CENTER FOR CANCER RESEARCH

LUNG CANCER:
Precision Medicine Strategy

Curtis Harris
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NIH NATIONAL CANCER INSTITUTE

Lung cancer

Precision Medicine: LUNG CANCER

Report of the Surgeon General, 2014

Premature deaths caused by smoking and exposure to secondhand smoke, 1965-2014

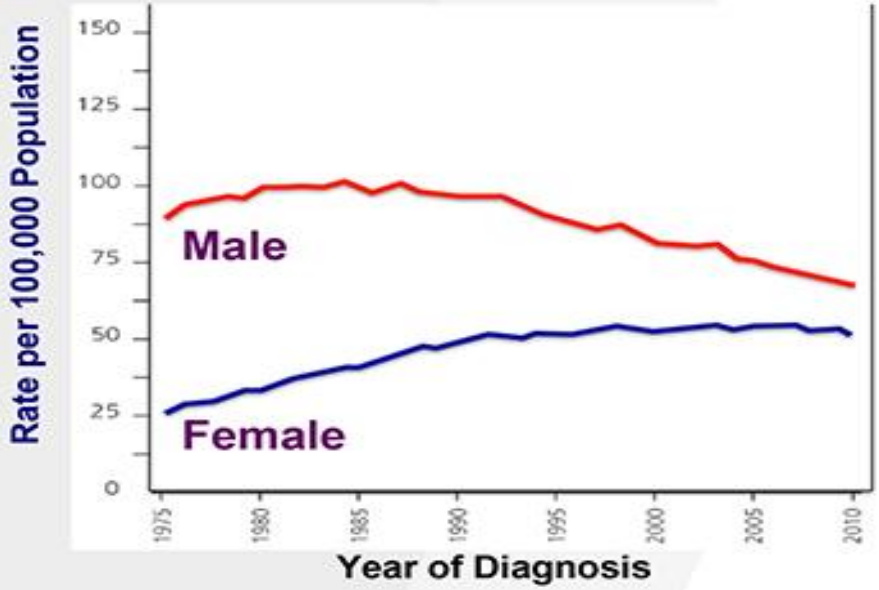
Cause of death	Total
Smoking-related cancers	6,587,000
Cardiovascular and metabolic diseases	7,787,000
Pulmonary diseases	3,804,000
Conditions related to pregnancy and birth	108,000
Residential fires	86,000
Lung cancers caused by exposure to secondhand smoke	263,000
Coronary heart disease caused by exposure to secondhand smoke	2,194,000
Total	20,830,000

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

Report of Surgeon General, Executive Summary, 2014

Cancer Statistics (ACS), 2014

Lung & Bronchus

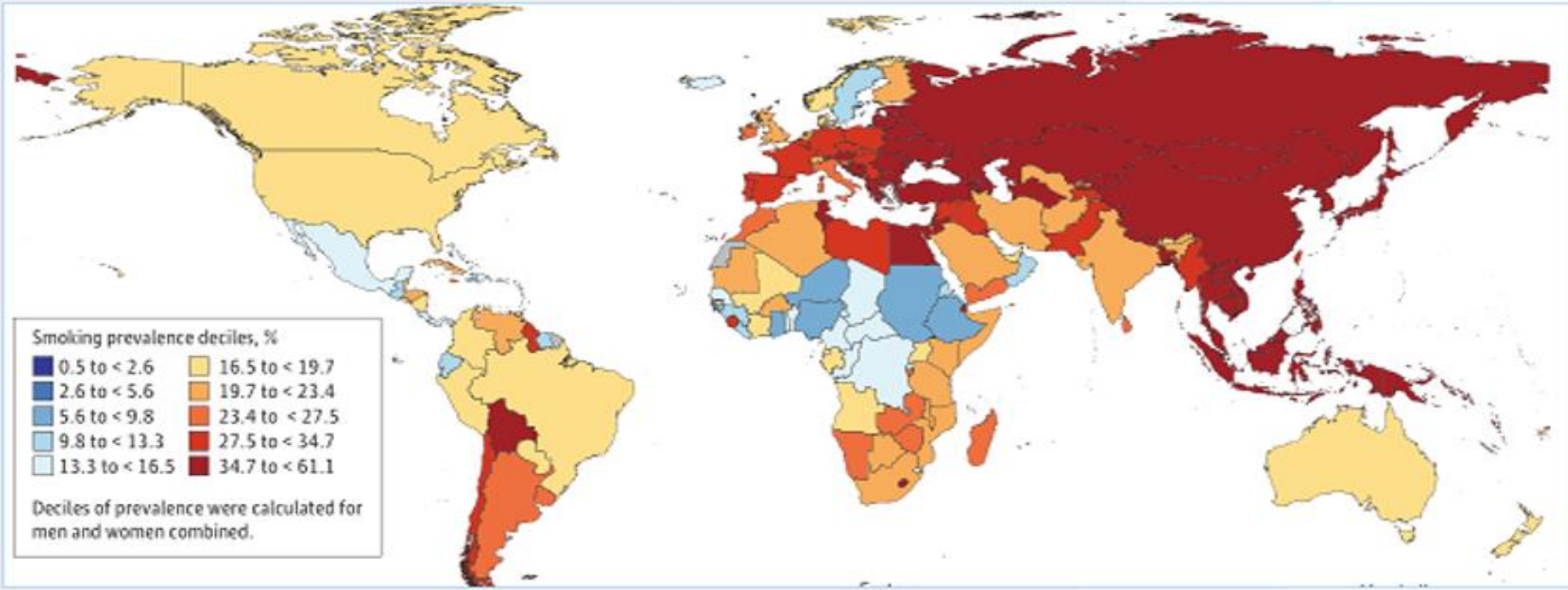


Siegel, R., et al., CA Cancer J Clin, 64: 9-29, 2014

Smoking prevalence

Smoking Prevalence and Cigarette Consumption in 187 Countries, 1980-2012

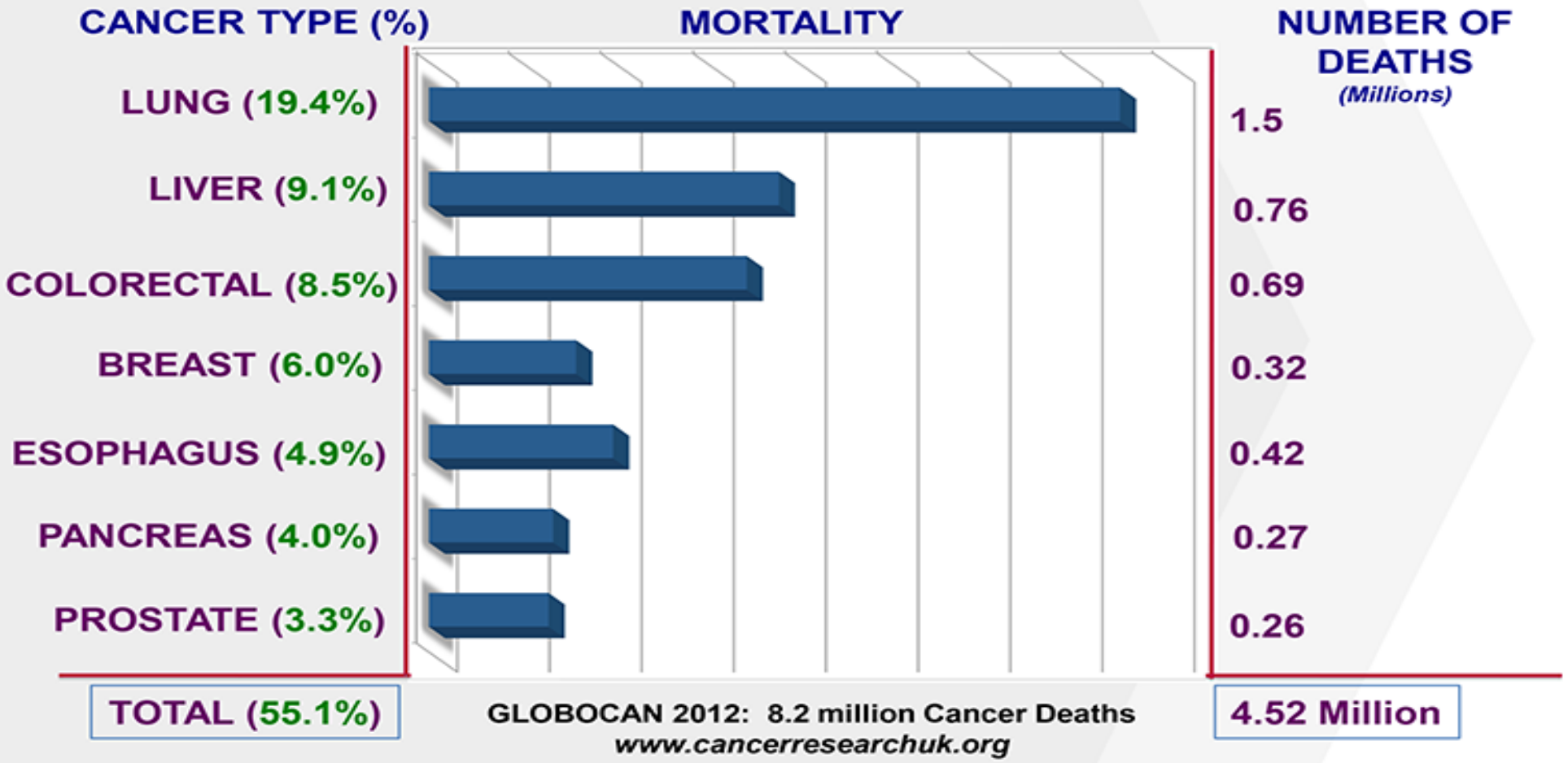
- **Estimate Age-Standardized Prevalence of Daily Smoking in 2012 among Men**



Ng, M., et al., JAMA, 311(2): 183-192, 2015

Cancer deaths

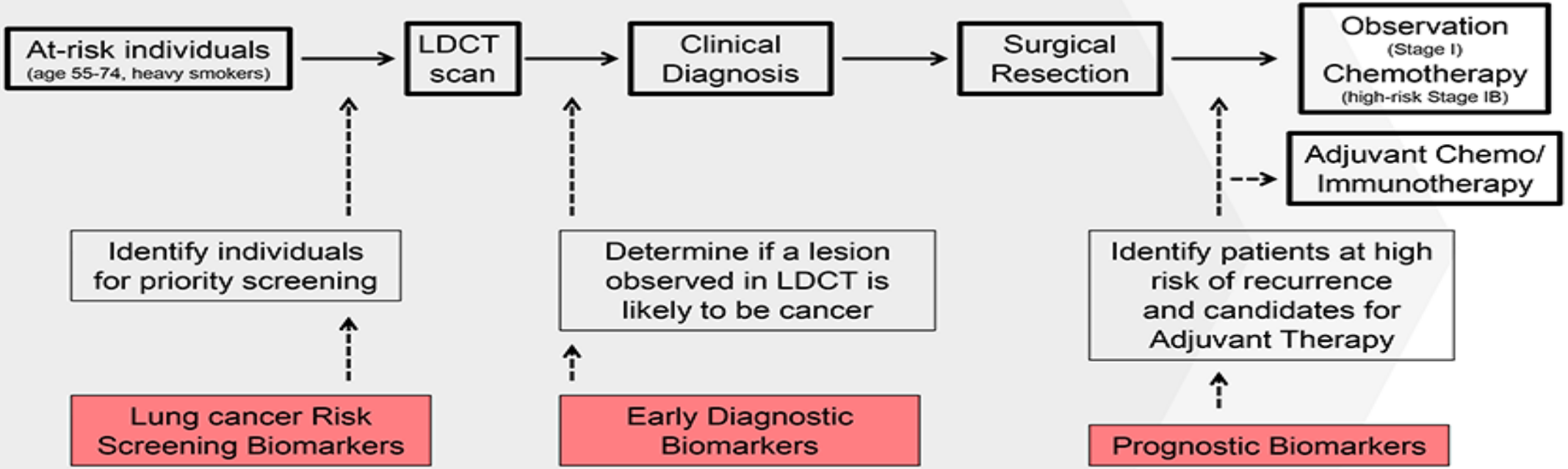
LHC Investigators are Studying Major Worldwide Lethal Types of Human Cancer



GLOBOCAN 2012: 8.2 million Cancer Deaths
www.cancerresearchuk.org

Early stage lung cancer

Early Stage Lung Cancer: Unmet needs



Precision medicine

PRECISION MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

> "Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."
>
> — President Barack Obama, State of the Union Address, January 20, 2015

Collins F and Varmus H. NEJM 372: 793-5, 2015

Towards Precision Medicine and a Molecular Taxonomic Classification of Disease

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Towards Precision Medicine and a Molecular Taxonomic Classification of Disease

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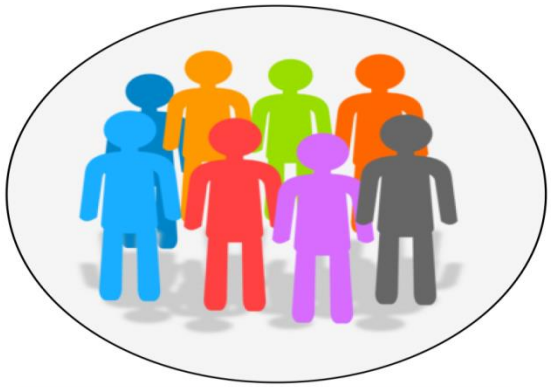
Traditional Medicine



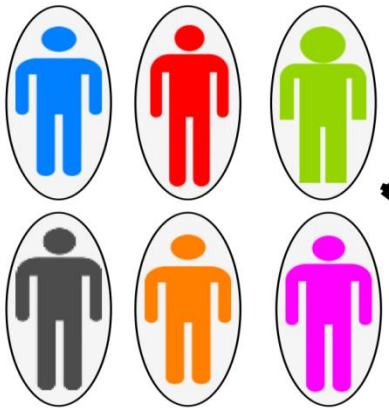
Lifestyle, medical & family history

Signs & Symptoms

Standard lab tests & imaging

Precision Medicine

- **Multi-layered**
- **Individual-centric**
- **Interconnected**

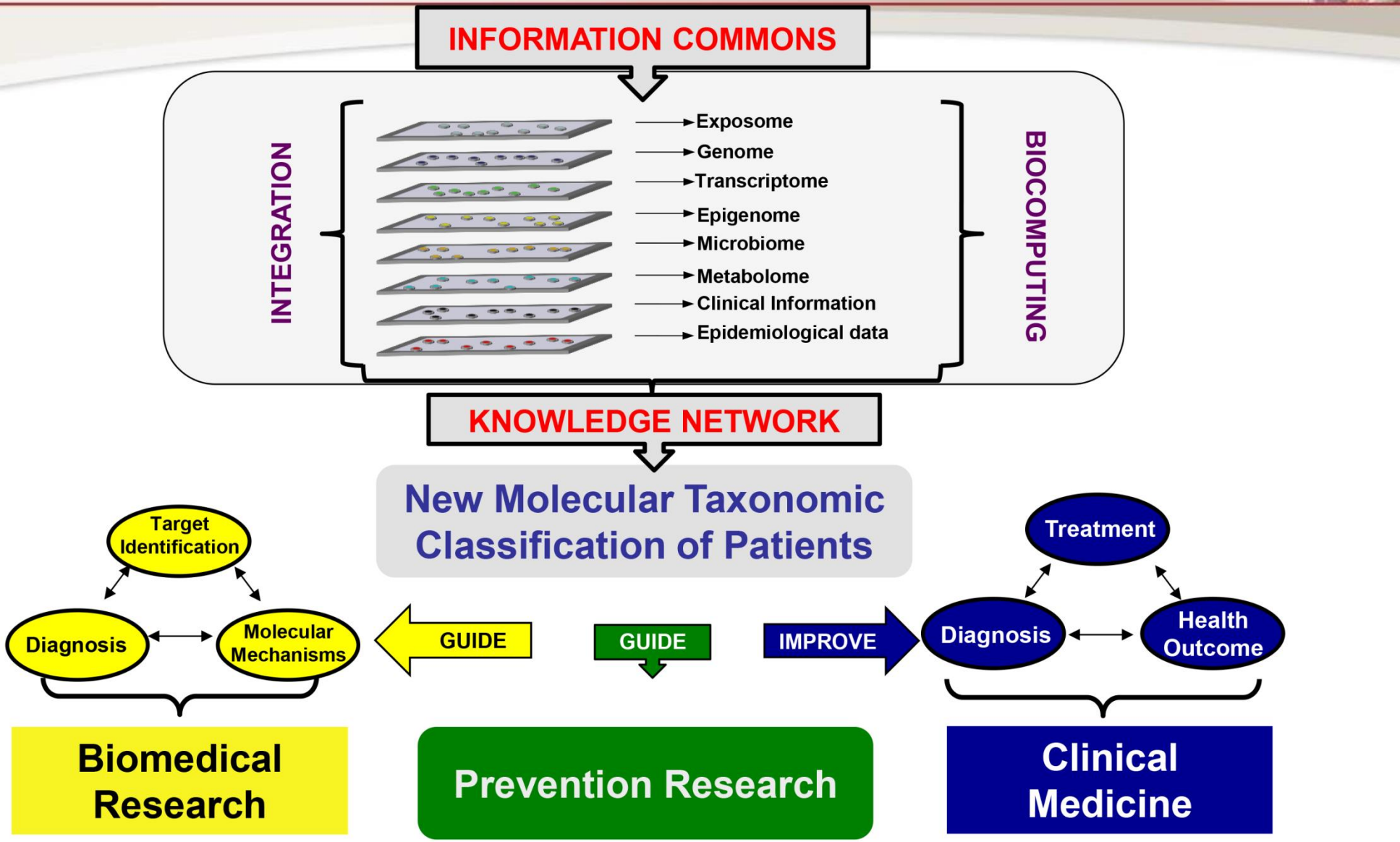


INFORMATION COMMONS

- Exposome
- Genome
- Transcriptome
- Microbiome
- Epigenome
- Metabolome
- Clinical Information
- Epidemiological data

- Lifestyle & family history
- Signs & Symptoms
- Standard lab tests & imaging

A Precision Medicine Research Strategy



Modified: Toward Precision Medicine, National Research Council, National Academy of Science, 2011

Exposome: p53 Tumor Suppressor is at the Crossroads of the Exposome and Cancer Genome

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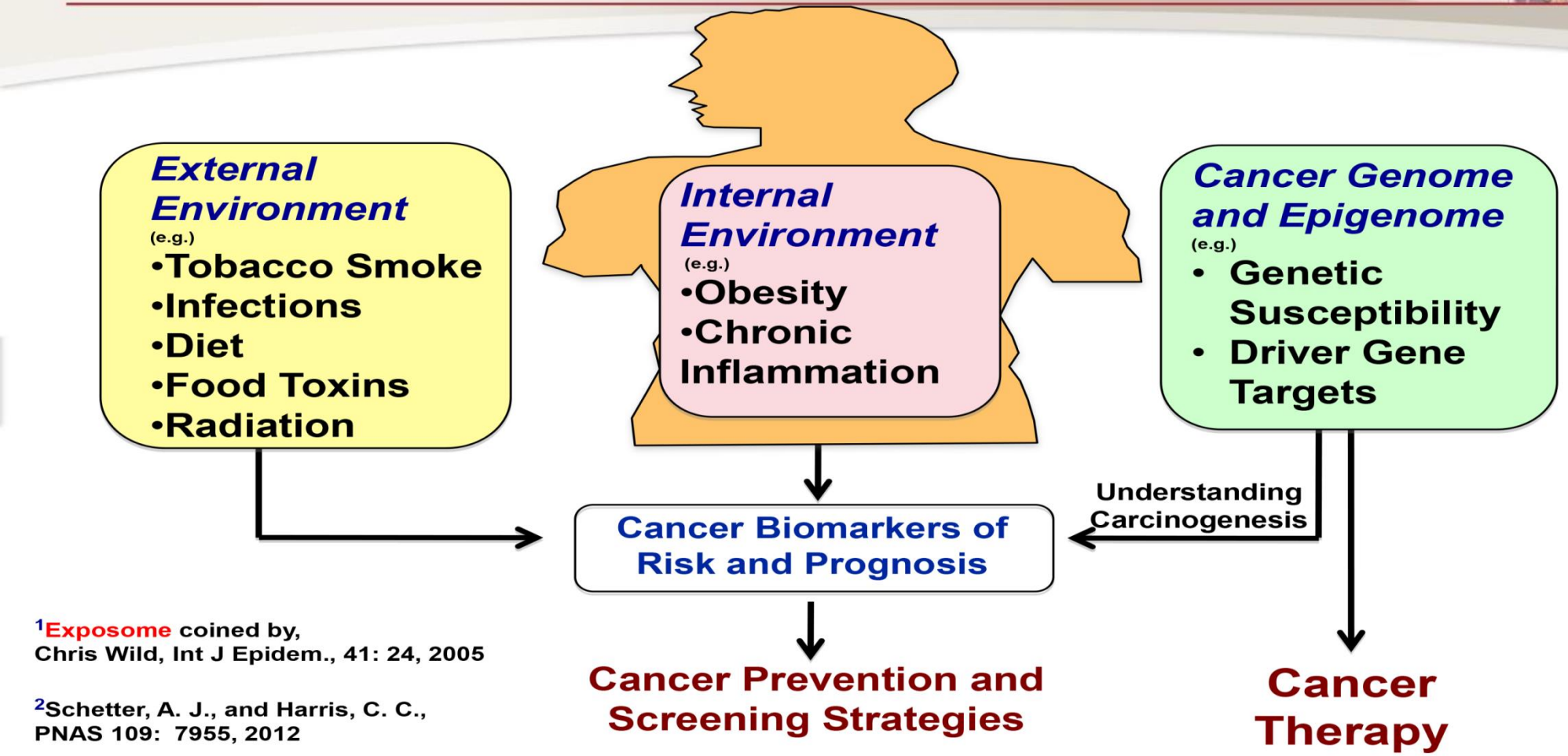
Exposome[1]: p53 Tumor Suppressor is at the Crossroads of the Exposome and Cancer Genome[2]

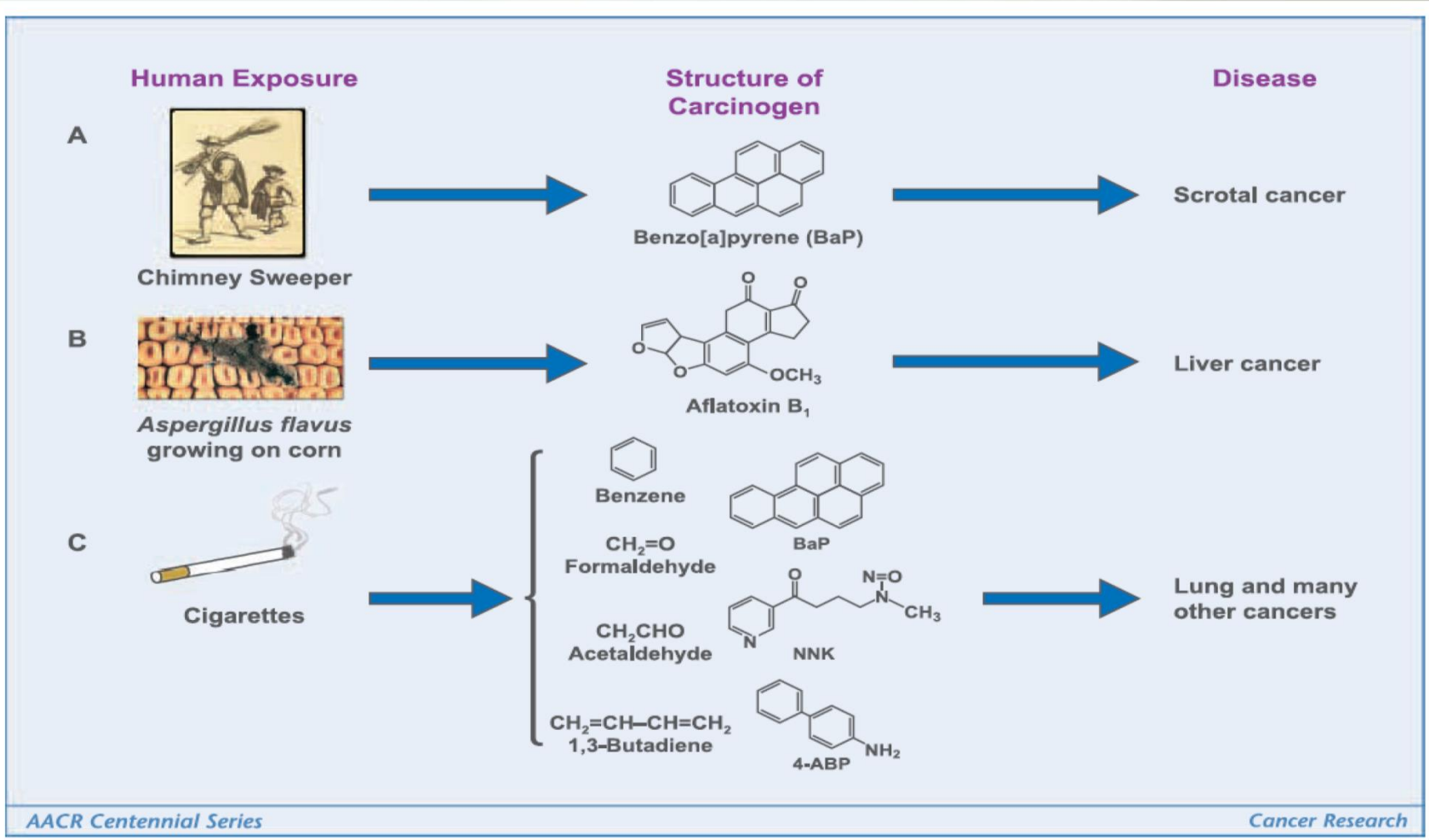


[1]Exposome coined by,
Chris Wild, Int J Epidem., 41: 24, 2005

[2]Schetter, A. J., and Harris, C. C.,
PNAS 109: 7955, 2012

Examples of Chemical Agents Causing Cancer

Examples of Chemical Agents Causing Cancer



TP53 mutations

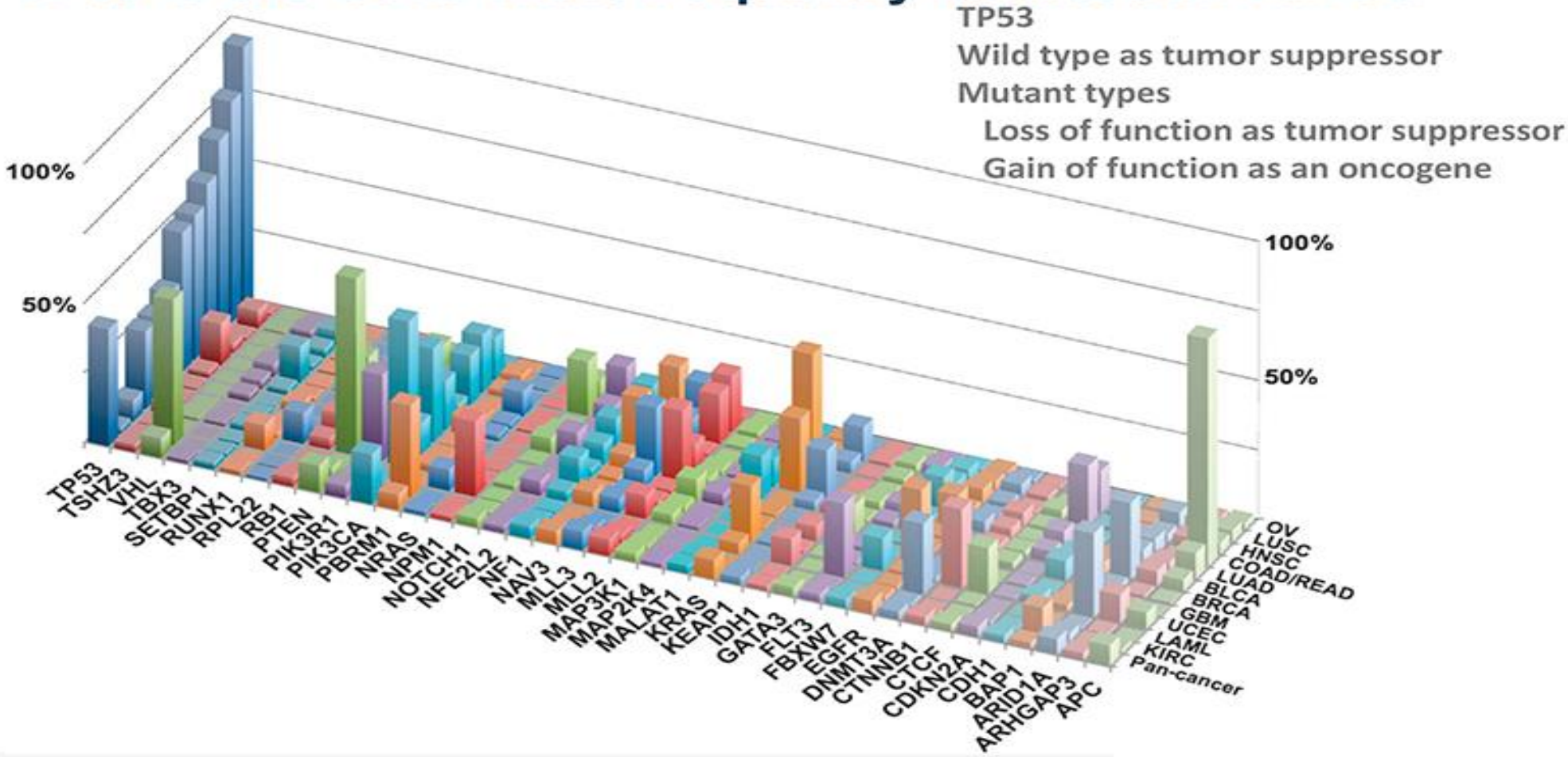
Exposome: Examples of Chemical and Physical Agents Causing Cancer and related TP53 Mutations in Human Cancer

Carcinogen/ (exposure)	Target organ	Base substitution		Distinctive
		IARC database	In Vitro Human Cell Assays	Hotspots (codons)
Aflatoxin B1 (dietary contam.)	Liver	G to T	G to T	249 (3rd base)
PAH (B[a]P) (smoking)	Lung	G to T with Strand bias	G to T with Strand bias	157, 158, 273
UV radiation (sunlight)	Skin	CC to TT	CC to TT	248, 278
Aristolochic Acid (dietary contam.)	Urothelium	A to T with Strand bias	A to T with Strand bias	131, 209, (280)

- Hsu, I.C.....Harris, C.C., Nature, 350: 427-428, 1991
- Bressac, B.....Ozturk, M., Nature, 350: 429-430, 1991
- Hollstein, M., Sidransky, D., Vogelstien, B., and Harris, C.C., Harris, Science, 253: 49-53,1991
- Greenblatt, M.....Harris, C.C., Cancer Res., 54: 4855-78, 1994

Gene mutations

TP53 is the Gene most frequently Mutated in Cancer

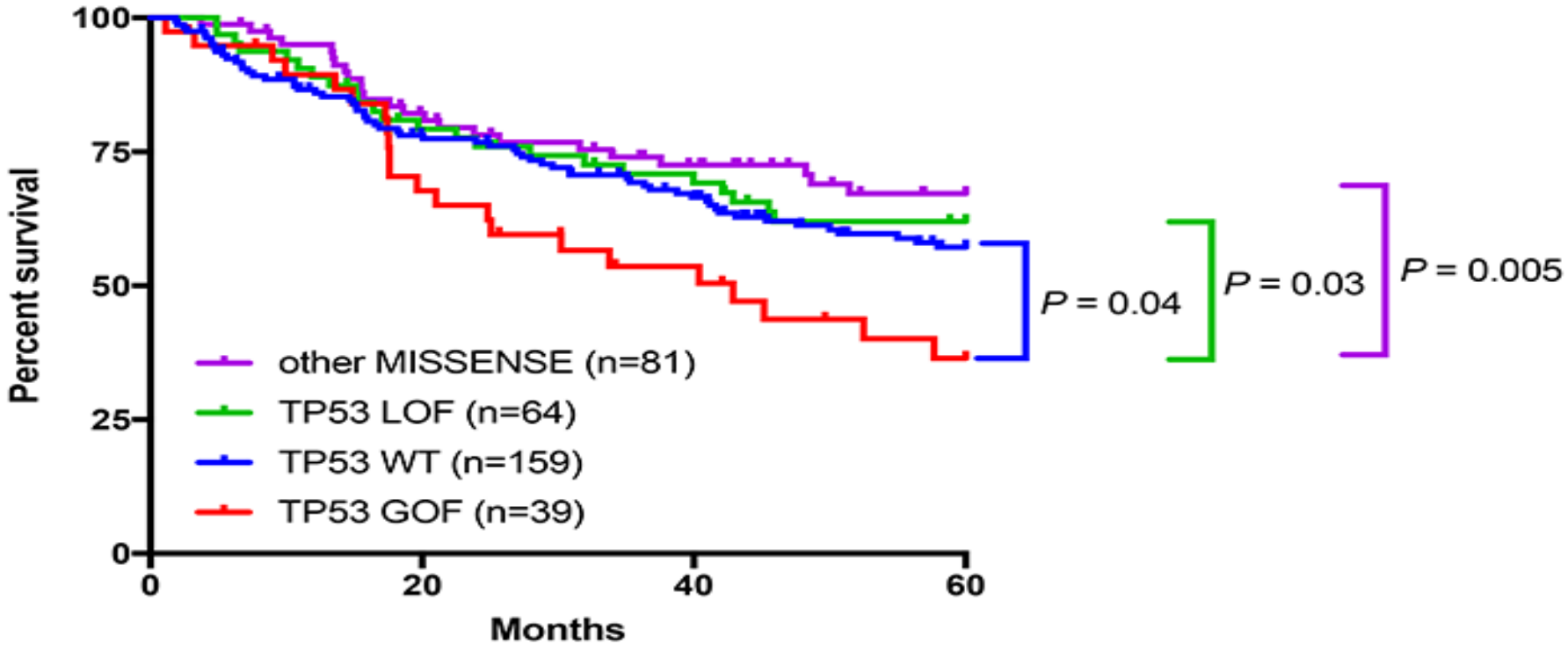


Genes most frequently mutated in various types of cancer in the TCGA Pan-Cancer study.
Data were generated by analysis of the mutations released by Kandoth et al. Nature 2013.

Soussi & Wiman, 2015

Survival curve

Gain of Function(GOF) TP53 Mutations are Associated with Poor Prognosis of Lung Cancer Patients



$HR_{GOFvsallothers}$: 1.8; CI, 1.0-3.0; *P*= 0.034

Adjusted for patient age, race, sex, and smoking history, and tumor histology, and stage.
Dataset of 352 surgical cases of NSCLC analyzed by TP53 capture sequencing

Robles A and Harris CC, NCI-MD Case Control Study

Chronic Inflammation and Infection can increase Cancer Risk

Chronic Inflammation and Infection Can Increase Cancer Risk

Inherited > Acquired

Disease	Tumor Site
Hemochromatosis	Liver
Crohn's Disease	Colon
Ulcerative Colitis	Colon
Familial Pancreatitis	Pancreas

Global Impact

- 2 million human cancers per year are related to infection
- Other causes of inflammation are associated with many more cancers per year (e.g. smoking 6 million cancers/year)

World Cancer Report, IARC, WHO, 2014

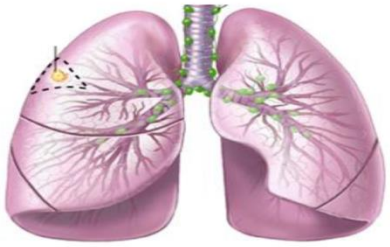
Acquired > Inherited

Disease Agent	Tumor Site
Viral	
Hepatitis B	Liver
Hepatitis C	Liver
Bacterial	
Helicobacter Pylori	Gastric
PID	Ovary
Parasitic	
S. hematobium	Urinary Bladder S. japonicum Colon
Liver Fluke	Liver
Chemical, Physical, and Metabolic Examples	
Acid reflux	Esophagus
Obesity	Multiple sites
Smoking	Multiple sites

Health Disparity: Increase Expression of Serum Pro-Inflammatory cytokines is associated with Lung Cancer Risk, Diagnosis and Survival

Health Disparity:
Increased Expression of Serum Pro-Inflammatory Cytokines is Associated with Lung Cancer Risk, Diagnosis and Survival

Increased Risk → Diagnosis → Poor Survival



↑ IL-8, ↑ CRP (EA)

JNCI 103: 1112, 2011

↑ IL-8, ↑ IL-6 (AA, EA)
↑ IL-1B & IL-10 (AA)

JNCI 103: 1112, 2011
J. Thoracic Oncol, 2014

↑ IL-6 & -8 (AA, EA), ↑ MBL-2 (EA)
↑ TNFα (EA), ↑ IL-10 & IL-12 (AA)

CEBP: 215, 2010
JNCI 99: 1401, 2007
J. Thoracic Oncol, 2014

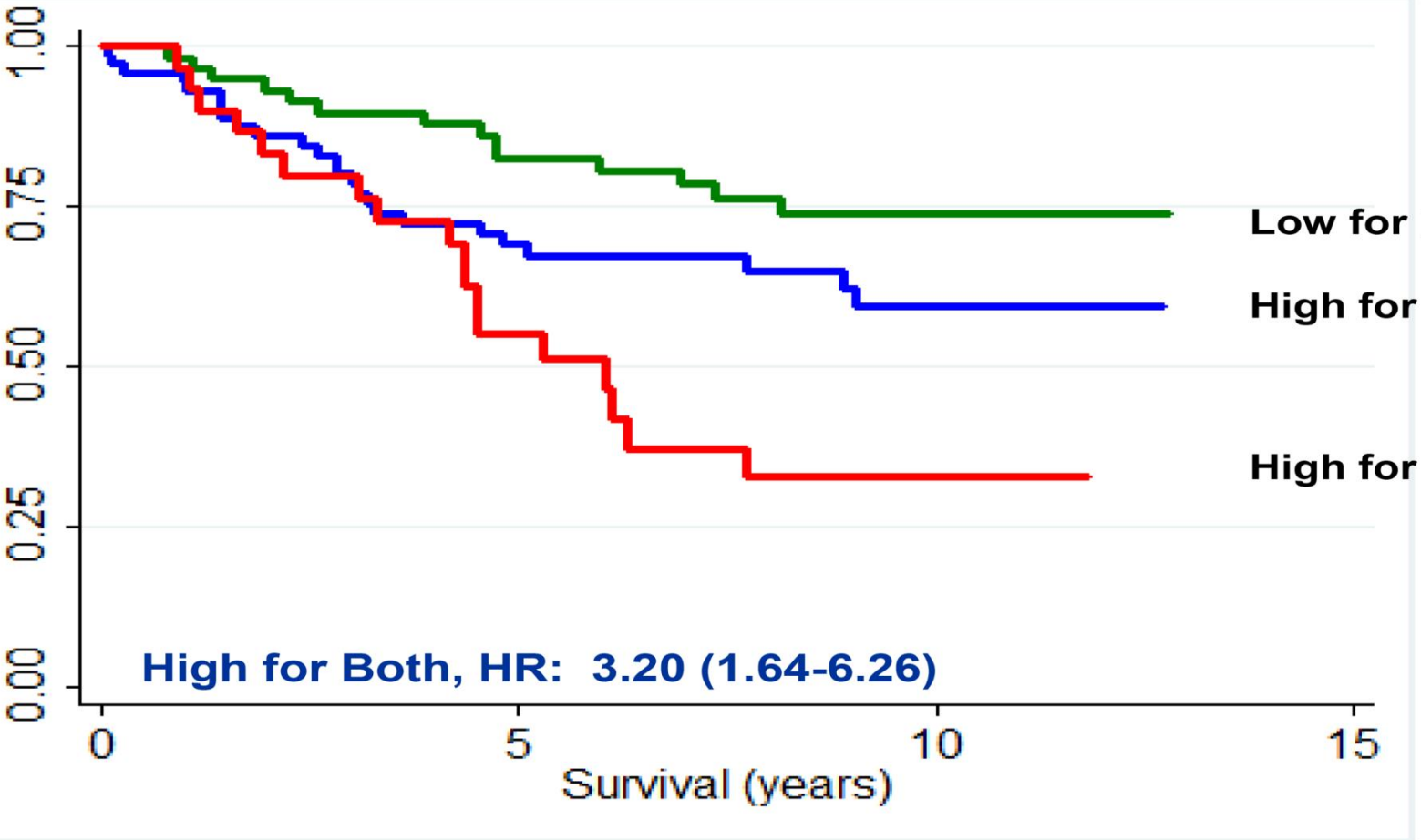
Health Disparity:
EA, European-American
AA, African-American

Collaboration: Ann Schwartz

Combination of Serum IL-6 and IL-8 is a robust Prognostic Classifier of Stage I Lung Cancer

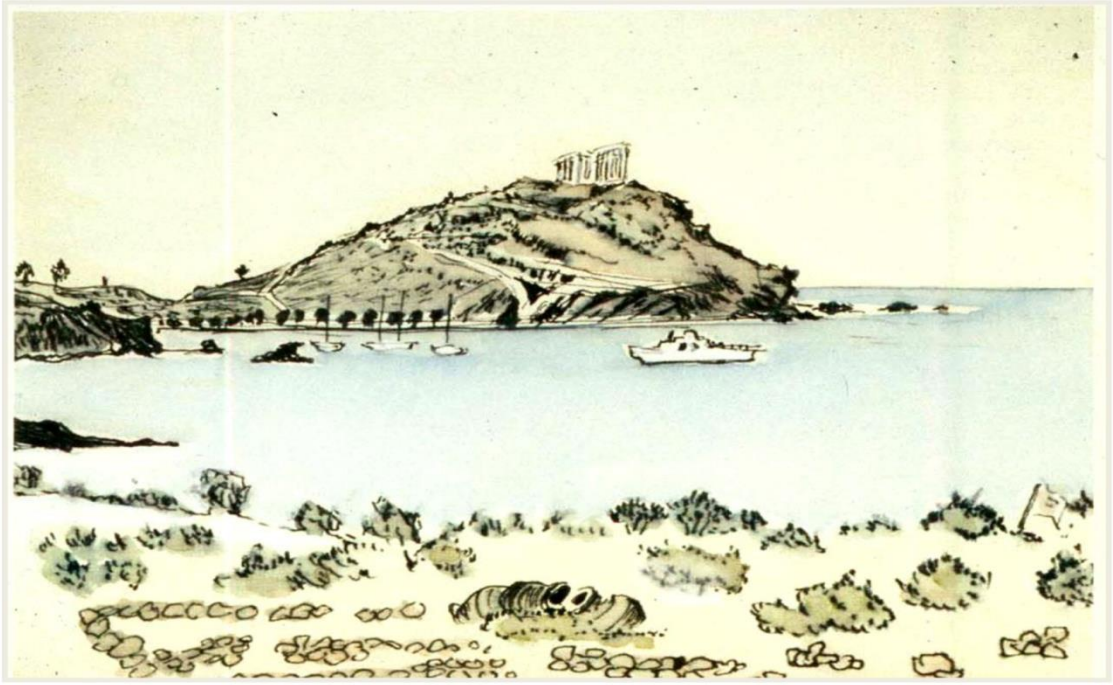
Combination of Serum IL-6 and IL-8 is a Robust Prognostic Classifier of Stage I Lung Cancer

Sharon Pine Brid Ryan



Involuntary Smoking (Exposure to Secondhand or Environmental Tobacco Smoke is Carcinogenic to Humans

"INVOLUNTARY SMOKING (EXPOSURE TO SECONDHAND OR 'ENVIRONMENTAL' TOBACCO SMOKE) IS CARCINOGENIC TO HUMANS" (Host Factors in Human Carcinognesis, IARC MONOGRAPH 183, 2002)



Hirayama, T., Cape Sunion,Greece,1981

Some men have constitutions that are like wooded mountains running with springs, others like those with poor soil and little water, still others like land rich in pastures and marshes, and yet others like the bare, dry earth of the plain.

Hippocrates

Airs, Waters, Places

1993-CH

Molecular Epidemiology of Lung Cancer in Never Smokers

Molecular Epidemiology of Lung Cancer in Never Smokers

Hypothesis:

- Childhood exposure to second-hand smoke and genetic alterations in innate immunity increase lung cancer risk in never smoking adults

Conclusions:

- Parental secondhand smoke exposure during childhood is associated with dose-dependent increased lung cancer risk among never smokers in two cohorts.
  - Especially among those with an *MBL-2* haplotype with a hyperactive innate immune system
  - Early age of onset of lung cancer

Susan Olivo-Marston

Cancer Epi Bio Prev., 18: 3375-83, 2009

Collaboration with Jen Jin and Ping Yang, Mayo Clinic

Precision Medicine: Information Commons

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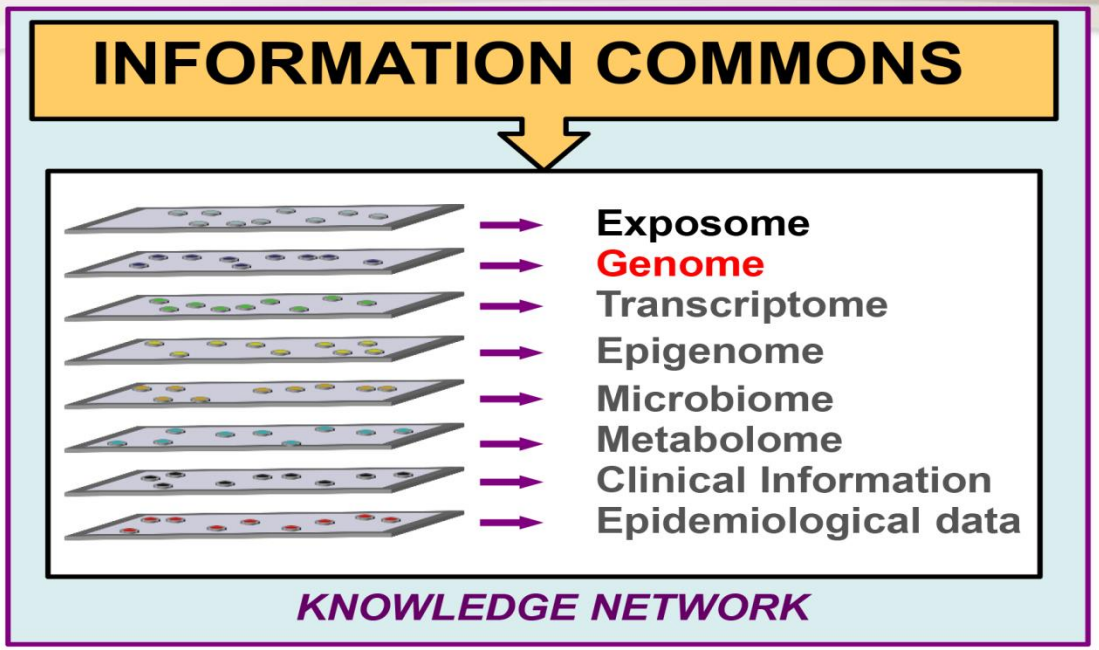

Modified: Toward Precision Medicine, National Research Council, National Academy of Science, 2011

Knowledge of Non-Small Cell Lung Cancer has Evolved Substantially in Recent Decades

Knowledge of Non-Small-Cell Lung Cancer has Evolved Substantially in Recent Decades

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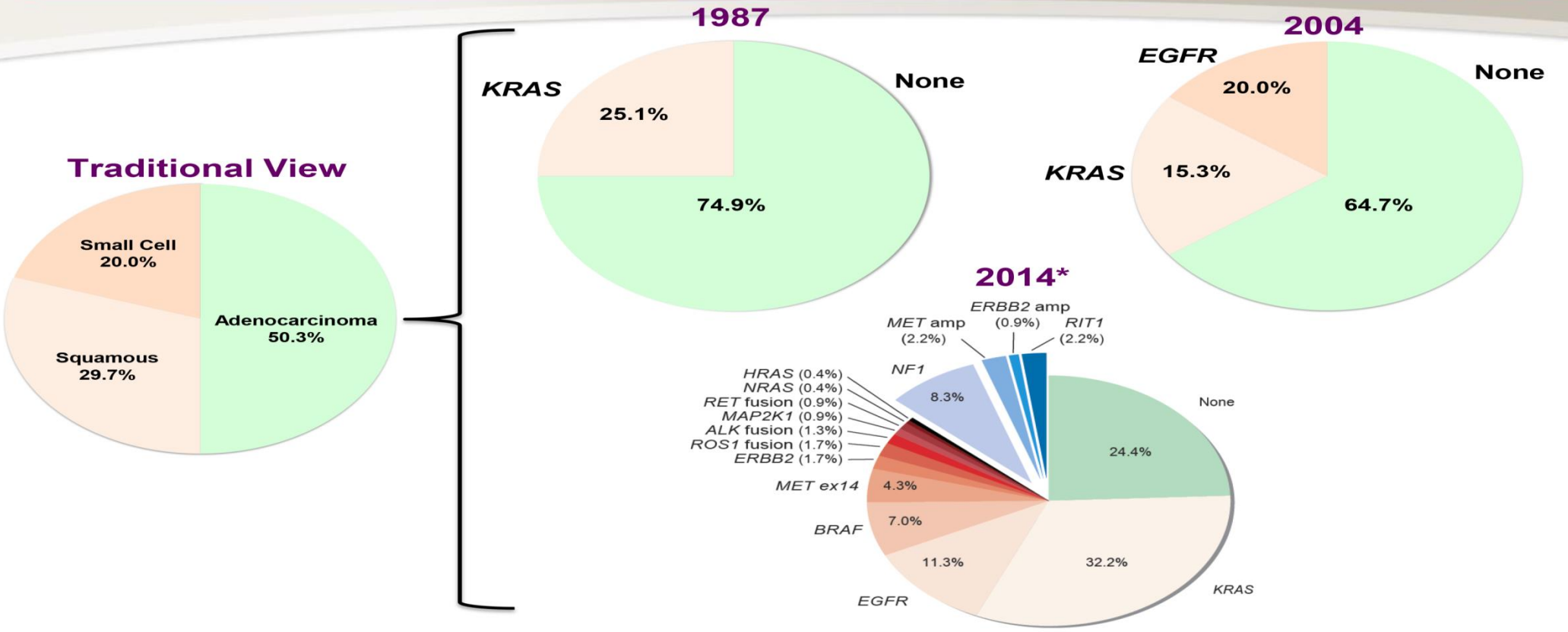


*The Cancer Genome Atlas Network, Nature, 2014

Epigenome: Micro RNA and Cancer

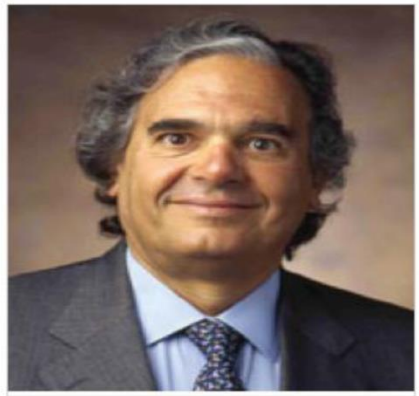
Epigenome: MicroRNA and Cancer

- **MicroRNA**
  - Small non-coding RNAs that are evolutionarily conserved and regulate gene expression.
  - Protein output of hundreds of genes are repressed by each microRNA destabilizing mRNA and to a lesser extent inhibiting translation of mRNA.

Victor Ambros

Gary Ruvkun

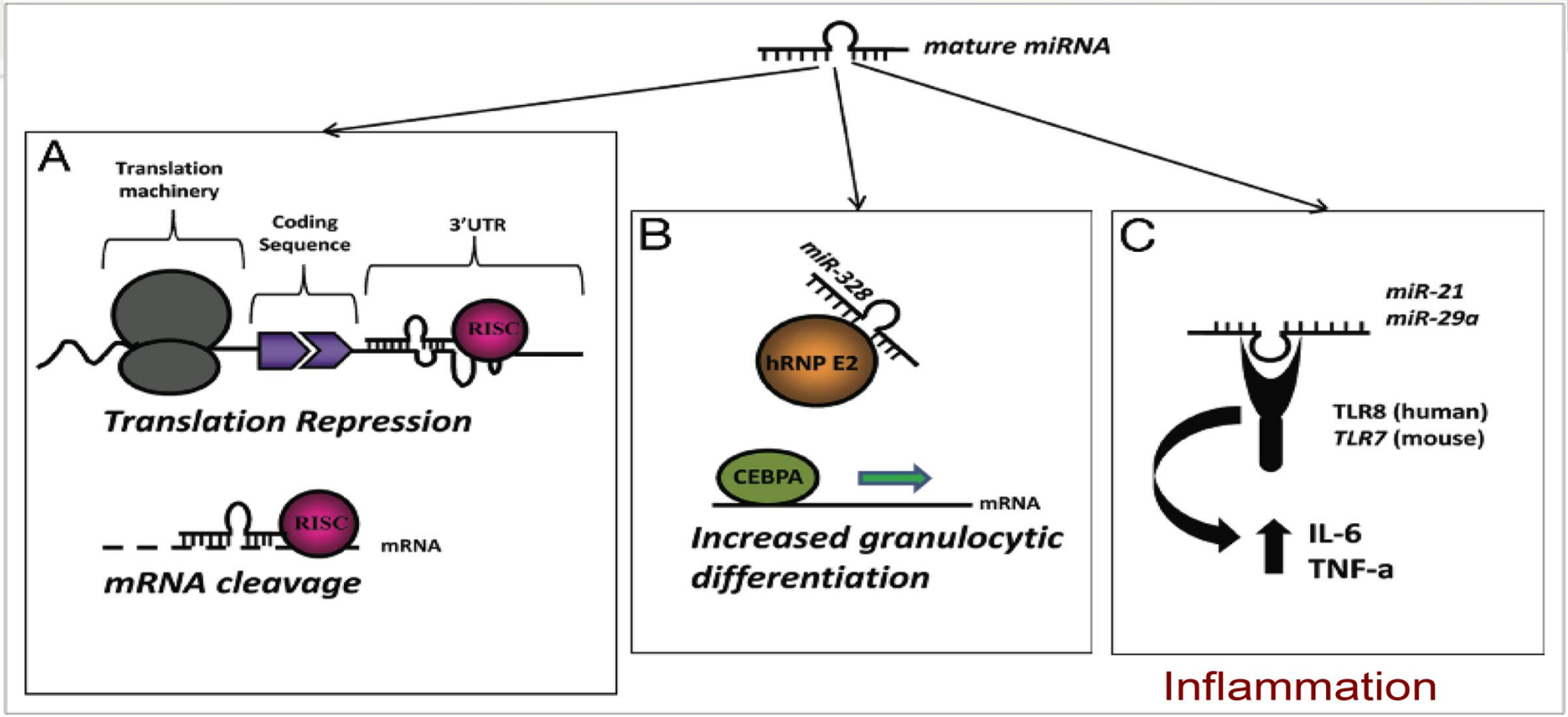
- **Human Cancer**
  - MicroRNAs are differentially expressed in human cancers.
  - MicroRNAs can predict risk, diagnosis, prognosis and therapeutic outcome.



Carlo Croce

Different Mechanisms of Action of Mature micro RNAs

Different Mechanisms of Action of Mature microRNAs

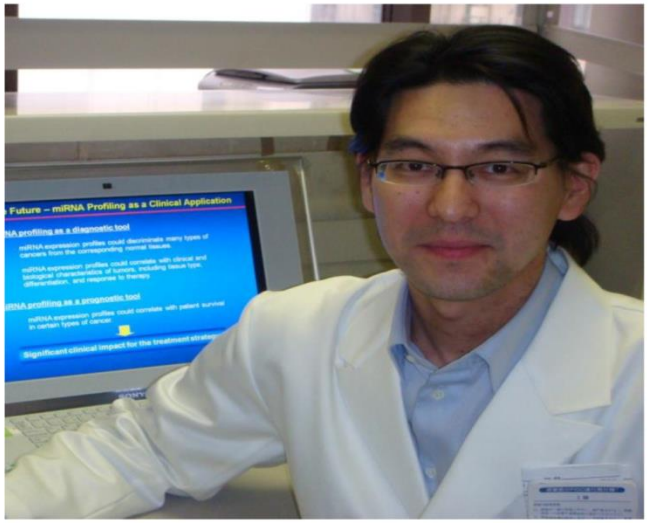


Fabbri, M., et al., RNA Biology, 10:2, 169-174, 2013

Hypothesis: Micro RNAs are Associated with Lung Cancer Diagnosis and Prognosis

Hypothesis: MicroRNAs are Associated with Lung Cancer Diagnosis and Prognosis

- miRNAs profiles were significantly different both between primary lung cancers and corresponding non-cancerous lung tissues and among different histological types of lung cancer.
- Increased mir-21, mir-155 and mir-106b, and decreased let-7 were each associated with diagnosis and prognosis including stage 1 lung cancer.



Nozumu Yanaihara

let-7: confirmed studies by Takahashi and Slack

Yanaihara et al., Cancer Cell, 9:189, 2006

Epigenome: Commonly Up-Regulated micro RNAs in Carcinomas

Epigenome: Commonly Up-Regulated microRNAs in Carcinomas

miR	N	Tumor Type
miR-21	6	Breast Colon Lung Pancreas Prostate Stomach
miR-17-5p	5	Breast Colon Lung Pancreas Prostate
miR-191	5	Colon Lung Pancreas Prostate Stomach
miR-29b-2	4	Breast Colon Pancreas Prostate
miR-223	4	Colon Pancreas Prostate Stomach
miR-128b	3	Colon Lung Pancreas
miR-199a-1	3	Lung Pancreas Prostate
miR-24-1	3	Colon Pancreas Stomach
miR-24-2	3	Colon Pancreas Stomach
miR-146	3	Breast Pancreas Prostate
miR-155	3	Breast Colon Lung

microRNAs shared by the signatures of six solid cancers*

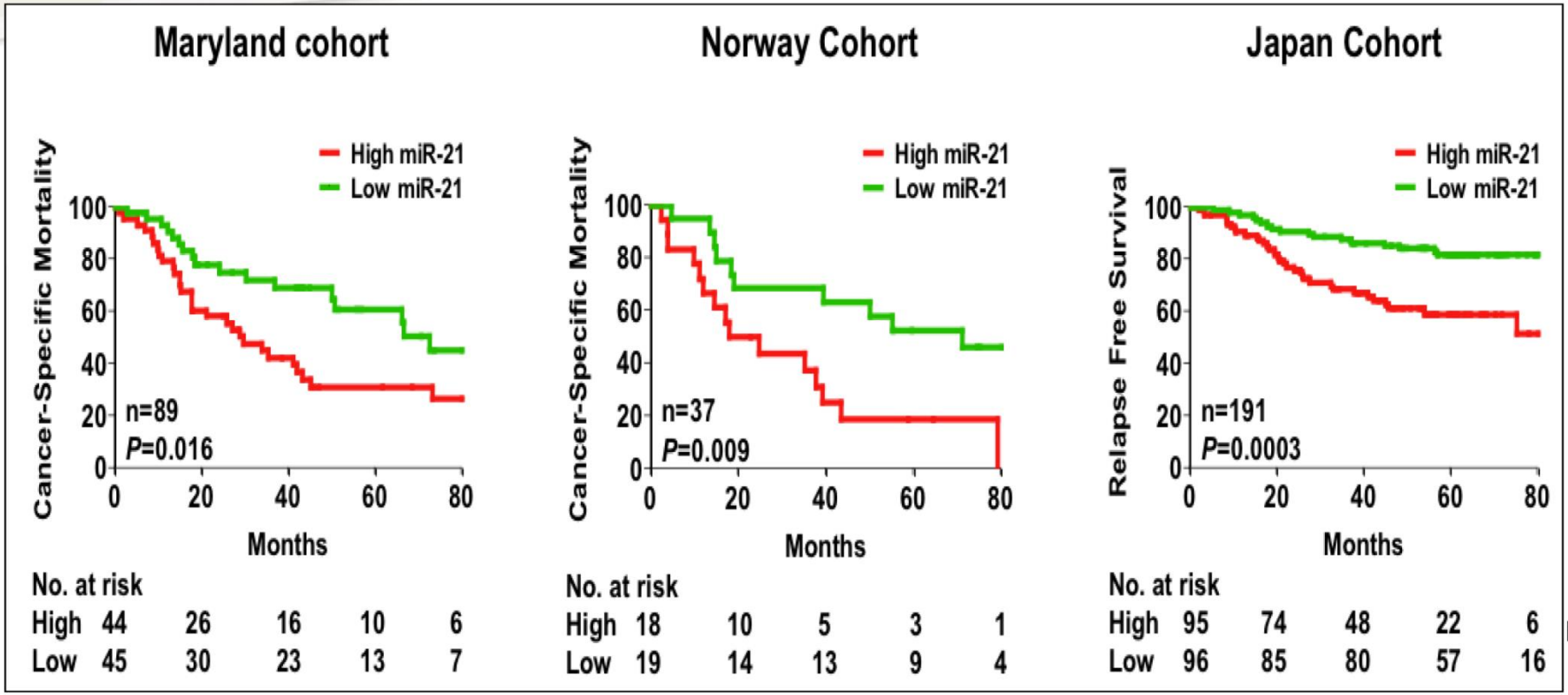
miR-21 is both up-regulated in 18 major cancers and a biomarker of poor survival in 14

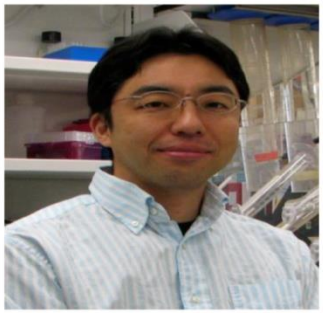
*The list includes 21 commonly up-regulated microRNAs in three or more (N) types of solid cancers (p-value=2.5×10^{-3}).

Volinia et al., PNAS 103: 1-5, 2006

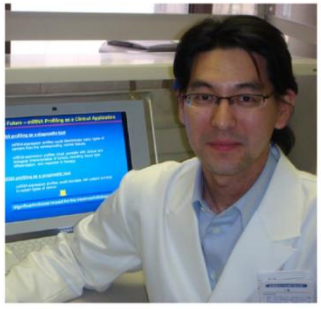
Increased miR-21 Expression in Human Lung Cancer is Associated with Poor Prognosis in Three Cohorts

Increased *miR-21* Expression in Human Lung Cancer is Associated with Poor Prognosis in Three Cohorts





Motonobu Saito



NozumuYanaihara

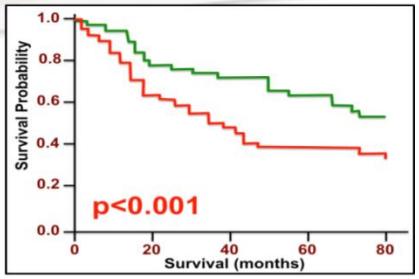
Yanaihara *et al.* Cancer Cell 9:189, 2006

Saito *et al.* Clinical Cancer Res. 17:1875, 2011

Increased miR-21 Expression is Associated with Poor Prognosis in Multiple Types of Cancer

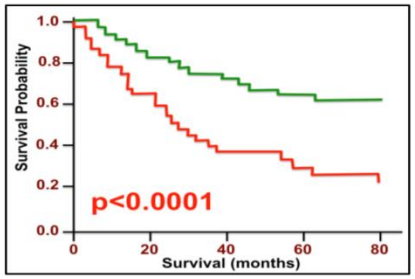
Increased *miR-21* Expression is Associated with Poor Prognosis in Multiple Types of Cancers

Lung Cancer



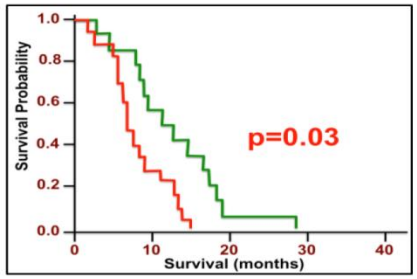
(Saito, M. et al. Clin Cancer Res., 2011)

Colon Cancer



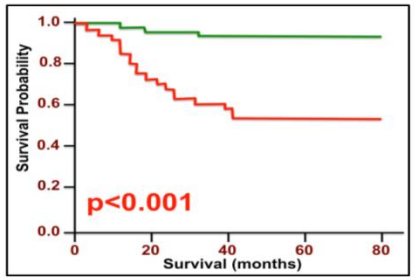
(Schetter et al. JAMA 2008)

Pancreatic Cancer



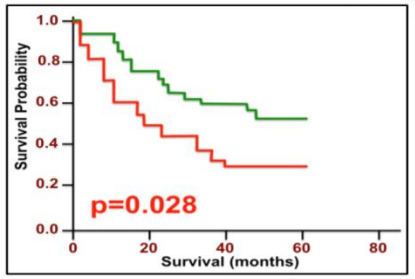
(Giovannetti, E., et al., Cancer Res. 2010)

Breast Cancer



(Yan et al, RNA 2008)

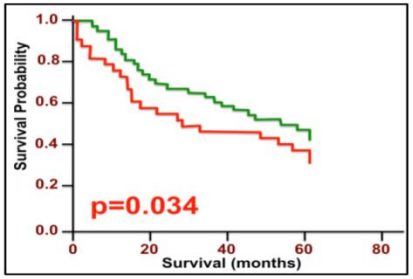
Melanoma



(Jiang *et al*, Acta Histochem., 2011)

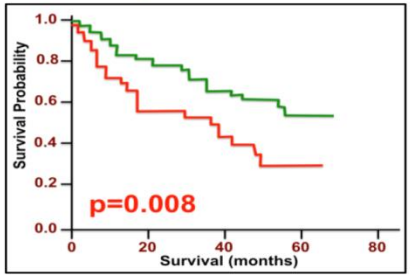
Low miR-21 Expression
High miR-21 Expression

Head & Neck Cancer



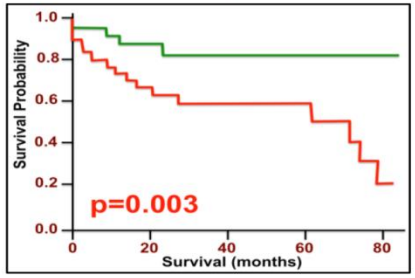
(Avissar, et al., Carcinogenesis 2009)

Tongue Cancer



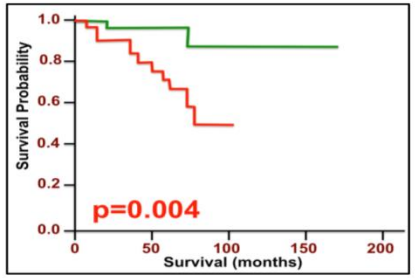
(Li, J. et al. Clin Cancer Res. 2009)

Astrocytoma



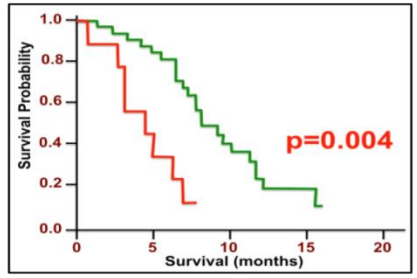
(Zhi, F. et al. Eur J Cancer 2010)

Chronic Lymphocytic Leukemia



(Rossi, S. et al., Blood 2010)

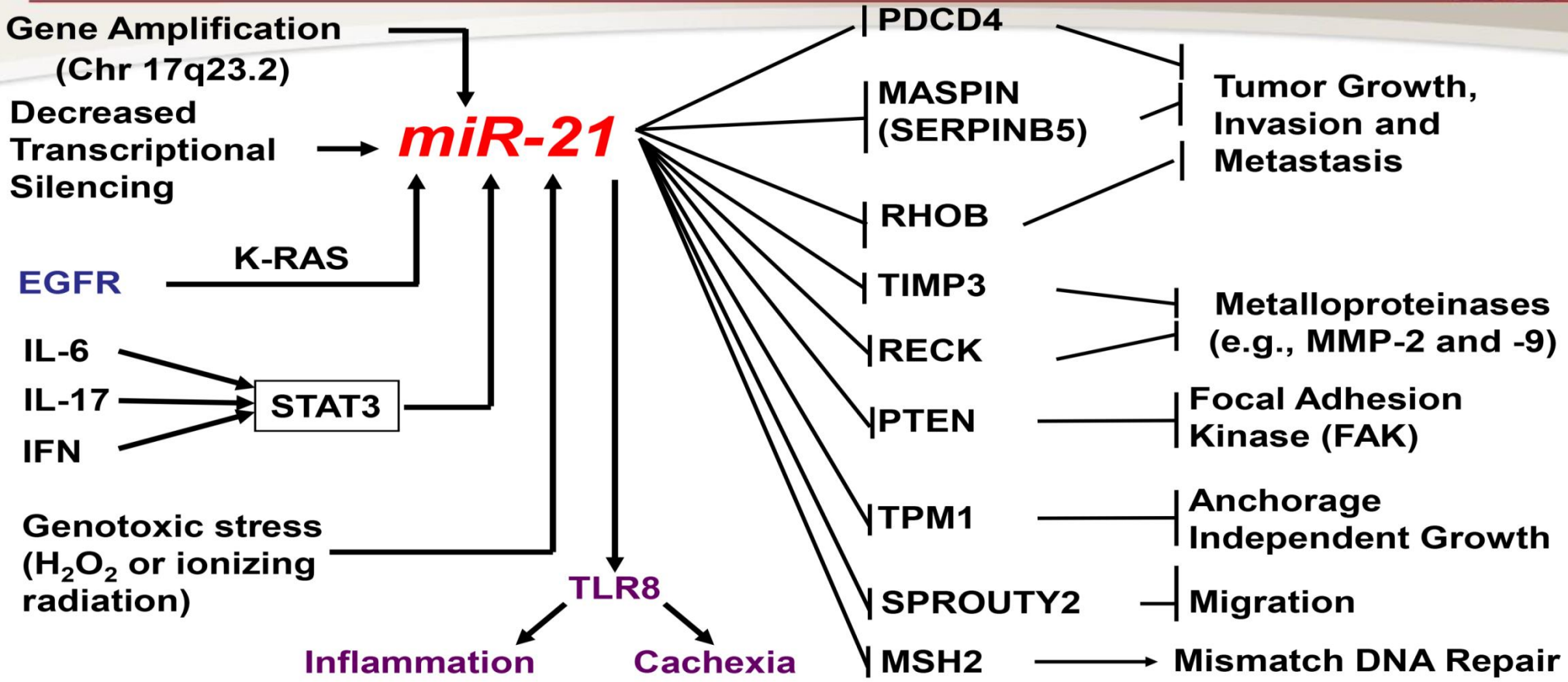
Gastric Cancer



(Jiang J. et al., PLoS ONE 2011)

Examples of the Mechanistic Underpinning of miR-21 in Human Cancer

Examples of the Mechanistic Underpinning of *miR-21* in Human Cancer

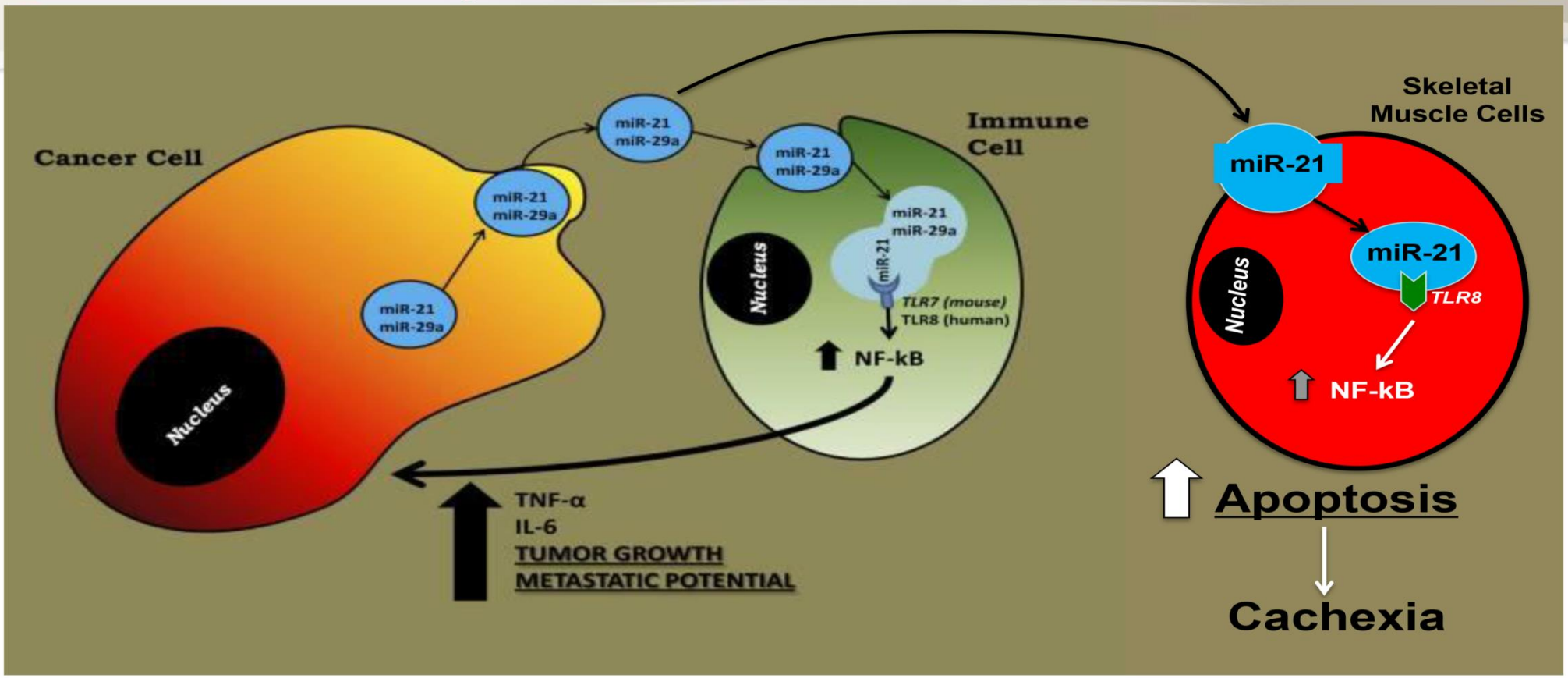


Seike ….Harris, PNAS 106: 12085-90, 2009
Schetter and Harris, Carcinogenesis 31: 37-49, 2010
Fabbri and Croce, RNA Biology 10: 169-174, 2013
He and Croce, PNAS 111: 4525-29, 2014

miRNAs are secreted by Cancer Cells in Exosomes and can Reach and Bind TLR8 Receptors in the Endosomes of Surrounding immune and Muscle Cells

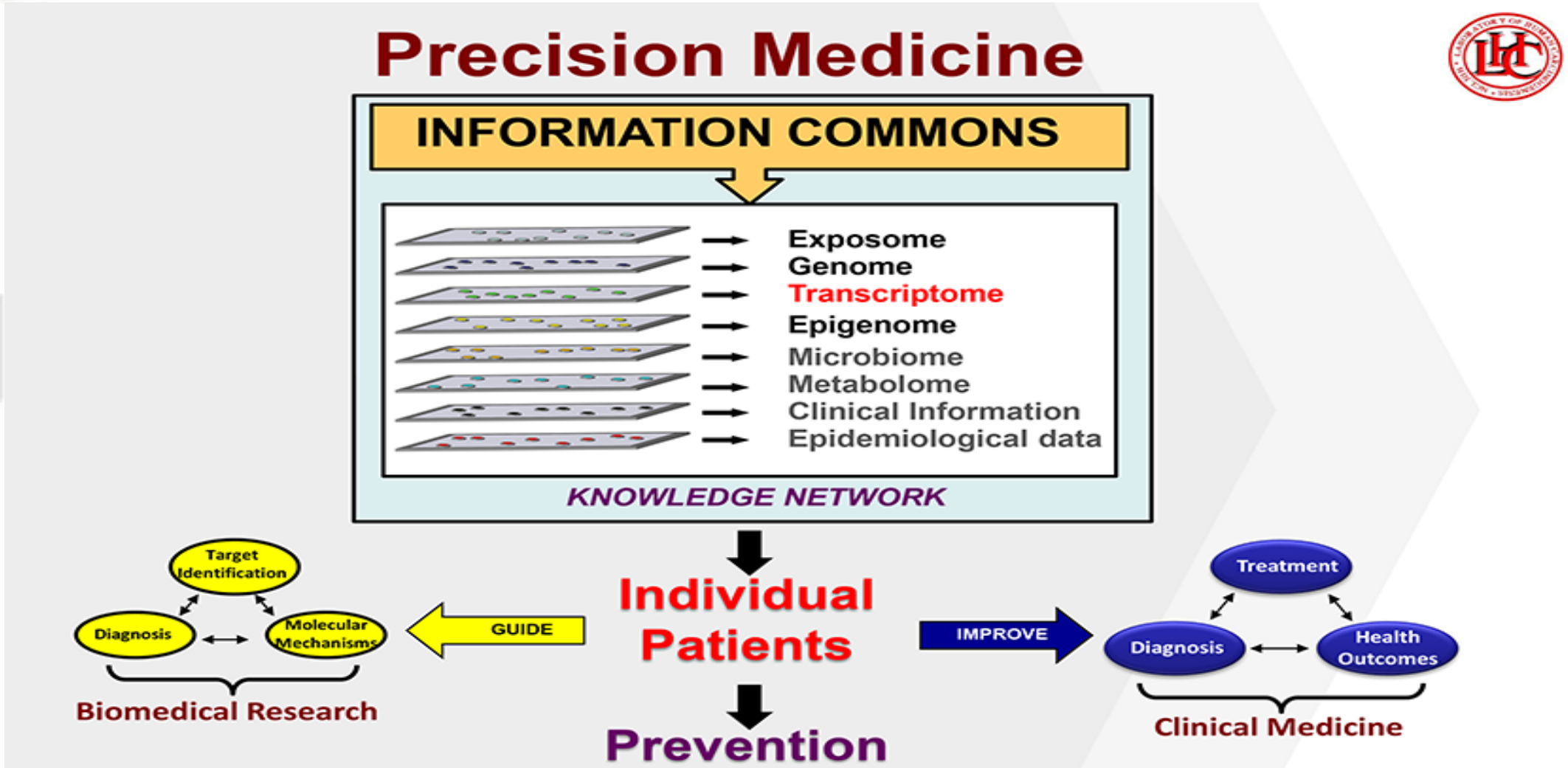
MiRNAs are Secreted by Cancer Cells in Exosomes and can Reach and Bind TLR8 Receptors in the Endosomes of Surrounding Immune and Muscle Cells

CENTER FOR CANCER RESEARCH



Fabbri, M., et al., PNAS, 109(31): E2110-E2116, 2012
He, W.A., et al., PNAS, 111: 4525-9, 2014

Precision medicine transcriptome



 Modified: Toward Precision Medicine, National Research Council, National Academy of Science, 2011

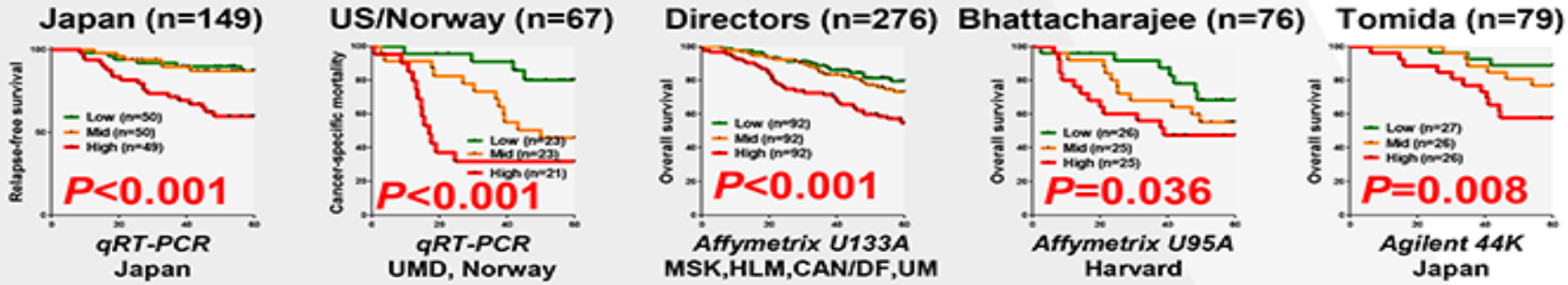
4-Gene classifier

The Performance of the 4-gene Classifier (Increased XPO1, BRCA1and HIF1a and Decreased DLC1) in 12 Independent Cohorts of Stage I ADC

4-gene

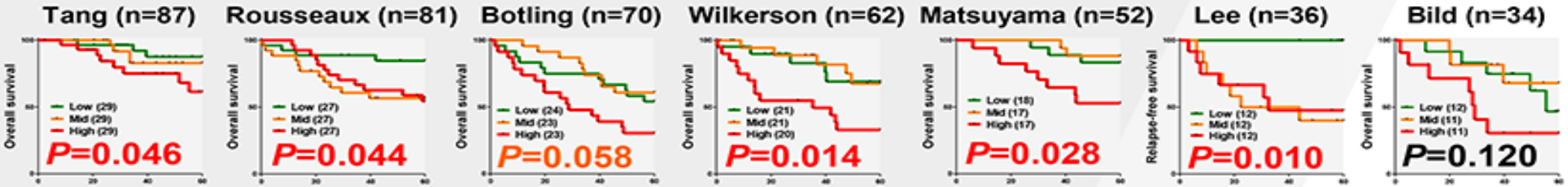
- Lowest tertile
- Middle tertile
- Highest tertile

5 original cohorts of stage I adenocarcinoma



- Akagi, I, Okayama, H et al, Cancer Res 73:3821-32, 2013

7 new cohorts of stage I adenocarcinoma



- Okayama, H, Schetter, A ...Harris CC Cancer Epi Prev Biomarker 23:2884-94, 2014.

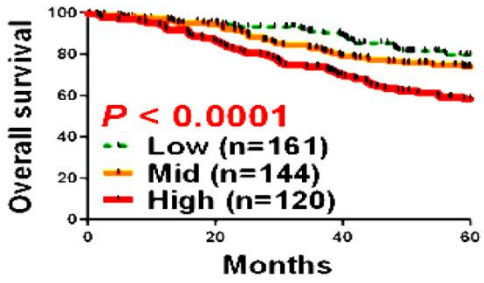
Meta-analysis

Meta-Analysis of the 4-gene Prognostic Classifier (Increased XPO1, BRCA1 and HIF1a and Decreased DLC1) in 12 Independent Cohorts of Stage I Patients

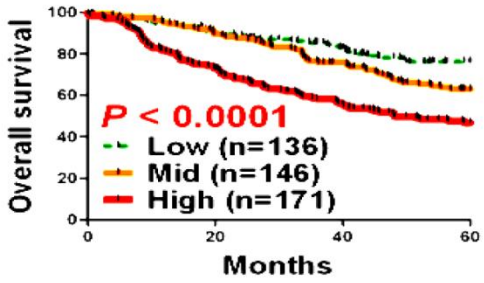
- 883 Stage I Patients

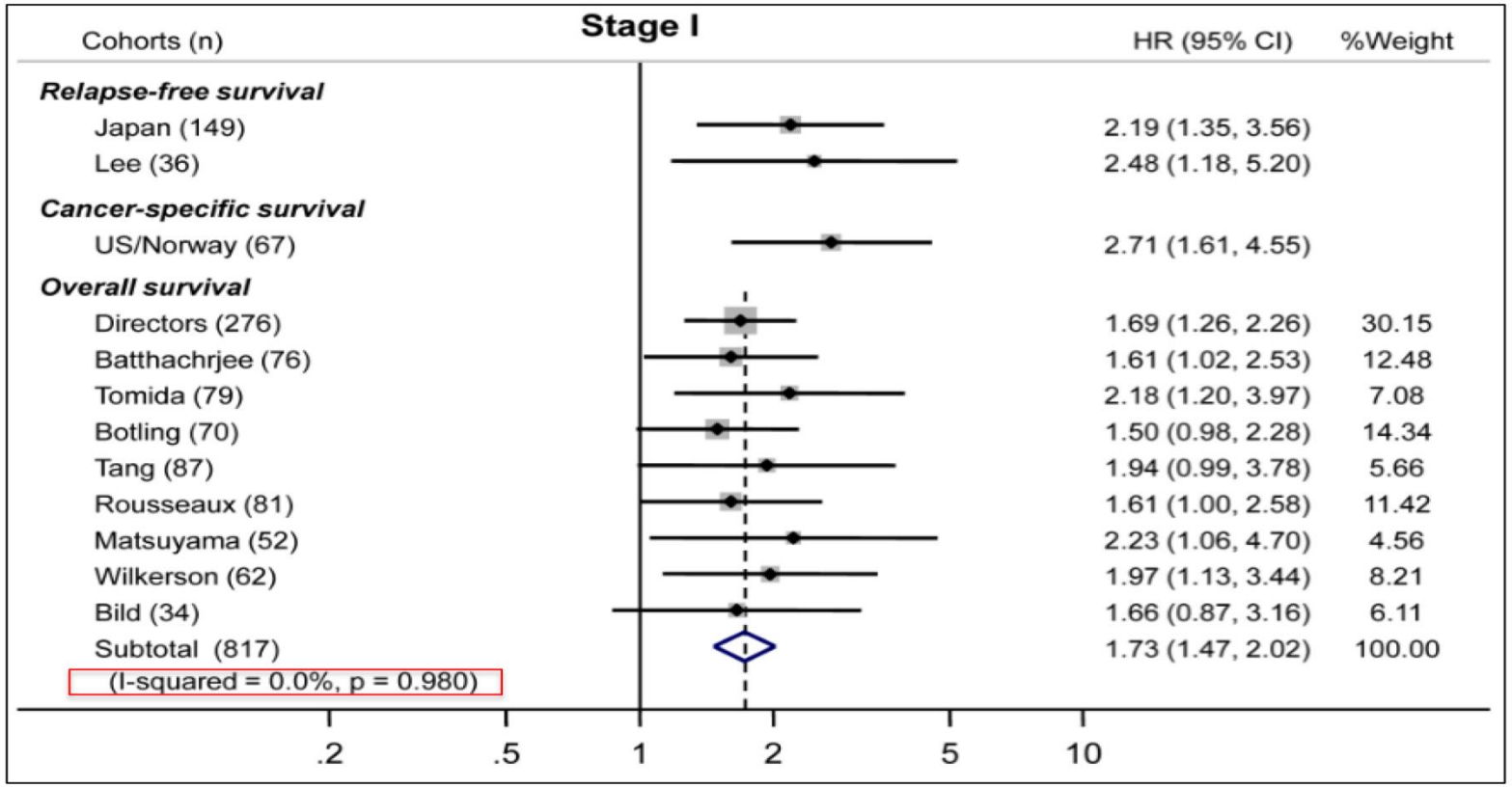
- Combined models included 9 datasets (n=817) with overall survival information

4-gene in Stage IA



4-gene in Stage IB





Okayama, H, Schetter, A ...Harris CC Cancer Epi Prev Biomarker 23:2884-94, 2014.

Mechanistic Cancer Biomarkers

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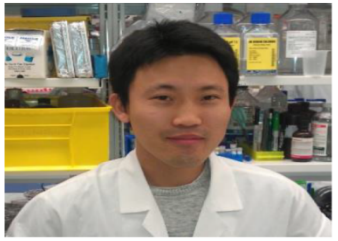
Mechanistic Cancer Biomarkers: Proof of Principle in Lung Adenocarcinoma

- **Hypothesis: The combination of protein-coding genes that are mechanistically related to lung cancer and the non-coding mir-21 is a better prognostic classifier than either alone**



Hiro Okayama

Ichiro Akagi

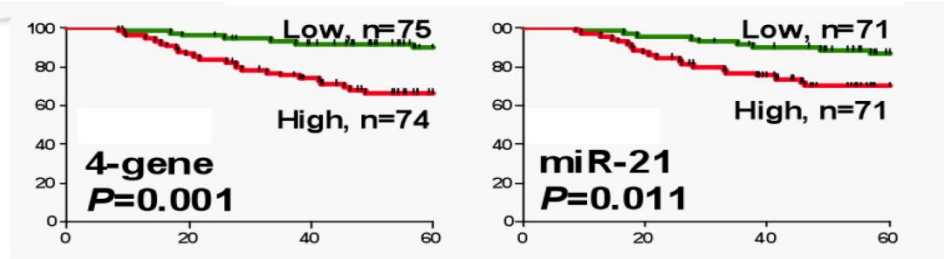
Akagi et al, Cancer Res. 73: 3821-32, 2013

Prognosis of Stage I Lung Adenocarcinoma

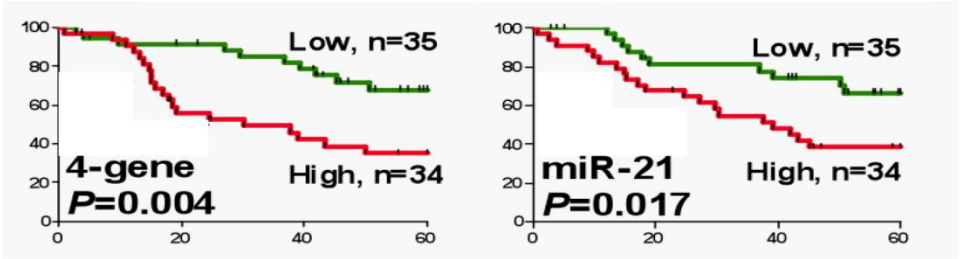
CENTER FOR CANCER RESEARCH

Hypothesis: The Combination of miR-21 and Four Coding Genes (Increased XPO1, BRCA1 and HIF1a and Decreased DLC1) Predicts Prognosis of Stage I Lung Adenocarcinoma

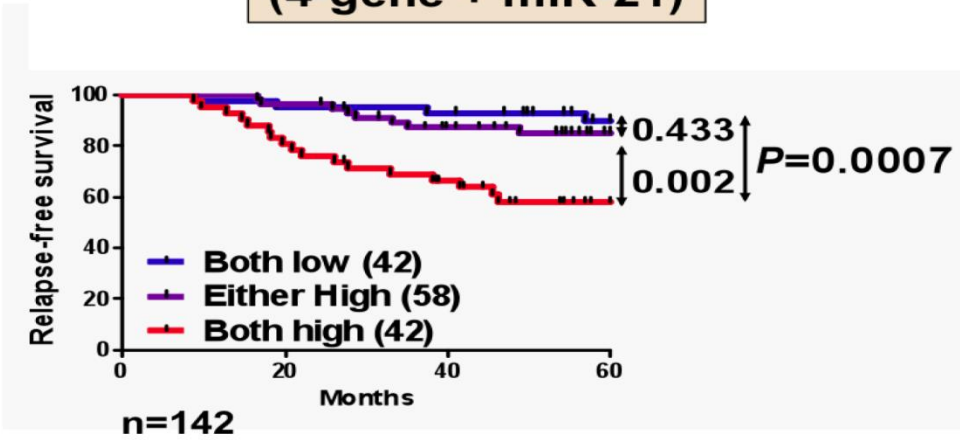
Japan (Stage IA > IB)



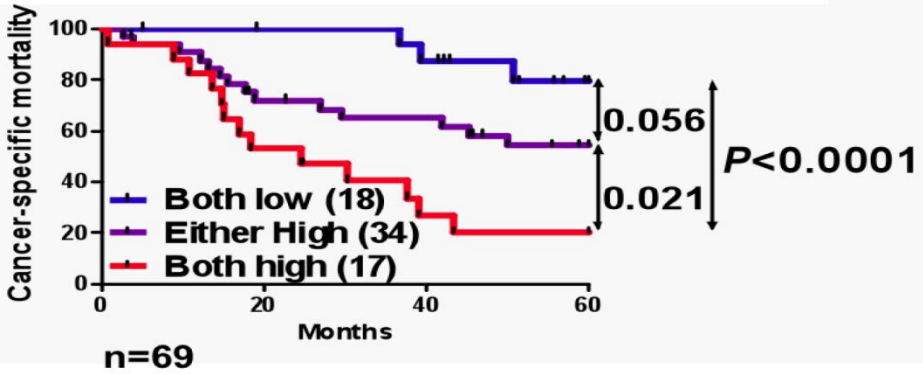
US/Norway (Stage IB > IA)



Combined (4-gene + miR-21)



Combined (4-gene + miR-21)



Early stage cancer

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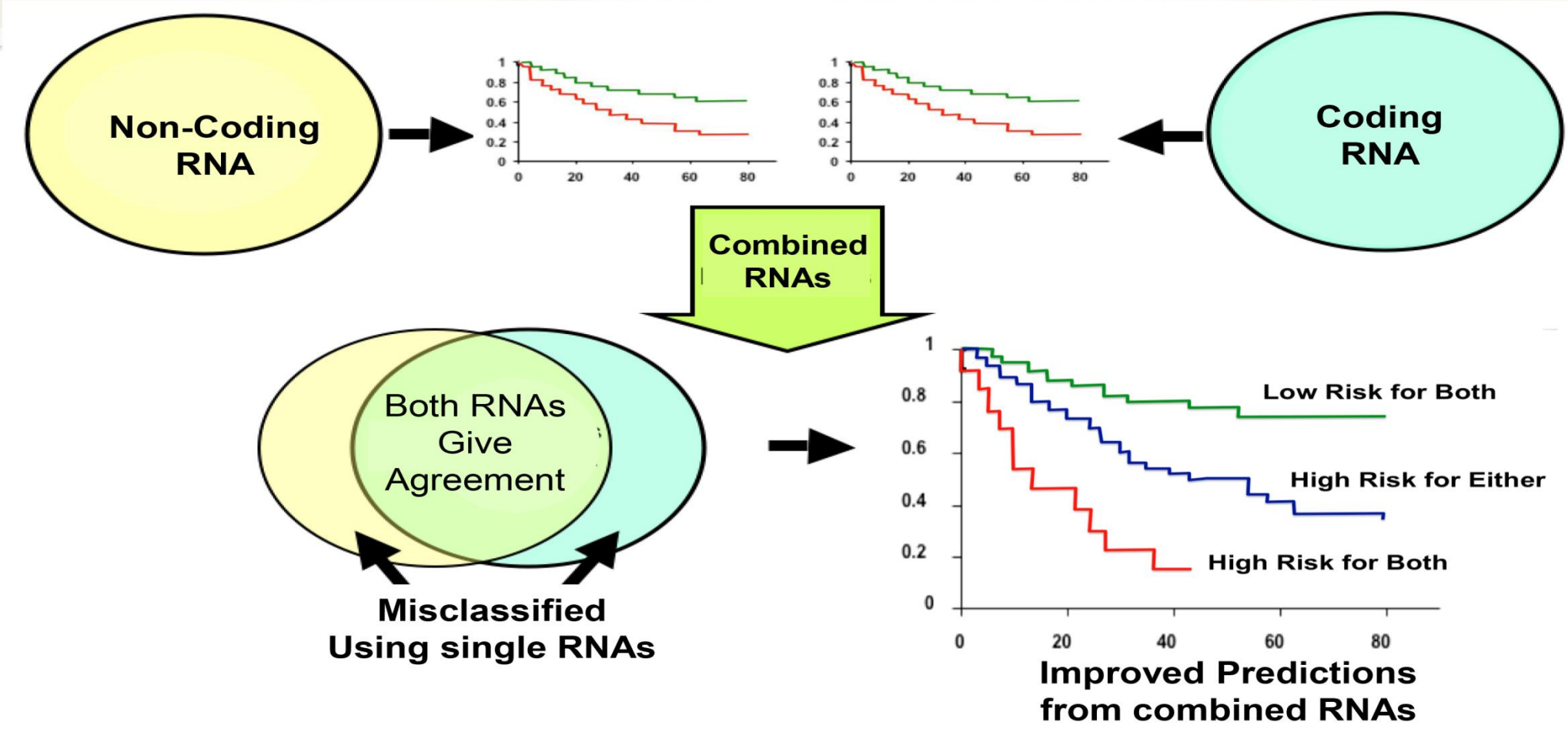
Principle: The Combination of Protein Coding and Non-Coding Gene Expression is a more Robust Prognostic Classifier of Early Stage Cancer



Further proof of Principle

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Further Proof of Principle

- **Colon Carcinoma**

  Schetter et al Clin. Cancer Res 15: 5878, 2009.

- **Esophageal Adenocarcinoma**

  Nguyen et al Clin. Cancer Res 16: 5824, 2013

- **Esophageal Squamous Cell Carcinoma**

  Zhao et al Int J Cancer 132: 2901, 2013

- **Lung Adenocarcinoma**

  Akagi et al Cancer Res 73: 3821, 2013

- **Breast Adenocarcinoma**

  Volinia et al P.N.A.S. 110:7413, 2013

Epigenome

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Precision Medicine

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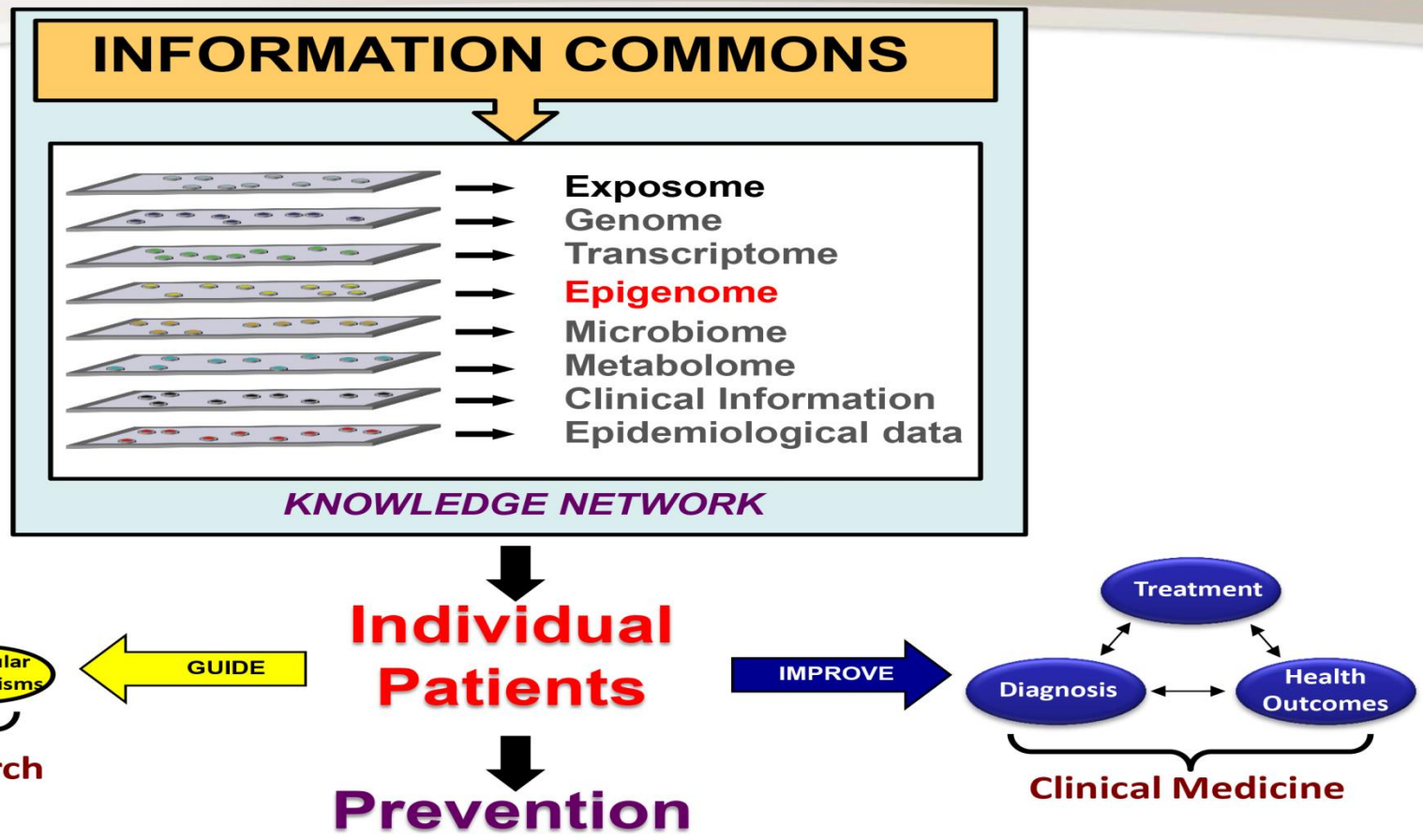

Modified: Toward Precision Medicine, National Research Council, National Academy of Science, 2011

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EPIGENOME: DNA METHYLATION

HYPOTHESIS:

An integrated biomarker classifier of stage I lung adenocarcinoma based on independent mRNA, microRNA and DNA methylation biomarkers, will further improve the prognostic classification

Ana Robles

Robles a et al., J. Thoracic Oncology 10: 1037-48, 2015

Epigenetic signature

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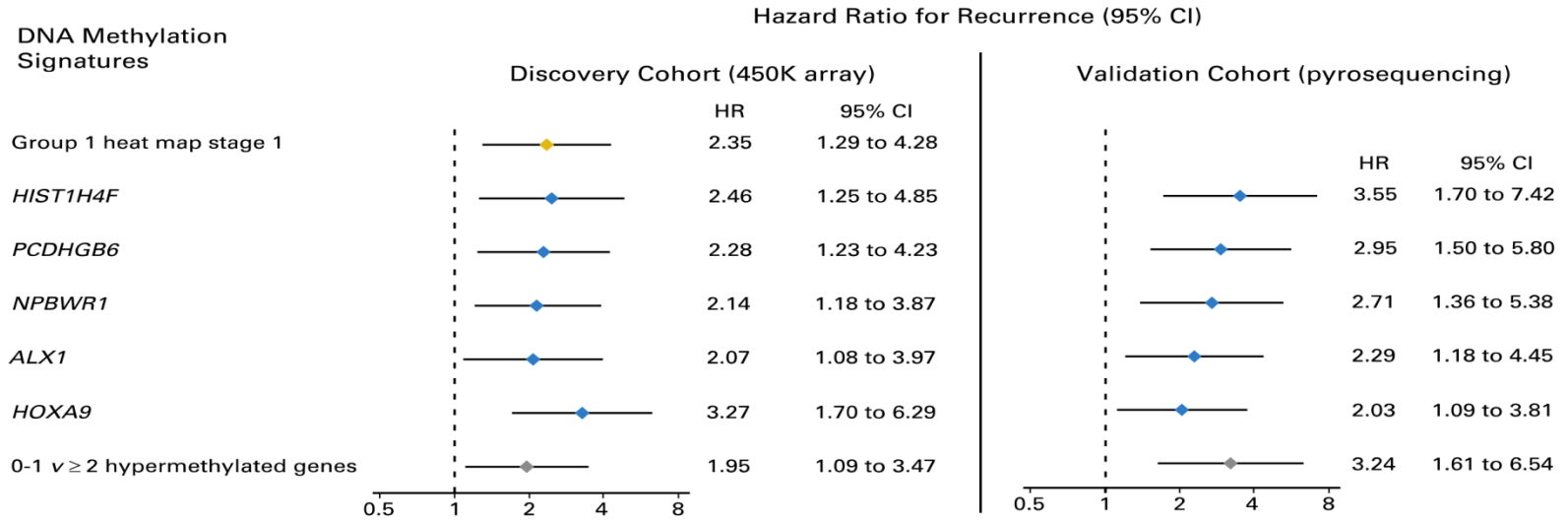
DNA Methylation in NSCLC is a Prognostic Epigenetic Signature

A Prognostic DNA Methylation Signature for Stage I Non–Small-Cell Lung Cancer

Juan Sandoval, Jesus Mendez-Gonzalez, Ernest Nadal, Guoan Chen, F. Javier Carmona, Sergi Sayols, Sebastian Moran, Holger Heyn, Miguel Vizoso, Antonio Gomez, Montse Sanchez-Cespedes, Yassen Assenov, Fabian Müller, Christoph Bock, Miquel Taron, Josefina Mora, Lucia A. Muscarella, Triantafillos Liloglou, Michael Davies, Marina Pollan, Maria J. Pajares, Wenceslao Torre, Luis M. Montuenga, Elisabeth Brambilla, John K. Field, Luca Roz, Marco Lo Iacono, Giorgio V. Scagliotti, Rafael Rosell, David G. Beer, and Manel Esteller

(J Clin Oncol 2013;31(32):4140-7).



Stage I NSCLC (ADC, SCC)

Combined score

An Increasing Combined Score of Mechanistic Biomarkers Conferred Greater Risk for Poor Outcome in Stage 1 Lung Cancer, and Within Stage 1A/1B Subgroup Analysis

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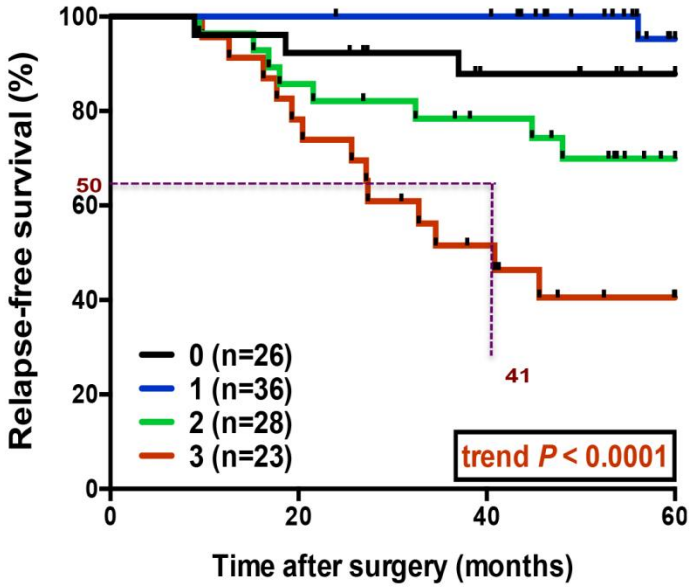
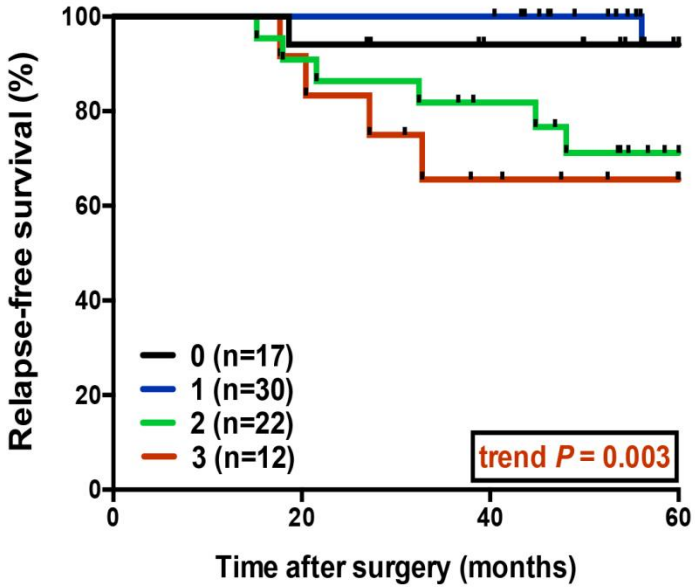
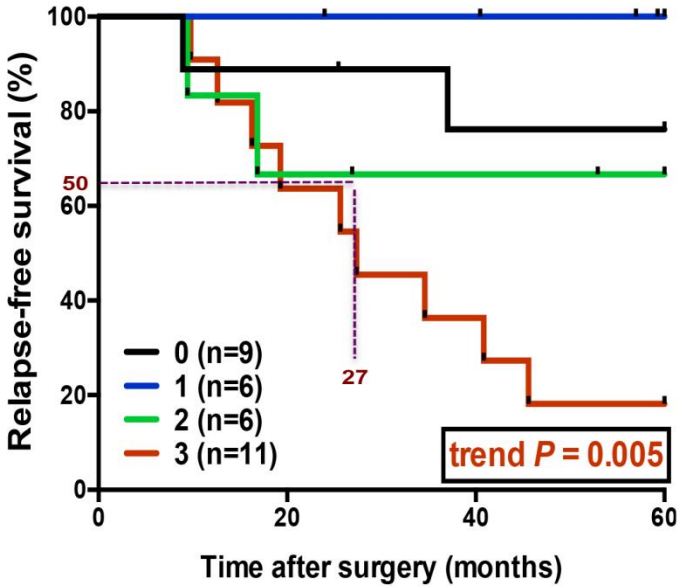
Stage 1



Stage 1A



Stage 1B



- Cases were categorized according to the combined number of high values for HOXA9 methylation, miR-21 (Clin. Cancer Res. 2011;17:1875-82) and 4-gene signature (Cancer Res. 2013;73:3821-32) and HOXA9 promoter methylation(J. Thoracic Oncology 10: 1037-48, 2015.
- *P* values calculated by log-rank test for trend.

Metabolome

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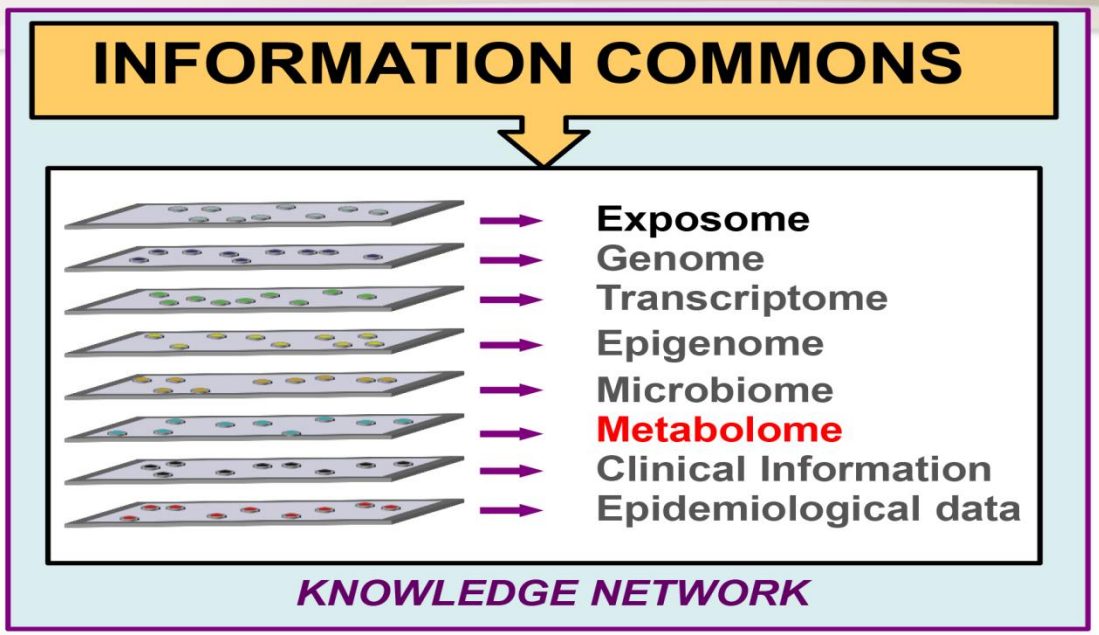
Precision Medicine



Modified: Toward Precision Medicine, National Research Council, National Academy of Science, 2011

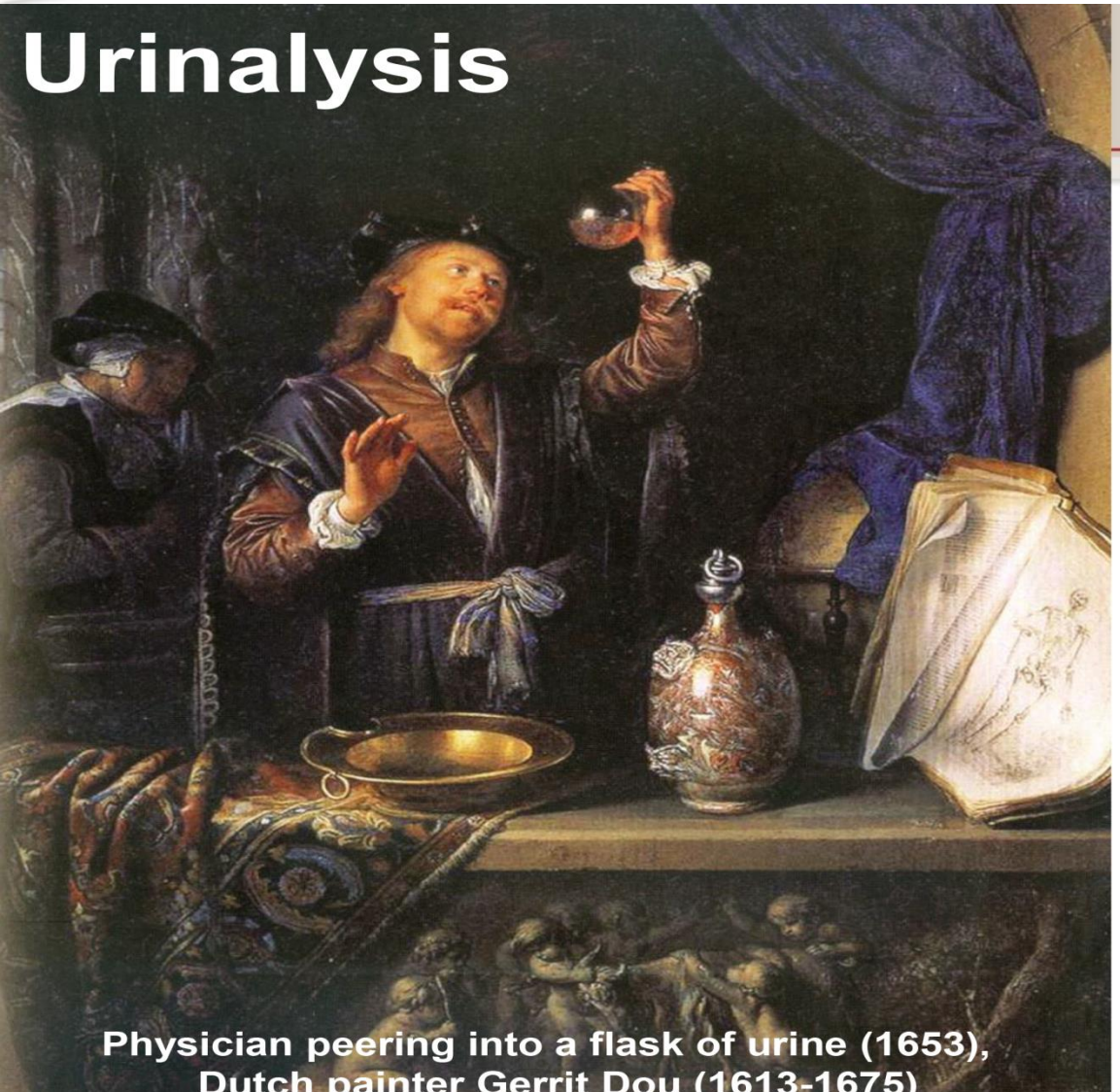
Tumor Metabolism and Metabolome

Hypothesis: Unbiased metabolomics will discover biomarkers associated with the risk, diagnosis, prognosis and therapeutic outcome of lung cancer.

Majda Haznadar

Ewy Mathe

Urinalysis



Physician peering into a flask of urine (1653), Dutch painter Gerrit Dou (1613-1675)

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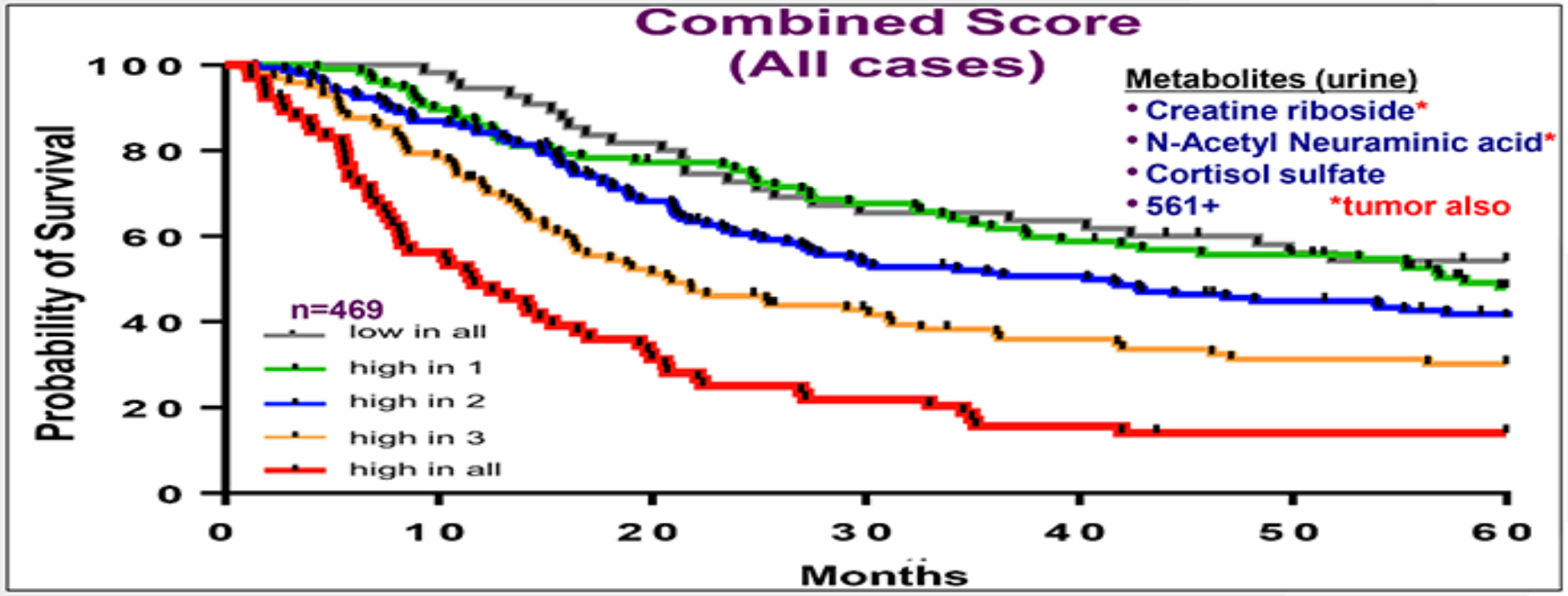
- **Hippocrates tasted urine in the diagnosis of disease in his patients.** ***(460-370, BC)***
- **Physiologist J. A. Armstrong writes, "From a liquid window through which physicians felt they could view the body's inner workings, urine led to the beginnings of laboratory medicine…"**

Lung cancer metabolome

Lung Cancer Metabolome and Prognosis



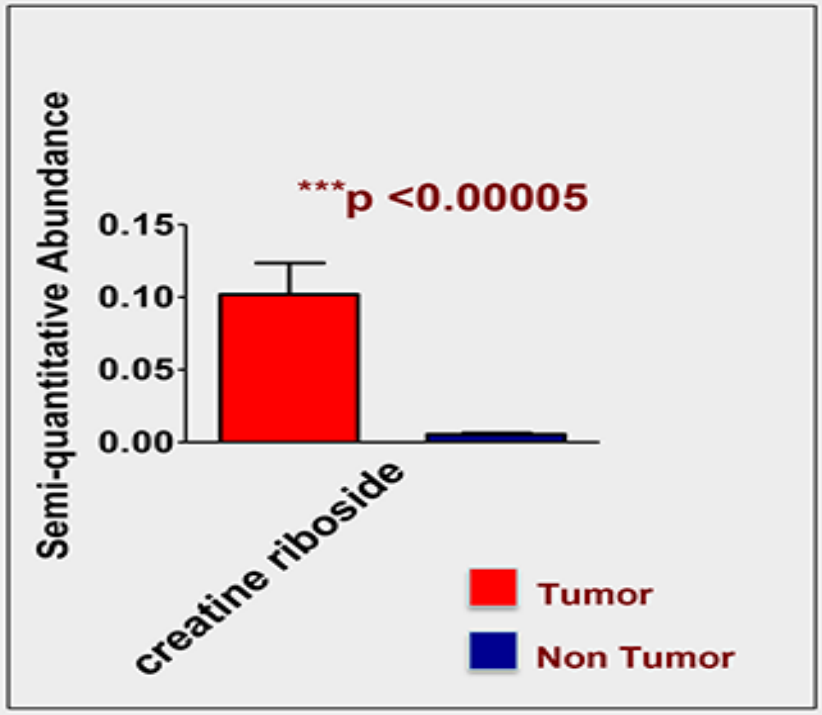
	HR (95% CI)	P
Reference	1	1.00
High in 1	1.10 (0.67-1.75)	0.75
High in 2	1.36 (0.86-2.14)	0.19
High in 3	1.84 (1.15-2.94)	0.01
High in all	3.65 (2.34-6.00)	<0.00001

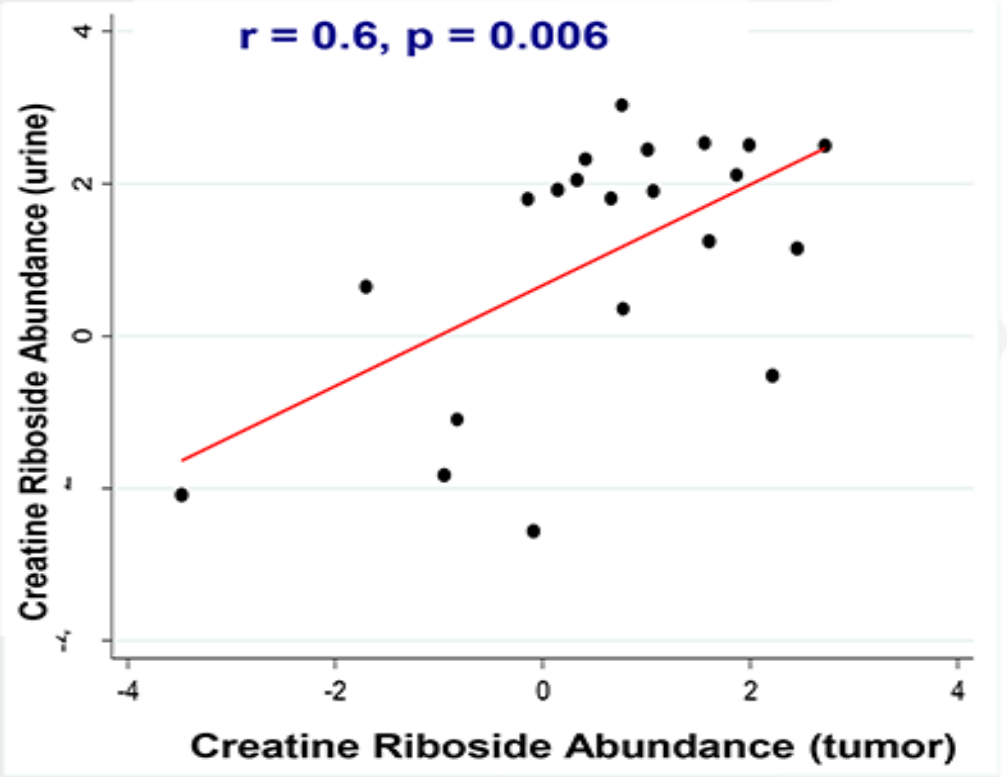
Mathe, E...Harris, CC, Cancer Res., 74: 3259-70, 2014

Creatine ribose

Creatine Ribose is Positively Correlated in Cancer and Urine

Lung Adenocarcinoma
(targeted UPLC-MS/MS)
N = 48 (Tumor), 48 (Non Tumor)





Creatine Riboside and NANA

High Levels of Creatine Riboside and NANA are Associated with Increased Lung Cancer Risk

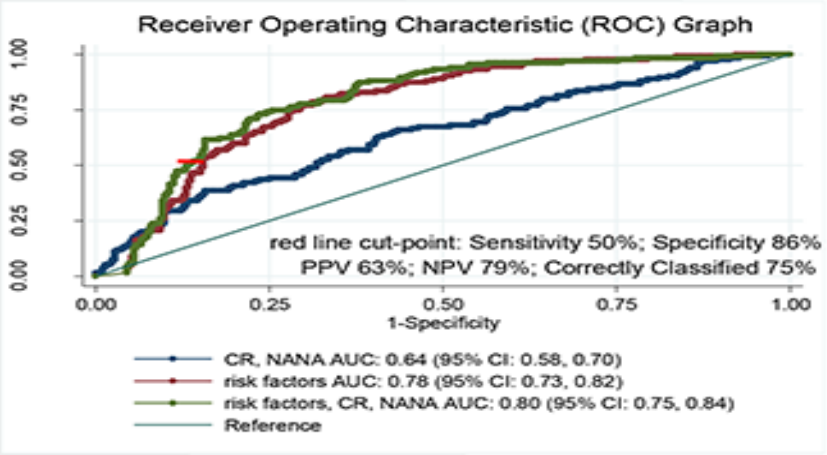
Nested Lung Cancer Case-Control Study

- Prospective Southern Community Cohort Study (SCCS)
- 178 cases, 351 controls
- The majority adeno- and squamous-cell carcinoma histologies
- 53% African Americans, 42% European Americans
- Individually matched controls randomly selected in a 2:1 ratio to cases using incidence density sampling among cohort members matched by age (+/- 2 years), sex, race, recruitment site, menopausal status (women), and date of sample collection (+/- 6 months)

			Univariate		Multivariate*
Metabolite	Controls %	Cases %	OR (95% CI)	P	OR (95% CI)
$Referent_{low}$			1		
$Creatine\ riboside_{high}$	25	39	2.0 (1.3, 3.0)	0.001	1.9 (1.0, 3.6)
N-$acetylneuraminic\ acid_{high}$	25	39	2.0 (1.3, 3.0)	0.001	2.0 (1.1, 3.6)

Levels dichotomized into high and low based on the 75th percentile of population control abundances (low = referent)

* Multivariate conditional logistic regression adjustated for age, BMI, income, education level, prior history of COPD, family history of lung cancer, smoking status and pack years. Individually matched controls selected in 2:1 ratio to cases using date of sample collection (+/- 6 months).



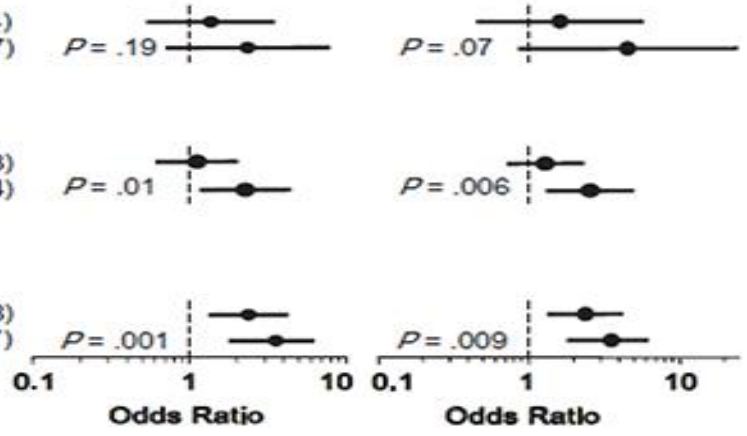
Haznadar M, ... Harris CC. CEBP 25:978-86, 2016

IL-8 and CRP

The Combination of Serum IL-8 and CRP is a Robust Marker of Lung Cancer Risk

Association of high IL-8 and CRP serum levels with lung cancer risk in PLCO study

IL-8 and CRP levels by smoking category	No. of case patients and control subjects: Reference (low IL-8 and low CRP)	No. of case patients and control subjects: Comparison to reference	Odds Ratio (95% CI)
Never			
High IL-8 and low CRP or high CRP and low IL-8	9/34	19/57	1.32 (0.50 to 3.54)
High IL-8 and high CRP	9/34	9/15	2.28 (0.66 to 7.87)
Former			
High IL-8 and low CRP or high CRP and low IL-8	59/71	132/144	1.13 (0.73 to 1.73)
High IL-8 and high CRP	59/71	100/71	1.76 (1.09 to 2.84)
Current			
High IL-8 and low CRP or high CRP and low IL-8	23/49	102/97	2.39 (1.33 to 4.28)
High IL-8 and high CRP	23/49	79/57	3.33 (1.77 to 6.27)



Pine SR, ... Harris CC. JNCI 103: 1112-1122, 2011

Creatine riboside and NANA

High Levels of Creatine Riboside and NANA are Associated with Lung Cancer Risk in European Americans

EUROPEAN AMERICANS (N = 74 cases)

			Univariate		Multivariate*	
Metabolite‡	**Controls %**	**Cases %**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
$Referent_{low}$			1			
$Creatine\ riboside_{high}$	15	31	2.7 (1.3, 5.4)	0.005	12.2 (2.2, 69.6)	0.005
$N\text{-acetylneuraminic acid}_{high}$	24	46	2.8 (1.5, 5.2)	0.001	10.1 (2.2, 46.8)	0.003

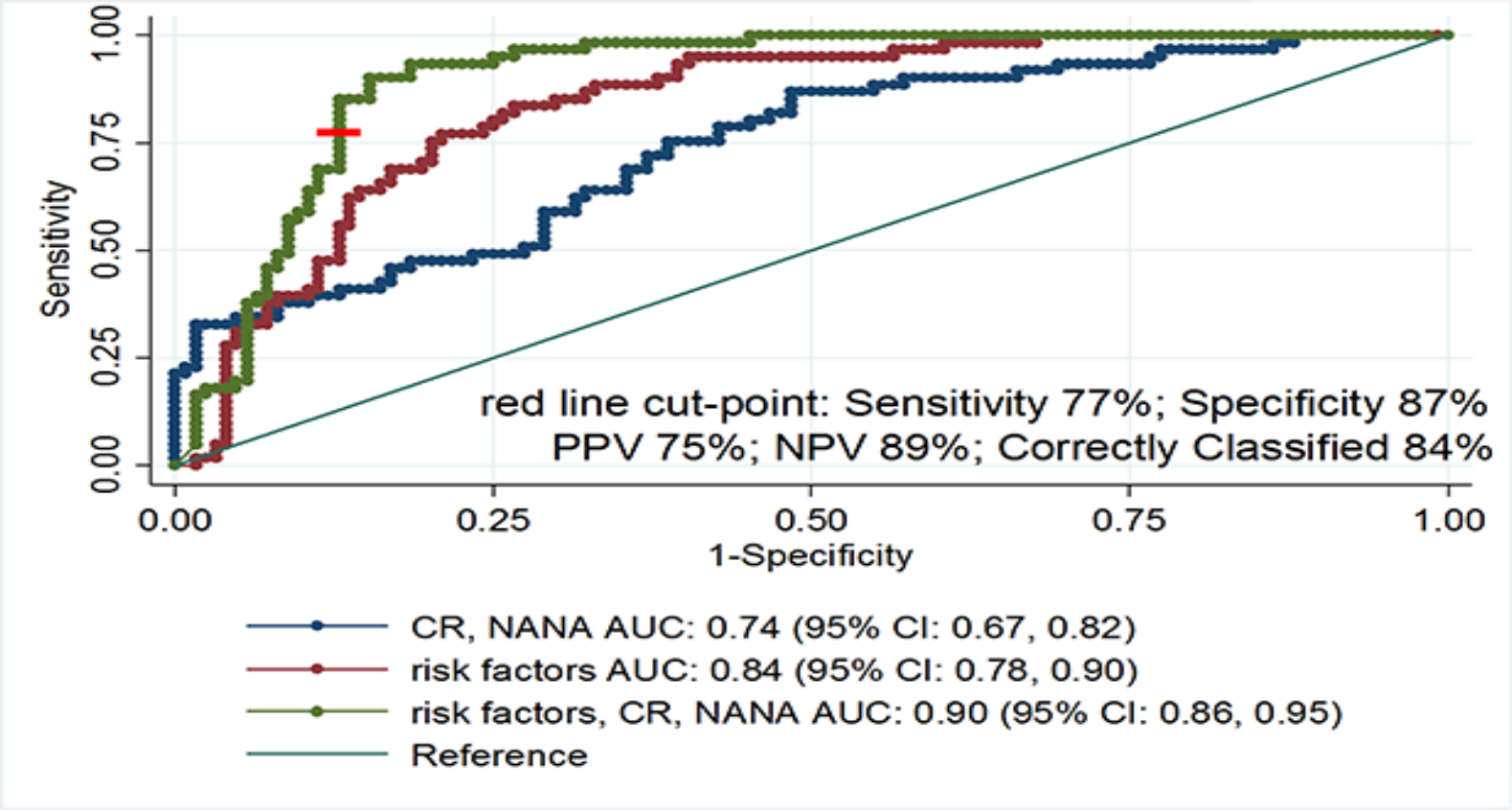
AFRICAN AMERICANS (N = 96 cases)

			Univariate		Multivariate*	
Metabolite‡	**Controls %**	**Cases %**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
$Referent_{low}$			1			
$Creatine\ riboside_{high}$	34	46	1.6 (1.0, 2.7)	0.06	1.0 (0.5, 2.1)	0.96
$N\text{-acetylneuraminic acid}_{high}$	26	33	1.4 (0.8, 2.4)	0.20	1.0 (0.4, 2.4)	0.95

Haznadar M, … Harris CC. CEBP 25: 978-86, 2016

Creatine riboside and NANA

Creatine Riboside and NANA May Be Able to Refine Screening Decisions in High Risk European Americans



Haznadar M, … Harris CC. CEBP 25:978-86, 2016

Low-dose CT

Low-Dose CT Screening for Lung Cancer Detects Early Stage and Reduces Mortality

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 4, 2011 VOL. 365 NO. 5

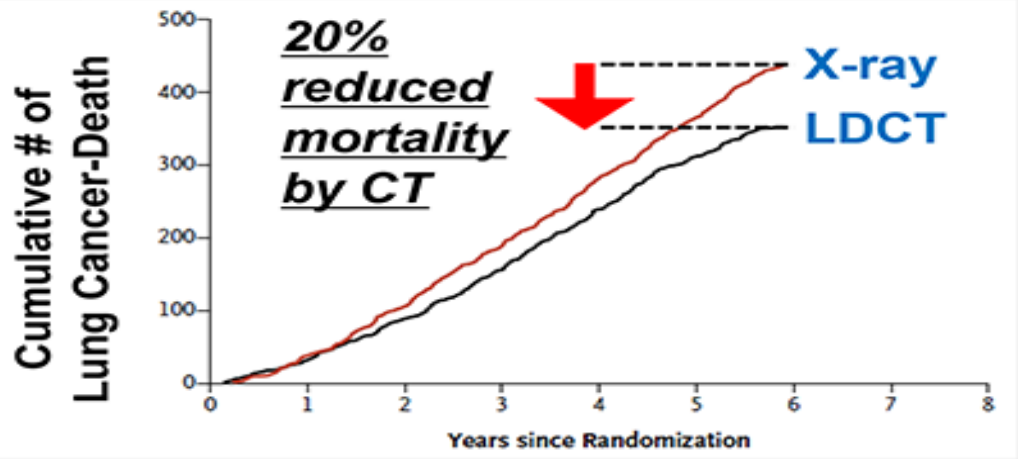
Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

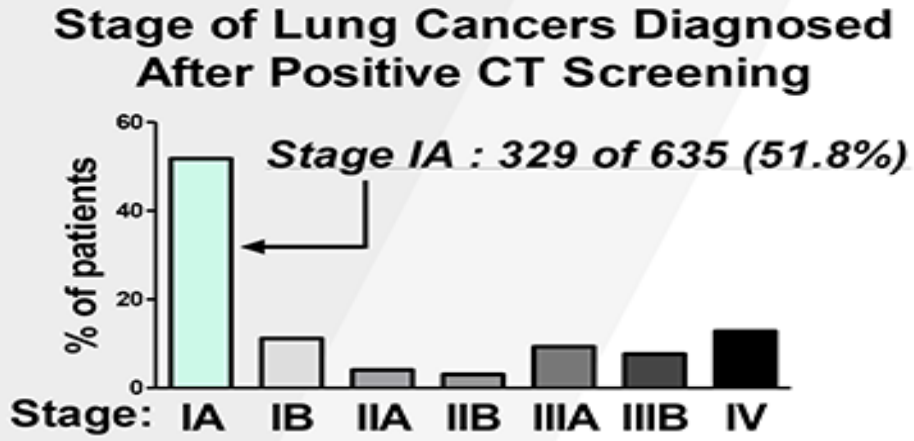
The National Lung Screening Trial Research Team*

n=53,454 participants
Current/former heavy smokers, 55-77 y.o.

X-ray	LDCT
n=26732	n=26722

Low-Dose CT
- False Positive Rate = 96.4%

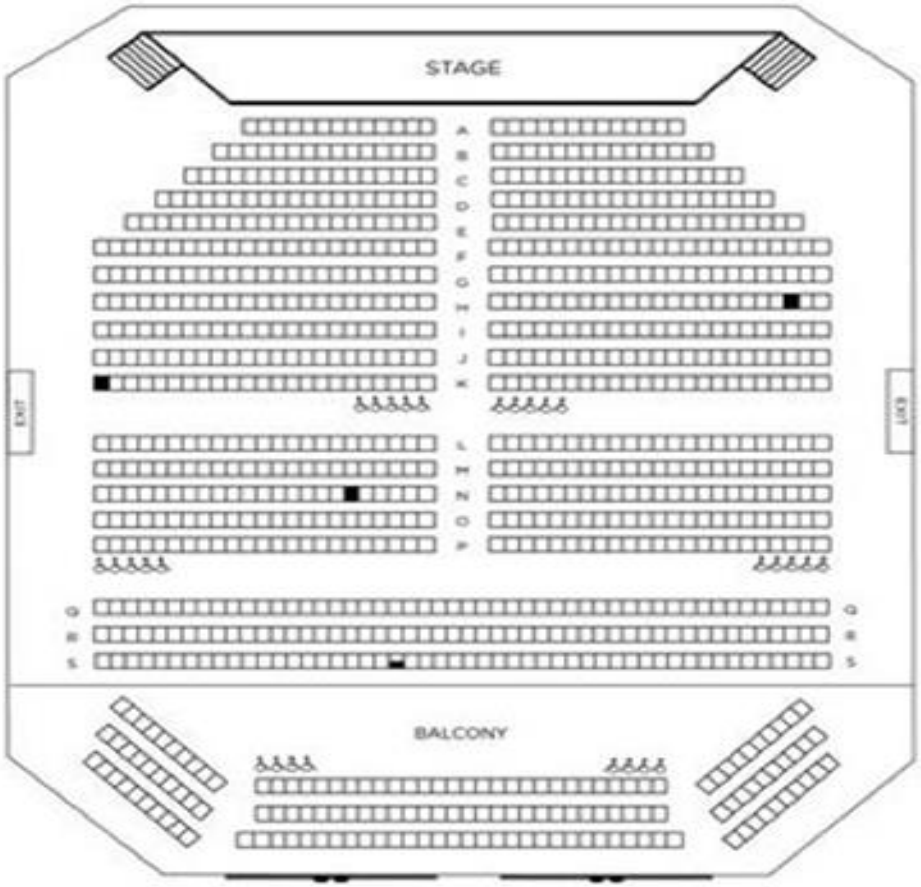




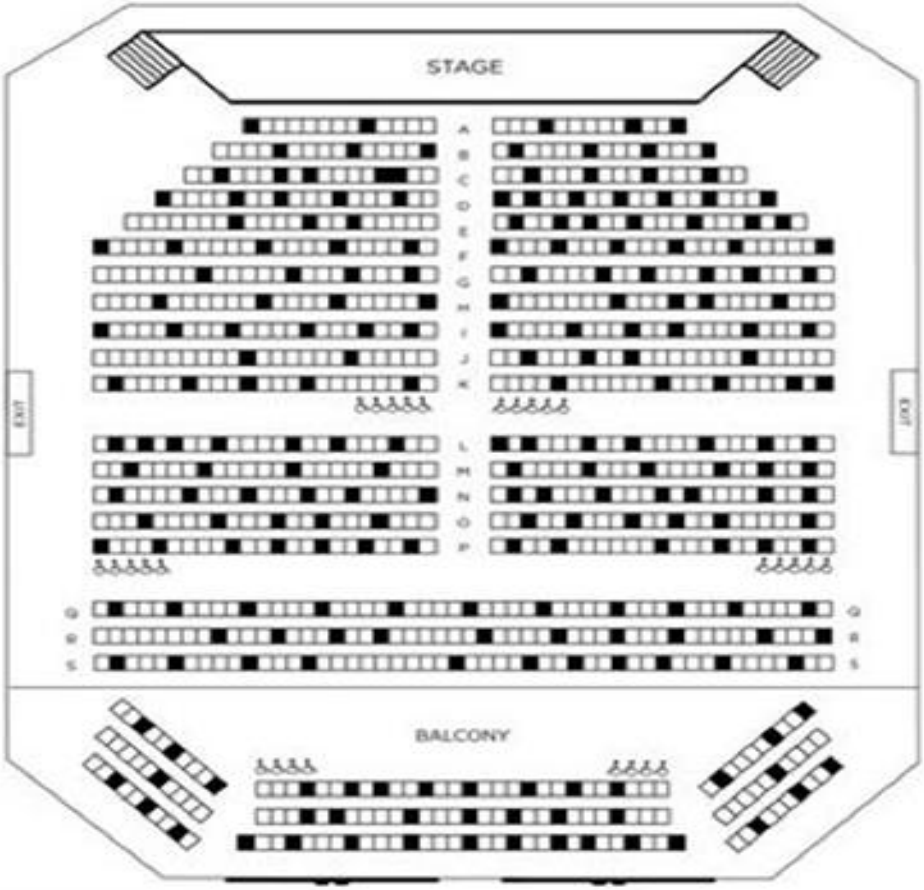
Spiral CT

Analogy of the Number of Lung Cancer Deaths Averted with Annual Spiral CT Scans, Compared to the Total Number of Scans Done

Lung Cancer

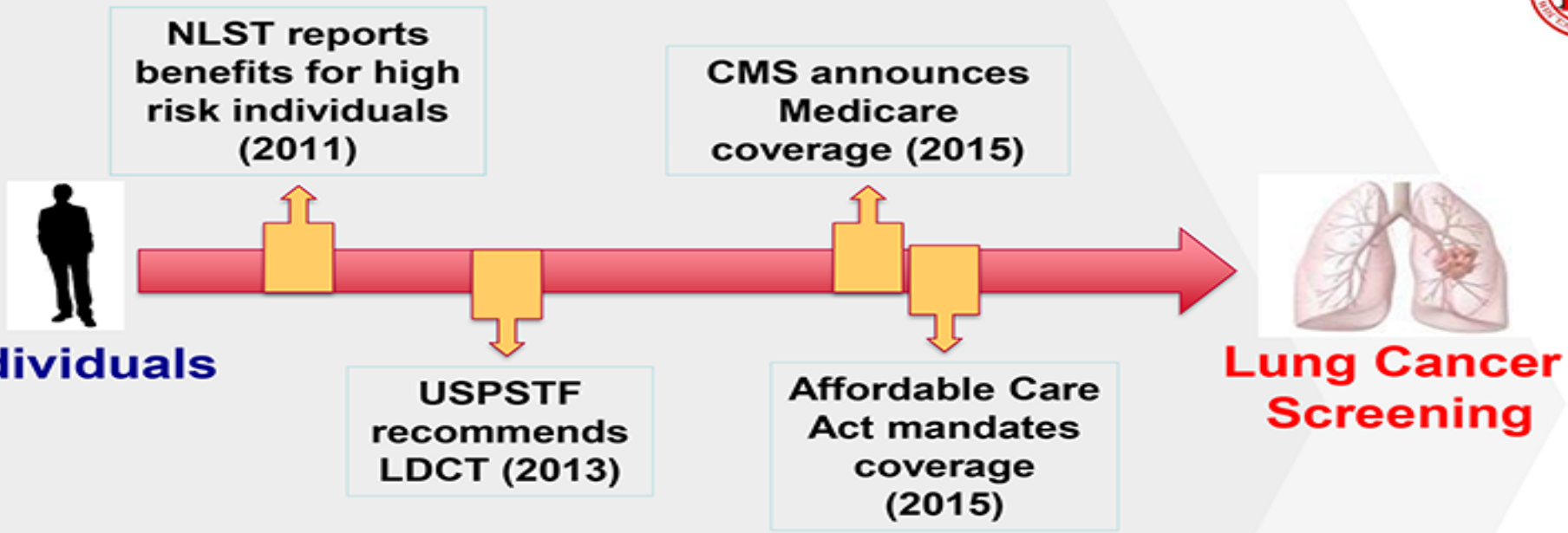


False Positive



Low dose computed tomography

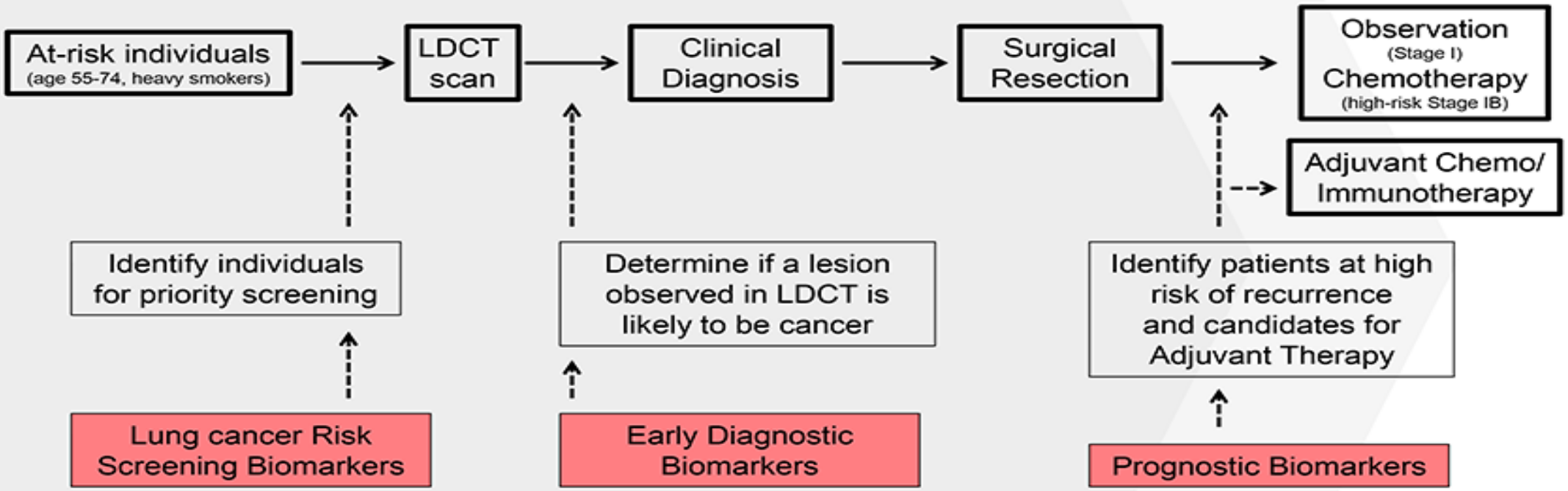
Low-Dose Computed Tomography (LDCT)



- High risk: age 55-74, 30 pack-year history, quit within 15 years or current smoker
  - Need to identify high risk individuals outside criteria?
  - Need to identify individuals within the criteria and prioritize those with the greatest risk?
- 8.8 million Americans were LDCT-eligible (2010)

Early stage lung cancer

Early Stage Lung Cancer: Unmet needs

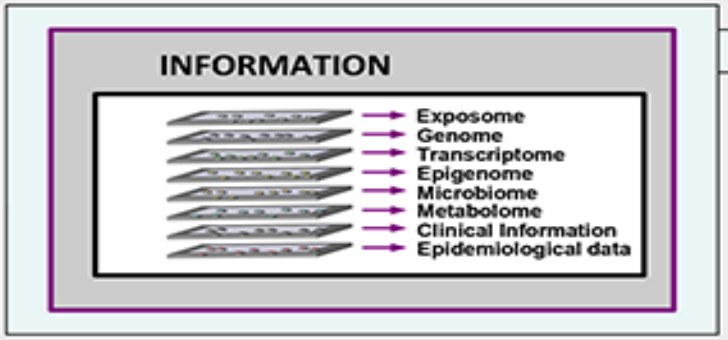


Precision medicine

A Goal of Precision Medicine is to Identify 25% of Stage I Lung Cancer Patients whose Cancer will recur

Stage I patients after curative surgery

25% of stage I patients recur and die of disease.



- Decrease False Positive Rate of 96.4%
- Decrease Financial Cost
- Improve Patient Care
- Guide Mechanistic Studies

Stage IA
<3cm, N0

Stage IB
3-5cm, N0

Surgery *Surgery*

Low risk **High risk**

Observe

Adjuvant immuno- and chemo-therapy

High risk patients who may have occult metastasis

Collaborators

COWORKERS AND COLLABORATORS

- Ichiro Akagi
- Majda Hazandar
- Teruhide Ishigame
- Ewy Mathe
- Rintaro Noro
- Hiro Okayama
- Ana Robles
- Brid Ryan
- Aaron Schetter
- Nozumo Yanaihawa
- Carlo Croce
- Akihiko Gemma
- Frank Gonzalez
- Aage Haugen
- Ke Yang
- Takashi Kohno
- SY Leung
- Sharon Pine
- Masahiro Seike
- Kouya Shiraishi
- Jun Yokota