CURE-TB Strategy and the Stratified Medicine Trial Design

September 9th, 2019

INTERTB Meeting

St. George's Hospital, University of London

Rada Savic, Patrick Phillips, and Payam Nahid

On behalf of the CDC-TBTC CURE-TB protocol team

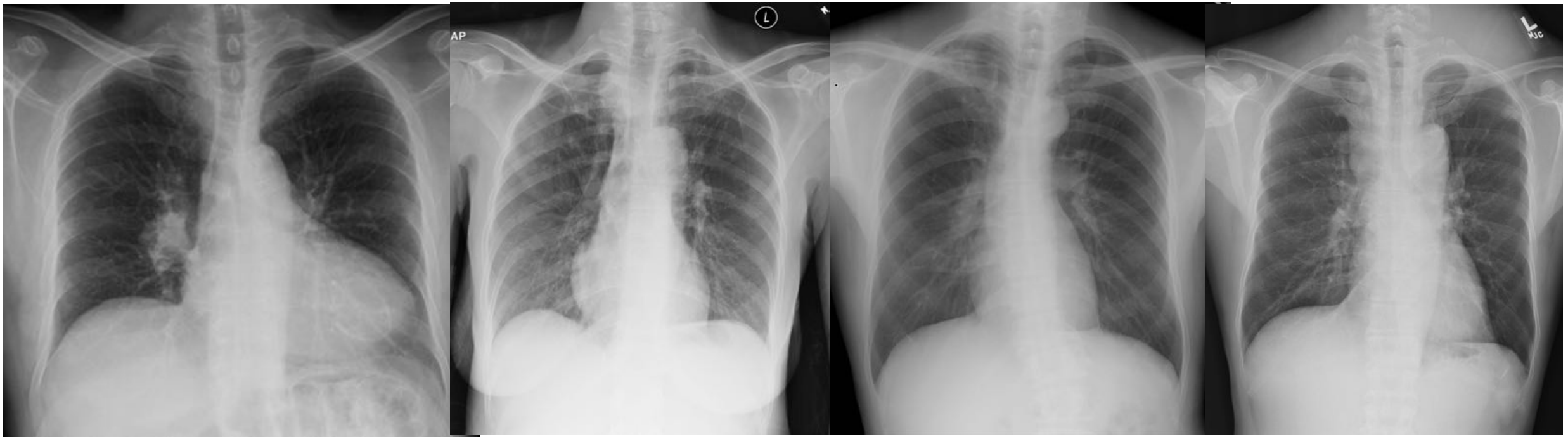
Cancer versus Consumption

A brief journey through the approaches to patient care in cancer of the lung and TB of the lung

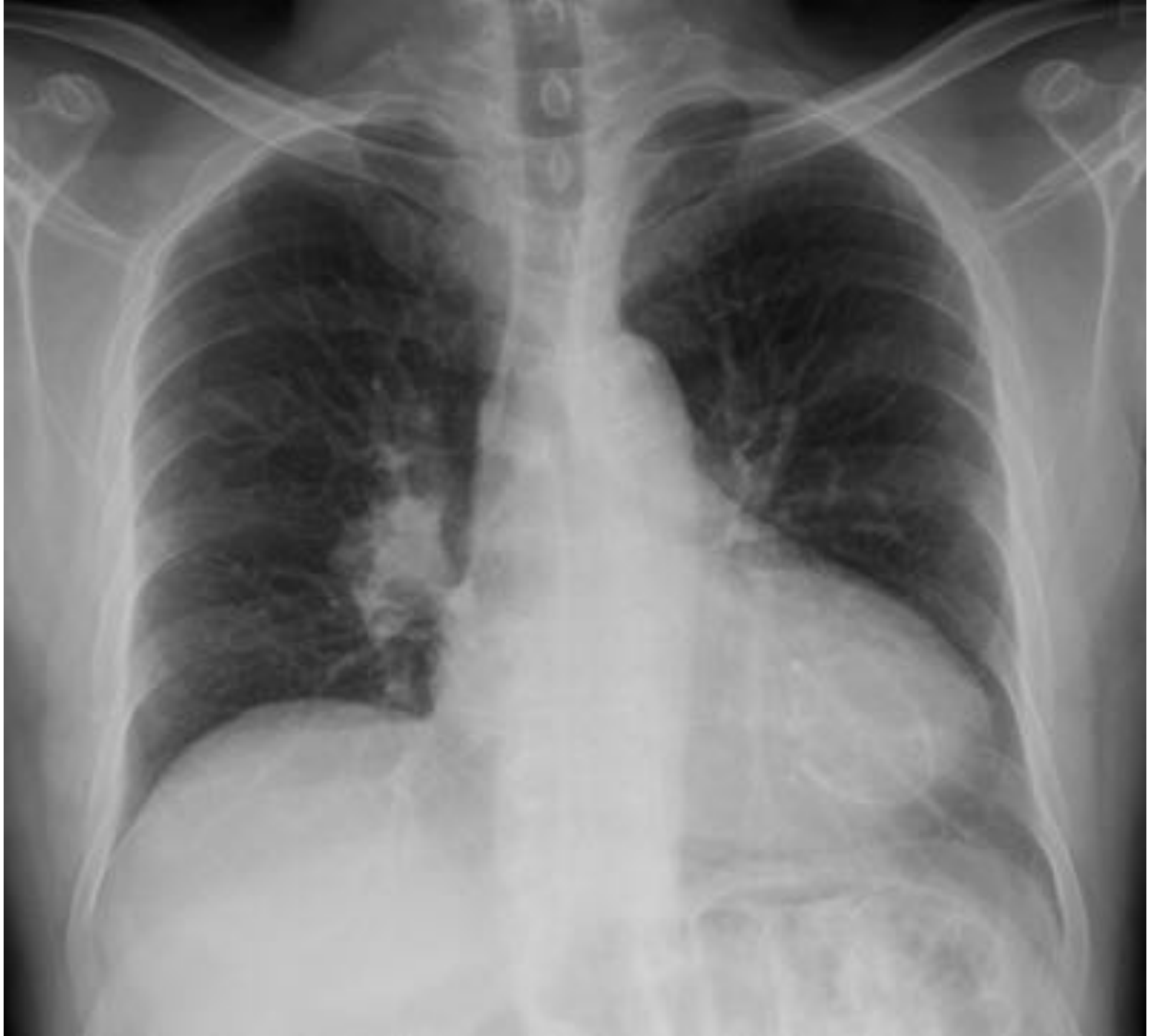
Deidentified images courtesy of

Khai Vu, MD
Associate Professor
Department of Radiology and Biomedical Imaging
Zuckerberg San Francisco General Hospital
University of California, San Francisco

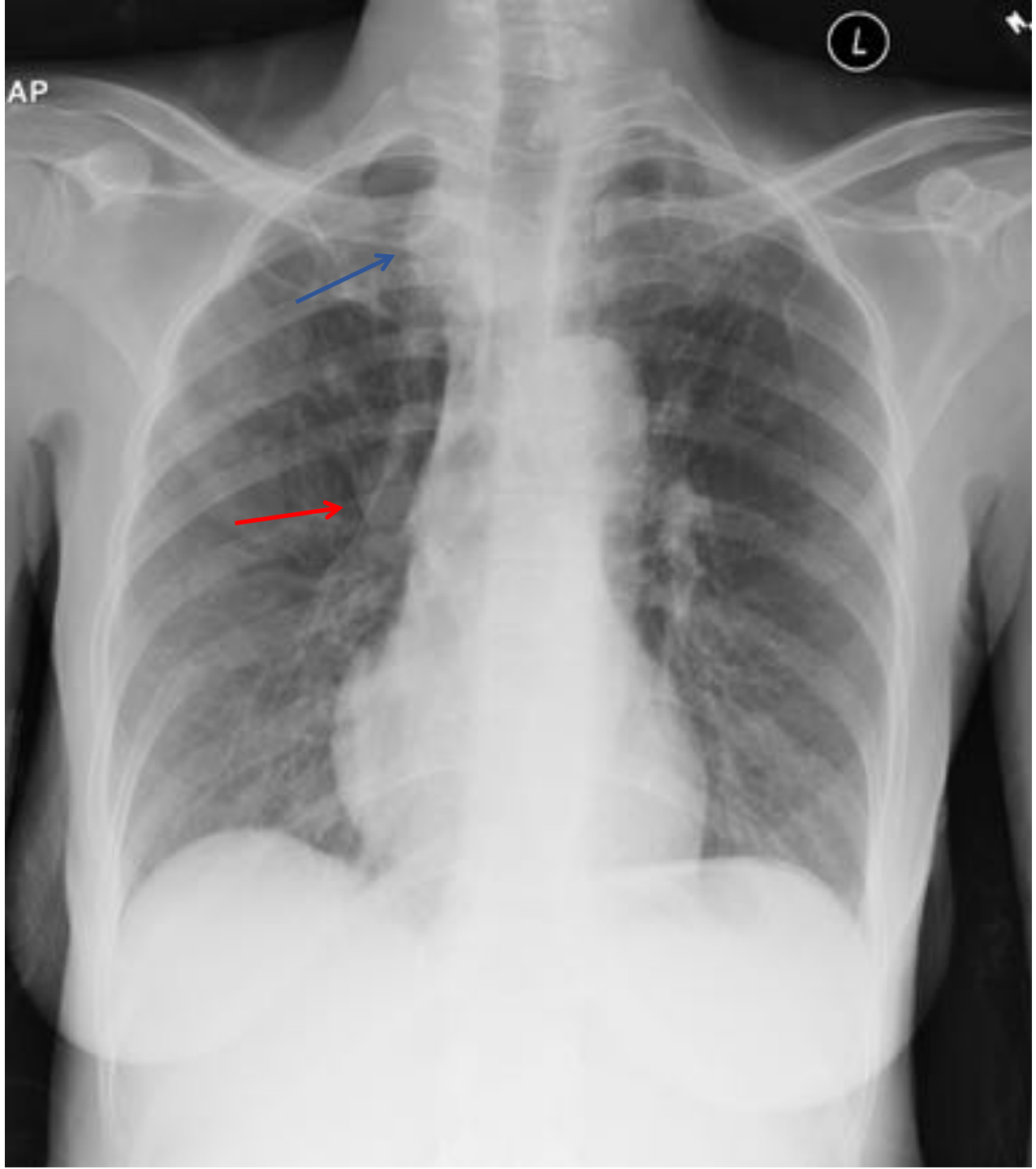
An Oncology Program View of Patient Care



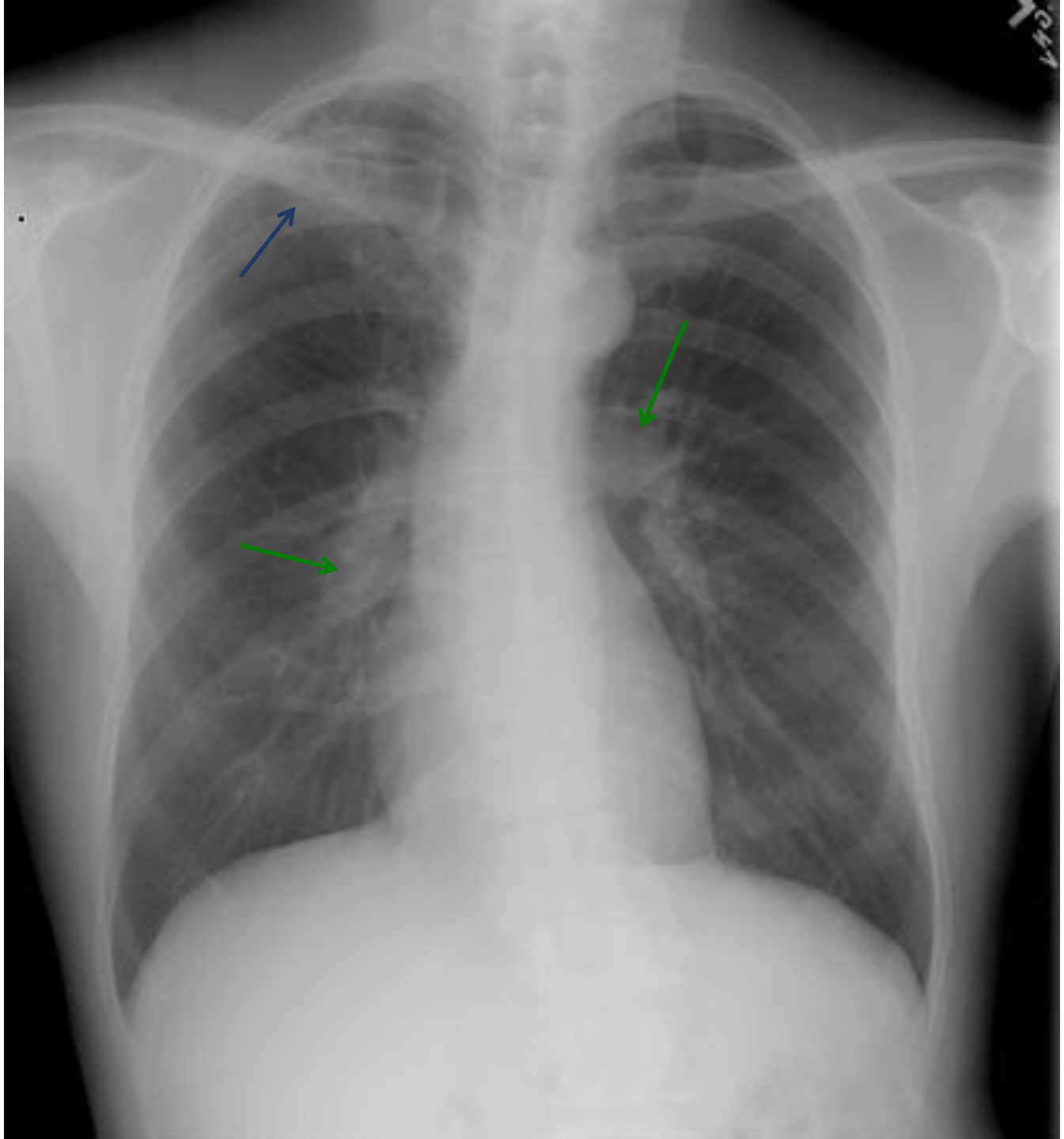
Four patients with newly diagnosed adenocarcinoma of the lung



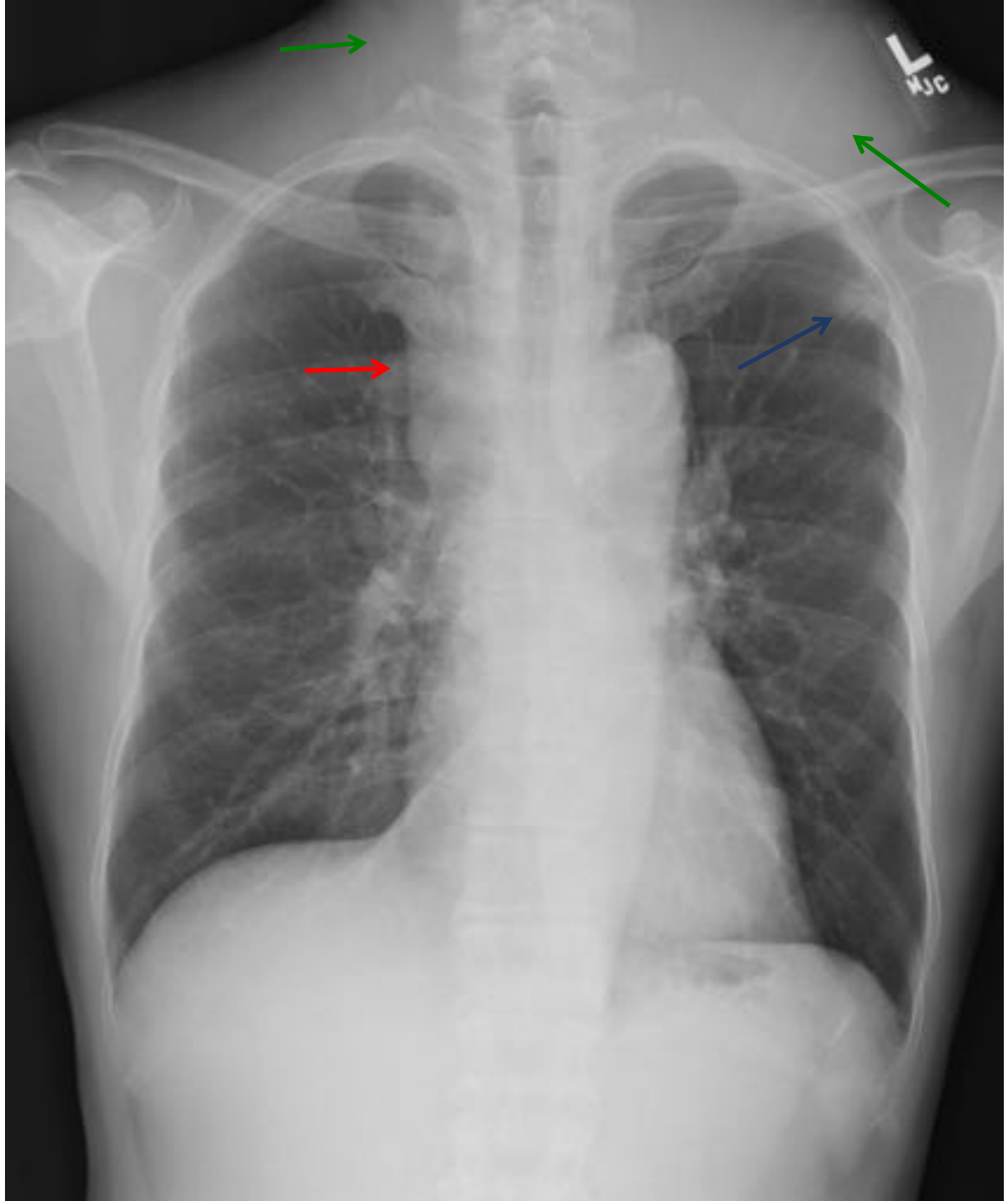
AdenoCA-Stage 1
Posterior right hilar mass



AdenoCA Stage 2
Right upper lobe para-mediastinal mass (Blue arrow)
Right hilar adenopathy (orange arrow)



AdenoCA Stage 3
Right apical mass (Blue arrow)
Bilateral hilar adenopathy (Green arrows)



AdenoCA-Stage 4

Left upper lobe nodule (Blue arrow)

Contralateral para tracheal adenopathy (Orange arrow)

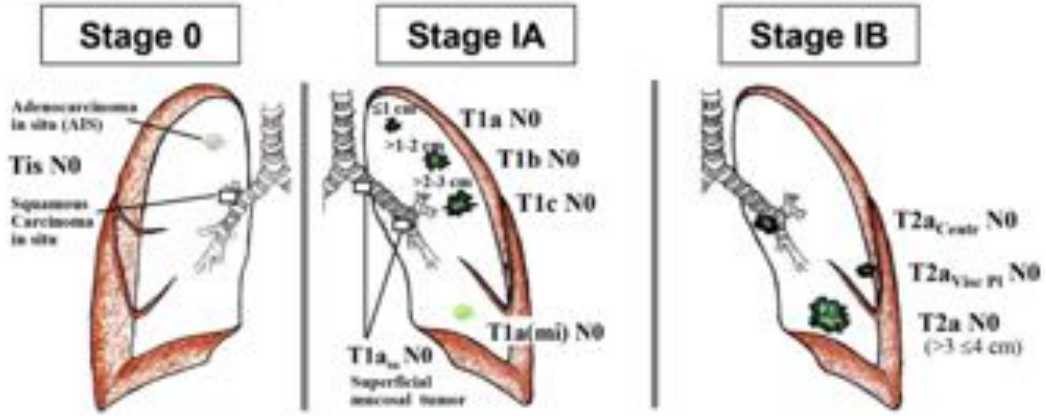
Bilateral neck LAD (green arrows)

Lung Cancer Stage Classification (8th Edition)

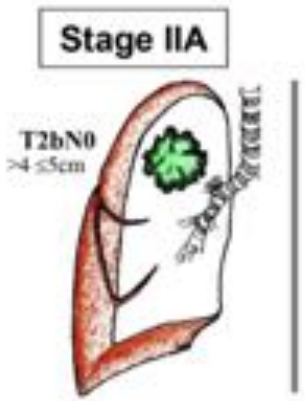
General Note:
All Stage I-III tumors are M0

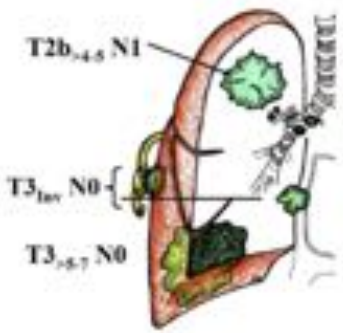
Tx, Nx should be used only if no information at all is available about T or N stage (including no clinical staging information).

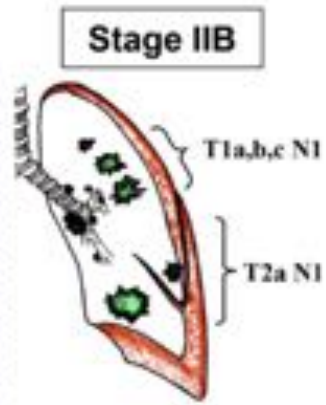
Mx is not allowed, because symptoms and physical exam information is always available.

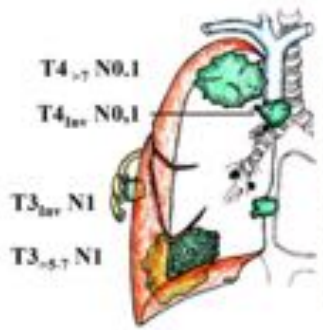


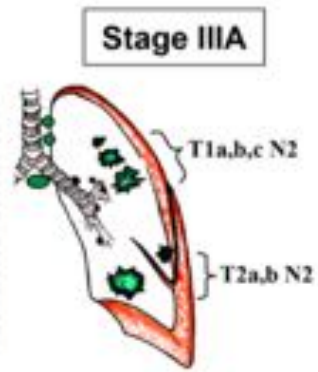
Using CT, PET, bronchoscopy, biopsies and tissue pathology, among other techniques, stages are confirmed

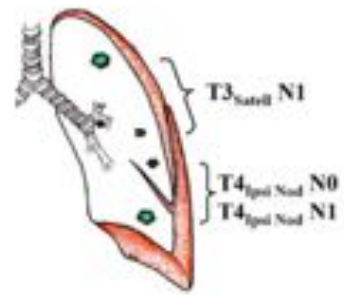




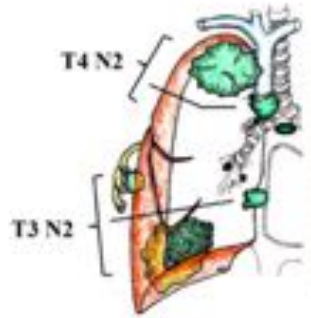


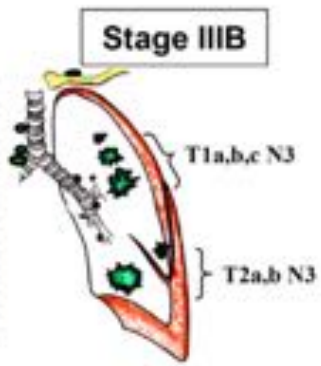


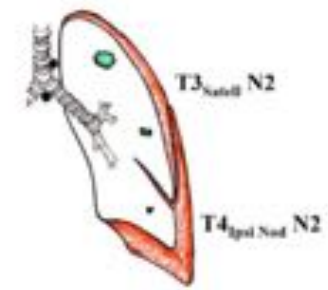


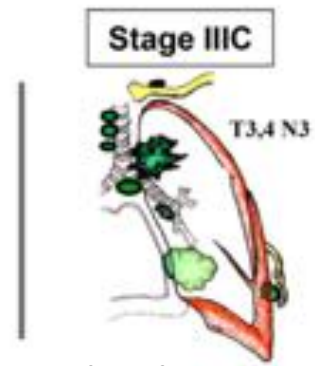


Specific Notes:
Tumor size defined as largest dimension of the solid (imaging, c-stage) or invasive (p-stage) component
Direct extension of the primary tumor into an adjacent node counts as nodal involvement
Extension of a nodal metastasis into a T structure does not count for the T category
The highest T category is used when there is a discrepancy between T by size or by other factors









Detterbeck et al., Chest 2017

Lung Cancer Stages and Treatments

Stage 1: Localized

Stage 2: Larger (> 5 cm) or spread to local lymph nodes

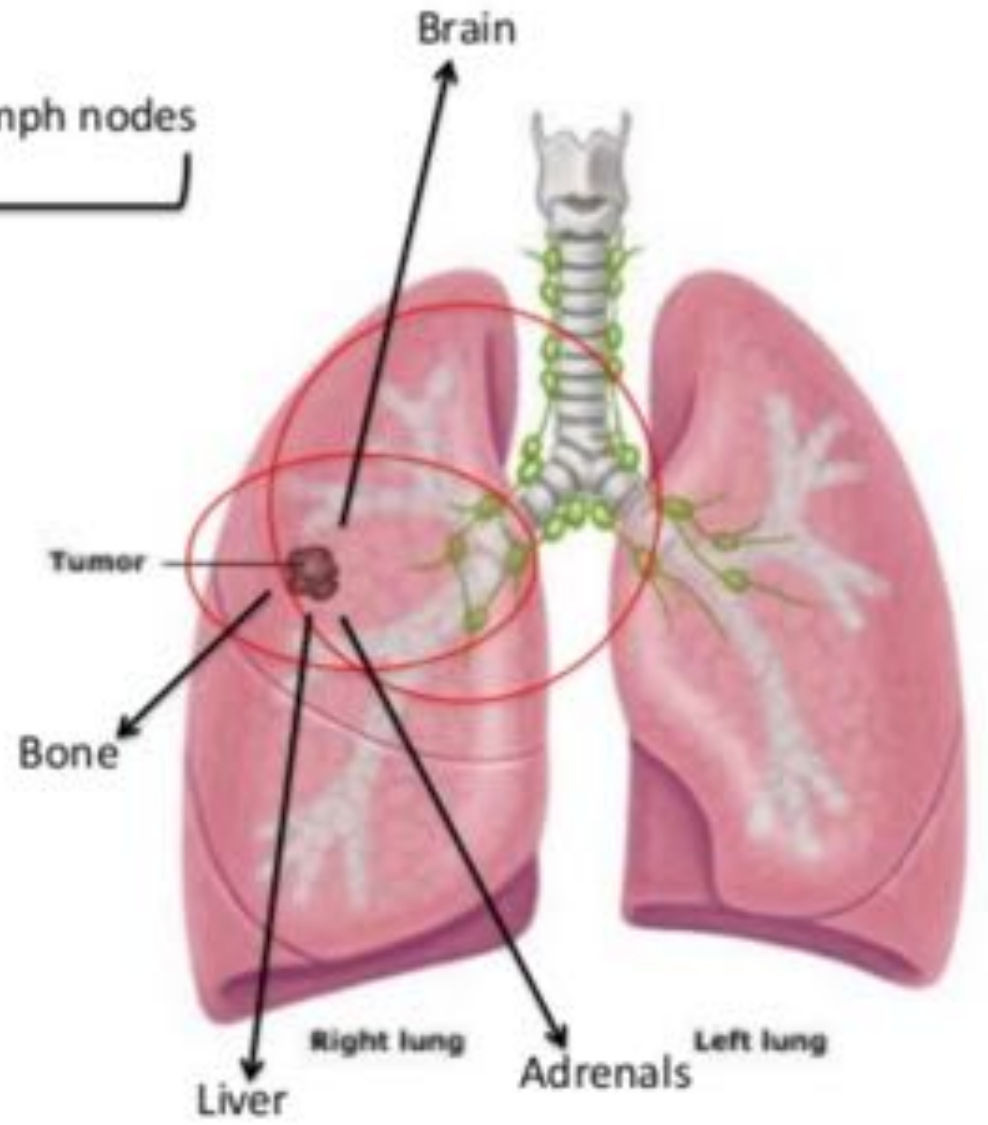
Surgery, +/-chemotherapy

Stage 3: Locally advanced

Chemotherapy and radiation, +/- surgery

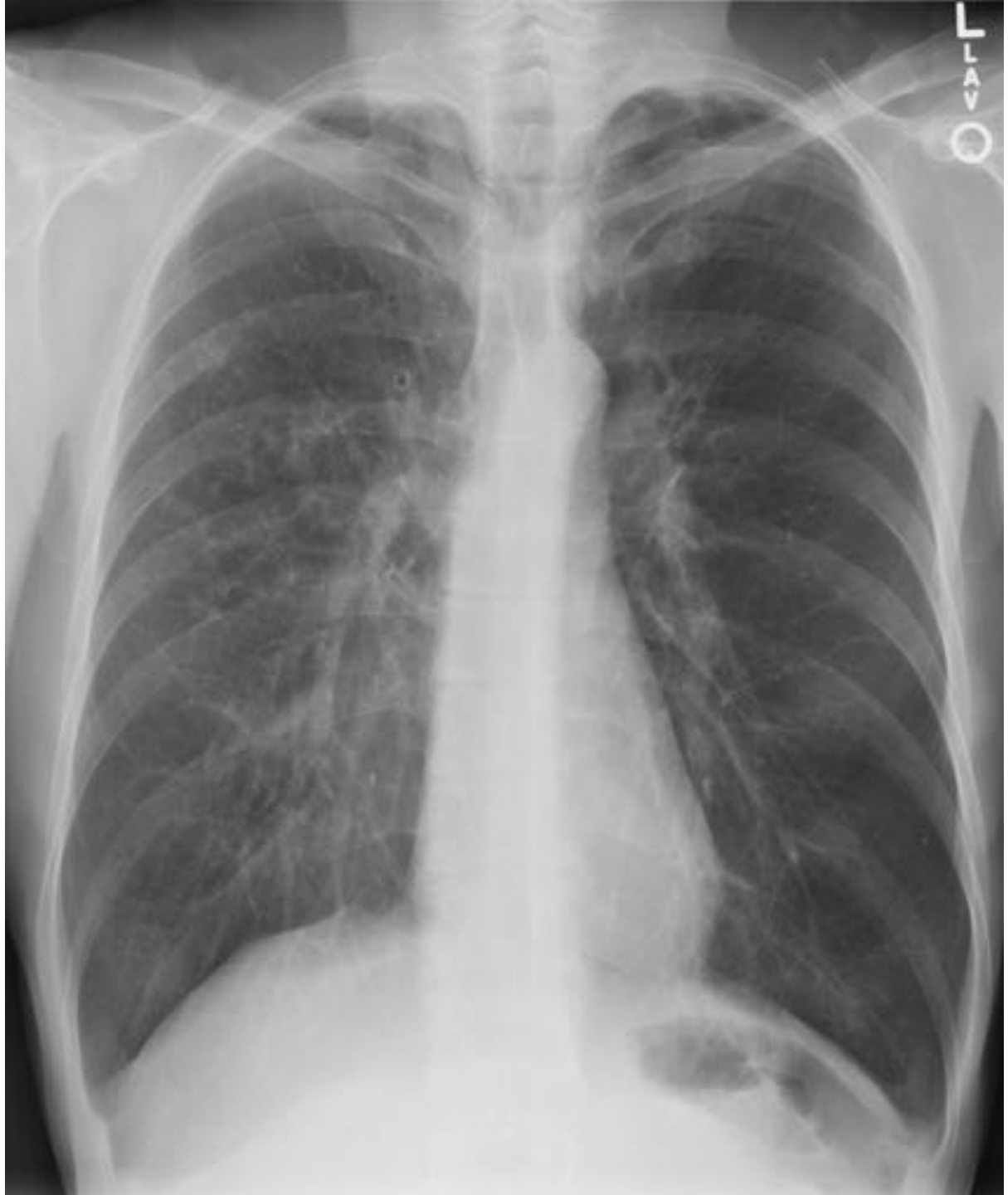
Stage 4: Advanced/metastatic

Chemotherapy +/- palliative radiation

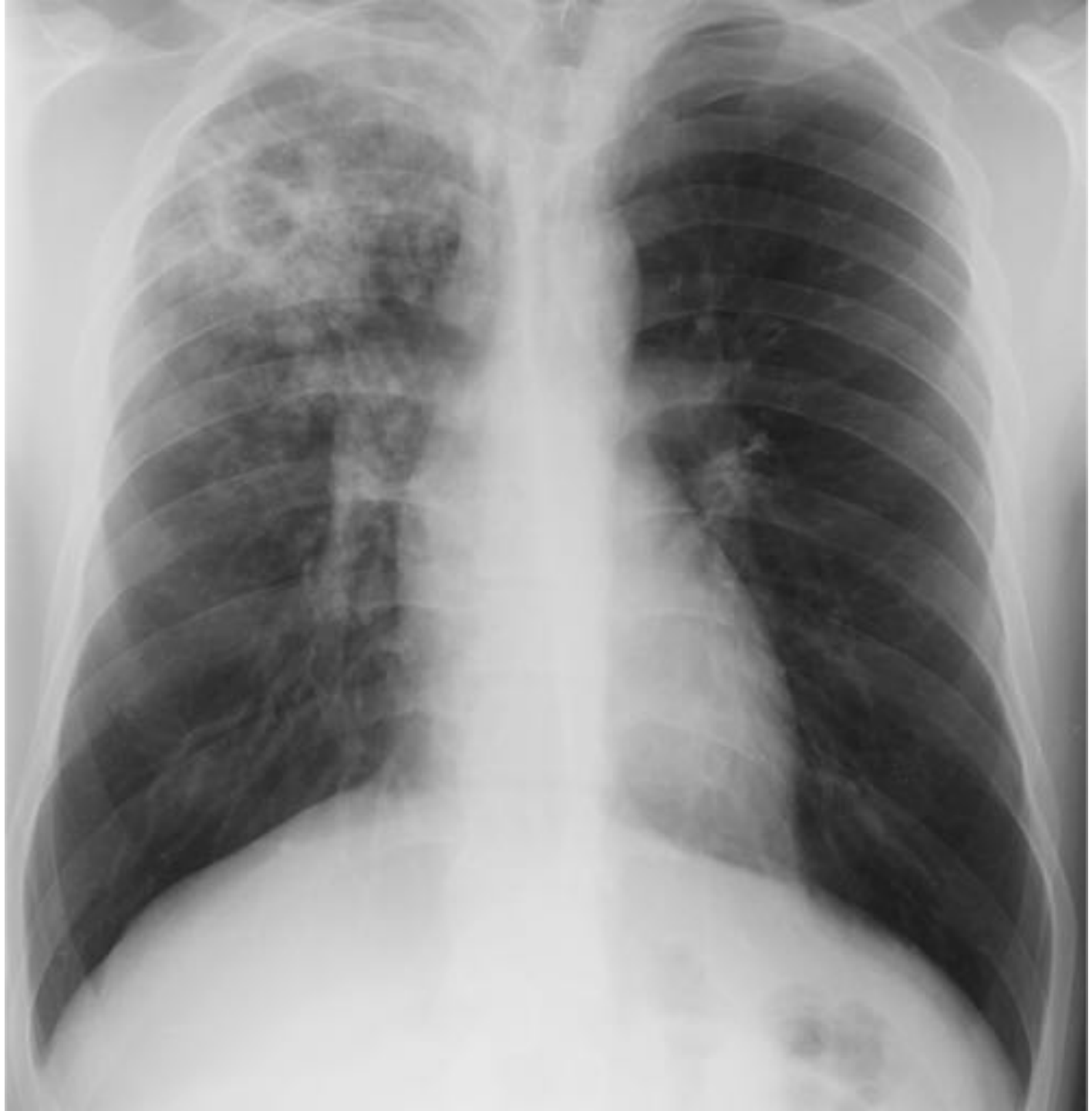


Barbie, Health and Medicine, 2013

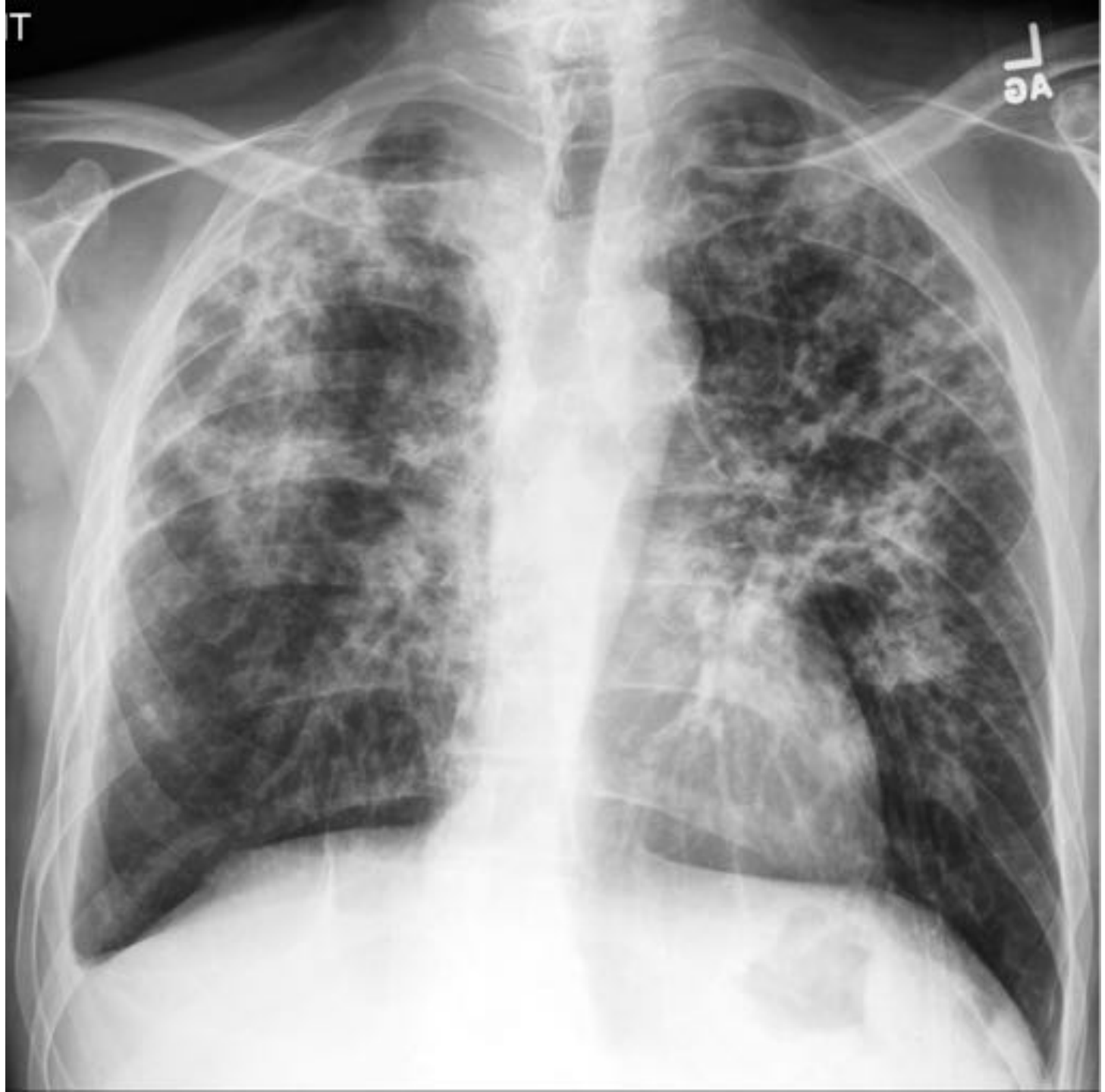
A TB Program View of Patient Care



Smear/ Culture / Xpert confirmation
Diagnosis: Active TB
Plan: 2HRZE/4HR



Smear/ Culture / Xpert confirmation
Diagnosis: Active TB
Plan: 2HRZE/4HR



Smear/ Culture / Xpert confirmation
Diagnosis: Active TB
Plan: 2HRZE/4HR

?

We'll extend treatment when we need to, but does this apply to contemporary regimens?

- Iterative trials have reduced the duration of rifamycin-based regimens giving us an evidence base on which to extend treatment for defined periods of time, applied on case by case basis, as needed (still not a great approach).
- But what about new regimens and new trials? 2HPZE/2HP (S31)? BPaL regimen (NixTB)? Or entirely new chemical entities for pan-TB regimens developed for 2 months? or 3 months? Will we know whether extension is safe, tolerable and effective? When to use it? For how long to extend?
- And do we ever seek to reducing duration? If so, when? By how much?

What proportion of patients are cured with the 6-month standard regimen for drug-susceptible pulmonary TB?

99% - SHRZ/HR	Fox, 1981
95-99% - SHRZ/HR(Z)	FDA guidance for pulmonary TB trials, 2013
96% - SHR	EA/BMRC Study R 1972
95.1% (PP)	RIFAQUIN, Jindani et al. 2014
92%	NIRT, Jawahar et al. 2013
92% (PP)	REMoxTB, Gillespie et al. 2014
88.7% (PP)	OFLOTUB Phase III, Merle et al. 2014
85.6% (MITT)	RIFAQUIN, Jindani et al. 2014
84% (MITT)	REMoxTB, Gillespie et al. 2014
82.8% (MITT)	OFLOTUB Phase III, Merle et al. 2014

Terms and Conditions

Composite endpoints may include non-TB-related outcomes.

Investigators and protocol team not responsible for variable responses in the trial, or for the actions or inactions of regimens. Fees may apply.

MITT = Modified Intention-To-Treat; PP = Per Protocol

nature medicine

Article | OPEN | Published: 05 November 2018

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

Marjorie Z. Imperial, Payam Nahid, Patrick P. J. Phillips, Geraint R. Davies, Katherine Fielding, Debra Hanna, David Hermann, Robert S. Wallis, John L. Johnson, Christian Lienhardt & Rada M. Savic

Nature Medicine **24**, 1708–1715 (2018) | Download Citation

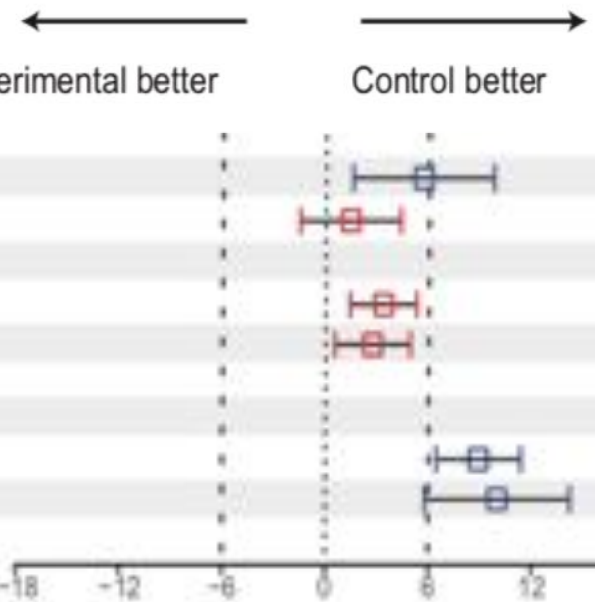
INFECTIOUS DISEASE

A stratified approach to tuberculosis treatment

Stratifying tuberculosis (TB) disease into minimal, moderate or severe disease may allow treatment duration to be tailored to disease severity. Minimal poor adherence is associated with poor treatment outcomes.

Gavin J. Churchyard

The current World Health Organization guidelines recommend using a standard 6-month regimen for treating all drug-susceptible pulmonary tuberculosis (TB), regardless of the extent of disease[1]. However, pulmonary TB has a spectrum of disease, ranging from minimal to severe. It has also long been recognized that 6 months of treatment may be unnecessarily long for a large majority of patients with drug-susceptible TB and that not all patients are cured with a 6-month standard regimen.



Validation Subgroups					
Smear 3+ and non-cavitary disease	394	23.1	17.3	5.8 (1.7, 9.9)	0.88
Smear ≤ 2+ and non-cavitary disease	706	19.6	18.0	1.5 (−1.4, 4.5)	0.02
Patient subgroups eligible for 4-month regimens: various definitions					
Smear < 2+ or non-cavitary disease	1591	19.9	16.5	3.4 (1.5, 5.4)	0.02
Smear < 2+ or Smear 2+ and non-cavitary disease	1186	19.1	16.3	2.8 (0.6, 5.0)	0.01
Hard to treat patient subgroups: various definitions					
Smear 3+ and cavitary disease	1162	26.4	17.6	8.8 (6.4, 11.3)	0.02
Smear 3+ and BMI < 17 kg/m^2	421	31.2	21.2	10 (5.8, 14.1)	0.68

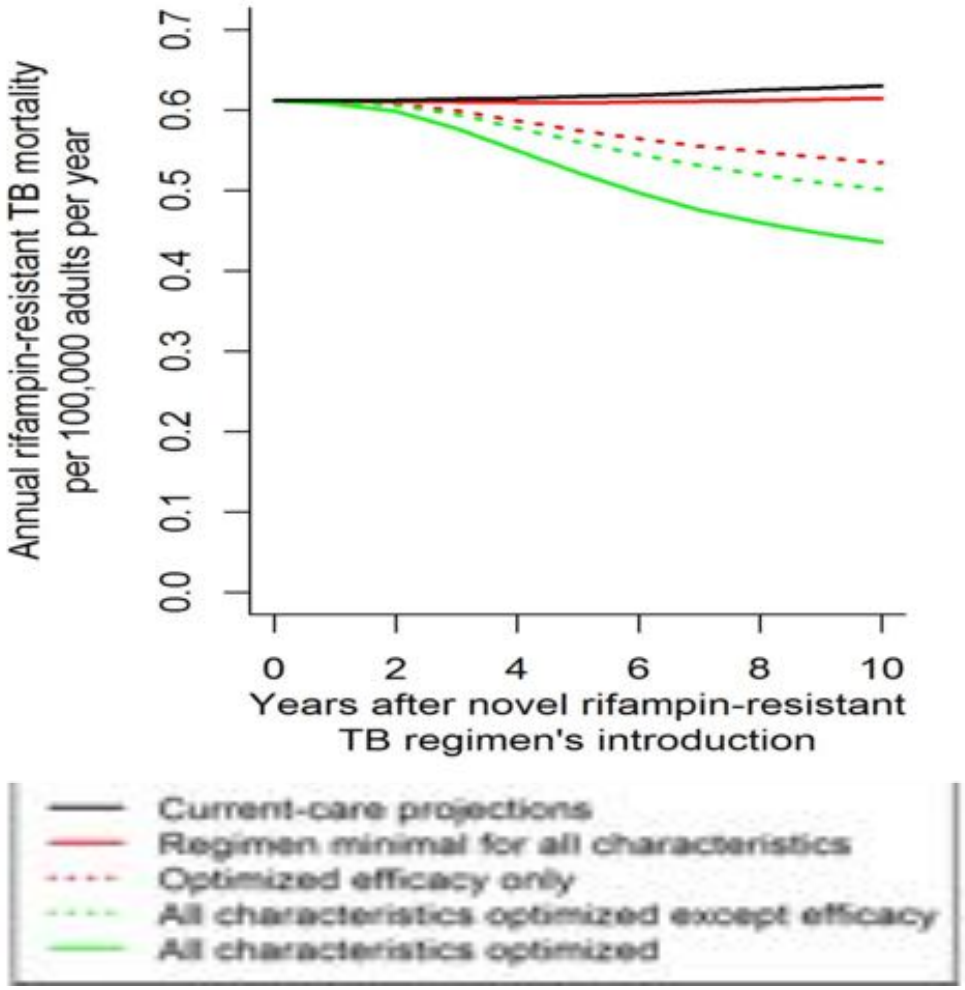
CURE-TB Strategy – Stratified Medicine for TB Care

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 a significant proportion of TB patients with less severe disease can be cured with shorter durations
2. **Enhancing cure rates for severe TB**
   - Achieve higher cure rates than is currently reported in the field and trials for TB overall, unfavourable outcomes are dominated by severe forms of the disease.
   - Stratification of risk using simple markers allows for programmatically relevant strategies.
3. **Patient-centered approach**
   - Selecting regimen with greater precision for burden of disease
4. **Alternative to “One Size Fits All” approach**
   - Patients in different risk groups receive different durations (or compositions) of regimens, but if stratification not feasible, ”one-size-fits-all” still available.

Epidemiologic model supports impact of enhancing efficacy over tx shortening

Regimen characteristic	Values modeled for novel RS TB regimen	Values modeled for novel RR TB regimen
Efficacy	• Minimal: 94% • Intermediate: 97% • Optimistic: 99%	Minimal: 76% Intermediate: 88% Optimistic: 94%
Barrier to resistance	• Minimal: 5% • Intermediate: 0.8% • Optimistic: 0%	Minimal: 10% Intermediate: 5% Optimistic: 0.8%
Preexisting novel-regimen resistance	• Minimal: 10% • Intermediate: 3% • Optimistic: 0%	Minimal: 15% Intermediate: 5% Optimistic: 0%
Medical contraindications	• Minimal: 11% • Intermediate: 5% • Optimistic: 0%	Minimal: 11% Intermediate: 5% Optimistic: 0%
Duration	• Minimal: 6 mo • Intermediate: 4 mo • Optimistic: 2 mo	Minimal: 20 mo Intermediate: 9 mo Optimistic: 6 mo
Tolerability/ease of adherence	• Minimal: 0% • Intermediate: 25% • Optimistic: 50%	Minimal: 0% Intermediate: 25% Optimistic: 50%



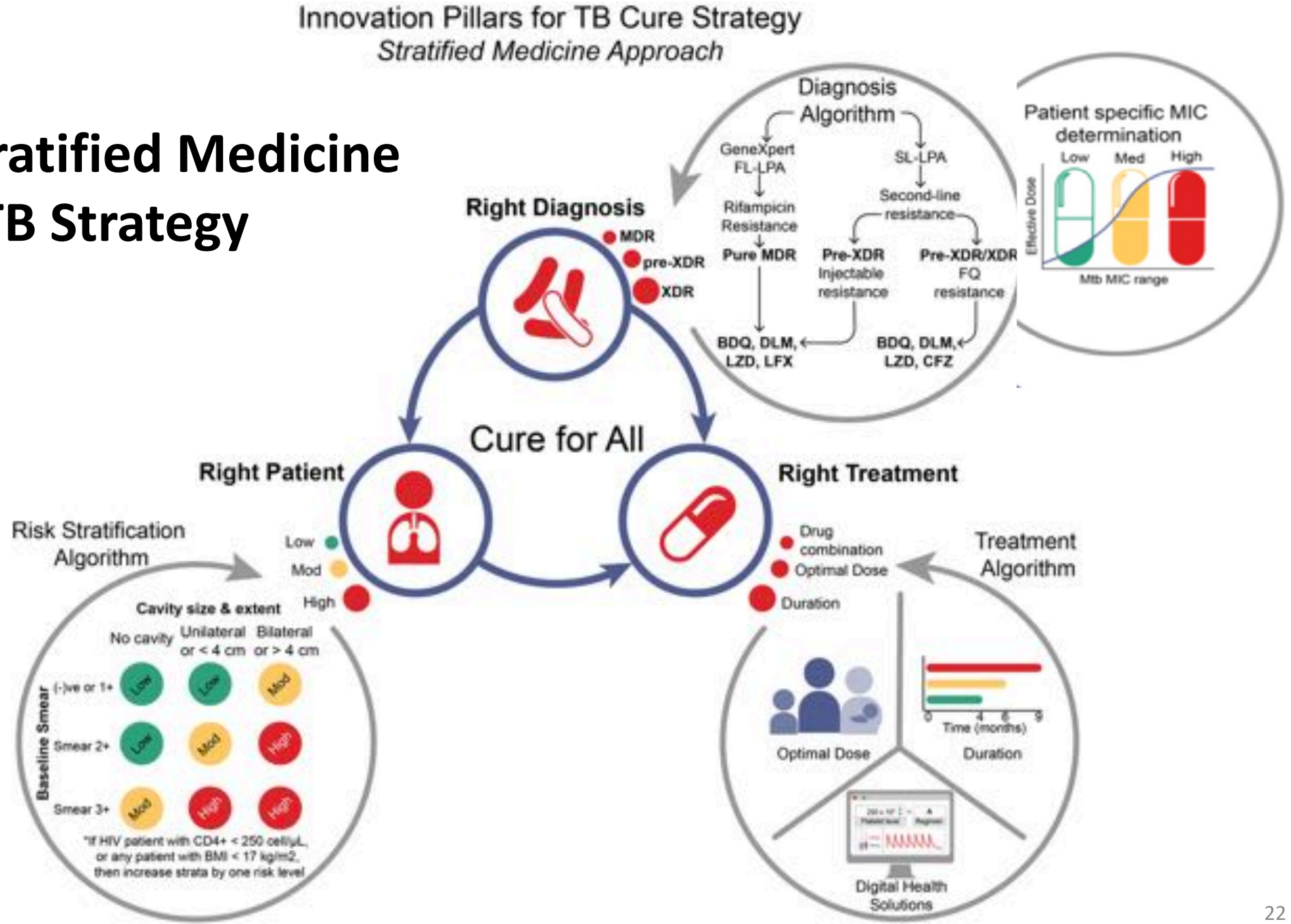
Emily A. Kendall Sourya Shrestha Ted Cohen Eric Nuermberger Kelly E. Dooley Lice Gonzalez-Angulo Gavin J. Churchyard Payam Nahid Michael L. Rich Cathy Bansbach Thomas Forissier Christian Lienhardt David W. Dowdy (2017) Priority-Setting for Novel Drug Regimens to Treat Tuberculosis: An Epidemiologic Model. PLOS Medicine 14(1): 2017

PLOS | MEDICINE

CURE-TB Strategy Trial

Stratified Medicine for Treatment of Drug-Susceptible TB: A randomized, open-label, controlled phase 3 clinical trial

Towards Stratified Medicine
The CURE-TB Strategy



CURE-TB Strategy Trial Hypotheses

A) Rifapentine-based regimen duration stratified based on baseline markers

- In previously untreated individuals with active drug-susceptible pulmonary tuberculosis treated with a regimen composed of rifapentine (P), isoniazid (H), pyrazinamide (Z) and ethambutol (E), given daily throughout, **with duration stratification based on baseline markers**, the proportion of participants who achieve durable cure (favorable outcome) will be superior to that observed in participants who are treated with a standard control regimen given daily throughout.

B) Rifapentine-based regimen duration stratified based on baseline and on-treatment markers

- In previously untreated individuals with active drug-susceptible pulmonary tuberculosis treated with a regimen composed of rifapentine (P), isoniazid (H), pyrazinamide (Z) and ethambutol (E), given daily throughout, **with duration stratification based on baseline markers with treatment extension based on on-treatment markers**, the proportion of participants who achieve durable cure (favorable outcome) will be superior to that observed in participants who are treated with a standard control regimen given daily throughout.

CURE-TB Strategy Trial Hypotheses

A) Rifapentine-based regimen duration stratified based on baseline markers

- In previously untreated individuals with active drug-susceptible pulmonary tuberculosis treated with a regimen composed of rifapentine (P), isoniazid (H), pyrazinamide (Z) and ethambutol (E), given daily throughout, **with duration stratification based on baseline markers**, the proportion of participants who achieve durable cure (favorable outcome) will be superior to that observed in participants who are treated with a standard control regimen given daily throughout.

B) Rifapentine-based regimen duration stratified based on baseline and on-treatment markers

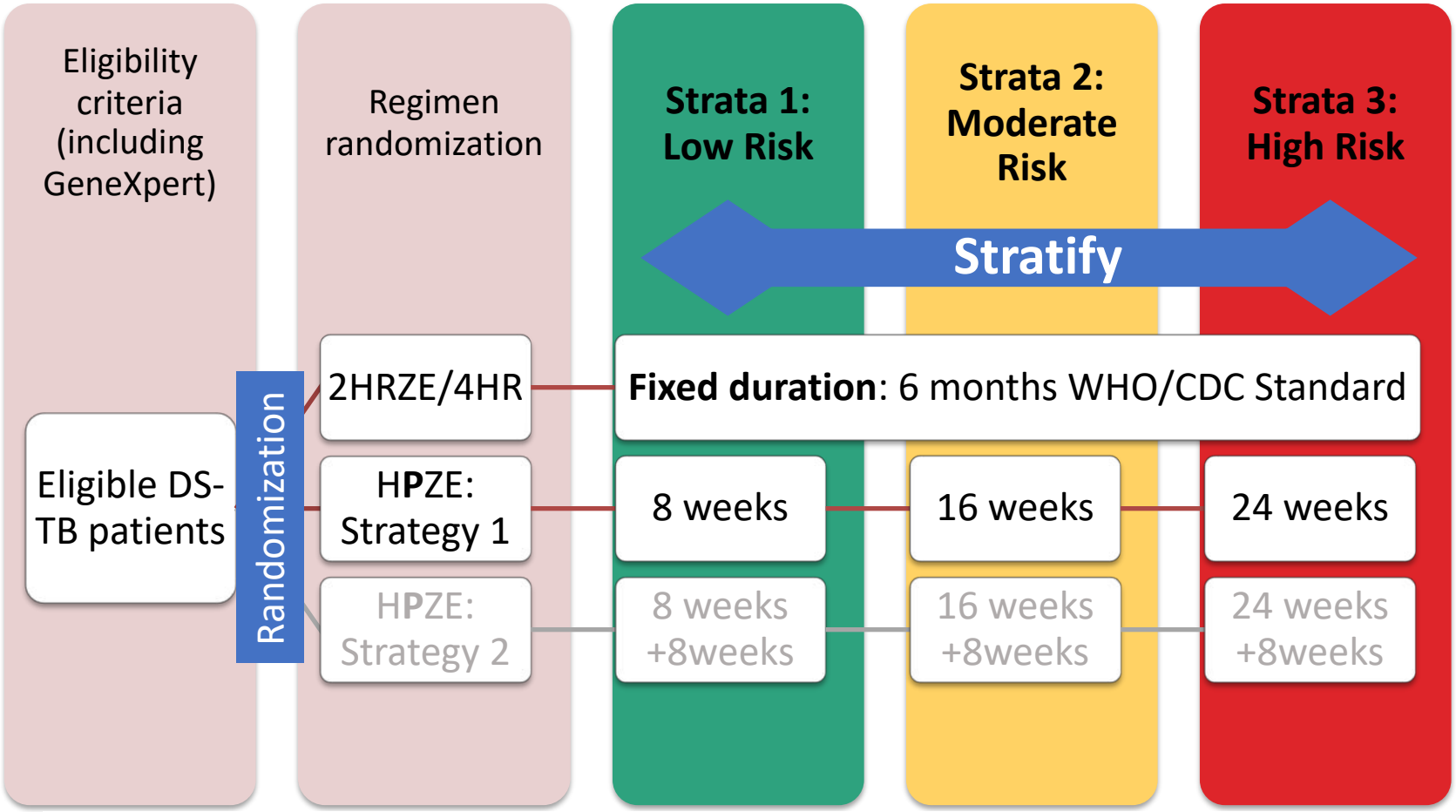
- In previously untreated individuals with active drug-susceptible pulmonary tuberculosis treated with a regimen composed of rifapentine (P), isoniazid (H), pyrazinamide (Z) and ethambutol (E), given daily throughout, **with duration stratification based on baseline markers with treatment extension based on on-treatment markers**, the proportion of participants who achieve durable cure (favorable outcome) will be superior to that observed in participants who are treated with a standard control regimen given daily throughout.

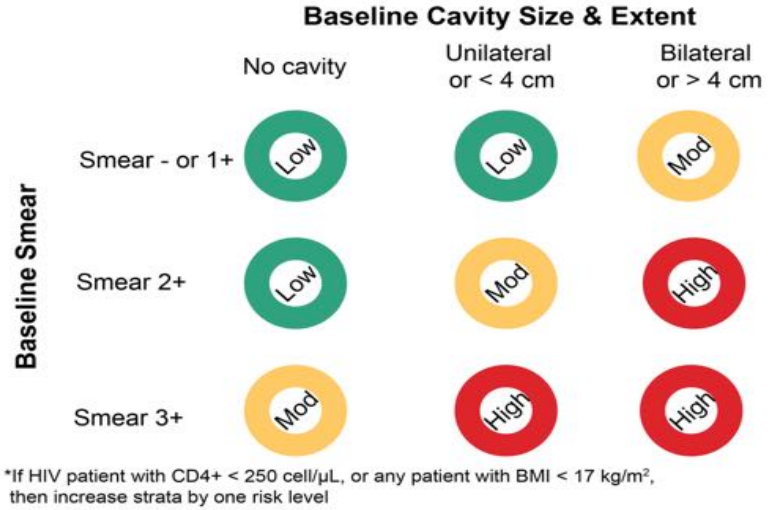
Design

- Build on results of TBTC S31
- An international, multicenter, randomized, controlled, open-label, 3-arm, phase 3 superiority trial (including strata-level non-inferiority tests).
- **Population**: Patients aged 10 years and older with newly diagnosed, previously untreated pulmonary tuberculosis
- **Number of Sites**: Multiple international sites of the Tuberculosis Trials Consortium.
- **Study Duration**: Duration per participant is approximately 18 months.

CURE-TB Strategy Trial in DS-TB

(Phase 3, Superiority, Pragmatic Trial to Cure All)





Strategy 1: Baseline Risk Markers

Strategy 2: Baseline/On Treatment Markers, with option to extend treatment by 8 weeks

H: Isoniazid, R: Rifampicin, P: 1200mg Rifapentine, Z: Pyrazinamide, E: Ethambutol

CURE-TB Strategy Protocol Development Progress

Topics addressed

- Leverage the systems, CRFs, protocol and experience of Study 31.
- CURE-TB proceeding regardless of S31 regimens meeting non-inferiority margins.
  - Impacts decisions around shortest duration feasible (e.g., 2 months versus 3 months)
- Design with S31 Regimen 2 (i.e., HPZE) for now.
- Define the all regimens by doses, not just duration, making up missed doses.
- Increase pragmatic features including the eligibility criteria
  - But acknowledging this is a first for testing stratified medicine principles in TB.
- Adherence measurement and enhancement is essential
  - DOT or other highly reliable approaches will be needed

Topics addressed

- Eligibility criteria:
  - HIV CD4 >100 threshold debated and remains
  - 12 years threshold reduced to 10 years
  - Lowered weight threshold from 40kg to 35kg
- For stratification markers, keep simple – smear grade or Xpert Ct, chest X-ray, HIV test, CD4 count, BMI, and sex
- For stratification system, use an algorithmic approach rather than table based approach. The TBTC systems for S31 can randomize and define strata assignments centrally.

Topics being addressed

- Focus on strategy 1 only, using baseline markers, dose counted, with duration possibly extended based on microbiology and adherence?
- Risk stratification algorithm development and refinement
- Can cycle thresholds be proxy for smear at baseline?
- In place of culture data, can cycle threshold be used for decision making on extension of continuation phase (most relevant to shortest regimen)?
- HIV ARV choice, should PK/DDI substudy to be built in for DTG with P1200mg daily?
- Configuring outcome definitions to be better fit for purpose for stratified medicine CURE-TB

Summary

- Lessons can be learned from the oncology field in stratifications of care
- A rich and robust evidence base now exists in TB to merit the conduct of a clinical trial to test stratified medicine approach to treating patients with greater precision than one-size-fit-all.
- Continued development of regimens with a one-size-fits-all viewpoint will continue to bring risk of failing to meet non-inferiority, driven by participants with highest burden of disease.
- Patient-centered at its core, stratified medicine allows for meaningful reductions in duration and toxicities for patients with minimal burden of disease, and maximally enhanced cure rates, reduced morbidity, transmission and drug resistance in patients with high burden disease
- Design of stratified medicine trials is underway, using field-friendly, immediately implementable tools for stratification.

CURE-TB Protocol Team

Rada Savic (Co-Chair)
Payam Nahid (Co-Chair)
Patrick Phillips (Trial Methodology)
Susan Dorman
April Pettit
Bob Belknap
John Johnson
Tony Garcia-Prats
Jennifer Green
Marjorie Imperial
Alvaro Schwalb
Mark Weiner
Alicia Wright
Barbara Seaworth
Harriet Mayanja-Kizza
Lindsay McKenna
Madeleine Lourens
Phan Ha
Nguyen Viet Nhung
Neil Martinson

<u>DCC Protocol Members</u>

Erin Bliven-Sizemore
Rosanna Boyd
Kia Bryant
Anne Purfield

With thanks to Katya Kurbatova, Kim Hedges, Lakshmi Peddareddy, and Yan Yuan for DCC contributions