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Clinical Utility of a Plasma-Based miRNA Signature Classifier Within Computed Tomography Lung Cancer Screening: A Correlative MILD Trial Study

Ugo Pastorino, M.D.

26-29 March 2014, Geneva, Switzerland

Organisers

IASLC International Association for the Study of Lung Cancer

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

NLST:

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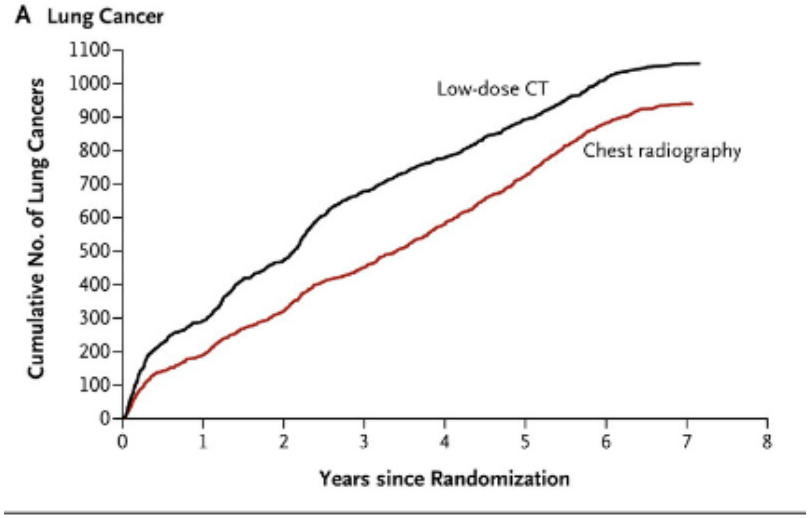

randomized screening trial
53,454 persons
3 rounds of LDCT annual screening vs CxR

20% reduction of lung cancer mortality
7% reduction all cause mortality

24.2% positive subjects
96.4% of these false positive

need to screen 320 subjects to prevent 1 lung cancer death

N Engl J Med 2011;365:395-409

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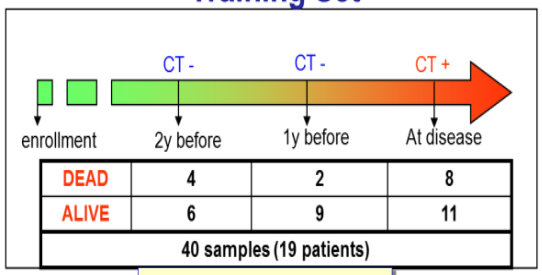
miRNA Signature Discovery & Initial Validation

Four miRNA ratios signatures (24 miRNAs)
Used to develop a single miRNA Classifier

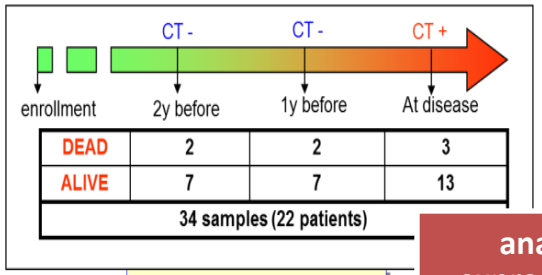
Training Set



DEAD	4	2	8
ALIVE	6	9	11
40 samples (19 patients)			

CONTROLS
5 POOLS
(28 individuals)

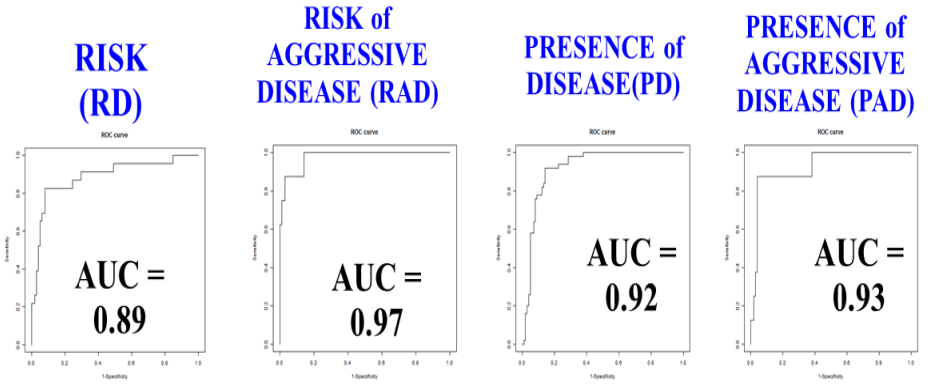
Validation Set



DEAD	2	2	3
ALIVE	7	7	13
34 samples (22 patients)			

CONTROLS
10 POOLS
(54 individuals)

analysis of relative expression ratios of 100 miRNAs
(starting from 378) detectable in plasma



Generation of the three-level miRNA signature classifier (MSC)

MSC	RD	RAD	PD	PAD
Low risk	-	-	-	-
Intermediate risk	+	-	+/-	-
	+/-	-	+	-
High risk	+/-	+	+/-	+/-
	+/-	+/-	+/-	+

PNAS

MicroRNA signatures in tissues and plasma predict development and prognosis of computed tomography detected lung cancer

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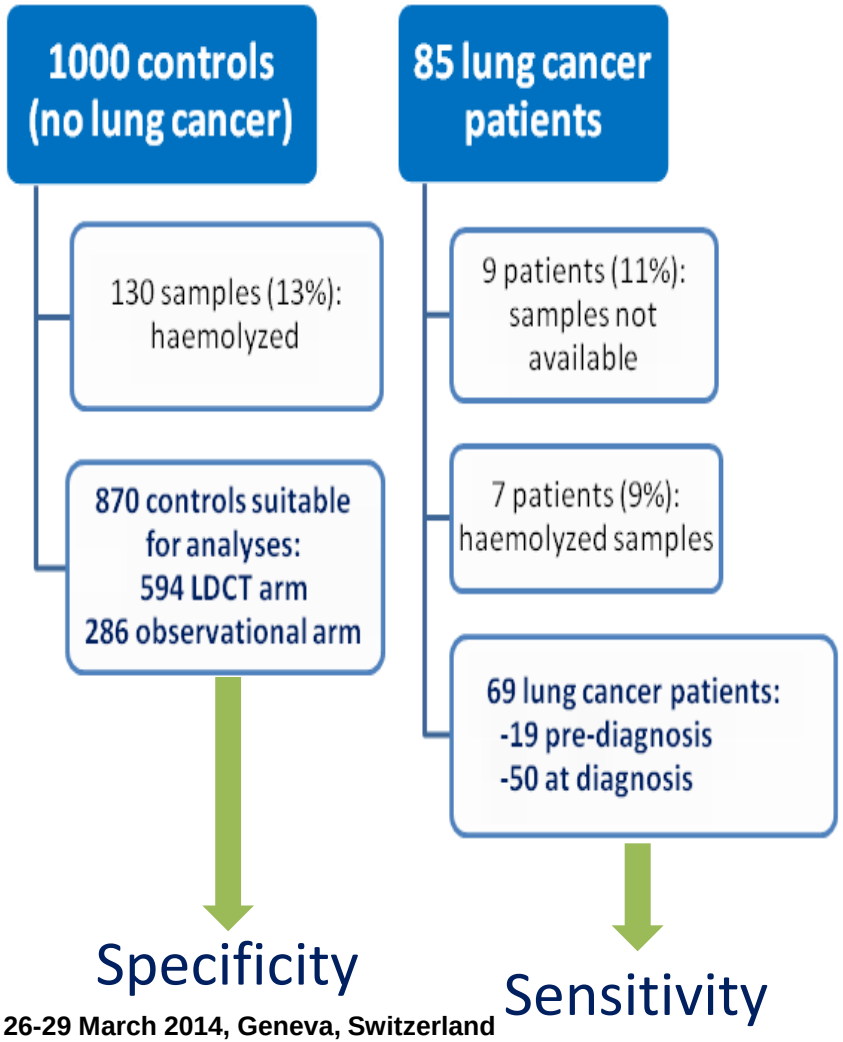
Clinical Validation Study – Multicentric Italian Lung Detection (MILD) Trial (2005-2012) [1]



- Specificity
  - 870 subjects **in both arms which did not have cancer** were examined to determine specificity of MSC
  - 594 subjects **in the LDCT arm which did not have cancer** were examined to assess the ability of MSC to reduce the false positive rate of LDCT
- Sensitivity

  69 patients **with lung cancer** from both arms of the trial were used to determine the sensitivity of MSC to detect cancer

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[1]Sozzi et al JCO, 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Clinical Utility of a Plasma-Based miRNA Signature Classifier Within Computed Tomography Lung Cancer Screening: A Correlative MILD Trial Study

Gabriella Sozzi, Mattia Boeri, Marta Rossi, Carla Verri, Paola Suatoni, Francesca Bravi, Luca Roz, Davide Conte, Michela Grassi, Nicola Sverzellati, Alfonso Marchiano, Eva Negri, Carlo La Vecchia, and Ugo Pastorino

Conclusion

This large validation study indicates that MSC has predictive, diagnostic, and prognostic value and could reduce the false-positive rate of LDCT, thus improving the efficacy of lung cancer screening.

J Clin Oncol 32.

Overall Diagnostic Performance of MSC[1]

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	Total	MSC (risk of lung cancer)		
		High (%)	Intermediate (%)	Low (%)
All subjects	939	63 (6.7)	159 (16.9)	717 (76.4)
No lung cancer	870	32 (3.7)	130 (14.9)	708 (81.4)
Lung cancer	69	31 (44.9)	29 (42.0)	9 (13.0)

Sensitivity: 87%
Specificity: 81%
NPV: 99%

MSC identified 8 of 9 **interval cancers** undetected by LDCT

MSC detected 9 of 11 (82%) lung cancers that occurred in the **observational arm**

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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

[1]Sozzi et al JCO, 2014

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MSC &Lung Cancer Stage

	Total	MSC (risk of lung cancer)		
		High (%)	Intermediate (%)	Low (%)
Lung cancer deaths[+]	19	12 (63.2)	6 (31.6)	1 (5.3) °
Lung cancer, stage I[‡]	37	14 (37.8)	19 (51.4)	4 (10.8)
Lung cancer, stage II-III[‡]	12	5 (41.7)	4 (33.3)	3 (25.0)
Lung cancer, stage IV[‡]	19	11 (57.9)	6 (31.6)	2 (10.5)

° plasma sample obtained 30 months before disease detection

increasing proportion of lung cancer deaths associated with Low, Intermediate and High MSC risk groups (p=0.0336)

MSC risk groups are not significantly associated with varying tumor stage (p=0.40) and histology (p=0.45)

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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

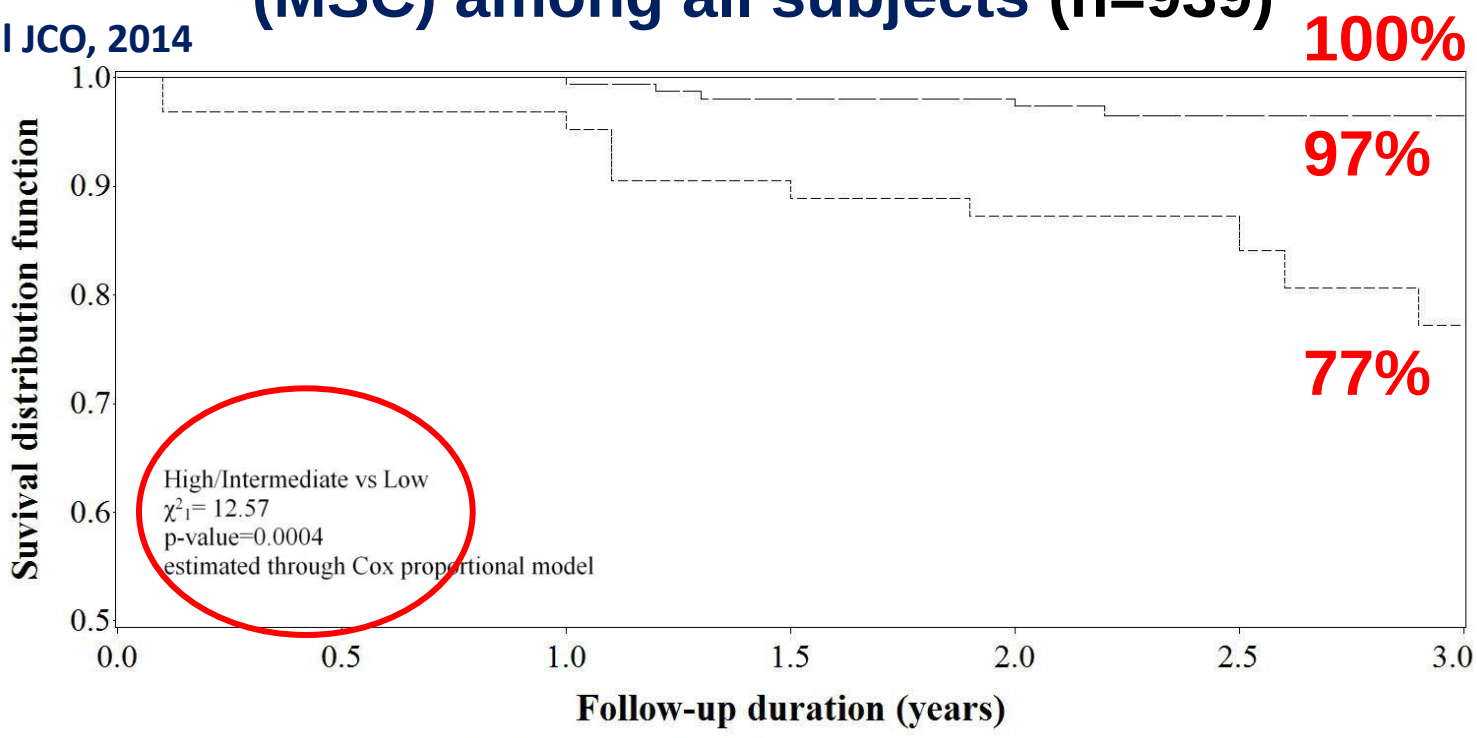
594 subjects in LDCT arm without lung cancer

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

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

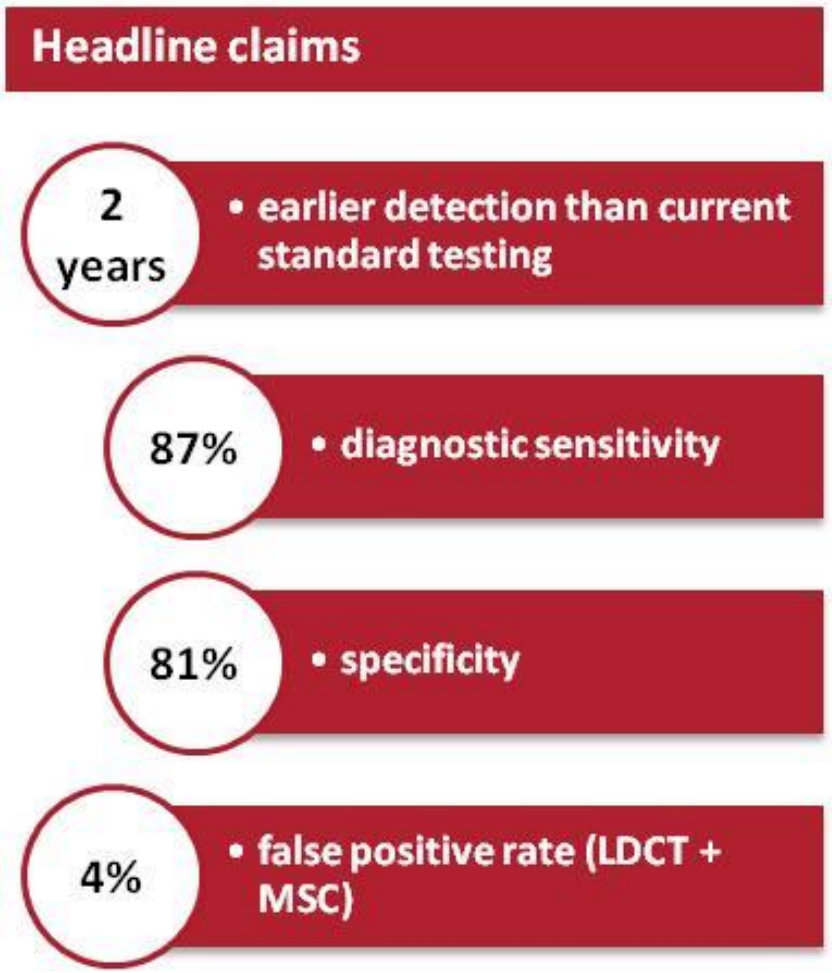


MiRNA signature classifier		baseline	1 year	2 years	3 years
High					
	Events*	0	2	8	11
	Number at risk	63	61	53	22
Intermediate					
	Events*	0	0	3	5
	Number at risk	159	156	149	39
Low					
	Events*	0	0	0	0
	Number at risk	717	715	710	83

*No death occurred due to other causes in lung cancer-free subjects.

MSC Performance

- MSC detects up to two years before a tumor may be found by LDCT scans
- MSC performance
  - determine the likelihood of a patient developing lung cancer with 87% sensitivity and 81% specificity.
  - identify high-risk patients, revealing both the presence and aggressiveness of the disease, and who is at risk of developing it.
  - false positive rate of only 4% (when used together with LDCT) compares very favorably with 96.4% in LDCT scans alone, the current standard in lung cancer detection.
  - Follow modulation of miRNA signatures in blood of patients at different stages in their lung cancer history (study in progress).



Conclusions

- LDCT screening has proven to reduce LC mortality
- False positive results are frequent & PPV is low
- Circulating miRNA test has diagnostic & prognostic value
- Combined use of LDCT & miRNA may improve performance
- Large-scale prospective validation studies are needed

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