One Size Does Not Fit All

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Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this activity

One Size Does *Not* Fit All

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Co-Medical Director

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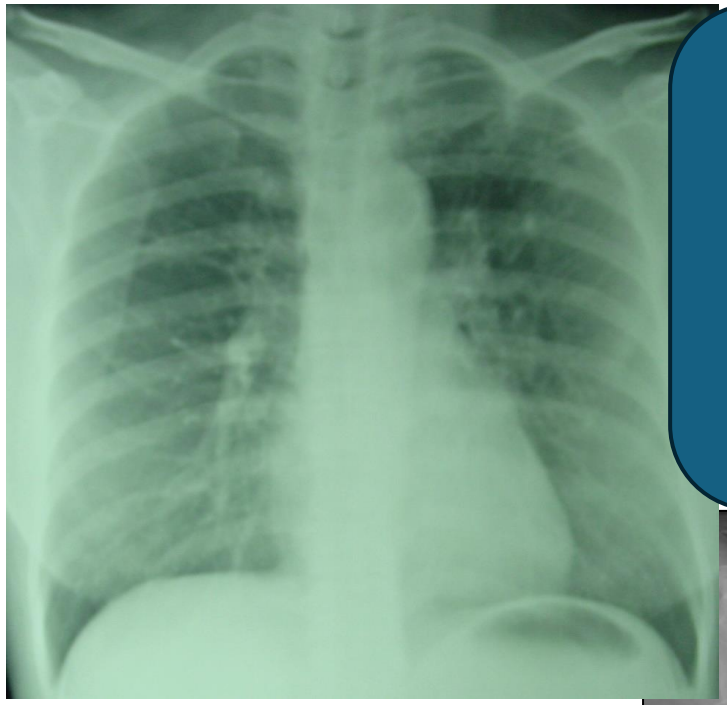
One size for everyone?

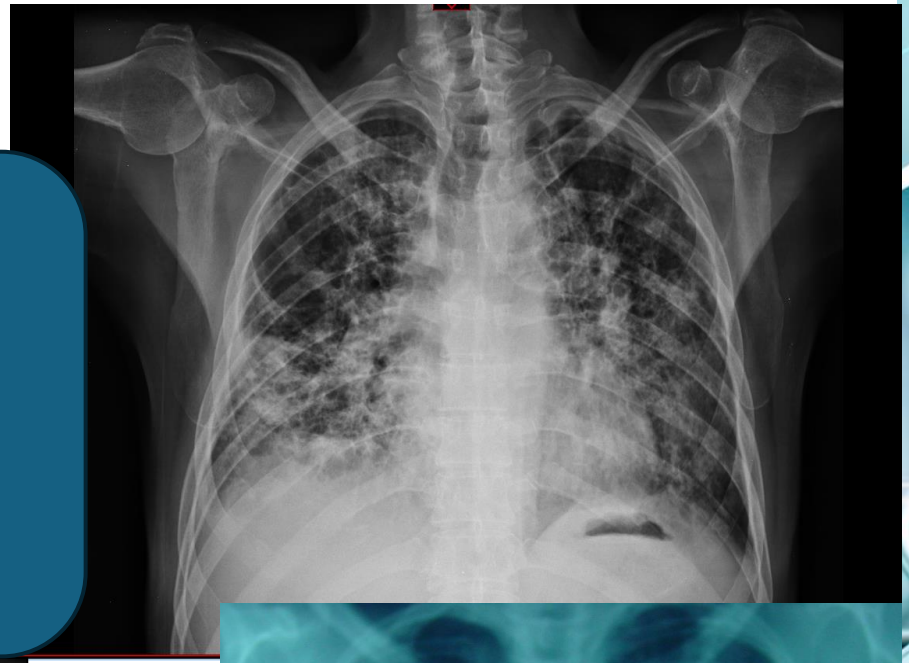


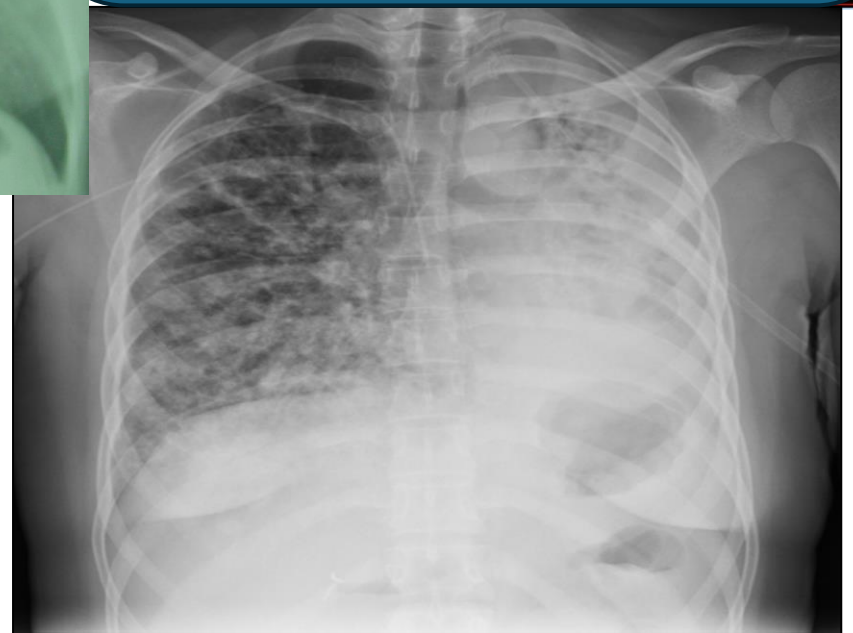
Standard duration:

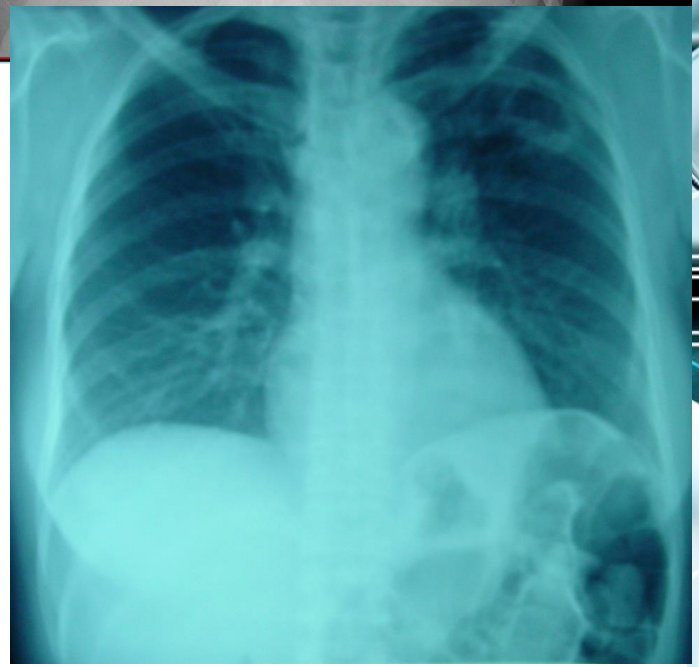
6 months RIPE (Drug Sen TB)

6 months RPE + moxi (INH R)

6 months BPAL (MDR TB)
6 months BPALM (MDR TB)







One Size for everyone…

- Current TB Guidelines suggest **Standard dose:**
  - Rifampin/rifabutin/rifapentine
  - INH
  - Bedaquiline
  - Pretomanid
  - Linezolid
  - Moxifloxacin

How can we give each person what they really need?

Optimized dosing

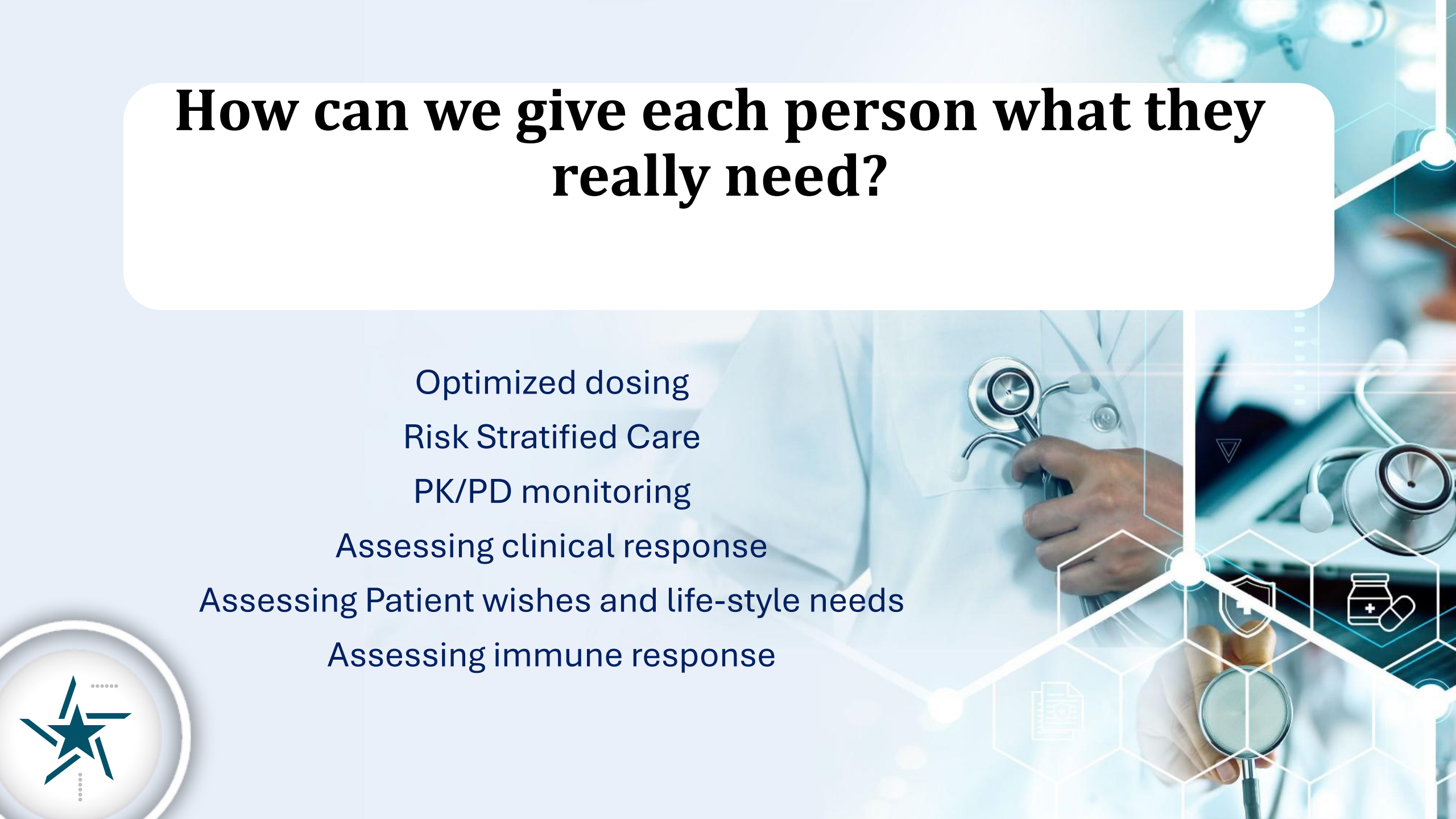
Risk Stratified Care

PK/PD monitoring

Assessing clinical response

Assessing Patient wishes and life-style needs

Assessing immune response



Where we are with attempting to individualize care?

- Nurse Case Management – VDOT – patient-based therapy
- Assessment of co-morbid conditions, medications, lifestyle
- Informal provider-based assessment of extent of disease
- Serum Drug level monitoring
- Assessment of treatment response for treatment duration
  - Clinical
  - Bacteriological
  - Radiographic

Treatment Shortening: Drug Susceptible TB Disease

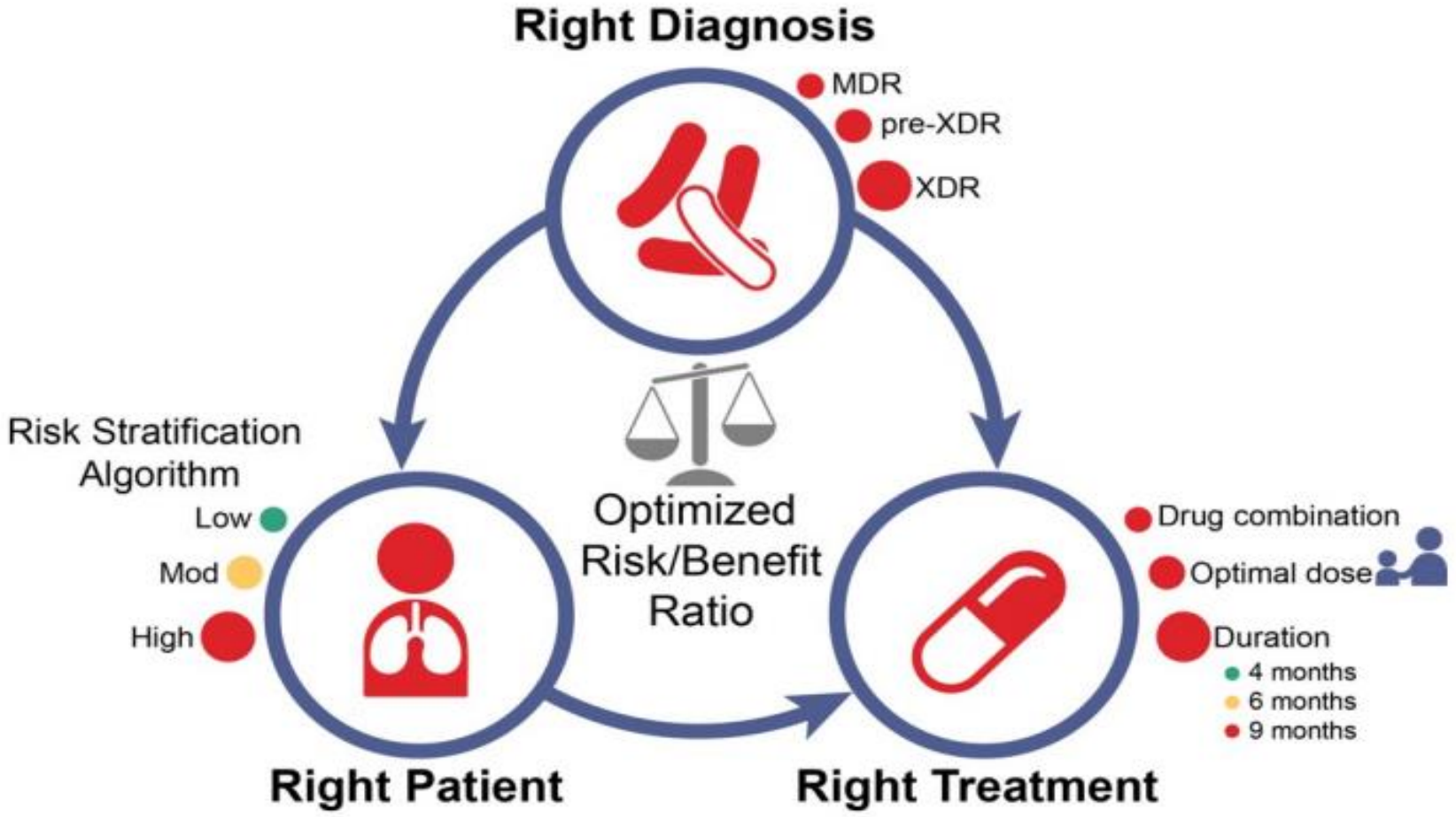
- **TB Trial Consortium Study 31**
  - 4 months of Rifapentine, INH, Moxifloxacin, PZA
- **Shine Trial**
  - 4 months for drug susceptible, limited disease in children
  - RIPE x 2; RI x 2

Treatment Shortening: MDR or RR TB

- **BDQ, Pretomanid, Linezolid plus moxifloxacin (BPALM) x 6 months**
- **BDQ, Pretomanid, Linezolid (BPAL) x 6 months**

Stratified Care – Precision Medicine

Giving each patient what they need



With gratitude to Dr. Rada Savic for sharing her work a number of subsequent slides are hers or from her publications.

ARTICLES
https://doi.org/10.1038/s41591-018-0224-2
OPEN
nature medicine
Corrected: Publisher Correction

A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis

Nov 2018

Marjorie Z. Imperial[1,11], Payam Nahid[1,11], Patrick P. J. Phillips[1], Geraint R. Davies[2], Katherine Fielding[3], Debra Hanna[4,5], David Hermann[5], Robert S. Wallis[6], John L. Johnson[7,8], Christian Lienhardt[9,10] and Rada M. Savic[1*]

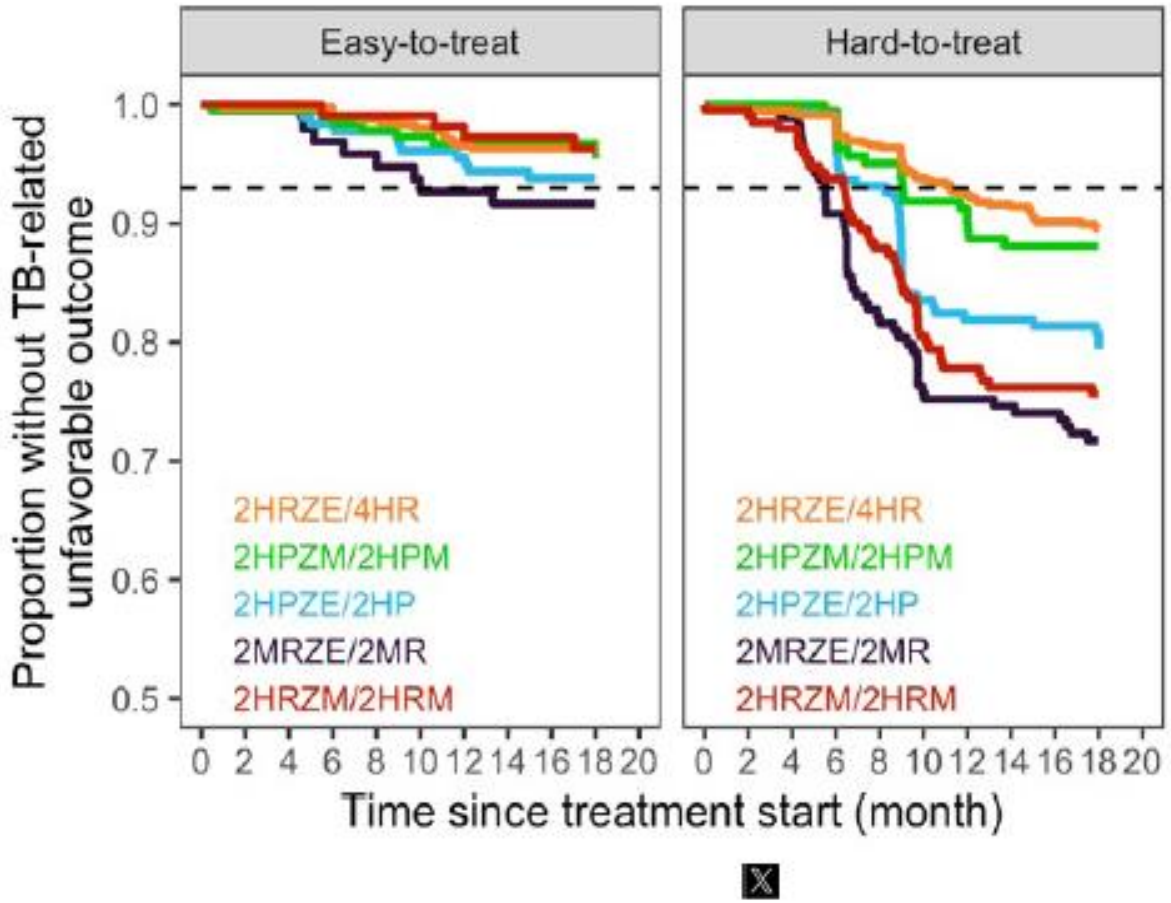
Individual patient-level pooled data analysis from Phase 3 trials

DMID 01-009 Johnson et al. 2009 Am J Respir Crit Care Med [NCT00130247]	OFLOTUB Merle et al. 2014 N Engl J Med [NCT00216385]	REMoxTB Gillespie et al. 2014 N Engl J Med [NCT00864383]	RIFAQUIN Jindani et al. 2014 N Engl J Med [ISRCTN44153044]	Study 31 Dorman et al. 2021 N Engl J Med [NCT02410772]
2HRZE/4HR	2HRZE/4HR	2HRZE/4HR	2HRZE/4HR	2HRZE/4HR
2HRZE/2HR	$2HRZG_{HD}/2HRG_{HD}$	$2HRZM_{HD}/2HRM_{HD}$	$2M_{LD}RZE/4M_{LD}P_{LD}$	$2HP_{HD}ZE/2HP_{HD}$
		$2M_{HD}RZE/2M_{HD}R$	$2M_{LD}RZE/2M_{LD}P_{LD}$	$2HP_{HD}ZM_{HD}/2HP_{HD}M_{HD}$

6,959 patients with DS-TB

H = isoniazid
R = rifampin
Z = pyrazinamide
E = ethambutol
P = rifapentine
M = moxifloxacin
G = gatifloxacin
HD = high-dose (M/G: 400 mg QD; P: 1200 mg QD)
LD = low-dose (M/G: <400 mg QD; P: <1200 mg QD)

LESSONS FROM THE DS PHASE 3 TRIALS



Control

Successful 4-month regimen

Failed

Failed

Failed

Phase 3 clinical trials failed because of inadequate response
In hard-to-treat patients

(Imperial et al. 2018)

ORIGINAL ARTICLE

November 2021

Precision-Enhancing Risk Stratification Tools for Selecting Optimal Treatment Durations in Tuberculosis Clinical Trials

Marjorie Z. Imperial[1,2], Patrick P. J. Phillips[2,3], Payam Nahid[2,3], and Radojka M. Savic[1,2,3]

[1]Department of Bioengineering and Therapeutic Sciences; [2]University of California, San Francisco, Center for Tuberculosis, and [3]Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California, San Francisco, San Francisco, California

ORCID IDs: 0000-0001-7434-3012 (M.Z.I.); 0000-0002-6336-7024 (P. P.J.P.); 0000-0003-2811-1311 (P.N.); 0000-0003-3143-5579 (R.M.S.).

Six item risk score successfully grouped participants into **low, moderate and high-risk** requiring treatment durations of 4, 6 and greater than 6 months to reach a target cure of 93% when receiving standard dose rifamycin containing regimens

With current “one –duration-fits-all approaches:
High risk groups have a 3.7-fold and a 4-fold higher hazard risk of unfavorable outcomes compared with low and moderate risk groups.

Four-month regimens were noninferior to the standard 6-month regimen in the low-risk group

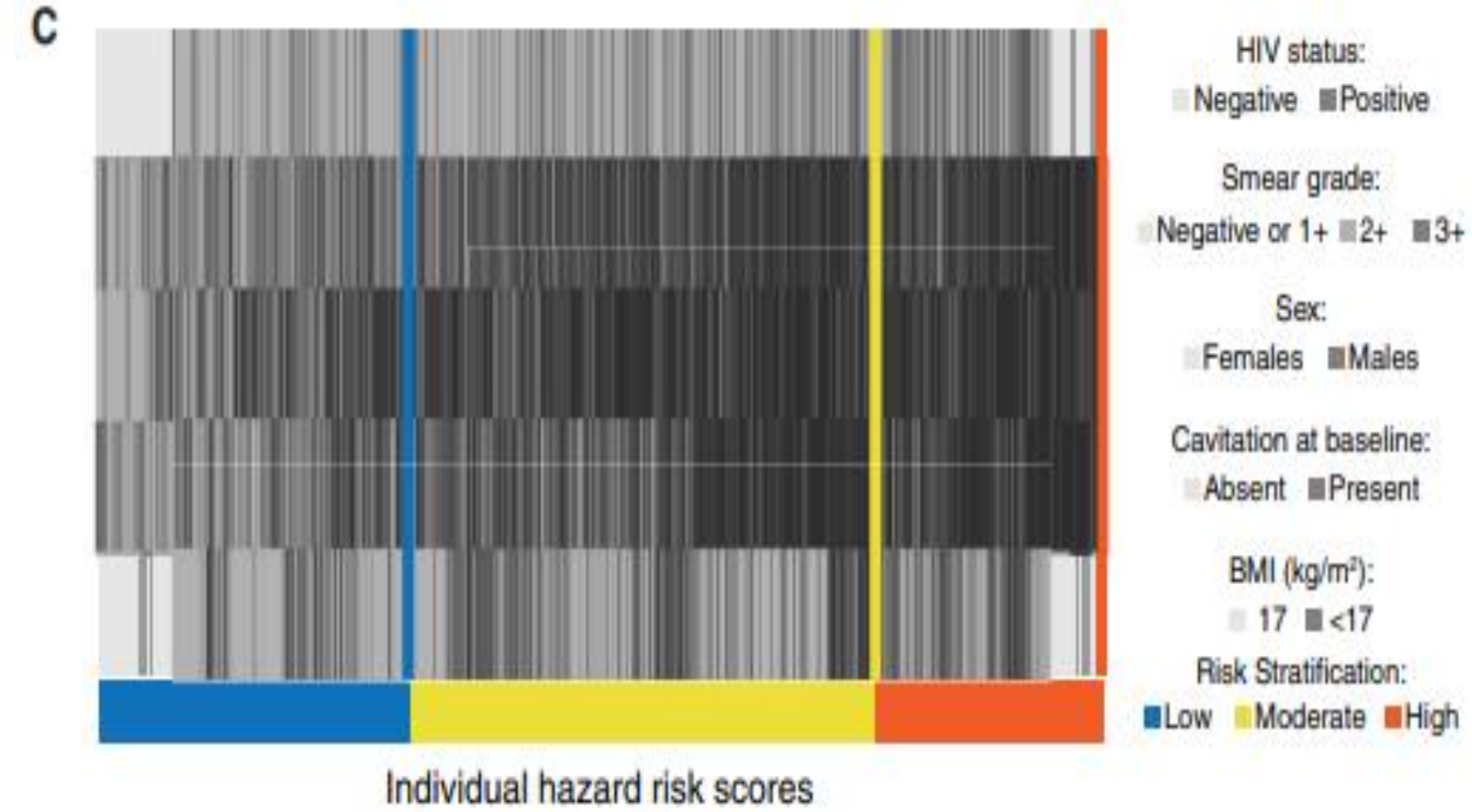
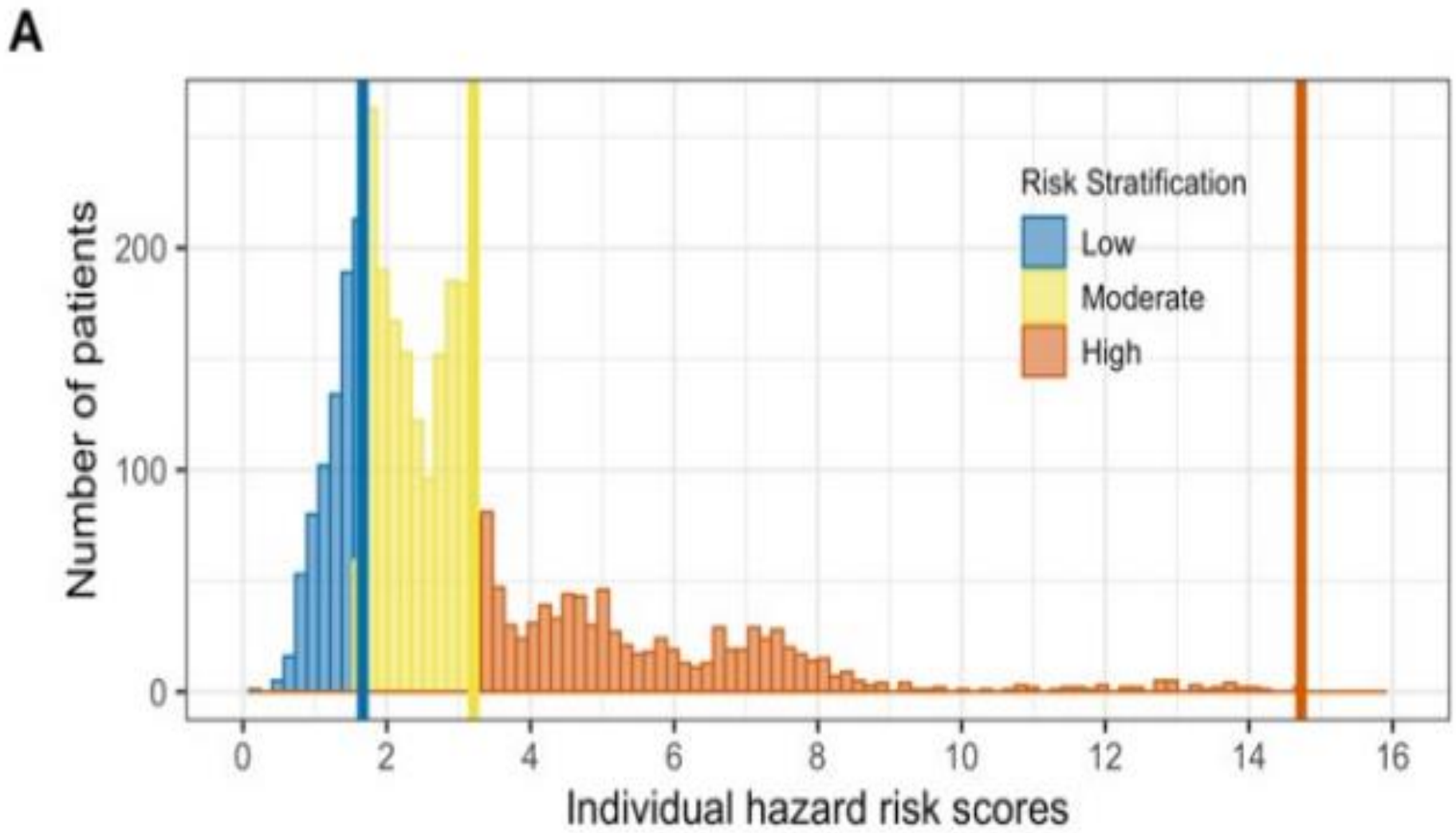


Figure 1. Distribution of individual risk scores, optimal treatment durations, and risk factors for target cure of 93% in the model development population. (*A*) Distribution of individual risk scores stratified by low-, moderate-, and high-risk groups. (*B*) Distribution of predicted optimal treatment durations for target cure rate of 93% stratified by low-, moderate-, and high-risk groups. (*C*) Heat map distribution of identified risk factors among low-, moderate-, and high-risk groups. All individuals are arranged on the *x*-axis from lowest risk score to highest risk score, and each column in each row (risk factor) represents a single individual. The low-risk group was defined as patients requiring less than or equal to 18 weeks of treatment, the moderate-risk group as requiring 19–24 weeks of treatment, and the high-risk group as requiring more than 24 weeks of treatment for a target cure rate of 93%. BMI = body mass index.

Imperial et al, Am J Resp Crit Care Medicine, Nov 2021

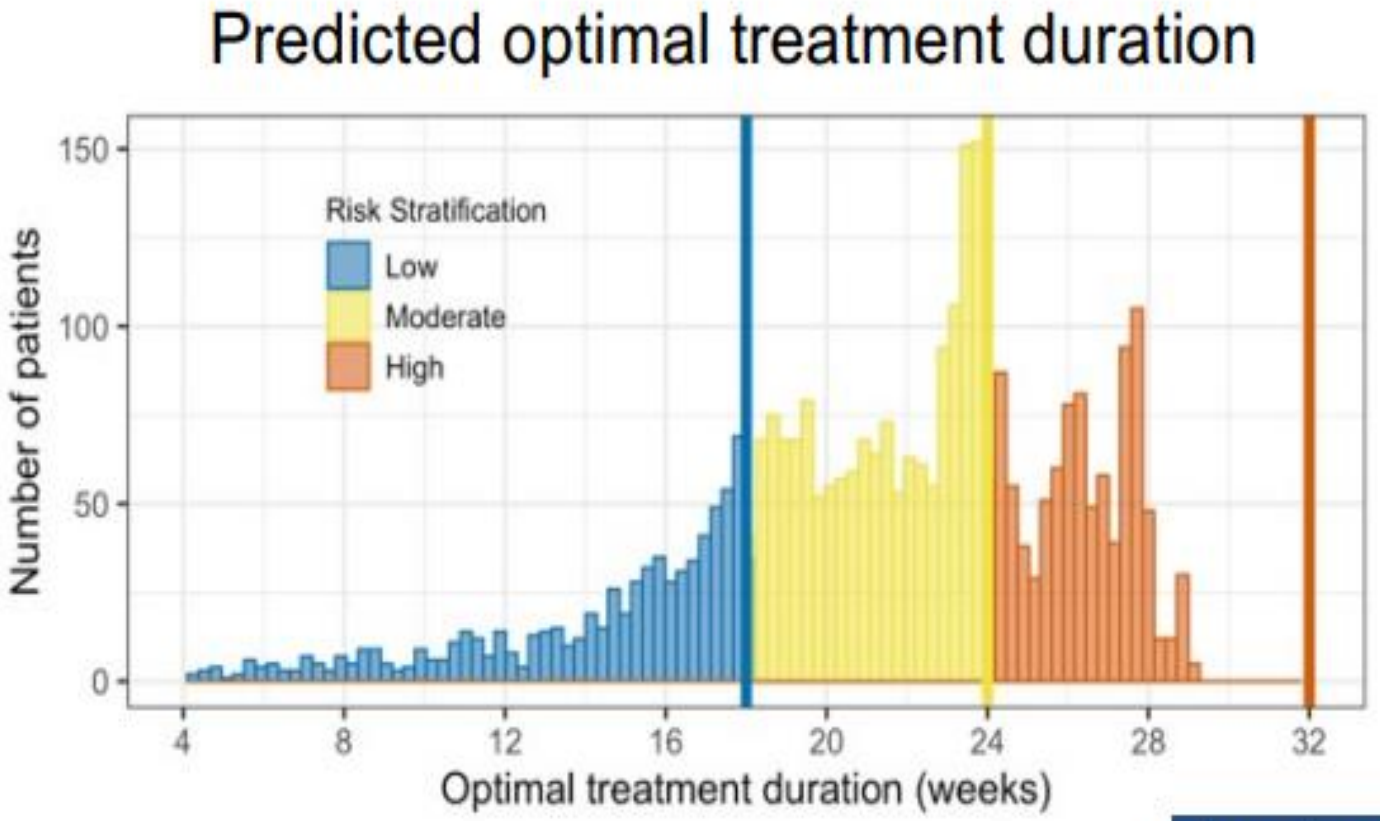
DISTRIBUTION OF PATIENT RISK SCORES



Imperial et al, Am J Resp Crit Care Medicine, Nov 2021

$$Risk\ Score = f_1(AUC) * f_2(Xpert) * f_3(Extent\ of\ Disease) * f_4(Age) * f_5(BMI) * f_6(Diabetes)$$

OPTIMAL DURATION FOR HRZE



American Journal of Respiratory and Critical Care Medicine

Home > American Journal of Respiratory and Critical Care Medicine > List of Issues > Volume 204, Issue 9

Precision-Enhancing Risk Stratification Tools for Selecting Optimal Treatment Durations in Tuberculosis Clinical Trials

Marjorie Z. Imperial [1,2], Patrick P. J. Phillips [2,3], Payam Nahid [2,3], and Radojka M. Savic [1,2,3]
+ Author Affiliations

UCSF

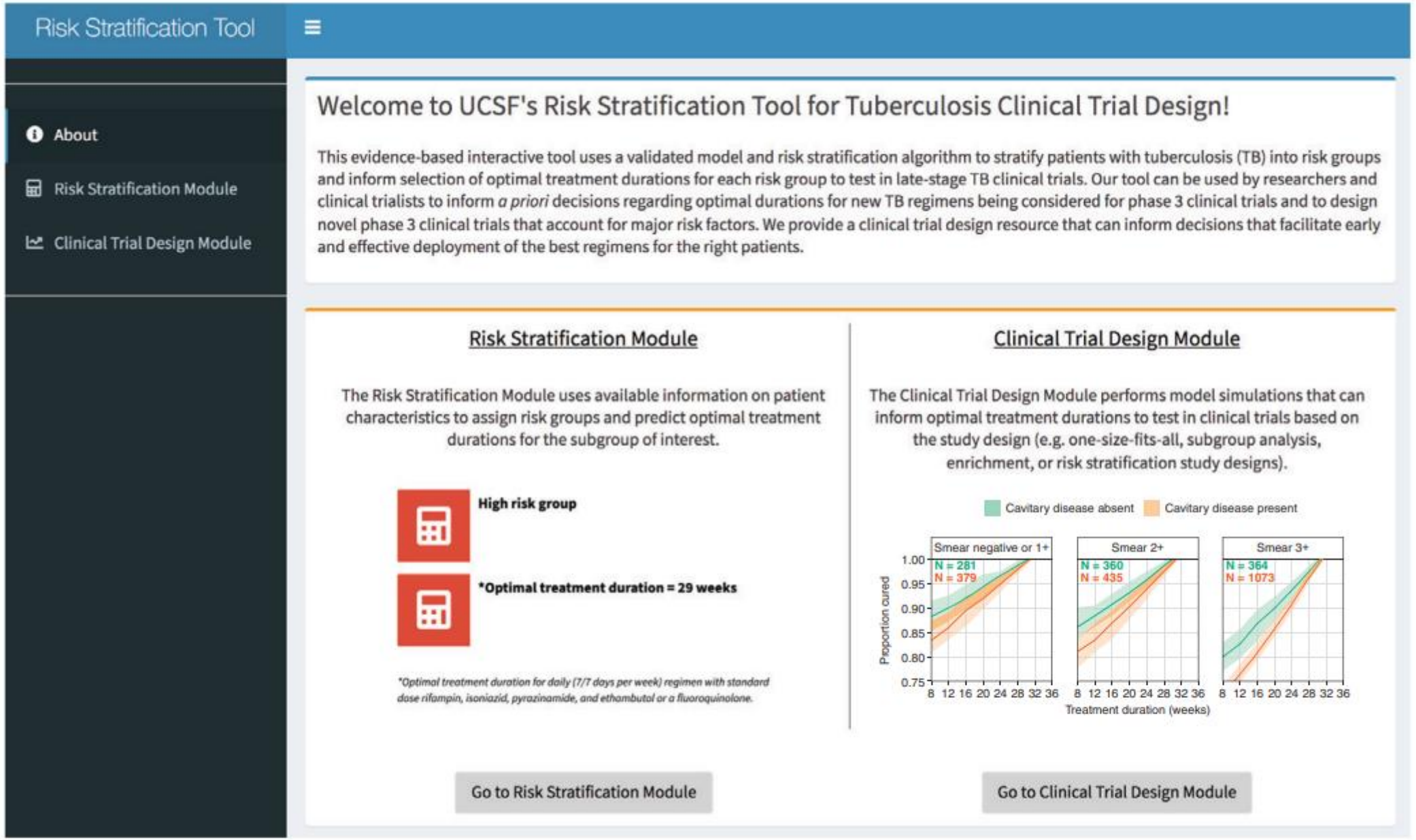


Figure 5. Interactive risk stratification tool. The "About" page in the web application that displays information on the Risk Stratification and Clinical Trial Design Module is shown. UCSF = University of California, San Francisco.

Imperial et al, Am J Resp Crit Care Medicine, Nov 2021

Risk factors for unfavorable outcomes for TBTC Study 31: 4-month RPT/INH/Moxi/PZA regimen

In RPT-Moxi regimen strongest driver of TB unfavorable outcome **was low rifapentine exposure**

Only other risk factors were **markers of disease severity**

Xpert MTB RIF cycle threshold

Extent of disease on baseline CXR

nature communications

Article

https://doi.org/10.1038/s41467-024-53273-7

Risk-stratified treatment for drug-susceptible pulmonary tuberculosis

Received: 14 May 2024

Accepted: 30 September 2024

Published online: 30 October 2024

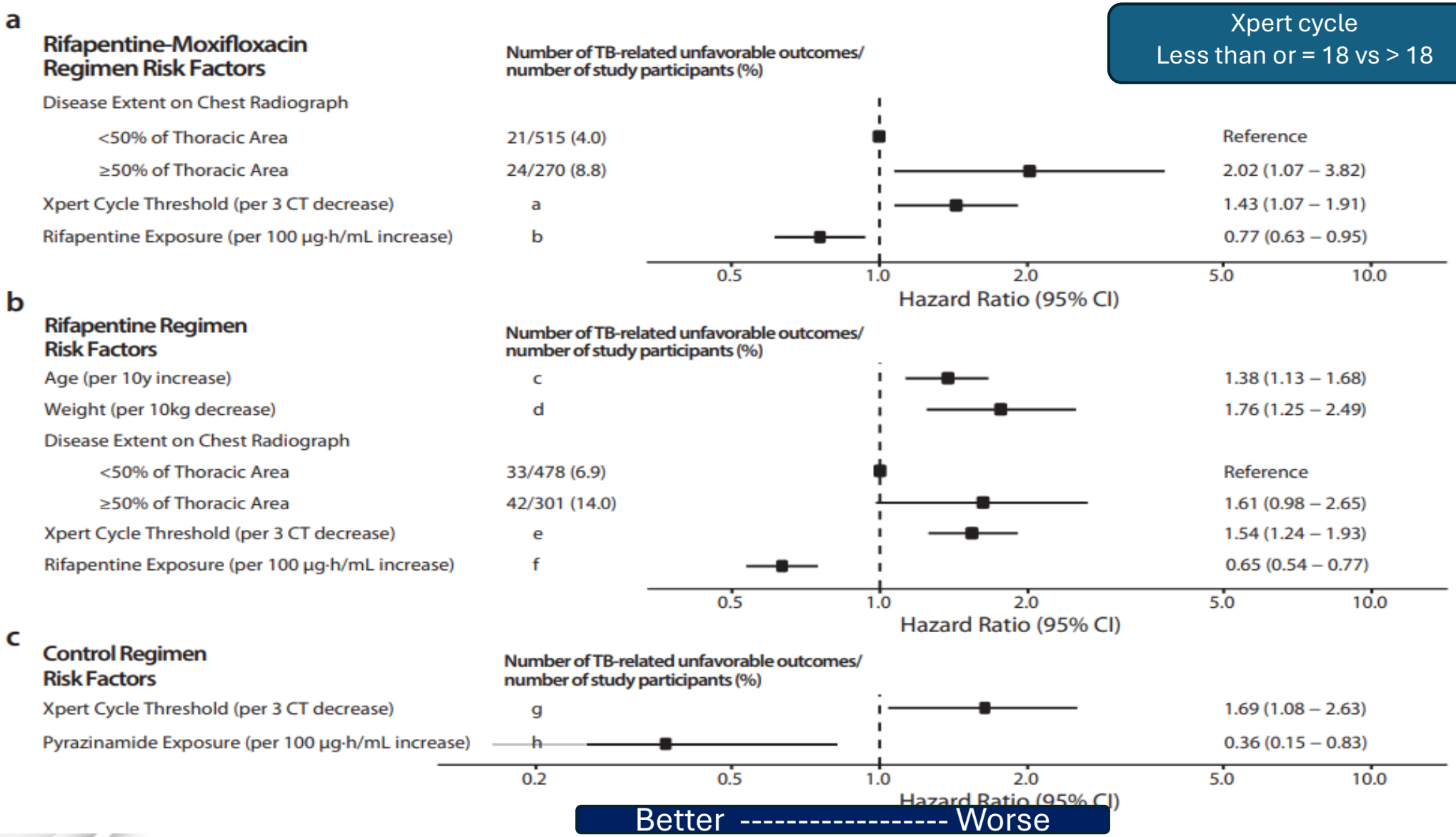
Check for updates

Vincent K. Chang[1,2], Marjorie Z. Imperial[1,2], Patrick P. J. Phillips[2,3], Gustavo E. Velásquez[2,4], Payam Nahid[2,3], Andrew Vernon[5], Ekaterina V. Kurbatova[5], Susan Swindells[6], Richard E. Chaisson[7], Susan E. Dorman[8], John L. Johnson[9,10], Marc Weiner[11], Erin E. Sizemore[5], William Whitworth[5], Wendy Carr[5], Kia E. Bryant[5], Deron Burton[5], Kelly E. Dooley[12], Melissa Engle[11], Pheona Nsubuga[10], Andreas H. Diacon[13], Nguyen Viet Nhung[14,15], Rodney Dawson[16], Radojka M. Savic[1,2] ✉, AIDS Clinical Trial Group* & Tuberculosis Trials Consortium*

Multivariable Hazard Ratios for TB Related Unfavorable Outcomes

Chang et al, Nature Communications October 2024

Xpert cycle
Less than or = 18 vs > 18



Better ---------- Worse

Stratified Medicine for TB Care (>35000 patient data base)

Bringing stratified medicine to TB – a paradigm shift in overall objectives in TB care

1. Reduce duration (and toxicity, cost, to programmes and patients)

- Treatment for severe disease may be longer, but ~70-75% of TB patients with less severe disease can be cured with shorter durations

2. Patient-centered approach

- Selecting regimen with greater precision for burden of disease

3. Enhancing cure rates for severe TB

- Achieve higher cure rates across the population, as unfavourable outcomes are dominated by severe forms of the disease.

4. Alternative to "One Size Fits All" approach in the field is feasible

- Novel diagnostics will enable simple implementation of stratified medicine

Med

CellPress

Perspective

Tuberculosis endotypes to guide stratified host-directed therapy

Andrew R. DiNardo,[1,*] Tomoki Nishiguchi,[1] Sandra L. Grimm,[2,3] Larry S. Schlesinger,[4] Edward A. Graviss,[5] Jeffrey D. Cirillo,[6] Cristian Coarfa,[2,3] Anna M. Mandalakas,[1] Jan Heyckendorf,[7,8,9] Stefan H.E. Kaufmann,[10,11,12] Christoph Lange,[7,8,9] Mihai G. Netea,[13,14] and Reinout Van Crevel[13,*]

TB Endotypes

Distinct molecular profiles, with specific metabolic, epigenetic, transcriptional, and immune phenotypes.

Characterized by either immunodeficiency or pathologic excessive inflammation.

DiNardo et al, Medicine 2, March 2021

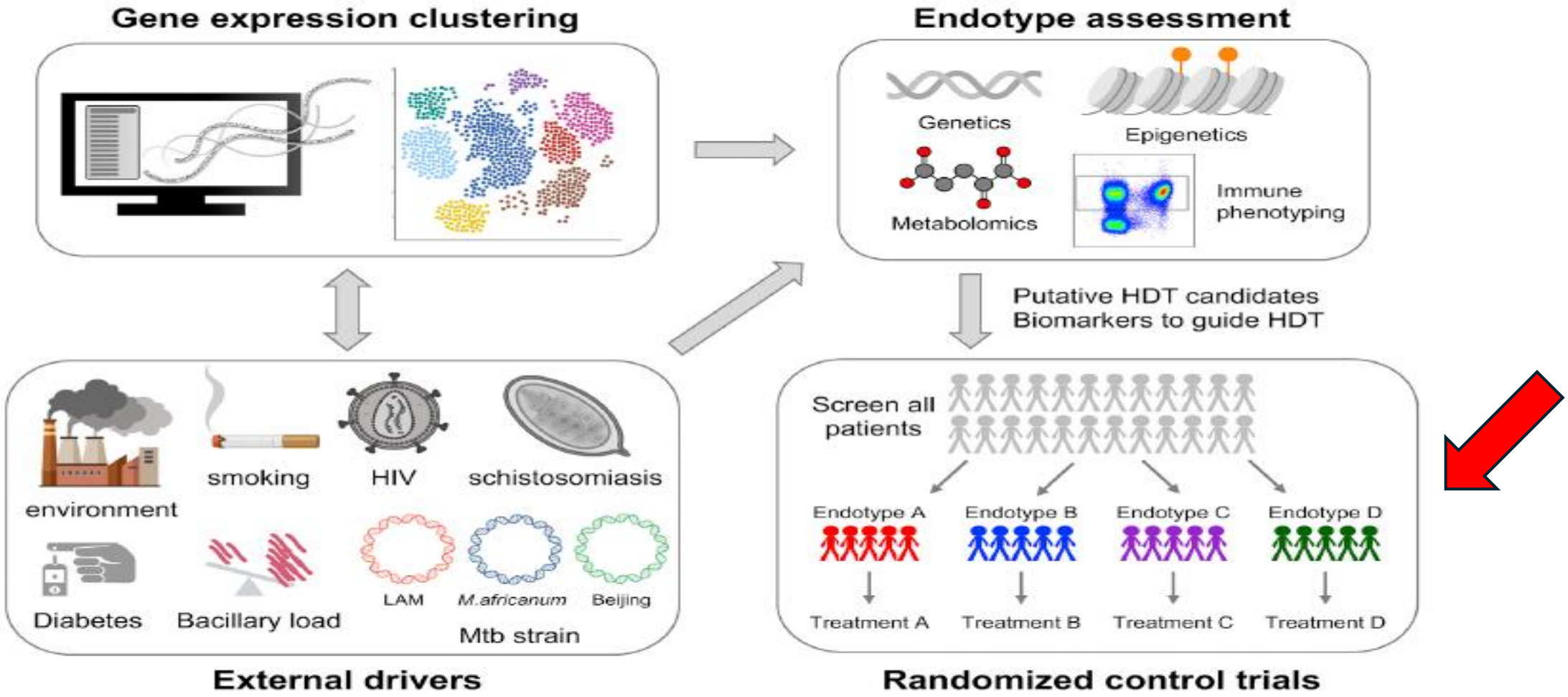


Figure 3. Unbiased clustering of publicly available data allows for identification of gene expression-derived dusters

Applying multimodal integration techniques, endotypes can be discovered and characterized on the basis of the their metabolic, epigenetic, genetic, and immune phenotype. Similarly, multimodal integration would clarify which epidemiologic factors are likely driving specific endotypes. Multimodal integration will identify the constellation of clinical epidemiology and biomarkers best suitable for treatment with putative HDT candidates that should be prospectively evaluated in umbrella and basket clinical trials.

Where should research be going? What does the TB Community Want?

- **Safety**

Efficacy

- **Tolerability**
  - Pill burden, side effects

Time

Duration, **home time**

One Size Does Not Fit All