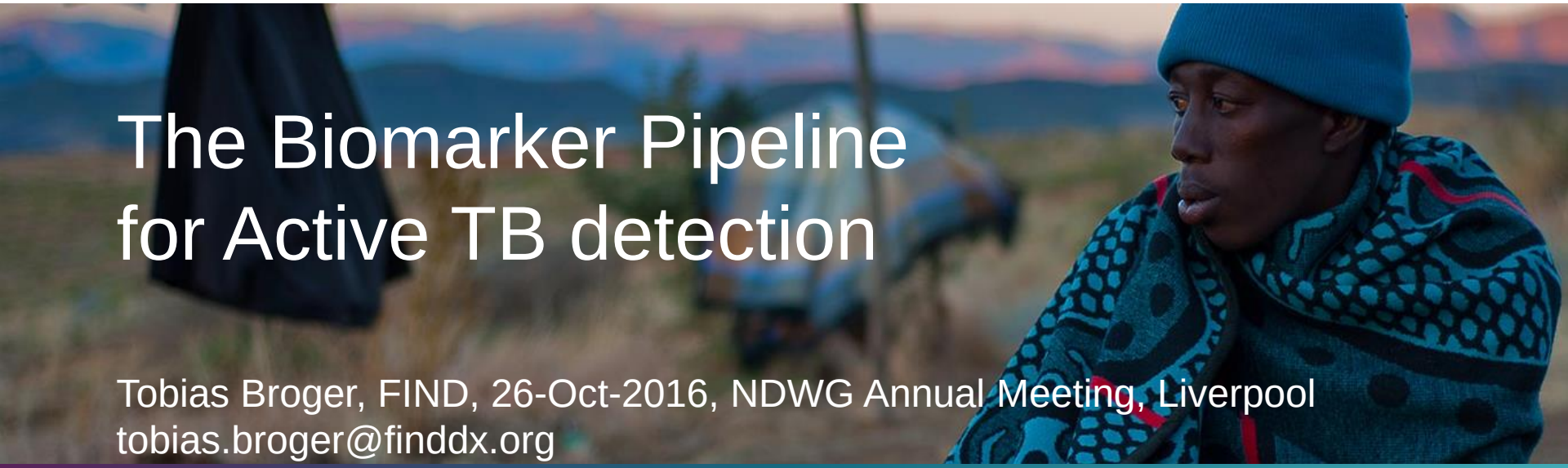
FIND

Centre international de TB McGill

McGill International TB Centre

Stop TB Partnership

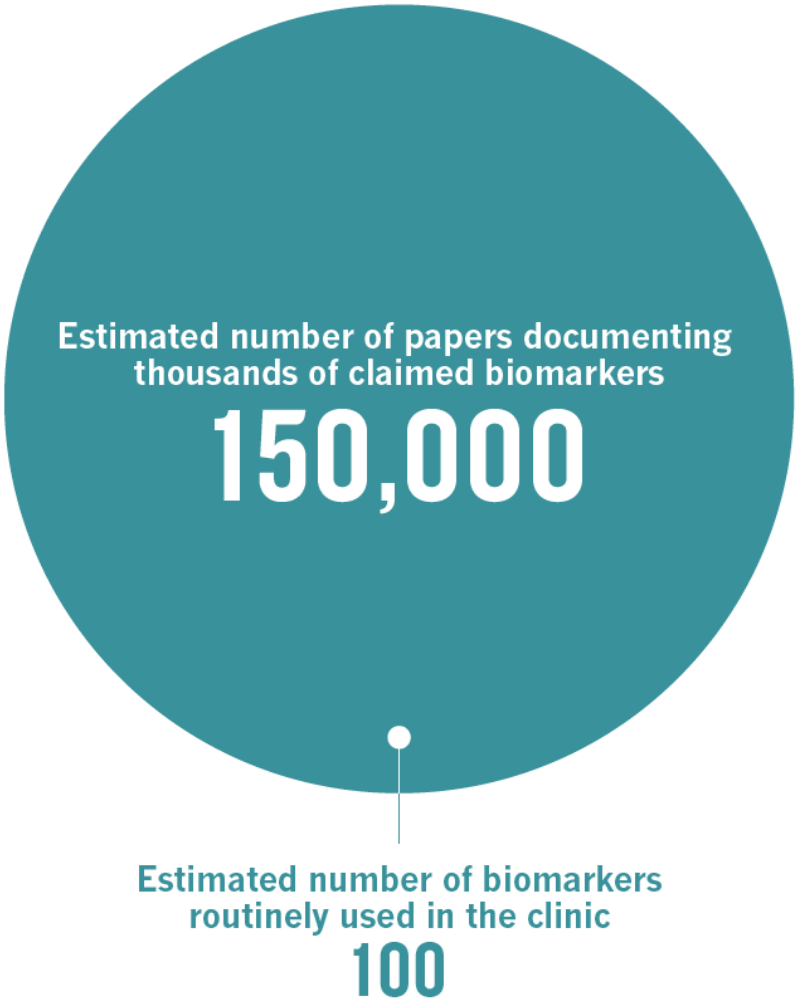
NDWG Biomarker Task Force



The Biomarker Pipeline for Active TB detection

Tobias Broger, FIND, 26-Oct-2016, NDWG Annual Meeting, Liverpool
tobias.broger@finddx.org

The problem: Many biomarker studies, limited impact



- Numerous reports on biomarkers from exploratory studies
- Often based on few, poorly characterized samples
- Limited independent confirmation and prospective validation
- Little translation into clinically useful tools
- Limited knowledge and data sharing
- Failure to articulate the intended use case

[Poste, Nature, 2011]

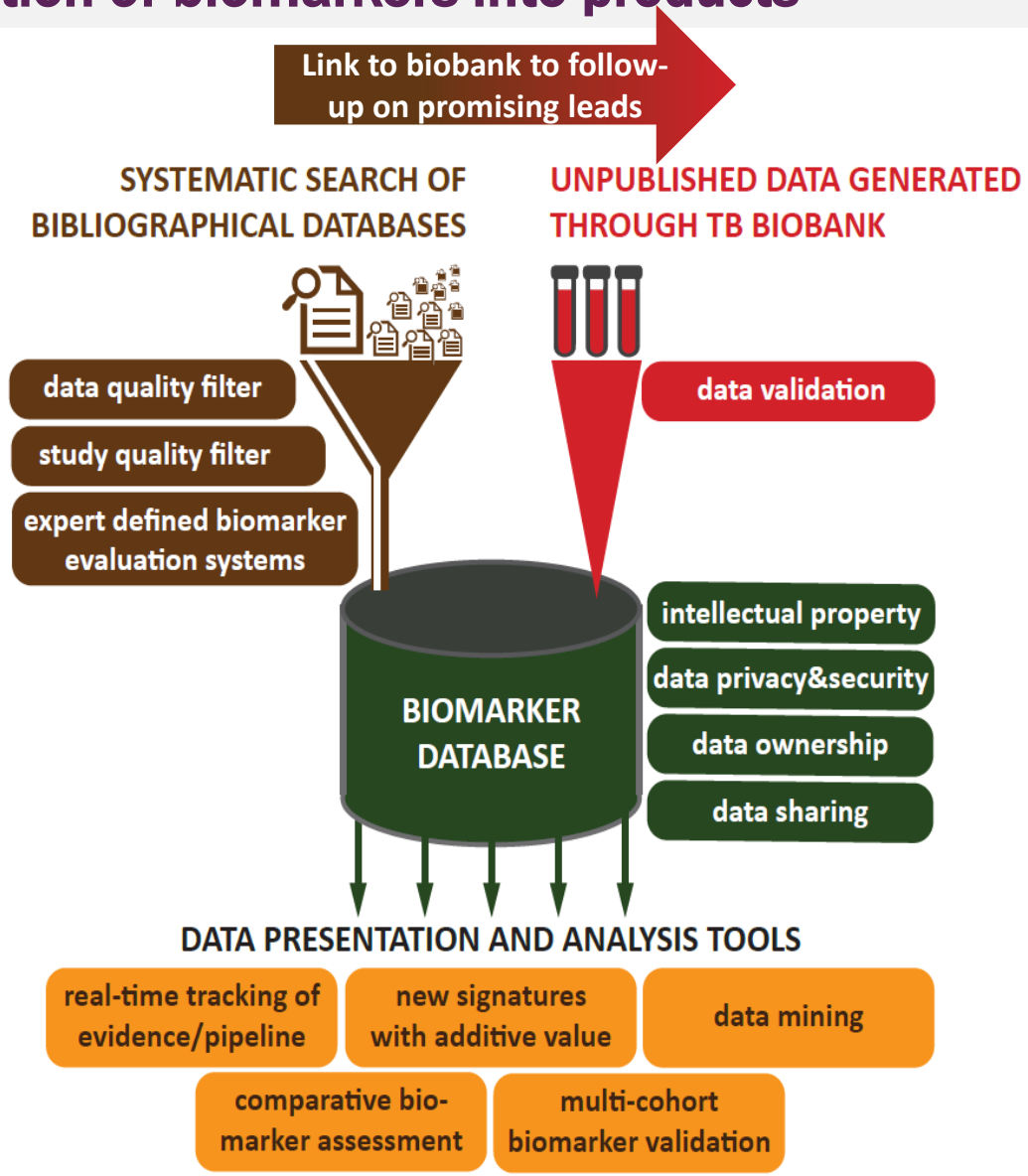
A TB Biomarker Database
to accelerate the translation of biomarkers into products

What data?

Quality Filter

How?

Why?



The intended use cases

TPP1: A non-sputum based TB diagnostic test for the purpose of initiating treatment

OR

TPP2: A triage test using a non-sputum sample that identifies patients for confirmatory testing

on-going systematic search!

Latent to Active Progression | **Active** | **Treatment Monitoring**

Based on WHO endorsed TPP: http://www.who.int/tb/publications/tpp_report/en/

«Active TB detection»: Relevant high-priority TPPs

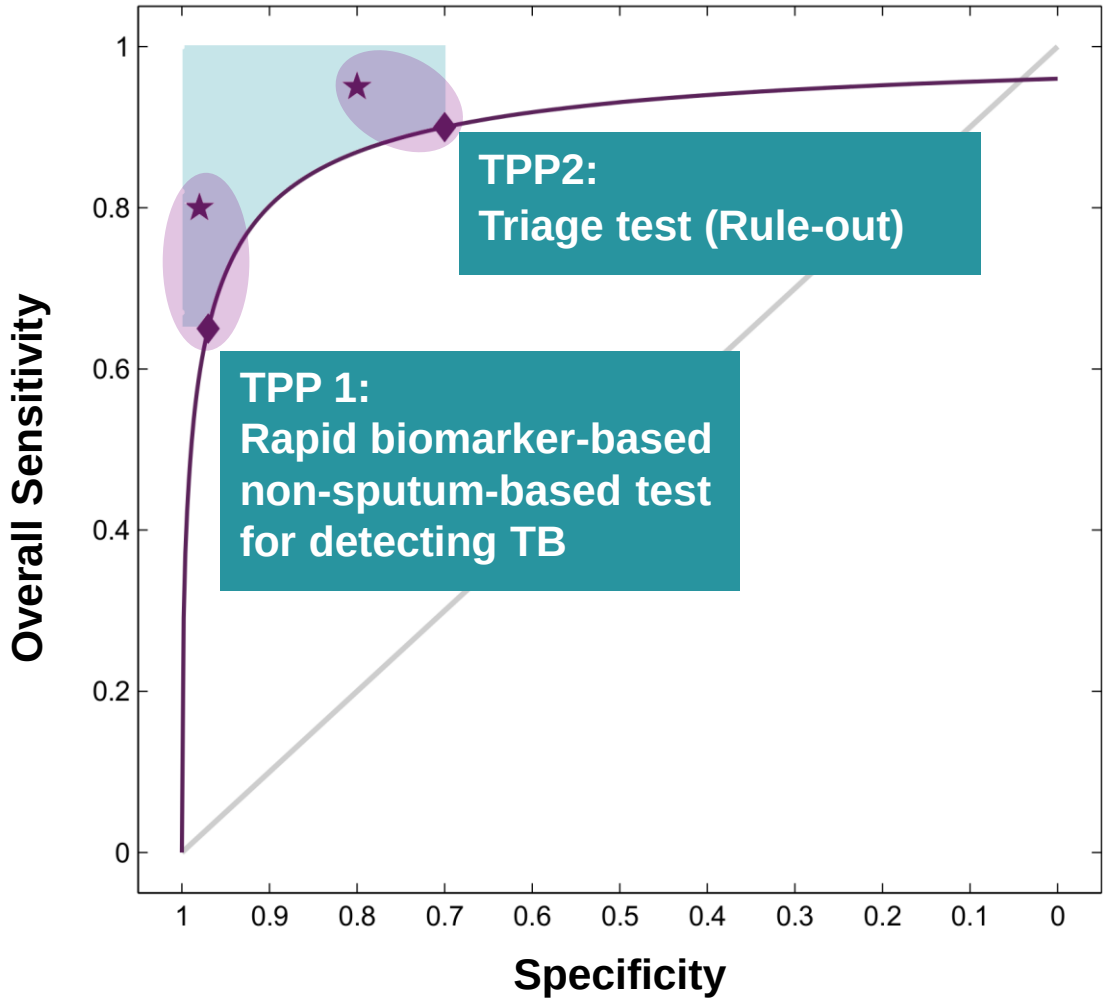
	TPP1: Non-sputum based detection test		TPP2: Triage test (Rule-out)	
Characteristic	**Optimal**	**Minimal**	**Optimal**	**Minimal**
Goal	• Biomarker based test • non-sputum samples • **for the purpose of initiating treatment**		• identify patients with any symptoms of or risk factors for active (pulmonary) TB • **rule-out disease or refer to confirmatory testing**	
Sensitivity	>80% overall ≥98% SS+ ≥68% S-C+	>65% overall (similar to smear microscopy)	>95% overall	>90% overall
Specificity	≥98%	≥98%	>80%	>70%
Time-to-result	<20 mins	<60 mins	<5 mins	<30 mins
Price	<US$ 4	<US$6	<US$1	< US$ 2
Instrument	Not needed	Small, portable, or handheld, <1 kg	Not needed	Small, portable, or handheld, <1 kg
Manual preparation of samples	Integrated or no manual preparation	Limited number of steps, no precise measuring	Integrated or no manual preparation	only 2 steps
Setting	Health post without lab and higher levels	Primary health-care clinics with lab or microscopy center or higher	Community or village level or higher levels	Health post or primary health-care clinics or higher

Based on WHO endorsed TPP: http://www.who.int/tb/publications/tpp_report/en/

Performance targets

Optimal targets ★

Minimal targets ◆



«Fill» the database with published evidence

Approach

- **Systematic literature search** to synthesize biomarker knowledge
- Search for all «target conditions»: risk of progression, detection of active TB, treatment monitoring
- Full-text extraction for **«detection of active TB»**

Goals

- Show the **status** of the TB biomarker pipeline
- Identify the **most promising biomarkers and biomarker classes** for POC test development
- Data input for the database

Included studies

- Studies reporting on **diagnostic performance of «non-DNA» biomarkers**
- Studies **≥30 participants or human samples**
- Published **2010 - 2015**

Included studies

Identification

5549 records identified through database searching + 8 from other sources

Screening

3417 records after duplicates removed

2253 excluded on the basis of title or abstract
- 1611 target condition
- 125 animal
- 161 language
- 91 index test
- 265 review

Eligibility

1164 full-text articles screened

876 excluded on the basis of title or abstract
- 56 target condition
- 3 animal
- 3 language
- 546 index test
- 10 no performance data
- 50 size ≤30 samples/participants
- 208 other

Included

288 studies included describing 413 biomarkers or signatures

preliminary unpublished

Included biomarkers per class

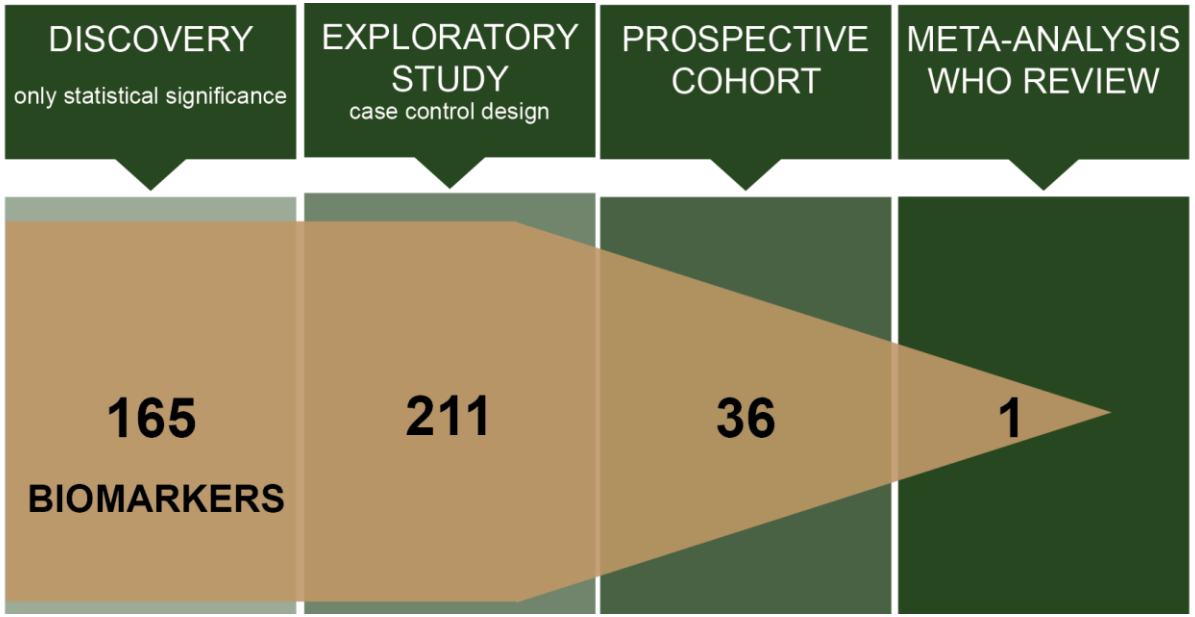
Biomarkers or Biomarker Signatures n=413	Host n=373	Protein biomarkers n=245	antibody
			cytokines
			protein peak
			enzymes
			cell surface protein
			glycoprotein
			lectin
			transmembrane protein
		Transcriptional biomarkers n=35	microRNA
			mRNA
			hematological markers
			metabolomic biomarkers
			other
	Pathogen n=40	Protein biomarkers n=12	antigens
			enzymes
			metabolic biomarkers
			transcriptional biomarkers
			mycolic acid
			lipid
			VOC
			other

Not for on-line publication

preliminary unpublished

The biomarker pipeline for active TB

Level of Evidence

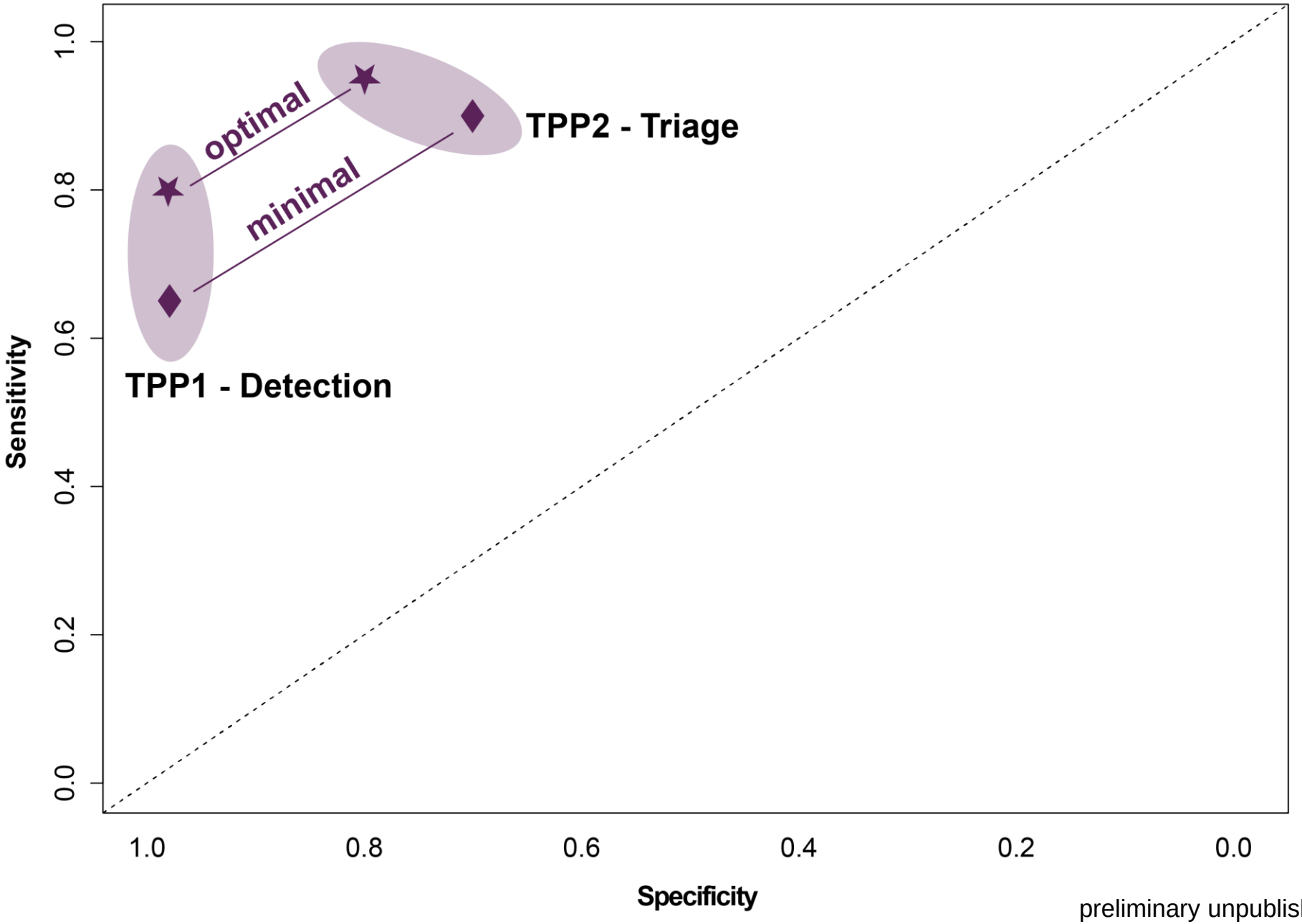


Quality of Evidence

	DISCOVERY	EXPLORATORY STUDY	PROSPECTIVE COHORT
REFERENCE STD CULTURE BASED?	67%	78%	84%
CONTROL GROUP Other Resp. Dis.?	18%	18%	77%
CONSECUTIVE SAMPLING?	17%	13%	26%
BLINDING?	15%	24%	49%
STUDY SIZE ≥100 ?	18%	53%	42%

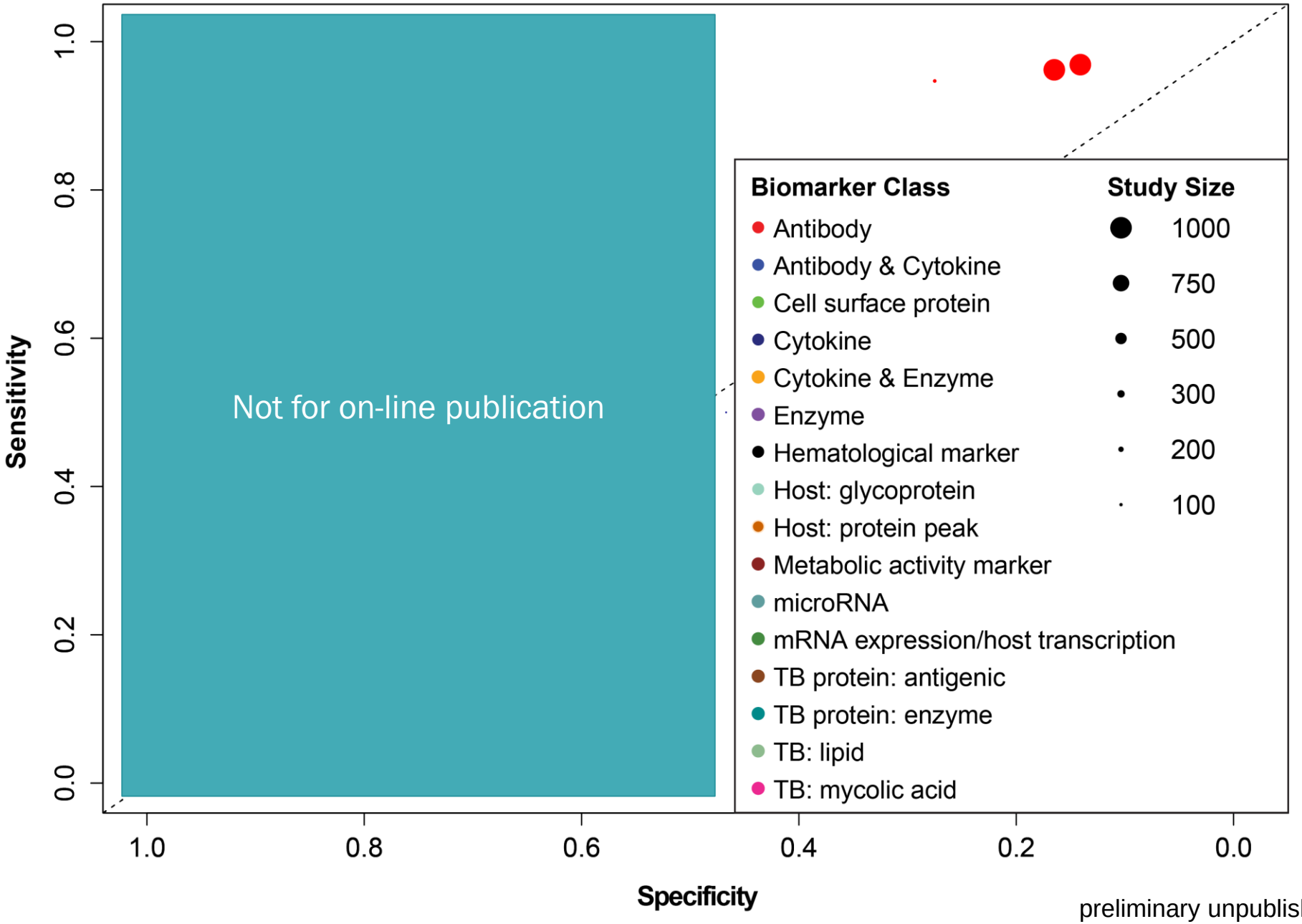
preliminary unpublished

Targets



preliminary unpublished

Blood biomarker entries with culture based reference std.



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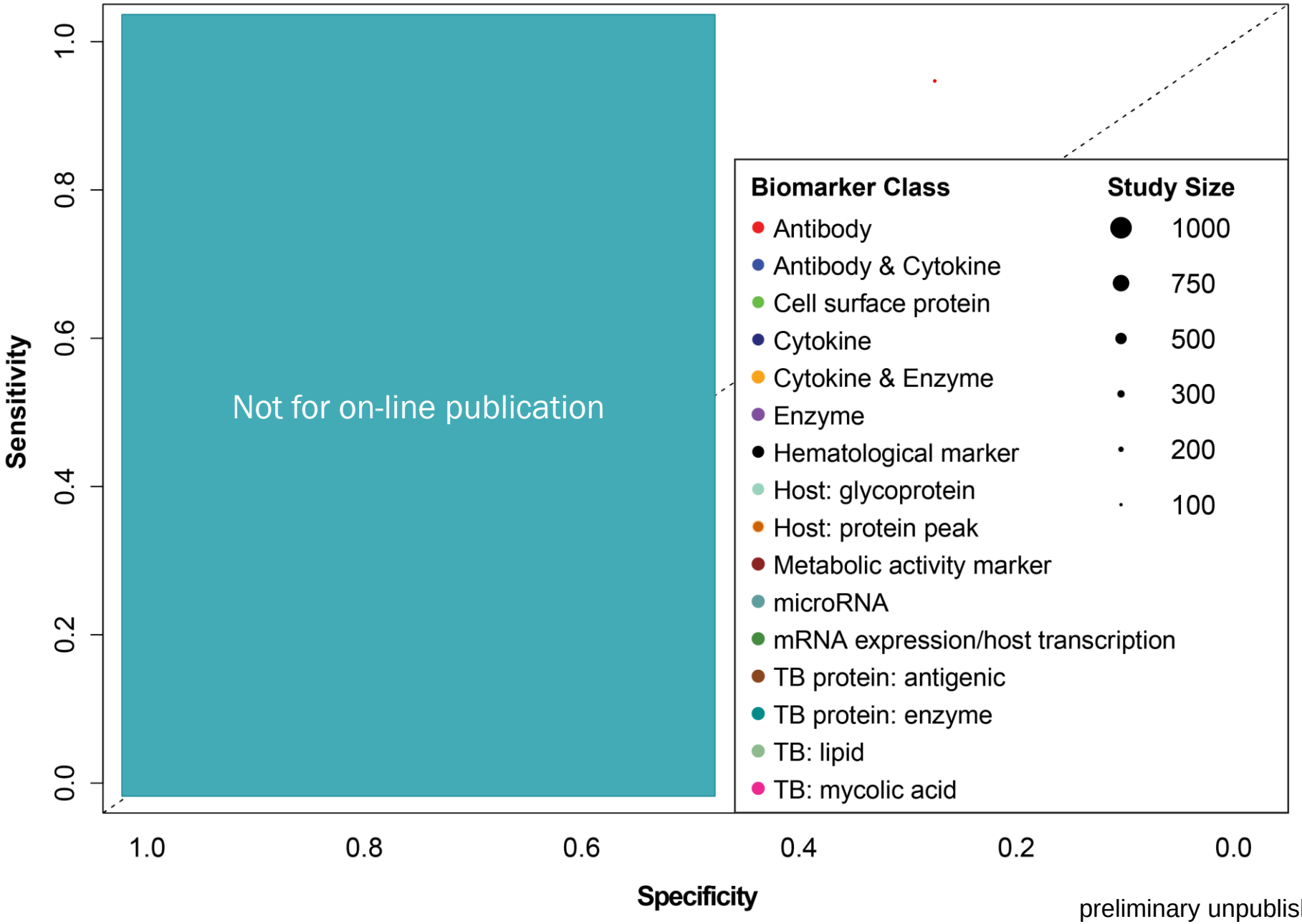
Blood biomarker entries with control group other respiratory disease (ORD)



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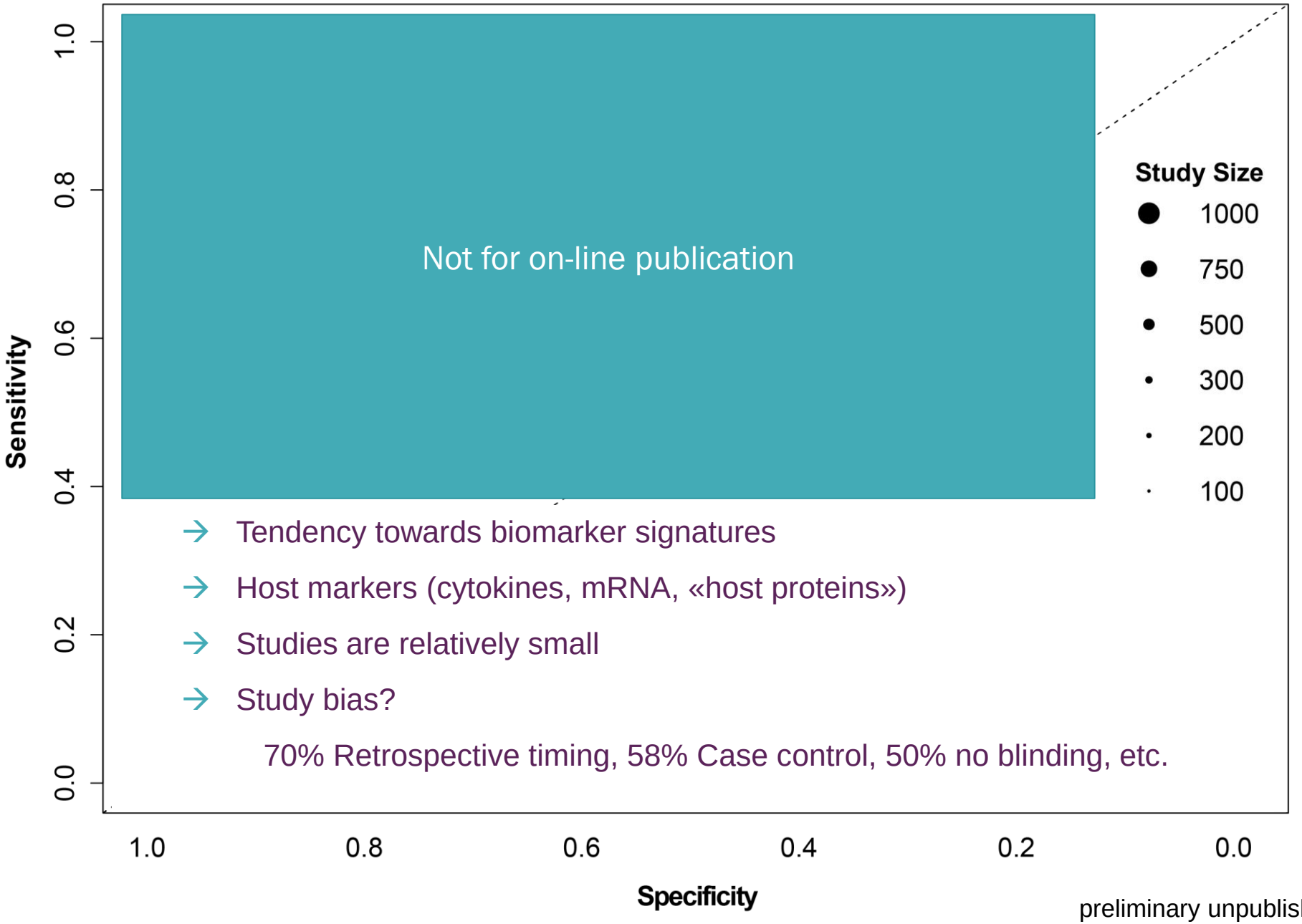


- → Tendency towards biomarker signatures
- → Host markers (cytokines, mRNA, «host proteins»)
- → Studies are relatively small
- → Study bias?

  70% Retrospective timing, 58% Case control, 50% no blinding, etc.

preliminary unpublished

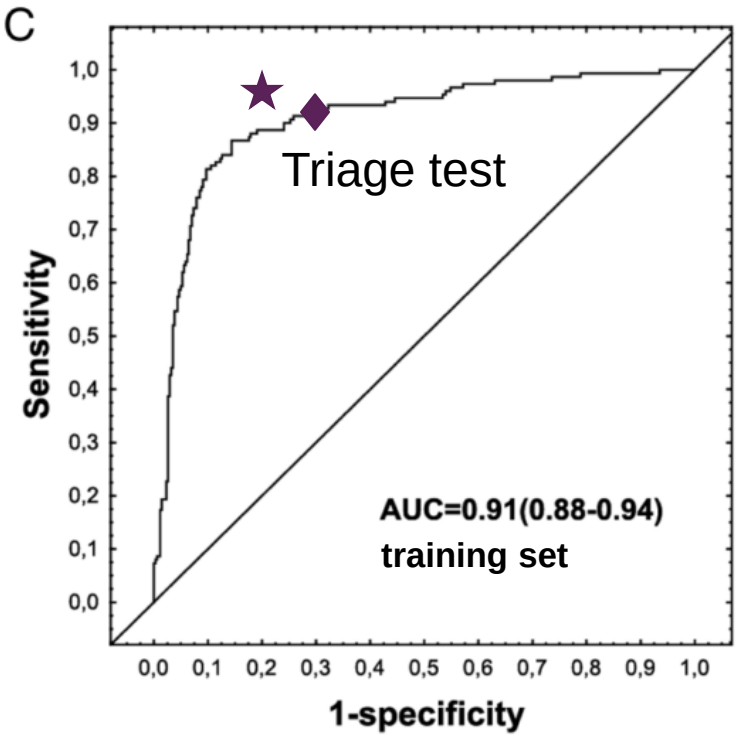
Example for high quality biomarker evidence: Host signature

Diagnostic performance of a seven-marker serum protein biosignature for the diagnosis of active TB disease in African primary healthcare clinic attendees with signs and symptoms suggestive of TB

Novel N Chegou,[1] Jayne S Sutherland,[2] Stephanus Malherbe,[1] Amelia C Crampin,[3] Paul L A M Corstjens,[4] Annemieke Geluk,[5] Harriet Mayanja-Kizza,[6] Andre G Loxton,[1] Gian van der Spuy,[1] Kim Stanley,[1] Leigh A Kotzé,[1] Marieta van der Vyver,[7] Ida Rosenkrands,[8] Martin Kidd,[9] Paul D van Helden,[1] Hazel M Dockrell,[10] Tom H M Ottenhoff,[5] Stefan H E Kaufmann,[11] Gerhard Walzl,[1] on behalf of the AE-TBC consortium

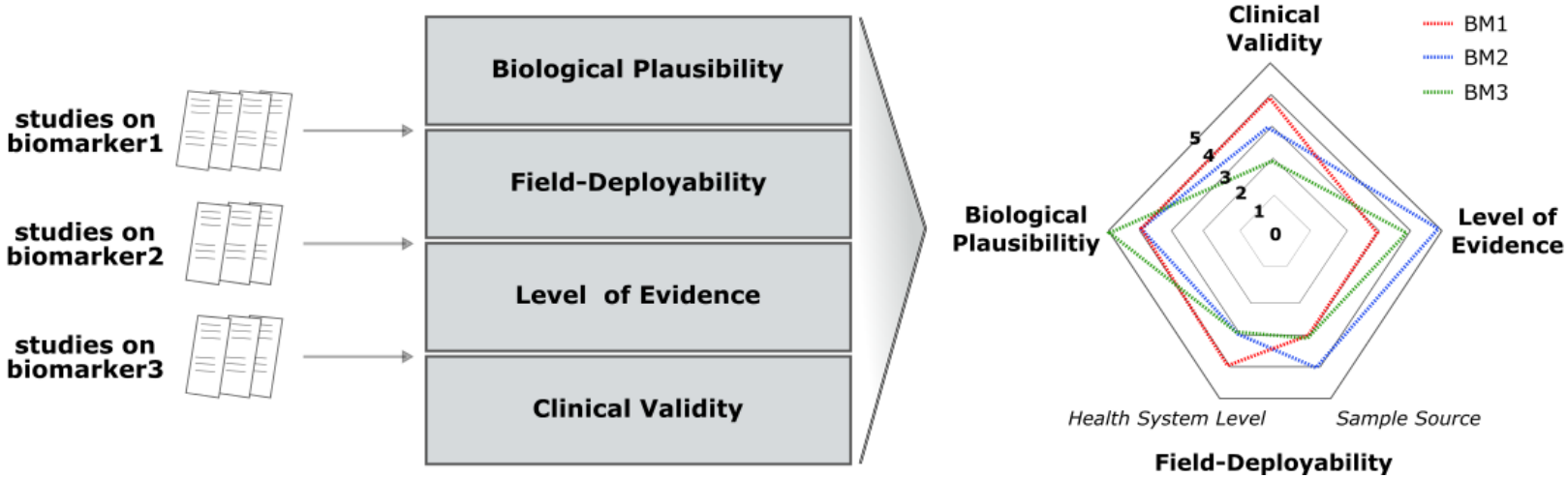
7-marker SIGNATURE
CRP
transthyretin
IFN-γ
Comp FH
Apo-A1
IP-10
SAA

- → n=716 (five African countries) ✓
- → Prospective cohort ✓
- → Adults with sympthoms ✓
- → Sensitivity 94%; Specificity 73% (test set)



Next steps

- Development of the TB Biomarker Database
- Development of a consensus-based biomarker evaluation and grading framework



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Thank you!

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McGill International TB Centre

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