Discussion abstract 24O

Plasma microRNA in screening (Dr. U. Pastorino)

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Disclosure

- **None for this abstract**

- **General: consultant (GSK-BIO, Merck-Serono), speaker (Eli-Lilly), research funding (Astra Zeneca)**

- **Thanks to Dr. Pastorino for preview of slides**

Screening and early detection
> biomarkers

- ❑ **NLST: CT screening level I evidence**
  - o <u>**IN:**</u> current or former (quit <15 years) smokers, 55-74 years, 30 pack-year history
  - o <u>**WITH:**</u> three annual rounds of low-dose CT screening
  - ➢ <u>**THAT:**</u> a 20% decrease in lung cancer-specific mortality
- ❑ **BUT ...need to screen 320 to prevent 1 lung cancer death**

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populations at risk

false pos findings

outcome of screen-detected cancers

Screening and early detection
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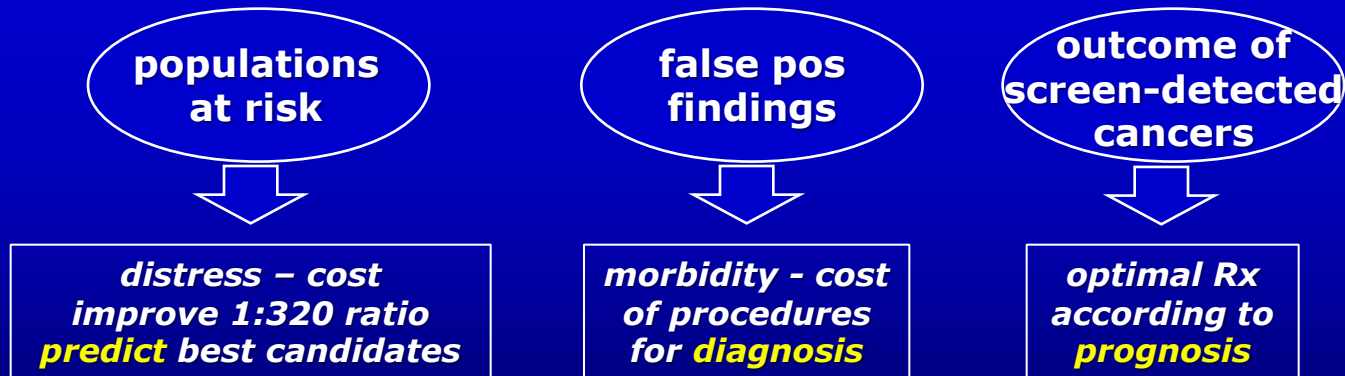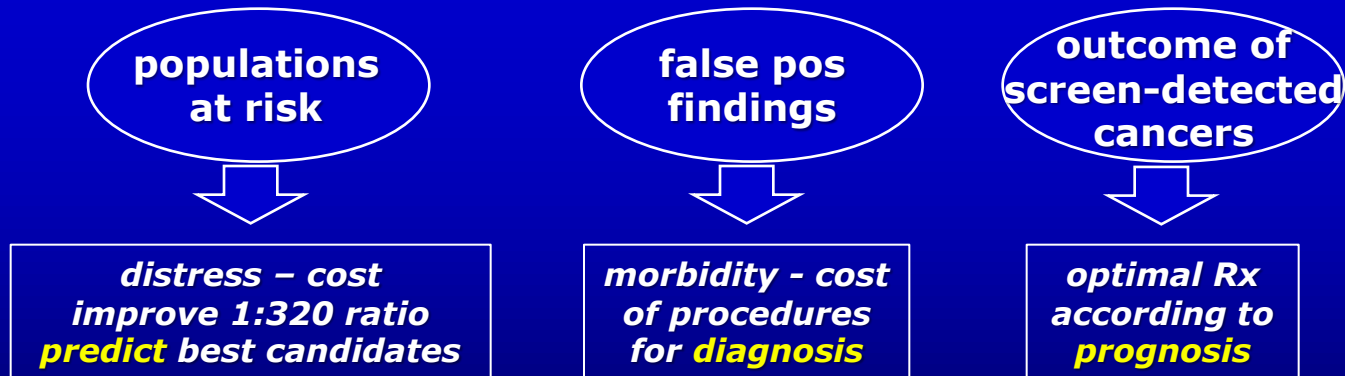| populations at risk	false pos findings	outcome of screen-detected cancers
distress – cost improve 1:320 ratio **predict** *best candidates*	*morbidity - cost of procedures for* **diagnosis**	*optimal Rx according to* **prognosis**

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Screening and early detection > biomarkers

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populations at risk	false pos findings	outcome of screen-detected cancers
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distress – cost improve 1:320 ratio *predict best candidates*	*morbidity - cost of procedures for diagnosis*	*optimal Rx according to prognosis*

"MSC has   predictive,   diagnostic &   prognostic   value"

Screening and early detection > biomarkers

❑ **Characteristics of early detection biomarkers**

❑ **"Predictive" aspect**

   o **help to improve definitions of populations at risk**

❑ **"Diagnostic" aspect**

   o **help in the DD of screen-detected nodules**

❑ **"Prognostic" aspect**

   o **help in therapy choice for best outcome of screen-detected nodules**

Screening and early detection > biomarkers

Very large number of early detection biomarker studies

❑ **Targets**

o **DNA: promoter hypermethylation, microsatellite instability, loss of heterozygosity (LOH), chromosomal aneusomy**

o **mRNA, micro RNA (miRNA)**

o **tumour-associated antibodies, antigens, proteomic profiles**

o **volatile organic compounds**

.

❑ **Specimens**

o **bronchial biopsies or lavage**

o **induced sputum**

o **buccal/nasal swabs**

o **plasma, serum, circulating tumour cells**

o **exhaled breath**

❑ **Phases**

o **early description**

o **small retrospective evidence**

o **large retrospective evidence from RCTs**

o **prospective testing**

o **large prospective validation in RCT**

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Screening and early detection > biomarkers

- ❑ **Many with high sensitivity and specificity (up to 100%) in feasibility studies**

- ❑ **None at present recommended as tests for screening**
  - ○ **lack of validation**
  - ○ **unsure if appropriate for risk individuals or very early stages**

- ❑ **Best candidates**
  - ○ **miRNAs**
    - ○ **high tissue specificity and incredible stability -> easily detectable and quantifiable in body fluids**
    - ○ **promising in work-up of LDCT detected nodules**
  - ○ **VOCs in exhaled breath**
    - ○ **non-invasive and repeatable**
    - ○ **moderate accuracy to distinguish lung cancer from controls**

Boeri et al, Proc Natl Acad Sci 108: 3713-3718, 2011
Shen et al, BMC Cancer 11: 374, 2011
Dragonieri et al, Lung Cancer 64: 166-170, 2009

Screening and early detection > biomarkers

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Screening and early detection
> defining populations at risk

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

Kovalchik et al, New Engl J Med 369:245-254, 2013

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Screening and early detection
> defining populations at risk

elcc — European Lung Cancer Conference

Time dependency analysis of diagnostic performance of MSC, at 6, 12, 18 and 24 months intervals between blood sampling and lung cancer diagnosis[1]

Months from blood sampling to lung cancer detection	SE	SP	PPV	NPV
6	83%	80%	18%	99%
12	86%	81%	22%	99%
18	86%	81%	23%	99%
24	87%	81%	25%	99%

[1] Heagerty PJ., Biometrics 2000, 2007

Screening and early detection
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➢ **MSC able to "sense" LC several years before CT detection**

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Screening and early detection
> the false positive problem

NLST	CT	XR
Positive result	18,146 (24.2%)	5043 (6.9%)
False pos result	17,497 (96.4%)	4,764 (94.5%)
Lung cancer	649 (3.2%)	279 (5.5%)

Implementation of LD-CT will be like an apple tree in fall

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Implementation of LD-CT will be like an apple tree in fall

WE HAVE TO PICK THE RIGHT APPLE

Screening and early detection
>reducing false pos: NELSON nodule approach

Table 3 NELSON follow-up protocol for non-calcified nodules at annual repeat screening

	Year 1	Year 2	Year 3
Volume	V_1	V_2	V_3
Percentage volume change: PVC (%) (solid nodules only)		$100 \times (V_2 - V_1)/V_2$	$100 \times (V_3 - V_1)/V_1$
Growth		PVC < 25%: no; PVC $\geq$ 25%: yes	PVC < 25%: no; PVC $\geq$ 25%: yes
Select lowest VDT (either VDT_v or VDT_d)			
VDT > 600 days: GROWCAT A		Annual CT year 4	Annual CT year 4
VDT 400–600 days: GROWCAT B		Annual CT year 3	Annual CT year 4
VDT < 400 days or new solid component in non-solid lesion: GROWCAT C		Refer to pulmonologist	Refer to pulmonologist

NELSON
Nederlands-Leuvens Longkanker
Screenings Onderzoek

➤ **In 1st and 2nd round of screening, 2.6% and 1.8% positive test results**

➤ **Yet, in 1st round, sensitivity was 94.6%, NPV 99.9%**

Xu et al, Lung Cancer 54: 177-184, 2006
Van Klaveren et al, N Engl J Med 361: 2221-2229, 2009

Screening and early detection
> reducing false positives

Complementary Diagnostic Performance of LDCT and MSC to Reduce False Positives

Increased specificity of identifying subjects without lung cancer

Subjects without lung cancer	TOTAL	MSC	
		High + Intermediate	Low
LDCT Administered	594	116	478
No nodule	248	49	199
Nodule diameter ≤ 5 mm	231	45	186
Nodule diameter > 5 - ≤ 10 mm	94	18	76
Nodule diameter > 10 mm	21	4	17

594 subjects in LDCT arm without lung cancer

346/594 subjects or 58% had a nodule detected by LDCT
This was reduced to 11% by MSC

115/594 subjects or 19.4% had a ≥ 5mm nodule which requires clinical action
This was reduced to 3.7% by MSC

Screening and early detection
> reducing false positives

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➢ **major reduction of nodules needing clinical action**
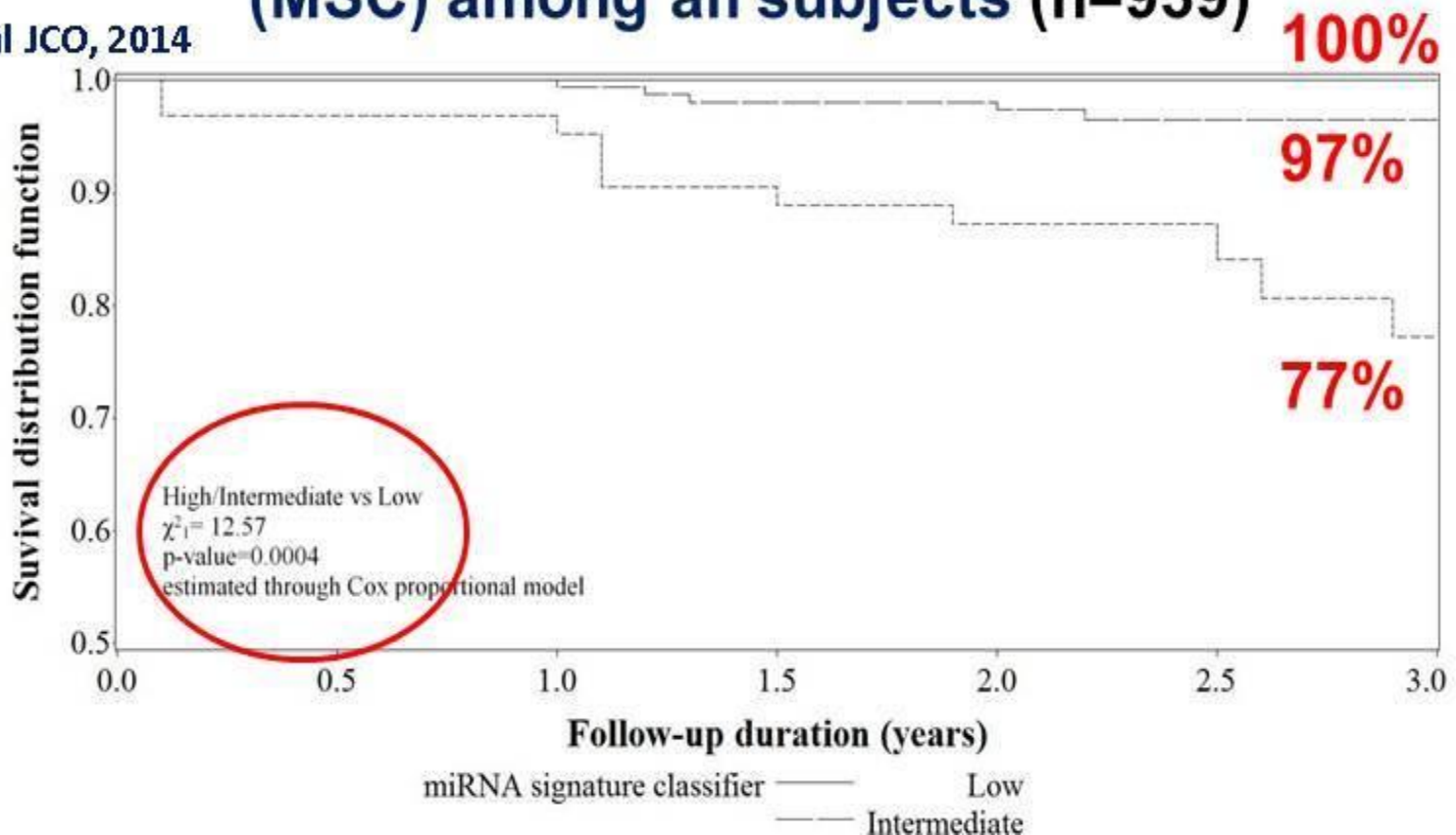
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Three-year survival from date of blood sample collection according to miRNA signature classifier (MSC) among all subjects (n=939)
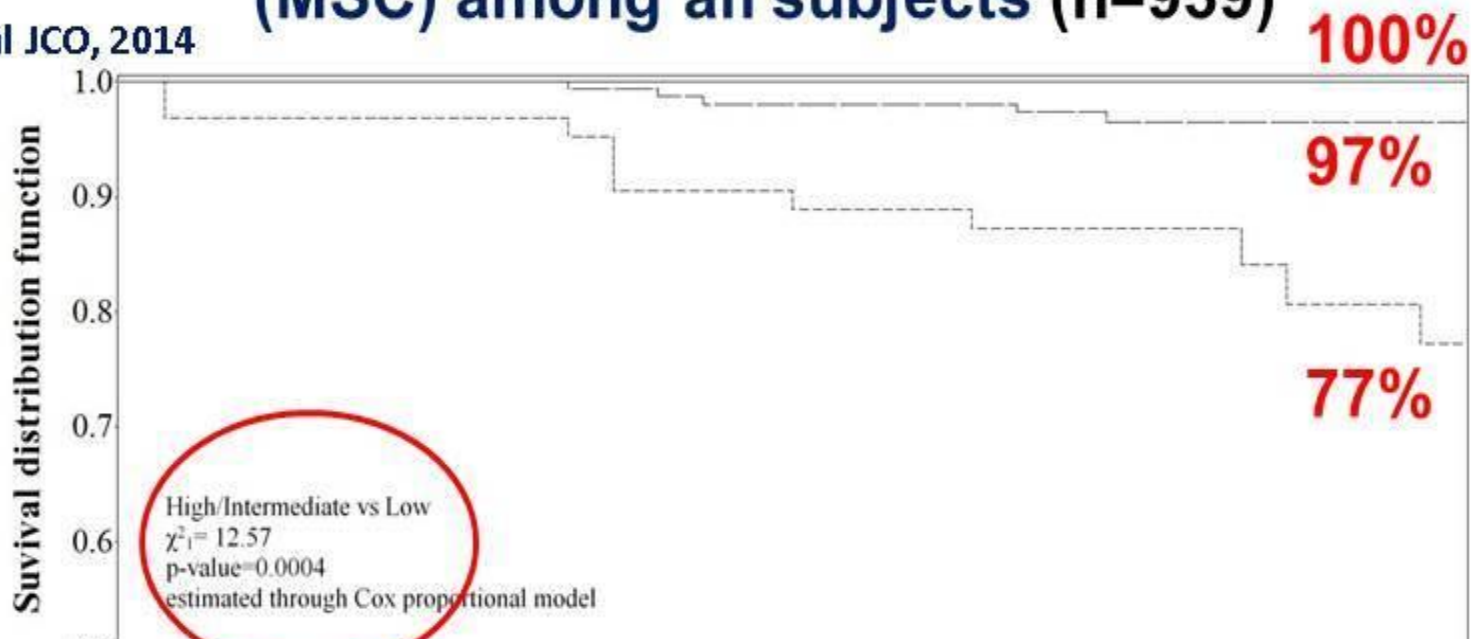
Sozzi et al JCO, 2014

High/Intermediate vs Low
$\chi^2_1 = 12.57$
p-value=0.0004
estimated through Cox proportional model

100%
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Suvival distribution function

> **prognostic classifier may help in adjuvant therapy decisions**

miRNA signature classifier —————— Low
— — Intermediate

Screening and early detection > biomarkers

❑ **Ideal early detection biomarker**

- o **permits large-scale screening**

- o **applicable on easily accessible specimens through non-invasive procedures**

- o **easy and reproducible quantification**

- o **high sensitivity and specificity**

- o **low cost**

- o **validation**

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Screening and early detection
> this miRNA work

❑ **Opportunities**

    o **modelling ± testing with more refined imaging features**

        o **2D: shape, margins, density of nodule**

        o **3D: growth pattern of nodule**

    o **validation in other cohorts**

    o **prospective demonstration of lowering of false positives, decrease in number-needed-to-screen, and further LC mortality reduction**

Thank you for your kind attention