Early Detection of Lung Cancer by a FISH-based Sputum Test
US Lung Cancer Statistic at Glance

Estimated New Cases by Sites, 2015

- Prostate: 221,200
- Breast: 188,000
- Colorectal: 120,000
- Lung & Bronchus: 240,000
- Other Cancers: 360,000
- Lung Cancer: 480,000

Estimated Deaths by Sites, 2015

- Prostate: 158,040
- Breast: 55,000
- Colorectal: 44,000
- Lung & Bronchus: 221,200
- Other Cancers: 188,000
- Lung Cancer: 240,000

Lung Cancer Diagnosis and Survival By Stage, 2004-2010

Stage at Diagnosis:
- Localized: 15%
- Distant: 22%
- Regional: 57%

5-Year Relative Survival:
- Localized: 54%
- Distant: 27%
- Regional: 4%
- UnStaged: Not shown

Early Detection Decreasing Lung Cancer Mortality

LOW DOSE CT SCAN (LDCT)

Screening Test for High Risk

NEGATIVE

INDETERMINATE

96% False Positive

POSITIVE

Early Detection

Reduced Mortality

Invasive Procedures

Healthcare Costs

Patient Anxiety

Radiation Exposure

Benign Nodules

Malignant Nodules

PET CT

Invasive Intervention

Clinical Dilemma

Benign Nodules

Radiological Surveillance

Malignant Nodules

The Unmet Need

- Reduce Invasive Tests
- Reduce CT Scans
- Increase Accuracy
- Aid in Early Detection

Improving LDCT Specificity
BioView LCD Test

Non-Invasive Test for Lung Cancer Detection

BioView Duet™ Imaging System
Enables to examine the same cell twice, once with morphology stain and once in FISH Scan

Cytogenetics Biomarkers
3p22.1 and 10q22.3 express numerical chromosomal alteration in malignant bronchial epithelial cells of lung tumor via Fluorescence In Situ Hybridization (FISH)

Induced Sputum
Non invasive specimen contains exfoliated bronchial cells from the lower respiratory tract and can be used for detecting cancerous cells as an aid for lung cancer diagnosis
Multi Center Clinical Study Design

**Study Objectives**
Evaluate LCD Test performance for the detection of lung cancer from induced sputum

**Study Population**
Subjects with 0.8-3cm pulmonary nodules suspected for lung cancer undergoing lung biopsy

- Participate
  6 Medical Centers in US and Israel
  3 Labs, 2 CLIA labs in US 1 in Israel
  **CRO Group:** ICON plc, USA

**Induced sputum**
BioView LCD TEST
Combined analysis of sputum cytology and Target-FISH on the same cell

- Positive
  % of Cancerous cells > cutoff

- Negative
  % of Cancerous cells < cutoff

**Lung biopsy** (Non-Surgical and Surgical)

- Positive
  Surgical and non-surgical biopsy confirm malignancy

- Determinate Negative
  1. Surgical biopsy rule out malignancy
  2. Detect Benign disease

- Indeterminate Negative
  non-surgical biopsy does not role out malignancy

**Follow up for 2 years**
1. Establish final diagnosis
2. Confirm nodule stability

**Final clinical Diagnosis**
- Lung Cancer
- Non Cancer
- Indeterminate
  Not Included

**LCD Test Result**
Compare
LCD Test Target-FISH Flow Chart

Sputum Collection & Processing

Papanicolaou Morphology Stain

De-staining & Applying LCD Probe

Combined Analysis
Morphology & FISH

Interpretation
Normal Vs. Abnormal Cell

Morphology Scan
"Lung Cells" Selection for Cytogenetic analysis

Target-FISH
FISH scan of "Lung Cells"

Reviewing Results

\[
\text{\% of Abnormal Cells} = \frac{22 \text{ (Abnormal Cells)}}{100 \text{ (Total Analyzed Cells)}}
\]

Sample Result

\[
\begin{align*}
\geq \text{ Cutoff} & \quad \Rightarrow \quad \text{POSITIVE SAMPLE} \\
< \text{ Cutoff} & \quad \Rightarrow \quad \text{NEGATIVE SAMPLE}
\end{align*}
\]
<table>
<thead>
<tr>
<th>GROUPS</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Enrolled Subjects</td>
<td>173</td>
<td></td>
</tr>
<tr>
<td>Excluded Subjects</td>
<td>57</td>
<td>32.95%</td>
</tr>
<tr>
<td>UnMet IE</td>
<td>11</td>
<td>6.36%</td>
</tr>
<tr>
<td>Biopsy not done</td>
<td>8</td>
<td>4.62%</td>
</tr>
<tr>
<td>Sputum Failure</td>
<td>28</td>
<td>16.18%</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>5.78%</td>
</tr>
<tr>
<td>Included Subjects</td>
<td>116</td>
<td>67.05%</td>
</tr>
<tr>
<td>Under Follow up</td>
<td>6</td>
<td>3.47%</td>
</tr>
<tr>
<td>Determinate Results</td>
<td>110</td>
<td>63.58%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>64</td>
<td>58.18%</td>
</tr>
<tr>
<td>Male</td>
<td>46</td>
<td>41.82%</td>
</tr>
<tr>
<td>Age, Years</td>
<td>64.7</td>
<td>(35-86)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>105</td>
<td>95.45%</td>
</tr>
<tr>
<td>Black</td>
<td>4</td>
<td>3.64%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1</td>
<td>0.91%</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Smoker</td>
<td>21</td>
<td>19.09%</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>65</td>
<td>59.09%</td>
</tr>
<tr>
<td>Former Smoker</td>
<td>24</td>
<td>21.82%</td>
</tr>
</tbody>
</table>
LCD Test Performance

LCD Test vs. Clinical Diagnosis

<table>
<thead>
<tr>
<th>LCD Test</th>
<th>Initial Biopsy</th>
<th>Follow Up</th>
<th>Final Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lung Cancer</td>
<td>No Cancer</td>
<td>Lung Cancer</td>
</tr>
<tr>
<td>Positive</td>
<td>62</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Negative</td>
<td>10</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>

In 9/11 subjects, LCD Test revealed cancerous cells within 17 to 402 days before the final diagnostic biopsy.

**CLINICAL DIAGNOSIS**
Biopsy Pathology Result and Nodule Stability

**Initial Biopsy Sensitivity:** 86.7% (79.5 - 94.0)

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>85.5% (77.8 - 93.1)</td>
<td>74% (57.5 - 90.6)</td>
<td>75.5% (67.4 - 83.5)</td>
<td>91% (84.7 - 97.4)</td>
<td>62.5% (84.7 - 97.4)</td>
<td>82.7% (75.7 - 89.8)</td>
<td>75.5% (67.4 - 83.5)</td>
</tr>
</tbody>
</table>
# Sensitivity: LCD Test vs. Lung Biopsy

## According to Radiologic Imaging Characteristics

<table>
<thead>
<tr>
<th>Nodule Location &amp; Size</th>
<th>All Patients</th>
<th>Cancer Patients</th>
<th>Initial Biopsy</th>
<th>LCD Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>110</td>
<td>83 (75%)*</td>
<td>[72] 86.7% (79.5 - 94.0)</td>
<td>[71] 85.5% (77.8 - 93.1)</td>
</tr>
<tr>
<td>Central</td>
<td>26</td>
<td>19 (73%)</td>
<td>[16] 84.2% (67.8 - 100.6)</td>
<td>[18] 94.7% (84.6 - 104.8)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>84</td>
<td>64 (76%)</td>
<td>[56] 87.5% (79.4 - 95.6)</td>
<td>[53] 82.8% (73.6 - 92.1)</td>
</tr>
<tr>
<td>&lt; 1.5 cm</td>
<td>30</td>
<td>17 (20%)</td>
<td>[14] 82.4% (64.2 - 100.5)</td>
<td>[14] 82.4% (64.2 - 100.5)</td>
</tr>
<tr>
<td>1.5 – 2.2 cm</td>
<td>42</td>
<td>33 (75%)</td>
<td>[27] 81.8% (68.7 – 95.0)</td>
<td>[30] 90.9% (81.1 -100.7)</td>
</tr>
<tr>
<td>≥ 2.3 cm</td>
<td>38</td>
<td>33 (75%)</td>
<td>[31] 93.9% (85.8 – 102.1)</td>
<td>[27] 81.8% (68.7 - 95.0)</td>
</tr>
</tbody>
</table>

* Percent of cancer patients /all patients
# Sensitivity: LCD Test vs. Lung Biopsy

## According to Lung Cancer Histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>Cancer Patients</th>
<th>Initial Biopsy</th>
<th>LCD Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>54</td>
<td>83.3% (73.4 - 93.3)</td>
<td>83.3% (73.4 - 93.3)</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>21</td>
<td>100.0% (100 - 100)</td>
<td>95.2% (86.1 - 104.3)</td>
</tr>
<tr>
<td>NOS</td>
<td>3</td>
<td>66.7% (13.3 - 120.0)</td>
<td>66.7% (13.3 - 120.0)</td>
</tr>
<tr>
<td>Small Cell Lung Cancer</td>
<td>3</td>
<td>100.0% (100 - 100)</td>
<td>100.0% (100 - 100)</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>50.0% (-19.3 - 119.3)</td>
<td>50.0% (-19.3 - 119.3)</td>
</tr>
</tbody>
</table>
# Sensitivity: LCD Test vs. Lung Biopsy

## According to Lung Cancer Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cancer Patients</th>
<th>Initial Biopsy</th>
<th>LCD Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>39</td>
<td>87.2% (76.7 - 97.7)</td>
<td>87.2% (76.7 - 97.7)</td>
</tr>
<tr>
<td>II</td>
<td>8</td>
<td>100.0% (100 - 100)</td>
<td>75.0% (45.0 - 105.0)</td>
</tr>
<tr>
<td>III</td>
<td>17</td>
<td>88.2% (72.9 - 103.5)</td>
<td>82.4% (64.2 - 100.5)</td>
</tr>
<tr>
<td>IV</td>
<td>17</td>
<td>82.4% (64.2 - 100.5)</td>
<td>94.1% (82.9 - 105.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>50.0% (-19.3 - 119.3)</td>
<td>50.0% (19.3 - 119.3)</td>
</tr>
</tbody>
</table>
Conclusion

THE LCD TEST MAY BE USEFUL AS A DECISION SUPPORT TOOL AT CRITICAL POINTS OF CLINICAL DILEMMA FOR SUBJECTS WITH HIGH RISK OF CANCER

- **INCREASE NODULES MANAGEMENT ACCURACY**
- **REDUCE INVASIVE TESTS**
  Small nodules 8-22 mm with moderate probability
  LCD Test detect 44/50, Initial biopsy detect 41/50
- **REDUCE CT-SCANS FREQUENCY**
  LCD Test detects 17/22 benign nodules ≤ 22 mm
  and 6/7 central benign lesions
- **AID IN EARLY DETECTION**
  LCD Test detects cancer in 9/11 subjects after initial negative non-surgical biopsy