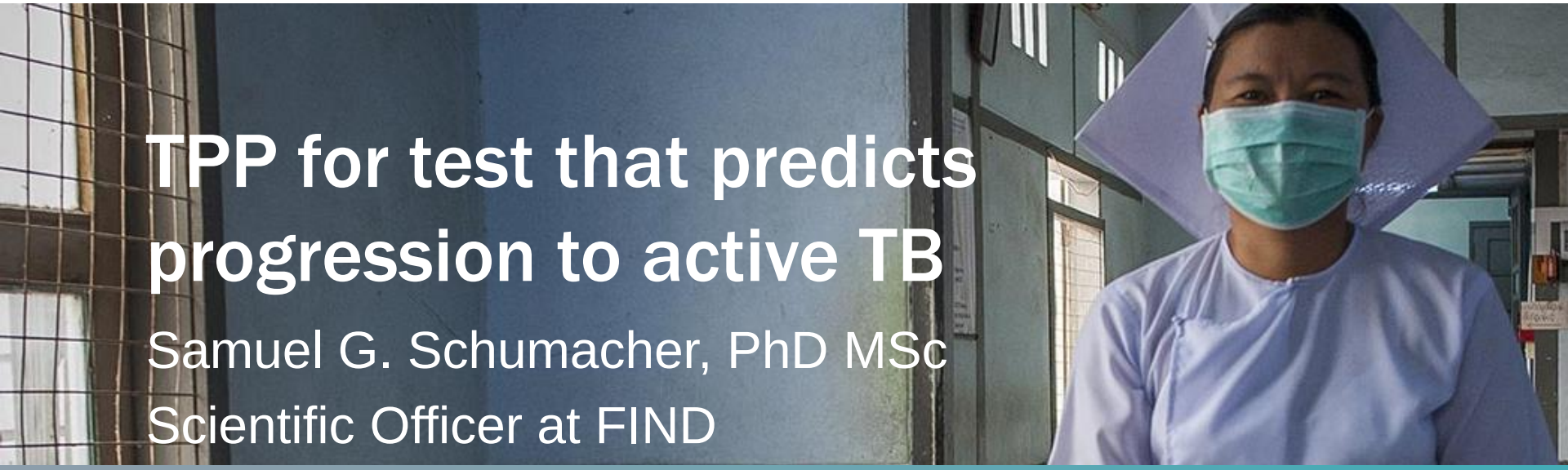
FIND

Because diagnosis matters



TPP for test that predicts progression to active TB

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Outline

Focus on areas with most disagreement in survey

1. Intended use / goal / target condition
2. Performance targets
3. Cost

TPP

Time horizon

- 5 years

Targets

- Optimal: aspirational, ambitious
- Minimal: feasible but important improvement

1. Intended use / goal / target condition

Goal / target condition

Rationale for 2-year time horizon

- Performance targets for predictive test only meaningful in reference to a specified time horizon
- 2 years reasonable pragmatic choice because
  - ~60% of progression occurs in first 2 years (~45% in year 1)
  - Most promising approach to predicting progression may be via detection of incipient TB (which by definition will be relatively close to onset of active disease)
  - Late progression may occur due to precipitating factors, which cannot be predicted in advance
  - Feasibility for conducting studies and getting timely results

Ruling-out active TB

- Remove as requirement from ’optimal’?

2. Performance targets

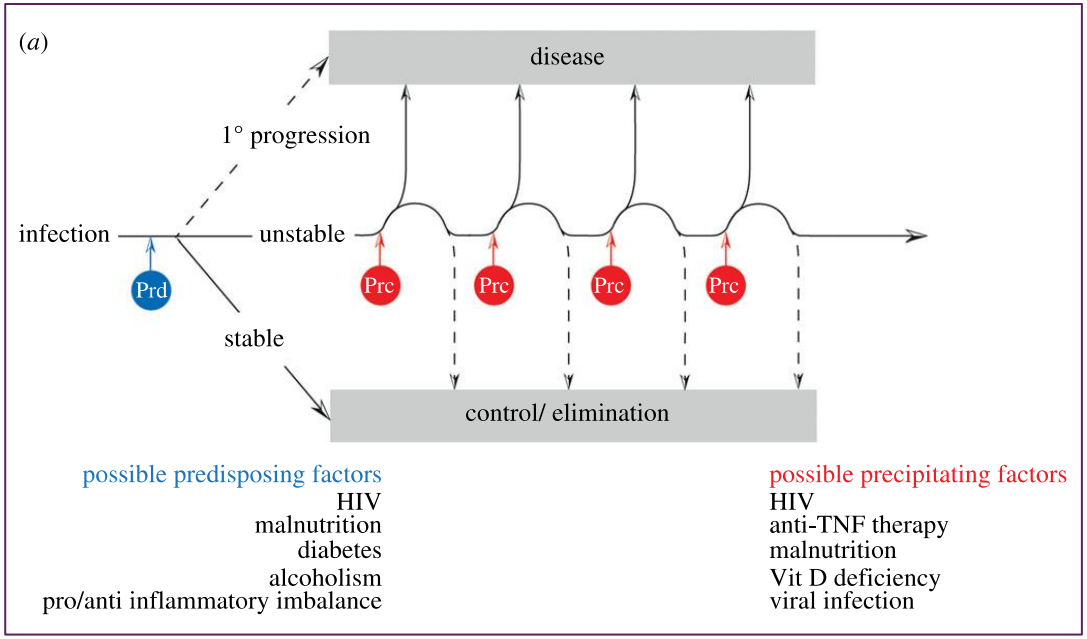
Performance targets

- 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)

- Premise: risk/benefit-profile is key, PPV and NNTT useful metrics for the determination of performance targets
  - 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: use sensitivity/specificity (or LR+/-) as performance metrics, since these are independent of incidence (picked based on desired PPV and NNTT)

Expectations for performance targets for prediction (vs diagnosis)

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



2-step approach to determining performance targets

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

- Look at groups for whom IPT is currently recommended by WHO
- Estimate PPV/NNTT in those groups

Step 2. Assess what combinations of sensitivity/specificity are compatible with acceptable values of PPV and NNTT

- PPV/NNTT ~ Se(RoP) + Sp(RoP) + RoP + Eff(Rx)
- Look at contours of PPV/NNTT across combinations of Se/Sp
- Investigate differences between key subgroups

2-step approach to determining performance targets

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

- Look at groups for whom IPT is currently recommended by WHO
- Look at estimates of Sens/Spec/LR+ and PPV/NNTT in those groups

Two-prong approach of LTBI management for low and high TB burden countries

COUNTRY GROUP	AT RISK POPULATIONS	TESTING ALGORITHM
High-income and upper middle-income countries with an estimated TB incidence rate of less than 100 per 100 000 population	Strongly recommended for the following risk groups: 1) People living with HIV; 2) Adults and children who are household or close contacts of pulmonary TB cases; 3) Clinical indications – patients with silicosis; patients initiating anti-TNF treatment; patients on dialysis; transplant patients.	Exclude active TB using TB investigations. A positive IGRA or TST test result is required to diagnose LTBI.
Resource-limited and other middle-income countries with an estimated TB incidence rate of more than 100 per 100 000 population	1) People living with HIV; 2) Children under 5 years of age who are household contacts of a TB case.	Exclude active TB using TB investigations. An LTBI test is not required prior to LTBI treatment, but is encouraged for people living with HIV. IGRA should not replace TST.


Articles

Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis

Molebogeng X Rangaka, Katalin A Wilkinson, Judith R Glynn, Daphne Ling, Dick Menzies, Judith Mwansa-Kambafwile, Katherine Fielding, Robert J Wilkinson, Madhukar Pai

Predictive accuracy of TST/IGRA

		Sensitivity	Specificity	PPV*	NNTT*
Rangaka / Kik	TST	72% / 58%	41% / 64%	2.4% / 3.2%	41 / 31
	IGRA	72% / 80%	50% / 56%	2.9% / 3.6%	35 / 28

- 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

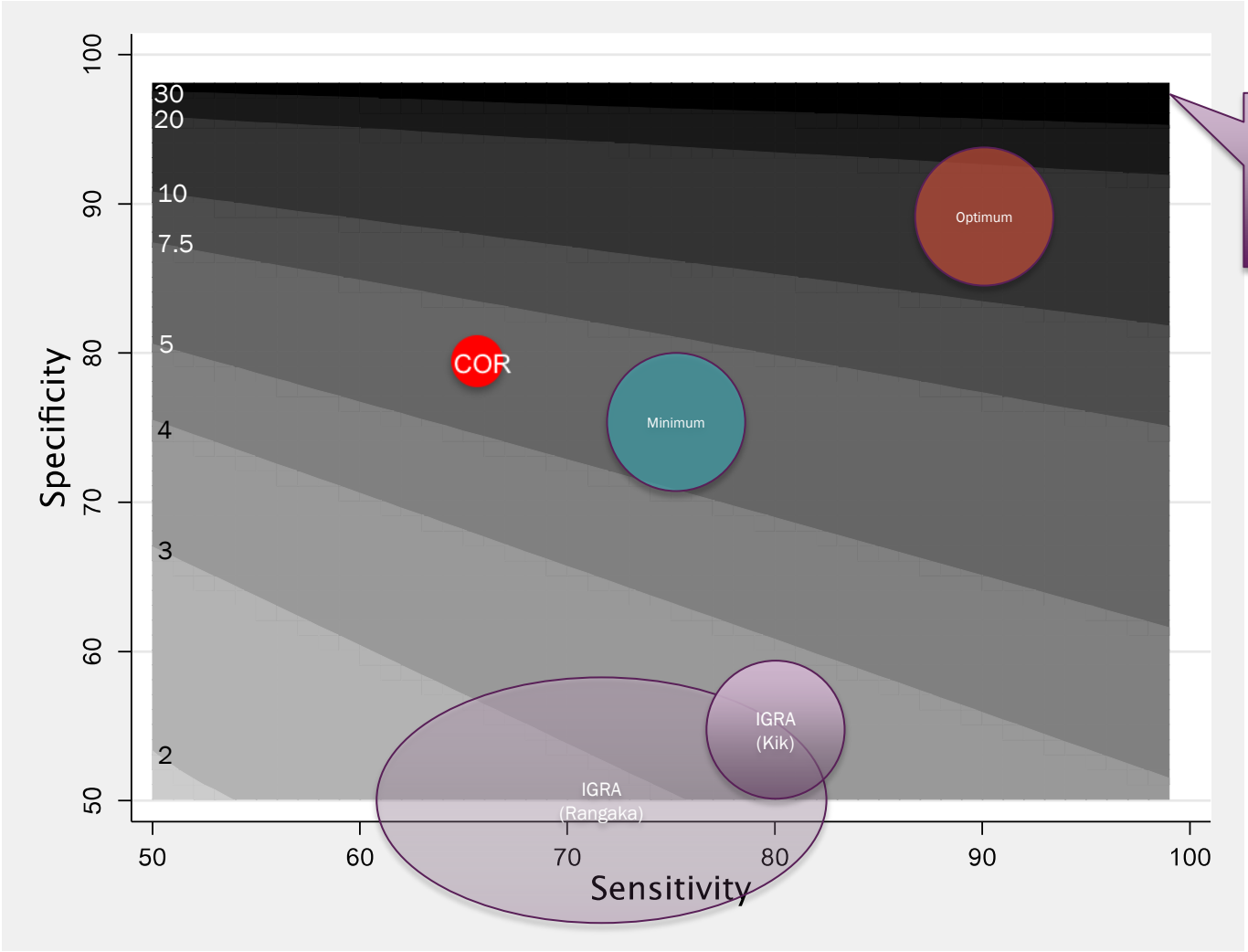
*Based on 2% incidence

2-step approach to determining performance targets

Step 2. Assess what combinations of sensitivity/specificity are compatible with acceptable values of PPV and NNTT

- PPV/NNTT ~ Se(RoP) + Sp(RoP) + RoP + Eff(Rx)
- Look at contours of PPV/NNTT across combinations of Se/Sp
- Investigate differences between key subgroups

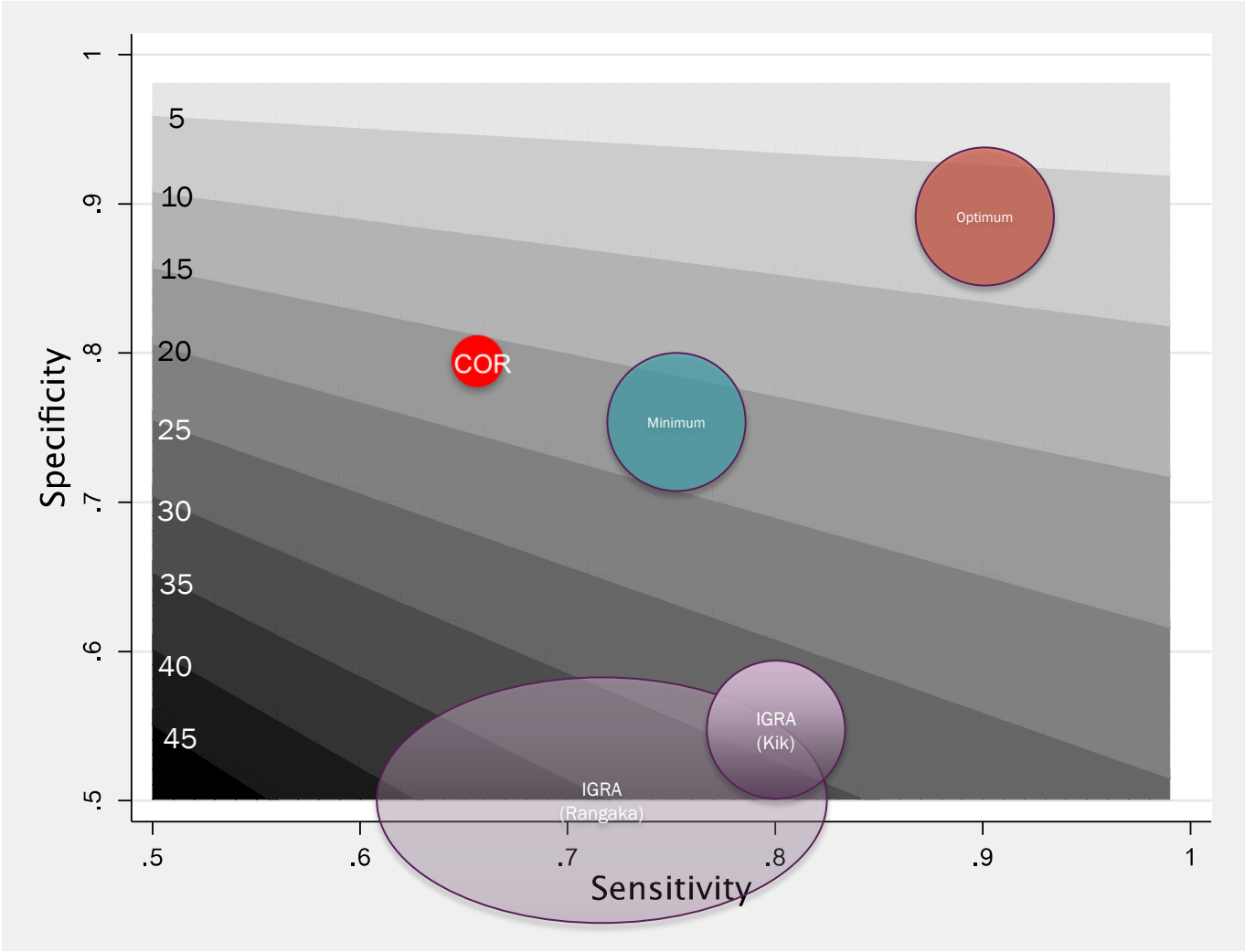
‘Positive Predictive Value’ according to Sens/Spec for risk of progression



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

cumulative incidence: 2%

‘Number Needed to Test & Treat’ according to Sens/Spec for risk of progression



cumulative incidence: 2%

Conclusion

- Need to spell out rationale behind targets in sufficient detail (perhaps including figures)
- Reaching a very high PPV is impossible
- Specifying performance targets as LRs (representing contours) may be preferable to Sens/Spec
- Proposed minimum target represents an important improvement and seems achievable within 5-year time horizon of TPP

List of topics for discussion

1. Intended use / goal / target condition
   - 2-year time horizon
   - Ruling-out active TB
2. Performance targets
3. Cost
4. Target population
5. Test type (read-out)