TPP for test that predicts progression to active TB

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1st July 2016
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
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 precipitating factors at time of testing

![Diagram showing the progression from infection to disease, including possible predisposing and precipitating factors.]

- Possible predisposing factors:
  - HIV
  - malnutrition
  - diabetes
  - alcoholism
  - pro/anti inflammatory imbalance

- Possible precipitating factors:
  - HIV
  - anti-TNF therapy
  - malnutrition
  - Vit D deficiency
  - viral infection

Esmail 2014
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

<table>
<thead>
<tr>
<th>COUNTRY GROUP</th>
<th>AT RISK POPULATIONS</th>
<th>TESTING ALGORITHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-income and upper middle-income countries with an estimated TB incidence rate of less than 100 per 100,000 population</td>
<td>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.</td>
<td>Exclude active TB using TB investigations. A positive IGRA or TST test result is required to diagnose LTBI.</td>
</tr>
<tr>
<td>Resource-limited and other middle-income countries with an estimated TB incidence rate of more than 100 per 100,000 population</td>
<td>1) People living with HIV; 2) Children under 5 years of age who are household contacts of a TB case.</td>
<td>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.</td>
</tr>
</tbody>
</table>
# Predictive accuracy of TST/IGRA

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV*</th>
<th>NNTT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rangaka / Kik</td>
<td>TST</td>
<td>72% / 58%</td>
<td>41% / 64%</td>
<td>2.4% / 3.2%</td>
</tr>
<tr>
<td></td>
<td>IGRA</td>
<td>72% / 80%</td>
<td>50% / 56%</td>
<td>2.9% / 3.6%</td>
</tr>
</tbody>
</table>

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