LEARNING OBJECTIVES

- To learn about screening, diagnosis and staging of breast cancer

Screening

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Siemens Scientific Advisory Board Member (2017)

Research collaboration with Philips

The aim of screening

- Detect a disease early in an asymptomatic stage
- Give early intervention and management
- Reduce the impact of a disease that has already occurred (secondary prevention)

Guidelines on the principles and practice of screening according to Wilson and Jungner (WHO 1968)

The disease

- Severe
- High prevalence in a preclinical stage
- The natural history of the disease known
- Long period between between first sign and manifest disease

The test

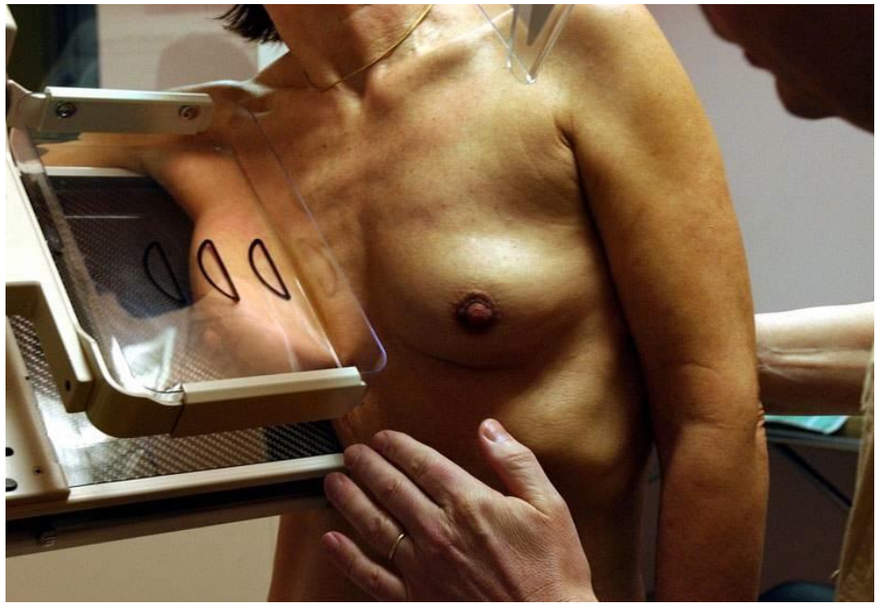
- Acceptable sensitivity and specificity
- Simple and cheap
- Safe and acceptable

The treatment

- Possible treatment
- Effective, safe and acceptable

Randomised trials of breast cancer screening with mammography

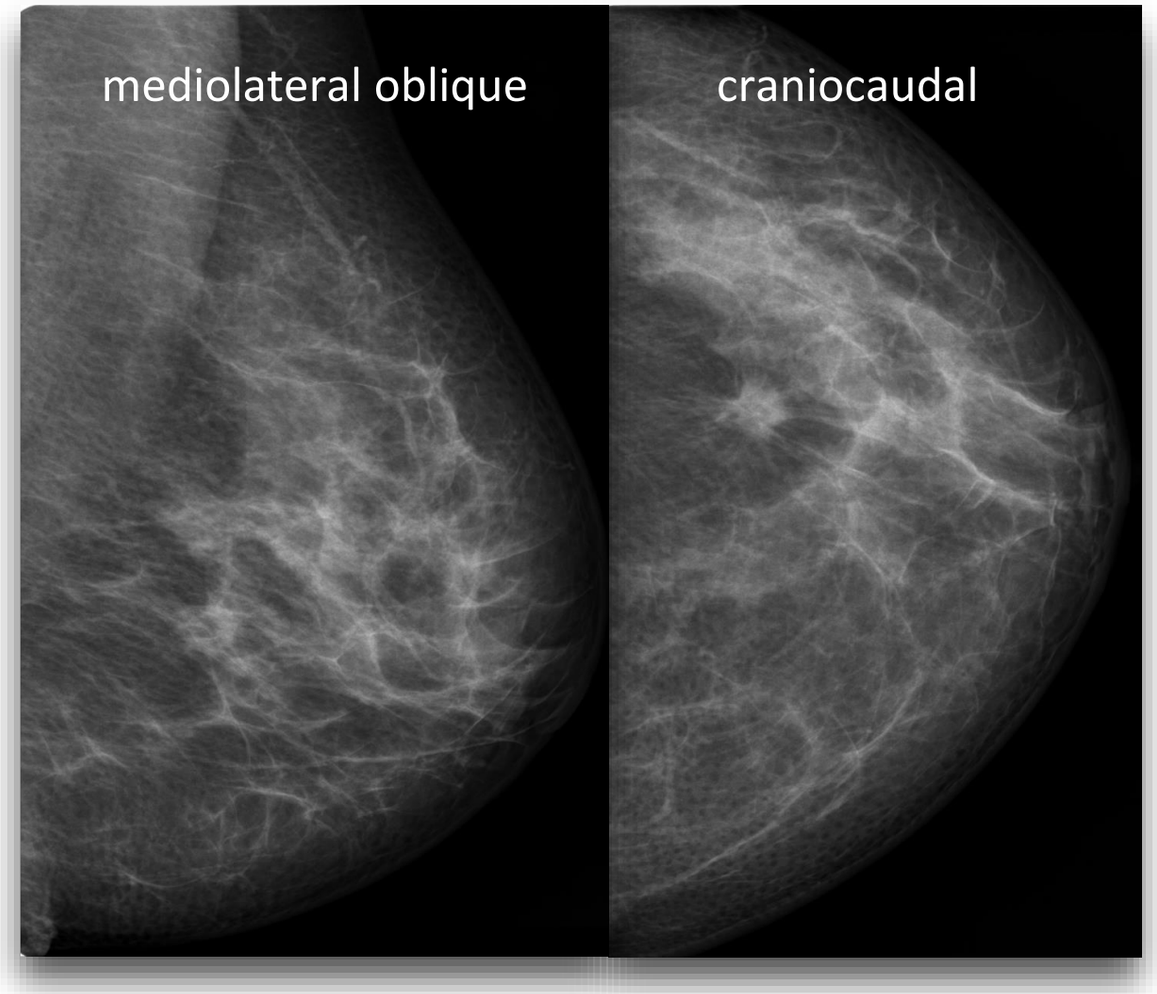
- New York HIP (1963)
- Malmö I and II (1976)
- Swedish Two County (1977)
- Edinburgh (1978)
- Canada I and II (1980)
- Stockholm (1981)
- Göteborg (1982)
- UK Age trial (1991)



- Initiation of a population based screening programmes
- In Europe: 1986 to 2008

Mammography screening programmes

- Two-view mammography
- Target age 50–69
- Biennial screening intervals
- Double reading



Sweden: Age 40–74 with 1.5–2 year interval

UK: Age 50–70 with 3 year interval

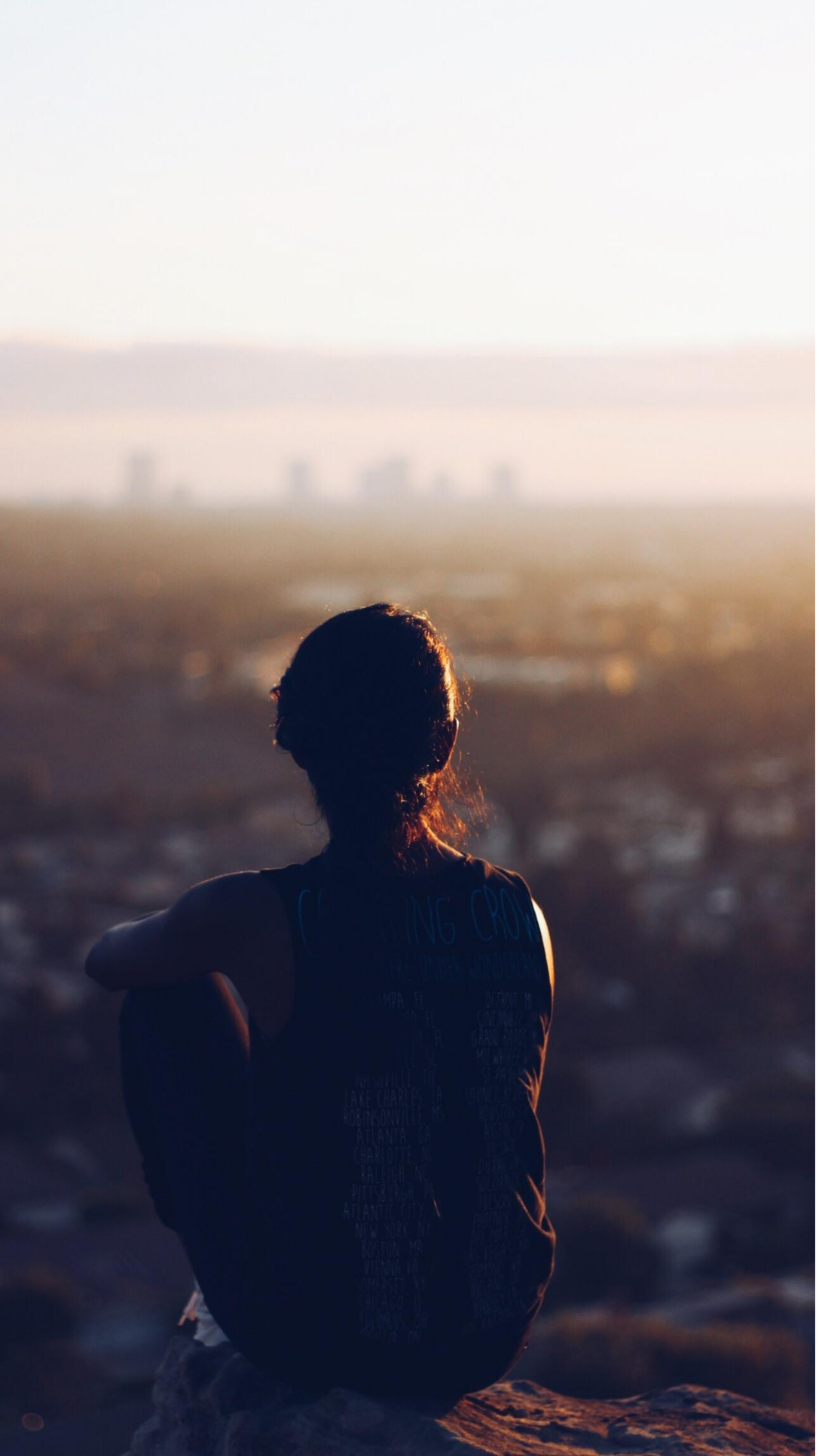
Mammography screening

Benefits

- Reduction in mortality
- Reduced suffering from metastatic disease
- Breast conserving surgery
- Feeling of security

Harms

- False positives
- Overdiagnosis
- Anxiety
- Limitation: False negatives



False positives (FP)

- 80–90% of recalled women are FP
- Breast cancer-specific psychological distress that may endure for up to 3 years
- Recall rates:
  - prevalence screening <7%
  - incidence screening <5%

Bond et al. Health Technol Assess 2013
Bolejko et al. Cancer Epidemiol Biomarkers Prev 2015

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Overdiagnosis

- The detection of a cancer that would never have been found were it not for the screening test

The consequence:

- Women become cancer patients with psychological and treatment side effects
- A breast cancer diagnosis is associated with comorbidity: increased risk of dying of various causes (pulmonary circulation, suicide, heart failure, and gastrointestinal disease)

Riihimäki et al. Ann Oncol 2012

Estimates of overdiagnosis in screening

- <5% (Paci et al, J Med Screen 2004; Duffy et al, Breast Cancer Res 2005)
- 11% (Peeters et al, Int J Epidemiol 1989)
- 15–25% (Kalager et al, Ann Intern Med 2012)
- 50% (Zahl et al, BMJ 2004)

Screening for breast cancer with mammography (Review)

Gøtzsche PC, Jørgensen KJ

- Review of RCTs
- Screening is likely to reduce breast cancer mortality by about 15%
- But 30% overdiagnosis and overtreatment
- 2000 invited women screened for 10 years:

  1 BC death prevented

  10 women overdiagnosed and overtreated

  200 women with FPs

Cochrane Database of Systematic Reviews 2011

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The mammography screening controversy

- The rate of overdiagnosis
- The effect on breast cancer mortality

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UK Independent Panel Review (Lancet 2012)

- Review of RCTs
- Reduction of breast cancer mortality about 20% (invited)
- Overdiagnosis: 11% (invited), 19% (attending)
- If 10,000 women aged 50 are invited to screening for 20 years:

43 BC deaths prevented

129 women overdiagnosed and overtreated

1 breast cancer death prevented

3 women overdiagnosed and overtreated

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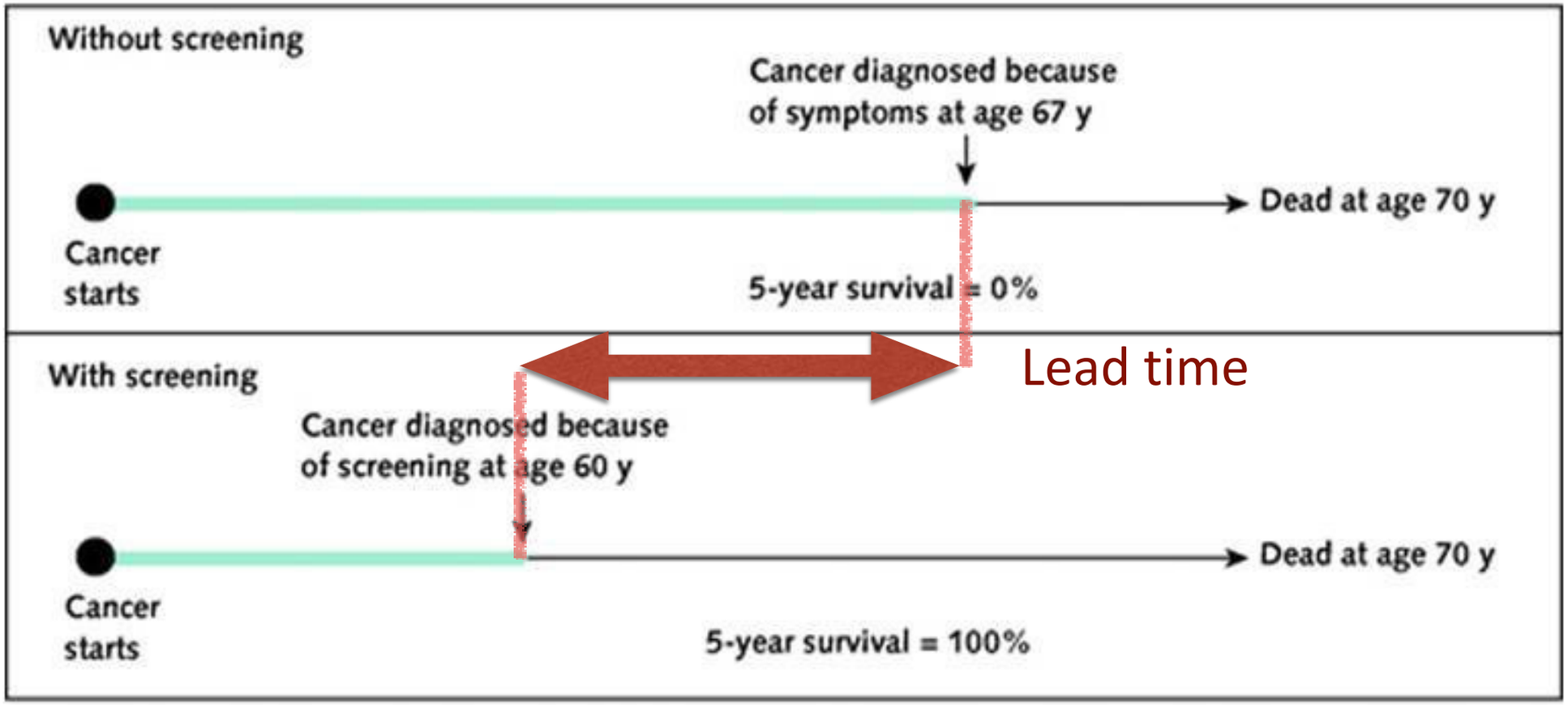
Lead time bias



- The earlier diagnosis does nothing to change the course of the disease
- People in the invited group appears to survive longer

To study screening efficacy: disease specific mortality rates, not survival rates!

O. Wegwarth et al., Ann Intern Med 2012

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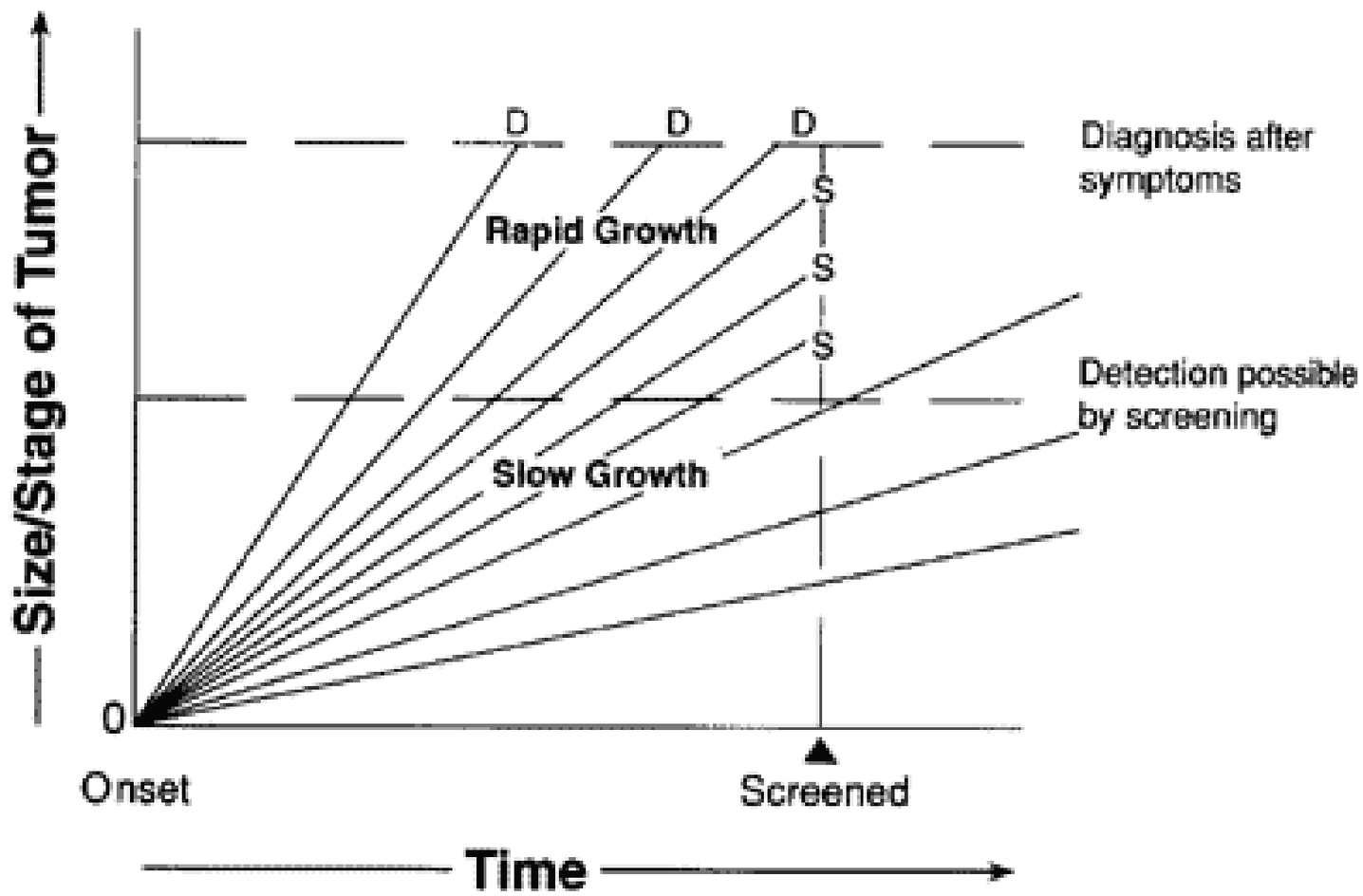
Length time bias



- Screening is more likely to pick up slower-growing, less aggressive cancers
- Can lead to the perception that cancer screening leads to a better outcome when it has no effect

Interval cancers

- Symptomatic cancers diagnosed in the interval between two screening examinations
- ”False” or ”true” interval cancers
- More aggressive with poorer prognosis
- Strong indicator on how successful your screening programme is

SCREENING DM
2013

SCREENING DM
2014

3 months later
lump in the breast

PAD: 12 mm IDC trippel negative G3

Zoom: 85% (-)
2013-03-21, 13:56:02
40 mm, 0,009 dGy, 28 kV, 69 mAs

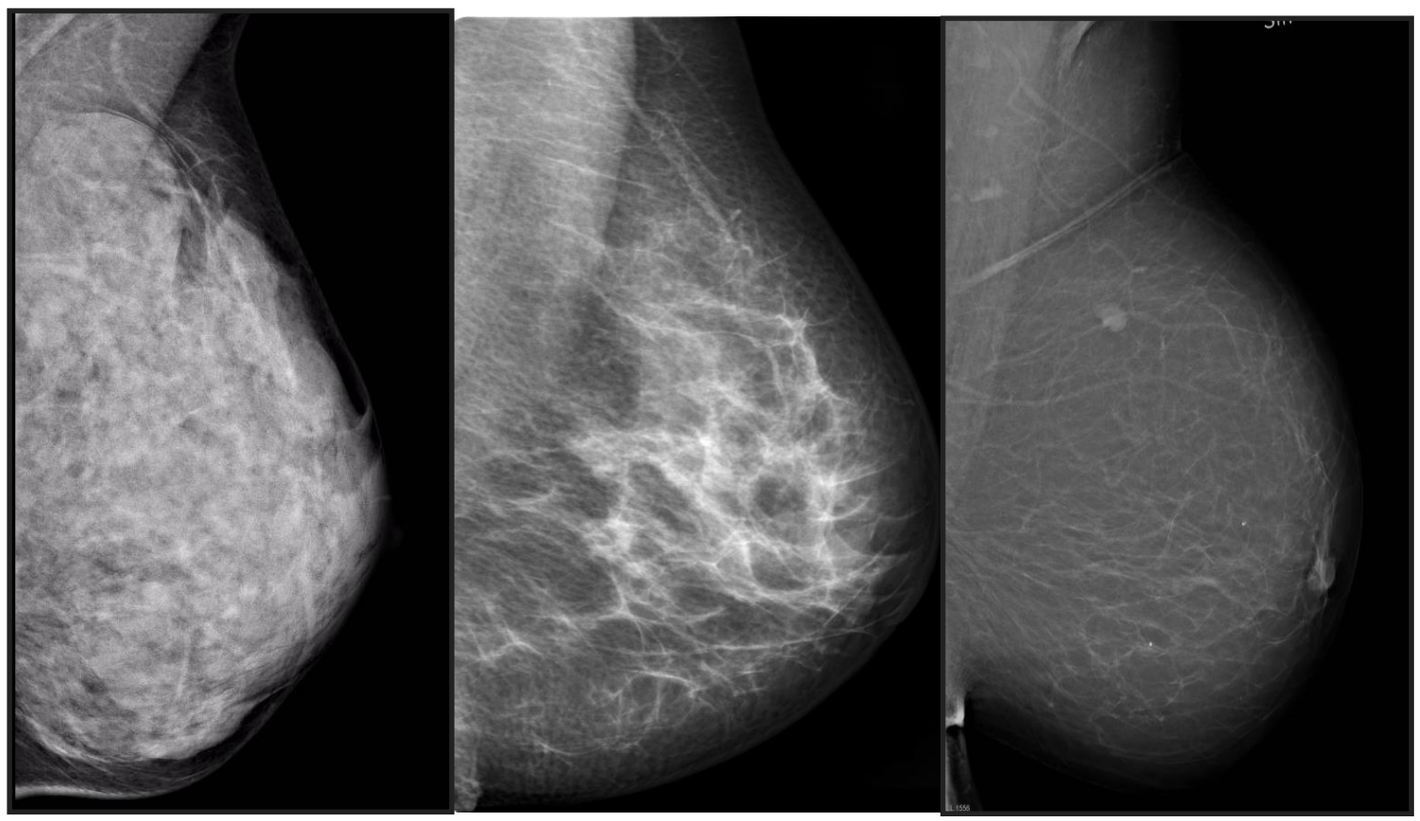
sin

2014-10-09, 13:40:16
31 mm, 0,0098 dGy, 27 kV, 69 mAs

Dist = 1.165cm

The limitation of mammography

DENSE → FATTY



Up to 1/3 of all cancers may be missed

Sensitivity: range 30–95%

Birdwell et al. Radiology 2001
Laming D, et al. J Med Screen 2000
Bochud FO, et al. Med Phys 1999
Carney PA, et al. Ann Intern Med 2003

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Future perspectives of breast cancer screening

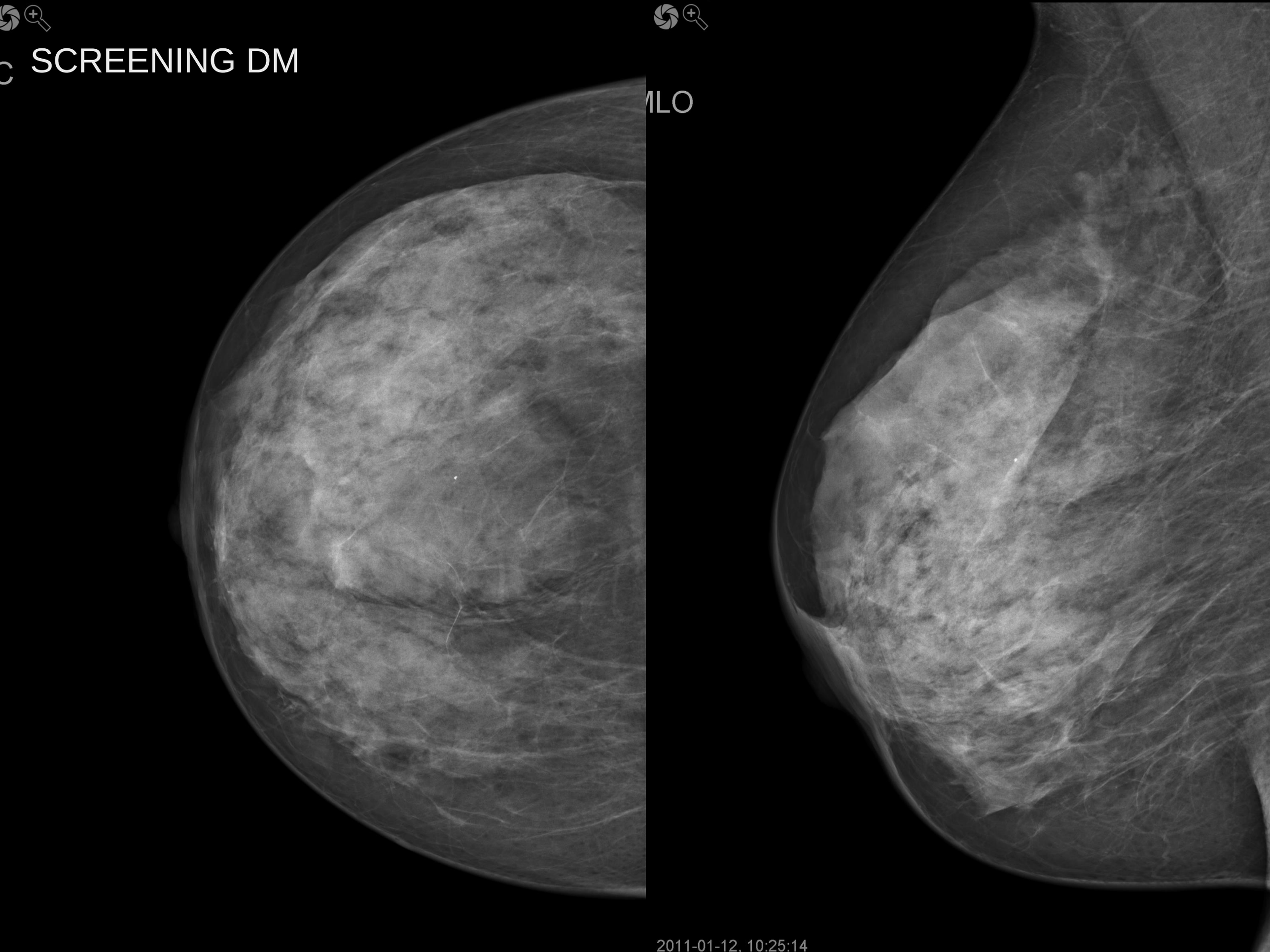
- Breast tomosynthesis (”3D-mammography”)
- Ultrasonography
- Liquid biopsy
- Individualized screening
- Machine learning

Tomosynthesis screening trials

- Three population-based screening trials in Europe: Oslo, STORM, Malmö (+30% cancers detected, slight elevation in recall rates)
- Several retrospective non-population based screening trials in the US (reduction in recall rates)
- RCTs in Europe are ongoing: RE-TOMO (Reggio Emilia, Italy), TOBE-study (Bergen, Norway)

Skaane et al. Radiology 2013
Lång et al. Eur Radiol 2015
Houssami et al. Lancet Oncol 2016

Rose et al. AJR 2013
Haas et al. Radiology 2013
Friedewald et al JAMA 2014
McCarthy et al J natl Cancer inst 2014
Greenberg et al AJR 2014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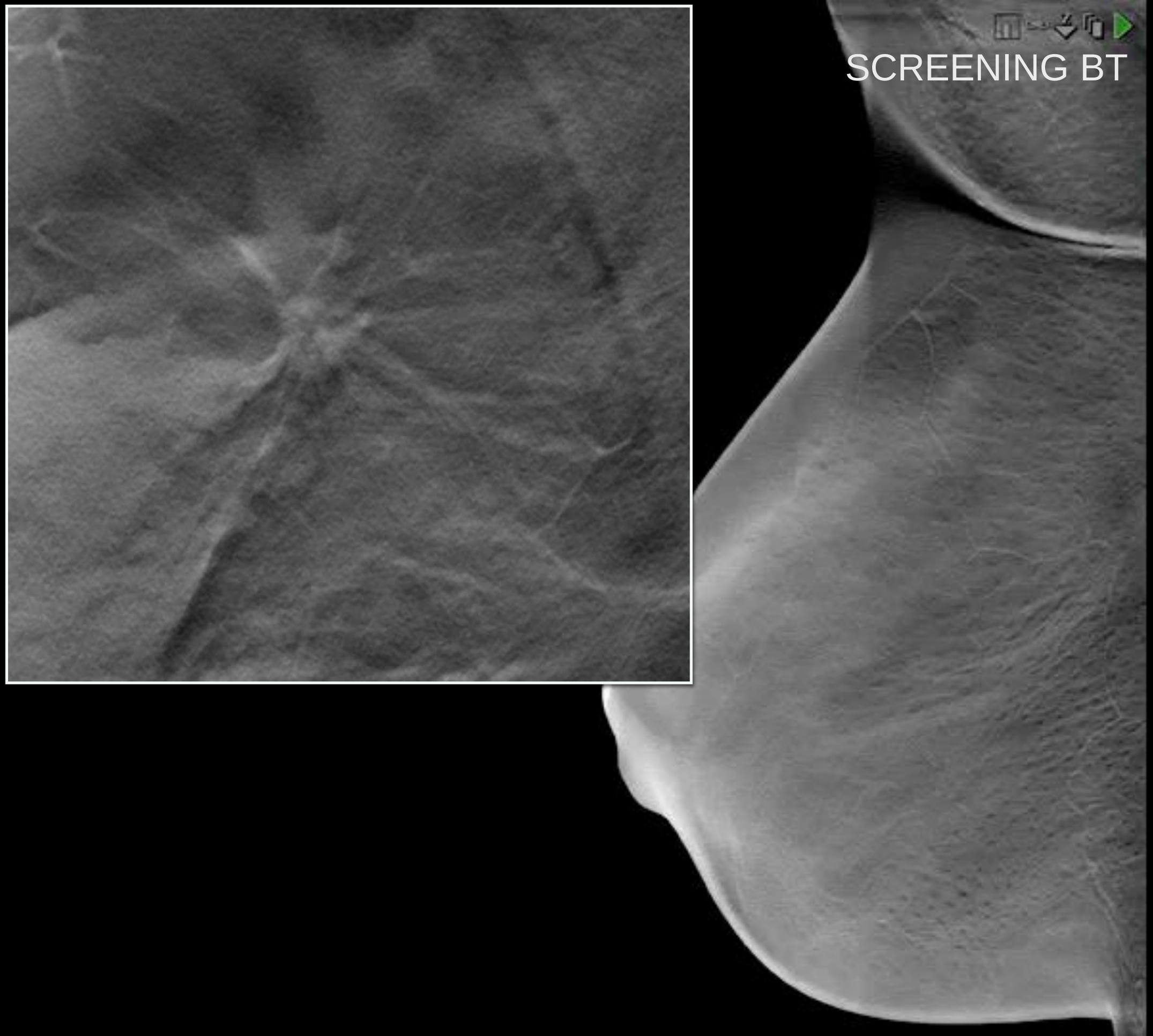
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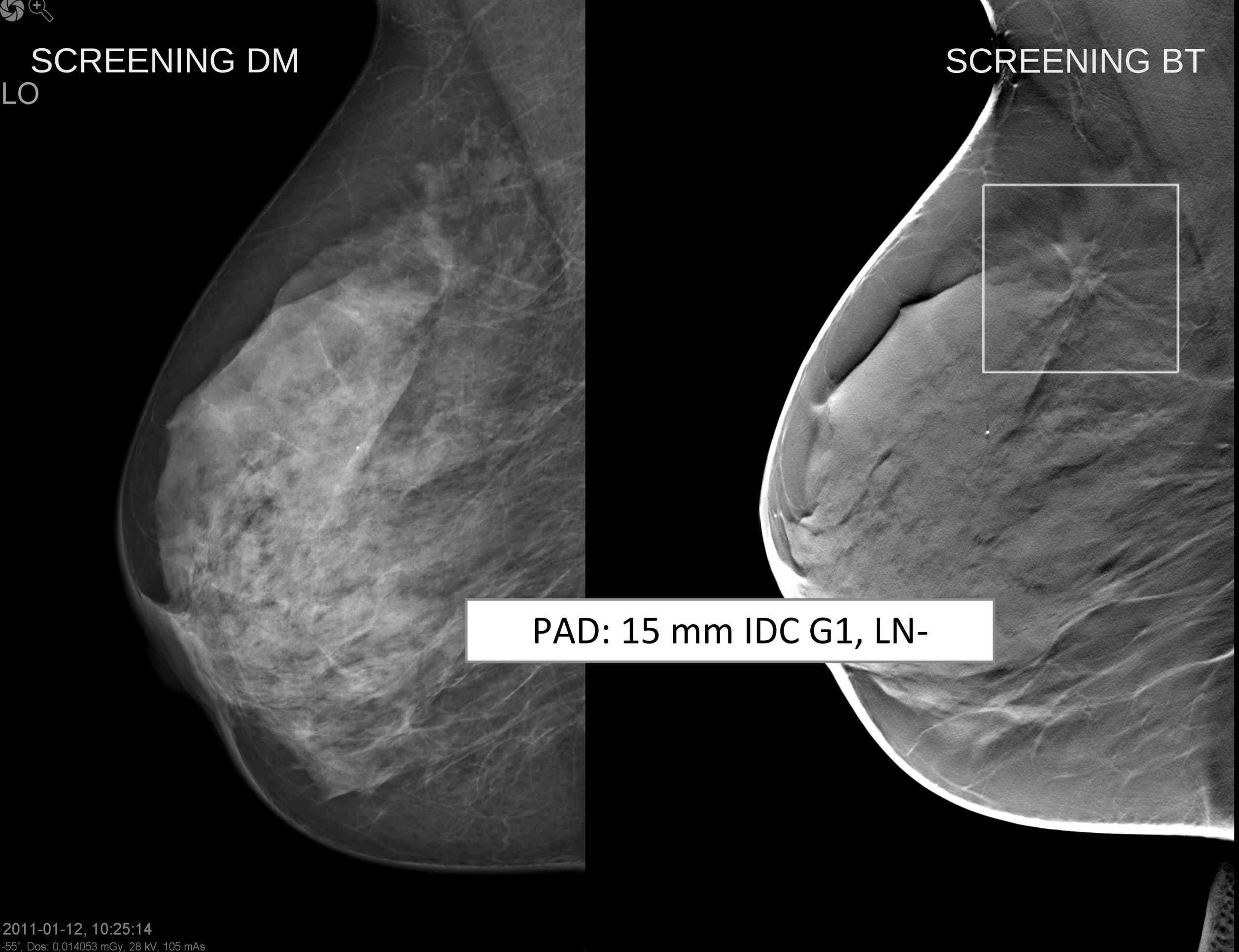
SCREENING DM
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SCREENING BT
PAD: 15 mm IDC G1, LN-
2011-01-12, 10:25:14
-55°, Dos: 0,014053 mGy, 28 kV, 105 mAs

Ultrasound in screening

THE LANCET

< Previous Article Volume 387, No. 10016, p341–348, 23 January 2016 Next Article >

Articles

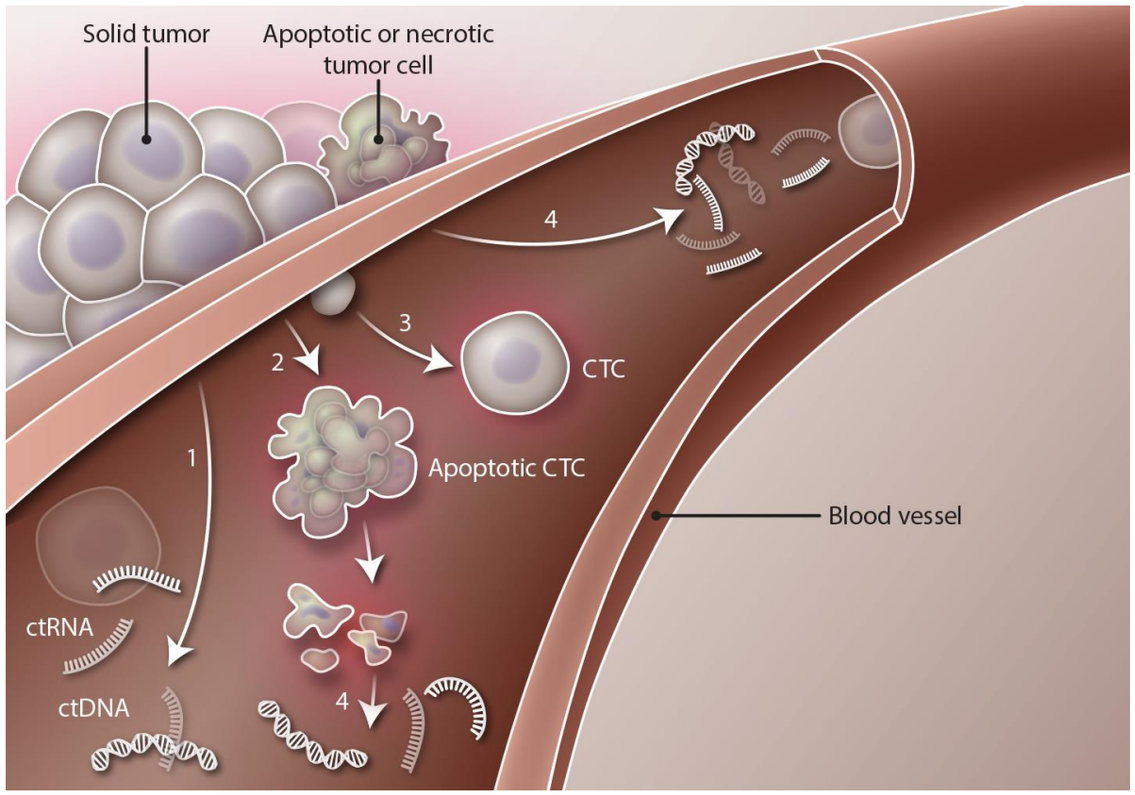
Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial

Prof Noriaki Ohuchi, PhD, Akihiko Suzuki, PhD, Prof Tomotaka Sobue, MD, Masaaki Kawai, PhD, Seiichiro Yamamoto, PhD, Ying-Fang Zheng, PhD, Yoko Narikawa Shiono, PhD, Hiroshi Saito, PhD, Prof Shinichi Kuriyama, PhD, Eriko Tohno, PhD, Tokiko Endo, PhD, Prof Akira Fukao, PhD, Prof Ichiro Tsuji, PhD, Prof Takuhiro Yamaguchi, PhD, Prof Yasuo Ohashi, PhD, Mamoru Fukuda, PhD, Takanori Ishida, PhD for the J-START investigator groups

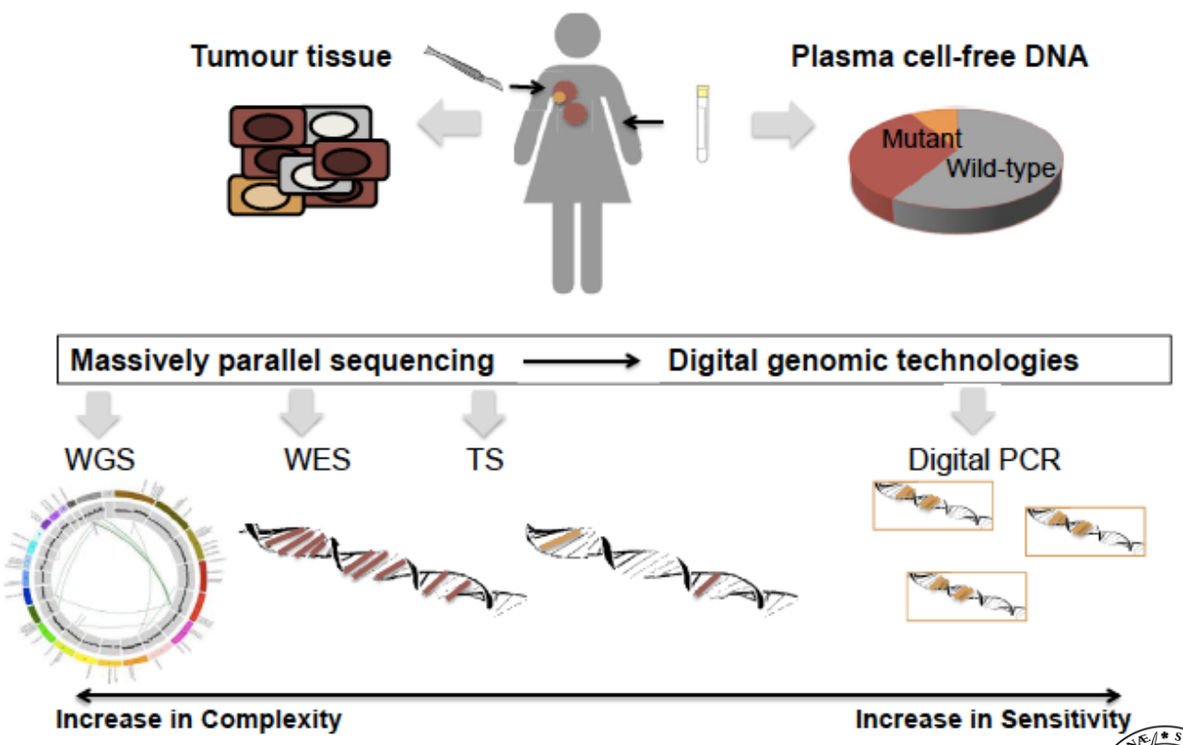
Published Online: 04 November 2015

- RCT, 72,000 women
- Increased sensitivity but decreased specificity

Liquid biopsy

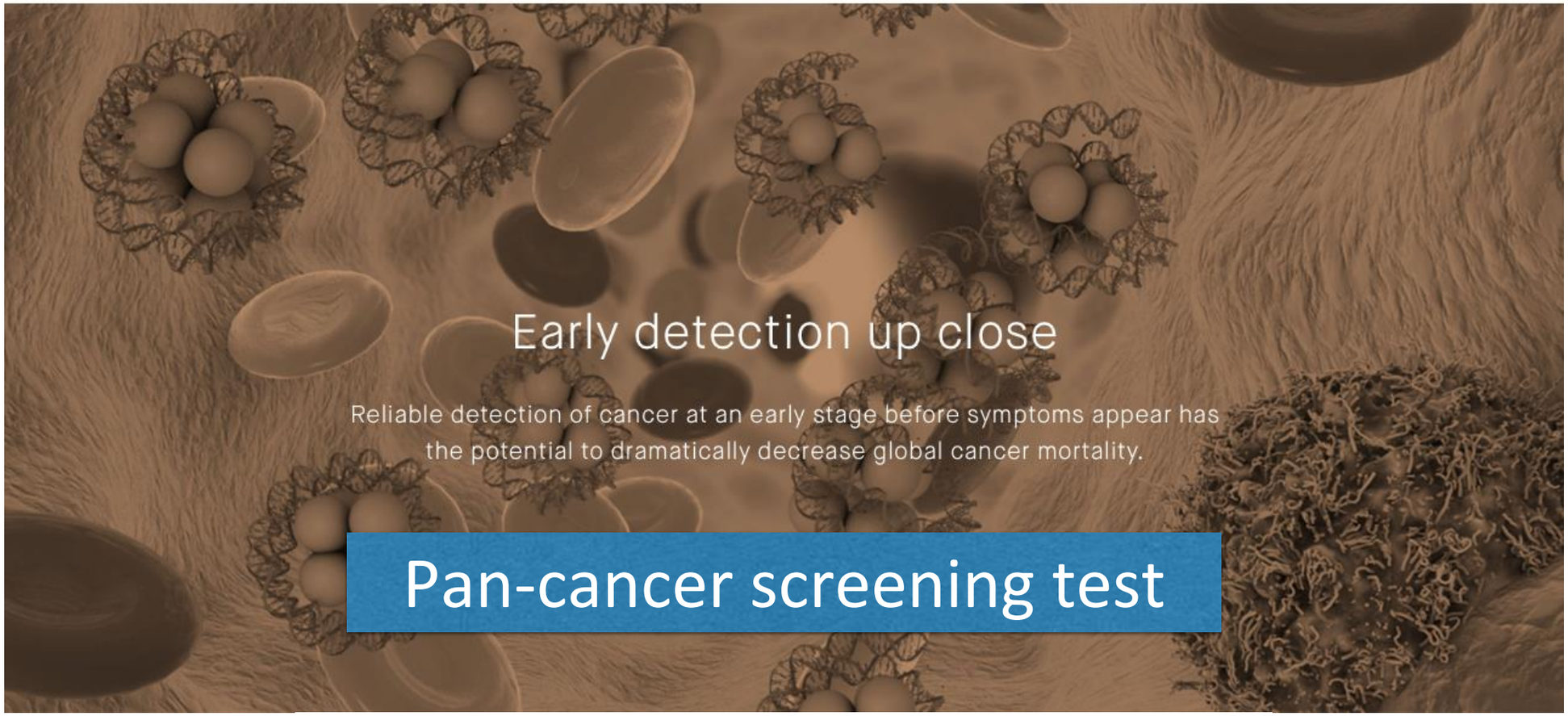


- Detection of circulating fragment of tumour DNA
- Sequence the DNA searching for cancer specific mutations or chromosomal alterations



GRAIL

Science Careers About Join the Team



Pan-cancer screening test

illumina BILL GATES SUTTER HILL VENTURES

ARCH Venture Partners BEZOS EXPEDITIONS

GV

”…aim to massively decrease cancer mortality by detecting the disease at a curable stage.”

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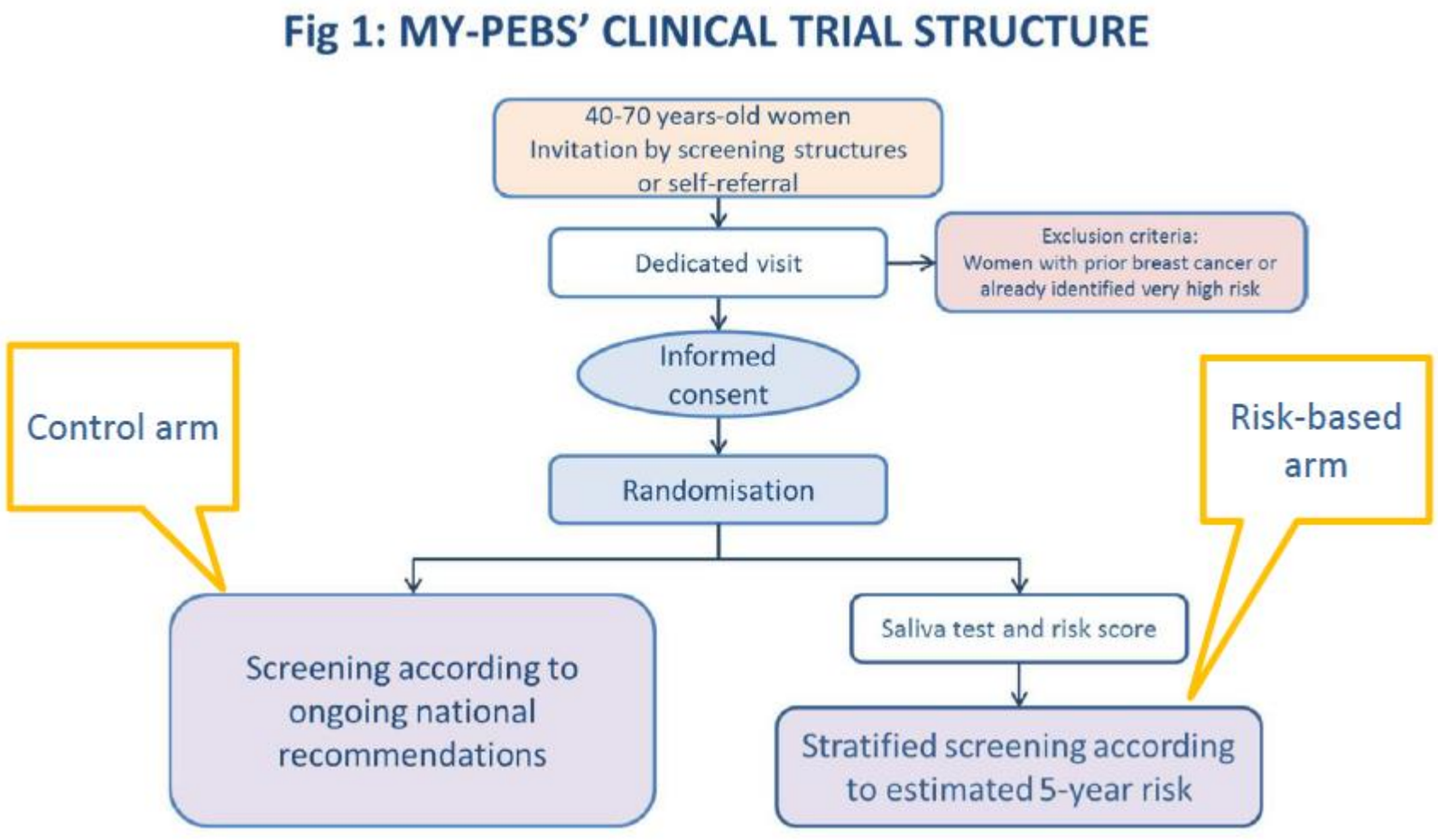
Personalized breast cancer screening

- Stratification based on personalized breast cancer risk and breast density
- MyPEBS: a 7-year long European H2020 project starting 2018



Machine learning

Large scale deep learning for computer aided detection o
mammographic lesions

Thijs Kooi [a,*], Geert Litjens [a], Bram van Ginneken [a], Albert Gubern-Mérida
Clara I. Sánchez [a], Ritse Mann [a], Ard den Heeten [b], Nico Karssemeijer [a]

[a] Diagnostic Image Analysis Group, Department of Radiology, Radboud University Medical Center, Nijmegen, The Netherlands
[b] Department of Radiology, University Medical Centre Amsterdam, Amsterdam, The Netherlands

”…..a deep learning model in the form of a Convolutional Neural Network (CNN) trained on a large data set of mammographic lesions outperforms a state-of-the-art system in Computer Aided Detection (CAD).”

”….human readers and CNN have similar performance.”

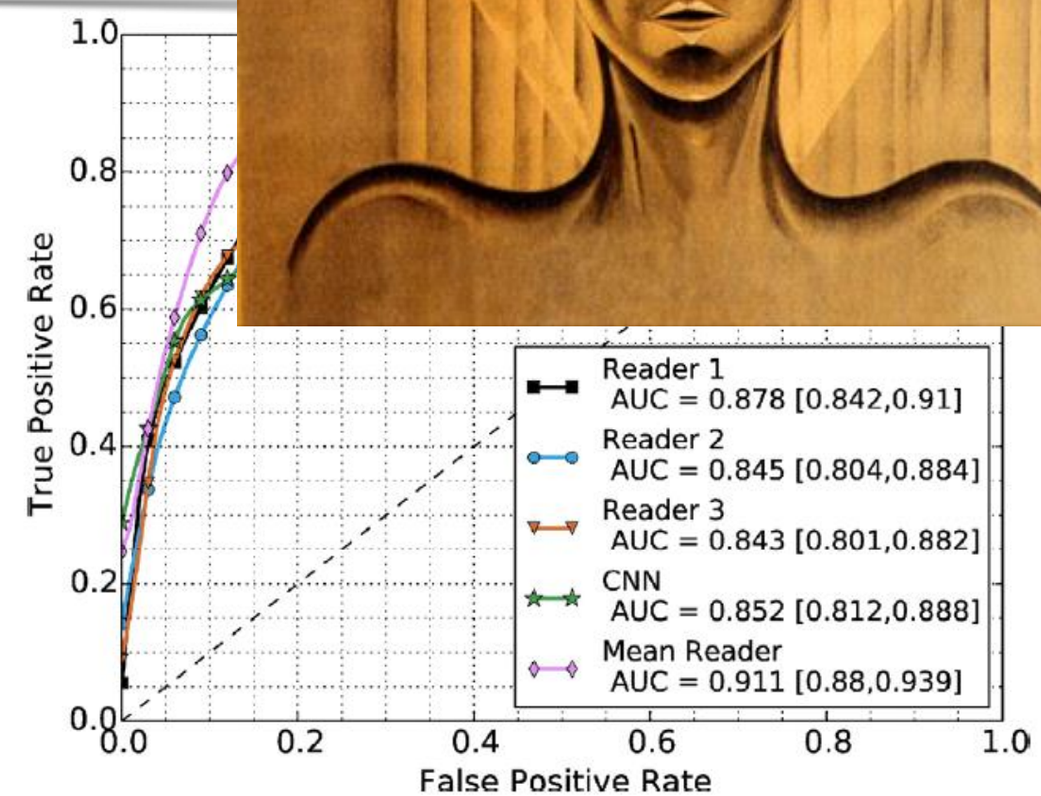


Fig. 12. Comparison between the CNN and three experienced readers on a patch level.

T. Kooi et al. Medical Image Analysis 2017

Summary

- Breast cancer screening programmes are implemented in most countries in Europe
- Screening interval: age 50–69, mammography with 2 year interval
- RCTs: Reduction in breast cancer mortality by 20%
- Overdiagnosis rate 11%
- False positives is a drawback in screening
- The screening policy will most likely be modified in the future with new techniques and individualized screening

Thank you for your attention

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