NLST
methodological considerations

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overview

- Process standardization
  - Image acquisition
  - Screen interpretations
  - Results communication
- Outcomes data collection
- Endpoint verification
- Implications for public policy
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>kV</td>
<td></td>
</tr>
<tr>
<td>Gantry rotation time</td>
<td></td>
</tr>
<tr>
<td>mA (Regular – Large patient values)</td>
<td></td>
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<tr>
<td>mAs (Reg – Lg)</td>
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<tr>
<td>Scanner effective mAs (Reg – Lg)</td>
<td></td>
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<tr>
<td>Detector collimation (mm) - T</td>
<td></td>
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<tr>
<td>Number of active channels - N</td>
<td></td>
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<tr>
<td>Detector configuration – N · T</td>
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<tr>
<td>Collimation (operator console)</td>
<td></td>
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<tr>
<td>Table incrementation (mm/rotation) - I</td>
<td></td>
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<tr>
<td>Pitch ([mm/rotation]/ beam collimation – I/NT</td>
<td></td>
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<tr>
<td>Table speed (mm/second)</td>
<td></td>
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<tr>
<td>Scan time (40 mm thorax)</td>
<td></td>
</tr>
<tr>
<td>Nominal reconstructed slice width</td>
<td></td>
</tr>
<tr>
<td>Reconstruction interval</td>
<td></td>
</tr>
<tr>
<td>Reconstruction algorithm</td>
<td></td>
</tr>
<tr>
<td># Images/data set (40 cm thorax)</td>
<td></td>
</tr>
<tr>
<td>CTDI vol (Dose in mGy)</td>
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</tr>
</tbody>
</table>

- **CT Technique Chart**
  - Standardized 18 parameters
  - 14 CT scanners: 4-64 channels
  - 120-140 kV; mAs < 80 (CTDIvol 2-3mGy)
  - Nominal slice thickness: ≤ 2.5 mm
- Equipment certification annually
- Routine CT phantom calibration
- QC: DICOM headers | visual QC
- CXR techniques from CRFs and machine output: mR/mAs vs. kV

*Cagnon CH. Acad Radiol 2006; 13: 1431-1441.*
<table>
<thead>
<tr>
<th>NLST CT Technique Chart</th>
<th>Siemens 64 Sensation</th>
<th>GE – VCT (64)</th>
<th>Toshiba Aquilion</th>
<th>Philips MX8000 16 slice</th>
</tr>
</thead>
<tbody>
<tr>
<td>kV</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
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<tr>
<td>Gantry rotation time</td>
<td>0.50 sec</td>
<td>0.50 sec</td>
<td>0.50 sec</td>
<td>0.5 sec</td>
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<tr>
<td>mA (Regular – Large patient values)</td>
<td>50-100</td>
<td>50-100</td>
<td>80-160</td>
<td>75-150</td>
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<tr>
<td>mAs (Reg – Lg)</td>
<td>25-50</td>
<td>25-50</td>
<td>40-80</td>
<td>37.5-75</td>
</tr>
<tr>
<td>Scanner effective mAs (Reg – Lg)</td>
<td>25-50</td>
<td>27-53</td>
<td>26.7-53.3</td>
<td>25-50</td>
</tr>
<tr>
<td>Detector collimation (mm) - T</td>
<td>0.6 mm</td>
<td>0.625</td>
<td>2 mm</td>
<td>.75 mm</td>
</tr>
<tr>
<td>Number of active channels - N</td>
<td>32</td>
<td>64</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Detector configuration – N · T</td>
<td>32 x 0.6 mm</td>
<td>64 x 0.625</td>
<td>16 x 2 mm</td>
<td>16 x .75 mm</td>
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<tr>
<td>Collimation (operator console)</td>
<td>64 x 0.6 mm</td>
<td>.625/.984/39.37</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Table incrementation (mm/rotation) - I</td>
<td>19.2 mm</td>
<td>39.37 mm</td>
<td>48 mm</td>
<td>18 mm</td>
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<tr>
<td>Pitch ([mm/rotation]/ beam collimation – I/NT</td>
<td>1.0</td>
<td>0.984</td>
<td>1.5</td>
<td>1.5</td>
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<tr>
<td>Table speed (mm/second)</td>
<td>38.4 mm/sec</td>
<td>78.74 mm/sec</td>
<td>96 mm/sec</td>
<td>36 mm/sec</td>
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<tr>
<td>Scan time (40 mm thorax)</td>
<td>11 sec</td>
<td>5.1 sec</td>
<td>4.2 sec</td>
<td>11 sec</td>
</tr>
<tr>
<td>Nominal reconstructed slice width</td>
<td>2 mm</td>
<td>2.5 mm</td>
<td>2 mm</td>
<td>2 mm</td>
</tr>
<tr>
<td>Reconstruction interval</td>
<td>1.8 mm</td>
<td>2.0 mm</td>
<td>1.8 mm</td>
<td>1.8 mm</td>
</tr>
<tr>
<td>Reconstruction algorithm</td>
<td>B30</td>
<td>STD</td>
<td>FC 10</td>
<td>B or C</td>
</tr>
<tr>
<td># Images/data set (40 cm thorax)</td>
<td>223</td>
<td>200</td>
<td>223</td>
<td>223</td>
</tr>
<tr>
<td>CTDI vol (Dose in mGy)</td>
<td>1.9 – 3.8 mGy</td>
<td>2.2 – 4.4 mGy</td>
<td>2.7 – 5.4 mGy</td>
<td>1.9 – 3.8 mGy</td>
</tr>
</tbody>
</table>

= Modifiable parameters on technologist console
radiation dose

- **Whole body effective dose** (weighted average dose to each organ)
  - Low dose helical CT: 1.5 mGy
  - Mammogram: 0.7 mGy
  - CXR: 0.01 mGy

- **Low dose helical CT**: estimates of organ specific dose
  - Lung: 4 mGy
  - Breast: 4 mGy
  - Red bone marrow, stomach, liver and pancreas: each ~1 mGy

- **Screening mammogram organ specific dose**:
  - Breast: 4 mGy
  - Other organs: < 0.1 mGy

- **CXR**: effective dose ~ 0.1 mSv

image interpretation findings

- Non-calcified nodule(s) or masses ≥ 4 mm
  - Anatomic location, slice #; diameters; margins, attenuation

- Other findings:
  - Micronodules < 4 mm
  - Atelectasis, segmental or greater
  - Pleural thickening | effusion
  - Hilar | mediastinal adenopathy
  - Significant cardiovascular abnormality (CM, CAD, valvular calcification)
  - Interstitial fibrosis
  - Significant other findings above | below diaphragm
• Non-calcified nodule(s) or masses ≥ 4 mm
  • Anatomic location, slice #; diameters; margins, attenuation

• Other findings:
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  • Atelectasis, segmental or greater
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  • Hilar | mediastinal adenopathy or masses
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  • Interstitial fibrosis
  • Significant other findings above | below diaphragm
interpretation results

- [-] Screen
  No significant findings – or –
  Minor incidental findings not significant for lung cancer

- [-] Screen
  Significant findings unrelated to lung cancer
  [Some form of diagnostic recommendation required; e.g., echocardiogram for suspected pulmonary hypertension]

- [+] Screen
  Findings potentially related to lung cancer
  [diagnostic recommendation of some form required]
1 Some nodules 4-10 mm may go directly to biopsy or other tests in ABNORMAL pathways.

2 No growth is defined as < 15% increase in overall diameter OR no ↑ in solid component.
Solid or Part-solid Nodule >10 mm

- Biopsy: Percutaneous, Bronchoscopic, Thoracoscopic, Open
  - DCE-CT
    - Enhance <15 HU
    - Enhance ≥15 HU
      - ▲ Activity
        - Non ▲ Activity
          - Low Dose TSCT at 3-4 Months¹
            - Per Protocol
          - TSCT at 6-12 months
      - TSCT at 6-12 months
    - FDG-PET
      - ▲ Activity
      - No ▲ Activity
        - Reserve for nodules considered highly likely to be BENIGN [polygonal shape, 3D shape ratio > 1.78]
diagnostic pathways
[+] CXR

Nodule on CXR

Confirm

• CXR ± Special Views
• LDCT

Small Nodule

• F/U CXR 3-6 months
• LDCT 3-6 months
• Diagnostic chest CT

Large Nodule

• Diagnostic chest CT
• FDG-PET or PET-CT
• Biopsy

No nodule

• Diagnostic chest CT
• FDG-PET or PET-CT
• Biopsy

Nodule 4-10 mm or enlarging

• LDCT 3-6 Months
[or High Suspicion protocol]

Nodule >10 mm or enlarging

High Suspicion Nodule Protocol

Continue Annual Screen
Study interpretation within 1 month

Results reporting to
  • Participant
  • Primary physician (or documented participant refusal)

Diagnostic algorithms served as guidelines

3-month | annual FU to determine management & results
outcomes collection

- [+] screens
  - Diagnostic procedures (CPT) | complications (ICD.9)
  - Diagnoses: lung cancer | other cancer (ICD-0-3) | other Dx (ICD.9)

- Lung cancers
  - ICD-0-3 (histology and grade) | size | anatomic location
  - Clinical and pathologic stage (AJCC 6th Edition)
  - 1st line lung cancer treatment(s)
  - Time of progression or 2nd primary lung cancer

- Death certificates | time and cause of death

- Sample of [-] screen significant other & [-] screen no/minor abnl
endpoint verification

- Independent endpoint verification committee (chair + 4 members)
- EVP review dictated by a selection algorithm
  - Cause of death (ICD-10) on death certificate
  - Review blinded to screening arm and official death certificate
  - Arbitration for disparity between: DC & chair | between EVP members
- Selection algorithm intended to capture
  - All lung cancer deaths (reported or death certificate)
  - Death following a [+ ] screen
  - Deaths following diagnostic evaluation of [+ ] screen
  - Cause of death = COPD
- Sub-sample of cases not included in the algorithm underwent EVP
implications of NLST

- Efficacy proven under ideal conditions
  - Institutions with sophisticated medical resources
  - Multidisciplinary team for management follow-up
  - High risk population
  - Rigorous image quality
  - Standardized interpretation | communication
  - Systematic follow-up & outcomes collection
  - Endpoint verification
implementation prerequisites

- Consistent definitions of [+ ] screen
  - All nodules | minimum size thresholds?
  - All evolving nodules?

- **Controlled** vocabulary & consistent feature description
  - Anatomic location
  - Size
  - Consistency

- Guidelines for work-up & communication of screening findings

- Types and degree of follow-up

- CAD | image analysis
GGN: Focal opacity of increased attenuation within which normal structures remain visible

Solid: Focal opacity of increased attenuation that completely obscures underlying structures

Part-solid: Focal opacity containing both solid and GG components
## Classification of Adenocarcinoma

<table>
<thead>
<tr>
<th>IASLC</th>
<th>ATS</th>
<th>ERS 2011</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAH (typically ≤ 5 mm)</td>
<td></td>
<td>GGN</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma in situ (AIS)¹</td>
<td></td>
<td>GGN</td>
<td></td>
</tr>
<tr>
<td>Minimally invasive ADC (MIA)²,³</td>
<td></td>
<td>Part-solid</td>
<td></td>
</tr>
<tr>
<td>Invasive ADC, lepidic predominant</td>
<td></td>
<td>Part-solid</td>
<td></td>
</tr>
<tr>
<td>Invasive ADC, acinar predominant</td>
<td></td>
<td>Part-solid</td>
<td></td>
</tr>
<tr>
<td>Invasive ADC, papillary predominant</td>
<td></td>
<td>Part-solid to solid</td>
<td></td>
</tr>
<tr>
<td>Invasive mucinous adenocarcinoma</td>
<td></td>
<td>Solid</td>
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<table>
<thead>
<tr>
<th>Classification</th>
<th>CT Description</th>
<th>Prognosis</th>
</tr>
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<tbody>
<tr>
<td>AAH (typically ≤ 5 mm)</td>
<td>GGN</td>
<td>Pre-malignant</td>
</tr>
<tr>
<td>Adenocarcinoma in situ (AIS)¹</td>
<td>GGN</td>
<td>100% survival</td>
</tr>
<tr>
<td>Minimally invasive ADC (MIA)¹,²,³</td>
<td>Part-solid</td>
<td>~100% survival</td>
</tr>
<tr>
<td>Invasive ADC, lepidic predominant</td>
<td>Part-solid</td>
<td>~90 5-Yr progression free survival</td>
</tr>
<tr>
<td>Invasive ADC, acinar predominant</td>
<td>Part-solid</td>
<td>multiple factors</td>
</tr>
<tr>
<td>Invasive ADC, papillary predominant</td>
<td>Part-solid to solid</td>
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<td>Invasive mucinous adenocarcinoma</td>
<td>Solid</td>
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¹ Rarely mucinous histology; ² Maximum diameter ≤ 30 mm; ³ Invasive component ≤ 5 mm

nodule characterization

- 2007: Part-solid
- 2010: Part-solid | larger
  - Increasing opacification
  - Increasing “mass”
  - Linear reticulation
  - Cysts
  - Air bronchograms
  - Convex margins

Invasive adenocarcinoma, acinar predominant
Round to oval-shaped malignant glands invading a fibrous stroma.
computer aided diagnosis

4-2006:
Diameters: 24 x 11 mm
Volume: 2805 mm³

dD = 27%  |  dV = 112%

3-2007:
Diameters: 24 x 14 mm
Volume: 5955 mm³
## NLST ACRIN biospecimen repository

### Specimens collected at 3 annual screening time points (N = 10,200)
- Purpose: validation of biomarkers of early detection
- Biorepository open to scientific community | 2-step peer-review process

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Samples</th>
<th>Number Participants</th>
<th># Participants with ≥ 1 sample</th>
<th>% Participants with ≥ 1 sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>108,666</td>
<td>10,218</td>
<td>10,133</td>
<td>99.17%</td>
</tr>
<tr>
<td>Buffy coat</td>
<td>108,891</td>
<td>10,218</td>
<td>10,132</td>
<td>99.16%</td>
</tr>
<tr>
<td>Urine</td>
<td>55,332</td>
<td>10,247</td>
<td>10,168</td>
<td>99.23%</td>
</tr>
<tr>
<td>Sputum cell pellet</td>
<td>39,544</td>
<td>8,336</td>
<td>8,173</td>
<td>99.04%</td>
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<tr>
<td>Remnant tissue TMA</td>
<td>(NLST trial wide)</td>
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</table>
looking forward
lessons from mammography implementation

- Establish **cost-effectiveness**
- Optimal **risk cohorts** for CT-screening
- **Standardize practices**
  - Acquisition parameters and radiation dose
  - Interpretation and communication practices
  - Follow-up documentation
- Determine what **molecular biomarker(s)**
  - Identify high risk individuals who may benefit from screening
  - Motivate more aggressive evaluation of [+] screen
- Establish appropriate venues for screening within broader programs of risk modification and smoking cessation
Thank you