



Review

Precision medicine in resistant Tuberculosis: Treat the correct patient, at the correct time, with the correct drug



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SUMMARY

Human genomic mapping has advanced molecular medicine health care and created a transformative paradigm shift towards Precision Medicine. In 2015, President Obama launched the PM initiative, encapsulated as “unique individualized data-driven treatments”. Since then, this field is rapidly advancing both curative treatment and disease prevention by accounting for both individual and environmental variability. While a substantial evidence for accelerating adoption of Precision Medicine in other spheres of medicine exists, application of Precision Medicine in infectious diseases is far more complex.

One of the most warranted applications of precision healthcare is in the management and treatment of Drug-resistant Tuberculosis. Application of Precision Medicine to Drug-resistant Tuberculosis could potentially change the landscape of treatment and prevention of a disease affecting vulnerable patients in impoverished communities. Poorly diagnosed and treated Drug-resistant Tuberculosis not only leads to increased mortality and morbidity but also increased transmission of DR-TB strains, fuelling ongoing high incidence rates and further infection.

A Precision medicine model using individual clinical case histories used in conjunction with Mycobacterium Tuberculosis infection genomic data will better guide health care practitioners in more appropriate drug selection, and an individualized management approach. This viewpoint deliberates the intricacies of adopting a PM approach in the management of DR-TB. If applied correctly, we postulate that the research, application, and deployment of PM in DR-TB management may address the fundamental rule of PM in infectious disease: *to treat the correct patient, at the correct time, with the correct drug.*

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Introduction

Human genomic mapping has advanced molecular medicine health care and created a transformative paradigm shift towards Precision Medicine (PM). By harnessing the data generated by the dynamic interplay between genomics, metabolomics, proteomics, and microbiomes, the “one size fits all”, approach to treatment is questioned. This novel bioinformatics and machine learning-approach is rapidly evolving allowing the design of more accurate treatment modalities, no longer aimed at just disease, but tailored to individual patient’s health profile.

In 2015, President Obama launched the PM initiative, encapsulated as “unique individualized data-driven treatments”. Since then, this field is rapidly advancing both curative treatment and disease prevention by accounting for both individual and

environmental variability. The National Institute of Health (NIH) defines PM as a new treatment and prevention method based on the understanding of the individual gene, environment, and lifestyle.¹ In clinical literature reviews, the term “precision” has been used interchangeably with “personalized” and “individualized”.^{2,3} Although these terms are similar, “precision” emphasizes the integration of diagnosis, prevention and treatment strategies whilst considering individual variability.

The concept of precision-based medicine is not new. The PM model has been applied to curative and preventative health care in many civilizations. Avicenna, a famous traditional Persian medicine scientist, practicing about 1000 years ago dedicated a chapter in his “The Canon of Medicine” highlighted several factors relevant to the choice and prescription of medication in the fashion of personalized medicine. Avicenna said that “Any medication will have different effects on different bodies, organs of a person, at two different time points in one person’s body, and in one organ at two different time points”.⁴

This concept has been applied to many everyday situations in current medical practice. Everyday use of precision healthcare

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occurs with prevention of Rhesus disease in newborns, detecting genetic basis for hypersensitivity in prior to Clopidogrel and Maraviroc use.⁵ Furthermore, selection of appropriate and efficacious drugs based on specific gene mutations is now common practice in routine care within public health programmes, such as detecting anti-microbial sensitivity to bacteria and fungi, including pre-antiretroviral drug resistance and genetic susceptibility to cancer therapy.⁶ Furthermore, the role of PM in customizing individual care in rare conditions has been established in sub-specialties like molecular oncology rheumatology and clinical genetics.⁷ Wilson's disease and cystic fibrosis have long adopted PM approaches in clinical care.

Donor agencies such as the NIH continues to invest in large research programmes aimed at optimizing PM use in these conditions for improved health outcomes.^{8,9} While a substantial evidence for accelerating adoption of PM in other spheres of medicine exists, application of PM in infectious diseases is far more complex. This is largely due to the magnitude and impact of infectious diseases such as TB, malaria, and HIV; the epidemiological need for control of these diseases using effective therapeutic strategies while limiting spread of drug resistance, limited availability of drugs, and the need to prolong lifespan of available drugs.^{10,11} The application of these diagnostic advances in genomics and the subsequent generation of high-value bioinformatics data is changing the landscape for public healthcare.

Can we apply PM in DR-TB?

One of the most warranted applications of precision healthcare is in the management and treatment of drug-resistant Tuberculosis (DR-TB). Application of PM to DR-TB could potentially change the landscape of treatment and prevention of a disease affecting vulnerable patients in impoverished communities. Poorly diagnosed and treated DR-TB not only leads to increased mortality and morbidity but also increased transmission of DR-TB strains, fueling ongoing high incidence rates and further infection.¹² Individual clinical case histories used in conjunction with MTB (*Mycobacterium Tuberculosis* infection) genomic data will better guide health care practitioners in more appropriate drug selection, and an individualized management approach. This has potential to translate to optimized patient outcomes while possibly reducing side effects by excluding potentially toxic drugs.¹³ This viewpoint deliberates the intricacies of adopting a PM approach in the management of DR-TB. If applied correctly, we postulate that the research, application, and deployment of PM in DR-TB management may address the fundamental rule of PM in infectious disease: to treat the correct patient, at the correct time, with the correct drug.

The role of Biobanks

The establishment of integrated, accessible, searchable genomic data from reputable biobanks, inclusive of data from high prevalence settings is critical to support a PM approach for DR-TB. Benchmarks from successful biobanks ranges from the all-inclusive "All of Us Research Program" biobank, the Cambridge Blood and Stem Cell Biobank (CBSB) and the Juvenile Dermatomyositis National Cohort Biomarker Study and Repository for Idiopathic Inflammatory Myopathies.^{14–22} These biobanks have catalyzed landmark studies that have shifted our understanding of disease pathogenesis, prevention and treatment. Biobanks have also impacted on biotechnological and medical innovation as advances in technology have resulted in cost reductions in information technology, data storage and sequencing of samples.

Hence, the goal of a DR-TB biobank should be to further understand the host genetic and environmental factors that enhances susceptibility to DR-TB disease and adverse treatment outcomes.

Such a biobank should be made accessible to researchers globally, particularly in areas with high disease burden. In addition, it should aim at developing molecular-based classification and diagnostic procedures. A DR-TB biobank must also assist in understanding the correlation between an individual patient's genotype or phenotype and specifically drug treatment response. Benchmarking on existing biobanks we suggest the development of a DR-TB accordingly (Table 1).

The role of patients should also be taken into consideration. Recent literature has demonstrated that patients are no longer viewed as donors, but they are now viewed as actual collaborators in the concepts, design, development and the ongoing operation and governance of biobanks.²³

In order to obtain reliable genomic correlations with the state of disease, high volumes of samples need to be biobanked. The actual number of samples needed to provide statistically significant results will vary across different study designs and cohorts. The only way to acquire such high numbers within a reasonable time-frame would be to facilitate multi-centre research. This will prove valuable as biomarker/profile descriptions should be documented across different populations and not restricted to one population. Presently, organized *Mtb* biobanks are scanty.²⁴ Existing TB biobanks created from specific studies include the TB Immunology Group Research Tissue Bank, the Global Alliance for TB Drug Development and the World Health Organization Special Programme for Research and Training in Tropical Diseases.^{25–27} Although a range of samples has been collected, differing data are collated, and the limitation is that most of these studies do not have sets of correlated phenotypic, genomic and clinical data. Currently, the CRYPTIC project and ReSeqTB are multinational programs that aim to collect and curate whole genome sequencing data with corresponding phenotypic DST and clinical outcome data, from both the public and private sectors.^{28,29}

Analysis of genomic data

The analysis and interpretation of the volumes of data generated from sequence analysis remain a major restriction to many laboratories, as skill and expertise to interpret such results is very limited. To assist with this challenge, investigators have therefore utilized sequencing data to compile libraries of drug resistance mutation databases and online tools, such as TBdreaMDB, MUBII-TB-DB, and others, to rapidly analyze raw sequence data and predict resistance.^{30–32} Although these tools exist, there are limitations, and periodic updates must regularly be performed to include novel resistance-conferring mutations as discovered.

For the analysis of data from biobanks to be successful, protocols that define the use of biobanks for TB are essential. These protocols should adopt common technical standards for specimen collection, storage, annotation, long-term preservation of biospecimens and for data collection and management. At the outset, the biobank will require a substantial amount of resources. Procedures should be put in place for prospective collection of samples. In addition, networking via a multidirectional flow of information, expertise, and biological materials should exist between TB centers and research institutions. Samples must be made available to allow efficient research to be conducted, for new libraries to be created and current libraries expanded.³³ This will enable variation across global populations and will impact and influence clinical decision making. Provision must also be made for adequate follow-up and retrieval of information and clinical data on participants.

Clinical decision making using genomic data must involve the interplay between existing knowledge, individualised patient details, clinical care and experiential learning. In order to define and translate clinical genetics into healthcare, a PM multidimensional model is required. In order to advance PM, genomic medicine

Table 1
Characteristics of a DR-TB BIOBANK.

Details of Biobank	Details of donors	Details of clinical samples
<p><i>Biobank existence</i></p> <ul style="list-style-type: none"> • 1–4 years • 5–9 years • ≥10 years <p><i>Biobank contents</i></p> <ul style="list-style-type: none"> • Biological samples only • Genomic data only • Both biological samples with genomic data <p><i>Area of research</i></p> <ul style="list-style-type: none"> • Infection or prevention studies • Transmission studies • Genetic studies <p><i>Sample size</i></p> <ul style="list-style-type: none"> • 500–1000 • 1001–10 000 • 10 001–100 000 • ≥100 000 <p><i>Cohort areas</i></p> <ul style="list-style-type: none"> • Local epidemiology • Diverse geographical regions 	<p><i>Age of donor</i></p> <ul style="list-style-type: none"> • Adults only • Children only • Both adults and children <p><i>Medical History</i></p> <ul style="list-style-type: none"> • Immunization history • INH prophylaxis • Risk Stratification • Concurrent medication <p><i>Previous History of TB</i></p> <ul style="list-style-type: none"> • Date of Diagnosis • Susceptible versus resistant • Anti-TB regimen • Completed or not? • Evidence of culture conversion <p><i>Single disease or Co-existing diseases</i></p> <ul style="list-style-type: none"> • HIV co-infection • Auto immune diseases • Chronic diseases 	<p><i>Type of sample</i></p> <ul style="list-style-type: none"> • Sputum, blood, lymph node aspirates, urine, pleural fluid, gastric washings, cerebral spinal fluid, joint fluid, bone marrow aspirates, biopsy material, stool and urine <p><i>Point of sample collection</i></p> <ul style="list-style-type: none"> • Prior to anti-TB medication or antibiotics • Whilst on anti-TB medication or antibiotics • After anti-TB medication completed <p><i>Microbiological data</i></p> <ul style="list-style-type: none"> • Microscopy • Culture • Immunochromatographic/Rapid antigen tests • Susceptibility testing • Microscopic observation drug susceptibility (MODS) assays • Interferon gamma tests • Serology <p><i>Molecular data</i></p> <ul style="list-style-type: none"> • LPA tests • Xpert MTB/RIF assay • Sequencing data • <i>Mtb</i> (<i>Mycobacterium Tuberculosis</i>) strain derivative characterization

specialists will be required to work with a multidisciplinary team including clinicians, infectious disease specialists, microbiologists, pharmacists, counsellors and biobanker managers to create new clinical workflows. As genomic research becomes more relevant to clinical medicine, understanding and learning will be the ultimate step to translate biobanking knowledge to actual practice.

2018 is heralded as the year of Artificial intelligence (AI).³⁴ New developments and enhancements with machine learning algorithms should lead to more efficient bioinformatics support which collates data in real-time against published sequencing data, providing immediate clinical significance and precision-guided therapeutic options.³⁵ This big data can be refined with bio-computational and bio-informatics analyses with machine learning algorithms that have the power to discriminate DR-TB genetic mutations (which can occur in isolation or together) and push DR-TB treatment into a new frontier in PM. Data networking with other similar biobanks globally can allow for the use of machine learning and artificial intelligence for easily accessible, real-time analysis and interpretation.

Role of PM in stratification of TB disease risk and for targeted treatment and prevention

Patient stratification can be based on biomarkers from the host and /or the pathogen (*Mtb*). Studies have demonstrated that biomarkers can provide information that may guide clinical decision making. Table 2 lists selected studies that have utilized the concept of biomarkers in TB. Host Biomarkers can enable the clinician to either determine the risk of disease, diagnose current or past infection, identify progression and severity of any disease detected and predict response to treatment. These biomarkers may play a critical role in stratifying patients according to LTBI (latent TB infection) vs Active *Mtb* Infection, resistant vs susceptible *Mtb* infection, cure vs possible reactivation. In this manner, an early, precise diagnosis can be achieved. In addition, pathogen biomarkers such as strain type may predict progression and severity of

existing disease. Using a biomarker selection model may enable guided treatment strategies that prevent adverse events and lead to favorable outcomes.

Precision management

Despite recent advances in TB diagnostics, the gold standard for diagnosing DR-TB remains conventional culture-based drug susceptibility testing (DST). For PM to improve the current method of DR-TB diagnosis, additional synergistic TB diagnostics that allow for timely and accurate detection must be incorporated into a PM model. Genetic based diagnostics can determine both known resistance-associated loci and other loci on the MTB genome and thus create a more detailed patient-level drug susceptibility testing. The use of next-generation sequencing and computational technology platforms are now more affordable and accessible. The costs associated with researching and deploying PM protocols in the diagnosis of DR-TB are now more affordable and this is a key factor in driving the use of PM in DR-TB research and management forward.⁵⁴

Currently, MDR-TB regimen composition and duration, as well as the efficacy of drugs is based primarily on observational studies. Limited randomized controlled trials have been conducted, and therefore evidence for the use of these drugs in the regimen is graded as an overall quality of low or very low. A paradigm shift from the “one size fits all” treatment approach to a PM approach can enable the design of optimal therapeutic strategies for individual patients. These regimes can be created with a combination of existing drugs, as well as drugs in the pipeline, that are tailored to benefit the patient with less side effects and drug interactions. Although these individualized treatment regimens may improve patient management, experts in the field have warned that a targeted use of anti-TB drugs may inadvertently contribute to the emergence of drug resistance.¹³ It is important to note that even with the best clinical care, a patient that is being treated with anti-TB

Table 2
Discovering biomarkers of diagnosis, risk and response in MTB: a subset of studies.

Study group	Sample type	Finding	Ref
Biomarkers for diagnosis			
To differentiate patients with Active MTB infection vs LTBI infection	Blood	<ul style="list-style-type: none"> Measurements of EGF, VEGF, sCD40L, MIP-1β, TGF-α or IL-1α in supernatants from QuantiFERON assays can be developed as a rapid diagnostic for active TB. 	Chegou (2009) ³⁶
To determine the presence of a neutrophil-driven blood transcriptional TB signature	Blood	<ul style="list-style-type: none"> There exists a role of type I IFN-$\alpha\beta$ signaling in the pathogenesis of TB 	Berry (2010) ³⁷
The identification of TB biomarkers in human urine samples	Urine	<ul style="list-style-type: none"> Urine biomarkers hold promise for the development of new point-of-care diagnostic 	Young (2014) ³⁸
To differentiate patients with Active MTB infection vs LTBI infection	Blood (Proteomic analysis)	<ul style="list-style-type: none"> Antibody Fc functional profiles, selective binding to FcγRIII, and distinct antibody glycosylation patterns are unique in patients with LTBI and can be utilized as a diagnostic. 	Lu (2016) ³⁹
Diagnostic performance of a seven-marker serum protein biosignature for the diagnosis of active TB	Blood	<ul style="list-style-type: none"> Identification of a seven-marker host serum protein biosignature for the diagnosis of TB disease irrespective of HIV infection status or ethnicity in African primary healthcare clinic attendees. 	Chegou (2017) ⁴⁰
Quantification of circulating <i>Mtb</i> antigen peptides.	Blood	<ul style="list-style-type: none"> Antigen peptides allow rapid diagnosis of active disease and treatment monitoring 	Liu (2017) ⁴¹
New synthetic lipid antigens for diagnosis of TB		<ul style="list-style-type: none"> New synthetic lipid antigens allow rapid serological diagnosis of TB 	Jones (2017) ⁴²
Biomarkers of Risk			
To differentiate active infection from Healthy patients	Blood	<ul style="list-style-type: none"> The presence of HLA-DQB10503 was shown to be significantly present in 78 patients with TB, but not present in patients without TB 	Goldfield (1998) ⁴³
Risk of developing PTB (Pulmonary Tuberculosis) in HIV positive patients	Blood	<ul style="list-style-type: none"> HLA DRB1 homozygosity among HIV-positive patients is associated with a reduced risk of developing PTB but increased risk of Pleural effusions 	Louie (2004) ⁴⁴
HIV infected adults on ARV's at risk of PTB	Blood (PMBC)	<ul style="list-style-type: none"> The ratio of monocytes to lymphocytes (ML ratio) identified patients at risk of Active PTB who were initiated on ARV's 	Naranbhai (2014) ⁴⁵
Risk of developing active TB	Blood	<ul style="list-style-type: none"> Whole blood TB risk signature of 16 Genes prospectively identified people at risk of developing active TB Possibility for targeted intervention to prevent the disease. 	Zac (2016) ⁴⁶
Risk of developing TB	Blood	<ul style="list-style-type: none"> T-cell activation is an immune correlate of risk in BCG vaccinated infants 	Fletcher (2016) ⁴⁷
Biomarkers of response			
Risk of development of active TB	Blood	<ul style="list-style-type: none"> Screening of blood RNAseq profiles identified signatures of Active TB risk > 1 year before diagnosis 	Petruccioli (2016) ⁴⁸
Risk of developing TB	Blood	<ul style="list-style-type: none"> Enhanced expression of T-Cell activation markers with high risk of developing TB Conversely high levels of Ag85A antibodies and high frequencies of IFN-gamma specific T-Cells were associated with decreased risk of TB Infection 	Petruccioli (2016) ⁴⁸
Risk of developing TB	Blood	<ul style="list-style-type: none"> CD27-IFN-gamma-CD4+ cells as a possible predictive marker of Active TB Infection. T-Cell responses to TB Latency antigens including heparin-binding hemagglutinin and DOSR-regulon-encoded antigens was also correlated with protection. 	Petruccioli (2016) ⁴⁸
Risk of progression of disease	Blood (PBMC)	<ul style="list-style-type: none"> Progressors had lower PBMC proportions of CD4+ T-Cells, NKT cells and B-Cells, higher levels of IL-18, lower gene expression of Bc12 and higher CCR7 levels 	Sutherland (2011) ⁴⁹
Risk of susceptibility to infection	Blood	<ul style="list-style-type: none"> HLA-DRB1 alleles differentially modulate the various cytokine responses to <i>Mtb</i> antigens in a susceptible host May influence the cellular and humoral immune responses to <i>Mtb</i> infection 	Selvaraj (2007) ⁵⁰
Patients with Active MTB disease	Blood	<ul style="list-style-type: none"> <i>Mtb</i>-specific CD8+ T cells are found in high frequency in infected individuals and are restricted predominantly by HLA-B alleles 	Lewinsohn (2007) ⁵¹
Patients with Active MTB disease vs un-infected patients	Blood (Transcriptomic analysis)	<ul style="list-style-type: none"> Active TB 664-transcript signature and a treatment specific 320-transcript signature significantly diminished after two weeks of treatment and continued to diminish until six months. 	Bloom (2012) ⁵²
Biomarkers of successful treatment response		<ul style="list-style-type: none"> Transcriptional signatures changes were readily detectable two weeks after treatment initiation. 	
F15/LAM4/KZN (KZN) family of <i>Mtb</i> Isolates that evolved from MDR to XDR	Clinical isolates (Proteomics analysis)	<ul style="list-style-type: none"> Demonstrated that this strain shows greater adhesion and invasion into host tissues 	Ashiru (2010) ⁵³

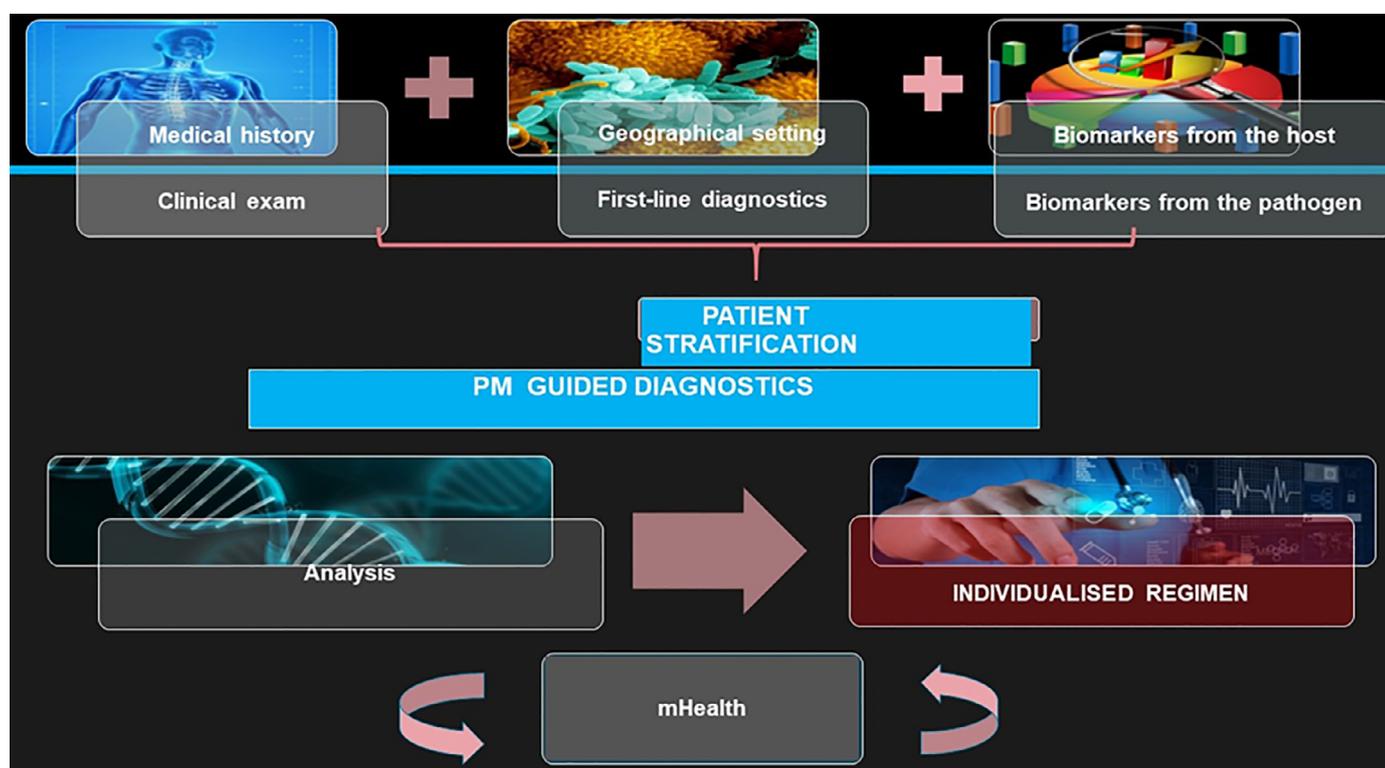


Fig. 1. A PM Model for DR-TB.

drugs for MDR-TB has a 44% risk of developing XDR-TB.⁵⁵ Although studies have demonstrated that resistance in new TB drugs are low, there has been emergence of resistance in repurposed drugs, such as linezolid.⁵⁶

A PM model should not only take the individual patient into consideration but also the geographical setting. Drug resistance varies across different settings and therefore outcomes from an individualized regimen will vary in different settings as well. An ideal PM model should comprise of several standardized regimens that are not only based on a drug resistance profile, but on a host of parameters that take the geographical setting, disease burden and health system infrastructure into account (Fig. 1). A computer algorithm can be used to determine allocation of patients to one of several individualized regimens. Selection for each category such as medical history, clinical examination, diagnostics, biomarkers from both the host and the pathogen etc., in a checklist format, with subheadings in a “drop-down box” format, can be fed into a computer algorithm that will utilize data analysis tools and bioinformatics based on existing evidence, to facilitate placement of a patient in the most suitable individualized regimen category (Fig. 2). Ultimately the algorithm should provide clear guidance on what drugs or drug combinations to use that support then best treatment outcome.

Once the PM model for diagnosis and management has been applied and the patient is placed into a category, incorporating mobile technology (mHealth) advances will also enable researchers to address issues such as treatment and adherence monitoring and surveillance at a personal level, with possible better treatment outcomes. Mobile technology can also assist in documentation of adverse effects and facilitate more rapid patient clinical reviews. Although mHealth studies evaluating different implementation strategies are limited, the added use of mHealth in a PM model may be highly beneficial in DR-TB.^{57,58}

Ethical considerations

A crucial ethical consideration for implementation of a PM driven TB service is the balance between individual versus public benefit.⁵⁸ On one hand, the ethics of having widespread access to PM technology in low-income high TB burden settings may be questionable given the limited formulary, high cost and poor availability of alternative therapies. Alternatively, failure to explore a PM derived approach to endemic infectious diseases will be a major limitation in developing new drugs, technologies and strategies aimed at mitigating the severe morbidity and mortality associated with these conditions

Despite this, the success of PM driven advances in therapeutics relies heavily on bio-ethical considerations that would potentially balance responsible, open access to specimens and biologically generated data against indiscriminate use of this resource for financial gains. Initially one needs to decide on who would sponsor the biorepository/database. Thereafter, there must be clarity on the ownership of samples and associated intellectual property rights. Would samples belong to the patient/participant in a trial, the researcher, the sponsor, or the state? Consent for long-term tissue storage, an important component of biobanking, will enable exposure of data and specimens to newer advances in scientific discovery – with anticipated benefits to the contributing population.^{59–61}

Ideally, a robust governance structure with representation from civil society, ethicists, religious bodies, the pharmaceutical sector and scientists, among others would be ideal in gatekeeping and access over biodata and repository. A steward/custodian of the database needs to be appointed. However, even in such a case there are still privacy concerns regarding gatekeepers’ access to patient records. Access to other parties must also be taken into consideration: Should access be given to other researchers, the private sector and health insurers also?

Check	General	Medical History	Clinical examination	First Line Diagnostics
<input checked="" type="checkbox"/>	Age	Existing medical conditions	Vital signs	Chest X-Ray
<input checked="" type="checkbox"/>	Gender	Previous history of TB	Lymphadenopathy	Sputum Microscopy
<input checked="" type="checkbox"/>	Address	Immunization history	General examination	HIV testing
<input checked="" type="checkbox"/>	Occupation	INH prophylaxis	Respiratory system examination	STI testing
<input checked="" type="checkbox"/>	Dependants/contacts	Concurrent medication	Cardiovascular examination	Bloods

Check	Biomarkers: Pathogen	Biomarkers: Host	Geographical Setting	Companion Diagnostics
	Strain Type	Antibody profiles	Algeria	Genetic based
	Virulence	TB risk signature	Angola	Phenotypic based
	Adhesion/invasion profile	HLA	Botswana	Minimal Inhibitory concentrations
		T cell activation markers	South Africa	Sequencing
		ML ratio	Germany	Novel Technologies

Fig. 2. Example of an algorithm for individualized regimen placement.

Block-chain technology advancements in database construction offers further protection of patient privacy.⁶² However, this also depends on who should be given access to the data/samples. Blockchain secured genomic data management platform, offers new opportunities for management, storage and sharing of discrete secure immutable blocks of data of interest.^{63,64} Moreover, artificial intelligence machine learning-driven automated biobanking and digital pathology services can harmonize quality assurance methods, minimize subjectivity and improve reproducibility among global biobank libraries.⁶⁵ This would facilitate research-relevant specimen selection by investigators and information sharing in an integrated network approach. Introduction of PM to DR-TB will require clinical governance, regulatory governance, human rights and laws to be taken into careful consideration. Expert panels must be formed to guide clinical decision making, independently evaluate outcomes and modify approaches based on factors such as co-morbidities, pharmacovigilance, efficacy and toxicity while also addressing ethical and medico-legal relevance.

Can we implement a PM strategy in DR-TB?

Before we move to programmatic implementation of PM in the DR-TB context, this strategy must be tested in randomized controlled clinical trials against the current standard of care, in different settings. The goal of such trials would be to determine if such a strategy is superior, equivalent or non-inferior. To this end, there are several ethical issues implicit in such research. If PM is established as being superior to prevailing standard of care early in a trial, consideration must be given to what stopping rules must be applied. Decisions must be made regarding whether those prevailing of care should be transitioned immediately to a PM model of care. Clarity must be provided on the post-trial obligations of the sponsors and researchers. Many questions should be raised before a PM model of care is implemented (Fig. 2). A major concern for clinical trials conducted in low income settings is that if superiority is established, these countries have a limited opportunity to implement a PM based model as the standard of care due to prohibitive financial factors as well as systemic gaps.

Furthermore, it is important to note that patients with DR-TB are in the minority compared to patients with drug sensitive TB who are in the majority. From a public health perspective, one can argue that PM will only bring benefit to the minority of patients with DR-TB and efforts should be directed at improving access to care for patients who have drug sensitive TB and thereby improve

their outcomes. It is well recognized that poverty is a determinant of health care and inequities in health care must be addressed, particularly in vulnerable populations. Is it then more feasible to focus on the economic, geographical, social and cultural barriers to health care than implementation of a PM approach? Integration of TB services as part of primary health care, the concept of decentralization and the construction of community-based TB care model may modify treatment services. Addressing capacity strengthening and funding for TB control programmes together with the extension of basic microscopy services and point of care diagnostics may offer more value in the TB care cascade.

Conclusion

Robust analytics, next generation sequencing and large-scale biological datasets are increasingly being integrated into the diagnosis, treatment, and control of DR-TB. For DR-TB, the mere convergence of new technologies does not translate to precision medicine. It is essential to understand that the use of PM in DR-TB needs to be incremental and objective driven including aspects of conventional practice of medicine. Genomic data requires effective integration with other factors such as clinical and radiological data to compose a complete individualized biological database. The interoperability of this data will most likely be decided upon by each country or organization and depends on its societal framework and burden of DR-TB disease. However, it is these differences between cultures, legal frameworks, economic conditions and health priorities that have potential to lead to a diversity of PM models globally, especially in infectious disease. To provide scientific evidence that will turn the concept of PM into a reality for DR-TB, development of rigorous research programs and both medical and non-medical multidisciplinary teams are needed. If the correct policies and technologies are applied, PM has the potential to improve treatment outcomes and decrease the transmission of DR-TB, and in doing so: Treat the correct patient, at the correct time, with the correct drug.

Declaration of interest

There are no conflicts of interest.

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