Lung Cancer Screening & Smoking Cessation

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Lung Cancer Screening – Transformative Change in Lung Cancer Care

- Lung cancer is the most common cause of cancer death worldwide – >1.6 million deaths per year (20,500 Canadians)
- Modest improvement in 5 year survival over the last two decades (<18%)
- Screening with low dose CT scan shown to reduce lung cancer mortality by 20% in high risk smokers (NLST)

Cost-Effectiveness of Screening

Site	Modality	Age range	Frequency	Incremental cost-effectiveness ratio
Breast cancer	Mammography	50-69	Biennial	$28,921/QALY[1]
		40-49	Biennial	$86,029/QALY
		70-74	Biennial	$106,153/QALY
Colorectal cancer	FIT	50-74	Annual	$4,350/QALY[2] $6,229/QALY[3]
Prostate cancer	PSA test	55-69	Every 4 yrs	net loss of QALYs[4] (negative ICER)
Lung cancer	Low-dose CT	55-74	Annual*	US$81,000/QALY[5]

* NLST trial protocol: 3 annual screens

1. Pataky, Phillips, Coldman, Peacock. J Cancer Policy. 2014
2. Heitman, Au, Hilsden, Manns. CADTH. 2009
3. Telford, Levy, Sambrook *et al*, CMAJ, 2010
4. Pataky, Gulati, Etzioni, *et al*. Int J Cancer. 2014
5. NLST Research Team. NEJM. 2014

US Preventive Services Task Force

B Grading (*High certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial*)
Recommends annual Low-dose Computed Tomography (LDCT) screening be provided/offered to those

- 55 to 80 years with a
- ≥30 pack-years smoking, Quit <15 years
- generally healthy, candidate for surgery

Ann Intern Med. 2014 Mar 4;160(5):330-8.

CMS Issues Final Decision to Cover Lung CT Screening

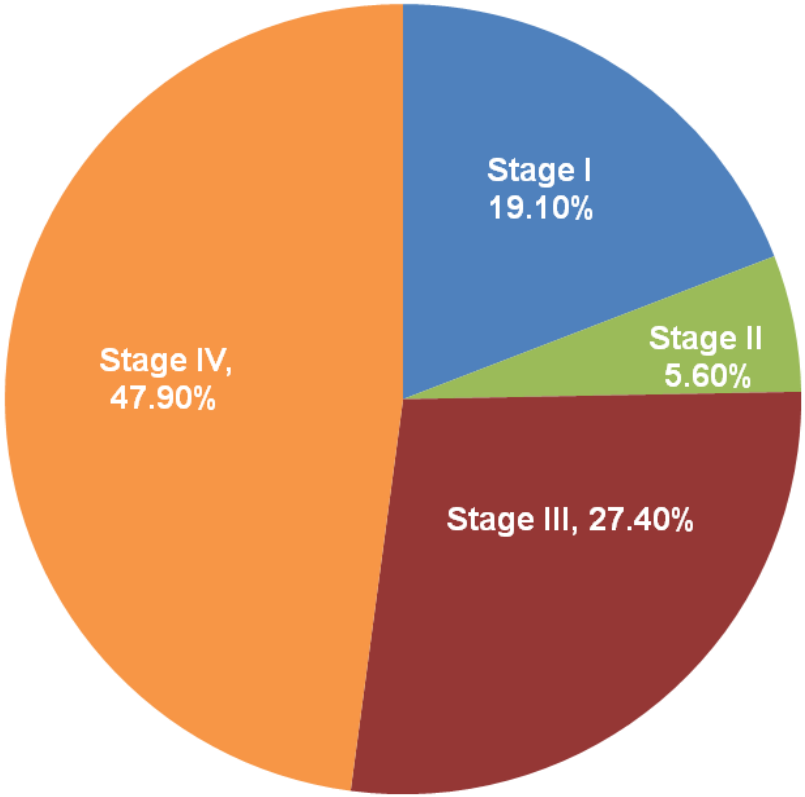
By **The ASCO Post**
February 25, 2015, Volume 6, Issue 3

- 55 to 77 years with a
- ≥30 pack-years smoking
- Quit <15 years

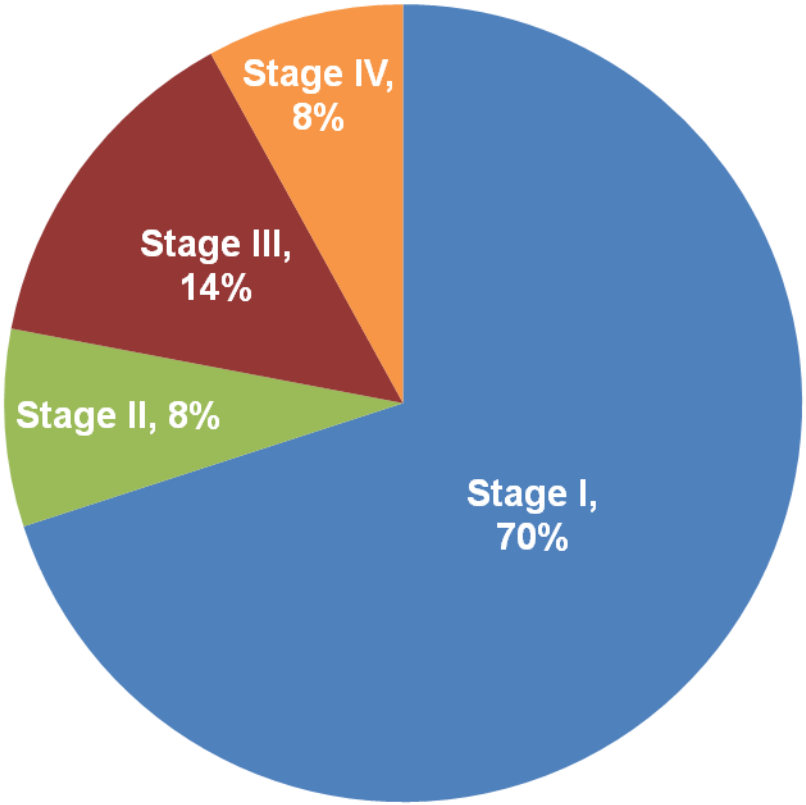
CMS = Centers of Medicare and Medicaid Services

Implication of Stage Shift On Clinical Care

No Screening
5 yr Survival < 18%



LDCT Screening
5 yr Survival >60% (Stage I)



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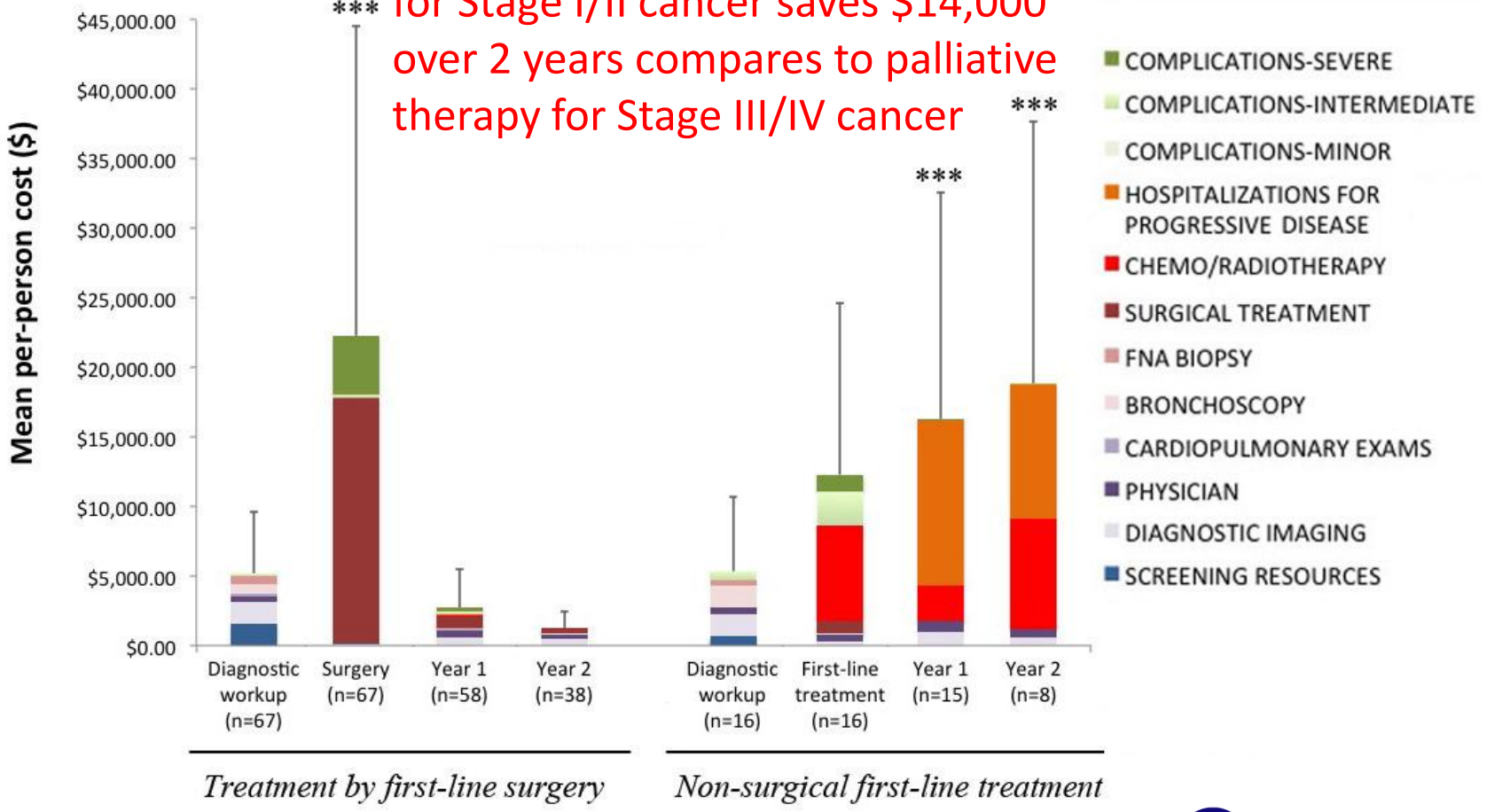
LDCT Screening Saves Money & Improves Outcome

Surgery ± adjuvant chemotherapy for Stage I/II cancer saves $14,000 over 2 years compares to palliative therapy for Stage III/IV cancer



Cressman et al . J Thorac Oncol 2014

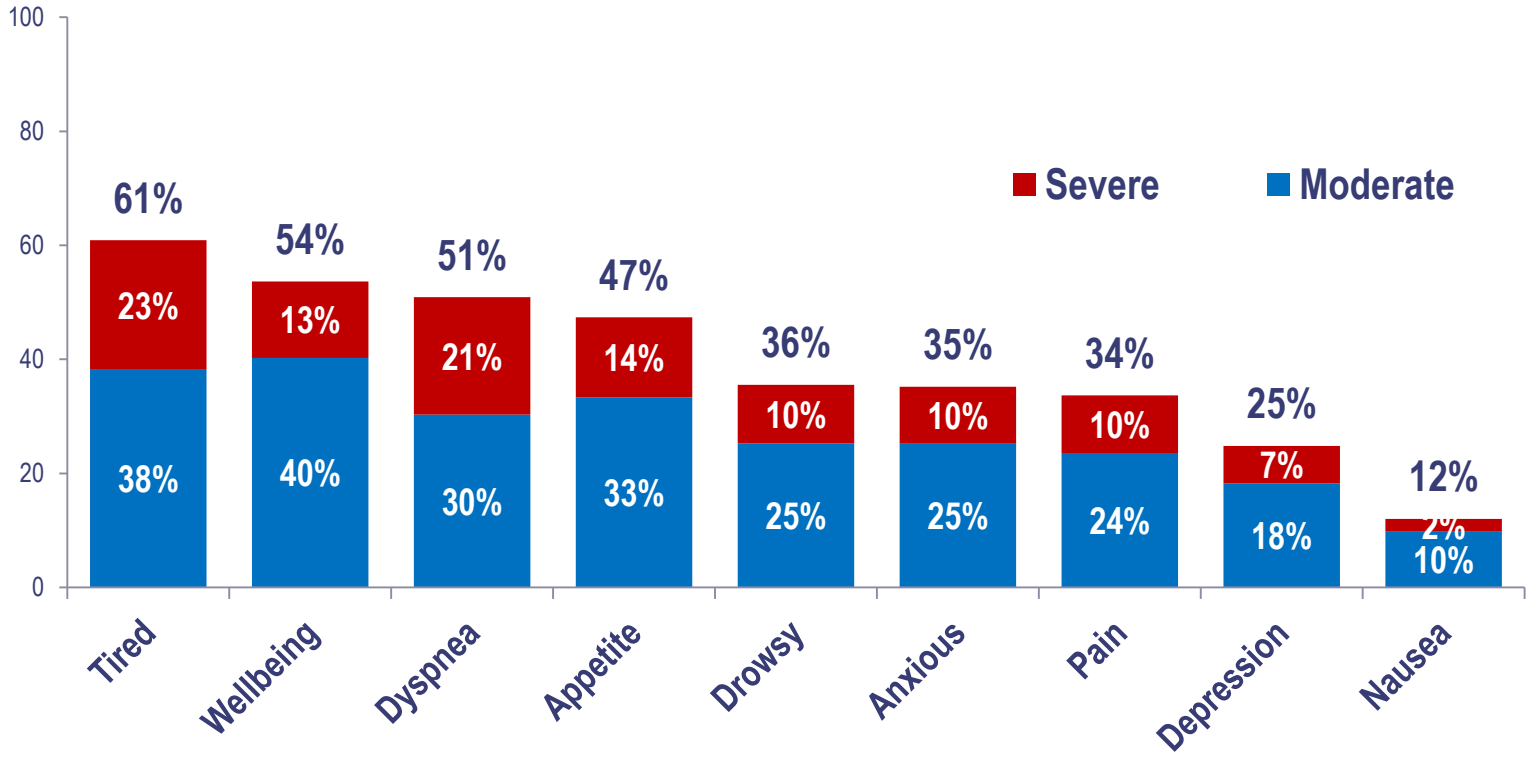
Cost of Targeted Therapy

Agent	Target	FDA-Approved Indication	Monthly or Per-Cycle Cost
Imatinib	BCR-ABL	CML	$6,982
Dasatinib	BCR-ABL	CML	$9,817
Nilotinib	BCR-ABL	CML	$9,163
Bosutinib	BCR-ABL	CML	$9,817
Sorafenib	VEGF, multikinase	RCC, HCC	$10,555
Sunitinib	VEGF, multikinase	RCC, GIST	$11,957
Everolimus	mTOR	RCC, breast	$8,984
Temsirolimus	mTOR	RCC	$6,355
Pazopanib	VEGF, multikinase	RCC	$7,778
Bevacizumab	VEGF	RCC, colon, lung	$11,684
Erlotinib	EGFR	Pancreatic, NSCLC	$5,756
Cetuximab	EGFR	Colon, head/neck	$24,092
Lapatinib	HER2	Breast	$5,120
Trastuzumab	HER2	Breast	$5,295
Brentuximab	CD30	Hodgkin lymphoma	$16,768*
Crizotinib	ALK1	NSCLC	$11,946
Ipilimumab	CTLA-4	Melanoma	$36,540†
Vemurafenib	BRAF	Melanoma	$12,282
Ruxolitinib	JAK2	Myelofibrosis	$8,400
Lenalidomide	IMID	Myeloma	$10,103

HM Kantarjian et al. JCO May 6, 2013

Symptom Burden Of Patients With Advanced Lung Cancer

ESAS symptom profile for all diagnosed Ontario Lung Cancer Patients in FY2009



Prepared by Cancer Informatics
Data sources: OCR, ESAS
Cohort: ESAS assessments done in FY2009

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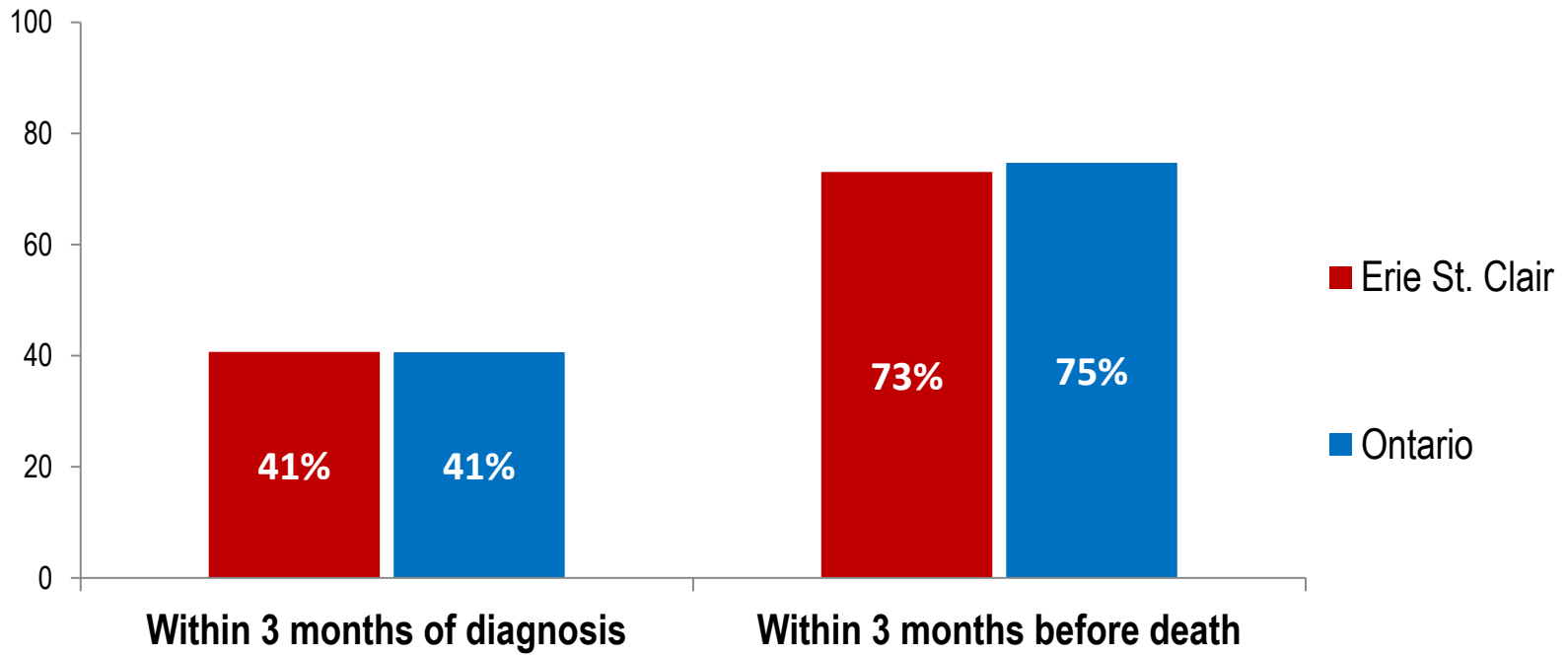
Lung Cancer Patients Access Emergency Department at a High Rate

Proportion of lung cancer patients who visited the emergency department within 3 months of diagnosis or within 3 months before death



Prepared by Cancer Informatics
Data sources: OCR, NACRS
Notes: Cause of death is not known

Courtesy of Bill Evans

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Factors That Influence QALY Gained with LDCT Screening

Sensitivity Analyses (NLST):

- Lung cancer risk
- Cost of CT examination ($285 in US)
- Number of follow-up CTs for “positive” screen, screening interval & duration
- Smoking cessation rate (current smokers)
- Incidental findings

B Black et al. N Engl J Med 2014;371:1793-802.

Screening 60% of Highest Risk Subjects Prevented 88% of Lung Cancer Deaths

Quintile of 5-Year Risk of Lung-Cancer Death	Participants	Lung-Cancer Cases		Lung-Cancer Deaths		Positive Screening Results		Number of False Positives per Prevented Lung-Cancer Death†	Number Needed to Screen†‡
		Total No.	Stage I†	Total No.	Prevented†	Total No.	False Positive†§		
	no. (%)		*no. (%)*		*no. (%)*		*no. (%)*		
All quintiles	26,604 (100)	1083	530 (48.9)	354	88 (24.9)	10,151	9484 (93.4)	108	302
Quintile 1: 0.15–0.55%	5,276 (19.8)	71	40 (56.3)	20	1 (5.0)	1,699	1648 (97.0)	1648	5276
Quintile 2: 0.56–0.84%	5,310 (20.0)	105	59 (56.2)	35	10 (28.6)	1,879	1806 (96.1)	181	531
Quintile 3: 0.85–1.23%	5,396 (20.3)	182	84 (46.2)	45	13 (28.9)	2,024	1911 (94.4)	147	415
Quintile 4: 1.24–2.00%	5,314 (20.0)	263	132 (50.2)	73	31 (42.5)	2,123	1973 (92.9)	64	171
Quintile 5: >2.00%	5,308 (20.0)	462	215 (46.5)	181	33 (18.2)	2,426	2146 (88.5)	65	161

N Engl J Med 2013;369:245-54.

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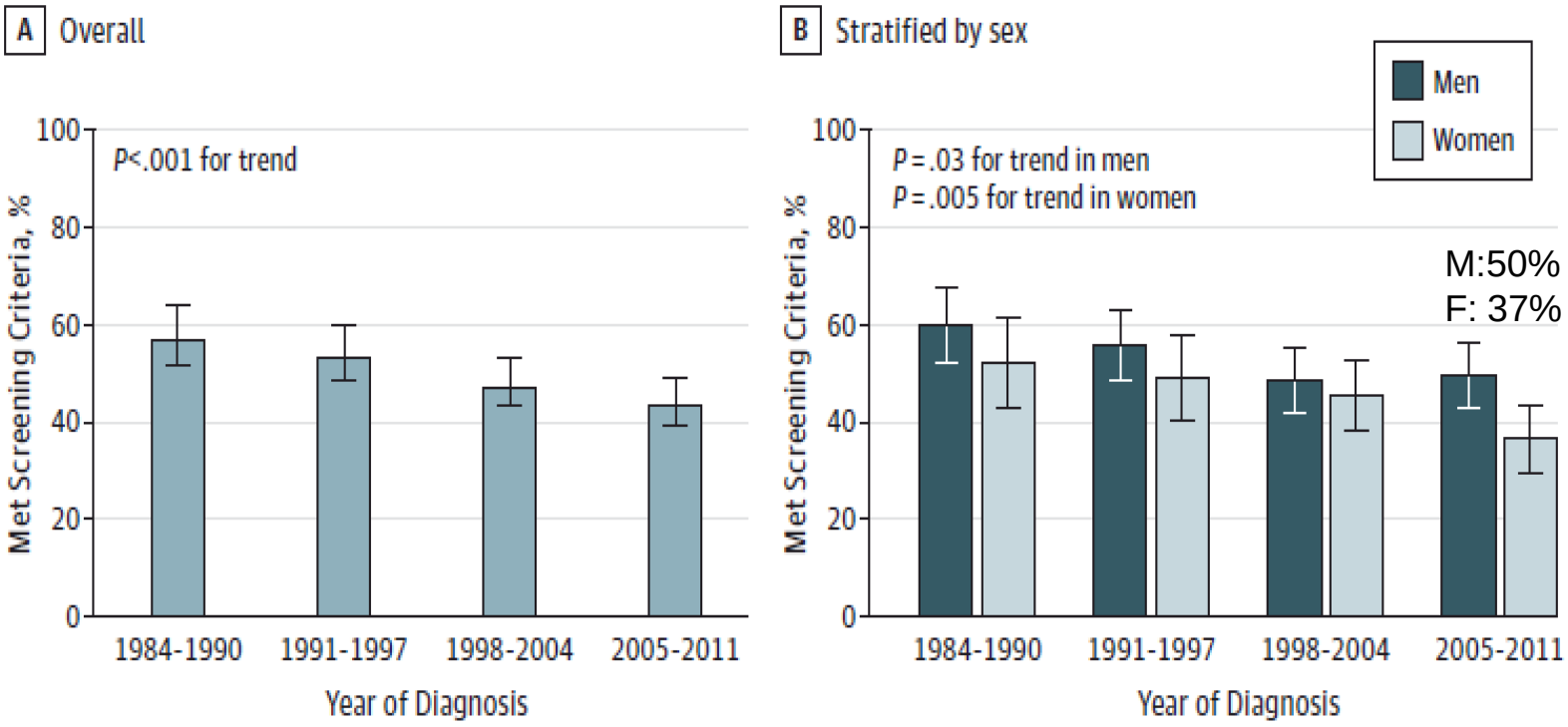
Increasing Number of Lung Cancer Patients Would Not Meet the USPSTF Screening Criteria (Age 55-80, ≥30 PY)



Yi Wang et al. JAMA February 24, 2015.

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Importance Of Sensitive Risk Identification & High Screening Uptake

Sensitivity of Risk Predictor	Participation Rate	Potential Impact At Population Level
80%	70%	56%
40%	70%	28%
40%	30%	12%

Accurate Risk Prediction Tool

Predictors: Risk ⬆ NEJM 2013;368:728-36

- ⬆ age
- Δ race/ethnicity
- ⬇ education (SES)
- ⬇ BMI
- ⬆ personal history of cancer
- ⬆ family history of lung cancer
- ⬆ COPD

7 non-smoking

4 smoking

- ⬆ smoking status, ⬆*intensity*, ⬆duration & ⬇quit-time

PLCOm2012 Predictive Performance : AUC = 0.80

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$NLST_{criteria}$ vs. $PLCO_{M2012}$

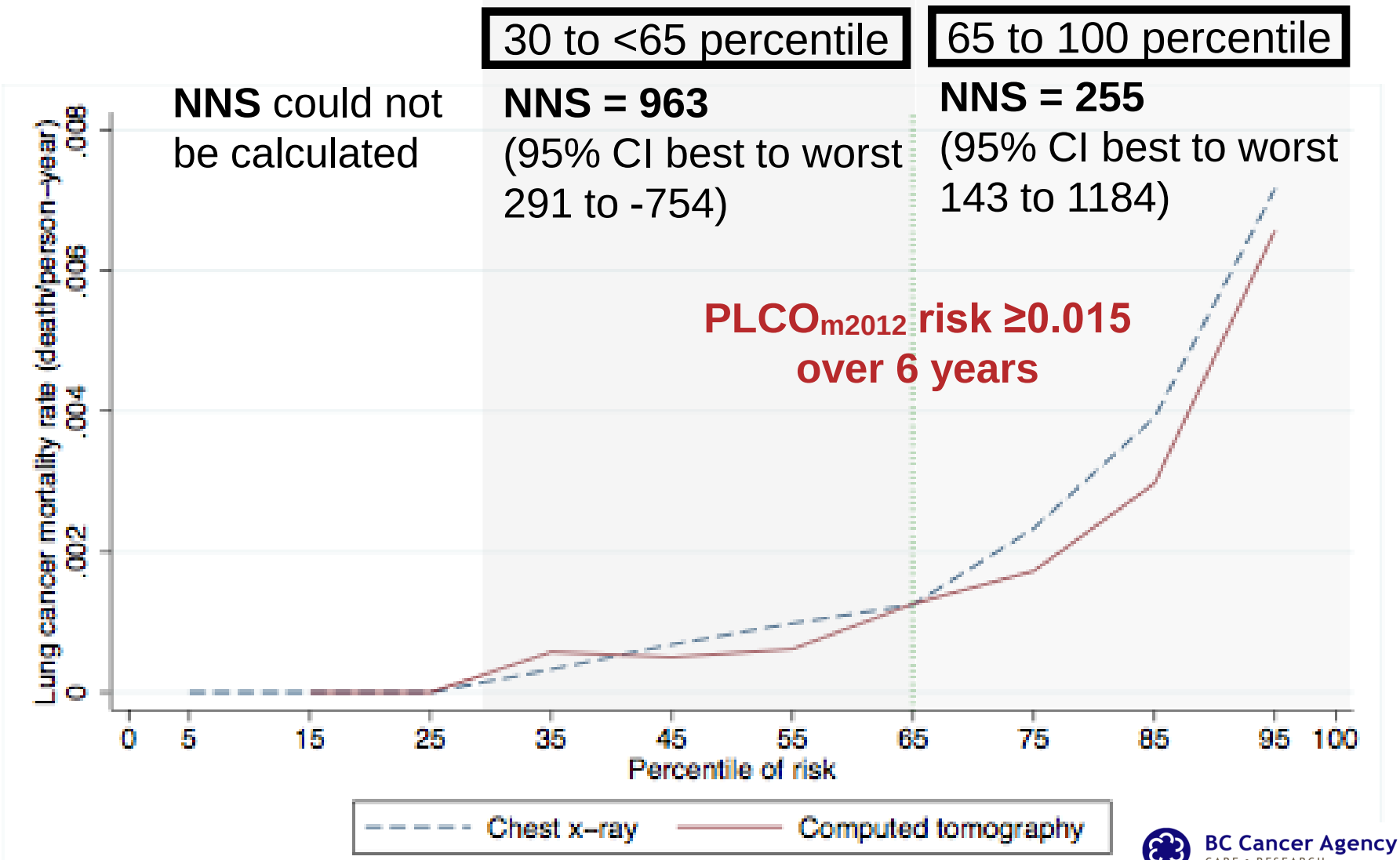
	NLST criteria Age 55-74, ≥30 PY	$PLCO_{M2012}$	P-value
Sensitivity	71.1%	83.0%	p<0.0001
Specificity	62.7%	62.9%	p=0.536
PPV	3.4%	4.0%	p=0.011
AUC in PLCO intervention arm	0.67	0.80	p<0.001

41.3% Fewer lung cancers missed with PLCO Model vs NLST

Tammemagi et al. N Engl J Med 2013;368:728-36

Lung cancer mortality rates in NLST intervention arms by $PLCO_{m2012}$ model risk deciles. **Number needed to screen to avert 1 lung cancer death.**

Tammemagi et al. PLOS Med December 2014



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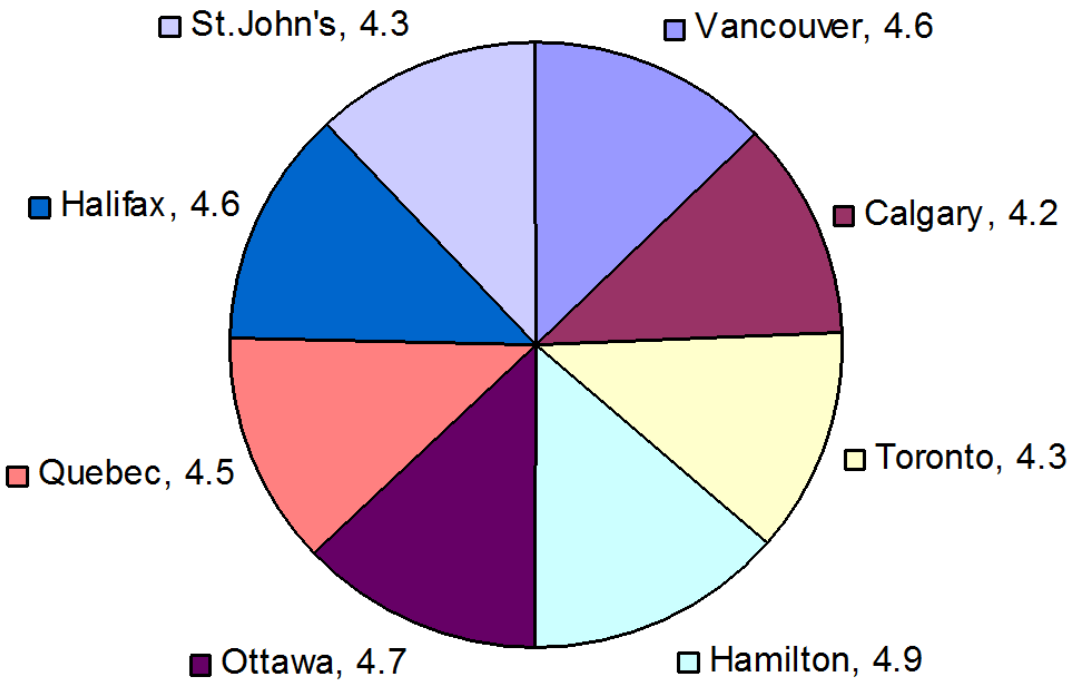
Pan-Canadian Early Detection Study

Average 3-year lung cancer risk 4.5% N=2537



114 Lung Cancers Expected Over 3 Years

110 cancers (4.3%) diagnosed in 36 months

Study Population Demographics Ever Smokers

	PLCO N= 85,717	NLST N= 53,452	Pan-Canadian Study N= 2537
Male	58%	59%	55%
Age (Median, yrs)	62	60	62
Race/Ethnicity			
White	83%	90%	97%
Black	5%	4%	0.6%
Hispanic	2%	1%	-
Asian	3%	2%	1.2%
Other	-	-	1.2%
Education			
≤HS	31%	30%	42%
≥ College	69%	70%	58%
Current Smokers	20%	48%	62%
Median Pack-years	29	48	50
Any first degree relative w/ LCA	12%	22%	33%

Study vs Population Demographics Ever Smokers Age 55-74

	PanCan	Canada	Ontario	British Columbia
Male : Female	55% : 45%	49% :51%	45% : 55%	49:51
Race/Ethnicity Non-White	3%	24%*	29%*	49%
Education ≤HS ≥ College	 42% 58%	 50% 50%	 44% 56%	 53% 47%
Current Smokers	62%	12%	13%*	8%
Median Pack-years	50	42	38	40

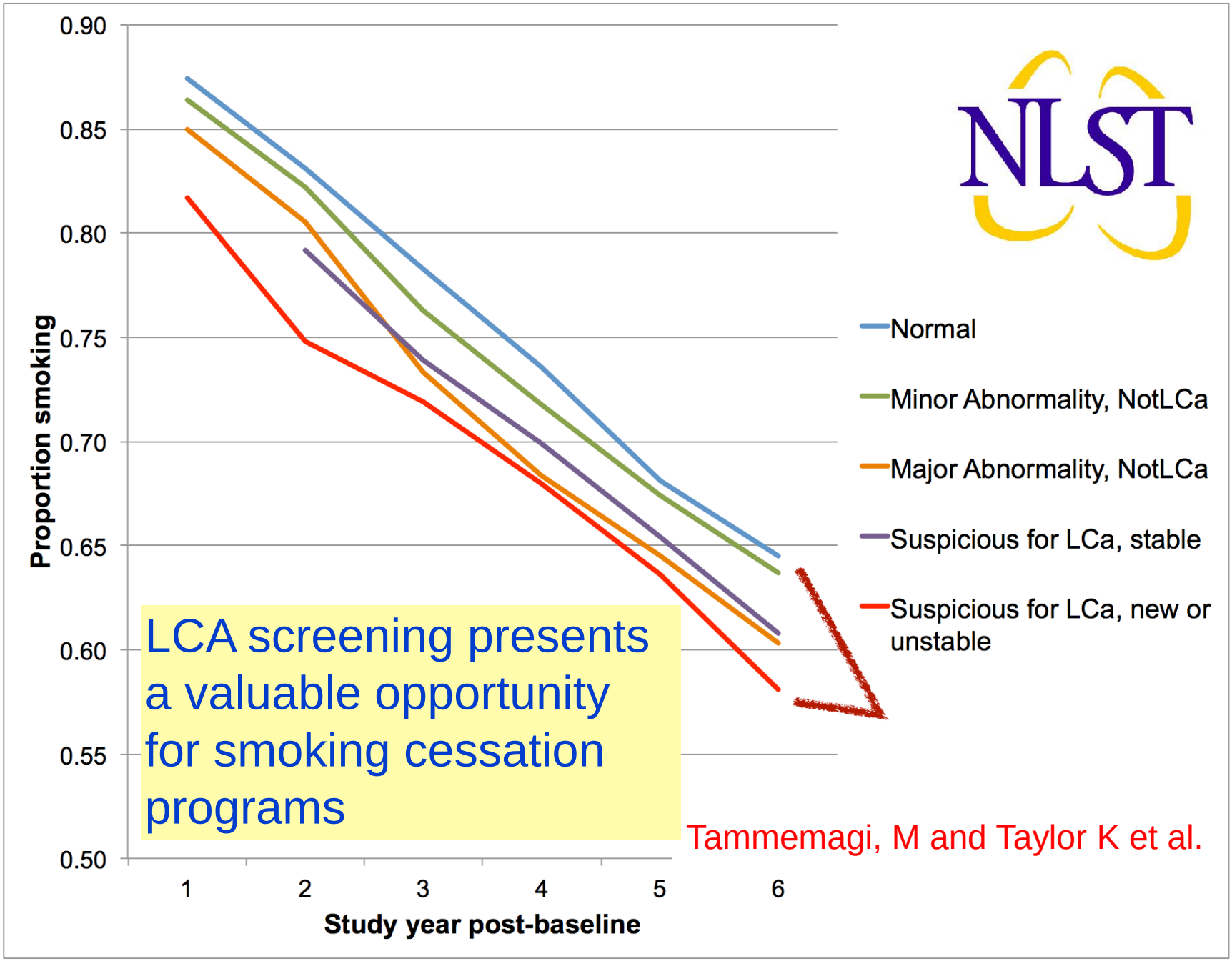
* Stat Canada 2011

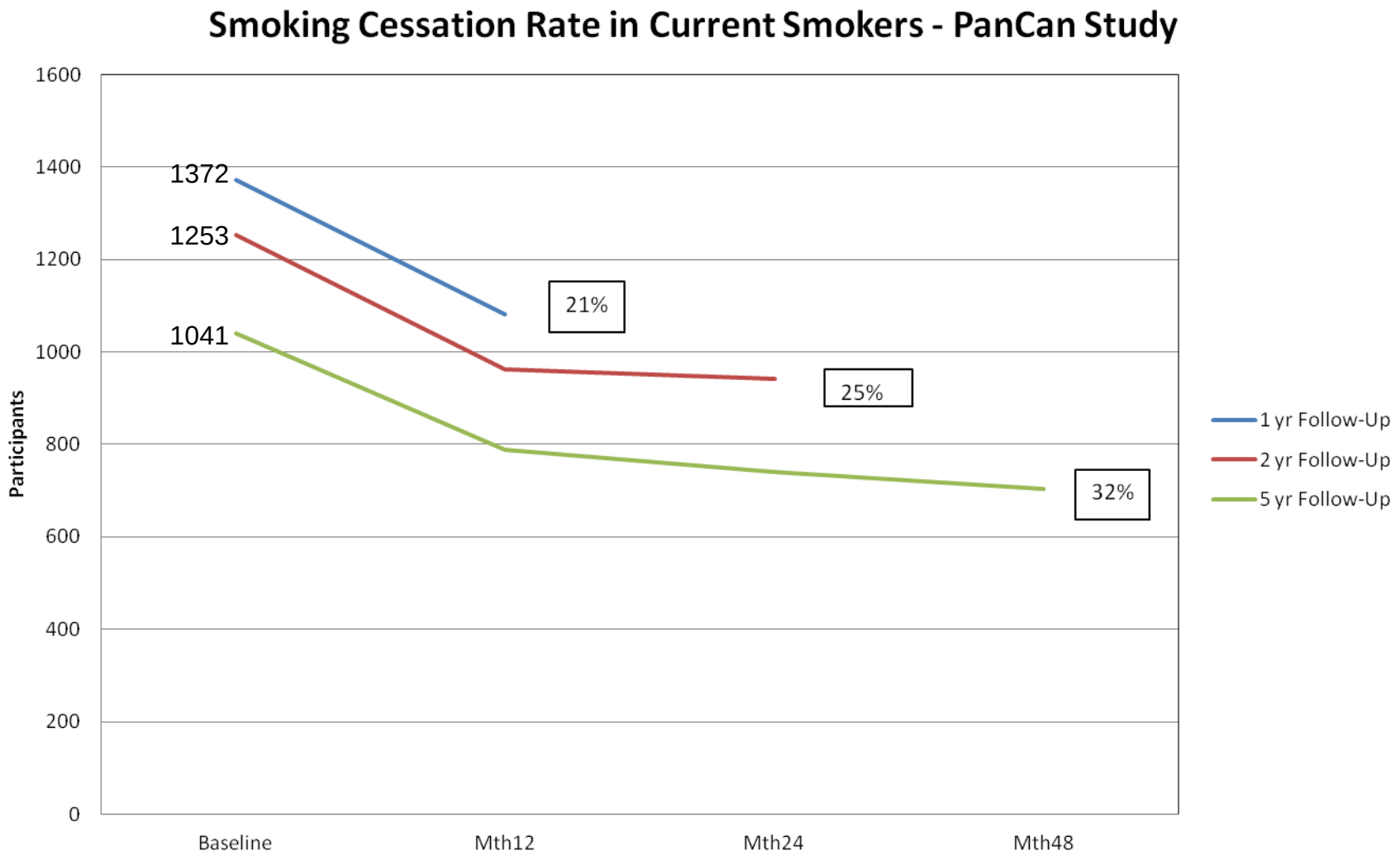
Smoking Cessation Rate In Randomized LDCT Trials

	Un-screen Arm	CT Arm
DLCST 2009	11.8%	11.9% 17.7% (CT+)
NELSON 2010	14.6%	12.6%*

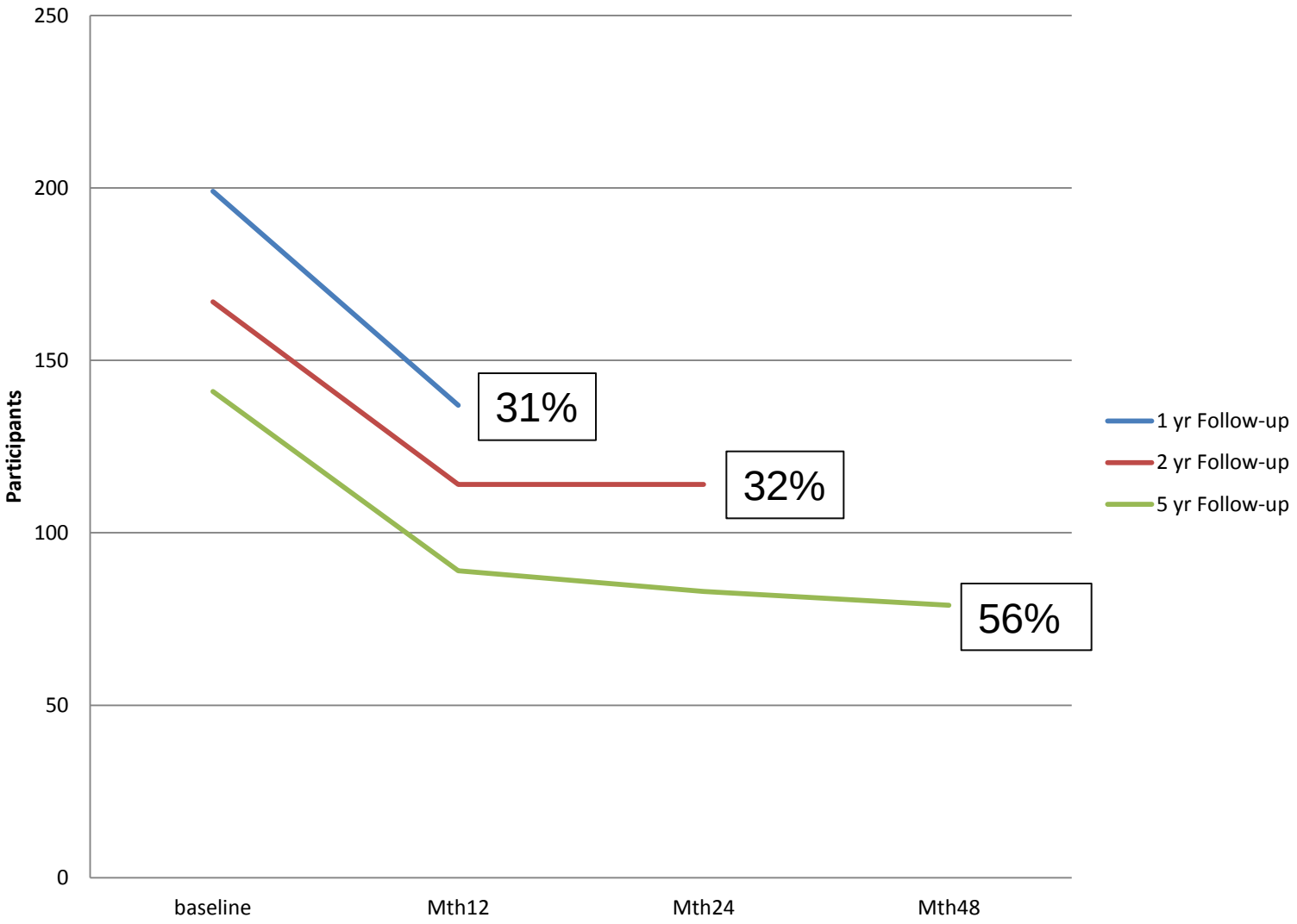
- Subjects with positive CT excluded from analysis
- Spontaneous annual smoking cessation rate in general population: 3% to 7%

Thorax 2009: 64:388-392; & 2010;65:600-605.
M Fiore et al. 2000


0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
Proportion smoking
1
2
3
4
5
6
Study year post-baseline
Normal
Minor Abnormality, NotLCa
Major Abnormality, NotLCa
Suspicious for LCa, stable
Suspicious for LCa, new or unstable
NLST
LCA screening presents a valuable opportunity for smoking cessation programs
Tammemagi, M and Taylor K et al.


Smoking Cessation Rate in Current Smokers - PanCan Study
Participants
1600
1400
1200
1000
800
600
400
200
0
1372
1253
1041
21%
25%
32%
Baseline
Mth12
Mth24
Mth48
1 yr Follow-Up
2 yr Follow-Up
5 yr Follow-Up

Smoking Cessation Rate in Vancouver LDCT Screening Cohort



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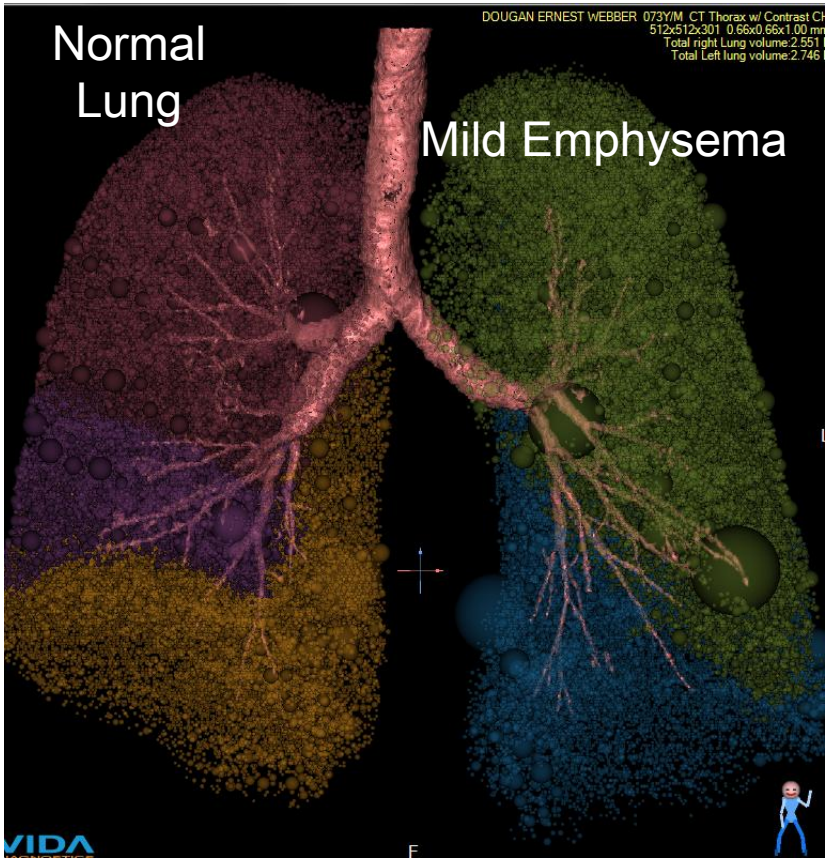
Smoking Cessation Method BCCA-LHS

Method	Proportion
Cold Turkey or will power	38.8%
Champix or Buproprion	30.6%
Nicotine replacement	24.5%
Other (hypnosis, laser, book)	6.1%

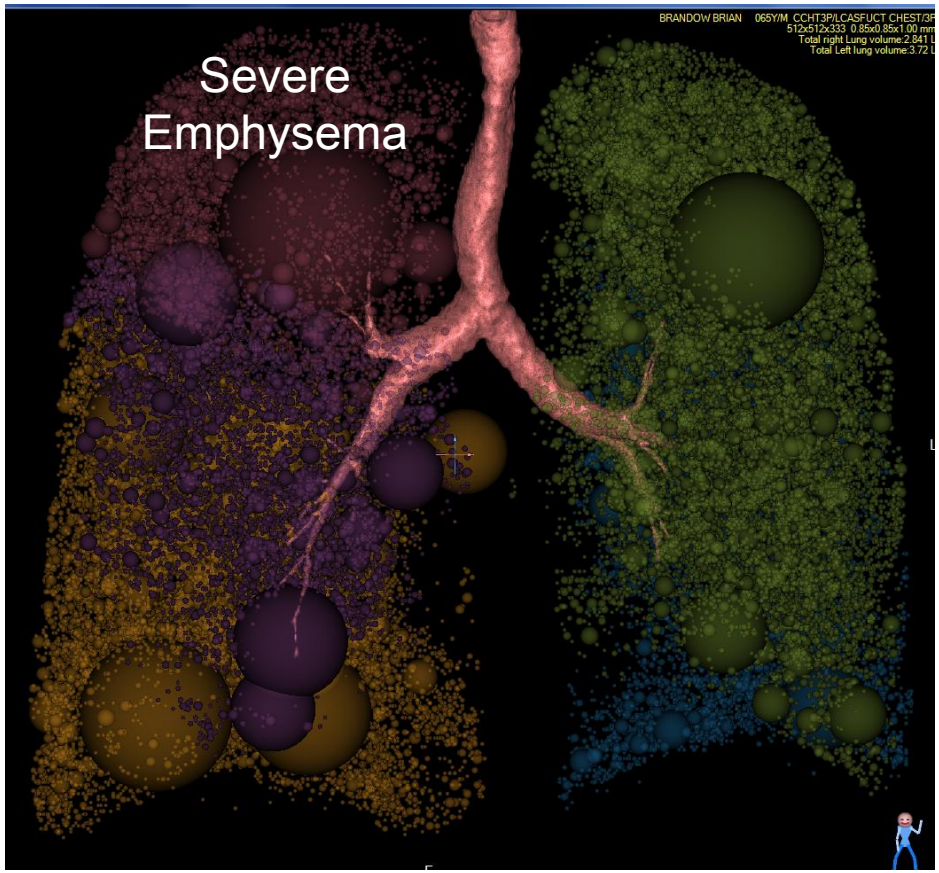
Smoking Cessation vs Screening

- Spontaneous quit rate 3% to 7%
- Cost of pharmacotherapy: $250 - $664 per smoker
- Cost of CT screening for 2 yrs. $453
- Average smoking cessation rate in LDCT screening program 20% (31% 12 month quit rate in BCCA - 40% without drugs)

CT Image For Behavioral Modification

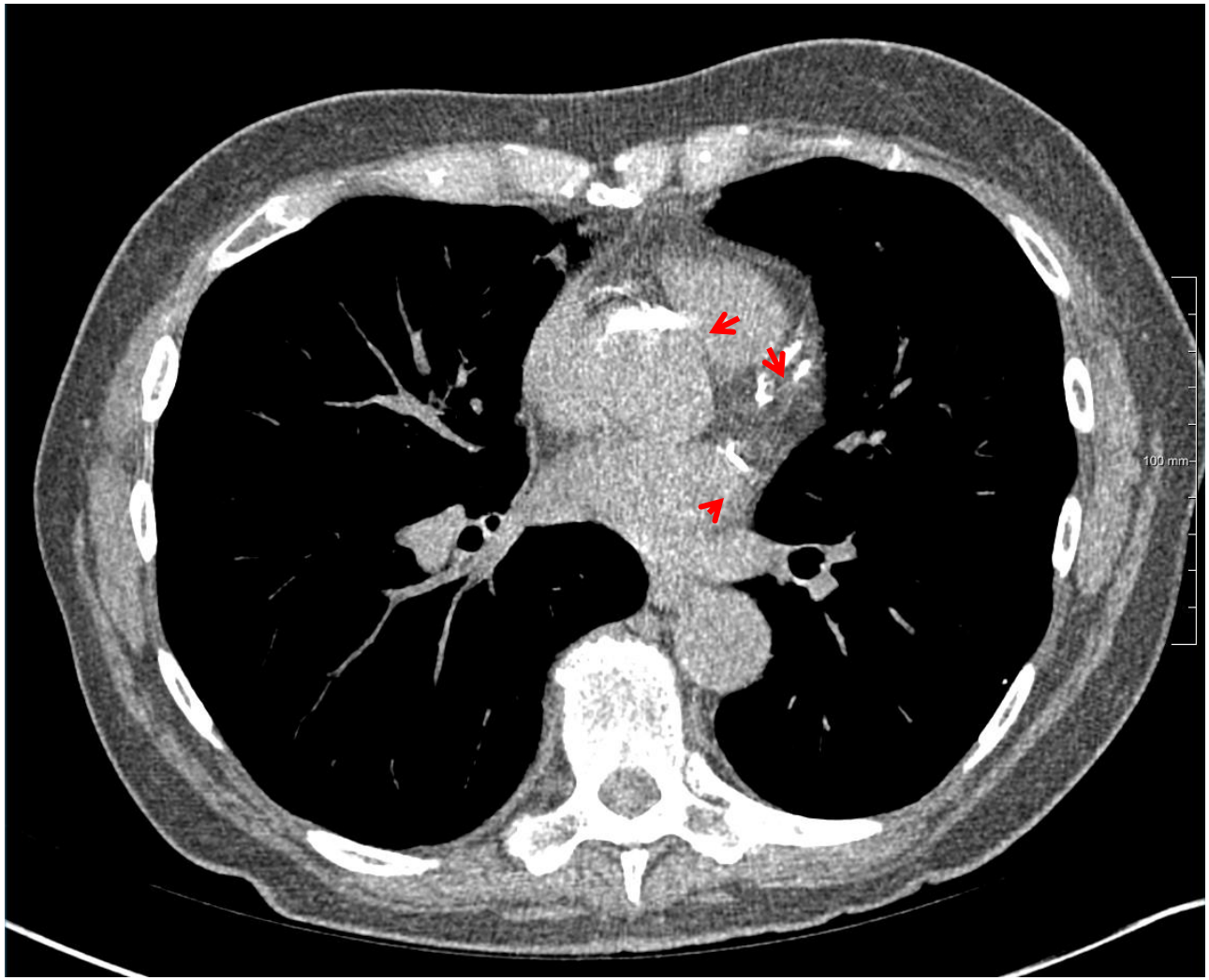


Mild COPD



Severe COPD

CT Image For Behavioral Modification



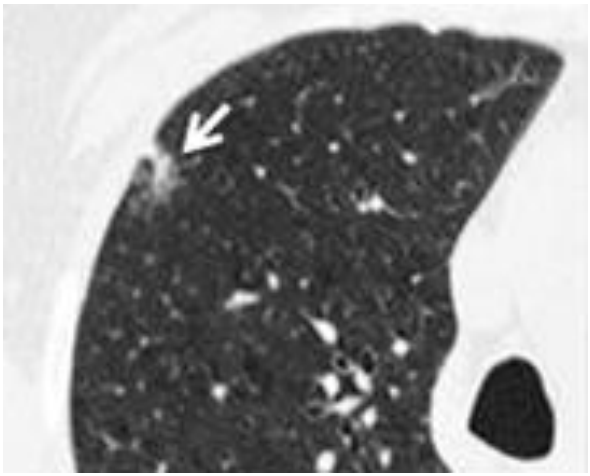
Radiation Risk

- Radiation dose 0.7 mSv with new dual source, ultrafast, ultra-low dose scanner
- Background radiation 2 – 8 mSv/yr
- Standard CT 8 mSV
- PET CT 8 to 12 mSV

- Proper nodule management protocol & personalized screening interval reduces downstream investigations & radiation exposure

Management Of Screen Detected Lung Nodules

Solid



Semi-Solid

Non-Solid

LungRADS

http://www.acr.org/Quality-Safety/Resources/LungRAD

Category	Category Descriptor	Category	Findings	Management	Probability of Malignancy	Estimated Population Prevalence
Incomplete	-	0	prior chest CT examination(s) being located for comparison part or all of lungs cannot be evaluated	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed	n/a	1%
Negative	No nodules and definitely benign nodules	1	no lung nodules nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules	Continue annual screening with LDCT in 12 months	< 1%	90%
Benign Appearance or Behavior	Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	solid nodule(s): < 6 mm new < 4 mm part solid nodule(s): < 6 mm total diameter on baseline screening non solid nodule(s) (GGN): < 20 mm OR ≥ 20 mm and unchanged or slowly growing category 3 or 4 nodules unchanged for ≥ 3 months			
Probably Benign	Probably benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	solid nodule(s): ≥ 6 to < 8 mm at baseline OR new 4 mm to < 6 mm part solid nodule(s) ≥ 6 mm total diameter with solid component < 6 mm OR new < 6 mm total diameter non solid nodule(s) (GGN) ≥ 20 mm on baseline CT or new	6 month LDCT	1-2%	5%
Suspicious	Findings for which additional diagnostic testing and/or tissue sampling is recommended	4A	solid nodule(s): ≥ 8 to < 15 mm at baseline OR growing < 8 mm OR new 6 to < 8 mm part solid nodule(s: ≥ 6 mm with solid component ≥ 6 mm to < 8 mm OR with a new or growing < 4 mm solid component endobronchial nodule	3 month LDCT; PET/CT may be used when there is a ≥ 8 mm solid component	5-15%	2%
		4B	solid nodule(s) ≥ 15 mm OR new or growing, and ≥ 8 mm part solid nodule(s) with: a solid component ≥ 8 mm OR a new or growing ≥ 4 mm solid component	chest CT with or without contrast, PET/CT and/or tissue sampling depending on the *probability of malignancy and comorbidities. PET/CT may be used when there is a ≥ 8 mm solid component.	> 15%	2%
		4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy			
Other	Clinically Significant or Potentially Clinically Significant Findings (non lung cancer)	S	modifier - may add on to category 0-4 coding	As appropriate to the specific finding	n/a	10%

Lung-RADS Classification

Lung-RADS Category	Baseline Screening	Subsequent Screening
1	No nodules; nodules with calcification	No nodules; nodules with calcification
2	Solid/part solid: <6 mm GGN: <20 mm -	Solid/part solid: <6 mm GGN: <20 mm or unchanged/slowly growing Category 3–4 nodules unchanged at ≥3 mo
3	Solid: ≥6 to <8 mm Part solid: ≥6 mm with solid component <6 mm GGN: ≥20 mm	Solid: New ≥4 to <6 mm Part solid: New <6 mm GGN: New ≥20 mm
4A	Solid: ≥8 to <15 mm Part solid: ≥8 mm with solid component ≥6 and <8 mm	Solid: Growing <8 mm or new ≥6 and <8 mm Part solid: ≥6 mm with new or growing solid component <4 mm
4B	Solid: ≥15 mm Part solid: Solid component ≥8 mm	Solid: New or growing and ≥8 mm Part solid: ≥6 mm with new or growing solid component ≥4 mm
4X	Category 3 or 4 nodules with additional features; imaging findings that increase suspicion of malignancy	Category 3 or 4 nodules with additional features; imaging findings that increase suspicion of malignancy

GGN = ground-glass nodule.
* Size is the average diameter rounded to the nearest whole number. Growth is a size increase >1.5 mm.

- **Potentially avoid 46% to 52% follow-up chest CTs for false-positive screen & reduce invasive diagnostic procedure by 23% compared to NLST**
- **Lung-RADS missed 9.2% to 16.2% lung cancers compared to NLST**

Pinsky et al. Ann Intern Med 10 February 2015

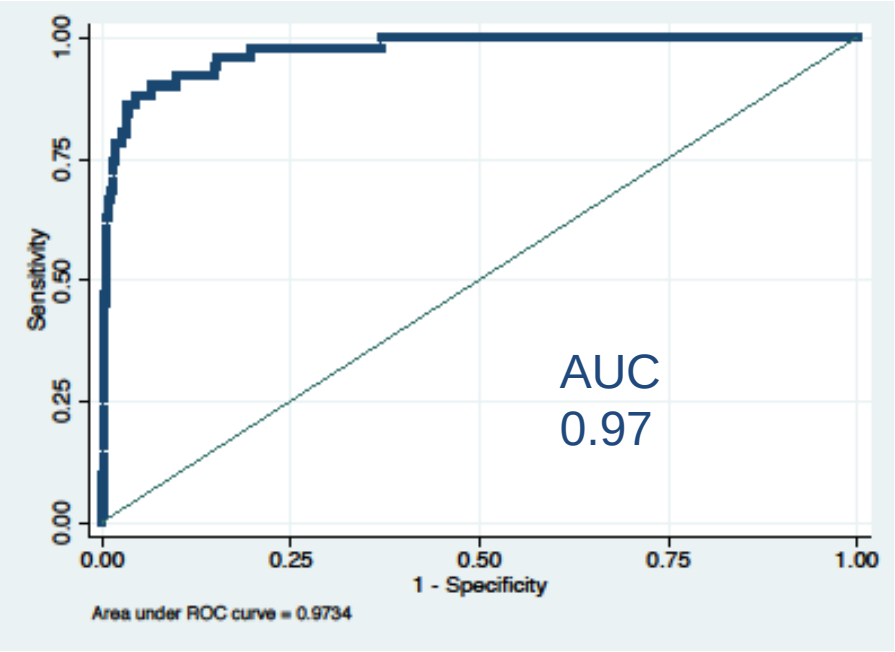
PanCan Lung Nodule Malignancy Risk Calculator

Nodule Calculator

Age:	Age
Sex:	Male / Female
Family history of lung cancer?	No / Yes
Emphysema?	No / Yes
Nodule Size: (Dimension in millimeters)	mm mm
Nodule Type (choose only one):	
1) Groundglass/nonsolid	No / Yes
2) Semisolid	No / Yes
3) Solid	No / Yes
Upper Lobe Location?	No / Yes
Spiculation?	No / Yes
Nodule Count: Enter the total number of nodules.	count

Calculate Probability | Clear

Probability that nodule is lung cancer = % %



	≤10 mm	GGN	Sub-solid
AUC	0.94	0.92	0.93

N Engl J Med 2013;369:908-17 & 369:2061-2

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Eur Radiol
DOI 10.1007/s00330-015-3689-0

CHEST

Predictive Accuracy of the PanCan Lung Cancer Risk Prediction Model -External Validation based on CT from the Danish Lung Cancer Screening Trial

Mathilde M. Winkler Wille · Sarah J. van Riel · Zaigham Saghir · Asger Dirksen · Jesper Holst Pedersen · Colin Jacobs · Laura Hohwü Thomsen · Ernst Th. Scholten · Lene T. Skovgaard · Bram van Ginneken

- Confirm high accuracy of PanCan model
- AUC 0.87

Positive Screen Definition

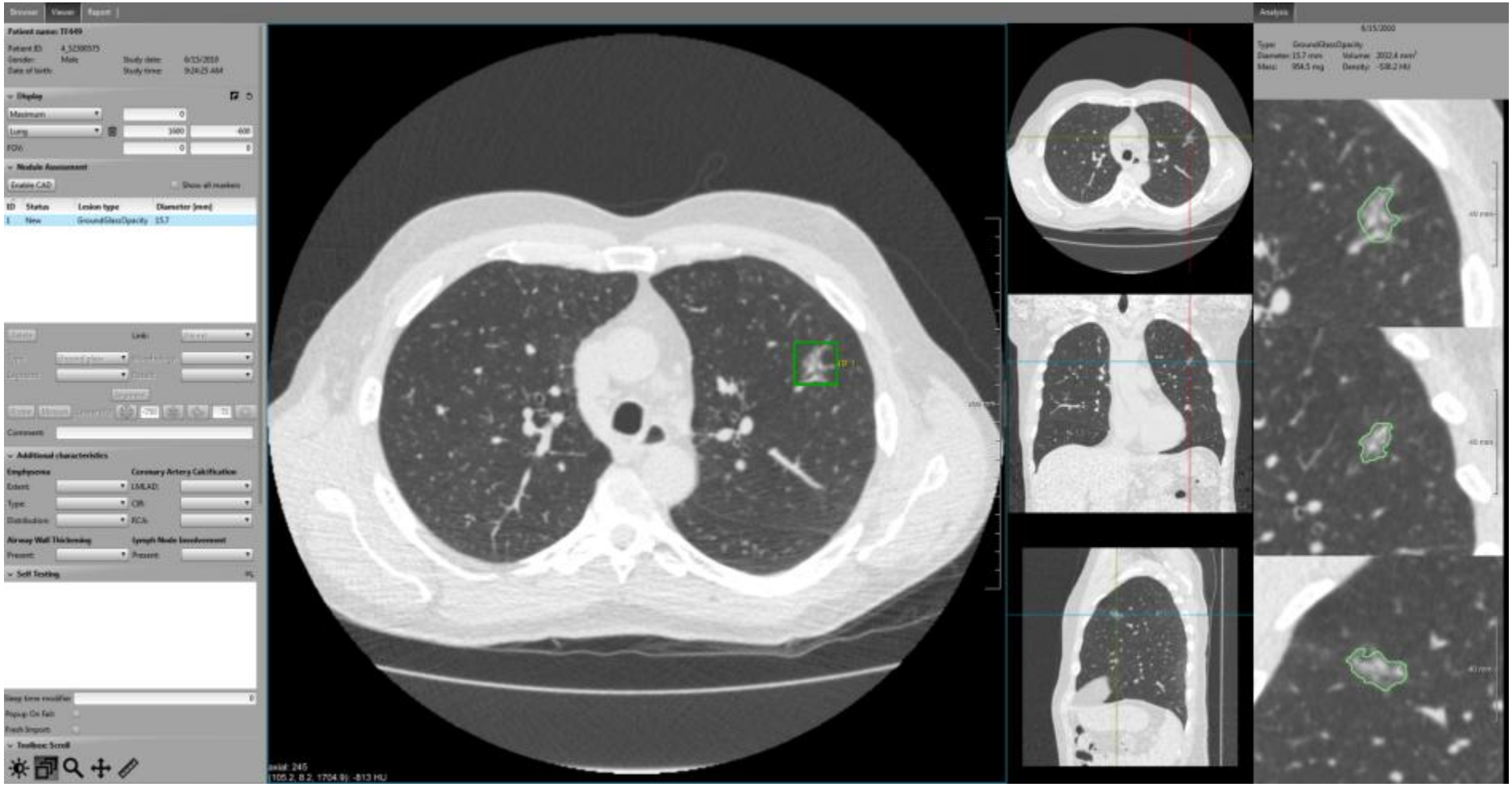
	NLST ≥4 mm	Lung-RADS Cat ≥3	PanCan ≥1.5% Malignancy Risk
Sensitivity	93.5	84.9	89.1
Specificity	73.4	87.2	88.4
PPV	3.8	6.9	9.9
NPV	99.9	99.8	99.8

Pinsky et al. Ann Intern Med 10 February 2015

Variability Of Scan Interpretation In NLST

- Median false-positive rate (FPR) 27.1%
- Aggregate sensitivity 96.5% for radiologists with FPR > median and 91.9% for radiologists with FPR <median Radiology 2013; 268:865-73
- Higher FPRs increase costs and utilization of health care resources and increase chance of harms with follow-up investigations
- Lower sensitivity may result in missing the chance for cure

Computer-aided detection and automated measurement software to reduce variability & facilitate nodule management recommendation



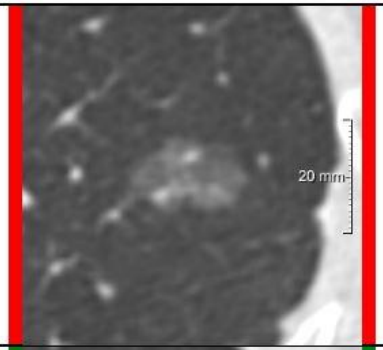
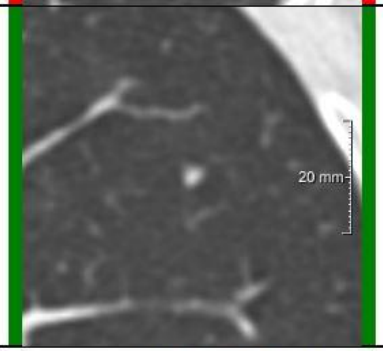
Bram van Ginneken et al.

Generation of High Quality Standardized Report in < 3 min

Chest Screening Report

Name	3348
Sex	F
Age	60
ID	3348
Visit	Visit 3
CT Scan Date	Nov 30, 2009
Signed off by	Vancouver-user
Comments	

LungRADS Assessment Category 2 based on nodule ID 2. Management: continue annual screening with LDCT in 12 months

		Finding	Baseline Dec 10, 2007	Visit 2 Jan 07, 2009	Visit 3 Nov 30, 2009	Comments
1		Location	Slice 58	Slice 58	Segment L1/2, Slice 62	
		Status	New	Old	Old	
		Result		Growing	Growing	
		Type	GroundGlassOpacity	GroundGlassOpacity	GroundGlassOpacity	
		Equivalent Diameter	13.0 mm	16.3 mm	17.7 mm	
		Mass	348.2 mg	626.4 mg	886.5 mg	
		Axis long/short	14.4 / 10.4 mm	20.3 / 13.3 mm	23.6 / 12.6 mm	
		Description			Well defined	
		Volume doubling time		401 d	941 d	
		Mass doubling time		465 d	653 d	
		Malignancy probability	12.54%	23.08%	43.83%	
2		Location	Slice 107	Slice 109	Slice 118	
		Status	New	Old	Old	
		Result		Smaller	Growing	
		Type	Solid	Solid	Solid	
		Equivalent Diameter	3.5 mm	3.3 mm	3.6 mm	
		Mass	12.0 mg	12.7 mg	16.1 mg	
		Axis long/short	2.8 / 1.1 mm	3.8 / 3.1 mm	3.8 / 2.7 mm	
		Description				
		Volume doubling time		-1873 d	988 d	
		Mass doubling time		4817 d	955 d	
		Malignancy probability	0.06%	0.23%	0.23%	
	Lymph Node Involvement	Present	No	No	No	
	Coronary Artery Calcification	LMLAD	None	None	None	
		CIR	None	None	None	
		RCA	None	None	None	
Emphysema	Extent	Mild (5-25%)	Trivial (<5%)	Mild (5-25%)		
	Type	Centrilobular	Centrilobular	Centrilobular		
	Distribution	Diffuse	Diffuse	Diffuse		
Airway Wall Thickening	Present	No	No	No		

BC Cancer Agency
CARE & RESEARCH
An agency of the Provincial Health Services Authority

Canadian Landscape

- In the absence of public policy, opportunistic screening has sprung up in private clinics, and physicians are increasingly requesting CT scans for smokers with respiratory symptoms such as cough.
- Pan-Canadian network supported by the Canadian Partnership Against Cancer (CPAC) developed a framework for lung cancer screening in Canada in 2013-2014.
- Cancer Care Ontario (CCO) released their guidelines for “Screening High-Risk Populations for Lung Cancer” in September 2013. Advertized for screening program lead
- Alberta is starting a 5-year pilot project.

British Columbia Projections

- 174,000 potential screenees
- 39,000 LDCTs annually (equivalent capacity with 2 new CT scanners 7 hours a day, 5 days a week for 48 weeks)
- Detailed budget being worked out
- Cost offset by ad hoc screening, treatment savings, decrease symptoms burden and hospital resource utilization, increase smoking cessation

Policy Option – No Screening (Maintain Status Quo)

Advantages

- No added start up infrastructure costs to the health care system

Disadvantages

- Ignores the positive evidence of clinical benefits of lung cancer screening using LDCT for at-risk individuals
- No change in the poor outcome of lung cancer patients (5 year survival <18%)
- No alternative to current mostly palliative treatment and end of life care with escalating health care costs
- No alternative to escalating targeted drugs costs

Policy Option – Defer Decision

Consider publically funding LDCT in future when additional trials have been completed.

- Additional trials likely will not have sufficient power to negate the positive findings of NLST
- Lack of a decision is a decision to encourage opportunistic lung cancer screening without proper quality assurance or outcome evaluation

Policy Option – Organized Provincial Program

Advantages

- Improve lung cancer outcome
- Shift from mainly palliative treatment and end of life care to curative therapy
- Decrease symptom burden and hospital resource utilization

Disadvantages

- Modest start-up infrastructure costs for program implementation
- Potential harm of overdiagnosis, investigation for false-positive screen, false assurance of false negative screen: *similar to all other screening programs such as screening mammography or colonoscopy*

Synergy Between Screening & Smoking Cessation Programs

- QuitNow (database and ongoing participation)
- Current smokers ≥55 yrs randomized to standard smoking cessation program (counseling + pharmacotherapy) versus smoking cessation program + LDCT versus counseling + LDCT
- LDCT – emphysema picture + coronary artery calcification
- Cost effectiveness analysis

Lung Cancer Screening

- Shift from palliative treatment to curative treatment
- Optimize lung cancer screening pathway
  - Evaluate selection criteria for screening
  - Computer vision technology promising tools to improve scan interpretation & provide smoking cessation aid
- Integrated smoking cessation & screening program will enhance success of both