NEUE BIOMARKER FÜR DIE FRÜHERKENNUNG

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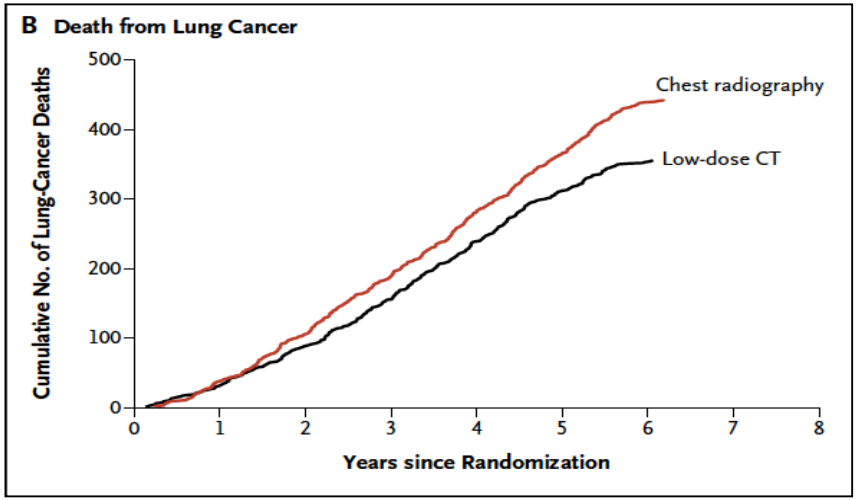
LungenClinic Grosshansdorf

Airway Research Center North (ARCN)

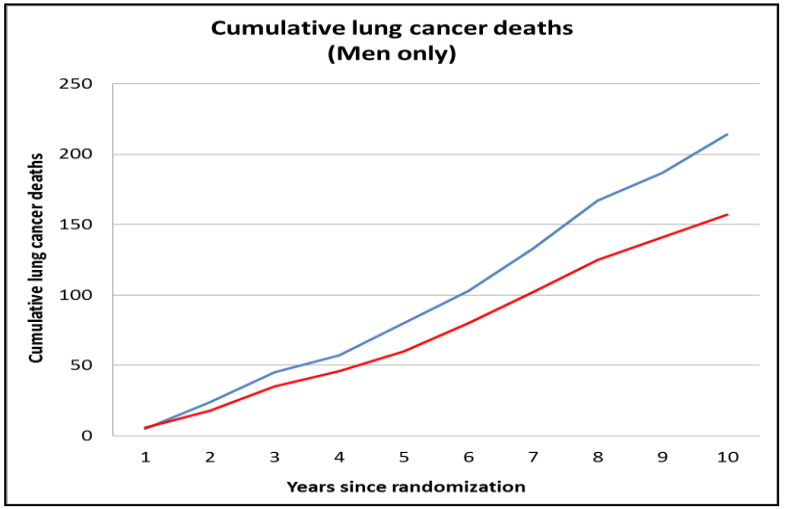
THEMA 1

SCREENING – DIE GUTE BOTSCHAFT

Mortalität Lungenkarzinom



Mortalität Lungenkarzinom (Männer)



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NLST Research Team, NEJM 20111; de Koning H et al, WCLC 2018

SCREENING – DAS PROBLEM

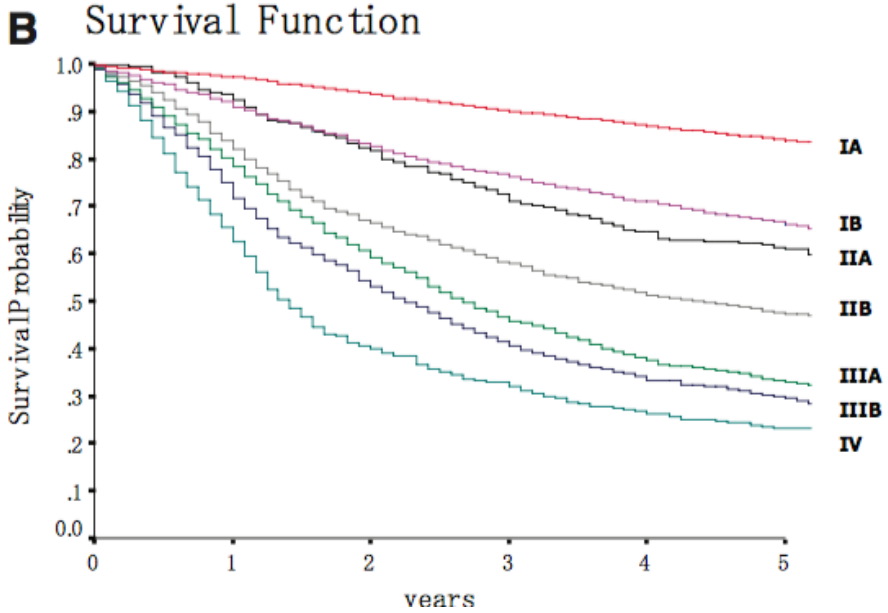
NLST	NELSON
24.2% positive Befunde	2.7% positive Befunde
davon	davon
96.4% Falsch positiv	60% Falsch positiv

THEMA 2

LUNGENCLINIC
GROSSHANSDORF

EIN GRUNDSÄTZLICHES PROBLEM IN DER THORAXONKOLOGIE

Trotz kurativem Ansatz begrenzte Prognose



12.620 resected patients

Stage (p)	5 year OS rate
Ia	83.9%
Ib	66.3%
IIa	61.0%
IIb	47.4%
IIIa	32.8%
IIIb	29.6%
IV	23.1%

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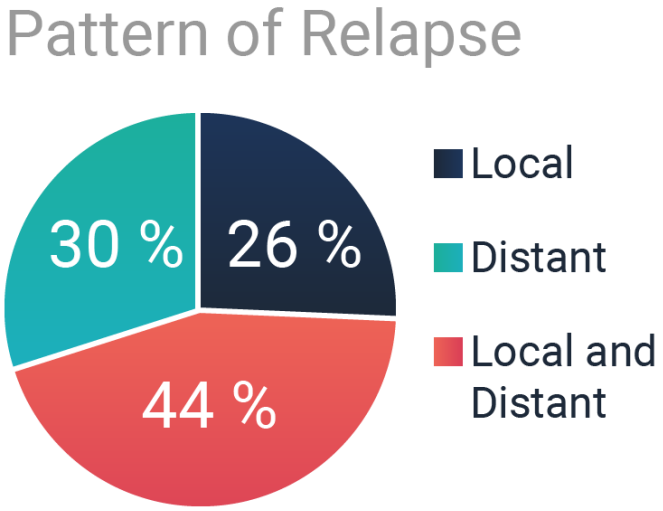
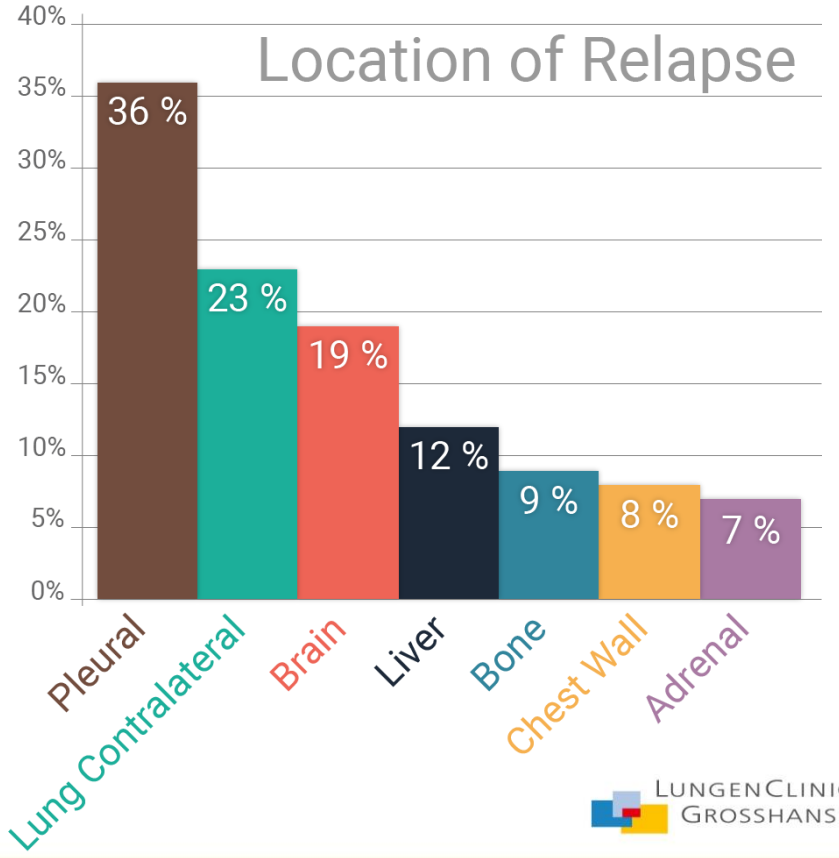
Asamura H et al, J Thorac Oncol 2008; 3: 46-52

PATTERNS OF RELAPS IN RESECTED NSCLC

- 257 Relapses in 1445 resected patients





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Lou Feiran et al. J Thor Cardiovas Surg 2013; 145: 75-82

WIE KÖNNEN WIR DAS SCREENING EFFEKTIVER MACHEN?

- Bessere Definition von Risikopatienten
- Bessere Diagnostikalgorithmen
- Nutzung von KI (globale Informationsnetze)
- ...
- Kombination mit alternativen Risikomarkern

5 GOLDENE PRINZIPIEN FÜR BIOMARKER BEIM LUNGENKARZINOM

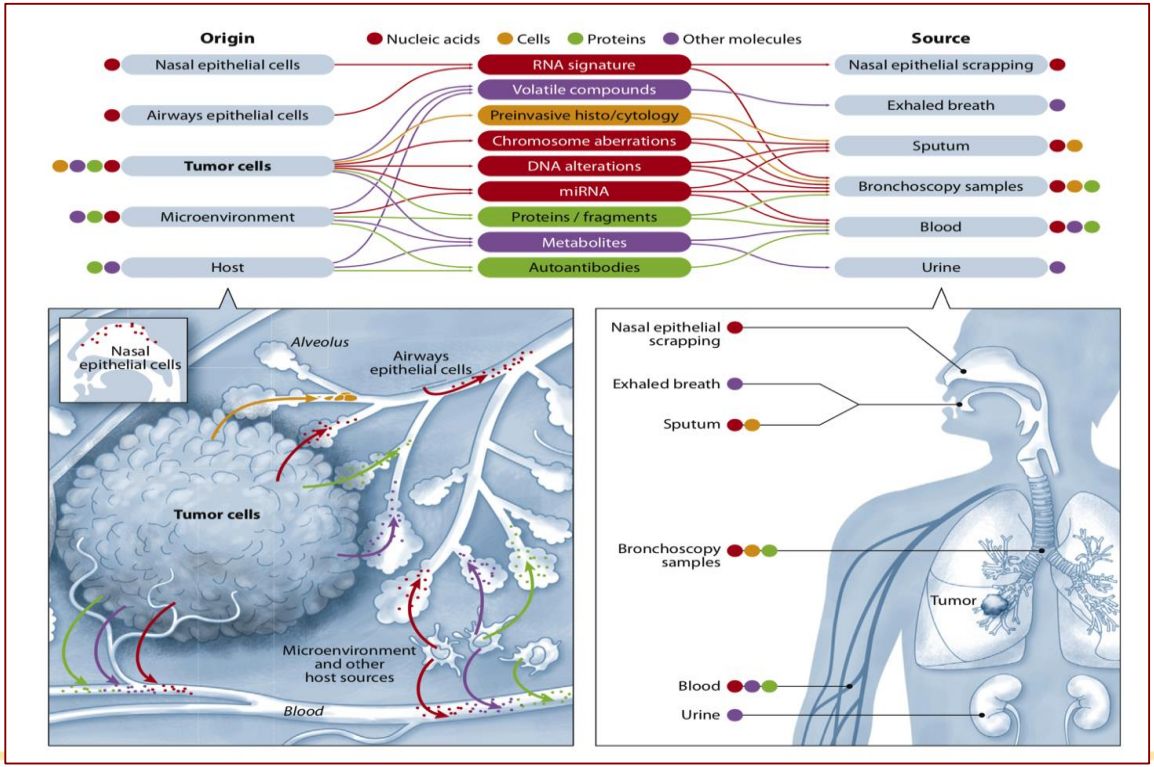
SEIJO LM ET AL, JTO 2018

1. Ein geeignetes Target (idealerweise)
2. Stabiler Marker
3. Klar definierte Validierung + Reproduzierbarkeit
4. Prospektive Testung in verschiedenen Kohorten
5. Randomisierte Testung zur Bestätigung der Überlegenheit

Table 1. Principles to Optimize the Research on Development of Lung Cancer Biomarkers

• Principle 1: Select the molecular approach guided by the intended use
• Principle 2: Look for stable analytes that are minimally dependent on storage time, temperature, pH, and enzymatic or oxidative stress
• Principle 3: The analyte should be measured with accuracy, precision, and robustness. Thoroughly test for reproducibility across sources of variability, laboratories, conditions, etc.
• Principle 4: Test the biomarker in multiple cohorts in the clinical context in which it will be considered for use (screening, nodule management). Case-control studies are discouraged, whereas prospective cohort studies and, eventually, observational registries are favored though less convenient
• Principle 5: Conduct the tests in larger cohorts to demonstrate superiority over standard of care, reduction of cost, and reduction of false-positive and false-negative rates

BIOMARKER ZUR FRÜHERKENNUNG BEIM LUNGENKARZINOM



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Seijo LM et al, JTO 2018

LAUFENDE STUDIEN

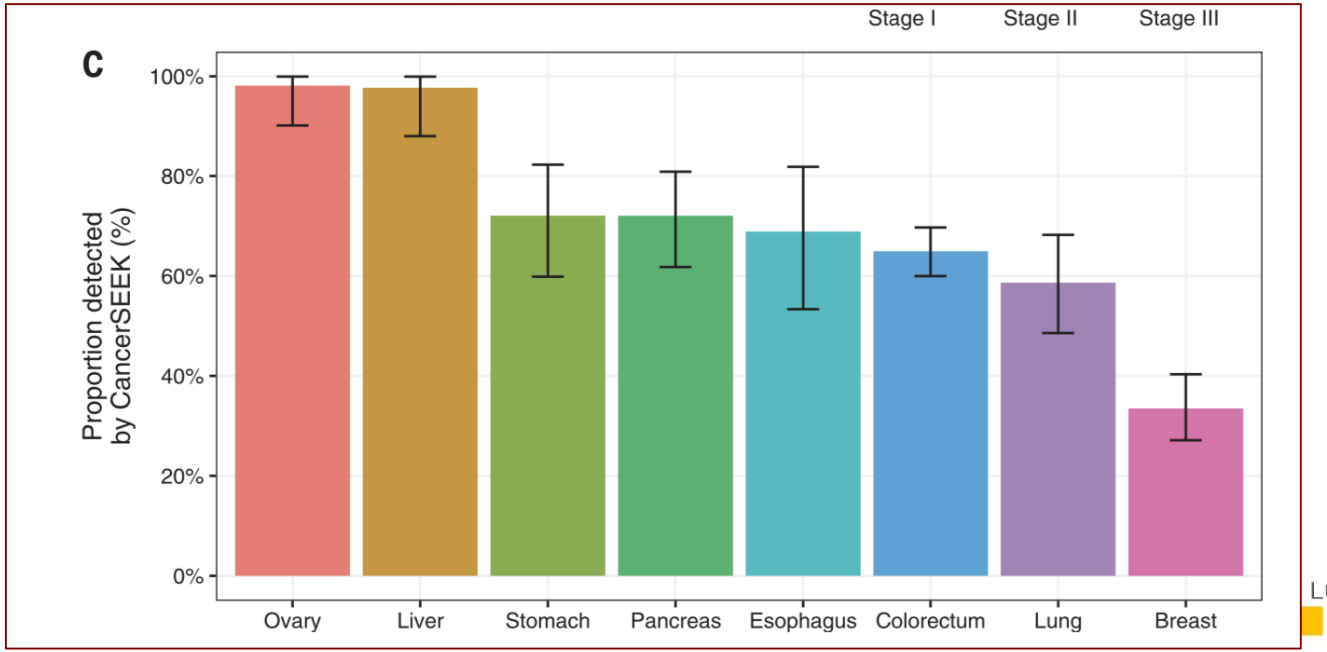
SEIJO LM, JTO 2018

Candidates	Biomarker	Target	Phase 1 Discovery, prediction	Phase 2 Assay validation	Phase 3 Retrolongitudinal	Phase 4 Clinical validation*	Phase 5 Clinical utility	References	Trial
SERUM/PLASMA									
Specific proteins/autoantibodies	Three proteins (CEA, CA-125, and CYFRA 21–1) and 1 AAb (NY-ESO-1)	RMS						40	
	Two proteins (LG3BP and C163A) and clinical features	DIPN						59	NCT01752114
	Seven AAbs (p53, NY-ESO-1, CAGE, GBU4-5, SOX2, HuD, and MAGE A4)	RMS						33,34	NCT01700257
		DIPN						38	
	Six proteins (CEA, CA-125, SCC, CYFRA 21–1, NSE, and proGRP)	DIPN						116	
	Complement fragment C4d	RMS						41	
		DIPN						42	
MiRNA	Ratios among 24 miRNAs	RMS						44, 117	NCT02247453
		DIPN							
	Signature of 13 microRNA + 6 for normalization	RMS						69, 118, 119	COSMOS II trial
		DIPN							
	Signature of 2 microRNA	DIPN						120	
DNA methylation	SOX2 and PTGER4 methylation	DIPN						121	
Circulating tumor nucleic acids	Circulating tumor DNA; NGS technology	RMS						113	NCT02889978
	Circulating tumor DNA; NGS technology	DIPN						122	
	Circulating tumor DNA; Ion Torrent DNA Sequencing technology	DIPN						123	
	Circulating tumor DNA; TEC-Seq technology	RMS						124	
	Signature of 29 genes (RNA)	DIPN						125	
	ctDNA mutation and proteins (CA-125, CEA, CA19-9, PRL, HGF, OPN, MPO, and TIMP-1)	DIPN						51	
TUMOR/AIRWAY EPITHELIUM									
Chromosome aberrations	Chromosome regions copy number or fusions (FISH)	DIPN						126	
mRNA gene expression classifier	Twenty three gene classifier	DIPN							NCT01309087 NCT00746759
SNPs	20 SNPs for COPD and clinical features	RMS						127	
SPUTUM, BREATH AND URINE									
DNA methylation	SHOX2 and RASSF1A methylation	RMS						128	
MiRNA	Signature of 3 microRNA	DIPN						129	
Exhaled breath	VOC- Nanoparticle Biometric Tagging (NBT)	DIPN							
	VOC- Field Asymmetric Ion Mobility Spectrometry (FAIMS)								NCT02612532
Tumor cells	>700 morphological features (by Cell CT)	RMS							
		DIPN							
	Buccal nanocytology	RMS						130	
	Porphyrin differential uptake by tumor cells	RMS						131	
Unrine markers	Metabolites	RMS						84	

RMS: risk management in screening context; DIPN: diagnosis of indeterminate pulmonary nodules; *DECAMP-1 and DECAMP-2 trials (NCT01785342 and NCT02504697) are currently recruiting patients in order to test some of these biomarkersAAB Autoantibody.

CANCER SEEK – EIN BEISPIEL

Kombinierte Testung von zirkulierenden Proteinen und Mutationen an 1005 Patienten mit frühen Karzinomen



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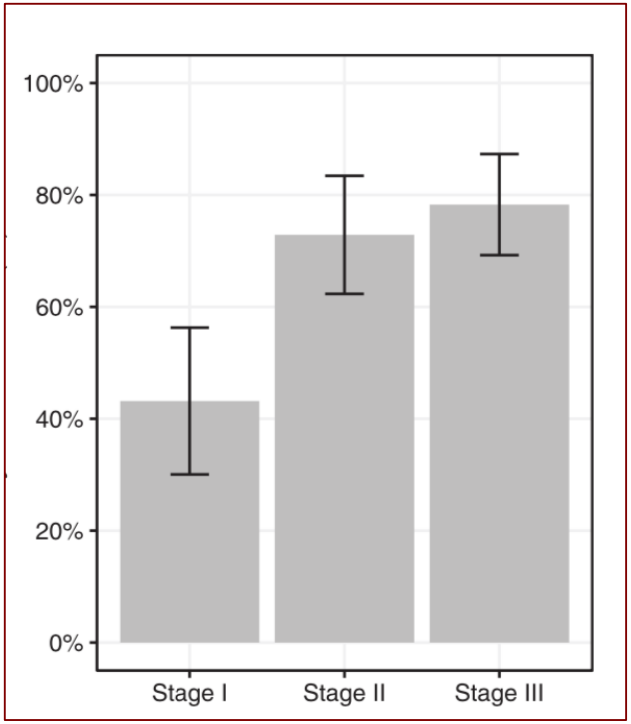
Cohen J et al, Science 2018

CANCER SEEK UND STADIEN



LUNGENCLINIC GROSSHANSDORF

Cohen J et al, Science 2018

Blood microRNA assay and LDCT reduce unnecessary LDCT repeats in lung cancer screening: results of bioMILD trial

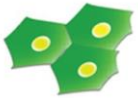
Ugo Pastorino,
Fondazione IRCCS Istituto Nazionale dei Tumori
Milan, Italy

Origin of blood the 24 BioMILD microRNAs

Lung cancer

Cluster miR-17-92
miR-21
miR-106a
miR-320
miR-660

Endothelial



miR-126

Fibroblasts

miR-145
miR-221

Skeletal MC

miR-320
cluster miR-17-92
miR-106a
miR-133a
miR-221

Smooth MC

miR-28-3p
miR-145

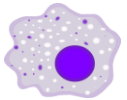
Lymphocytes

miR-92a
miR-101
miR-30b

Monocytes

miR-197
miR-660

Macrophages



miR-19b
miR-21
miR-140-5p
miR-197
miR-660

Granulocytes

miR-19b
miR-140-5p
miR-142-3p
miR-148a
miR-486-5p

Platelets

miR-17
miR-28-3p
miR-126
miR-145
miR-486-5p
miR-451

Hematopoietic:

miR-16
miR-140-3p

less than 20% from LC cells

BioMILD trial: AIMS

- evaluate the utility of blood microRNA and LDCT for prediction of individual LC risk
- assess the feasibility and safety of longer screening intervals in subjects with double negative baseline LDCT and microRNA
- reveal potential damage of 3-year LDCT interval: stage I LC, resection rates, interval cancer

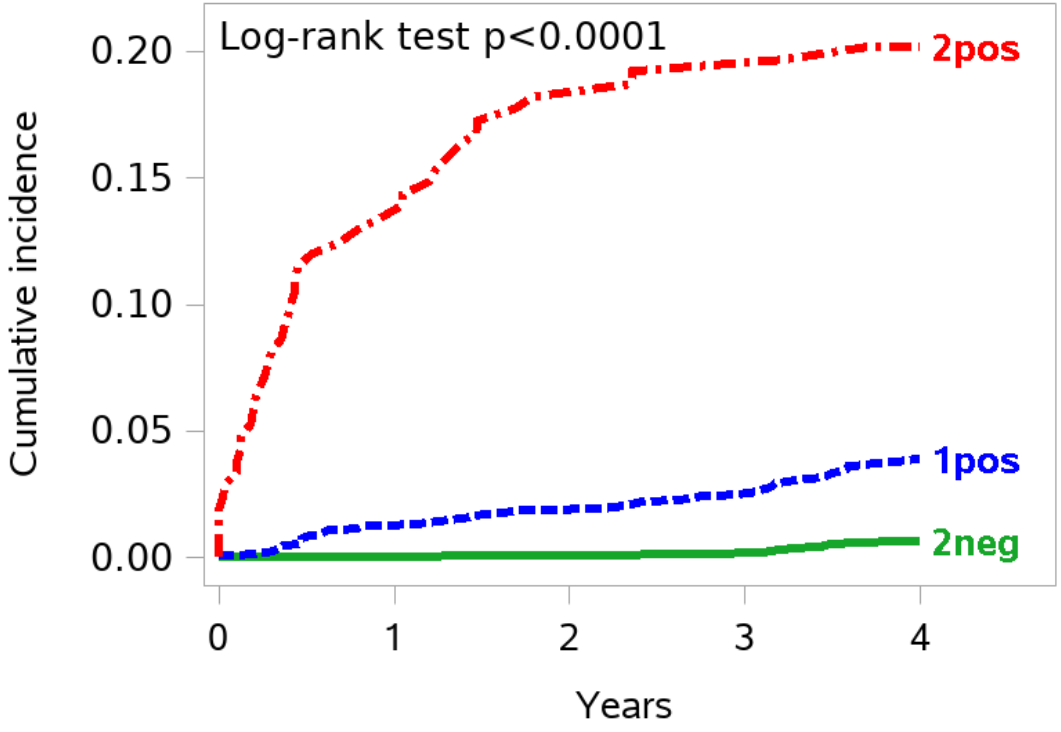
Risk profile	2neg	1pos	2pos
LDCT	0-112 mm^3 negative	≥ 113 mm^3 Ind / pos	≥ 113 mm^3 Ind / pos
	AND	OR	AND
miRNA	low	Interm / high	Interm / high

LDCT interval

	3 years	1 year	3 - 6 mos
LDCT	0-112 mm^3 negative	113-260 mm^3 indeterminate	>260 mm^3 positive
	AND	OR	OR
miRNA	low	intermediate	high

MILD bioLD
Multicentric Italian Lung Detection
Progetto multicentrico per la diagnosi precoce del tumore polmonare

Lung cancer incidence

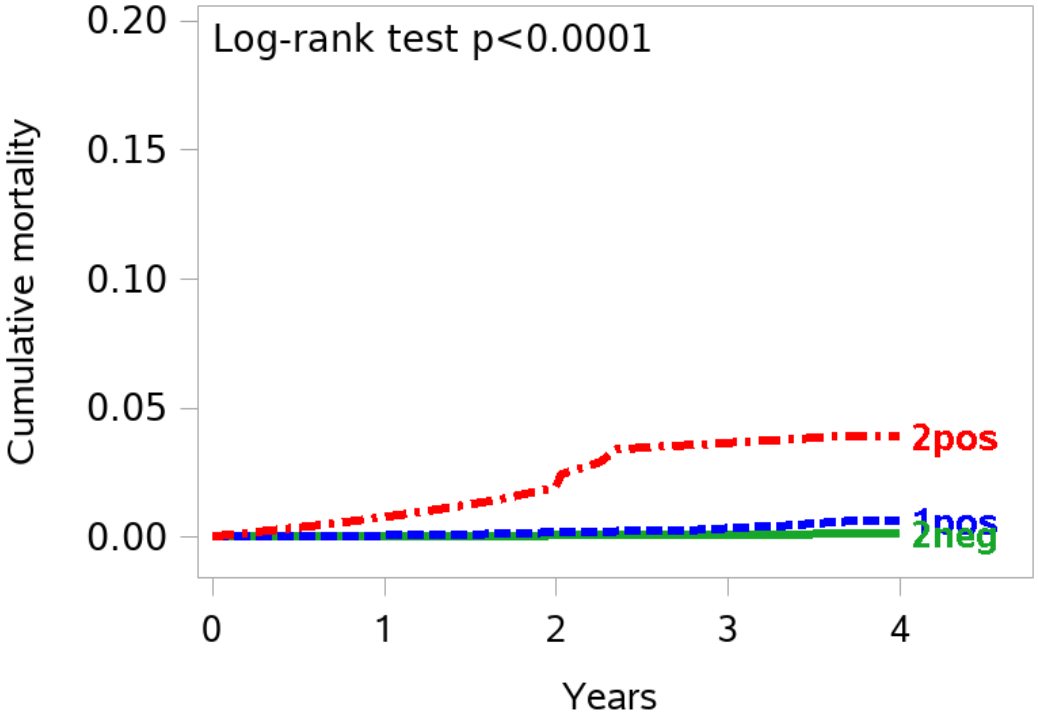


	Lung Cancer incidence HR* (95%CI)
2neg	**1.00** (ref.)
1pos	**5.96** (3.38-10.52)
2pos	**36.64** (20.31-66.11)

* Adjusted for age, sex and pack-years.

Log-rank test 2neg vs. 1pos	<0.0001
Log-rank test 1pos vs. 2pos	<0.0001

Lung cancer mortality



	Lung Cancer mortality HR* (95%CI)
2neg	**1.00** (ref.)
1pos	**4.67** (1.26-17.24)
2pos	**32.24** (8.55-121.60)

* Adjusted for age, sex and pack-years.

Log-rank test 2neg vs. 1pos	0.0103
Log-rank test 1pos vs. 2pos	<0.0001

EIN NORDDEUTSCHES PROJEKT IN ENTWICKLUNG

Hanse – Studie: Coming soon...

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UND WAS GIBT ES ZUR REZIDIVERKENNUNG?

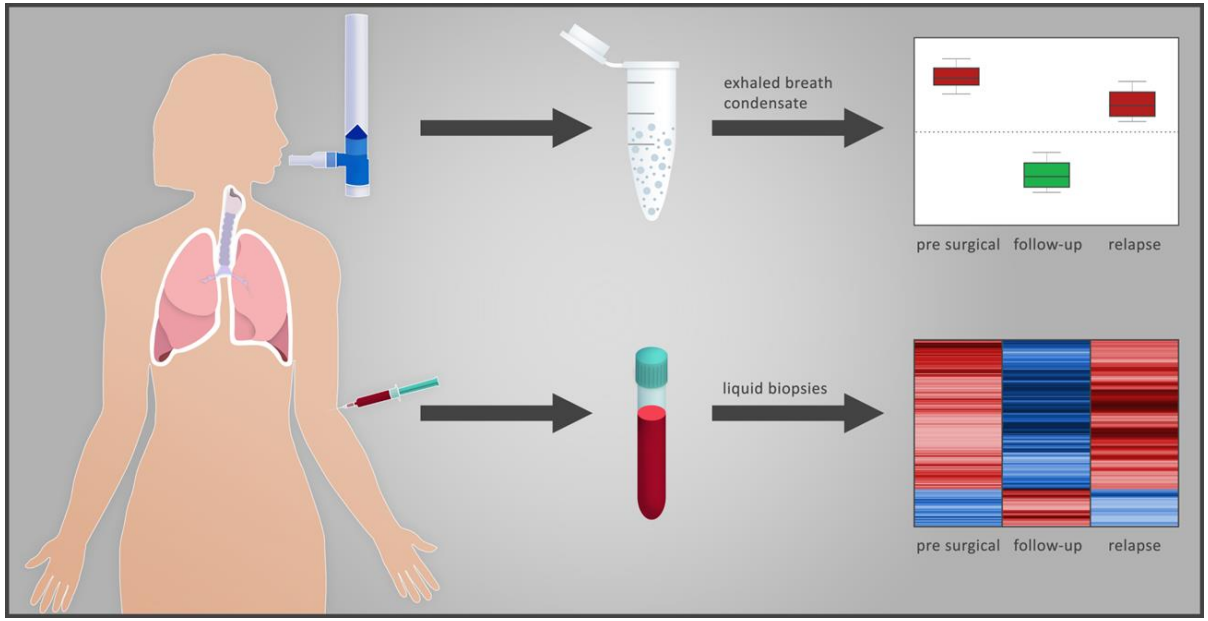
EMoLung – Concept:
Monitoring of NSCLC patients based on liquid biopsies and exhaled breath condensates

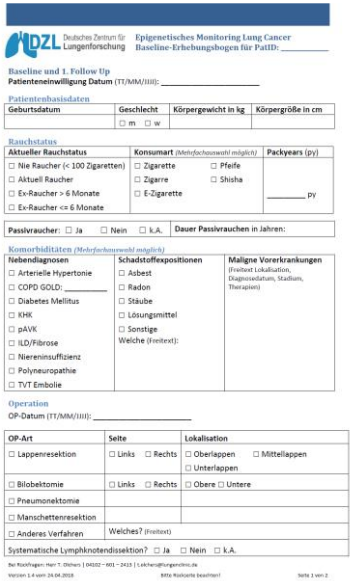
Martin Reck
On behalf of the DZL Lung Cancer Working Group

EMoLung-Concept

Objectives:

- Improvement of disease control by extension of conventional imaging strategies
- Generation of a well characterized patient cohort (Stage I, II, IIIA+B)
- Development of an algorithm allowing the detection of early relapse → early detection of lung cancer





Epigenetisches Monitoring Lung Cancer
Baseline-Erhebungsbogen für PatID: _____

Baseline und 1. Follow Up
Patienteneinwilligung Datum (TT/MM/JJJJ): _____

Patientenbasisdaten

Geburtsdatum	Geschlecht	Körpergewicht in kg	Körpergröße in cm
	☐ m ☐ w		

Rauchstatus

Aktueller Rauchstatus	Konsumart (Mehrfachauswahl möglich)	Packyears (py)
☐ Nie Raucher (< 100 Zigaretten)	☐ Zigarette ☐ Pfeife	
☐ Aktuell Raucher	☐ Zigarre ☐ Shisha	
☐ Ex-Raucher > 6 Monate	☐ E-Zigarette	_____ py
☐ Ex-Raucher <= 6 Monate		

Passivraucher: ☐ Ja ☐ Nein ☐ k.A. | Dauer Passivrauchen in Jahren:

Komorbiditäten (Mehrfachauswahl möglich)

Nebendiagnosen	Schadstoffexpositionen	Maligne Vorerkrankungen (Freitext Lokalisation, Diagnosedatum, Stadium, Therapien)
☐ Arterielle Hypertonie	☐ Asbest	
☐ COPD GOLD: _____	☐ Radon	
☐ Diabetes Mellitus	☐ Stäube	
☐ KHK	☐ Lösungsmittel	
☐ pAVK	☐ Sonstige	
☐ ILD/Fibrose	Welche (Freitext):	
☐ Niereninsuffizienz		
☐ Polyneuropathie		
☐ TVT Embolie		

Operation
OP-Datum (TT/MM/JJJJ): _____

OP-Art	Seite	Lokalisation
☐ Lappenresektion	☐ Links ☐ Rechts	☐ Oberlappen ☐ Mittellappen ☐ Unterlappen
☐ Bilobektomie	☐ Links ☐ Rechts	☐ Obere ☐ Untere
☐ Pneumonektomie		
☐ Manschettenresektion		
☐ Anderes Verfahren	Welches? (Freitext)	

Systematische Lymphknotendissektion? ☐ Ja ☐ Nein ☐ k.A.

Bei Rückfragen: Herr T. Dichen | 04102 – 601 – 2415 | t.eichen@lungenclinic.de
Version 1.4 vom 24.04.2018 Bitte Rückseite beachten! Seite 1 von 2

Targets of EBCs

Role of GATA6 and NKX2-1 in lung cancer

FOXA2 regulates EMT and invasion in human lung cancer cells (Tang et al, Cell Res 2011)

Nkx2-1 controls lung ADC differentiation and restricts metastatic ability (Winslow et al, Nature 2011)

Focal amplification of *NKX2-1* (14q13.3) in human ADC (Weir et al, Nature 2007)

GATA6 is strongly expressed in colon, pancreatic and ovarian cancers (Caslini et al, Oncogene 2006; Zhong et al, Plos One 2011; Belaquli et al, Neoplasia 2010))

Cytoplasmic accumulation of NKX2-1 in human lung cancers (Fujita et al, Lung cancer 2003)

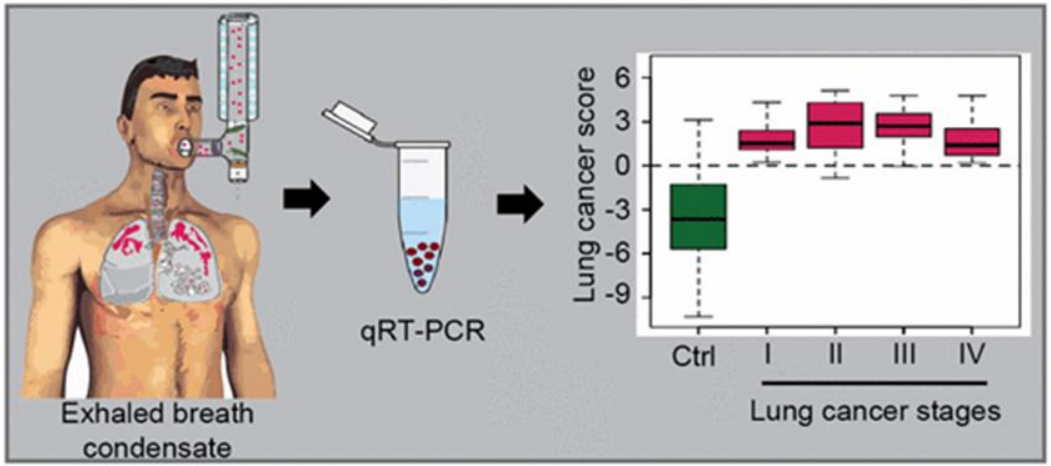
GATA6 promoter is not methylated in human lung caners (Gou et al, Clin Cancer Res, 2004)

Nkx2-1 enhances proliferation and angiogenesis (Pelosi G, Am J Surg Pathol. 2001; Puglisi et al., Mod Pathol 1999; Kwei et al, Oncogene 2008)

Nkx2-1 haploinsufficiency induces mucinous adenocarcinoma of the lung (Maeda et al, JCI 2012)

EMoLung-Concept: Monitoring of NSCLC patients

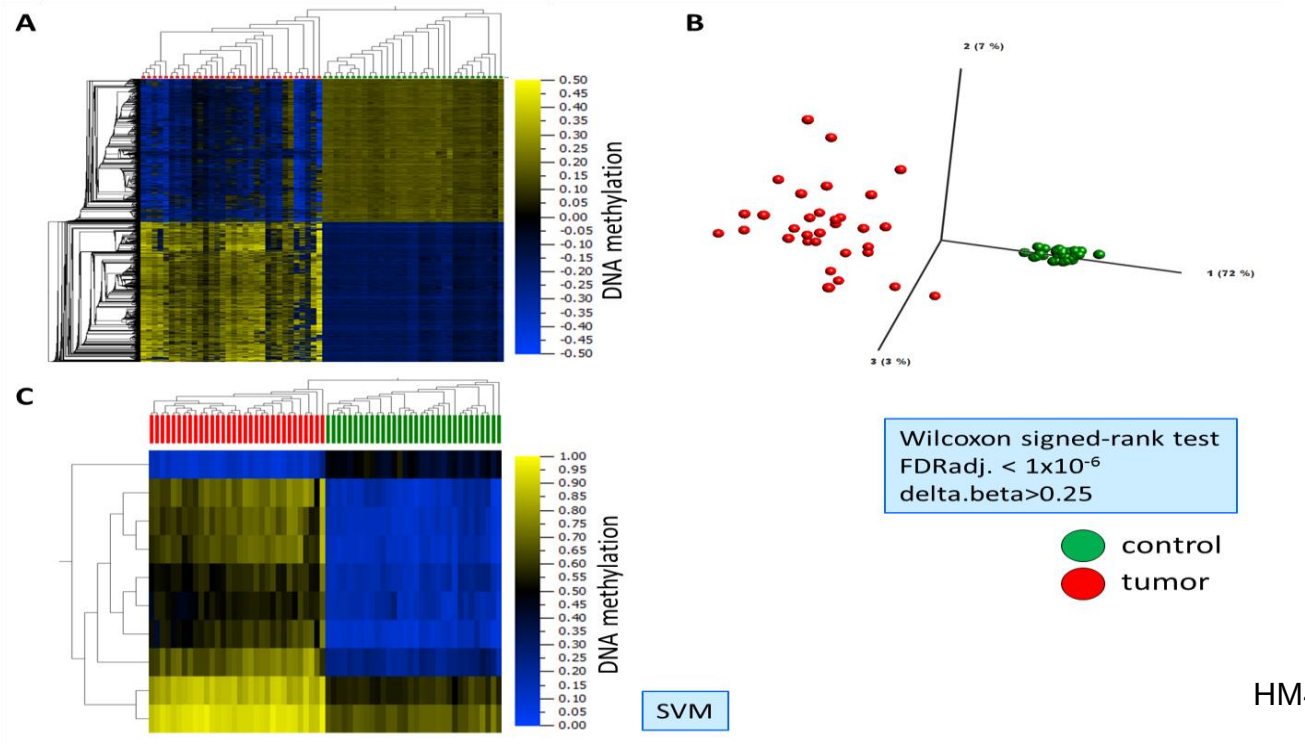
NON-INVASIVE LUNG CANCER DIAGNOSIS BY DETECTION OF RNA-ISOFORMS IN EXHALED BREATH CONDENSATE



- **LC score – a useful tool for the detection of early stage Lung Cancer**

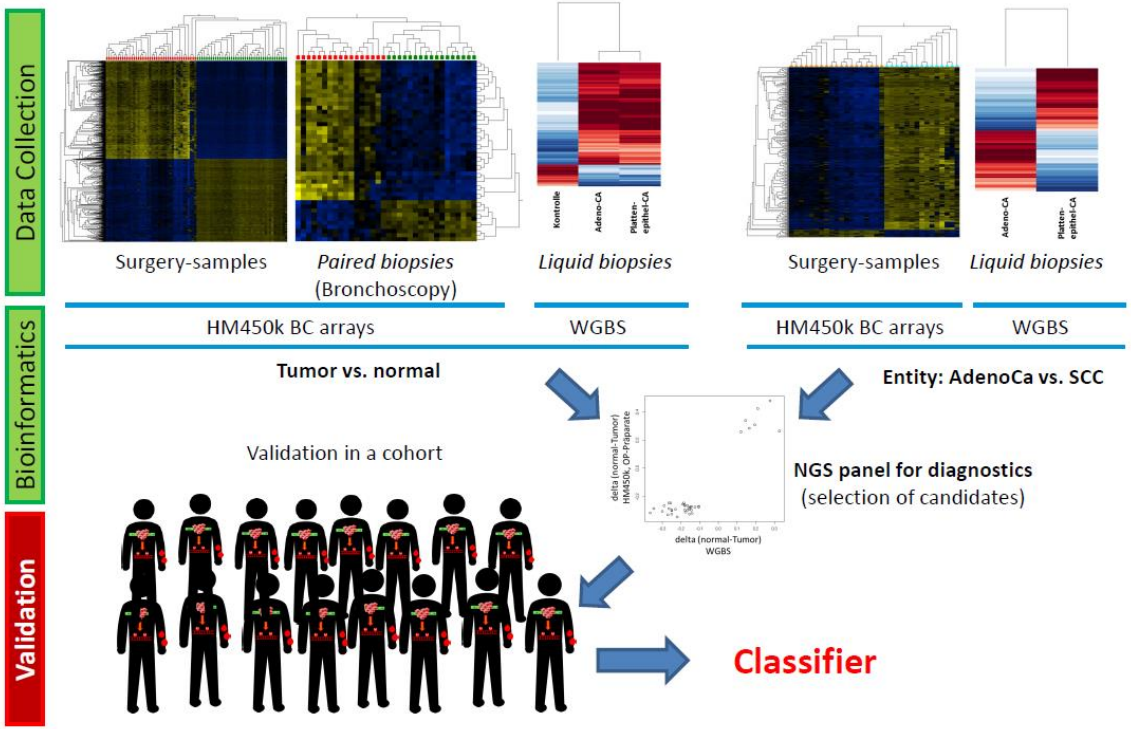
EMoLung-Concept: Epigenetic Diversity

Surgical Specimen: Tumor vs Control



EMoLung-Concept: Monitoring of NSCLC patients

DEVELOPMENT OF THE PLASMA PANEL



S. Scheufele , O. Ammerpohl

NGS EPI-panel (805 loci)

Classifier
Malignant vs non malignant
Adeno- vs Squamous
Rapid Progressor vs non rapid progressor

EMoLung-Concept: Monitoring of NSCLC patients

IDENTIFICATION OF EPIGENETIC SIGNATURE IN LIQUID BIOPSIES AND RNA BIOMARKERS IN EBCs ALLOWING THE IDENTIFICATION OF PATIENTS WITH RELAPSE

OBJECTIVES:

- Improvement of disease control by extension of conventional imaging strategies
- Generation of a well characterized patient cohort (Stage I, II, IIIA)

Collection of Blood and EBCs:

1.) before surgical resection

2.) 3 months after surgical resection

3.) time of relapse

EMO – LUNG

- Projekt läuft an 5 Standorten in Deutschland
- Aktuell 118 Patienten / viele Dropouts (46/118)
- Herzliche Einladung zur Teilnahme!
- Bitte Patienten zu Kontrolluntersuchungen schicken!

ZUSAMMENFASSUNG

- Screening senkt die Lungenkrebs Mortalität
- Hohe Rate an falsch positiven Ergebnissen problematisch
- Viele nicht invasive Marker in Prüfung
- Kombination von zirkulierenden Markern und CT-Screening interessant
- Marker zur Rezidiv Früherkennung in Prüfung

LUNGENCLINIC GROSSHANSDORF