Clinical Validation of the CAD4TB v7 system for the detection of CXR abnormalities associated with TB:

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On behalf of the PRIME TB team
PRIME TB Project

- Sponsored by the WHO STOP TB Partnership
- TBREACH funding mechanism (Wave 8)

Programmatic Aim:
To increase TB case-detection through engagement of private health providers in TB screening and diagnosis

Implementation Research Aim:
To clinically validate a new version of CAD4TB for the Ugandan population.
Introduction

- CXR has historically been one of the primary tools for diagnosing PTB.

- In the 1950-60s, developed countries held large scale screening campaigns using mobile Xray units to detect and treat patients with active TB disease.

- Mass screening campaigns were successful at detecting a large pool of prevalent TB cases, and resulted in significant reductions in TB burden.

- However, these campaigns were expensive and once the burden of TB was significantly reduced, were abandoned in favour of symptom screening.

- Currently used only for selected places e.g. immigration centers.
In developing countries with high TB burdens, mass screening with CXR was too expensive and logistically challenging to implement.

Moreover, CXR although highly sensitive has poor specificity and diverse intra- and inter-reader variability.

Thus, the policy for TB screening in these countries is based on symptom screening combined with sputum microscopy/Xpert testing to establish a diagnosis.

CXR was until recently, only recommended as a diagnostic tool to be used as part of clinical diagnosis for sputum negative TB.
However, the pendulum is swinging back in favour of CXR for TB screening for a number of reasons

▪ Several prevalence surveys demonstrated that a significant proportion of TB cases are asymptomatic, but detectable through CXR.

▪ Global priorities shifted from finding the most infectious cases to early diagnosis of all TB cases (the END TB Strategy).

▪ Advancements in digital radiography have led to reduced costs, better image quality, lower radiation dosage, and digital image transfer for telemedicine.

▪ Innovations have led to the development of computer-aided detection (CAD) software programs which can standardize the interpretation of CXRs reducing inter-reader variability and error.
# Considerations for use of CXR in TB screening

<table>
<thead>
<tr>
<th>Triage algorithm</th>
<th>Cost per true case detected</th>
<th>Yield of true-positive results</th>
<th>Yield of false-positive results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cough followed by microscopy</td>
<td>$</td>
<td>$</td>
<td>+</td>
</tr>
<tr>
<td>2. Cough followed by CXR followed by microscopy</td>
<td>$</td>
<td>$</td>
<td>+</td>
</tr>
<tr>
<td>3. Any TB symptom followed by microscopy</td>
<td>$</td>
<td>$</td>
<td>+</td>
</tr>
<tr>
<td>4. Any TB symptom followed by CXR followed by microscopy</td>
<td>$</td>
<td>$</td>
<td>+</td>
</tr>
<tr>
<td>5. CXR followed by microscopy</td>
<td>$</td>
<td>$</td>
<td>+</td>
</tr>
</tbody>
</table>

6. Cough followed by Xpert MTB/RIF testing

7. Cough followed by CXR followed by Xpert MTB/RIF testing

8. Any TB symptom followed by Xpert MTB/RIF testing

9. Any TB symptom followed by CXR, followed by Xpert MTB/RIF testing

10. CXR followed by Xpert MTB/RIF testing

CXR: chest X-ray.
Computer aided detection (CAD) systems detect three categories of radiographic abnormalities compatible with TB:

- textural abnormalities - diffuse changes in the lung parenchyma;
- shape abnormalities- changes in the boundaries of the lung and
- focal abnormalities- well-defined local lesions e.g. cavities.

Abnormality scores in each category are combined to produce an overall score for the presence/absence of active TB disease.

Score range is 0-100. Higher scores signify greater likelihood of TB.
TB Pathophysiology leads to a large diversity of pathologic changes in the lungs which vary with age, co-infection with HIV and severity of TB disease.

This leads to different patterns of abnormalities across populations.

Adequate utilisation of the CAD4TB system therefore requires adaptation of abnormality scores to individual populations with their own specific characteristics.

CAD Calibration before use in a specific setting is essential to ensure the accuracy, predictive values, overall yield, and requirements for further diagnostic testing are as expected.

Individuals recruited into the calibration study/studies must be representative of the population in which CAD will be implemented.

To determine the sensitivity and specificity of different CAD4TB v7 scores for the detection of bacteriologically confirmed tuberculosis (using Xpert MTB/RIF as the current standard) in the Ugandan population.

To determine the ideal threshold score to be used for the diagnosis of TB in the Ugandan population
## Study Participants

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Patients ≥15 years presenting to the outpatient department and HIV clinics at the two hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td><strong>HIV+ve patients:</strong></td>
</tr>
<tr>
<td></td>
<td>▪ All patients newly diagnosed with HIV.</td>
</tr>
<tr>
<td></td>
<td>▪ All patients returning to HIV care after being lost to follow-up for three months or more.</td>
</tr>
<tr>
<td></td>
<td>▪ Patients coming for ART refill visits with cough of any duration.</td>
</tr>
<tr>
<td></td>
<td><strong>HIV -ve patients:</strong></td>
</tr>
<tr>
<td></td>
<td>▪ Patients with cough of any duration plus one or more signs and symptoms of TB</td>
</tr>
<tr>
<td><strong>Exclusion Criteria</strong></td>
<td>▪ Patients who are unable to provide informed consent</td>
</tr>
<tr>
<td></td>
<td>▪ Patients already on TB treatment</td>
</tr>
<tr>
<td></td>
<td>▪ Female patients who were pregnant</td>
</tr>
</tbody>
</table>
Patient Flow Chart

- Patients attending OPD- (HIV test, Pregnancy test, WHO symptom screen)
- Patients attending HIV clinic – (Patient Questionnaire, WHO symptom screen)

Newly diagnosed HIV
Retuning to HIV care after ≥ 3/12
Any cough +/- chest pain, evening fevers, night sweats, weight loss

Chest X-ray
GeneXpert test

- MTB+/RR-: Treat for TB
- MTB+/RR+: Sputum for DST. Refer to MDR TB ward for start of second-line therapy.
- MTB-/Abnormal chest X-ray: Refer to physician for further evaluation and management
- MTB-/normal chest X-ray: Send home
Study Results

Screened N=1500

Enrolled
N=1363

Reasons for non-enrollment N=137
- Unproductive cough (%)=81(59.1)
- Declined to participate (%)=29(21.2)
- TB treatment(%)=4(2.9)
- Pregnant(%)=17(12.4)
- Mentally unstable(%)=5(3.7%)
- No enrollment data(%)=1(0.7%)

Gene xpert results
N=1345 (61 Xpert positive)

No chest xray results=11
No gene xpert results=6
Error gene xpert results=1
## Results: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall ( n=1344^\dagger (%) )</th>
<th>HIV + ( N=621(%) )</th>
<th>HIV – ( N=723(%) )</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>449(33.4)</td>
<td>215(34.6)</td>
<td>234(32.4)</td>
<td>0.38</td>
</tr>
<tr>
<td>Female</td>
<td>895(66.6)</td>
<td>406(65.4)</td>
<td>489(67.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Age median (iqr)</strong></td>
<td>42(30,52)</td>
<td>40(33,50)</td>
<td>41(27,56)</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Age group(\dagger ( n=1339 ))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24 years</td>
<td>196 (14.6)</td>
<td>57(9.2)</td>
<td>139(19.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>25-34 years</td>
<td>257(19.2)</td>
<td>123(19.9)</td>
<td>134(18.6)</td>
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</tr>
<tr>
<td>35-44 years</td>
<td>333(24.9)</td>
<td>203(32.9)</td>
<td>130(18.0)</td>
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</tr>
<tr>
<td>45-54 years</td>
<td>267(19.9)</td>
<td>139(22.5)</td>
<td>128(17.7)</td>
<td></td>
</tr>
<tr>
<td>&gt;55 years</td>
<td>286(21.4)</td>
<td>95(15.4)</td>
<td>191(26.5)</td>
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<tr>
<td><strong>BMI mean (sd) ( n=945 )</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
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<tr>
<td>Student</td>
<td>92(7.0)</td>
<td>14(2.3)</td>
<td>78(10.8)</td>
<td>&lt;0.01</td>
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<tr>
<td>Subsistence Farming</td>
<td>957(71.4)</td>
<td>459(74.2)</td>
<td>498(69.0)</td>
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<tr>
<td>Informal employment</td>
<td>217(16.2)</td>
<td>118(19.1)</td>
<td>99(13.7)</td>
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</tr>
<tr>
<td>Formal employment</td>
<td>75(5.6)</td>
<td>28(4.5)</td>
<td>47(6.5)</td>
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</table>
### Results: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall n=1344†</th>
<th>Positive N=621</th>
<th>Negative N=723</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous TB history†(n=1339)</strong></td>
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</tr>
<tr>
<td>Yes</td>
<td>159(11.9)</td>
<td>97(15.7)</td>
<td>61(8.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>20(4.6)</td>
<td>18(6.8)</td>
<td>2(1.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>429(95.6)</td>
<td>250(93.3)</td>
<td>179(98.9)</td>
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</tr>
<tr>
<td></td>
<td>893(66.4)</td>
<td>352(56.7)</td>
<td>541(74.8)</td>
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<tr>
<td><strong>Concomitant illness</strong></td>
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</tr>
<tr>
<td>Diabetes</td>
<td>18(1.3)</td>
<td>6(1.0)</td>
<td>12(1.7)</td>
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<tr>
<td></td>
<td>73(5.4)</td>
<td>15(2.4)</td>
<td>58(8.0)</td>
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</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
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<td>&lt;0.01</td>
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<tr>
<td><strong>Alcohol intake (n=1343)</strong></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>291(21.7)</td>
<td>135(21.8)</td>
<td>156(21.6)</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Tobacco use(n=1342)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>98(7.0)</td>
<td>49(7.9)</td>
<td>49(6.8)</td>
<td>0.43</td>
</tr>
</tbody>
</table>
### Results: Patient Characteristics (Xpert positives)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall n=1344† (%)</th>
<th>HIV + N=621 (%)</th>
<th>HIV – N=723 (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (80.0)</td>
<td>21 (80.8)</td>
<td>27 (79.4)</td>
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<tr>
<td><strong>Age median (iqr)</strong></td>
<td>42 (32,58)</td>
<td>37 (31,50)</td>
<td>45 (35,62)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24 years</td>
<td>5 (8.3)</td>
<td>1 (3.9)</td>
<td>4 (11.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>25-34 years</td>
<td>12 (20.0)</td>
<td>8 (30.8)</td>
<td>4 (11.8)</td>
<td></td>
</tr>
<tr>
<td>35-44 years</td>
<td>17 (28.3)</td>
<td>8 (30.8)</td>
<td>9 (26.5)</td>
<td></td>
</tr>
<tr>
<td>45-54 years</td>
<td>8 (13.3)</td>
<td>3 (11.5)</td>
<td>5 (14.7)</td>
<td></td>
</tr>
<tr>
<td>&gt;55 years</td>
<td>18 (30.0)</td>
<td>6 (23.1)</td>
<td>12 (30.0)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI mean (sd)</strong></td>
<td>19 (4)</td>
<td>20 (4)</td>
<td>19 (4)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
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<tr>
<td>Subsistence farming</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informal employment</td>
<td>42 (70.0)</td>
<td>17 (65.4)</td>
<td>25 (73.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>Formal employment</td>
<td>11 (18.3)</td>
<td>7 (26.9)</td>
<td>4 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>3 (5.0)</td>
<td>2 (7.7)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (6.7)</td>
<td>0 (0.0)</td>
<td>4* (11.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Previous TB history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (25.0)</td>
<td>7 (27.9)</td>
<td>8 (23.4)</td>
<td>0.77</td>
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</table>
### Results: Patient Characteristics (Xpert positives)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall n=1344†</th>
<th>Positive N=621</th>
<th>Negative N=723</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5(8.3)</td>
<td>3(11.5)</td>
<td>2(5.9)</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>55(91.7)</td>
<td>23(88.4)</td>
<td>32(94.1)</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25(41.7)</td>
<td>11(42.3)</td>
<td>14(42.3)</td>
<td>0.93</td>
</tr>
<tr>
<td>Tobacco use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13(21.7)</td>
<td>8(30.8)</td>
<td>5(14.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>Other Substance use</td>
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<tr>
<td>Yes</td>
<td>2(3.3)</td>
<td>1(3.9)</td>
<td>1(2.9)</td>
<td>0.54</td>
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<tr>
<td>CAD4TB AI prediction score</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median(iqr)</td>
<td>74(59,90)</td>
<td>73(48,88)</td>
<td>75(69,91)</td>
<td>0.14</td>
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<tr>
<td>ART</td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>21(32.4)</td>
<td></td>
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<tr>
<td>Newly diagnosed</td>
<td>3(11.5)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Missing</td>
<td>2(7.7)</td>
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<tr>
<td>CD4 Count median(iqr)</td>
<td>264(46,496)</td>
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</table>
## CAD4TB scores by HIV status and TB status

<table>
<thead>
<tr>
<th>CAD4TB score</th>
<th>HIV+ ve N=39</th>
<th>HIV-ve N=59</th>
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<tbody>
<tr>
<td></td>
<td>MTB+ n=26</td>
<td>MTB- n=13</td>
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<tr>
<td>≥0</td>
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<td>≥5</td>
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<td>≥90</td>
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<tr>
<td>≥95</td>
<td>1</td>
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</table>
### CAD4TB scores: Overall

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Sensitivity</th>
<th>95% CI</th>
<th>Specificity</th>
<th>95% CI</th>
<th># above cut off point</th>
<th># TB cases diagnosed</th>
<th>Proportion of TB cases diagnosed</th>
<th>Xpert positivity rate</th>
<th># Xpert tests saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0</td>
<td>100</td>
<td>94.1 - 100.0</td>
<td>0</td>
<td>0.0 - 0.3</td>
<td>1345</td>
<td>61</td>
<td>100</td>
<td>4.5</td>
<td>0</td>
</tr>
<tr>
<td>&gt;5</td>
<td>96.7</td>
<td>88.7 - 99.6</td>
<td>51.0</td>
<td>48.2 - 53.7</td>
<td>720</td>
<td>59</td>
<td>96.7</td>
<td>8.2</td>
<td>625</td>
</tr>
<tr>
<td>&gt;10</td>
<td>96.7</td>
<td>88.7 - 99.6</td>
<td>65.2</td>
<td>62.5 - 67.8</td>
<td>521</td>
<td>59</td>
<td>96.7</td>
<td>11.3</td>
<td>824</td>
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<tr>
<td>&gt;15</td>
<td>93.4</td>
<td>84.1 - 98.2</td>
<td>70.9</td>
<td>68.4 - 73.4</td>
<td>436</td>
<td>57</td>
<td>93.4</td>
<td>13.1</td>
<td>909</td>
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<tr>
<td>&gt;20</td>
<td>86.9</td>
<td>75.8 - 94.2</td>
<td>75.4</td>
<td>72.9 - 77.7</td>
<td>372</td>
<td>53</td>
<td>86.9</td>
<td>14.2</td>
<td>973</td>
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<tr>
<td>&gt;25</td>
<td>85.3</td>
<td>73.8 - 93.0</td>
<td>78.3</td>
<td>75.9 - 80.5</td>
<td>341</td>
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## CAD4TB scores: HIV+

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WHO Criteria for Diagnostics (90% Sens)

Proportion of TB cases diagnosed for various CAD4TB Scores

- Overall
- HIV+
- HIV-
Diagnostic Accuracy of CAD4TB

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Using a threshold score of 47% saves about 80% of all GeneXpert tests.
Considerations during threshold score selection.

CAD calibration analysis should be carefully interpreted in the context of the intended TB screening program.

Considerations for the most appropriate CAD threshold include:

- The prevalence of TB and of other relevant comorbidities in the population CAD is going to be used.
- Where CAD will be placed in the screening algorithm
- The goal of CAD use e.g.
  - a) If CAD is being used to maximize case detection. In this case it should be used as an early screening tool
  - b) If CAD is used to improve efficiency of a triage system? In this case, CAD should be preceded by earlier screening steps e.g. symptom screen.

- Finally, costs of over and under diagnosis at different CAD threshold scores should be calculated and taken into consideration when determining an appropriate threshold.
Uganda uses about 700,000 Xpert tests annually

Adding CXR with CAD4TB to the screening algorithm could significantly reduce the no. of Xpert tests needed with minimal reduction in the no. of TB cases diagnosed

Follow on benefits may include
- reduced sputum results TAT,
- reductions in pretreatment LFU and ultimately
- reduction in mortality

However, this has to be balanced against the cost of CAD, CXR maintenance and personnel to operate the CXR
Acknowledgements

- Stella Zawedde-Muyanja
- Christine Sekaggya
- Eva Laker
- Ahmed Ddungu
- Barbara Castelnuovo
- Jessica Masika
- Esther Nalugga
- Patricia Nerima
Thank you for listening.

For further questions or comments, please contact:
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