# Screening for Lung Cancer

# Beyond the NELSON update

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IASLC; Past Chair, Screening & Early Detection
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Pasr Head, Thoracic Oncology Assembly,
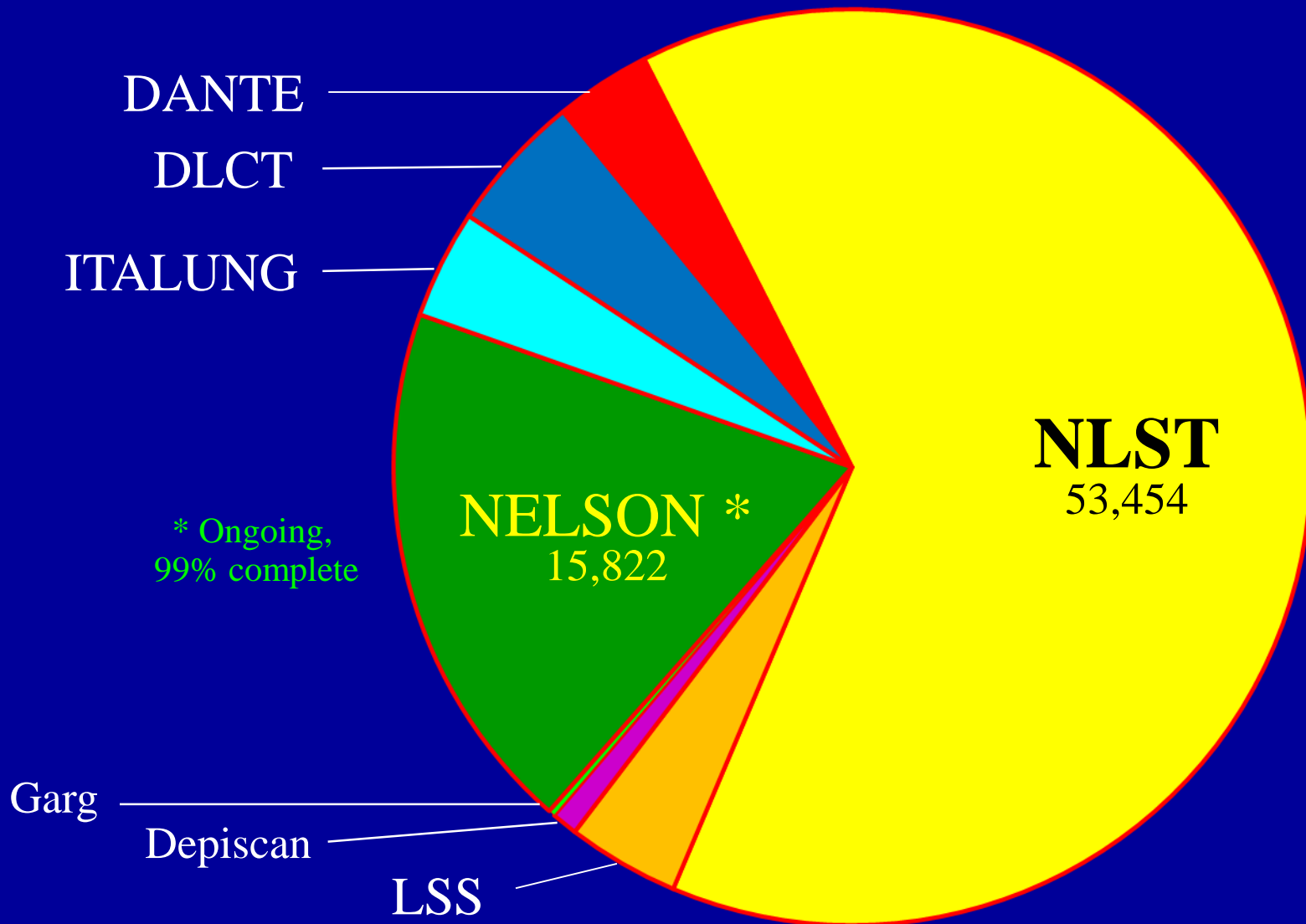European Respiratory Society
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# Presenter Disclosure

Advisor & honorarium from AstraZeneca, BI, BMS, FoundationMedicine, Gaurdant, Lilly, MSD, Novartis, Pfizer, Roche

# Points to Consider

1. **The benefit from Screening is proven**

2. **Screening reduces LC related mortality by 26%** (26% males; 40% females, NELSON Study 2018)

3. **Next task: IMPLEMENTATION**

4. **Challenges:**

   1. **Better cost-benefit**

   2. **SPN investigation**

   3. **Biomarkers** (Protein, DNA, miRNAs, Auto Abs, VOCs, EBC, others..)

# LDCT – Randomized Trials



DANTE

DLCT

ITALUNG

* Ongoing,
99% complete

Garg

Depiscan

LSS

NLST
53,454

NELSON *
15,822

**Screening for lung cancer: time for large-scale screening by chest computed tomography.**   Shlomi D, Ben-Avi R, Balmor GR, Onn A, Peled N.
**Eur Respir J. 2014 Feb 13.**

TABLE 6 Eligible criteria for lung cancer early detection by low-dose computed tomography, according to guidelines or recommendations issued in 2012–2013 by different organisations

| Guidelines by organisation | Date | Age years | Smoking history | Smoking cessation | Category/level[#] |
|---|---|---|---|---|---|
| NCCN [92] | Feb 2012 | 55–74 | ⩾30 pack-years | <15 years | 1 |
| | | ⩾50 | Any and one risk factor[¶] | | 2B |
| ALA [93] | Apr 2012 | 55–74 | ⩾30 pack-years | <15 years | NA |
| Collaborative work of ACCP, ASCO, NCCN [94] | May 2012 | 55–74 | ⩾30 pack-years | <15 years | 2B |
| AATS [95] | June 2012 | 55–79 | ⩾30 pack-years | Any active or former smoker | 1 |
| | | 50–79 | ⩾20 pack-years and added risk ⩾5% of developing lung cancer within 5 years[+] | | 2 |
| | | Any | Any and ⩾4 years remission after bronchogenic carcinoma | | 3 |
| ACS [96] | Jan 2013 | 55–74 | ⩾30 pack-years | <15 years | NA |
| French taskforce: IFCT, GOLF [97] | March 2013 | 55–74 | ⩾30 pack-years | <15 years | NA |
| ACCP [98, 99] | May 2013 | 55–74 | ⩾30 pack-years | <15 years | 2B |
| USPSTF [100] | July 2013 | 55–79 | ⩾30 pack-years | <15 years | B |

NCCN: National Comprehensive Cancer Network; ALA: American Lung Association; ACCP: American College of Chest Physicians; ASCO: American Society of Clinical Oncology; AATS: American Association for Thoracic Surgery; ACS: American Cancer Society; IFCT: Intergroupe Francophone de Cancérologie Thoracique; GOLF: Groupe d'Oncologie de Langue Française; USPSTF: US Preventive Services Task Force; NA: not applicable. [#]: refer to text; [¶]: radon exposure, occupational exposure (silica, cadmium, asbestos, arsenic, beryllium, chromium, diesel fumes, and nickel), cancer history (survivors of lung cancer, lymphomas, cancers of the head and neck, or smoking-related cancers), family history of lung cancer, disease history (chronic obstructive pulmonary disease or pulmonary fibrosis); [+]: such as chronic obstructive pulmonary disease with forced expiratory volume in 1 s of ⩽70% of predicted, environmental or occupational exposures, any prior cancer or thoracic radiation, genetic or family history.

# ESR/ERS white paper on lung cancer screening

Hans-Ulrich Kauczor[1,2], Lorenzo Bonomo[3], Mina Gaga[4], Kristiaan Nackaerts[5], Nir Peled[6], Mathias Prokop[7], Martine Remy-Jardin[8], Oyunbileg von Stackelberg[1,2] and Jean-Paul Sculier[9] on behalf of the European Society of Radiology (ESR) and the European Respiratory Society (ERS)

ABSTRACT   Lung cancer is the most frequently fatal cancer, with poor survival once the disease is advanced. Annual low dose computed tomography has shown a survival benefit in screening individuals at high risk for lung cancer. Based on the available evidence, the European Society of Radiology and the European Respiratory Society recommend lung cancer screening in comprehensive, quality-assured, longitudinal programmes within a clinical trial or in routine clinical practice at certified multidisciplinary medical centres. Minimum requirements include: standardised operating procedures for low dose image acquisition, computer-assisted nodule evaluation, and positive screening results and their management; inclusion/exclusion criteria; expectation management; and smoking cessation programmes. Further refinements are recommended to increase quality, outcome and cost-effectiveness of lung cancer screening: inclusion of risk models, reduction of effective radiation dose, computer-assisted volumetric measurements and assessment of comorbidities (chronic obstructive pulmonary disease and vascular calcification). All these requirements should be adjusted to the regional infrastructure and healthcare system, in order to exactly define eligibility using a risk model, nodule management and quality assurance plan. The establishment of a central registry, including biobank and image bank, and preferably on a European level, is strongly encouraged.
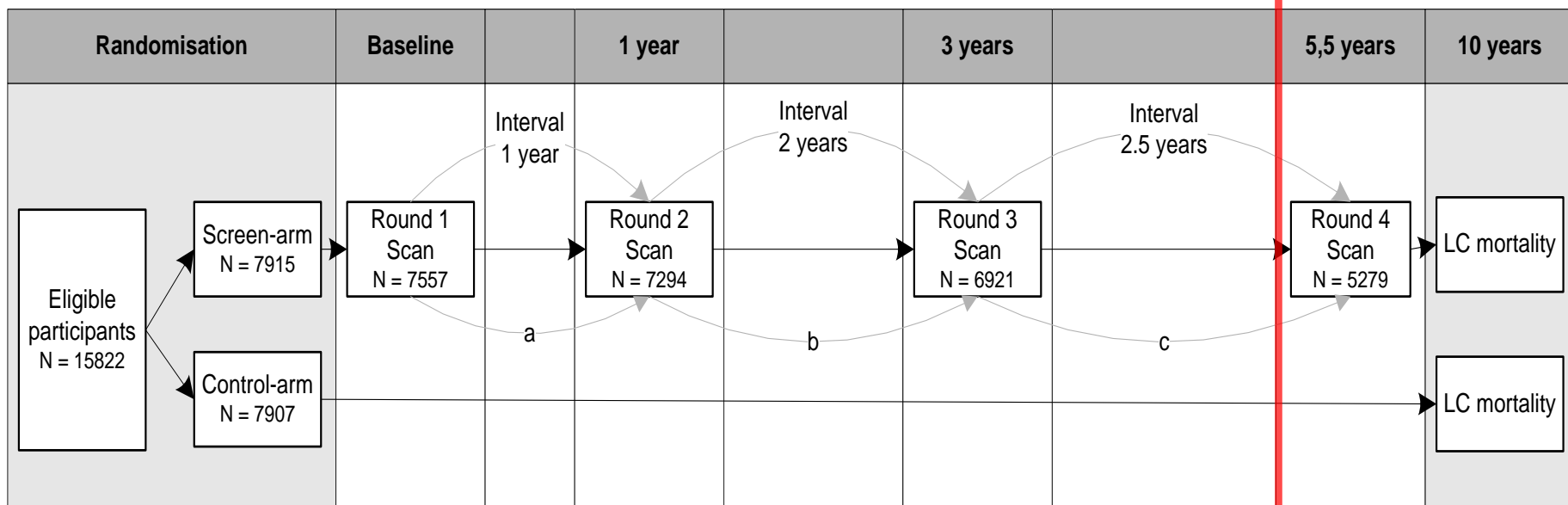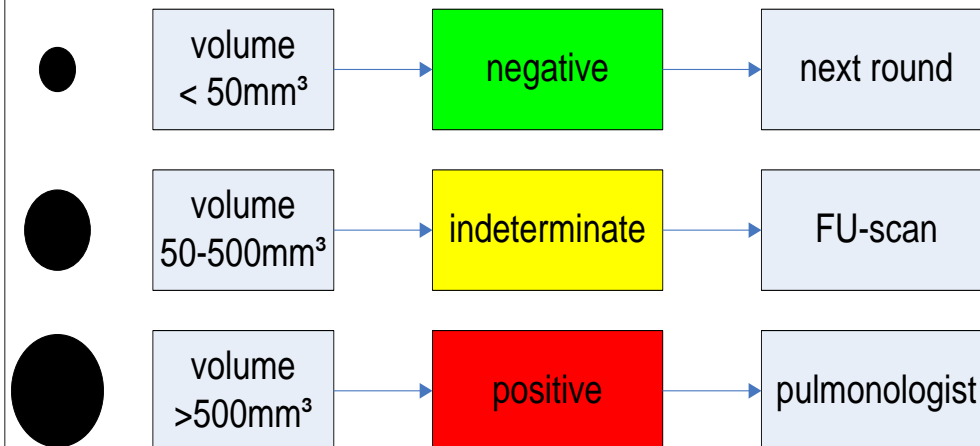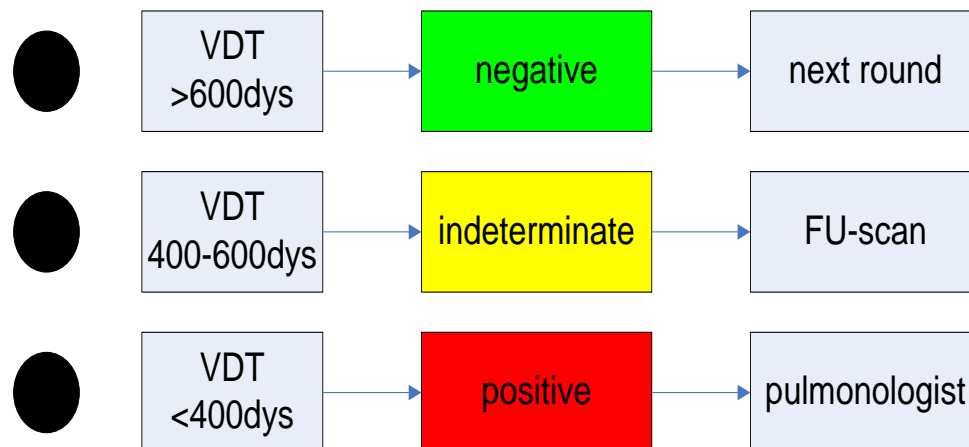
# Design NELSON trial

- 4 rounds of low-dose multi-slice computer tomography scanning
- Only trial with increasing length of the screening interval:
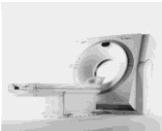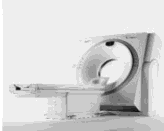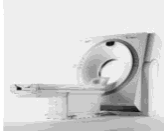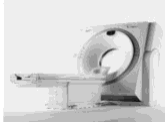  1 yr, 2 yr and 2.5 yr

| Randomisation | Baseline | | 1 year | | 3 years | | 5,5 years | 10 years |
|---|---|---|---|---|---|---|---|---|
| | | Interval 1 year | | Interval 2 years | | Interval 2.5 years | | |
| Eligible participants N = 15822 → Screen-arm N = 7915 | Round 1 Scan N = 7557 | | Round 2 Scan N = 7294 | | Round 3 Scan N = 6921 | | Round 4 Scan N = 5279 | LC mortality |
| | | a | | b | | c | | |
| Control-arm N = 7907 | | | | | | | | LC mortality |

R.J. van Klaveren, et al., *NEJM* 2009

# New nodule

| | | | |
|---|---|---|---|
| ● | volume < 50mm³ | negative | next round |
| ● | volume 50-500mm³ | indeterminate | FU-scan |
| ● | volume >500mm³ | positive | pulmonologist |

# Previously existing nodule

| | | | |
|---|---|---|---|
| ● | VDT >600dys | negative | next round |
| ● | VDT 400-600dys | indeterminate | FU-scan |
| ● | VDT <400dys | positive | pulmonologist |

Erasmus MC

Xu et al., Lung Cancer 2006

IASLC

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

IASLC 19th World Conference on Lung Cancer
September 23–26, 2018  Toronto, Canada

WCLC2018.IASLC.ORG

#WCLC2018

| | Year 1 | Year 2 | Year 4 | Year 6.5 | Year 10 |
|---|---|---|---|---|---|
| **Screen arm** n=7,900 | CT screening | CT screening | CT screening | CT screening | |
| | n=7,557 95.6% uptake | n=7,295 92.3% uptake | n=6,922 87.6% uptake | n=5,279 66.8% uptake | MORTALITY ANALYSES |
| **Control arm** n=7,892 | | Usual care (no screening) | | | |

NATIONAL LINKAGES
- Statistics Netherlands/ Belgium
- Dutch/ Belgium Cancer Registry
- Centre for Genealogy

CAUSE OF DEATH REVIEW

WCLC 2018

IASLC

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#WCLC2018

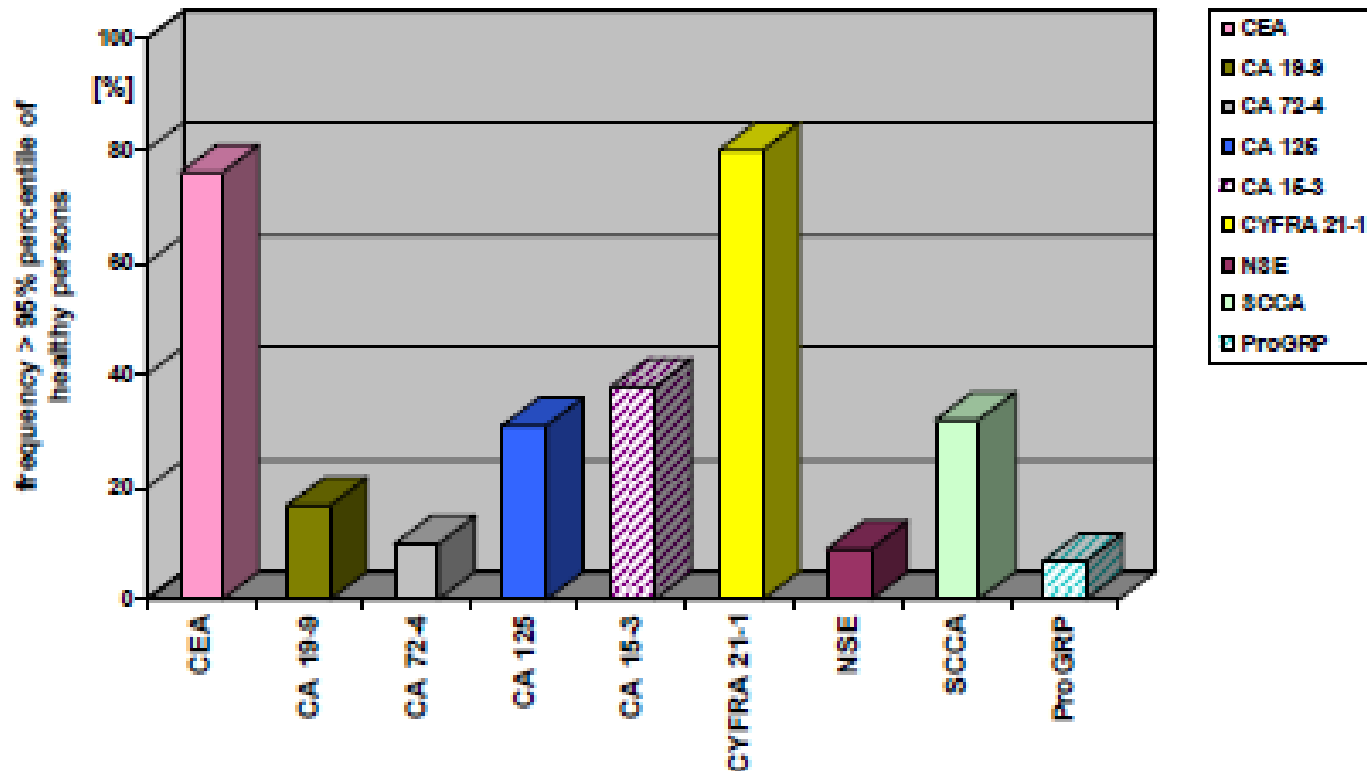| Lung cancer mortality rate ratio (95% CI) | Year 8 | Year 9 | Year 10 |
|---|---|---|---|
| MALES | **0.75** P=0.015 (0.59-0.95) | **0.76** P=0.012 (0.60-0.95) | **0.74** P=0.003 (0.60-0.91) |
| FEMALES | **0.39** P=0.0037 (0.18-0.78) | **0.47** P=0.0069 (0.25-0.84) | **0.61** P=0.0543 (0.35-1.04) |

10-year follow-up
December 31th 2015

WCLC 2018

# SO, WHAT NEXT ?
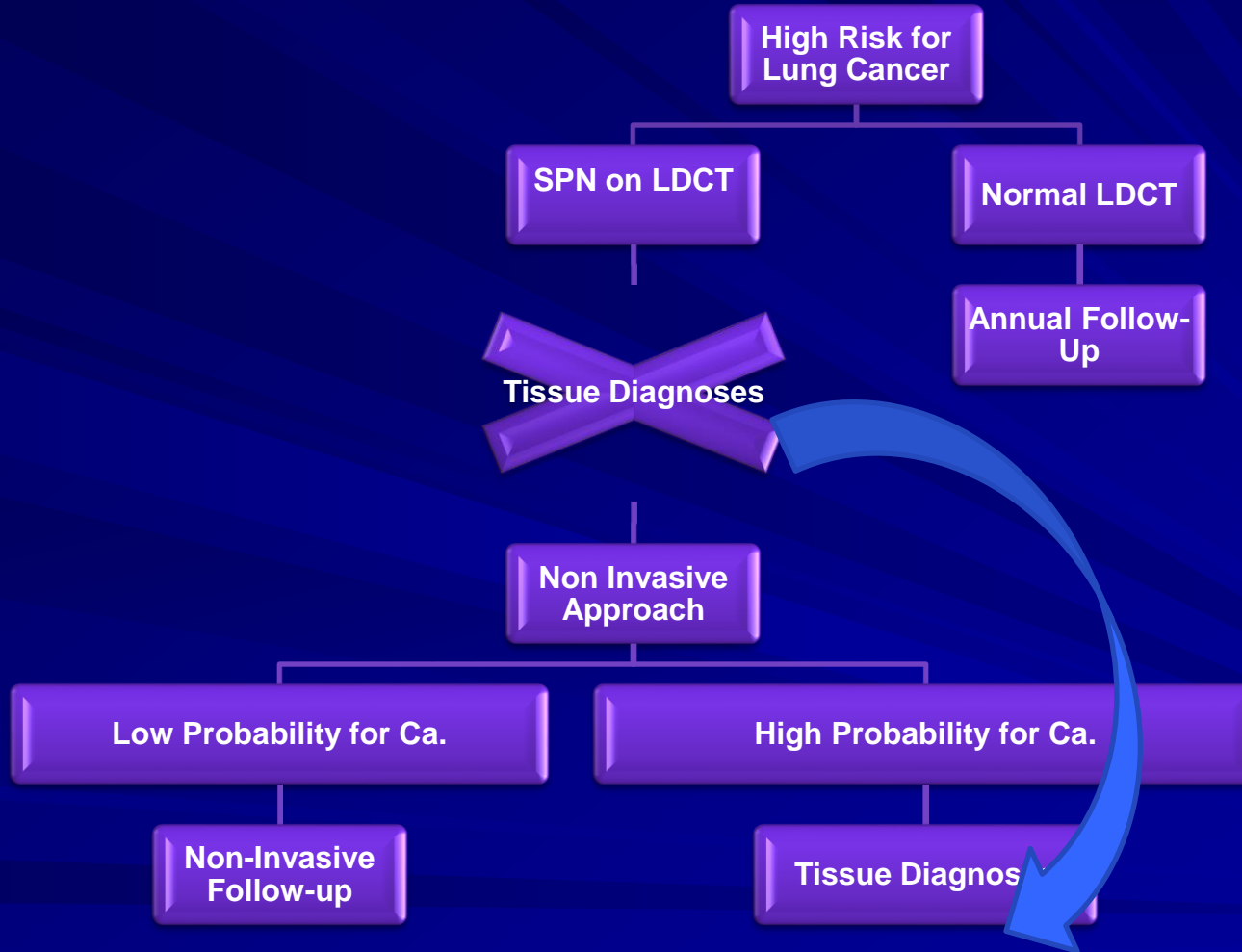
Release of Biomarkers in NSCLC Operable Stage I-IIIA

| marker | CEA | CA 19-9 | CA 72-4 | CA 125 | CA 15-3 | CYFRA 21-1 | NSE | SCCA | ProGRP |
|---|---|---|---|---|---|---|---|---|---|
| cut off | 2.5 ng/ml | 28.4 U/ml | 5.9 U/ml | 31.5 U/ml | 23.1 U/ml | 1.3 ng/ml | 20.0 ng/ml | 1.5 ng/ml | 50.0 pg/ml |

Release of Biomarkers in SCLC
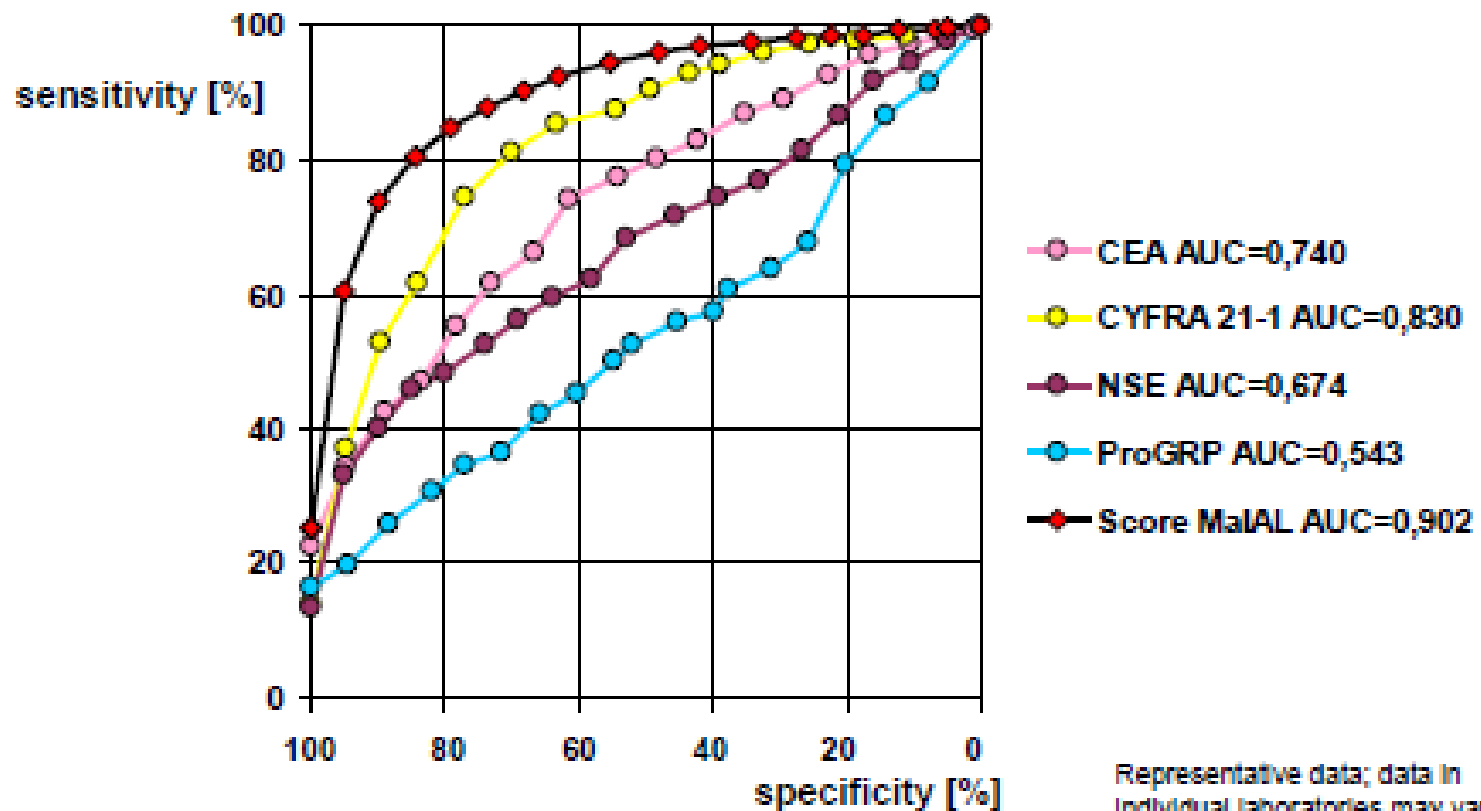Operable Stage LD

# Lung cancer patients serum markers

| | | N | SCC >2 ng/mL | ProGRP >50 pg/mL | NSE >25 ng/mL | CYFRA 21-1 >3.3 ng/mL | CEA >5 ng/mL | CA 15.3 >35 U/mL * |
|---|---|---|---|---|---|---|---|---|
| SCLC | Limited | 79 | 0% | 74.7% | 54.4% | 25.3 % | 36.7% | 6.7% (45) |
| | Extensive | 96 | 0% | 78.1% | 73.9% | 57.3% | 57.3% | 21.5% (51) |
| | TOTAL | 175 | 0% | 76.6% | 65.1% | 42.9% | 48% | 14.6% (96) |
| NSCLC | Squamous | 182 | 41.2% | 24.7% | 13.1% | 70.3% | 42.3% | 25.6% (133) |
| | ADK | 205 | 8.3% | 8.8% | 8.8% | 53.7% | 69.8% | 46.5% (198) |
| | LCLC | 19 | 10.5% | 21.1% | 15.8% | 52.6% | 26.3% | 14.3% (7) |
| | NSCLC | 66 | 10.6% | 10.6% | 6.1% | 53% | 47% | 52% (50) |
| | TOTAL | 472 | 21.4% | 15.7% | 10.4% | 60% | 54.2% | 39.4% (388) |

**ADK- Adenocarcinoma; LCLC: Large cell lung cancer**

**ROC Kurven Score**
**Benign Lung Diseases vs. Malignant Lung Diseases**

CEA AUC=0,740
CYFRA 21-1 AUC=0,830
NSE AUC=0,674
ProGRP AUC=0,543
Score MalAL AUC=0,902

Representative data; data in individual laboratories may vary.
Christine Gruber, JLabMed September 2008, 32 (5): 361-371

# Liquid Biopsy Definition
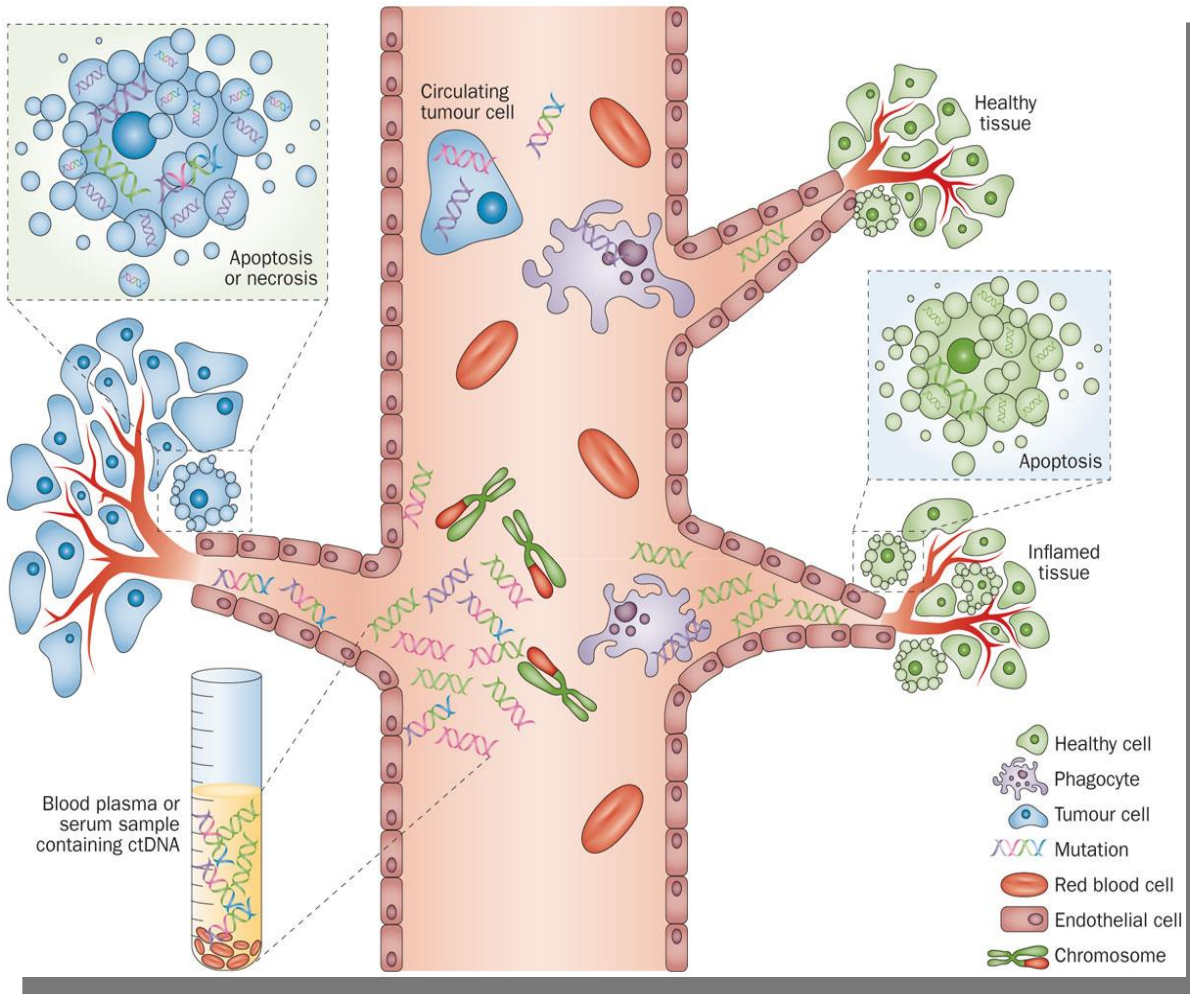


Detection of positive and negative biomarkers as circulating tumor cells (CTC) and cell-free circulating tumor DNA (ctDNA) from peripheral blood samples

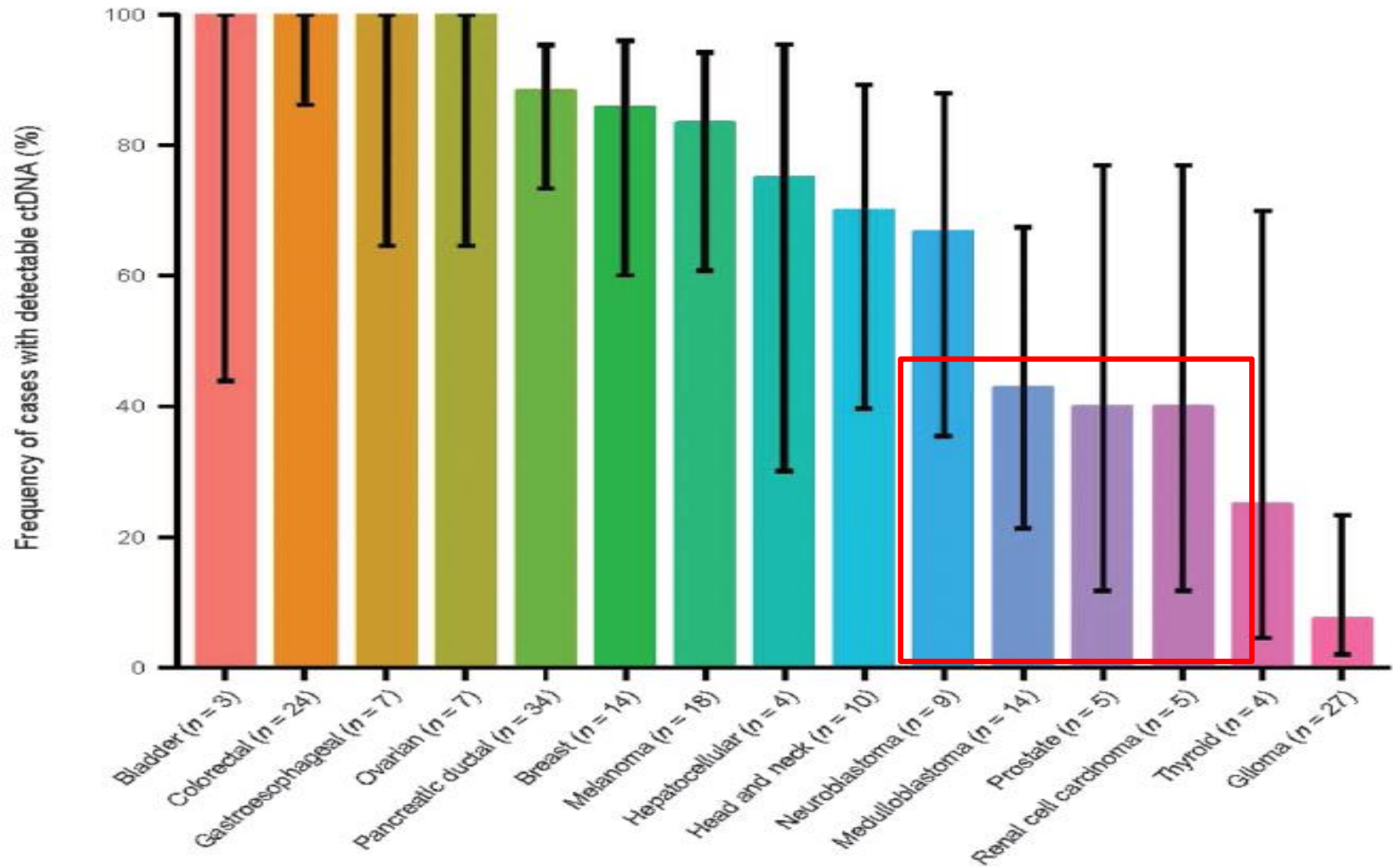Schwarzenbach et al. Nat Rev Cancer. 2011;11(6):426–437; Crowley et al Nat Rev Clin Oncol. 2013;10(8):472-484

# Circulating tumor DNA

## Technique sensitivity

| Technique | Sensitivity | Optimal Application |
|---|---|---|
| Sanger sequencing | > 10% | Tumor tissue |
| Pyrosequencing | 10% | Tumor tissue |
| Next-generation seqeuncing | 2% | Tumor tissue |
| Quantative PCR | 1% | Tumor tissue |
| ARMS | 0.10% | Tumor tissue |
| BEAMing, PAP, Digital PCR, TAM-Seq | 0.01% or lower | ctDNA, rare variants in tumor tissue |

Diaz et al. Clin Oncol. 2014;32(6):579–586

# Liquid biopsy

**ctDNA: Distribution in different tumors**



Bettegowda et al., Sci Transl Med. 2014;6(224):224ra24

# CancerSEEK performance for early detection

ctDNA mutation

&

CA-125
CEA
CA19-9
PRL
HGF
OPN
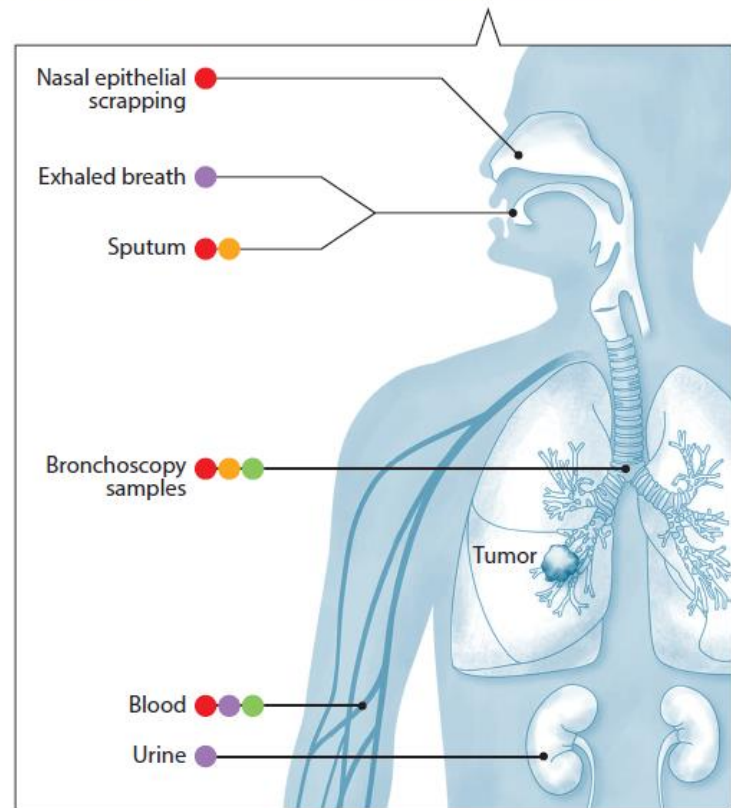MPO
TIMP1



J D Cohen; *Science* 2018

**Currently explored biomarker candidates**

Legend: ● Nucleic acids  ● Cells  ● Proteins  ● Other molecules

**Origin**
- Nasal epithelial cells
- Airways epithelial cells
- Tumor cells
- Microenvironment
- Host

**Biomarker candidates**
- RNA signature
- Volatile compounds
- Preinvasive histo/cytology
- Chromosome aberrations
- DNA alterations
- miRNA
- Proteins / fragments
- Metabolites
- Autoantibodies

**Source**
- Nasal epithelial scrapping
- Exhaled breath
- Sputum
- Bronchoscopy samples
- Blood
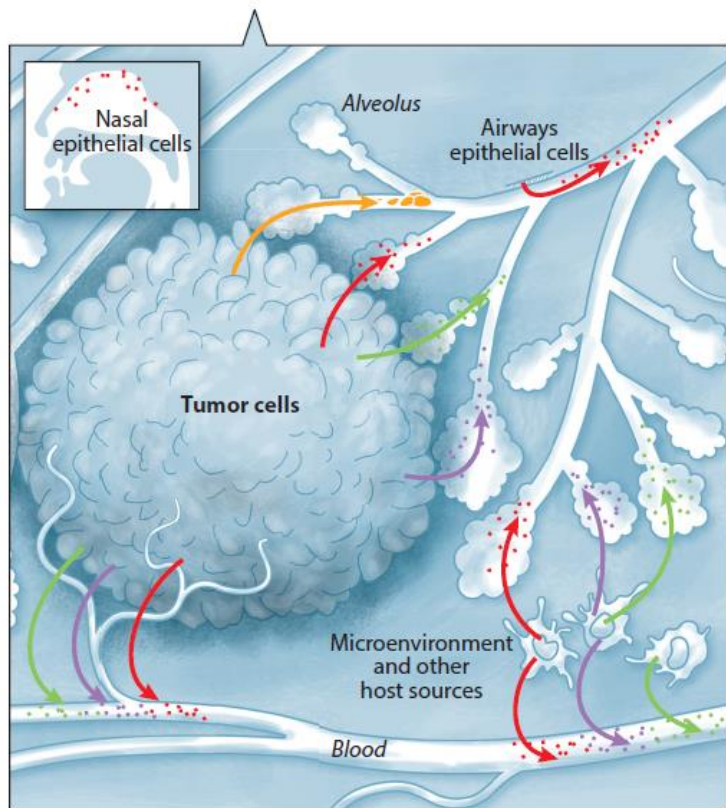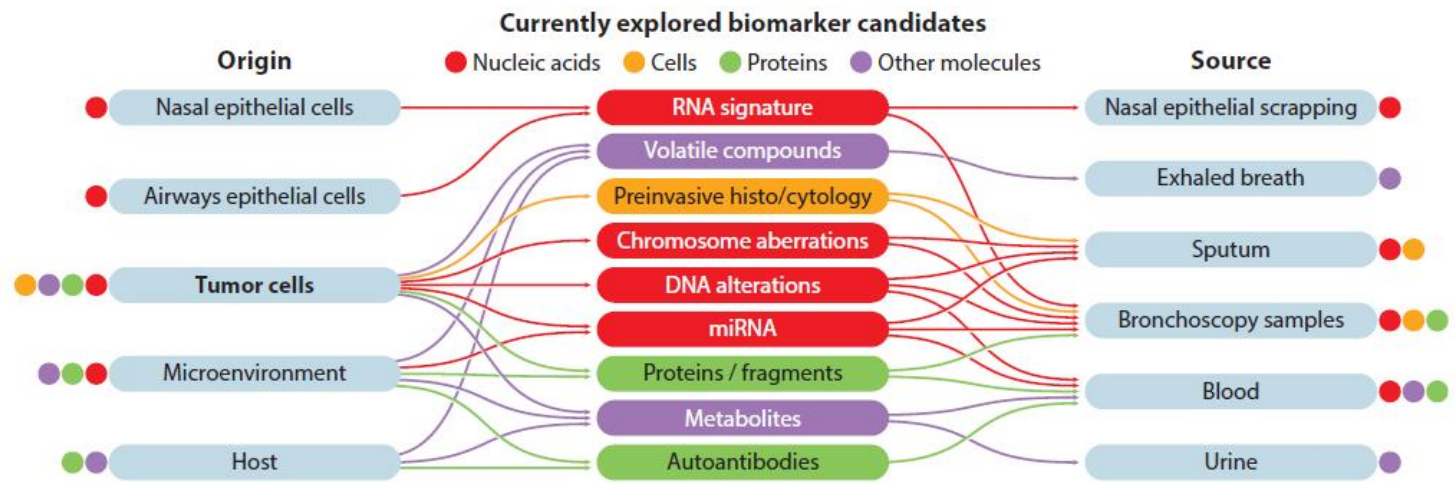- Urine

**Seijo L, Peled N et al, J Thoracic Oncology 2018; In Press**

# Take Home Message

- Screening for Lung Cancer is here to stay.
- Implementation is the current goal.
- Non-Invasive biomarkers are needed

**THANK YOU**