Early diagnosis of lung cancer

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Conflict of Interest Statement

- I declare that I have no financial or other conflicts of interest and that I have no relationships with any commercial interests.

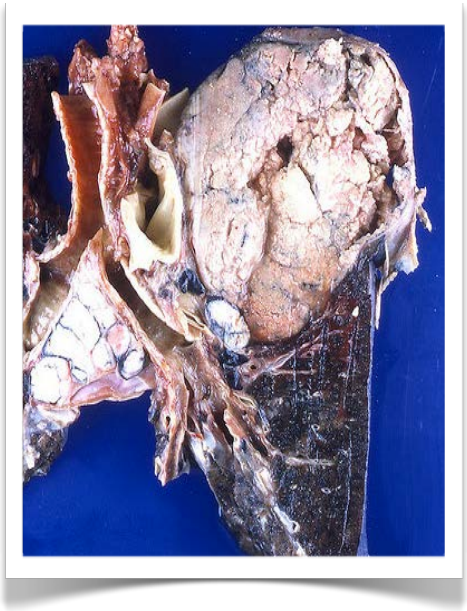
ClinicalTrials.gov Identifier:
NCT01925625

Michael Doherty

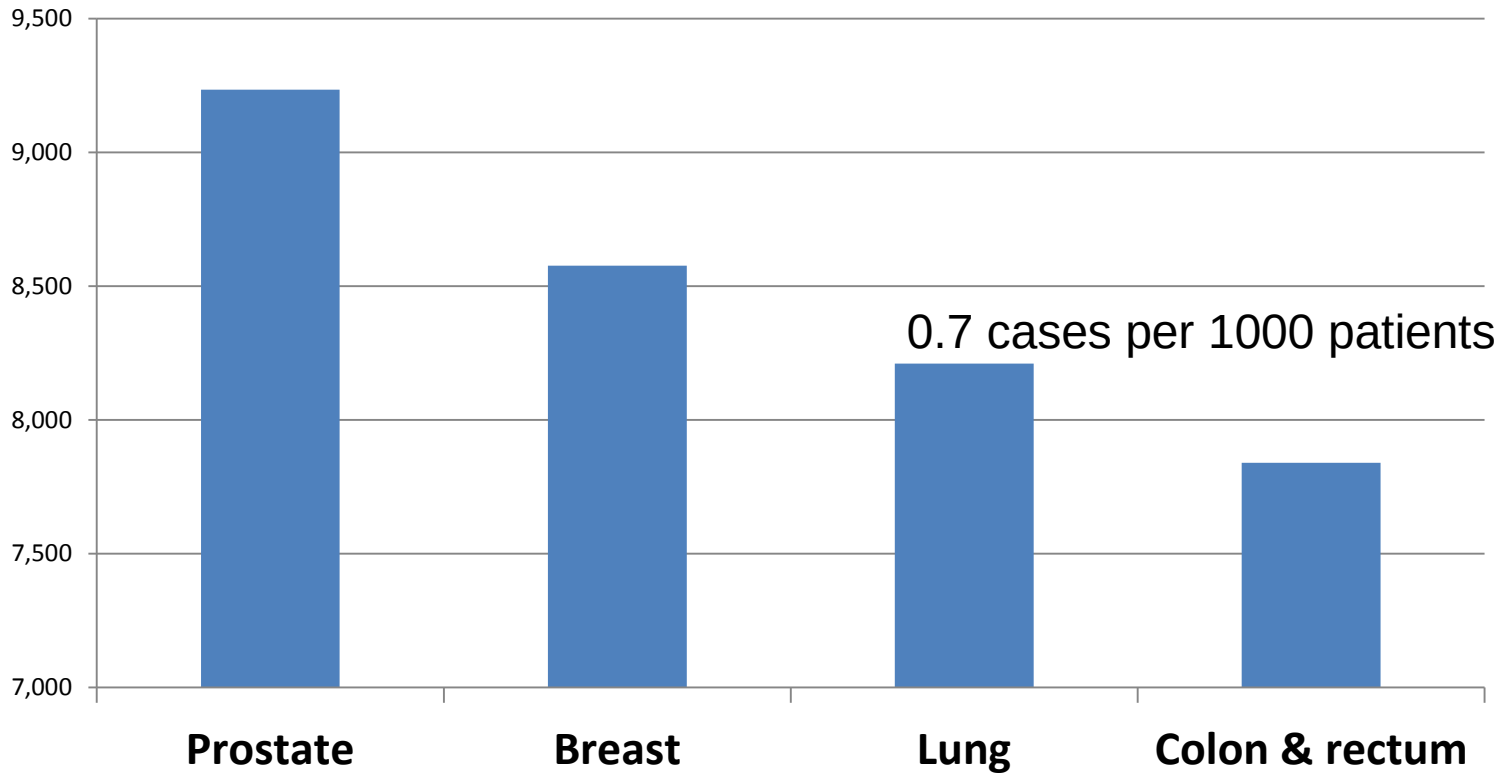
- October: A 56 year old factory worker consults his family physician with a smoker's cough that has been a bit worse than normal over the past week. He is otherwise well and there are no abnormal physical findings. His symptoms respond to a one week course of Amoxicillin.
- January: Normally the life and soul of the party he had been more subdued over the holidays. His wife persuades him to go back to his physician who arranges a CXR. After an initially suspicious result further tests confirm a stage III small cell lung cancer.
- May: Stops work and starts palliative care.
- October: Dies leaving his widow with 5 children still at school

The next 50 minutes

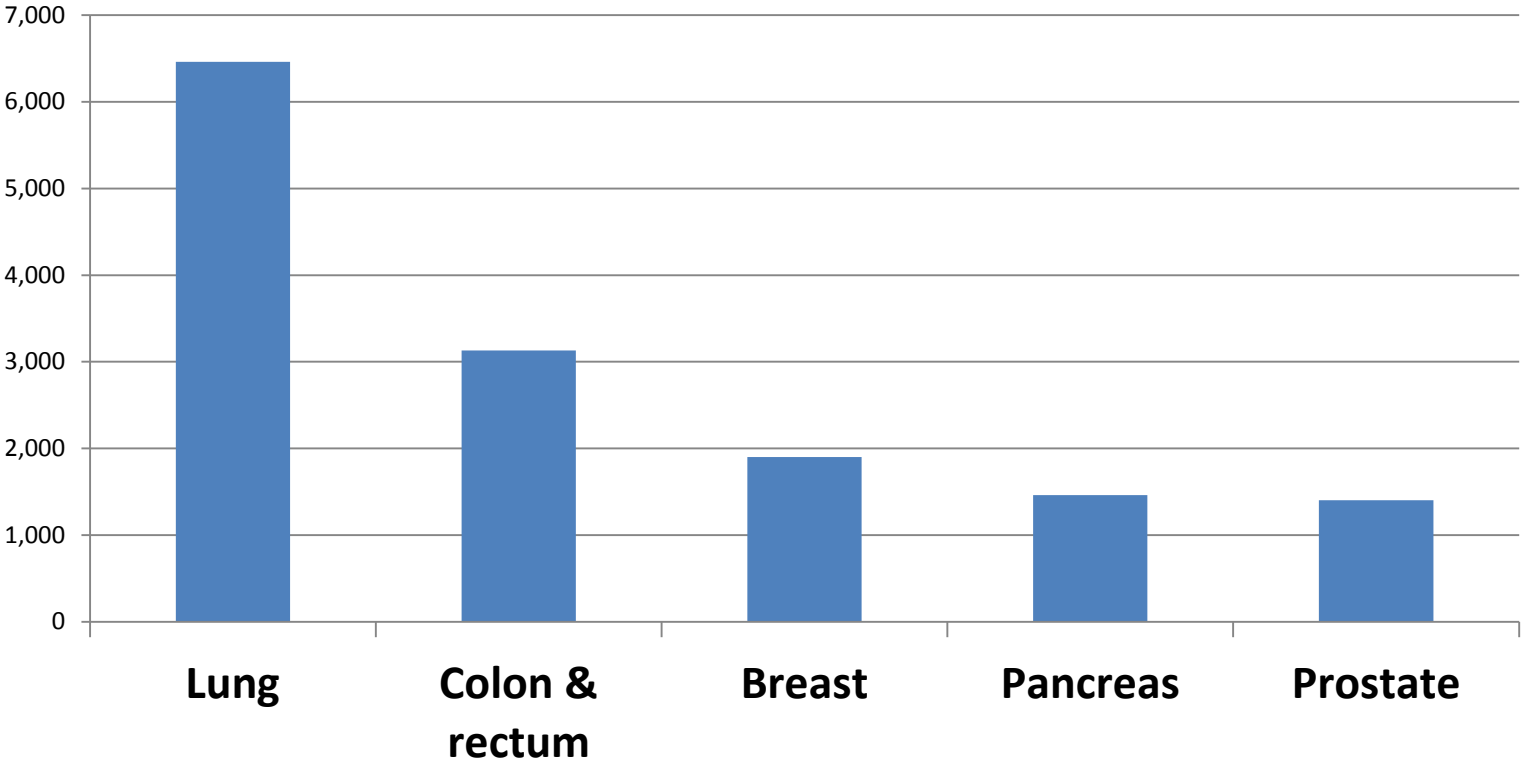
- Problem of Late Diagnosis
- Options for Earlier Diagnosis
  - More Effective Treatment
- A Large Trial in Scotland
  - Practice Based Research Networks
- Further work in Canada



New cases of Cancer in Ontario 2009



Deaths from cancers in Ontario 2009

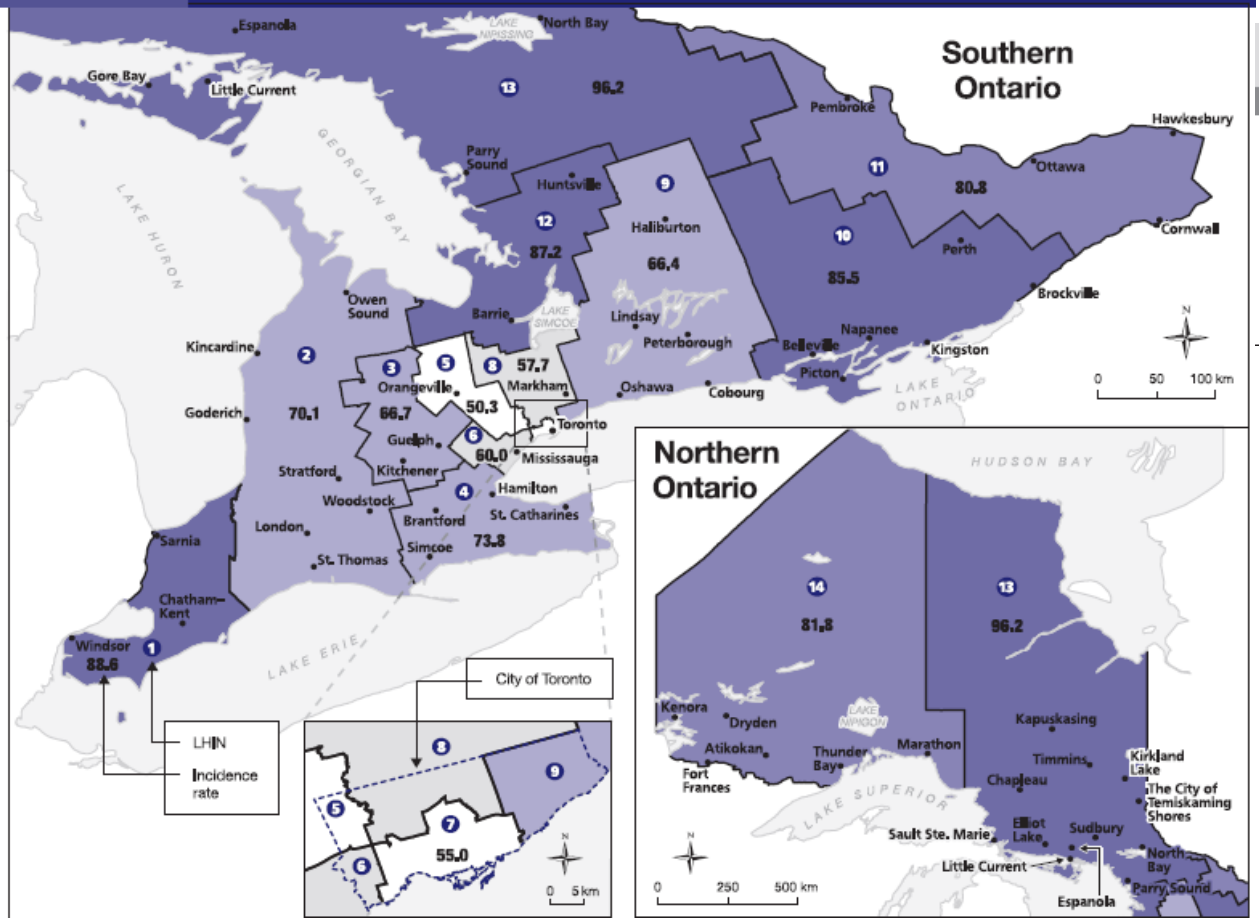


Poor prognosis: ~16% five-year survival, mostly due to late detection.
Prognosis improves if cancer is found at an early stage:

- 80-90% 5-year survival (Stage 1)
- Median survival of 6 months (Stage 4)

Geographical Variation in incidence

Exhibit 5.2 Age- and sex-standardized lung cancer incidence per 100,000 persons 20 years of age or older, by Local Health Integration Network (LHIN) of patient residence, in Ontario, 2003/04

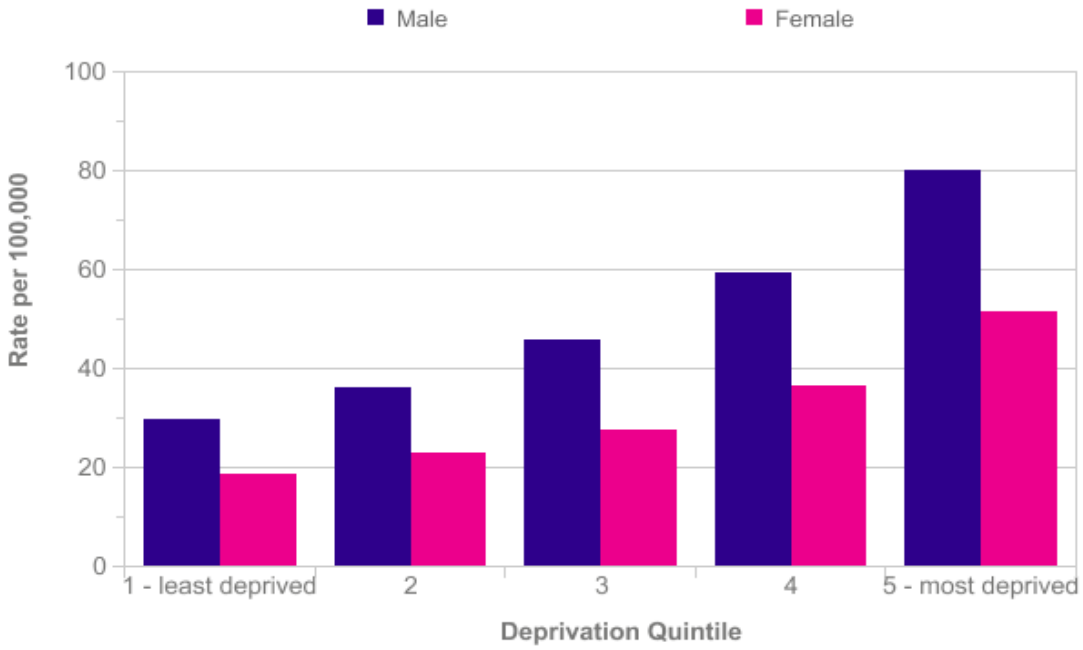


Age- and sex-standardized lung cancer incidence rate per 100,000 persons in the Overall Lung Cancer Cohort, by LHIN of patient residence, in Ontario, 2003/04

Ontario rate (OR) = 70.5 per 100,000 persons

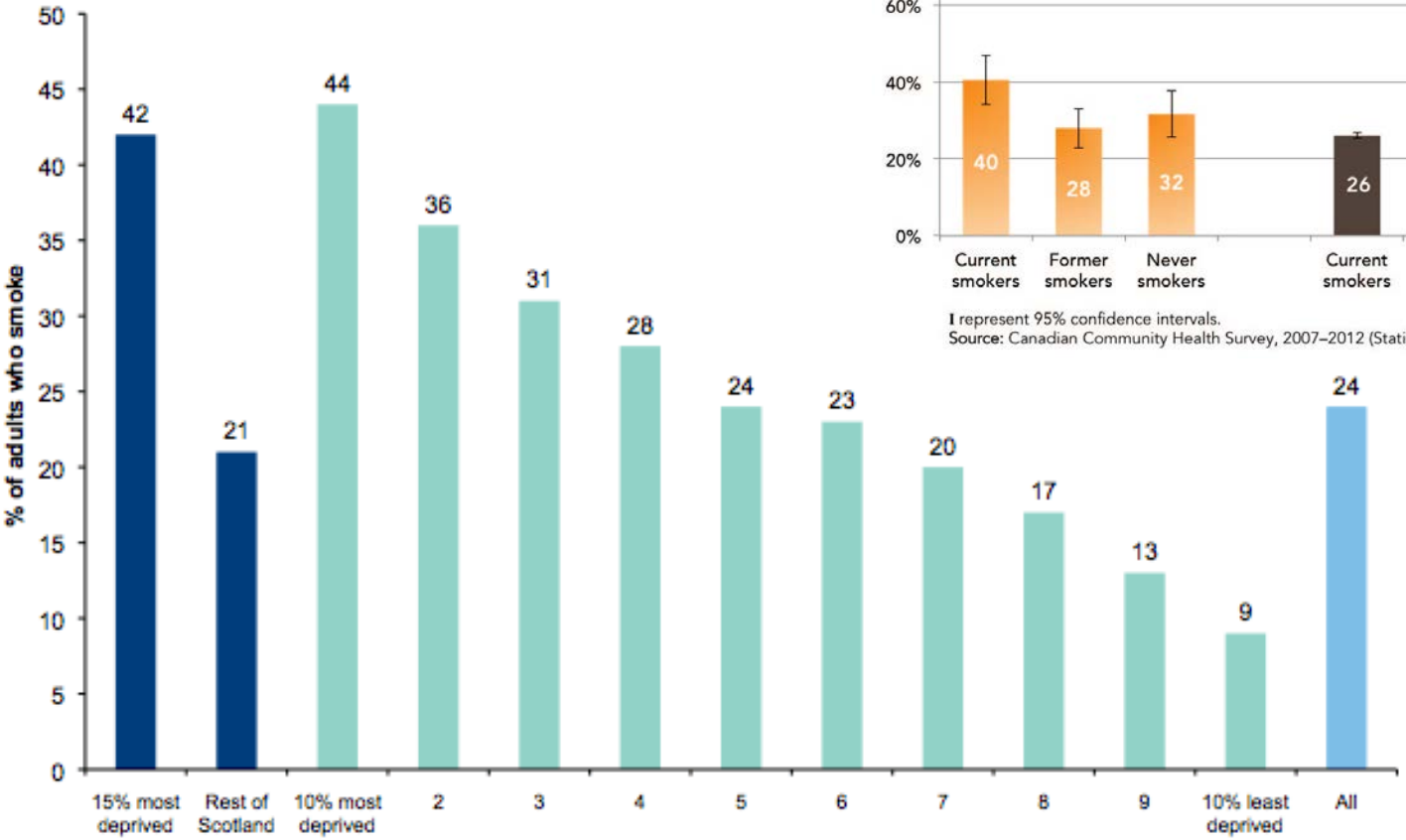
LHIN rate per 100,000 persons	LHIN rate compared to OR	Number of LHINs in each category
> 84.6	More than 20% above OR	4
77.2–84.6	10% to 20% above OR	2
63.9–77.1	Within 10% of OR	4
56.4–63.8	10% to 20% below OR	2
< 56.4	More than 20% below OR	2

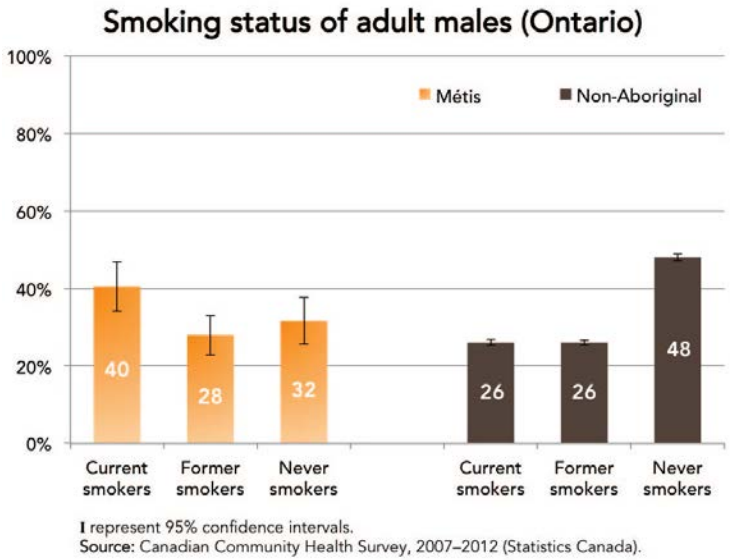
European Age-Standardised Mortality Rates by Deprivation Quintile, England



Cancer Research UK and National Cancer Intelligence Network. Cancer by deprivation in England: Incidence, 1996-2010, Mortality, 1997-2011. London: NCIN; 2014.

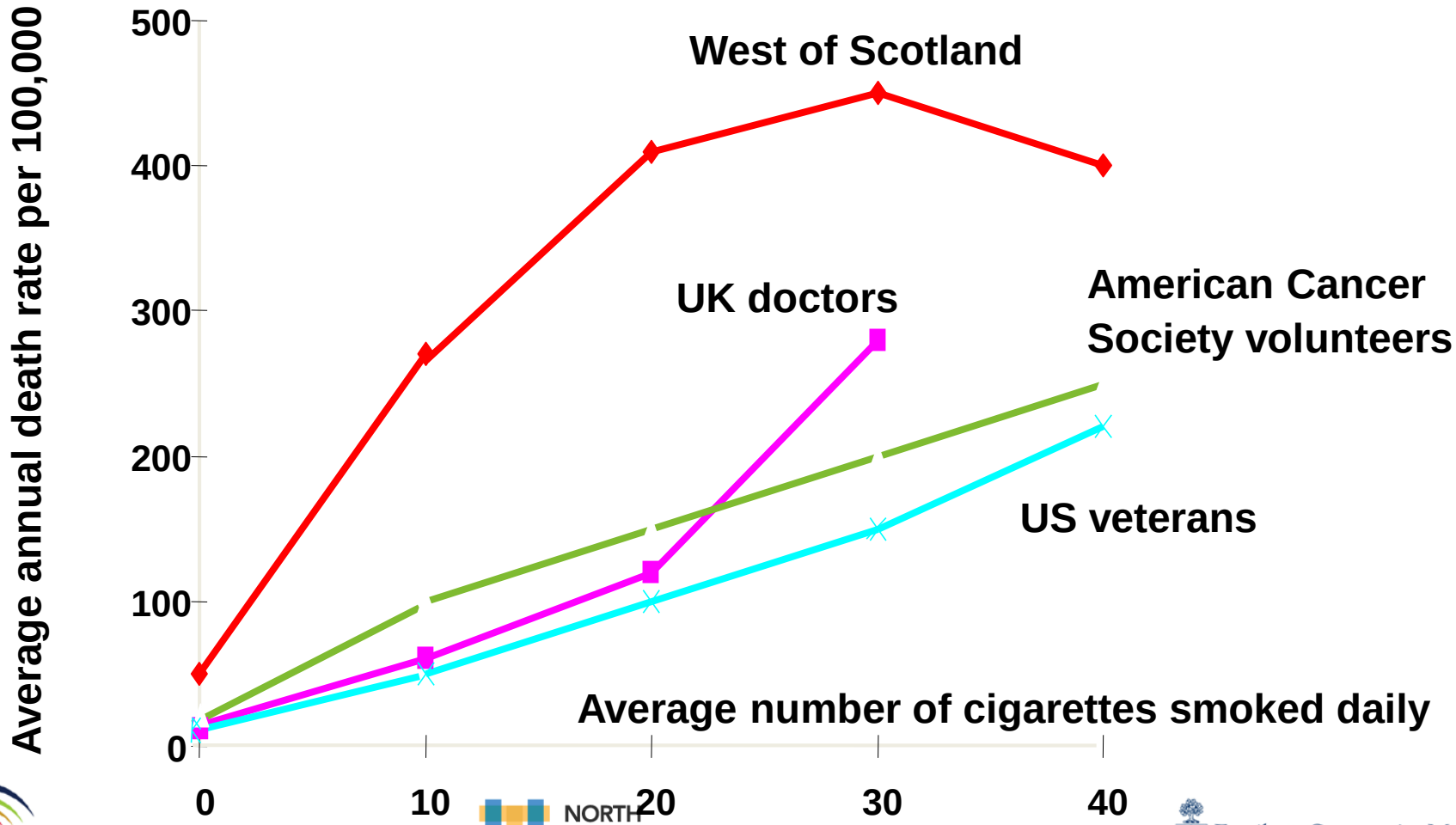
Percentage of respondents who smoke by Scottish Index of Multiple Deprivation 2009/2010 data,





cotland's People Annual report: Results from 2009/2010 Scottish Household Survey

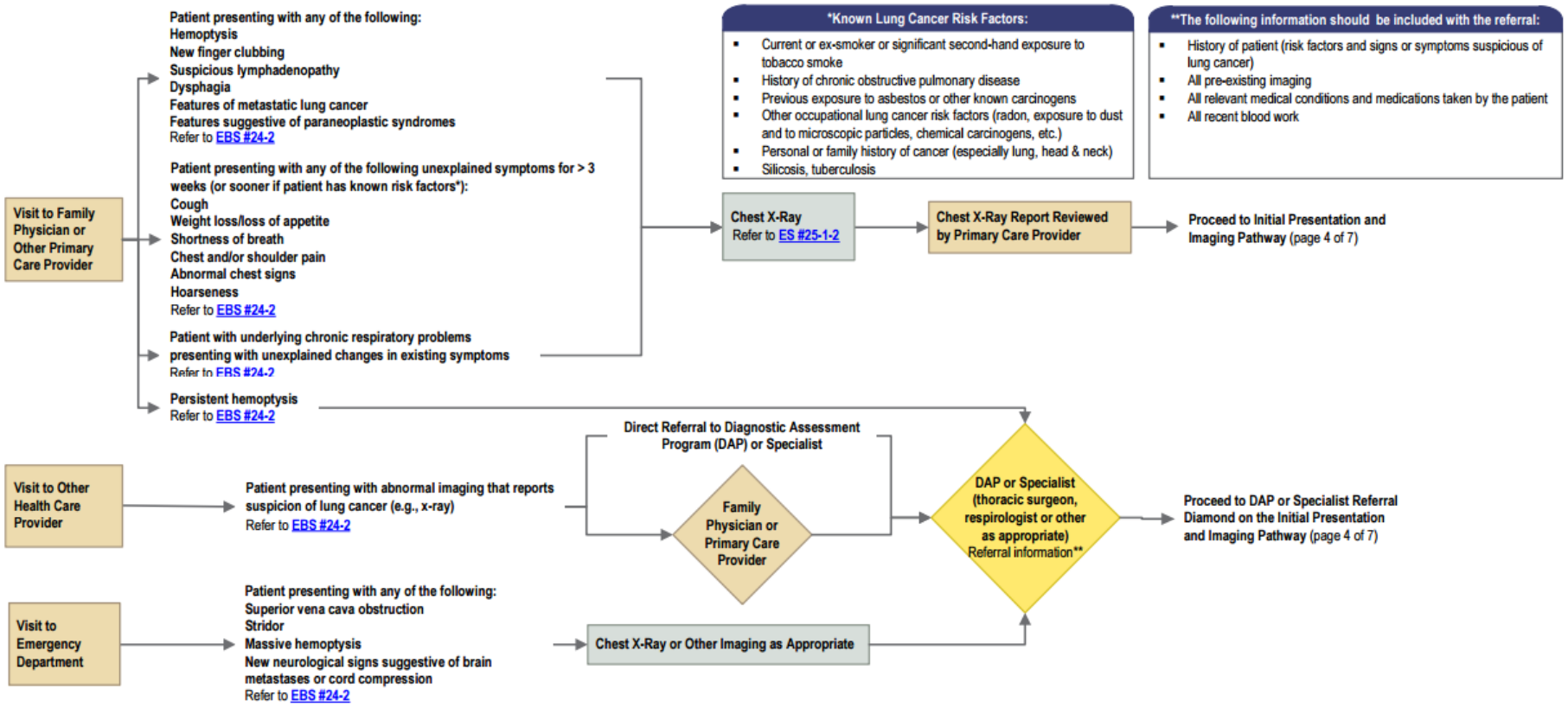
Not just smoking – diet and environment.



Cancer Care Ontario
Action Cancer Ontario

Lung Cancer Diagnosis Pathway

Disease Pathway Management Secretariat
Version 2012.02



Diagnosis is exceptionally difficult when the background risk is low.

Clinical features of limited value: 80% present at a late stage,

Positive predictive values (PPVs) for lung cancer for individual risk markers and for pairs of risk markers in combination (background risk of 1.8 per 1000)

Cough	Fatigue	Dyspnoea	Chest pain	Loss of weight	Loss of appetite	Thrombo-cytosis	Abnormal spirometry	Haemoptysis	
0.40 0.3, 0.5	**0.43** 0.3, 0.6	**0.66** 0.5, 0.8	**0.82** 0.6, 1.1	**1.1** 0.8, 1.6	**0.87** 0.6, 1.3	**1.6** 0.8, 3.1	**1.6** 0.9, 2.9	**2.4** 1.4, 4.1	PPV as a single symptom
0.58 0.4, 0.8	**0.63** 0.5, 0.9	**0.79** 0.6, 1.0	**0.76** 0.6, 1.0	**1.8** 1.1, 2.9	**1.6** 0.9, 2.7	**2.0** 1.1, 3.5	**1.2** 0.6, 2.6	**2.0** 1.1, 3.5	Cough
	0.57 0.4, 0.9	**0.89** 0.6, 0.3	**0.84** 0.5, 1.3	**1.0** 0.6, 1.7	**1.2** 0.7, 2.1	**1.8**	**4.0**	**3.3**	Fatigue
		0.88	**1.2** 0.9, 1.8	**2.0** 1.2, 3.8	**2.0** 1.2, 3.8	**2.0**	**2.3**	**4.9**	Dyspnoea
			0.95 0.7, 1.4	**1.8** 1.0, 3.4	**1.8** 0.9, 3.9	**2.0**	**1.4**	**5.0**	Chest pain
				1.2 0.7, 2.3	**2.3** 1.2, 4.4	**6.1**	**1.5**	**9.2**	Loss of weight
					1.7	**0.9**	**2.7**	**>10**	Loss of appetite
							3.6	**>10**	Thrombocytosis
								>10	Abnomal spirometry

Howie JG (1972) Diagnosis : the Achilles heel? J R Coll Gen Pract 1972:310–315
Hamilton W et al. Thorax 2005;60:1059-1065

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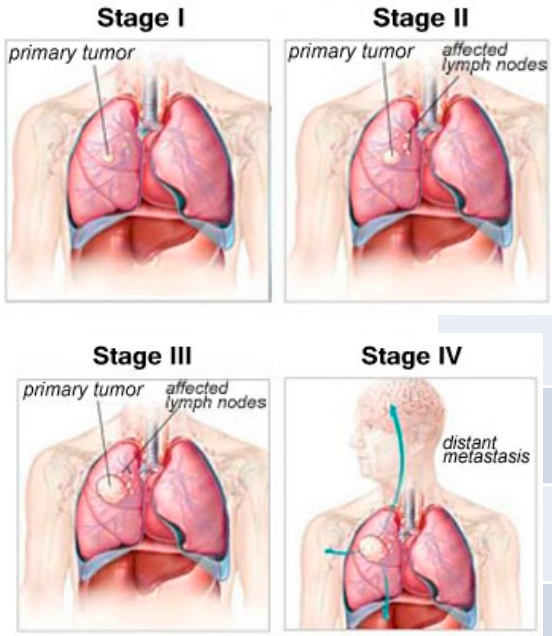
% 5 year survival by TNM staging (UK)

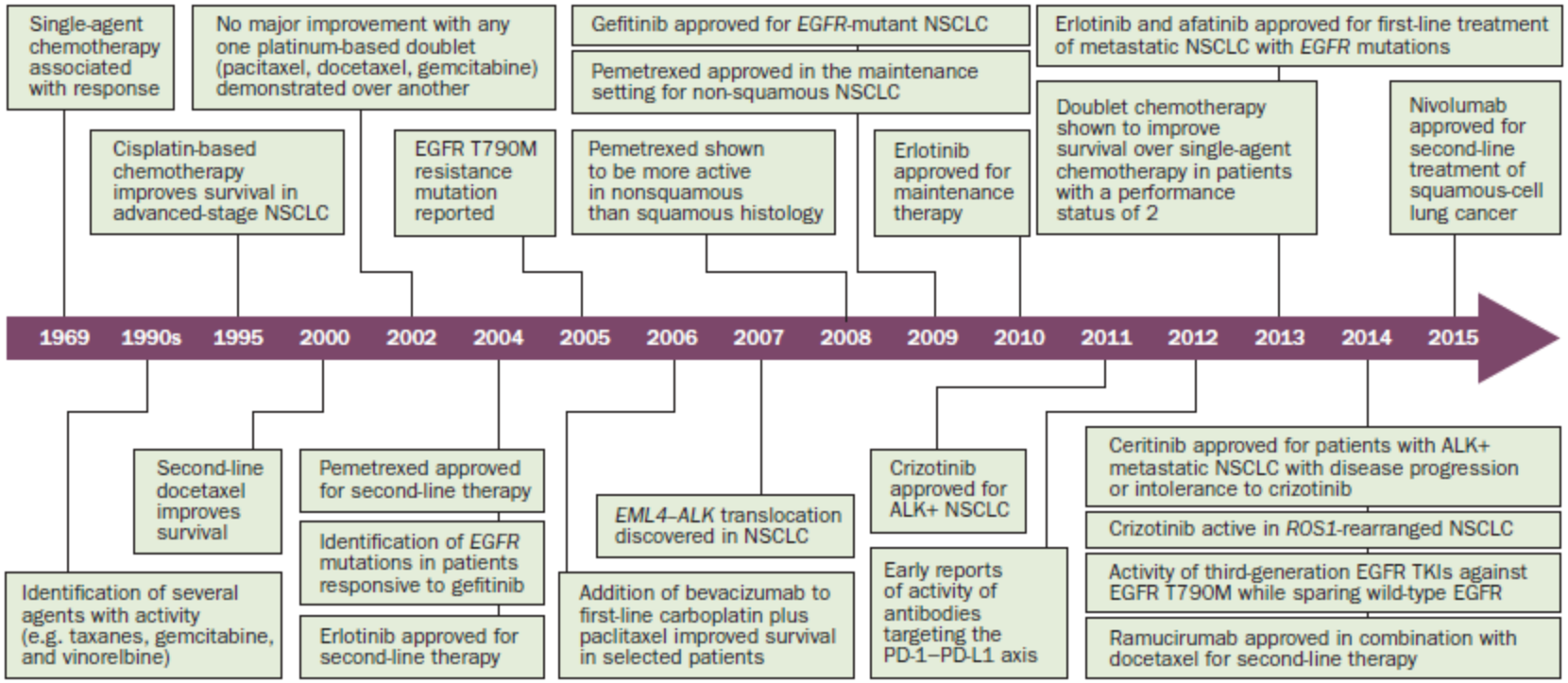
80%



Staging	Non small cell	Small cell
1A	58-73	38
1B	43-58	21
2A	36-46	38
2B	25-36	18
3A	19-24	13
3B	7-9	9
4	2-13	1

20%

Will lung cancer become a chronic disease if detected early?



Anish Thomas, Stephen V. Liu, Deepa S. Subramanlam and Giuseppe Giaccone Nature Oncology Reviews 2015

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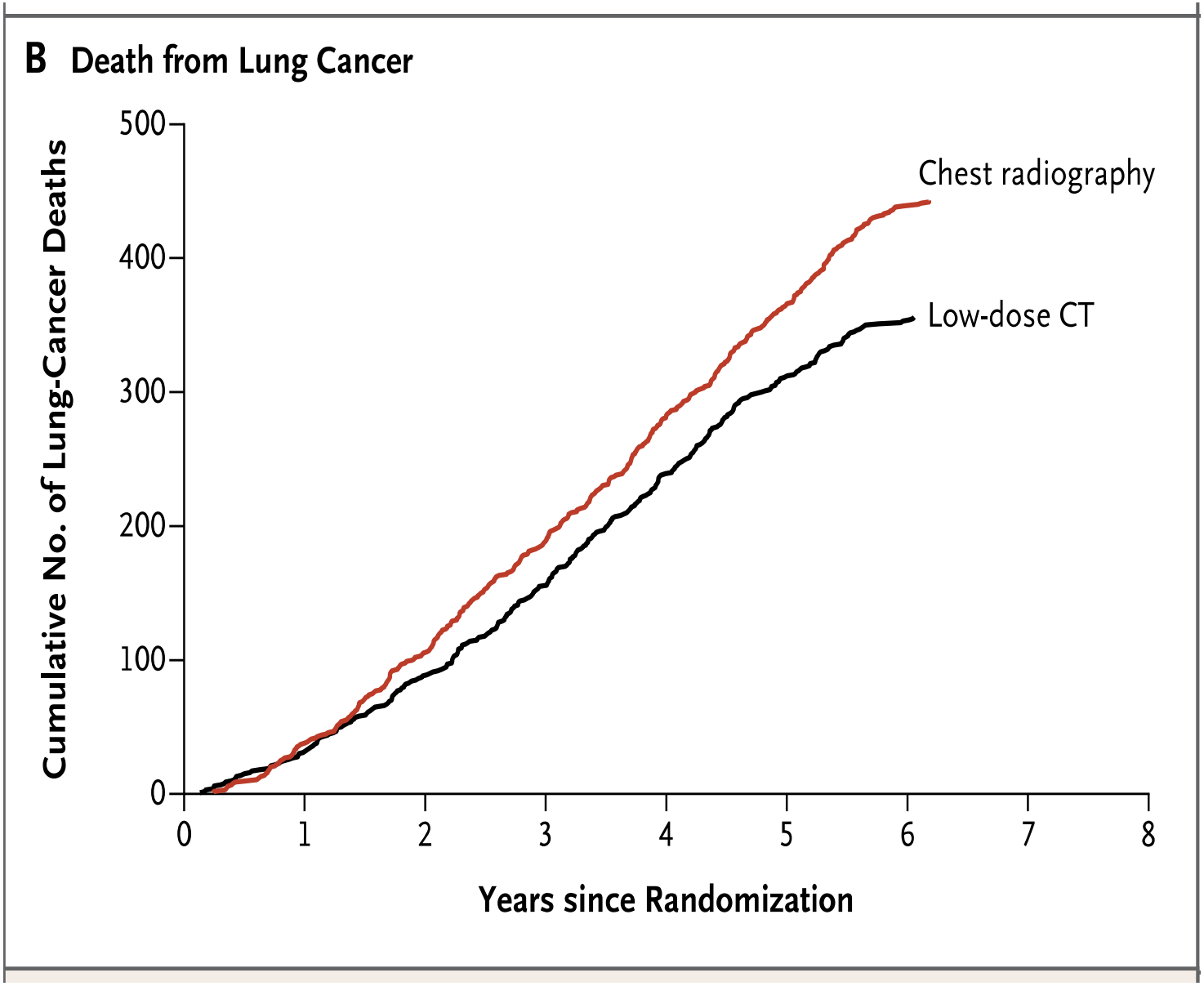



The NEW ENGLAND JOURNAL of MEDICINE

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

53,454 persons at high risk for lung cancer

3 Annual CT Scans

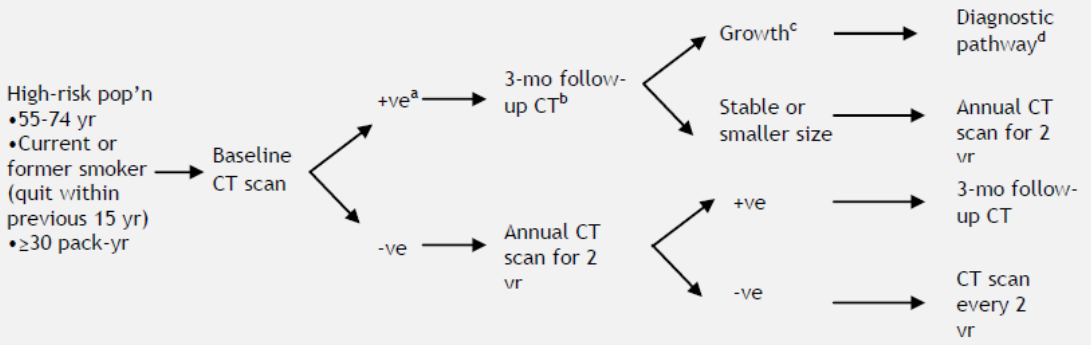
20% Reduction In Mortality

Cumulative number of lung cancer deaths recorded by the NLST

Canadian Task Force on Preventive Health Care 2016 Lung Cancer Screening Recommendations

We recommend screening for lung cancer among adults aged 55 to 74 years with at least a 30 pack-year smoking history, who smoke or quit smoking less than 15 years ago, with low-dose computed tomography (CT) every year up to three consecutive years. Screening should only be done in health care settings with access to expertise in early diagnosis and treatment of lung cancer. (Weak recommendation, low-quality evidence.)

Recommendation 3: Persons at high risk for lung cancer should commence screening with an initial LDCT scan followed by annual screens for 2 consecutive years, and then once every 2 years after each negative (-ve) scan.



[a]A positive (+ve) test is defined as a solid nodule ≥5 mm or a non-solid nodule (part solid or ground glass) ≥8 mm.
[b]If the nodule appearance dictates a different approach (e.g., bronchoscopy or PET), this can be chosen at the discretion of the reading physician.
[c]Doubling time of between 30 and 400 days.
[d]Lung Cancer Diagnosis Pathway (7).

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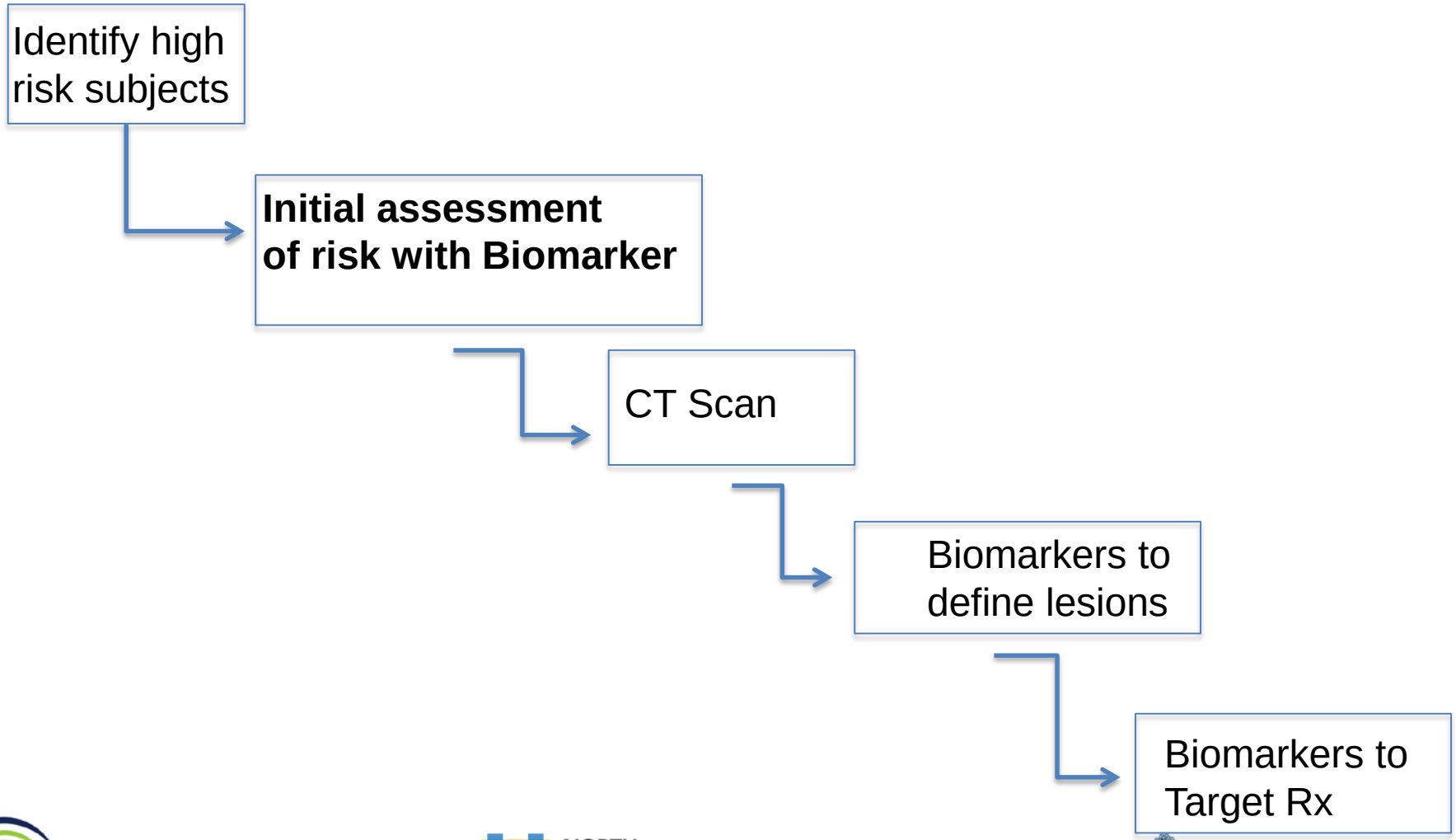
dicine
ONTO

Cancer detection and harms - NLST (averaged over 3 annual lung screens)

- 11.2% of screens were followed by one or more extra scan (additional radiation 7-10mSv compared to 0.5mSv with CXR).
- 0.9% of screens led to diagnosis of lung cancer (10-15% of which would not have appeared during remaining life).
- 0.5% of screens led to biopsy or bronchoscopy that did NOT find cancer.
- 0.3% of screens led to surgery that did not reveal lung cancer.

Potential Roles of Biomarkers in Lung cancer



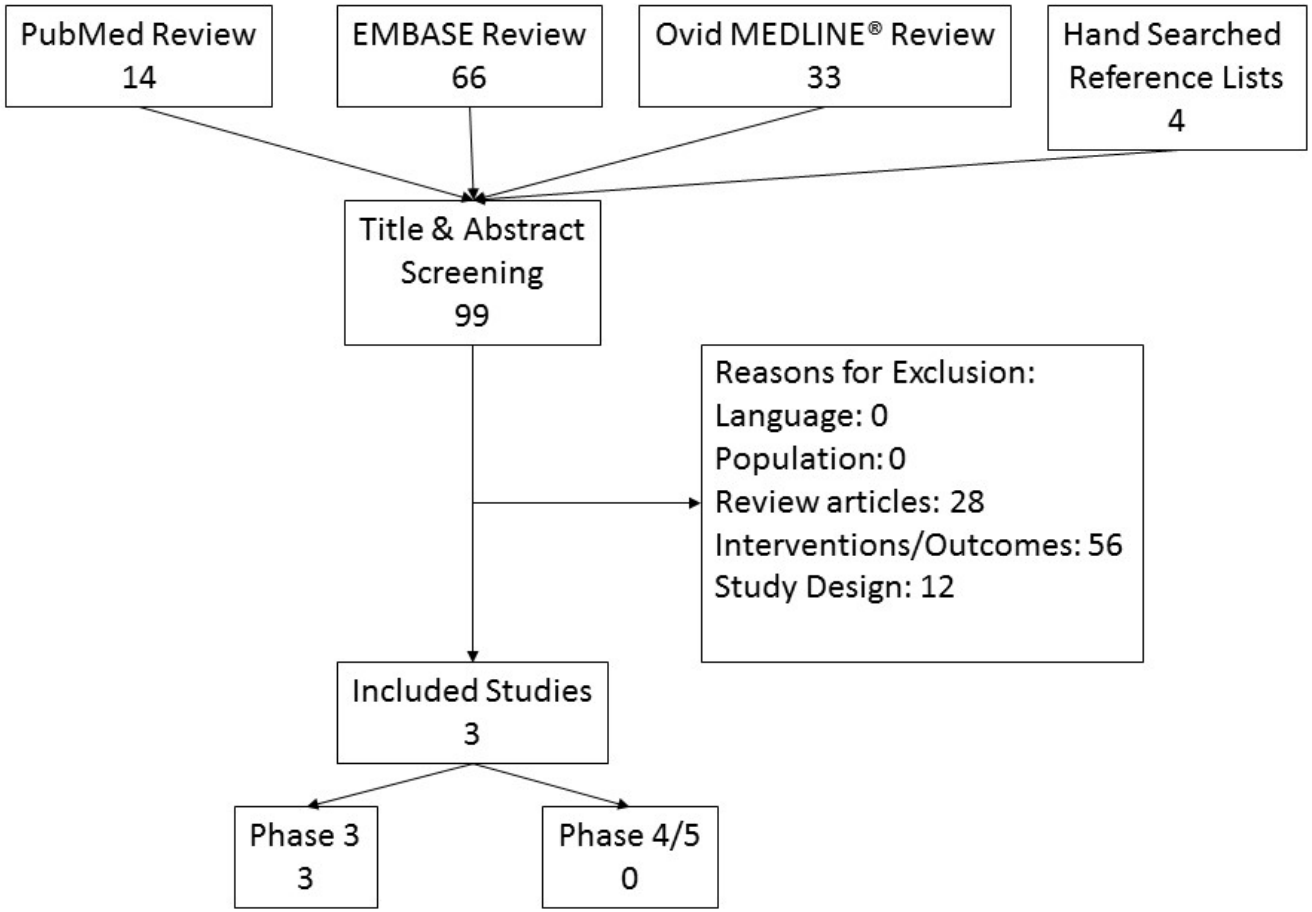
A Review of Blood-Based Biomarkers – Gavin Chu FY2

- 3 biomarker signatures in Phase 4 testing:
  - **EarlyCDT-lung** (antibody based assay)
  - **miR-test** (serum-based 34 miRNA signature),
  - **MSC** (plasma-based miRNA) test

- **Key questions:**

1. Diagnostic performance of **biomarker test individually**?
2. Diagnostic performance of each **biomarker test used in conjunction with LDCT**?
3. Any data in improving **lung-cancer mortality** and **all-cause mortality**?

Literature Review



Results: Diagnostic Performance Individually

Test	EarlyCDT-lung	MSC	miR-test
Sensitivity	41% (95% CI: 29-53%)	87% (95%CI: N/A)	78% (95%CI: N/A)
Specificity	87% (95% CI: 86-89%)	81% (95% CI: 79-84%)	75% (95% CI: 72-78%)
PPV	11% (95% CI: 7-15%)	27% (95% CI: 21-32%)	10% (95% CI: 7-14%)
NPV	97% (95% CI: 97-98%)	98% (95% CI: N/A)	98% (95% CI: N/A)
Positive LR	3.19	4.67	3.09
Negative LR	0.68	0.16	0.30

Rationale for the detection of Autoantibodies

Aberrant molecule → Auto-Antigen

Auto-Antigen → Auto-Immune response

Auto-Immune response → Circulating Auto-antibodies

Small [Auto-antigen] → **Large [Auto-antibody]**

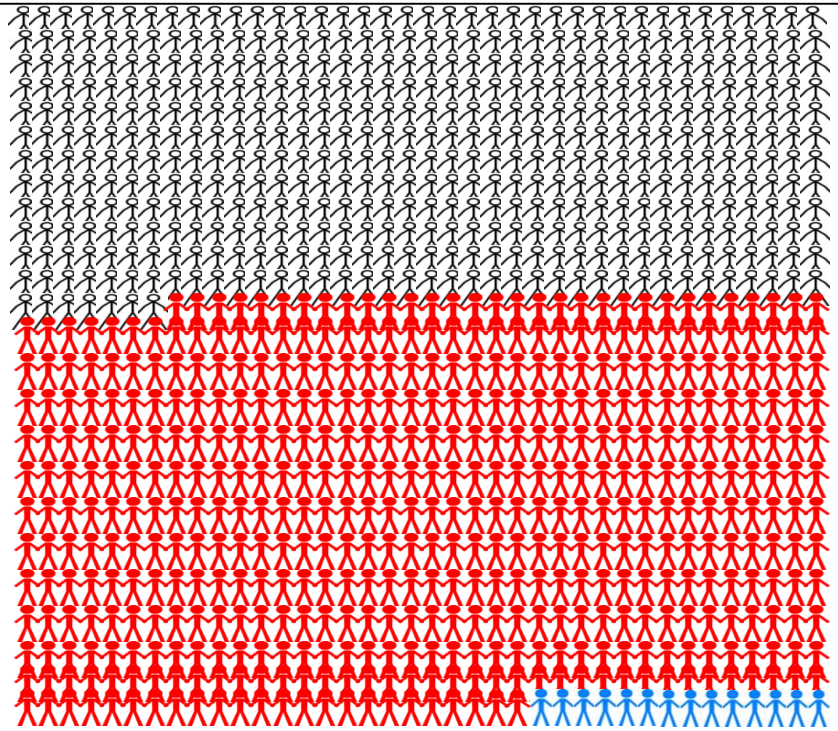
Small tumour bulk → **Measurable signal**

EarlyCDT-Lung concentrates 41% of the lung cancers in 8% of a high risk population

Assuming a 2% prevalence of lung cancer in a high risk population of 1000 patients...

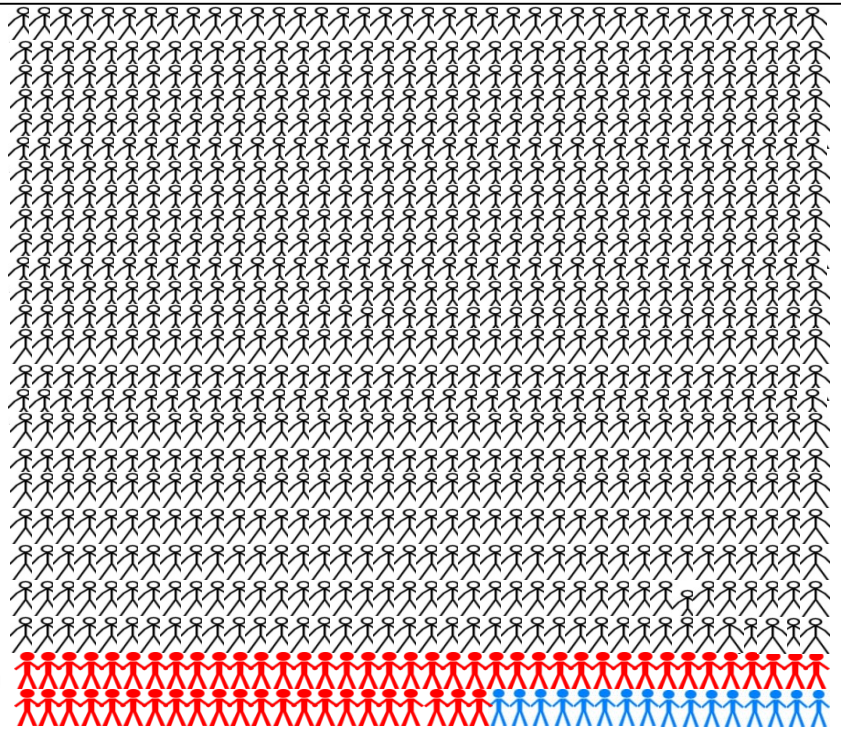
CT

490 patients will undergo unnecessary follow-up;
14 lung cancer identified



EarlyCDT-

69 patients will undergo unnecessary follow-up;
8 identified immediately, 8 more over next 2 years



Negative Result

False Positive

Detected Lung Cancer

CT

-False Positives
-Radiation Exposure
-Increased number of anxious patients

EarlyCDT-Lung

-5X better PPV and 7X fewer False Positives
-Non-invasive & less radiation risk

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*Performance of CT has been reported as 50% specificity and 70% sensitivity (Swensen et al 2002, 2005 & van Klausen et al 2009)
*EarlyCDT-Lung has been shown to reported to have a 87% specificity & 41% sensitivity

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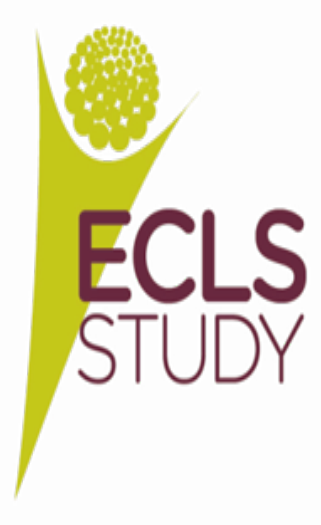
Phases of biomarker development

Preclinical Exploratory	***PHASE 1***	*Promising directions identified*
Clinical Assay and Validation	***PHASE 2***	*Clinical assay detects established disease*
Retrospective Longitudinal	***PHASE 3***	*Biomarker detects disease early before it becomes clinical and a "screen positive" rule is defined*
Prospective Screening	***PHASE 4***	*Extent and characteristics of disease detected by the test and the false referral rate are identified*
Cancer Control	***PHASE 5***	*Impact of screening on reducing the burden of disease on the population is quantified*

Margaret Sullivan Pepe et al. JNCI J Natl Cancer Inst 2001;93:1054-1061

Research Question

Is the EarlyCDT™Lung test effective in reducing the incidence of patients with late-stage lung cancer at diagnosis, compared with standard clinical practice?



$8M

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12 November 2012 Last updated at 01:07

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Lung cancer cases in Scotland predicted to double by 2040

Cases of lung cancer are predicted to more than double in the next 30 years, according to a cancer charity.

There could be about 12,000 people with lung cancer in Scotland in 2040, compared with about 5,500 today, research carried out on behalf of Macmillan Cancer Support has predicted.

Lung cancer is expected to rise 35 times faster among women than men.

More than twice as many women compared to men are expected to have the disease in Scotland in the future.

The research predicted there will be 95,000 women with the illness UK-wide by 2040

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NEWS

Screening trial of blood test for lung cancer is set to start in Scotland

BMJ 2012; 344 doi: 10.1136/bmj.e2312 (Published 26 March 2012)
Cite this as: *BMJ* 2012;344:e2312

Why do we need a trial?

'No Evidence' That Breast Cancer Screening Affects Death Rates Amongst Women

PA | Posted: 11/06/2013 07:11 BST | Updated: 12/06/2013 07:54 BST PRESS ASSOCIATION

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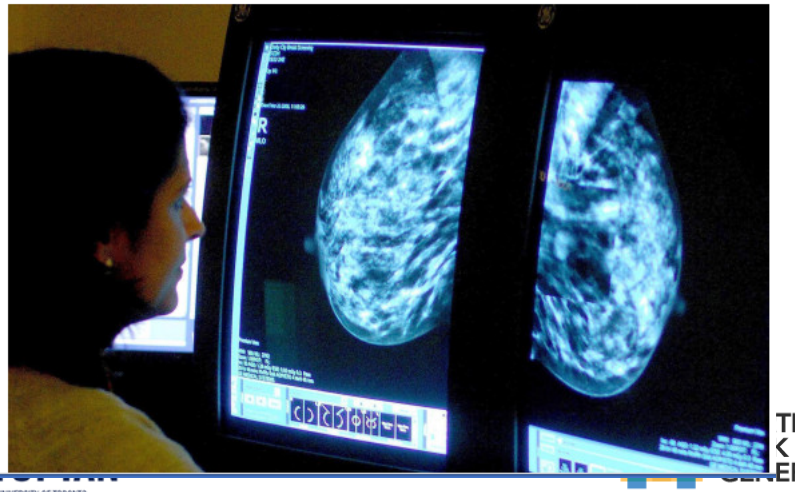
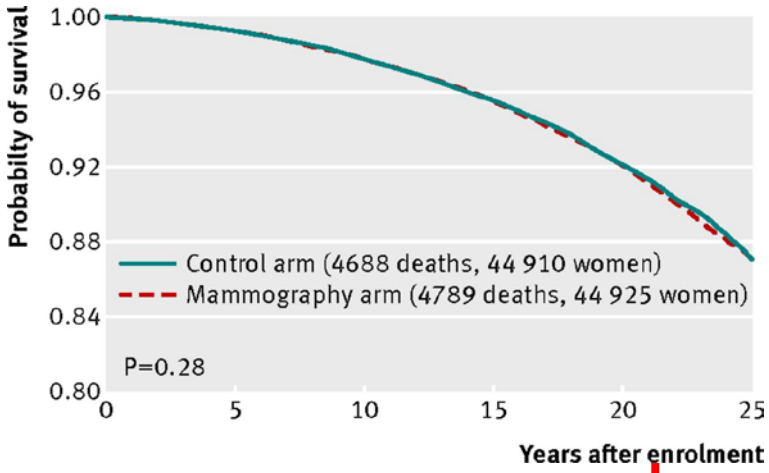
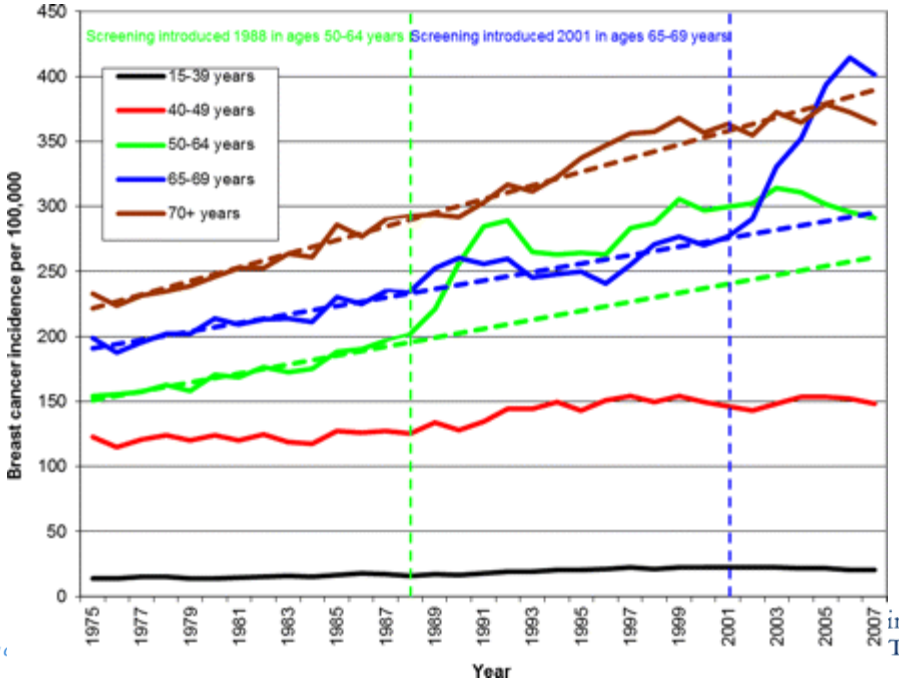
Breast cancer screening programmes have yet to show a reduction in the number of women who die from the disease, researchers said.

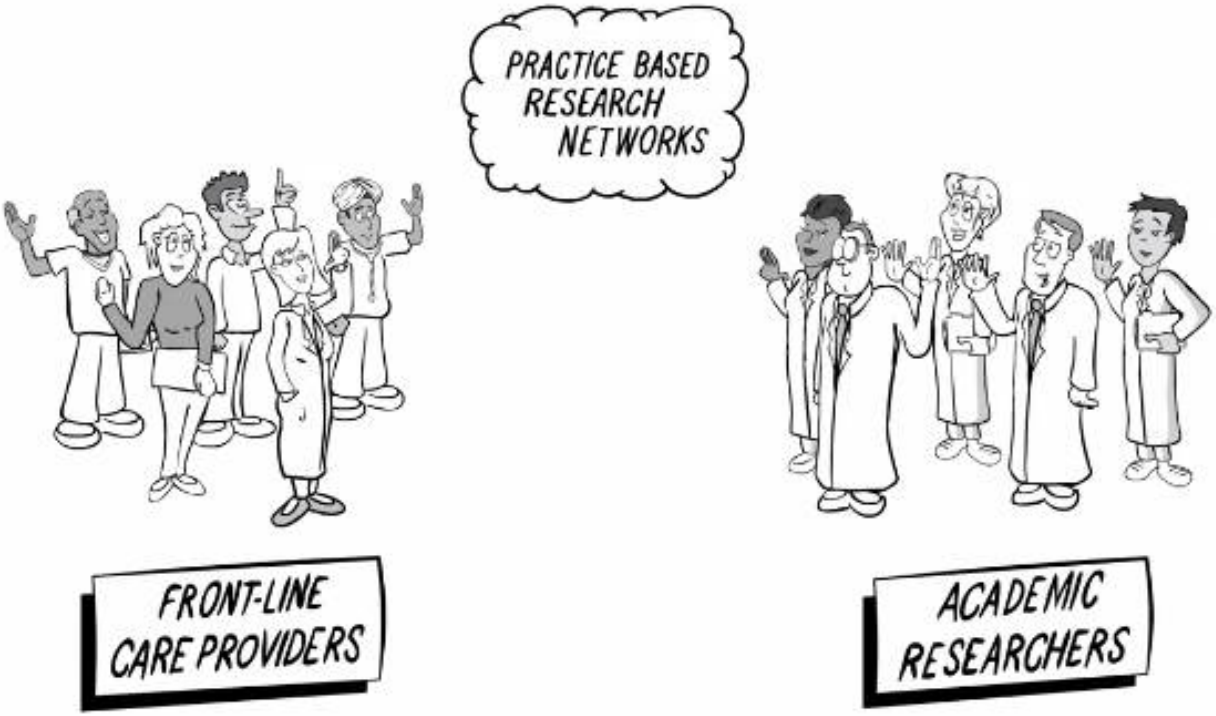
A new study suggests that there is "no evidence" that screening women for breast cancer has an effect on mortality.

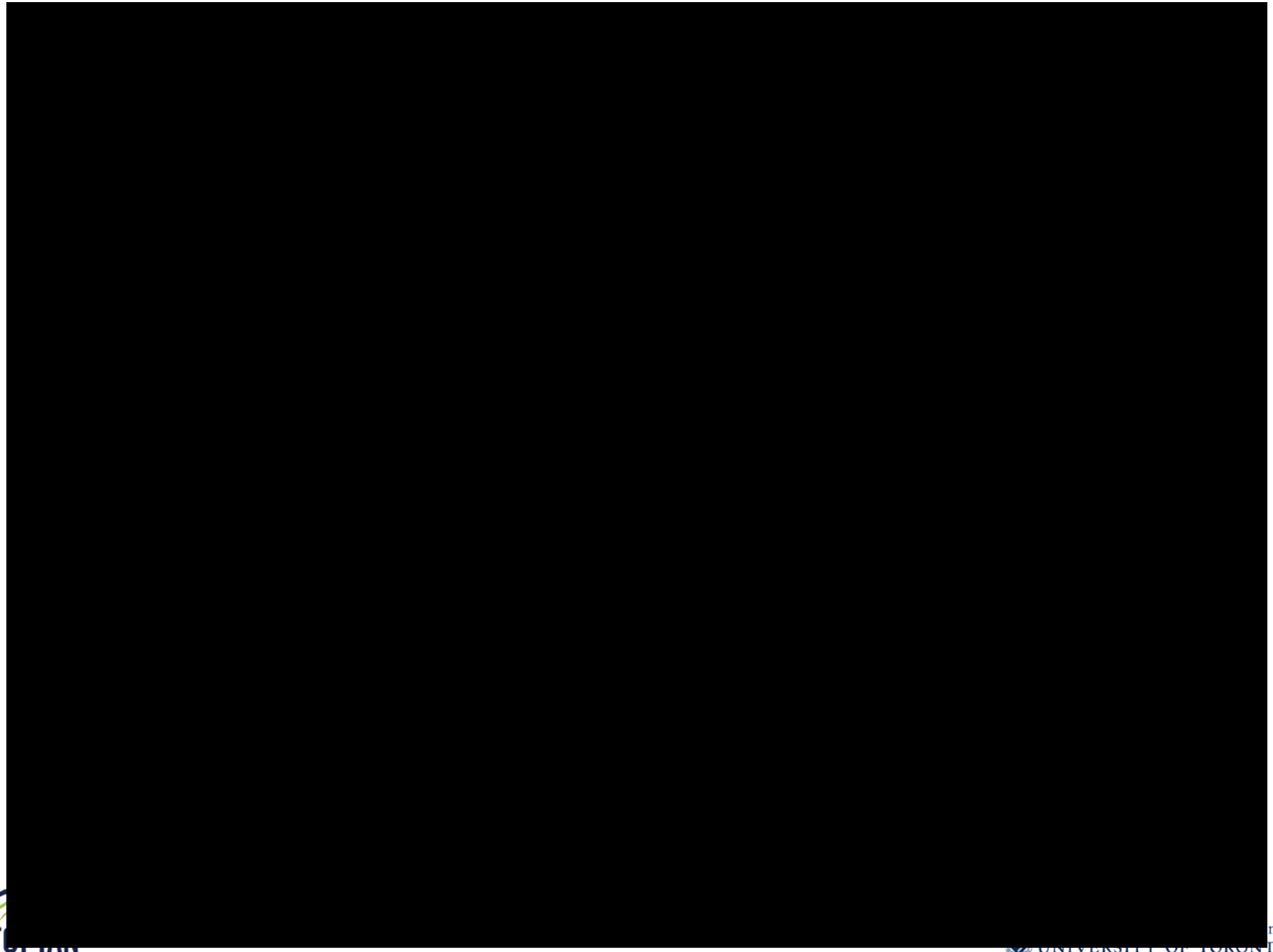






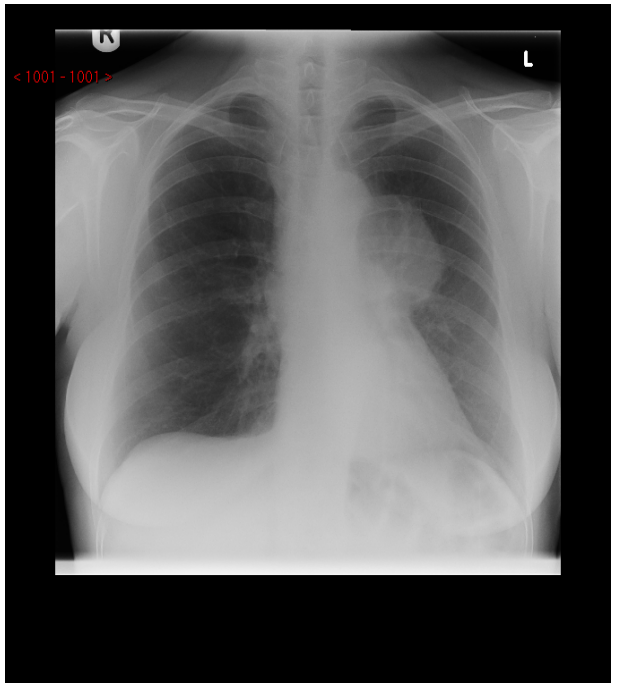
Practice Based Research Networks



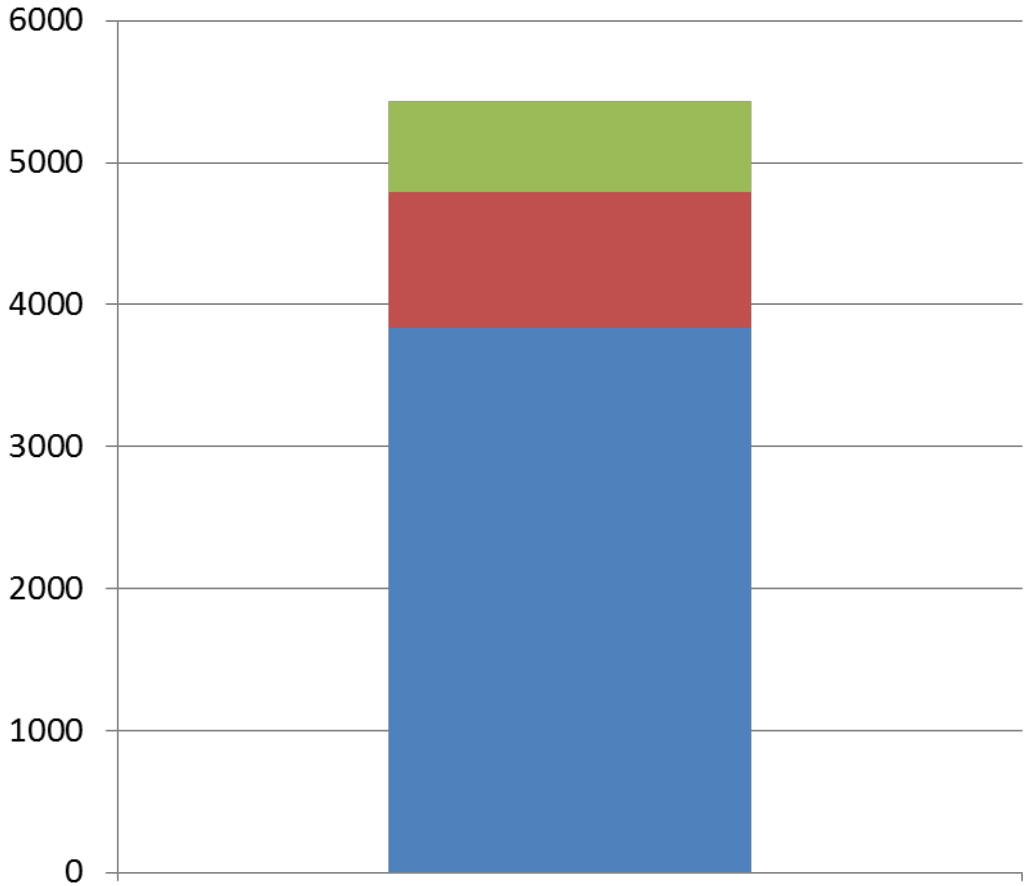


ECLS Study Subjects

- Electronic Medical Records Screened by PBRN
  - practices from most deprived quintile (200)
    - Greater Glasgow & Clyde
    - Tayside
    - Lanarkshire
- High risk(2%) patients aged 50-75
  - Current and recent smokers
    - 20 pack years
  - Family history Lung Ca
  - ECOG 1&2



Identifying patients at practice level n=5 437



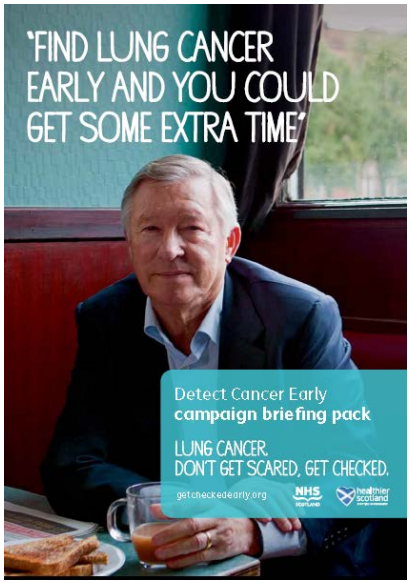
potentially eligible 640

in age group, low risk 960

patients outwith age group 3 837

Additional recruitment Strategies

- Awareness raising
- Practice letters & Calls
- GP computer based reminders
- Public spaces



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% Participants from eligible

If 60 practices need 26% participation

If 80 Practices need 20% participation

Pilot work in 4 deprived areas 34-42% say they would participate

KSO Research Limited

Methods- In Brief

Objective

to assess the effectiveness of EarlyCDTLung test in reducing the incidence of patients with late-stage lung cancer at diagnosis, compared with standard clinical practice.

Intervention

7 Antigen Early-CDT™ lung test

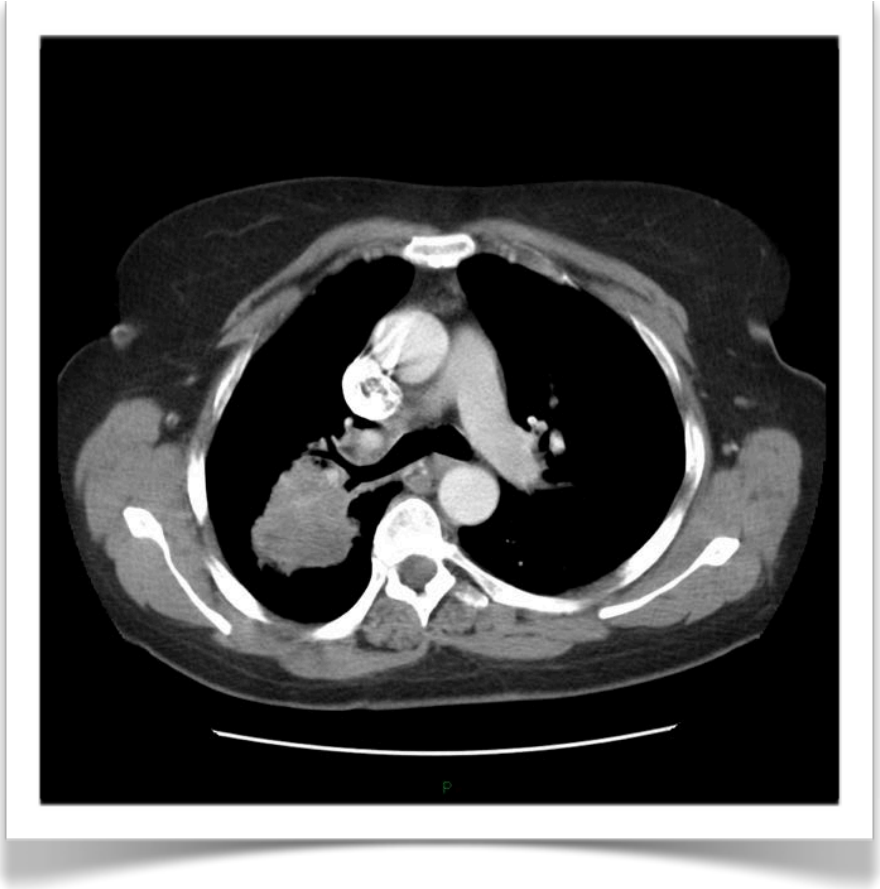
If +ve CT scan, baseline then 6 monthly for 24 months

(If –ve, no active surveillance, outcome data at 24 months)

Primary Outcome

Difference at 24 months after randomisation, between the number of patients with stage 3, 4 or unclassified lung cancer at diagnosis in the intervention arm, and those in the control arm in Scottish Cancer Registry.

ECLS Imaging



- Participants with positive test and a CXR that does not show malignancy will proceed to have 6 monthly CT chests for 24 months

Secondary Outcomes

- Costs
  - Health Service
  - Societal
- Longer follow up using Record Linkage
  - 5 years
  - 10 years
- Harms
  - 2PhDs on psychological & behavioural responses

Power

- With a sample size of 10,000 and
- a baseline annual late stage presentation rate of 1 200/100 000 = 1.2% and
- risk differences of 30%, 35% and 40% provide
- powers 0.71, 0.82 and 0.93 respectively with two-sided alphas of 0.05.

Annual Incidence of late stage cancer lower than anticipated in 1st 2 years

- 680/100 000 instead of 1 200/100 000
- Target increased to 12 000

Subjects vs Patients

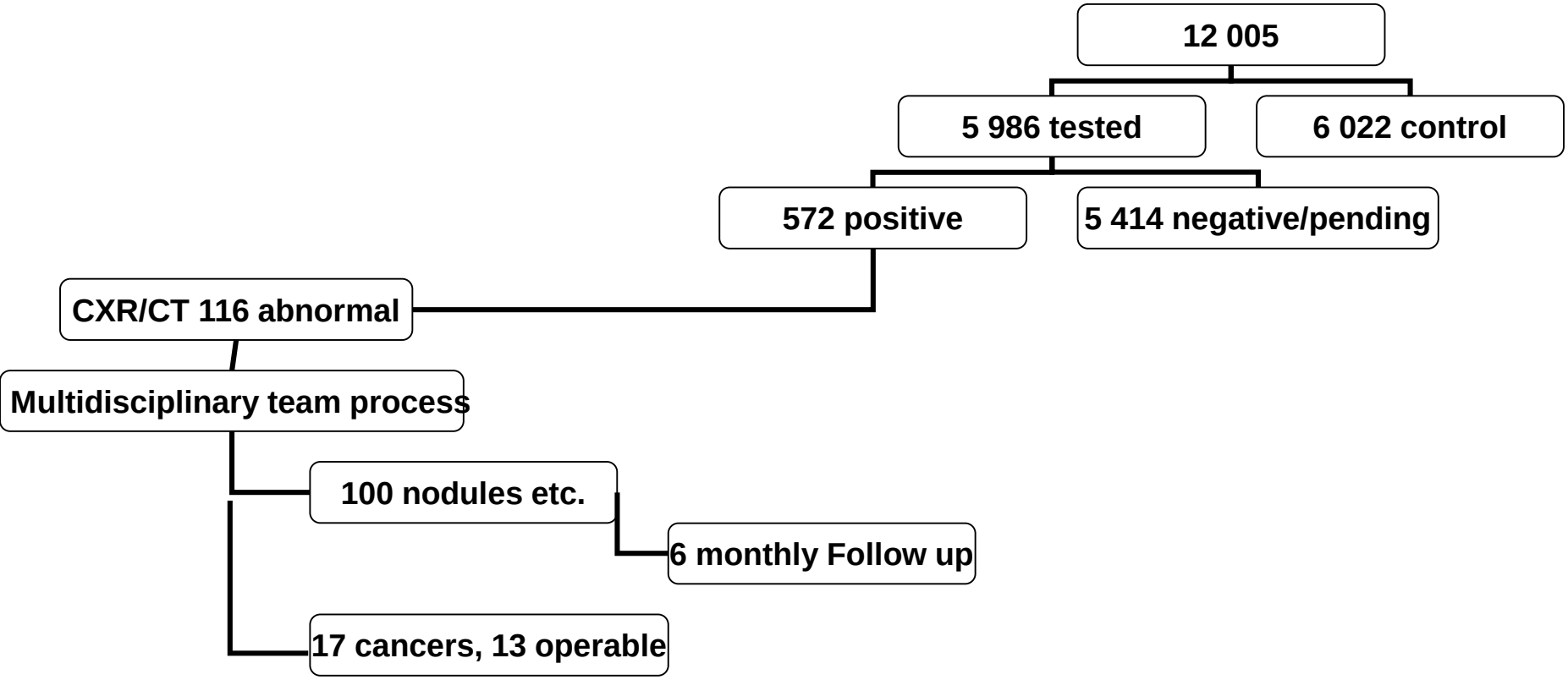
- **Subjects**
- People in the study
- Positive EarlyCDT test
- Normal CT or
- Small pulmonary nodules
- Looked after by the study

- **Patients**
- Positive EarlyCDT test
- Obvious tumour on CXR or CT
- Large pulmonary nodules
- Looked after by NHS

Progress 7.8.13- 31.5.16

- 12 005 Randomised(1:1)
- 572/5986 (9.6%) tests positive
  - 558 have had a CXR and 1st CT
  - 18 have had 24 month CT
  - 190 had one or more pulmonary nodules
- 263 incidental findings
- 27/251 nodules (1.1%) suspicious so far
- 16 participants in test arm confirmed as cancer so far (one with 2 primary lesions).
- 4/17 (24%) cancers late stage(3, 4 or unclassified)

Partial Consort Diagram



Provisional conclusions from early data

- GP Electronic Medical Record data able to identify >77K potential study subjects
- 16% Very hard to reach study subjects recruited
- Lower than expected annual incidence of late stage cancer - 680/100 000 not 1 200/100 000
  - Healthy Volunteer Effect
- Higher than expected Risk Difference 24% late stage not 80%
- Final results expected late 2018/early 2019

Estimate of test performance based on incomplete data

- Specificity - 90.7%
- Sensitivity - 81.3%
- PPV 2.8
- NPV 99.9
- Likelihood ratio of a positive test 8.8
- Likelihood ratio of a negative test 0.2

- Current estimates likely to **overestimate** sensitivity and LR+ve

Michael Doherty

- October: A 56 year old factory worker consults his family physician with a smoker's cough that has been a bit worse than normal over the past week. He is otherwise well and there are no abnormal physical findings. His symptoms respond to a one week course of Amoxicillin.
- October: His biomarker result returns with a positive test
- November: His CT scan shows a suspicious nodule.
- January: He has a partial lobectomy for a stage 2a small cell cancer
- April: Returns to work a non-smoker.
- July: Goes on holiday with his family.

Evening Telegraph

Tuesday, September 23, 2014

Uni study discovers Shirley's cancer

By Ane Hine

A woman discovered she had a tumour lurking in her lung — while taking part in an experimental research project at Dundee University.

When Shirley Dolan, 58, volunteered to take part in the Early Lung Cancer Detection Study, she had no idea the blood she submitted held a deadly secret.

If the tumour had been left undetected much longer, it would have radically reduced her chances of survival.

She said: "I never even had a cough. Without the test, we would never have known, and with lung cancer, by the time people feel symptoms, it is usually too late."

Shirley, from St Mary's, had been invited to participate in the cancer research programme by her GP because she belonged to a demographic — smokers and ex-smokers aged 50-75 — who are deemed high risk for the disease.

The study, which is being conducted in collaboration with researchers in Glasgow, Nottingham, NHS Scotland and the Tayside Clinical Trials Unit.

They hope to recruit a total of 10,000 participants from Tayside and Greater Glasgow and Clyde by January 2015.

"Lung cancer kills more people than any other cancer, with 5,000 people in Scotland dying from the disease every year," explained Dr Schembri.

"There are often few symptoms until the cancer has been growing for a long time and perhaps spread.

'I hope my story encourages others'

"So, out of every 10 people four have lung cancer, nine are unfortunately inoperable."

The study involves a simple blood test called EarlyCDT-Lung — which

Shirley with Dr Schembri.

Cancer study was lifesaver for Shirley

by **Graham Gibson**

A DUNDEE woman has cheated death after doctors discovered a five centimetre lung tumour — during what started out as no more than an experimental blood test.

Shirley Dolan, 58, felt fit and healthy when she signed up to a Dundee University study trying to detect early lung cancer.

Shirley, Macalpine Road, decided to donate a vial of blood after seeing members of her family die from cancer.

And she was left in fear for her life when her test results revealed the unknown tumour lurking in her lung.

Shirley said: "If it wasn't for the study it would have been too late. It saved my life.

"I didn't feel ill at all. I had no breathing problems and no issues and couldn't believe it when it happened. It was scary at the time, just like you were on another planet.

"The tumour was three to five cm, which was quite big, but it was still early enough to remove it. I probably wouldn't have had too long before it was too late.

"Now I don't need any chemotherapy. I'm clear because they removed it so early."

Shirley, a health care assistant at Ninewells, was diagnosed with lung cancer in May and received surgery in July.

She added: "I would recommend people become involved with tests such as this. The cure at the moment is finding it early and getting it removed because there is no cure."

ggibson@thecourier.co.uk

See full story on page 13


Shirley was shocked when a 5cm tumour was discovered in her lung but was relieved it was caught so early. *Picture: John Stevenson.*

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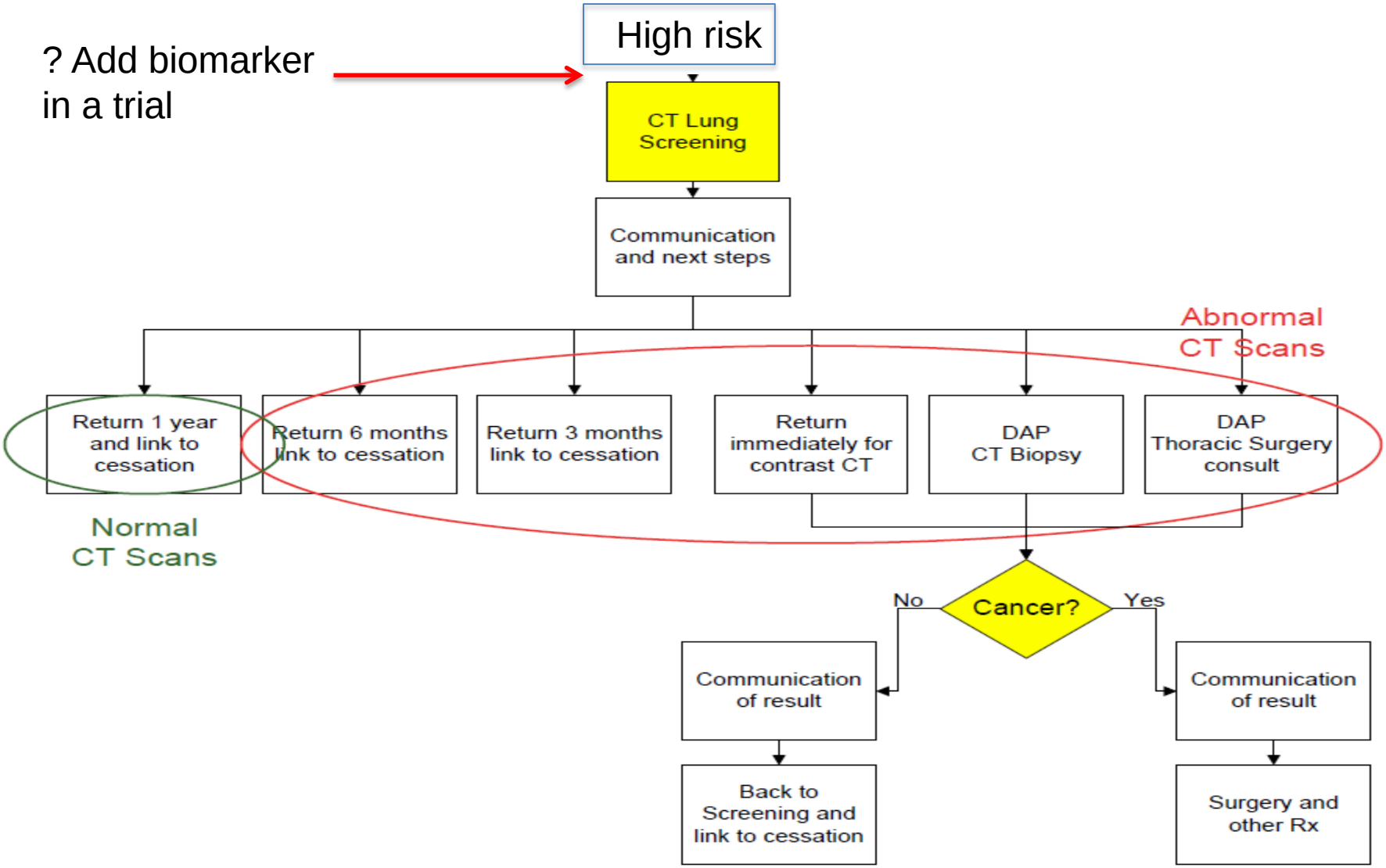
Planned Ontario Screening pathway



Research Question – Lead Mary Ann O'Brien

- What are the views of PCPs on their potential roles and informational needs in an organized LDCT screening program?

Methods

- Sampled PCPs from diverse health regions of Ontario and different practice models including family health teams and community health centres
- Conducted focus groups using modified Delphi method
- Developed a coding scheme then applied it systematically to interview transcripts

Results

Four groups with 33 PCPs and staff:

- 27 (82%) female;
- 21 (64%) physicians,
- 6 (18%) other health professionals,
- 6 (18%) administrative staff

Theme #1

Variable involvement of PCPs in identifying eligible patients for LDCT screening

- Greater involvement: e.g., running searches on EMR, applying algorithm, discussing pros and cons of LDCT
- **Generally Supportive**
- Lesser involvement: e.g., advertising screening in office
- **Concerned about additional workload**

Sample Quotations

"… I think we could very well be involved because our EMRs, we target smokers and we can run searches on our EMRs to find patients, exactly the ones you're looking for, so... we do it for other, you know... for all the big four, colon cancer and so on."

"[In] 10 to 15 minutes I cannot see myself conscientiously committing to doing anything else … I like our reminders… of the PAPs, the mammograms, the faecal occult blood. This could certainly be something else that's there. But I cannot conscientiously say that I'm going to be able to do this."

Are We Asking Patients if They Smoke?

Missing Information on Tobacco Use in Canadian Electronic Medical Records

Michelle Greiver, MD, Babak Aliarzadeh, MD, Christopher Meaney, MSc, Rahim Moineddin, PhD, Chris A. Southgate, BA, David T.S. Barber, MD, David G. White, MD, Ken B. Martin, MSc, Tabassum Ikhtiar, MD, Tyler Williamson, PhD

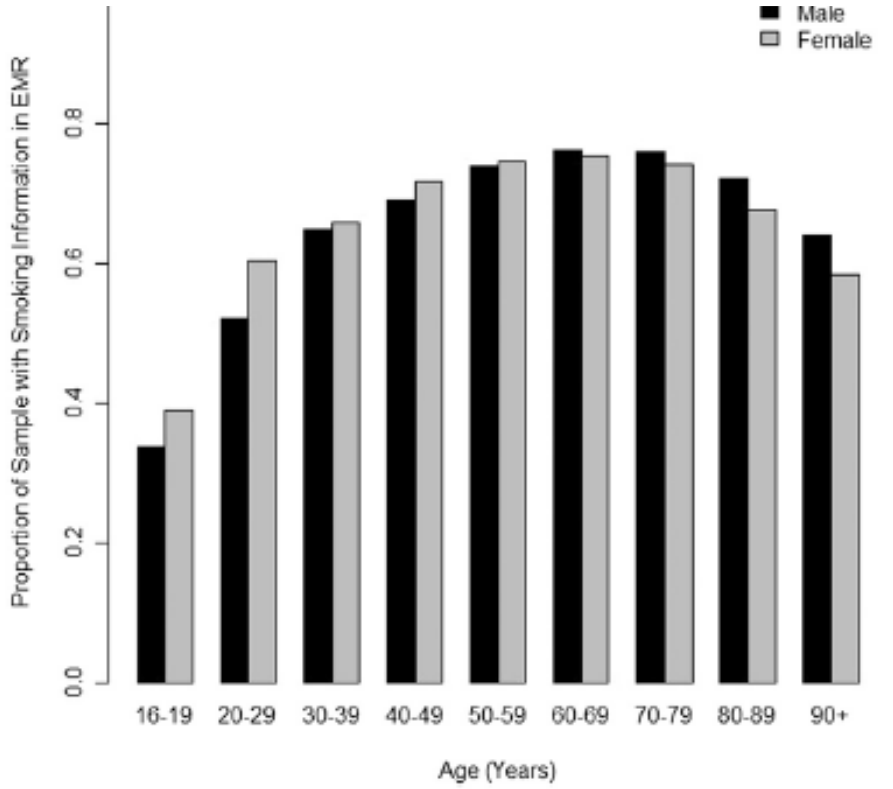


Figure 1. Proportion of sample with smoking information in electronic medical record (EMR) by age ranges and gender.

(Am J Prev Med 2015;49(2):264–268)

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Theme #2

Responsibility for follow up of positive LDCT findings should rest with a screening program not PCPs

Sample Quotation

"I, as a family doctor, would like to know that there was a 4 mm lesion found, it's been reviewed by a thoracic surgeon…and the recommendations are there."

Theme #3

Smoking cessation services are a key component of a lung cancer screening program

Sample Quotation

"… this is a phenomenal opportunity for those people who are identified as not being eligible for the low dose CT to have a discussion regarding smoking cessation. That's absolutely crazy not to use this as an opportunity."

Theme #4

PCPs have high information needs

- Evidence including potential benefits and harms such as false positive results
- Eligibility criteria
  - High risk
  - Identification of patients with multi-morbidities
- Details of a proposed screening process
- Communicating risk information to patients
- Follow up process when patients receive an abnormal result

Conclusions

- A future Ontario LDCT lung cancer screening program will need to consider the **wide variability in the roles** that PCPs envisioned for themselves.
- As **PCPs had extensive information needs**, a future program will need to develop information materials and learning opportunities tailored to identified needs.
- The existence of LDCT lung cancer screening program was seen **as a new opportunity to discuss smoking cessation** with patients. Therefore PCPs advocated that a potential program have explicit links to smoking cessation programs.

Should we nest a biomarker study in the Ontario Scheme?

- Are the Scottish results encouraging enough to consider extending to Ontario?
  - 76% operable V 20%
- Would EMR data quality in Canada be good enough?
- Do we need a PBRN to undertake this kind of study?
- What else would be needed?