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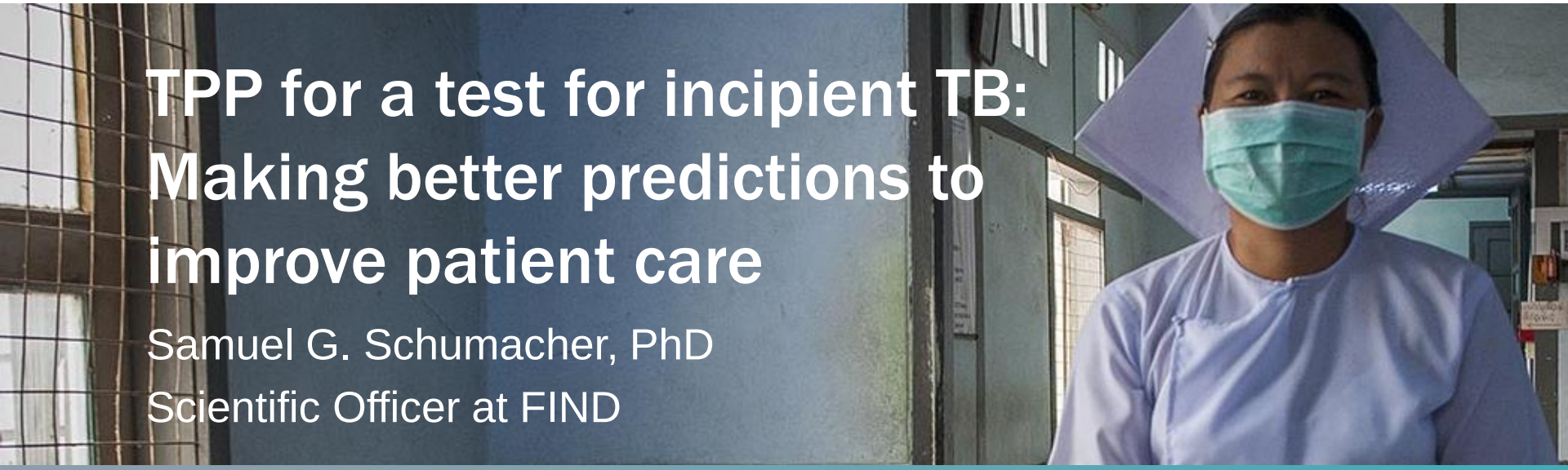
Because diagnosis matters



TPP for a test for incipient TB: Making better predictions to improve patient care

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47th Union World Conference on Lung Health, Liverpool,
NDWG Annual Meeting, 26 October 2016

Outline

1. TPP process and status
2. Performance targets
3. Next steps

1. TPP process and status

Step 1	• Drafted TPP by FIND and reviewed with experts
Step 2	• Meeting May 2015 with experts organized by NDWG, WHO and FIND >> revised document
Step 3	• Survey with a larger stakeholder group (May 2016)
Step 4	• FU meeting of NDWG LTBI taskforce (July 2016) >> revised document on FIND website
Step 5	• Final review in stakeholder meeting at WHO (Q1 2017) prior to finalization

2. Performance targets

Definitions & test conceptualization

Predict progression →

TB infection

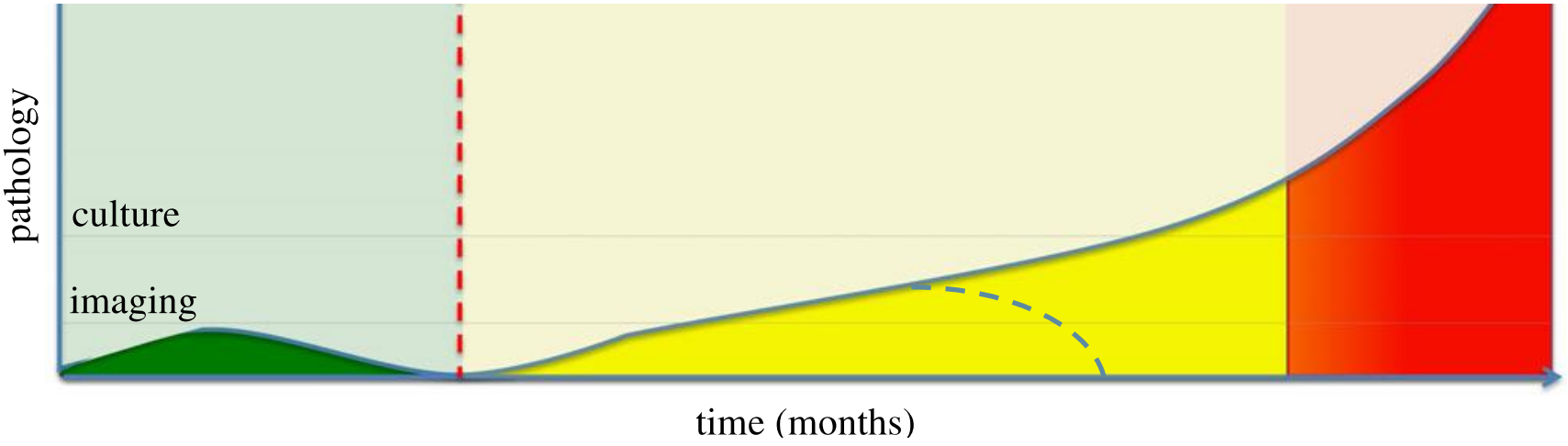
- Asymptomatic
- Positive TST / IGRA
- Without microbiological, radiological, or clinical evidence of active TB

~~Incipient TB disease~~

- Asymptomatic
- With
  - evidence of TB on radiographic and/or microbiological examination
  - or development of TB within “short” time after initial evaluation
- Subset of patients will not progress

TB disease

- Symptomatic
- With
  - positive microbiological test (confirmed TB)
  - or compatible clinical and/or radiology and/or histology for TB and started TB treatment (clinical TB)

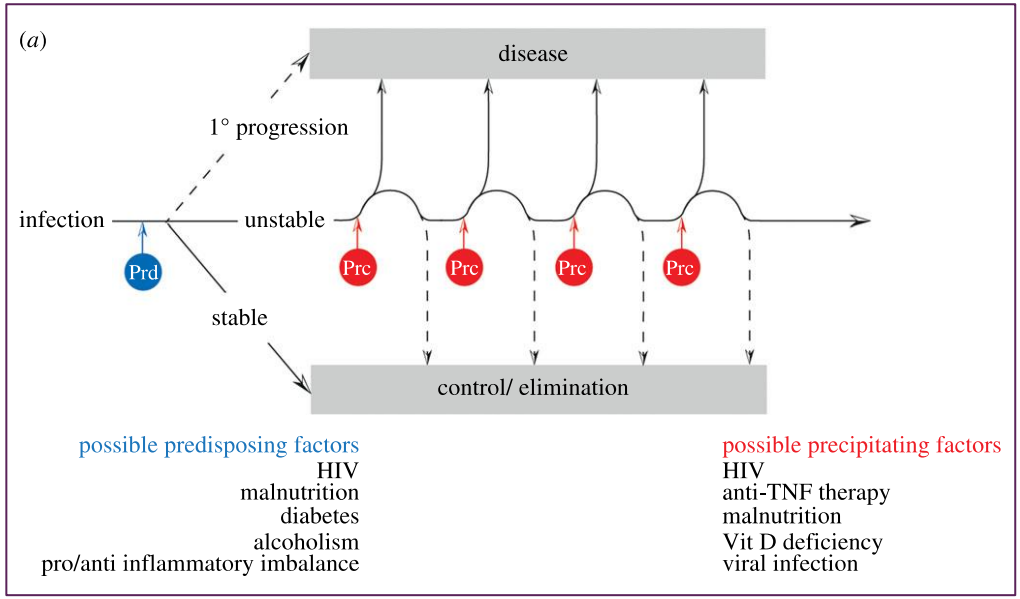


Adapted from Esmail 2014

Performance targets

Expectations for for prediction (vs diagnosis)

- Accuracy of prediction (prognosis) inherently lower than that of diagnosis
  - Statement about future vs present
  - Impossible to predict precipitating factors at time of testing



Esmail 2014

Reasons for imperfect Sensitivity (i.e. patient "supposed to stay healthy" but progresses)	Reasons for imperfect Specificity (i.e. patient "supposed to progresses" but stays healthy)
Precipitating factors "hitting" after testing	Prd/Prc factors removed/"addressed"
Reinfection	Self-cure
Hard to detect very early immune changes	Hard to find specific host immune response

Performance targets

Basic premises

- Key reason for limited uptake & adherence of IPT: risk/benefit-profile for preventive Rx not convincing for many (from perspective of patients, clinicians and PH) because
  - imperfect treatment (efficacy, duration, AEs etc.)
  - TST/IGRA accuracy for risk of progression very low (→ low PPV and high NNTT)

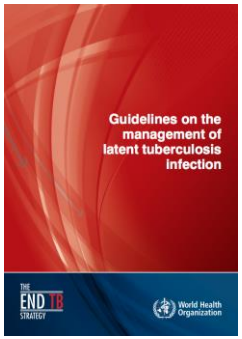
- Conceptualize desired performance based on PPV/NNTT
  - PPV captures patient perspective (If test+, how likely am I to have disease?)
  - NNTT captures clinician/PH perspective (If treating all test+, how many do I need to test and treat to prevent one case?)

- But specify performance targets using Sens/Spec
  - independent of incidence

Performance targets

Approach for setting targets

Step 1. Clarify what values of PPV and NNTT are currently found acceptable to patients/clinicians/policy makers



	Sensitivity	Specificity	PPV*	NNTT*
TST	58%	64%	3.2%	31
IGRA	80%	56%	3.6%	28

Source: SR by Kik et al. (prelim. results; unpublished)

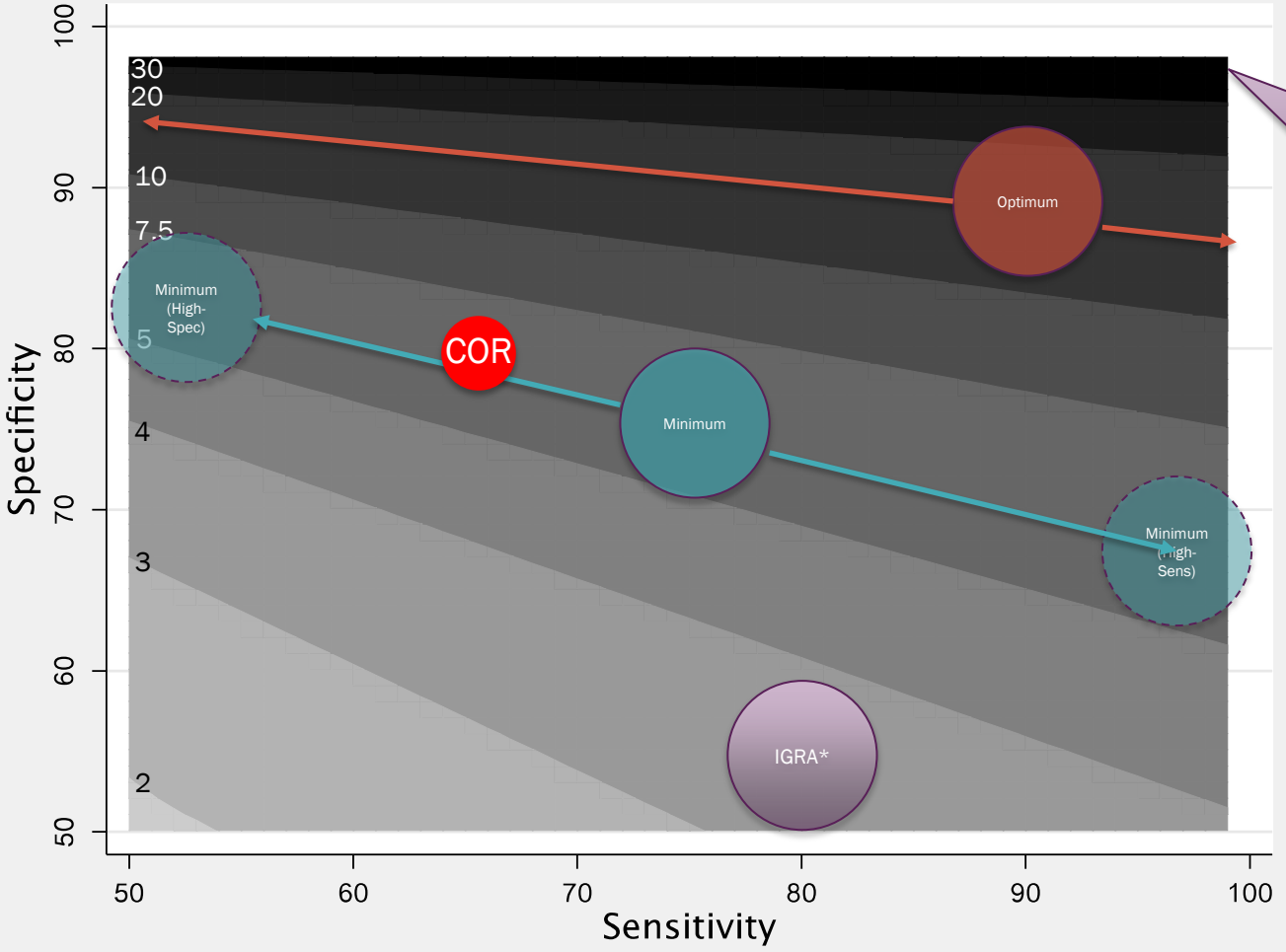
* Cumulative incidence of progression from TB infection to active TB: 2%; NNTT not considering imperfect treatment efficacy

Step 2. Defining combinations of sensitivity/specificity that are compatible with improved values of PPV and NNTT

- Minimal target: Increase PPV by factor of ~2 and (thus cutting NNTT by ~1/2) compared to IGRA
- Optimal target: Increase PPV by factor of ~5 and (thus cutting NNTT by ~1/5) compared to IGRA
- Use contour plots to assess combinations of sensitivity/specificity compatible with these proposed values of PPV/NNTT

What performance should we be aiming for?

PPV according to Sens/Spec for risk of progression



Note that a test with Se/Sp 99/99 would yield PPV=67%

Note: Cumulative incidence of progression from TB infection to active TB: 2%

* Based on updated, unpublished SR/MA by Kik et al.

Observations

1. Reaching a very high PPV is impossible for a test aiming to *predict* a *rare* event

2. Proposed minimum target represents an important improvement
(and seems achievable within 5-year time horizon of TPP)

3. Targeted PPV/NNTT can be achieved with various combinations of Sens/Spec (and preferences for trade-offs will vary between stakeholders)

4. Repeat testing is likely to increase both Sens and Spec

3. Next steps

- Publication of report of TPP survey results and Milan meeting
- Stakeholder meeting at WHO to achieve consensus and finalize TPP
- Publish WHO-endorsed TPP

Thank you

Thank you to:

- Claudia Denkinger
- NDWG LTBI taskforce
- TPP Survey participants