NAME OF THE STUDENT: GUNJAN DESHPANDE

PROGRAM ENROLLED: B.TECH BIOINFORMATICS AND DATA SCIENCE

ROLL NUMBER: BID 19006

TITLE OF THE PROJECT PROPOSAL: AI & MACHINE LEARNING ANALYSIS OF CAPTAIN OF ALL THESE MEN OF DEATH - TUBERCULOSIS

D Y PATIL DEEMED TO BE UNIVERSITY SCHOOL OF BIOTECHNOLOGY & BIOINFORMATICS NAVI MUMBAI

PART A : GENERAL INFORMATION

1) Project Title: AI & ML Analysis of The Captain of all these Men of Death - Tuberculosis
2) Priority Area (Proposed area of Work):Drug susceptibility testing and Software for docking target
3) Duration: 2.5 Years: 6+Months
4) Total Project Cost: Rs._____Lakhs
5) Project Summary- The Captain of all these Men of Death- Tuberculosis

This was the name given by John Bunyan to Tuberculosis. In this project we will be first performing the Drug Susceptibility Tests: The Absolute Concentration Method, The Resistance Ratio Method and The Proportion Method Identification Tests. In order to distinguish between different mycobacterial species as well to perform drug susceptibility and identification tests, culture examination becomes a necessity. Culture of sputum provides definitive diagnosis of tuberculosis by establishing the viability and identity of organisms. However, compared to other bacteria, which typically reproduce within minutes, M.tuberculosis proliferates extremely slowly (generation time 18-24 hours).

Materials required for the same would-be important task like Preparation of 1%CPC-NaCl : 1gm of cetylpyridinium chloride and 2gms of sodium chloride are dissolved in 100ml of sterile distilled water and distributed in 5 ml aliquots in sterile McCartney bottles. The stock solution should be stored in dark, away from sunlight at room temperature. Mucoid/mucopurulent sputum specimen consists of recently discharged material from the bronchial tree, with minimum amounts of oral or nasal material. The sputum specimen should have volume of approximately 5ml. Preparation of Sterile 4% NaOH solution: Weigh 10 grams of Sodium Hydroxide pellets and dissolve in 250ml of distilled water in a conical flask (500 ml capacity); sterilize in solution cycle in an autoclave at 15 psi for 20 min. Inoculation Procedures: Two slopes per specimen are inoculated each with one 5 mm loopful of the centrifuged sediment, distributed over the surface.

An additional slope containing pyruvate may be used to identify M. bovis. Bottle caps should be tightened to minimize evaporation and drying of media. Care should be taken to avoid using red hot loop and loop should be cooled before inoculation.

Also, we will be doing research work on Ayurvedic formula: a clinical study that evaluated the efficacy of Bhringarajasava found that the Ayurvedic formula provided relief from pain, fever, appetite loss, weight loss, breathing difficulty, and coughing. How to use Bhringarajasava Bhringarajasava 30ml mixed 30ml of water thrice a day (entire duration of treatment + additional 6,8 months). Review of various studies that appeared in the Journal of Intercultural Ethnopharmacology found that Ashwagandha can protect against side effects of TB drugs, also increasing their efficacy. One of the studies reviewed also proves that Ashwagandha can provide relief from symptoms like weight loss. Researchers investigating the effects of combined treatment with Ashwagandha and Chyawanprash also observed improvements in body weight, reduction in severity of symptoms, improvement in liver health, and better recovery. We will also be performing Biochemical tests by preparing reagents as indicated and check the expected biochemical test response by using appropriate positive and negative controls. Last but not the least Quality Assurance Programme will be performed as Quality assurance with regard to tuberculosis bacteriology is system designed to continuously improve the reliability, efficiency and use of the tuberculosis laboratory services. In order to achieve the required technical quality in laboratory diagnosis, a continuous system of quality assurance needs to be established.

6) Keywords:

Tuberculosis, Drug, Dry lab, Wet lab, Ayurveda, MDR and XDR.

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PART B : TECHNICAL DETAILS OF PROJECT

7) Introduction

a) Details of the project focusing on field demonstration with little R&D component.

Citing evidence from observations in humans, work in experimental animals, and inferences from related studies in other fields, the authors note that a "wealth of ecological associations link TB with malnutrition in populations affected by famine, war, natural disasters, poverty, mass migration, and confinement in prisons or ghettos." On a population basis, malnutrition ranks as the risk factor most commonly linked with TB, according to the forthcoming "Expanding the Global Tuberculosis Control Paradigm." Still, "the evidence [for that association] in humans is surprisingly thin from the perspective of scientific rigor," write J. Peter Cegielski and David N. McMurray in a review of human and animal studies published in the March 2004 issue of the International Journal of Tuberculosis and Lung Disease.

Citing results from survey of 4,000 TB cases across several European countries, published in the May 2007 issue of Emerging Infectious Diseases, Giovanni Battista Migliori, director of the WHO Collaborating Centre for TB and Lung Diseases, says XDR TB's mortality rate is up to 5 times greater than that of MDR TB.

It was previously thought that XDR TB, once acquired, might not be infectious beyond hospitals and other clinical settings. XDR TB bacteria were believed to be too weak to be broadly transmissible, presumably because the bacteria are so mutated that they're generally unhealthy.

At the national level, governments should take steps to create research-enabling environments that nurture and facilitate TB R&D. This will entail:

• developing country-specific TB research agendas and strategic plans to expand TB research at the country level through capacity-building and multisectoral partnerships;

• activating domestic financing mechanisms to increase funding for TB R&D; and

• streamlining regulatory processes for the expedited review of clinical trials and other research activities in order to advance research.

b) Details indicating how the project will benefit the population/ environment or a global phenomenon.

For centuries, TB has been linked anecdotally with environmental risk factors that go hand-in-hand with poverty: indoor air pollution, tobacco smoke, malnutrition, overcrowded living conditions, and excessive alcohol use. One of the world's leading killers, tuberculosis (TB) is nearly as old as humanity itself; fossilized evidence of this lethal infection has been found in a *Homo erectus* skeleton half a million years old. But look to a modern hospital in a developed country, and you'd be hard pressed to find more than a few cases TB drugs are a two-edged sword, says Tommie Victor, a professor of health sciences at Stellenbosch University in South Africa's Western Cape Province. They destroy the bacterium, but can also select for resistant bacteria against which those drugs are then ineffective. In the 1970s, the drugs had the upper hand, and TB seemed to be in decline. But funding and interest in TB control programs also declined, says Victor, and for the following 20 years no systematic monitoring of drug resistance was carried out. The situation changed dramatically with the arrival of HIV/AIDS in the 1980s, when transmission of TB and outbreaks of multidrug-resistant (MDR) TB increased around the globe.

Drug-susceptible TB cases can be cured with a standardized 6-month regimen of first-line antibiotics administered using the "directly observed treatment, short-course," or DOTS, protocol. Under the DOTS protocol, patients take their daily medication in the presence of a health care worker to ensure compliance. Considered one of the most effective clinical programs ever, DOTS is a cornerstone of the WHO Stop TB Strategy, which by 2015 aims to reduce the incidence of new TB cases to 50% of 1990 levels. (The long-term goal is to reduce annual TB incidence to fewer than 1 case per 1 million people by 2050.)

Confronting Environmental Risk Factors:

Those who argue in favor of risk factor interventions say these strategies offer broad population-level benefits. Consider smoking cessation, says Donald Enarson, senior advisor to the

International Union Against Tuberculosis and Lung Disease, an independent research and outreach group in Paris. Although its capacity to trigger TB among individuals is surely less than that of HIV/AIDS, smoking might actually trigger more TB cases on a population basis because people who smoke far outnumber those infected with HIV, he says.

When considering these factors, it's important to distinguish infection risks (i.e., situations that bring people who have TB in close contact with others) from those that accelerate disease progression among people who are already infected. For 40 years, crowding has been cited as a crucial infection threat in both industrialized and nonindustrialized countries. But this factor's unique contribution to TB risk is hard to quantify, concedes Lönnroth. "The relative risks [from crowding] vary with housing quality, TB prevalence in the community, and also with access to health care, which is associated with chance of early cure of infectious cases," he says.

Conserdering all these factors in mind we will be finding solutions for Making ethically appropriate treatment decisions in absence of DST and Ethical approach to scaling up MDR/XDR-TB treatment.

c) Objectives:

- Discuss reasons for and challenges with gap between diagnosis and treatment of drug-resistant TB and need to address this gap
- Explain the benefits of drug susceptibility testing in the absence of drug-resistant TB treatment
- Demonstrate why education and counselling forms an essential component of patient care in the absence of drug susceptibility testing (DST) and appropriate treatment for drug-resistant TB

Solution:

- Making ethically appropriate treatment decisions in absence of DST.
- Ethical approach to scaling up MDR/XDR-TB treatment

Vaccination of our livestock against TB and routine screening of livestock (e.g., on a yearly basis at the farms and also at the animal fairs) should be made mandatory. Our fight against TB will be incomplete without considering this zoonotic aspect of this deadly disease. To eliminate the potential zoonotic sources of TB, pasteurization of milk before marketing and organized goat/sheep abattoirs should be made mandatory under law; where milk samples and carcasses can be routinely tested/examined for TB; and the cause of TB possibly traced to the infected herds.

8) **Work Plan**

a) Methodology-

Sources of data :

The analyses of tuberculosis (TB) research funding in this policy paper drew on publicly available data from a number of sources. Estimates of TB research and development expenditures came from the survey data collected by the Treatment Action Group for its series of reports on global funding for TB research. The G-FINDER report produced by Policy Cures Research was the principal data source for expenditures in other global health R&D areas. Burden of disease measures (e.g. disabilityadjusted life-years) came from the Institute for Health Metrics and Evaluation's Global Burden of Disease study. Information on the outputs of new product pipelines for TB, HIV and malaria was collected from the public records of the United States (US) Food and Drug Administration, the European Medicines Agency and the WHO prequalification programme. Macroeconomic data on gross domestic product and measures of inflation came from the World Bank, the US Bureau of Labor Statistics, and the US Bureau of Economic Analysis. The United Nations Educational, Scientific and Cultural Organization (UNESCO) provided estimates of gross domestic expenditure on research and development (GERD).

How were data on TB R&D expenditures collected?

Each year since 2005, TAG has estimated global funding for TB R&D by surveying TB research funders across the world. The survey is sent to more than 200 known and potential funders of TB R&D in over 25 countries, and is available in six languages. Funders are asked to report disbursements made in a given fiscal year and denote spending by six categories of research: basic science, diagnostics, drugs, vaccines, operational and implementation research, and infrastructure/ unspecified projects. In addition, funders indicate whether they belong to the public, private, philanthropic or multilateral sectors. Private-sector companies may report anonymously in order to protect strategic and other proprietary information, although many participate in the survey openly. Survey recipients also note whether expenditures represent funding given to others, funding received from others or self-funded research.

How were the data on TB R&D expenditures handled?

The TAG survey asks recipients to report spending in local currencies, which TAG converts into US dollars using the interbank exchange rates published by OANDA. All dollar figures represent disbursements, or the actual transfer of funds, rather than commitments or budgetary allocations for future years. For the following analyses, all figures are reported in current (i.e. nominal) dollars of a given year unless otherwise noted. Where adjusted for inflation, the adjustment was made using the biomedical research and development price index (BRDPI), a measure of how much the budget of the US National Institutes of Health (NIH) must change each year to maintain purchasing power. The US Bureau of Economic Analysis developed and maintains the BRDPI for the NIH Office of Budget, and the BRDPI is commonly used as a measure of inflation for biomedical research in related studies.

Limitations:

Limitations also apply to the TB R&D funding data that form the heart of the following analyses. The comprehensiveness of estimates of TB R&D expenditure depends on the proportion of organizations funding TB research that participate in the TAG survey. This proportion cannot be calculated, because the true number of TB research funders worldwide is unknown. To address this limitation, TAG takes several steps to ensure that the survey has a wide reach and high yield. First, the sampling frame is updated annually, and each year TAG conducts outreach to organizations that have not previously participated in the survey. Most of these organizations do not have known TB R&D investments, but either support health research generally or invest in related diseases. Second, given the high degree of concentration of TB research funding, TAG makes a special effort to collect data from the 30 largest funders from one year to the next. In any given year, the top 30 funders of TB R&D account for more than 90% of known total spending. On average, the survey achieves a 95% response rate from the top 30 funders. Finally, 25 organizations have participated in each year of the TAG survey since 2009 and comprise a “core funders” group. For each of the following analyses, data were first analysed using the full TAG dataset and then re-analysed using only information from the 25 core funders to see whether the results differed. In all cases, the two datasets produced similar results.

b) Organization of work elements

- In- Silico analysis of TB
- Research of effect of TB on kids, adults, old people.
- Software for docking target , time , dry lab and wet lab experiments.
- Research /benefits and monitoring & purification of Ayurvedic medicine- wet lab experiment
- Analyzing the Biological derivatives of TB
- Perform Model Evaluation.
- Perform Model Performance Comparison.

c) Time schedule of activities giving milestones.

S.No	Name of Milestone	Expected Start (Month/Year)	Expected Completion (Month/Year)
1.	In- Silico analysis of TB	January 2023	March2023
2.	Wet-laboratory experiment	April 2023	September 2023
3.	Research /benefits and monitoring & purification of Ayurvedic medicine	October 2023	December2023
4.	Software for docking target	January 2024	March 2024

9) Details of raw materials/local resources needed in the project and/or available.

- Sputum smear
- 1%CPC-NaCl
- 4% NaOH
- 1 high end system from the school
- 1ml SDW with six 3 mm glass beads + 1 loopfull (3 mm internal diameter) of culture
- Hard-Disk to store the huge Dataset
- 1% aqueous barium chloride and 1% sulphuric acid (AR)

10) Indicate whether the project will help in maintaining environmental/ecological balances.

At the national level, countries should take steps to create research-enabling environments that nurture and facilitate TB R&D. This will involve reducing structural impediments to research where they exist, increasing TB research capacity, developing national strategic plans for TB research, and activating domestic research financing mechanisms. In creating research-enabling environments, countries can seek guidance from the detailed blueprint in the WHO Global action framework for TB research (the WHO Action framework). Priority steps to be taken include:

Streamlining regulatory processes for the review of clinical trials and other research activities in order to expedite research. This can involve creating a streamlined, predictable process for ethics and regulatory approvals, and providing a simple pathway for the transfer of biological samples, study drugs and other equipment in and out of a country. Lack of such logistical considerations can increase the cost and complexity of clinical trials and result in avoidable delays. The need to address these issues has been raised by many funders, industry groups, scientists and advocates as an important priority. The particular challenges will vary by setting, and there is much that countries can learn from one another in creating regulatory and administrative frameworks that facilitate research while ensuring the safety of research participants. At a minimum, countries should develop or enhance their capacity to evaluate products studied elsewhere, to allow for their importation for the benefit of their constituents.

11) Details of employment/revenue generation through the project in long term/development of entrepreneurship

The strategy should determine mechanisms to facilitate collaborations between researchers in different countries around common research goals, and promote multisite and multidisciplinary research. This should rely on existing or new international TB research networks and consortia dedicated to investigating specific questions of importance that combine discovery, preclinical, clinical and operational research. Such knowledge networks could complement existing international TB research networks by focusing on understudied areas. As outlined in the WHO Global action framework, these networks could be coordinated from a hub located in an institution with expertise in the relevant focus area.

A priority-setting exercise could improve the coherence of global and national TB R&D investments by helping to focus resources on pressing needs or neglected research areas (or both). The International TB research roadmap, published by WHO and the Stop TB Partnership in 2011, would offer a natural starting place. The Roadmap seeks to identify key research questions that need to be answered in order to achieve TB elimination, with a view towards encouraging investment in these topics. Updating the Roadmap in the context of the goals and targets of the End TB Strategy to reflect recent advances and the current state of TB science could be among the first priorities of the new global strategy for coordinating and advancing TB research. Importantly, the updated Roadmap should be linked with the wider landscape of country-specific TB research agendas, with special efforts to address socioeconomic barriers that are critical to reaching the missing TB cases, and mitigating the health and social impact of TB.

12) References in APA style

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PART C: BUDGET ESTIMATE SUMMARY

Items	**Budget**			
	Year 1/ months	**Year 2/ months**		**Total**
A. **Non-Recurring :** (1) Equipment (2) Plant & Machinery	-	-		
Sub-Total (A)	5000	1000		6000
B. **Recurring :** 1) Consumables 2) Travel 3) Other Costs/ Contingencies 4) Human Resource 5) Institutional Overhead Charges	-			
Sub-**Total** (B)	2500	3000		5500
Grand Total **(A + B)**				**11,500**