8-2019

Dynamic Prediction of Treatment Outcomes for Recurrent Tuberculosis Patients

Nicole Hayes
University of Arkansas, Fayetteville

Dynamic Prediction of Treatment Outcomes for Recurrent Tuberculosis Patients

By

Nicole Hayes

July 2019

University of Arkansas

Thesis Advisor: Dr. Shengfan Zhang

Thesis Reader: Dr. Kelly Sullivan

Abstract

Tuberculosis (TB) is a disease that affects people around the world, especially people in underdeveloped countries. TB is one of the top ten causes of death globally so improvement in understanding diagnosis and treatment of TB affected patients could lead to major improvements in world health. This thesis research evaluated relapse patients specifically, deeming a relapse patient as one who has either been cured or completed their last treatment and then is diagnosed with TB again.

This research uses dynamic predictive modeling, based upon the random forest algorithm, to predict treatment outcomes for recurrent TB patients using demographic and follow-up clinical data. The model identifies variables and time periods that are significant in predicting whether the patient will be cured. The model is applied to data provided by the Evaluation System of National Control Program of Tuberculosis in the Republic of Moldova. Our results reveal insights that could be used by physicians to improve treatment strategy and monitor patients more effectively throughout the treatment trajectory.

Acknowledgments

I would like to thank Dr. Shengfan Zhang for her collaboration and mentorship with me over the course of this project. She sparked my interest in research about application of Industrial Engineering techniques used in the medical field which lead to this research topic. I would also like to thank Maryam Kheirandish who helped provide the data for me and answered my questions along the way. Her own research has been a tremendous help in applying similar methods she used to recurrent TB patients. Lastly, I would like to say thank you to my senior design team in Industrial Engineering who worked alongside me in understanding how to implement machine learning techniques which helped me in achieving the following research.

This research was conducted with help from an Honors College Research Grant from the University of Arkansas so I would like to say thank you to the Honors College for support of undergraduate research endeavors like this one.

Table of Contents

1. Introduction

Tuberculosis (TB) is a disease that burdens people across the globe as "worldwide TB is one of the top 10 causes of death and the leading cause from a single infectious agent" (World Health Organization (WHO), 2019). TB has affected the world for centuries and although the mortality rate is dropping about 3% each year, "around 10 million people still fall ill with the disease each year (more adults than children, and more men than women)" (WHO, 2019). The prevalence of the disease suggests that any new discoveries or methods for detection or treatment of TB could have major impact for many countries, especially developing countries. One quarter of the world's population is infected with TB (CDC, 2018), yet funding towards TB prevention, diagnostic and treatment services still falls short of what is needed despite doubling from 3.3 billion dollars in 2006 to 6.9 billion dollars in 2018 (WHO, 2019).

Many TB patients become resistant to the drugs used for treatment, thus leading to a more difficult and expensive treatment pathway. Effective treatment of TB is crucial as it helps cure current patients and prevents spread of the disease. On average 10 to 15 people can be infected by a person with active TB who isn't treated, which explains how crucial treatment and detection is for the tuberculosis disease (WHO, 2014). The graphs in Figure 1 show a decrease in TB mortality rate that is more steep than the decrease in TB incidents, indicating that the treatment is probably improving thus better preventing death from the disease.

Global trends in estimated TB incidence and mortality rates, 2000–2017. Shaded areas represent uncertainty intervals.

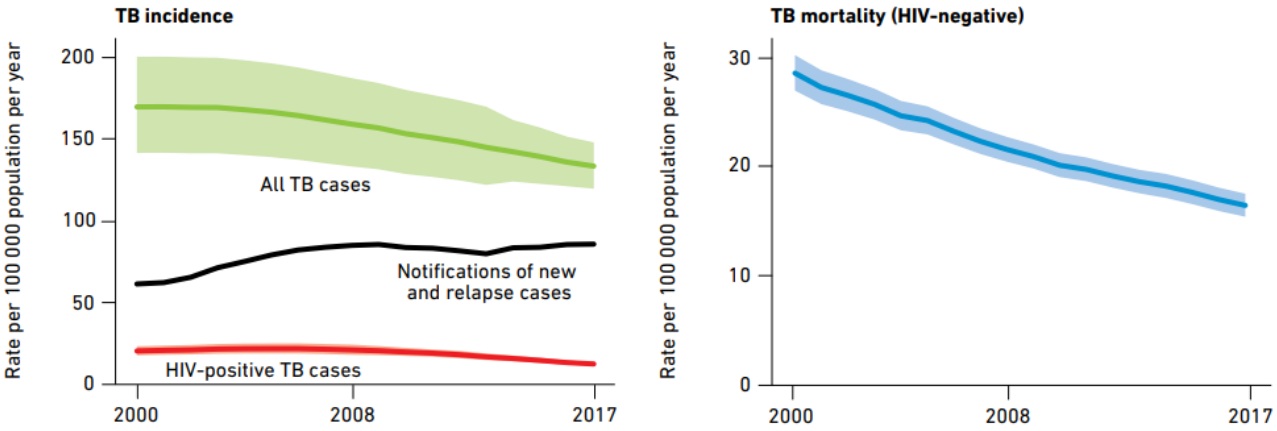


Figure 1. World Health Organization. (2019, March 3). Global trends in estimated TB incidence and mortality rates, 2000-2017 [Chart]. In *Global Tuberculosis Report 2018*. Retrieved from https://www.who.int/tb/publications/global_report/en/

In this research, we seek to predict treatment outcomes for TB patients with a relapse using demographic and follow-up clinical data and identify the time points that are most crucial during the two-year DOTS+ treatment period.

1.1 Key Definitions

This research focuses on TB relapse. WHO (2015) defines relapse patients as those who have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB cause by reinfection). The terms recurrent TB patient and relapse patient are used synonymously throughout this research. Directly Observed Treatment, Short Course (DOTS) is a government supported treatment strategy that lasts 6 to 8 months and includes use of anti-TB drugs for patients with positive sputum smears (WHO, 2014). This thesis research uses an expansion of that strategy known as DOTS+, a program endorsed by the WHO

in 2000 that improves upon DOTS by addressing patients with drug resistance (Grover & Takkar, 2008).

According to the CDC, it is important that all patients suspected of TB are examined for specimen collection and that the diagnosis involves smear, culture, and drug susceptibility testing. During diagnosis testing for TB, smear and culture tests have different functions; smear tests for the presence of acid-fast bacilli and culture tests for the growth of tubercle bacilli (CDC, 2016). The CDC (2016) also states that many TB patients have negative smears but with a subsequent positive culture. Because negative smears do not exclude TB, it is important to have both smear and culture results when confirming the existence of TB bacteria (CDC, 2016). Similar to TB diagnosis, patients (including those with TB relapse) undergoing treatment need to have regular smear and culture follow-up tests to track health status. Drug susceptibility is also initially tested to see if the patient is resistant to the first-line anti-TB drugs: isoniazid, rifampin, ethambutol, and pyrazinamide because these particular patients need different treatment strategies (CDC, 2016). Patients who have multi-drug resistance (MDR) are less likely to survive treatment. We evaluate patient outcomes at the end of 2 years using clinical test data because of the WHO guidelines that define MDR patient recovery as 2 years and non-MDR patient recovery as 9 months.

1.2 Machine Learning in Medicine

Machine learning algorithms are being used in many different avenues of the world today and medicine is emerging as one of the promising fields of opportunity. Before implementing machine learning, the capabilities the algorithms offer and other ways it has been implemented in medicine were researched in order to verify it was the right course of action for the data.

There are many articles describing the use of machine learning in medicine and one explains well that, "the key distinction between traditional approaches and machine learning is that in machine learning, a model learns from examples rather than being programmed with rules" (Rajkomar et al., 2019). The ability of machine learning algorithms to find patterns within data presents several clear opportunities for the Tuberculosis data. Finding patterns for when the patients are most susceptible to recover whether that be due to time periods or certain factors will be helpful to physicians in monitoring and treating future patients.

There are already many studies using machine learning in medicine, even in tuberculosis efforts specifically. For example, Sauer et al. (2018) seek to identify features associated with treatment failure and to predict which patients are at the highest risk of treatment failure. This study shows how physicians can use the insights found from machine learning to impact their future decisions for treatment strategy and timeline. After learning about the capabilities of machine learning, especially in medicine, a specific algorithm was chosen based on the appropriate fit for the data.

1.3 Research Goal and Thesis Organization

The goal of this research is to evaluate TB patient data during treatment to predict whether a recurrent TB patient will eventually become cured at the end of 24 months of treatment. The research seeks to identify indicators within the data that certain time epochs or predictors lead to a need for treatment change. A dynamic model is used at different follow-up time epochs after initiation of treatment in order to predict the recovery outcome of the patient at the end of 24 months.

The remainder of the thesis begins by explaining the data used for analysis and the steps taken to initialize the data and understand the baseline of the relapse patient data. The choice and implementation of the random forest algorithm is then explained alongside evaluation of the model accuracy at different time epochs. Then the results of the different models created and discussion of the research in general are included.

2. Methodology

This section presents a summary of the data (in section 2.1) and the dynamic prediction model (in section 2.2). Throughout this section the terms time 0, treatment initiation, and beginning of treatment are all synonymous to explain the time at which the patient comes in to start treatment for the most recent recurrent TB episode.

2.1 Data Source and Data Processing

We used data from 2009 to 2016 provided by the Informational Monitoring and Evaluation System of National Control Program of Tuberculosis in the Republic of Moldova. The raw dataset consists of 176,234 clinical records of 23,160 pulmonary tuberculosis patients. In this research, we focus on the subset containing only TB relapse patients. We select patients who had at least one occurrence of a "start of treatment" date later than an "end of treatment" date, indicating a relapse. In order to include only patients with true TB relapse (i.e., a patient who was declared cured or treatment completed but was found smear positive again), the data was narrowed by selecting only pre-status groups "Cured" and "Complete" in the last treatment. These distinctions decreased the number of records from over 500 to 281. Note that the number of patients who died at any point during the two-year follow-up period was very small (6 records), and thus we excluded these data in this study.

The baseline is considered only the information about the patient at time zero and includes the variables described in Table 1 of this section (Gender, Age, TB Group, Smear, Smear Grade, Culture, and Culture Grade). A demographic summary of the baseline of the

remaining 281 patients is provided in Table 1. All descriptions of the variables in the following chart are from WHO definitions for Tuberculosis (WHO, 2015).

Patients are guided to undergo regular smear and culture testing during the treatment follow-up period, i.e., at months 2, 4, 6, 9, 12, and 18 following treatment initiation. The data is evaluated at different time epochs which indicate how many months of data up to the prediction epoch are included in the model creation. For example, the 24-month epoch indicates the time from month 18 to just before the 24 month follow-up, but not including exactly at 24 months. Any follow-up results during this period are still used to predict the end of the 2-year recovery. The concept is close to land marking in the survival analysis which is when information is collected over time and added to the baseline information in an effort to add to the accuracy of the outcome prediction (Parast & Griffin, 2017). The time epochs are defined in Table 2 .

Table 1. Demographic Summary of Relapse Tuberculosis Patients at Baseline

Variables		Population		Description
Gender				
	Male	77.6%	(n= 218)	
	Female	22.4%	(n= 63)	
Age				Patients' age at the start of TB treatment
	Below 35	39.1%	(n= 110)	
	35-55	43.1%	(n= 121)	
	Above 55	17.8%	(n= 50)	
TB Group				INH' is susceptible to Rifampicin but not Isoniazid resistance. 'RIF' is susceptible to Isoniazid but not Rifampicin resistance. 'MDR is resistant to both and 'Pans' is susceptible to both.
	1 (Pans)	65.8%	(n= 185)	
	2 (INH)	3.2%	(n= 9)	
	3 (RIF)	2.8%	(n= 8)	
	4 (MDR)	28.1%	(n= 79)	
Smear				Smear shows the result of a sputum Smear test taken at the intitiation date of treatment.
	Positive	14.9%	(n= 42)	
	Negative	52.0%	(n= 146)	
	Unknown	33.1%	(n= 93)	
Smear Grade				Smear grade shows quantitative result of Smear test at intitiation date of treatment. "+3", "+2", "+1", and "1-9/100" show numerous, moderate, few, and rare number of acid-fast bacilli (AFB)s in stained smears respectively.
	1+	5.0%	(n= 14)	
	2+	2.1%	(n= 6)	
	3+	2.5%	(n= 7)	
	1-9/100	4.6%	(n= 13)	
	Unknown	33.8%	(n= 95)	
	Negative	52.0%	(n= 146)	
Culture				Culture shows the result of a sputum Culture test taken at the initiation date of treatment.
	Positive	33.8%	(n= 95)	
	Negative	63.7%	(n= 179)	
	Unknown	2.5%	(n= 7)	
Culture Grade				Culture grade shows quantitative result of Culture test at initiation date of treatment. "+3", "+2", and "+1" show numerous, moderate, and few number of acid fast bacilli (AFB)s in stained smears respectively.
	1+	10.7%	(n= 30)	
	2+	12.1%	(n= 34)	
	3+	5.3%	(n= 15)	
	0	71.9%	(n= 202)	

Table 2. Explanation of the Time Epochs used and how many Months are Included in the Model

Data Point	Months Included in Model
1	Baseline
2	0, 1
3	0, 1,2
4	0, 1,2,3
5	0, 1,2,3,4
6	0, 1,2,3,4,5
7	0, 1,2,3,4,5,6
8	0, 1,2,3,4,5,6,9
9	0, 1,2,3,4,5,6,9,12
10	0, 1,2,3,4,5,6,9,12,18
11	0, 1,2,3,4,5,6,9,12,18,24

2.2 Random Forest Algorithm

In medical applications, with patient data changing continuously, a model that changes alongside the data is necessary. After researching the most popular machine learning algorithms, the one that seemed most suitable for a variety of reasons was the random forest algorithm. We used Python version 3.7 for data analysis in this research. The coding language used was Python because there are many machine learning packages available to implement different machine learning algorithms. After manipulating the data into appropriate formats for Python, the code was then initialized to read the data. The random forest algorithm essentially pulls many decision trees together to create one model, thus yielding the name forest. The random forest algorithm can be used for either classification or regression and offers the ability to "measure the relative importance of each feature on the prediction" (Donges, 2018). The flexibility of random forests and the opportunity to evaluate the feature importance at different points throughout the model made it the algorithm chosen for implementation. The random forest was used as a classification model because the response variable "Final Status" is binary, taking on the value 1 for patients who are "Cured", and 0 for patients who are "Not Cured" at the end of the two-year treatment. A patient is deemed as cured if they have two consecutive negative smear or culture tests and are a non-MDR patient and 3 consecutive negative smear or culture tests if they are an MDR patient.

Machine learning can be used to predict future outcomes by creating a model based on historical data. It is necessary in model creation to split the data into a training set and a testing set. The training data set is what the algorithm uses to build the model and the testing set is used to validate or "test" the model. One of the many packages that Python allows access to is an automatic test--train--split package. The package randomly splits the data loaded into training and testing sets based on the entered parameters. For this particular data set, 70% of the data was designated for training and 30% of the data for testing to allow a big enough test result to evaluate (Srinidhi, 2018).

The Y-variable for every model run was the binary "Final Status" value mentioned previously, but the X-variables changed to account for the changes in timing and features included in the model. The data provided included features or predictors introduced in Table 1 from 11 different time epochs (beginning of treatment, 1, 2, 3, 4, 5, 6, 9, 12, 18, and 24 months after initiation of treatment). The first model created was the data from time zero only and then follow-up test results in the months following treatment initiation were added to create 11 different models to show dynamic prediction.

3. Results

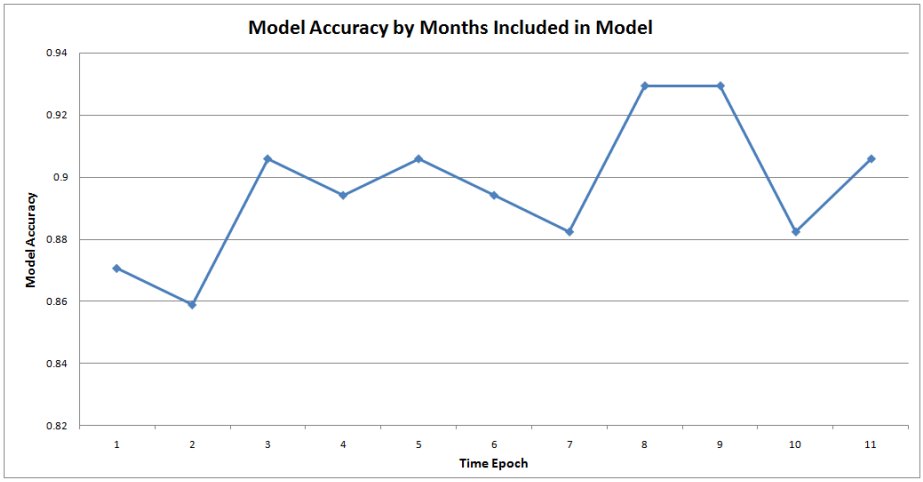
The results are all reported based on only the testing set of the data. The accuracy of the model at different prediction epochs with varying months of historical data available and included in

the model is shown below in Figure 2. The model accuracy was calculated using Equation 1, which is essentially the number of matches divided by the number of samples. In Figure 2, though the accuracy slightly oscillates, it remains high at every time epoch. This is interesting because we thought that as months of data were included within the model, the accuracy would significantly increase. The F1-scores for the model were also calculated since the data is very imbalanced, meaning that the patients fall more into one class than the other. The 281 patients overall fall into the "Not Cured" and "Cured" classes of Final Status in a ratio of 9 to 1 respectively. The F1-score is a weighted average of precision and recall and is a more appropriate metric to evaluate models with highly imbalanced data (Tilii, 2016). The F1-scores for each time epoch are in Table 3. The best value for an F1-score is 1 so the values in Table 3 show a high range of values, similar to the accuracy. The values in Table 3 do not show an evident trend as the months added to the models increase which again goes against our original hypothesis that model validity would increase as the data available increased.

Equation 1. Calculating Accuracy of Random Forest Model

$$\text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}}$$

Where: TP = True Positive; TN = True Negative; FP = False Positive; FN = False Negative



Data Point	Months Included in Model
1	Baseline
2	0, 1
3	0, 1,2
4	0, 1,2,3
5	0, 1,2,3,4
6	0, 1,2,3,4,5
7	0, 1,2,3,4,5,6
8	0, 1,2,3,4,5,6,9
9	0, 1,2,3,4,5,6,9,12
10	0, 1,2,3,4,5,6,9,12,18
11	0, 1,2,3,4,5,6,9,12,18,24

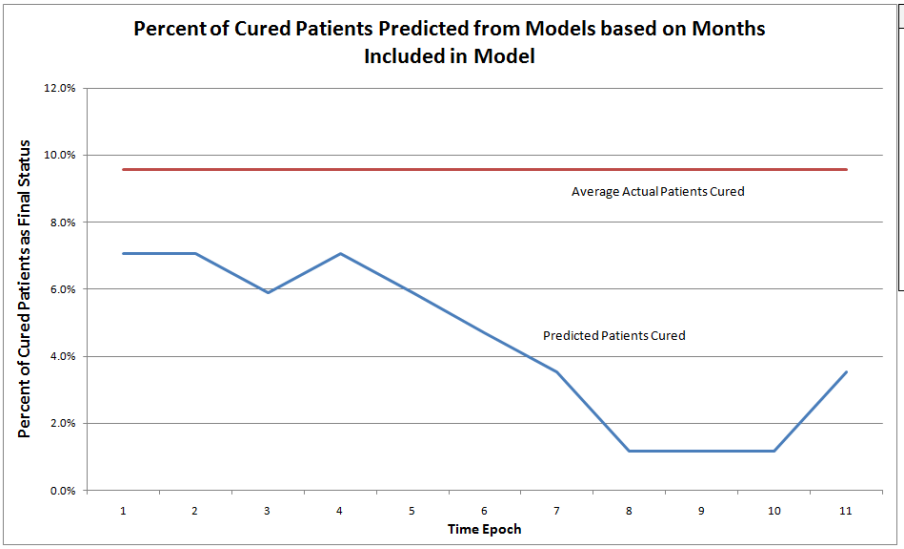
Figure 2. Model Accuracy based on Months of Data Included in Model Creation

Table 3. F1-score of Model based on Months of Data Included in Model Creation

Baseline	1	2	3	4	5	6	9	12	18	24
0.868	0.932	0.924	0.814	0.897	0.893	0.901	0.869	0.920	0.884	0.787

We next explored how the feature importance for each X-variable changes as the months included change. The complete table of the variable importance weights and how they change depending on the number of months of data included in the creation of the random forest models is presented in Figures A1-A12 of the appendix. One interesting aspect was the percent of cured patients and how that changed at each time interval. The percent of cured patients was calculated by evaluating the Y prediction values that the random forest generates for the testing set of data. The results for the percent of patients predicted to be "Cured" as the Final Status after the treatment is below in Figure 3.

This analysis is useful because it could show what point within the two-year treatment is most critical for recovery.



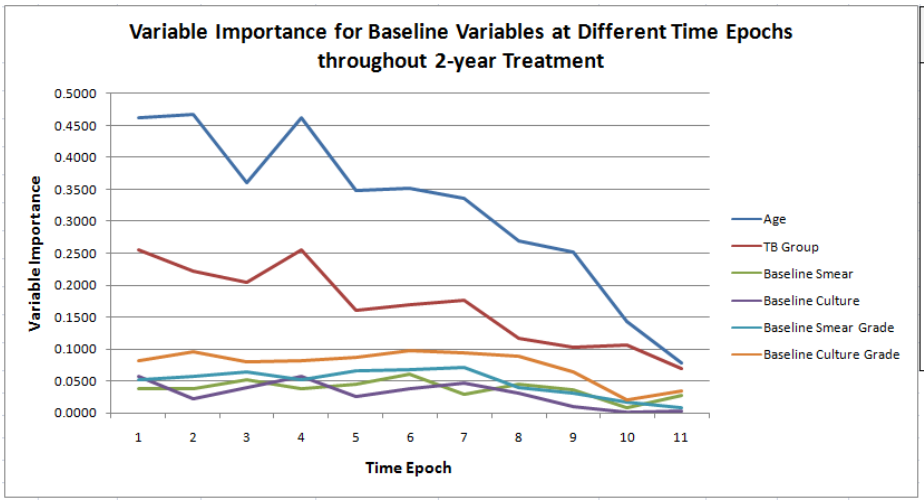
Data Point	Months Included in Model
1	Baseline
2	0, 1
3	0, 1,2
4	0, 1,2,3
5	0, 1,2,3,4
6	0, 1,2,3,4,5
7	0, 1,2,3,4,5,6
8	0, 1,2,3,4,5,6,9
9	0, 1,2,3,4,5,6,9,12
10	0, 1,2,3,4,5,6,9,12,18
11	0, 1,2,3,4,5,6,9,12,18,24

Figure 3. Percent of Cured Patients Predicted from Models based on Months Included in Model

The concerning thing about the results of Figure 3 is that the highest percent of cured patients predicted is about 7% which seems like a low recovery rate for a two-year treatment program. The "Average Actual Patients Cured" line was calculated by dividing the number of cured patients in the original data Final Status column by the total number of 281 patients in order to show a reference for the true recovery rate of this data. The dataset used to create the models includes drug-resistant patients so the recovery rate could be affected by the difficulty in treating those patients. The World Health Organization 2018 Global Report even stated that, "treatment success remains low, at 55% globally" and specifically "treatment success was less than 50% in The Republic of Moldova" for all TB cases (2019). The low recovery rate could also reflect the difficulty in treating recurrent patients. One interesting trend from the "Predicted

Patients Cured" line in Figure 3 is the higher recovery rate in the first 6 months of treatment than in the later months of treatment. This leads to insight that patients who don't recovery within the first 6 months are probably not going to recover in the months after the 6th month follow-up. The higher recovery rate in the early months and the high accuracy and F1-score at every month epoch creates the question whether the baseline data on its own is enough to accurately predict the treatment outcome of a patient at the end of the two-year treatment.

The results of the models along with the feature importance of each variable at every time point could help in making the treatment more impactful. The treatment may need to be altered, but until physicians understand how to alter it for relapse patients they cannot make any changes. Not only do these models provide initial insight into the treatment of relapse Tuberculosis patients, but the models can be built upon with future data added. The feature importance found and the recovery rate essentially provide initial understanding of what the recovery of a relapse Tuberculosis patient depends on most. Figure 4 below shows how the importance for the top significant variables and how they change depending on months of data included in the model creation. The breakdown of the top 15 most important variables and their rankings are provided in charts for each time epoch in the appendix.



Time Epoch	Months of Data Included in Model
0	Baseline
1	0, 1
2	0, 1,2
3	0, 1,2,3
4	0, 1,2,3,4
5	0, 1,2,3,4,5
6	0, 1,2,3,4,5,6
9	0, 1,2,3,4,5,6,9
12	0, 1,2,3,4,5,6,9,12
18	0, 1,2,3,4,5,6,9,12,18
24	0, 1,2,3,4,5,6,9,12,18,24

Figure 4. Variable Importance for Baseline Variables at Different Time Epochs throughout Two-year Treatment

In Figure 4, the interesting trend is that the variable importance for each variable decreases as variables are added to the model creation, which is intuitive since the other variables added each add a level of significance to the model, but the relative importance decreases as well. Age and TB group are the top two most significant variables at every time epoch, but their relative importance decreases in comparison to the other variables as more variables are added. In particular, smear and culture results become more important and the demographic variables become less important during later time epochs.

4. Discussion and Conclusions

The insights from applying random forest algorithms to predict outcomes for recurrent TB patients can be used to help physicians in understanding the diagnosis and treatment variables that affect the recovery of relapse Tuberculosis patients. That being said, there are still limitations to this research and areas for improvement in future endeavors involving similar topics.

One limitation of this research was the removal of death patients (N = 6) from the data before model creation. This removal could lead to bias within the evaluation, essentially indicating that a patient must be alive in order to be cured or not cured at the end of the 2-year treatment. This could create bias in the model since information about those patients is now missing. The choice to remove them came from the inherent behavior of the random forest algorithm, which grows in accuracy as the number of trees grows (Polamuri, 2017). With only 6 patients to build a decision tree from in the random forest, there was not enough data to accurately create a multinomial prediction as to whether the death patients would have been cured, not cured, or died at the 24 month time point. Further research could use truncated data for these particular patients in which if the patient is still alive, their data is used in model creation, and if they have died then their data is not used.

Another limitation of this study is that the classes for the response variable are imbalanced, meaning that one classification outweighs the other. Future research can explore other methods to fix this bias that comes from the imbalanced data, such as under-sampling or over-sampling.

Another interesting expansion to this research would be further evaluation of the variables of importance as outlined in each bar graph of the appendix for deeper understanding of why those variables change in significance the way that they do. There are certain trends in the importance that could be evaluated alongside the Tuberculosis disease trends to see how the treatment and the disease coincide at different time points.

The model accuracy and F1-scores did not significantly improve as months of data included in the model increased which reveals how important the baseline data is, even in the later months of treatment. The feature importance of the baseline variables (Figure 4) decreases both in importance and relative importance so future research as to why the relative importance specifically is decreasing could lead to insight into how the TB disease progresses in recurrent TB patients. The predicted cured patients created by the models already shows insight into how many patients are suspected to improve as treatment progresses, but with even more data, the accuracy of the model in predicting recovery rate will improve. Ultimately, machine learning techniques provided new perspective of the recurrent TB patient data which alongside physician knowledge could be used for future patients in deciding which type of treatment and the duration that is most appropriate for each patient.

5. References

Centers for Disease Control and Prevention. (2018, December 31). Data & Statistics | TB | CDC. Retrieved from https://www.cdc.gov/tb/statistics/default.htm

Centers for Disease Control and Prevention. (2016, May 4). Diagnosis of Tuberculosis Disease. Retrieved from https://www.cdc.gov/tb/education/corecurr/pdf/chapter4.pdf

Donges, N. (2018, February 22). The Random Forest Algorithm. Retrieved from https://towardsdatascience.com/the-random-forest-algorithm-d457d499ffcd

Grover, G. S., & Takkar, J. (2008, October). Recent Advances in Multi-Drug-Resistant Tuberculosis and RNTCP. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2763697/

Parast, L., & Griffin, B. A. (2017). Landmark estimation of survival and treatment effects in observational studies. *Lifetime data analysis*, *23*(2), 161–182. doi:10.1007/s10985-016-9358-z

Polamuri, S. (2017, May 22). How the Random Forest Algorithm Works in Machine Learning [Web log post]. Retrieved from https://dataaspirant.com/2017/05/22/random-forest-algorithm-machine-learing/

Rajkomar, A., M.D., Dean, J., Ph.D., &Kohane, I., M.D., Ph.D. (2019). Machine Learning in Medicine. *Machine Learning in Medicine, 380*(14), 1347-1358. doi:nejm.org

Sauer, C. M., Sasson, D., Paik, K. E., McCague, N., Celi, L. A., Fernandez, I. S., & .Illigens, B. M. (2018). Feature selection and prediction of treatment failure in tuberculosis. *PLOS ONE,* 1-14. doi:https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0207491&type=printable

Srinidhi, S. (2018, July 30). How to split your dataset to train and test datasets using SciKit Learn. Retrieved from https://medium.com/@contactsunny/how-to-split-your-dataset-to-train-and-test-datasets-using-scikit-learn-e7cf6eb5e0d

Tilii. (2016). Unbalanced data and cross-validation. Retrieved from https://www.kaggle.com/questions-and-answers/27589

World Health Organization. (2015, July 21). Definitions and reporting framework for tuberculosis. Retrieved from https://www.who.int/tb/publications/definitions/en/

World Health Organization. (2019, March 3). Global trends in estimated TB incidence and mortality rates, 2000-2017 [Chart]. In *Global Tuberculosis Report 2018*. Retrieved from https://www.who.int/tb/publications/global_report/en/

World Health Organization. (2019, March 03). Global tuberculosis report 2018. Retrieved from https://www.who.int/tb/publications/global_report/en/

World Health Organization. (2014, June 18). What is DOTS? Retrieved from https://www.who.int/tb/publications/dots-who-guide/en/

6. Appendix

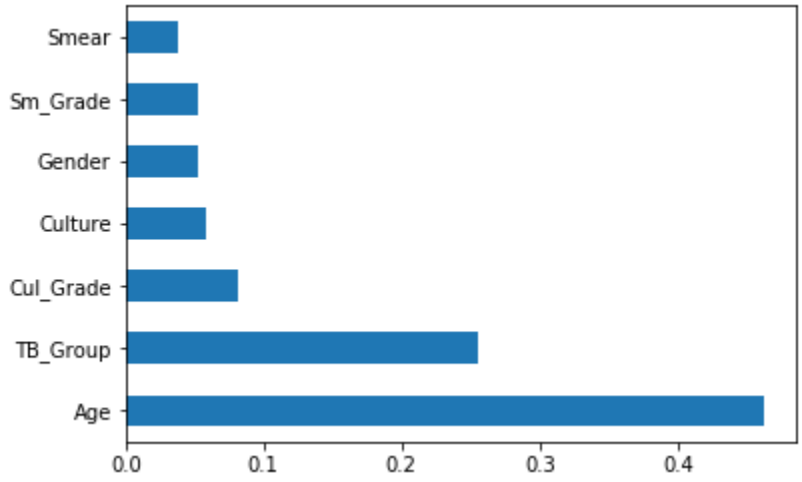


Figure A1. Top Variables of Importance at Baseline

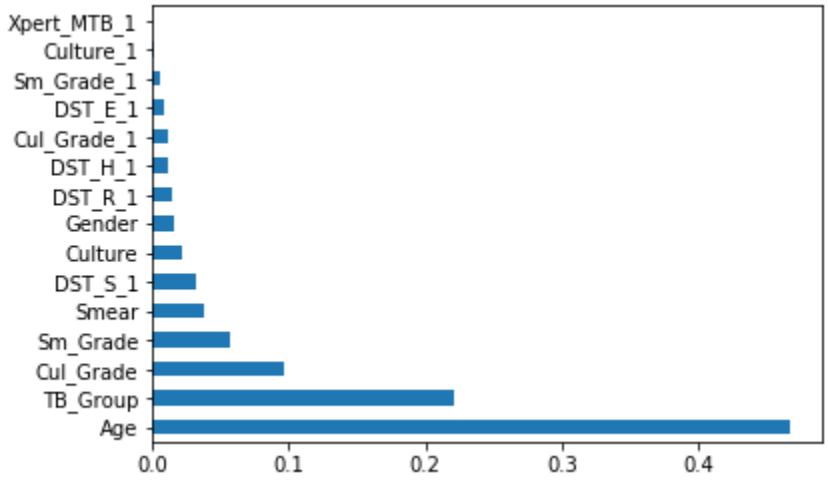


Figure A2. Top 15 Variables of Importance at 1 Month Time Epoch

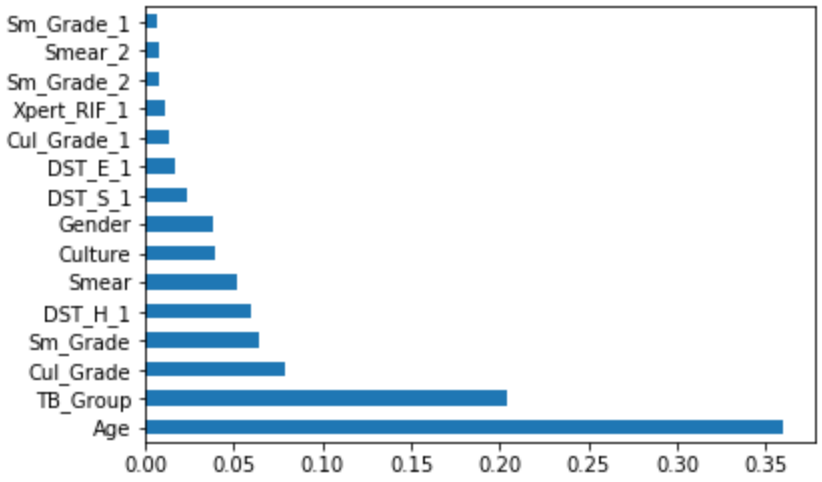


Figure A3. Top 15 Variables of Importance at 2 Month Time Epoch

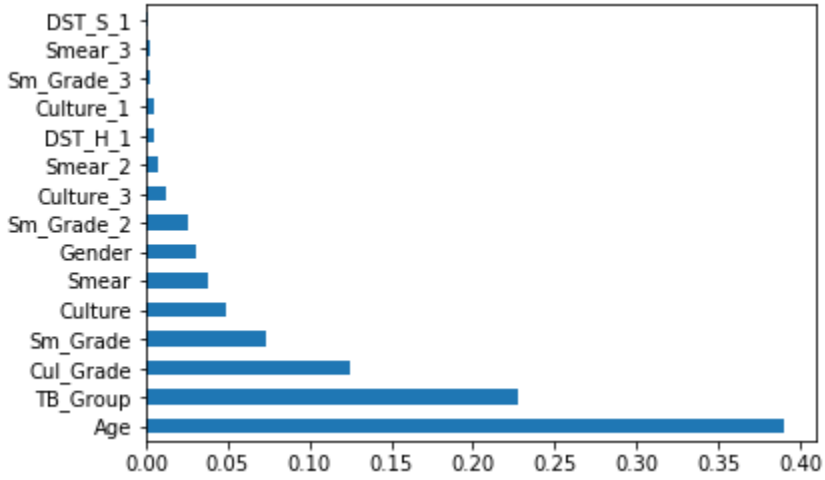


Figure A4. Top 15 Variables of Importance at 3 Month Time Epoch

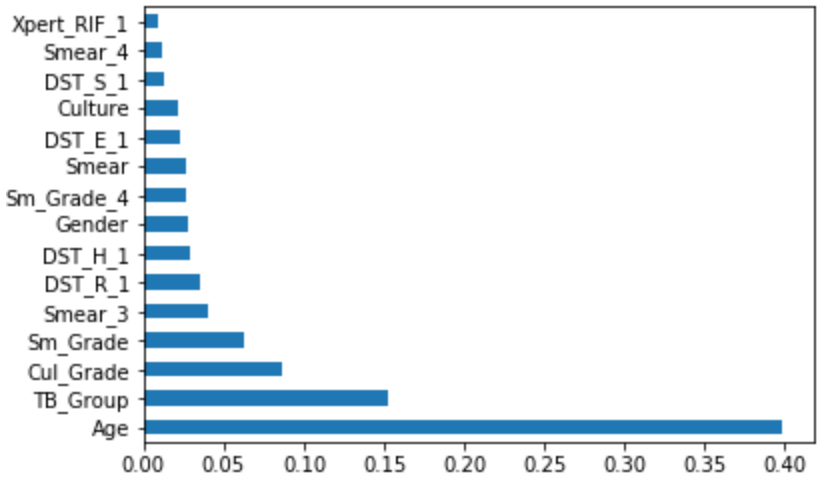


Figure A5. Top 15 Variables of Importance at 4 Month Time Epoch

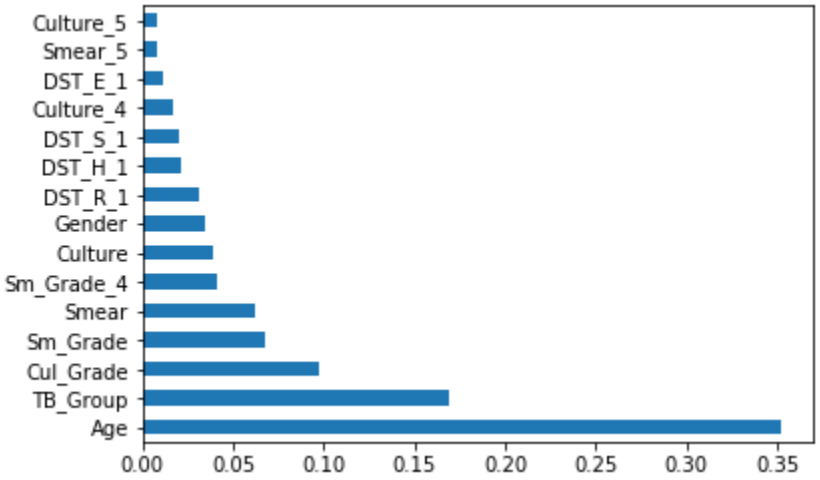


Figure A6. Top 15 Variables of Importance at 5 Month Time Epoch

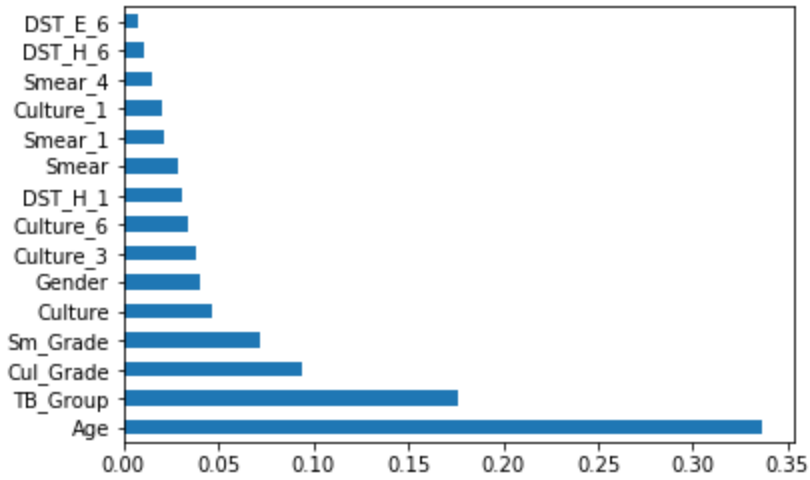


Figure A7. Top 15 Variables of Importance at 6 Month Time Epoch

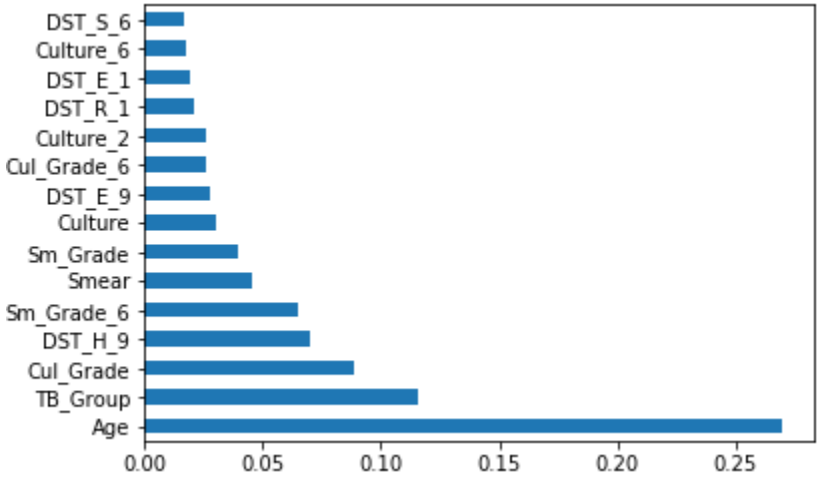


Figure A8. Top 15 Variables of Importance at 9 Month Time Epoch

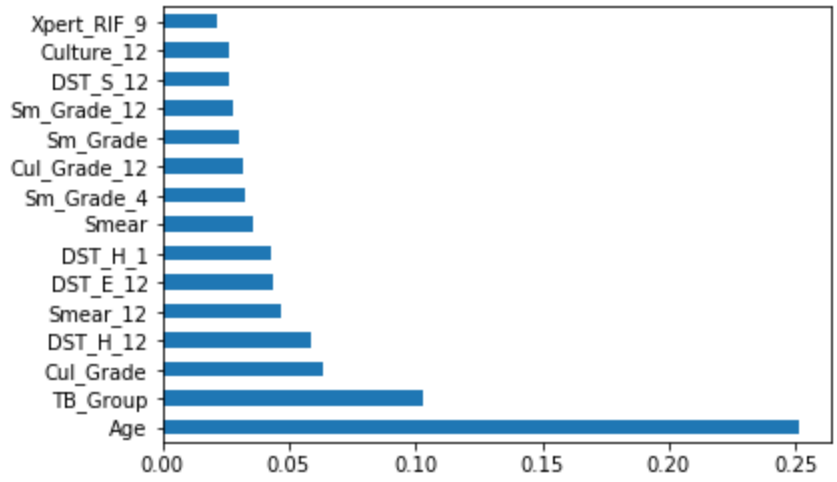


Figure A9. Top 15 Variables of Importance at 12 Month Time Epoch

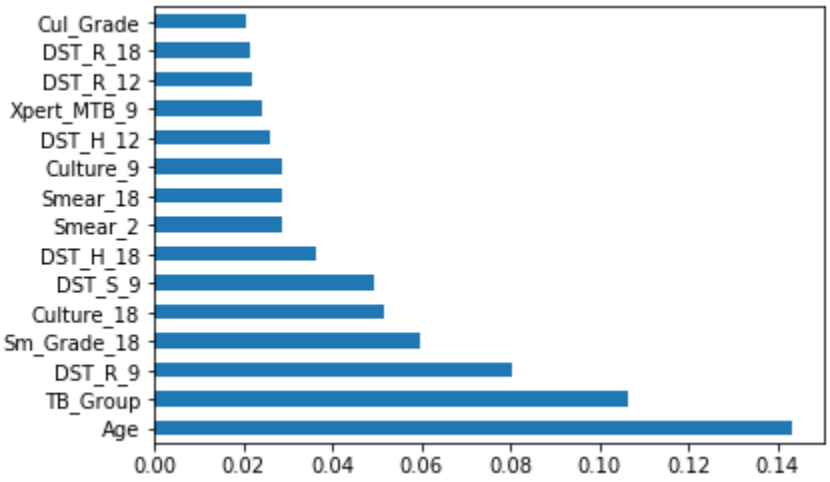


Figure A10. Top 15 Variables of Importance at 18 Month Time Epoch

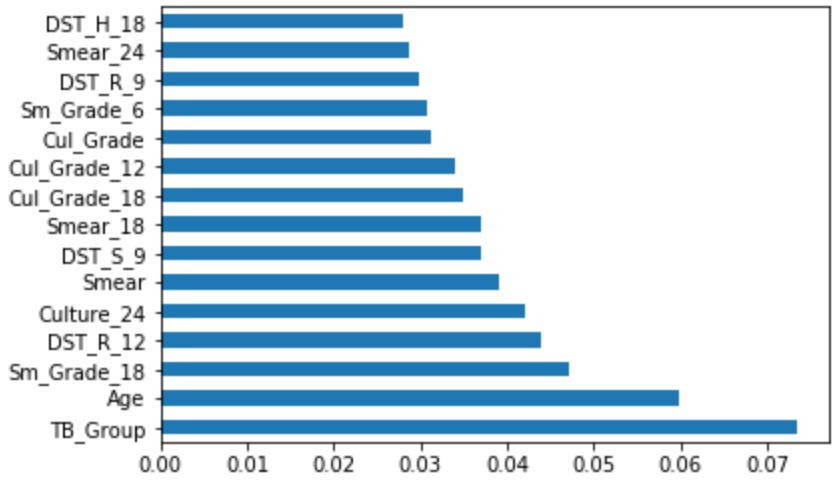


Figure A11. Top 15 Variables of Importance at 24 Month Time Epoch