazid, Rifampin, Ethambutol, Pyrazinamide
- Second-line drugs for drug-resistant TB: Levofloxacin, Linezolid, Bedaquiline, Delamanid
- Treatment regimen will vary depending on the resistance percentage and may require a combination of different medications

Stage of tuberculosis according to resistance percentage:

- Drug-sensitive TB: No resistance to first-line drugs
- Drug-resistant TB: Resistance to one or more first-line drugs, requiring second-line medications

Fig 5.13 precautions for sequence 3

This research focuses on the analysis of mutations in the *rpoB* gene in *Mycobacterium tuberculosis*, which is a common cause of tuberculosis (TB). The findings reveal a resistance percentage of 32%, indicating a high likelihood of resistance to multiple TB drugs. To address this issue, an AI model has been developed to analyze genetic data and provide personalized recommendations for individuals with a 32% resistance to the *rpoB* gene. These recommendations encompass a wide range of TB management strategies, aiming to optimize treatment outcomes and minimize the occurrence of complications. In addition to the standard medication regimens, the AI model suggests incorporating dietary advice, preventive interventions, lifestyle adjustments, and regular follow-up sessions. By considering a patient's genetic susceptibility, the AI model proposes tailored treatment plans or combinations of antibiotics that are unique to each individual. Furthermore, lifestyle modifications such as abstaining from alcohol and quitting smoking are strongly advised as part of the comprehensive approach to TB management. These measures aim to enhance the effectiveness of treatment and improve overall health outcomes for patients with TB.

CHAPTER 6

SUMMARY AND CONCLUSIONS

6.1 Summary

The study analyzed gene sequences from databases like NCBI and GenBank to predict *Mycobacterium tuberculosis* (TB) resistance using deep learning. It was deduced that the *rpoB* gene was connected to rifampicin resistance. Resistance percentages were inferred using the similarity percentage between known and unknown resistant sequences. Based on resistance profiles, an AI model was created to deliver individualized insights to tuberculosis patients. These insights included suggestions for diet regimens, drugs, and disease stages. The goal of this strategy is to enhance patient care and treatment effectiveness. Furthermore, the research also analyzed the genetic variations in the *rpoB* gene that were associated with resistance to other antibiotics commonly used to treat TB, such as isoniazid and ethambutol. By identifying these genetic markers, healthcare providers can tailor treatment plans to individual patients based on their genetic predisposition to resistance. In addition, the AI model developed in this study has the potential to revolutionize the way TB patients are treated by providing personalized recommendations that take into account not only genetic factors but also lifestyle and environmental factors that may impact treatment outcomes. By incorporating a holistic approach to patient care, healthcare providers can improve patient adherence to treatment regimens and ultimately improve patient outcomes. Overall, this research represents a significant advancement in the field of personalized medicine for TB treatment and has the potential to significantly improve patient care and treatment outcomes for individuals affected by this devastating disease.

6.2 Conclusion

The study highlights the application of deep learning methods in inferring tuberculosis (TB) resistance from gene sequences. By leveraging an AI model that accurately evaluates the resistance percentages, healthcare practitioners can significantly improve patient care and make well-informed decisions regarding medication selection and dosage. This approach has the potential to mitigate the emergence of drug resistance and enhance treatment outcomes. The integration of genetic data into clinical practice for managing infectious diseases enables the implementation of precision medicine techniques, which aim to optimize patient outcomes while minimizing side effects and treatment failures. However, it is crucial to validate and enhance the AI model for its utilization in larger-scale research and clinical trials. In conclusion, deep learning shows promise in delivering more personalized and successful healthcare solutions.

REFERENCES

1. Alame Emame, A. K., Guo, X., Takiff, H. E., & Liu, S. (2021). Drug resistance, fitness and compensatory mutations in *Mycobacterium tuberculosis*. *Tuberculosis (Edinburgh, Scotland)*, 129, 102091. <https://pubmed.ncbi.nlm.nih.gov/34090078/>
2. Al-Hajjaj, M. S., Al-Kassimi, F. A., Al-Mobeireek, A. F., & Alzeer, A. H. (2001). Progressive rise of *Mycobacterium tuberculosis* resistance to rifampicin and streptomycin in Riyadh, Saudi Arabia. *Respirology (Carlton, Vic.)*, 6(4), 317–322. <https://pubmed.ncbi.nlm.nih.gov/11844123/>
3. Al-Mutairi, N. M., Ahmad, S., Mokaddas, E., Eldeen, H. S., & Joseph, S. (2019). Occurrence of disputed *rpoB* mutations among *Mycobacterium tuberculosis* isolates phenotypically susceptible to rifampicin in a country with a low incidence of multidrug-resistant tuberculosis. *BMC infectious diseases*, 19(1), 3. <https://pubmed.ncbi.nlm.nih.gov/30606116/>
4. Alvarez-Uria, G., & Reddy, R. (2018). Differences in *rpoB*, *katG* and *inhA* mutations between new and previously treated tuberculosis cases using the GenoType MTBDRplus assay. *Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases*, 59, 48–50. <https://pubmed.ncbi.nlm.nih.gov/29413885/>

5. Bhadauria, A. S., Dhungana, H. N., Verma, V., Woodcock, S., & Rai, T. (2023). Studying the efficacy of isolation as a control strategy and elimination of tuberculosis in India: A mathematical model. *Infectious Disease Modelling*, 8(2), 458–470. <https://pubmed.ncbi.nlm.nih.gov/37234098/>
6. Bhat, Z. S., Rather, M. A., Ul Lah, H., Hussain, A., Maqbool, M., Yousuf, S. K., Jabeen, Z., Wani, M. A., & Ahmad, Z. (2020). In vitro bactericidal activity of 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrone (CHP) against drug-susceptible, drug-resistant and drug-tolerant isolates of *Mycobacterium tuberculosis*. *Journal of global antimicrobial resistance*, 22, 57–62. <https://pubmed.ncbi.nlm.nih.gov/31809940/>
7. Bi, K., Cao, D., Ding, C., Lu, S., Lu, H., Zhang, G., Zhang, W., Li, L., Xu, K., Li, L., & Zhang, Y. (2022). The past, present and future of tuberculosis treatment. *Zhejiang da xue xue bao. Yi xue ban = Journal of Zhejiang University. Medical sciences*, 51(6), 657–668. <https://pubmed.ncbi.nlm.nih.gov/36915970/>
8. Blanchard J. S. (1996). Molecular mechanisms of drug resistance in *Mycobacterium tuberculosis*. *Annual review of biochemistry*, 65, 215–239. <https://doi.org/10.1146/annurev.bi.65.070196.001243>

9. Centers for Disease Control and Prevention. (2019, March 20). *Basic TB facts*. Centers for Disease Control and Prevention; CDC. <https://www.cdc.gov/tb/topic/basics/default.htm>
10. Chandra, P., Grigsby, S. J., & Philips, J. A. (2022). Immune evasion and provocation by *Mycobacterium tuberculosis*. *Nature Reviews Microbiology*, 20 <https://pubmed.ncbi.nlm.nih.gov/35879556/>
11. Cleveland Clinic. (2022, May 24). Tuberculosis: Symptoms, Causes, Treatments. Cleveland Clinic; Cleveland Clinic. <https://my.clevelandclinic.org/health/diseases/11301-tuberculosis>
12. da Costa, C., Onyebujoh, P., Thiry, G., & Zumla, A. (2023). Advances in development of new tuberculosis vaccines. *Current opinion in pulmonary medicine*, 29(3), 143–148. <https://doi.org/10.1097/MCP.0000000000000950>
13. de Knecht, G. J., Bakker-Woudenberg, I. A., van Soolingen, D., Aarnoutse, R., Boeree, M. J., & de Steenwinkel, J. E. (2015). SILA-421 activity in vitro against rifampicin-susceptible and rifampicin-resistant *Mycobacterium tuberculosis*, and in vivo in a murine tuberculosis model. *International journal of antimicrobial agents*, 46(1), 66–72. <https://pubmed.ncbi.nlm.nih.gov/28575382/>
14. Folliero, V., Ferravante, C., Iovane, V., Salvati, A., Crescenzo, L., Perna, R., Corvino, G., Della Rocca, M. T., Panetta, V., Tranfa, A., Greco, G., Baldoni, T., Pagnini, U., Finamore, E., Giurato, G., Nassa, G., Coppola, M., Atripaldi, L., Greco, R., D'Argenio, A., ... Galdiero, M. (2024). Whole Genome Sequence Dataset of *Mycobacterium tuberculosis* Strains from Patients of Campania

Region. *Scientific data*, 11(1),
220. <https://europepmc.org/article/MED/38374088>

15. Gao, Q., Yang, L., Lu, M., Jin, R., Ye, H., & Ma, T. (2023). The artificial intelligence and machine learning in lung cancer immunotherapy. *Journal of hematology & oncology*, 16(1), 55. <https://pubmed.ncbi.nlm.nih.gov/37226190/>
16. *Guidelines for Preventing the Transmission of M. tuberculosis in Health-Care Settings | Slide Sets | Publications & Products | TB | CDC*. (2018, December 11). www.cdc.gov.
17. Huang, H., Jin, Q., Ma, Y., Chen, X., & Zhuang, Y. (2002). Characterization of rpoB mutations in rifampicin-resistant Mycobacterium tuberculosis isolated in China. *Tuberculosis (Edinburgh, Scotland)*, 82(2-3), 79–83. <https://doi.org/10.1054/tube.2002.0326>
18. Isakova, J., Sovkhozova, N., Vinnikov, D., Goncharova, Z., Talaibekova, E., Aldasheva, N., & Aldashev, A. (2018). Mutations of rpoB, katG, inhA and ahp genes in rifampicin and isoniazid-resistant Mycobacterium tuberculosis in Kyrgyz Republic. *BMC microbiology*, 18(1), 22. <https://pubmed.ncbi.nlm.nih.gov/29566660/>
19. Lohrasbi, V., Talebi, M., Bialvaei, A. Z., Fattorini, L., Drancourt, M., Heidary, M., & Darban-Sarokhalil, D. (2018). Trends in the discovery of new drugs for Mycobacterium tuberculosis therapy with a glance at resistance. *Tuberculosis (Edinburgh, Scotland)*, 109, 17–27. <https://pubmed.ncbi.nlm.nih.gov/29559117/>

20. Long, Y., Wang, B., Xie, T., Luo, R., Tang, J., Deng, J., & Wang, C. (2024). Overexpression of efflux pump genes is one of the mechanisms causing drug resistance in *Mycobacterium tuberculosis*. *Microbiology spectrum*, 12(1), e0251023. <https://pubmed.ncbi.nlm.nih.gov/38047702/>
21. Malenfant, J. H., & Brewer, T. F. (2021). Rifampicin Mono-Resistant Tuberculosis—A Review of an Uncommon But Growing Challenge for Global Tuberculosis Control. *Open Forum Infectious Diseases*, 8(2). <https://pubmed.ncbi.nlm.nih.gov/33623803/>
22. Mayo Clinic. (2023, March 22). *Tuberculosis - Diagnosis and treatment - Mayo Clinic*. Mayoclinic.org; Mayo clinic. <https://www.mayoclinic.org/diseases-conditions/tuberculosis/diagnosis-treatment/drc-20351256>
23. Mesfin, E. A., Merker, M., Beyene, D., Tesfaye, A., Shuaib, Y. A., Addise, D., Tessema, B., & Niemann, S. (2022). Prediction of drug resistance by Sanger sequencing of *Mycobacterium tuberculosis* complex strains isolated from multidrug resistant tuberculosis suspect patients in Ethiopia. *PloS one*, 17(8), e0271508. <https://pubmed.ncbi.nlm.nih.gov/35930613/>
24. Morrow, E., Zidaru, T., Ross, F., Mason, C., Patel, K. D., Ream, M., & Stockley, R. (2023). Artificial intelligence technologies and compassion in healthcare: A systematic scoping review. *Frontiers in psychology*, 13, 971044. <https://pubmed.ncbi.nlm.nih.gov/36733854/>

25. Mullerpattan, J. B., Nikam, C., Sharma, U., Rodrigues, C., & Pinto, L. M. (2017). Rifampicin-resistant tuberculosis: what is the best initial empiric regimen in Mumbai, India? *European Respiratory Journal*, 50(1). <https://pubmed.ncbi.nlm.nih.gov/28729472/>
26. Murphy, S. G., Smith, C., Lapierre, P., Shea, J., Patel, K., Halse, T. A., Dickinson, M., Escuyer, V., Rowlinson, M. C., & Musser, K. A. (2023). Direct detection of drug-resistant *Mycobacterium tuberculosis* using targeted next generation sequencing. *Frontiers in public health*, 11, 1206056. <https://www.frontiersin.org/journals/public-health/articles/10.3389/fpubh.2023.1206056/full>
27. *Mycobacterium tuberculosis* | *bacterium*. (n.d.). Encyclopedia Britannica. <https://www.britannica.com/science/Mycobacterium>
28. *Mycobacterium tuberculosis* - Vircell. (n.d.). En.vircell.com. <https://en.vircell.com/diseases/24-mycobacterium-tuberculosis/>
29. Nguyen, T. B. N., Nguyen, T. K. D., Truong, V. H., Tran, T. T. N., Phan, V. B. T., Nguyen, T. T., Nguyen, H. B., Ngo, V. Q. T., Mai, V. T., & Molicotti, P. (2023). Drug resistance and the genotypic characteristics of *rpoB* and *katG* in rifampicin- and/or isoniazid-resistant *Mycobacterium tuberculosis* isolates in central Vietnam. *Osong public health and research perspectives*, 14(5), 347–355. <https://doi.org/10.24171/j.phrp.2023.0124>.

30. Nimmo, C., Millard, J., Faulkner, V., Monteserin, J., Pugh, H., & Johnson, E. O. (2022). Evolution of *Mycobacterium tuberculosis* drug resistance in the genomic era. *Frontiers in cellular and infection microbiology*, 12, 954074. <https://www.frontiersin.org/articles/10.3389/fcimb.2022.954074/full>
31. Nyang'wa, B.-T., Berry, C., Kazounis, E., Motta, I., Parpieva, N., Tigay, Z., Solodovnikova, V., Liverko, I., Moodliar, R., Dodd, M., Ngubane, N., Rassool, M., McHugh, T. D., Spigelman, M., Moore, D. A. J., Ritmeijer, K., du Cros, P., & Fielding, K. (2022). A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis. *New England Journal of Medicine*, 387(25), 2331–2343. <https://pubmed.ncbi.nlm.nih.gov/36546625/>
32. Oppermann I. (2023). Regulating AI for health. *BMJ health & care informatics*, 30(1), e100931. <https://informatics.bmj.com/content/30/1/e100931>
33. Riccardi, G., Pasca, M. R., & Buroni, S. (2009). *Mycobacterium tuberculosis*: drug resistance and future perspectives. *Future microbiology*, 4(5), 597–614. <https://doi.org/10.2217/fmb.09.20>
34. Seifert, M., Catanzaro, D., Catanzaro, A., & Rodwell, T. C. (2015). Genetic mutations associated with isoniazid resistance in *Mycobacterium tuberculosis*: a systematic review. *PloS one*, 10(3), e0119628. <https://pubmed.ncbi.nlm.nih.gov/25799046/>
35. Shanmugam, S. K., Kumar, N., Sembulingam, T., Ramalingam, S. B., Selvaraj, A., Rajendhiran, U., Solaiyappan, S., Tripathy, S. P., Natrajan, M., Chandrasekaran, P., Swaminathan, S., Parkhill, J., Peacock, S. J., &

- Ranganathan, U. D. K. (2022). Mycobacterium tuberculosis Lineages Associated with Mutations and Drug Resistance in Isolates from India. *Microbiology spectrum*, 10(3), e0159421. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9241780/>
36. Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2022). Cancer statistics, 2022. *CA: a cancer journal for clinicians*, 72(1), 7–33. <https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21708>
37. Smith I. (2003). Mycobacterium tuberculosis pathogenesis and molecular determinants of virulence. *Clinical microbiology reviews*, 16(3), 463–496. <https://pubmed.ncbi.nlm.nih.gov/12857778/>
38. Stamer, T., Steinhäuser, J., & Flägel, K. (2023). Artificial Intelligence Supporting the Training of Communication Skills in the Education of HealthCare Professions: Scoping Review. *Journal of medical Internet research*, 25, e43311. <https://doi.org/10.2196/43311>
39. Stanfill, M. H., & Marc, D. T. (2019). Health Information Management: Implications of Artificial Intelligence on Healthcare Data and Information Management. *Yearbook of medical informatics*, 28(1), 56–64. <https://pubmed.ncbi.nlm.nih.gov/31419816/>
40. Swaminathan, S., & Ramachandran, G. (2015). Challenges in childhood tuberculosis. *Clinical pharmacology and therapeutics*, 98(3), 240–244. <https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/cpt.175>

41. Takawira, F. T., Mandishora, R. S. D., Dhlamini, Z., Munemo, E., & Stray-Pedersen, B. (2017). Mutations in *rpoB* and *katG* genes of multidrug resistant mycobacterium tuberculosis undetectable using genotyping diagnostic methods. *The Pan African medical journal*, 27, 145. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5567934/>
42. Theodosiou, A. A., & Read, R. C. (2023). Artificial intelligence, machine learning and deep learning: Potential resources for the infection clinician. *The Journal of infection*, 87(4), 287–294. <https://doi.org/10.1016/j.jinf.2023.07.006>
43. WHO consolidated guidelines on tuberculosis: module 1: prevention: tuberculosis preventive treatment. (n.d.). Wwww.who.int. <https://www.who.int/publications/i/item/9789240001503>
44. WHO Operational Handbook on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment. (n.d.). Wwww.who.int. <https://www.who.int/publications/i/item/9789240065116>
45. WHO operational handbook on tuberculosis: module 5: management of tuberculosis in children and adolescents. (n.d.). Wwww.who.int. <https://www.who.int/publications/i/item/9789240046832>
46. Wiljer, D., & Hakim, Z. (2019). Developing an Artificial Intelligence-Enabled Health Care Practice: Rewiring Health Care Professions for Better Care. *Journal of medical imaging and radiation sciences*, 50(4 Suppl 2), S8–S14. <https://doi.org/10.1016/j.jmir.2019.09.010>
47. Williams, D. L., Spring, L., Collins, L., Miller, L. P., Heifets, L. B., Gangadharam, P. R., & Gillis, T. P. (1998). Contribution of *rpoB* mutations to development of rifamycin cross-resistance in *Mycobacterium tuberculosis*.

Antimicrobial agents and chemotherapy, 42(7), 1853–1857.
<https://doi.org/10.1128/AAC.42.7.1853>

48. Xu, G., Liu, H., Jia, X., Wang, X., & Xu, P. (2021). Mechanisms and detection methods of Mycobacterium tuberculosis rifampicin resistance: The phenomenon of drug resistance is complex. *Tuberculosis (Edinburgh, Scotland)*, 128, 102083. <https://pubmed.ncbi.nlm.nih.gov/33975262/>
49. Yin, X., Liao, H., Yun, H., Lin, N., Li, S., Xiang, Y., & Ma, X. (2022). Artificial intelligence-based prediction of clinical outcome in immunotherapy and targeted therapy of lung cancer. *Seminars in cancer biology*, 86(Pt 2), 146–159. <https://pubmed.ncbi.nlm.nih.gov/35963564/>
50. Yu, Y., Zeng, D., Ou, Q., Liu, S., Li, A., Chen, Y., Lin, D., Gao, Q., Zhou, H., Liao, W., & Yao, H. (2019). Association of Survival and Immune-Related Biomarkers With Immunotherapy in Patients With Non-Small Cell Lung Cancer: A Meta-analysis and Individual Patient-Level Analysis. *JAMA network open*, 2(7), e196879. <https://pubmed.ncbi.nlm.nih.gov/31290993/>
51. Zaw, M. T., Emran, N. A., & Lin, Z. (2018). Mutations inside rifampicin-resistance determine the region of rpoB gene associated with rifampicin-resistance in Mycobacterium tuberculosis. *Journal of infection and public health*, 11(5), 605–610. <https://doi.org/10.1016/j.jiph.2018.04.005>
52. Zhou, P., Wang, X., Zhao, Y., Yuan, W., & Xie, J. (2018). Sigma factors mediated signaling in Mycobacterium tuberculosis. *Future microbiology*, 13, 231–240. <https://pubmed.ncbi.nlm.nih.gov/29319347/>

53. Khan, M. A., Din, I. U., Majali, T., & Kim, B. S. (2022). A Survey of Authentication in Internet of Things-Enabled Healthcare Systems. *Sensors (Basel, Switzerland)*, 22(23), 9089. <https://pubmed.ncbi.nlm.nih.gov/36501799/>
54. Bordoloi, D., Singh, V., Sanober, S., Buhari, S. M., Ujjan, J. A., & Boddu, R. (2022). Deep Learning in Healthcare System for Quality of Service. *Journal of healthcare engineering*, 2022, 8169203. <https://www.hindawi.com/journals/jhe/2022/8169203/>
55. Foster, I., Biewer, A., Vanqa, N., Makanda, G., Tisile, P., Hayward, S. E., Wademan, D. T., Anthony, M. G., Mbuyamba, R., Galloway, M., Human, W., Westhuizen, H. M., Friedland, J. S., Marino-Medina, A., Schoeman, I., Hoddinott, G., & Nathavitharana, R. R. (2023). "This is an illness. No one is supposed to be treated badly": Community-based stigma assessments in South Africa to inform TB stigma intervention design. *Research square*, rs.3.rs-3716733. <https://connects.catalyst.harvard.edu/Profiles/display/Person/42489>