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

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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

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)

Predict progression
Performance targets
Expectations 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

Reasons for imperfect Sensitivity (i.e. patient “supposed to stay healthy” but progresses)
- Precipitating factors “hitting” after testing
- Reinfection
- Hard to detect very early immune changes

Reasons for imperfect Specificity (i.e. patient “supposed to progresses” but stays healthy)
- Prd/Prc factors removed/“addressed”
- Self-cure
- Hard to find specific host immune response

Esmail 2014
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

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV*</th>
<th>NNTT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>58%</td>
<td>64%</td>
<td>3.2%</td>
<td>31</td>
</tr>
<tr>
<td>IGRA</td>
<td>80%</td>
<td>56%</td>
<td>3.6%</td>
<td>28</td>
</tr>
</tbody>
</table>

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: 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