

Precision medicine



PRECISION MEDICINE OF HUMAN LUNG CANCER

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NIH

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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.

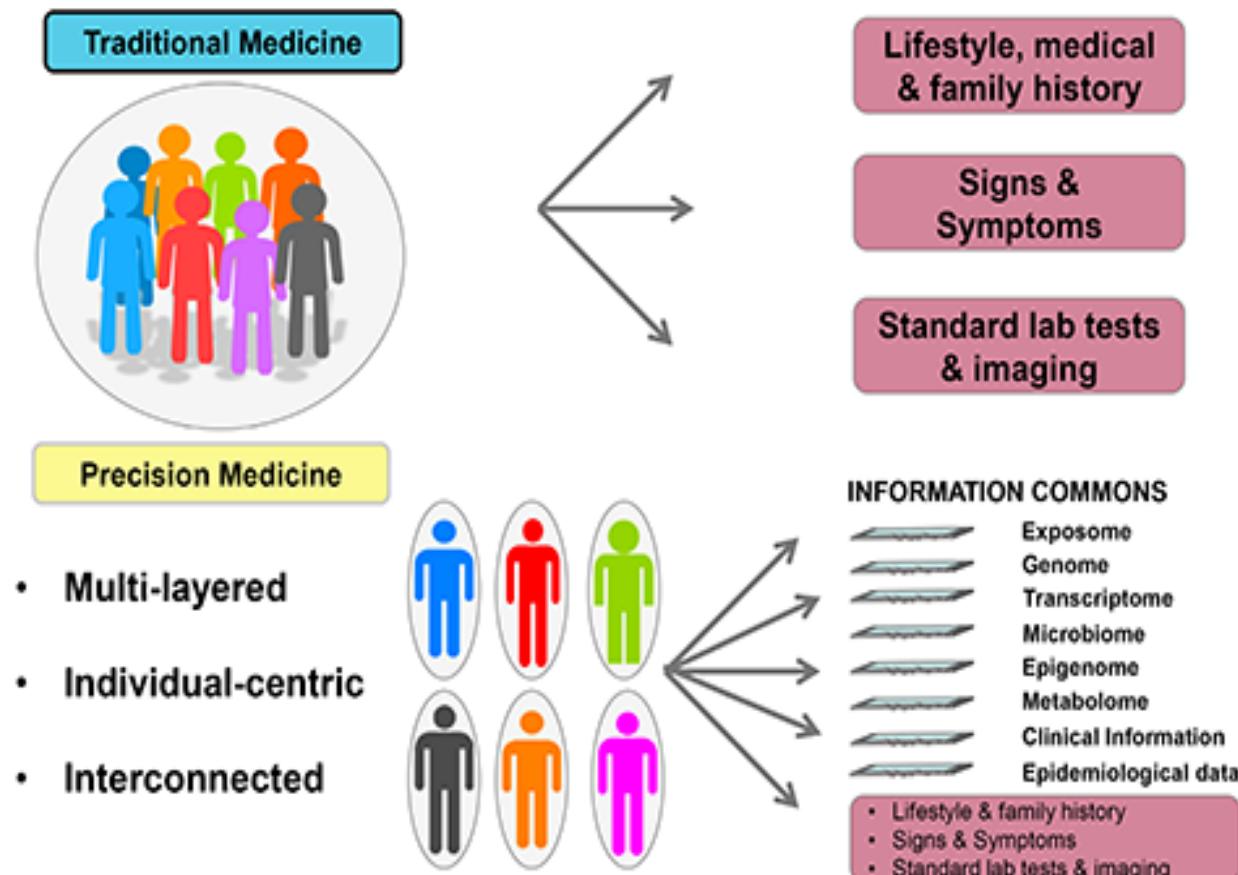
“Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”

— President Barack Obama, State of the Union Address, January 20, 2015

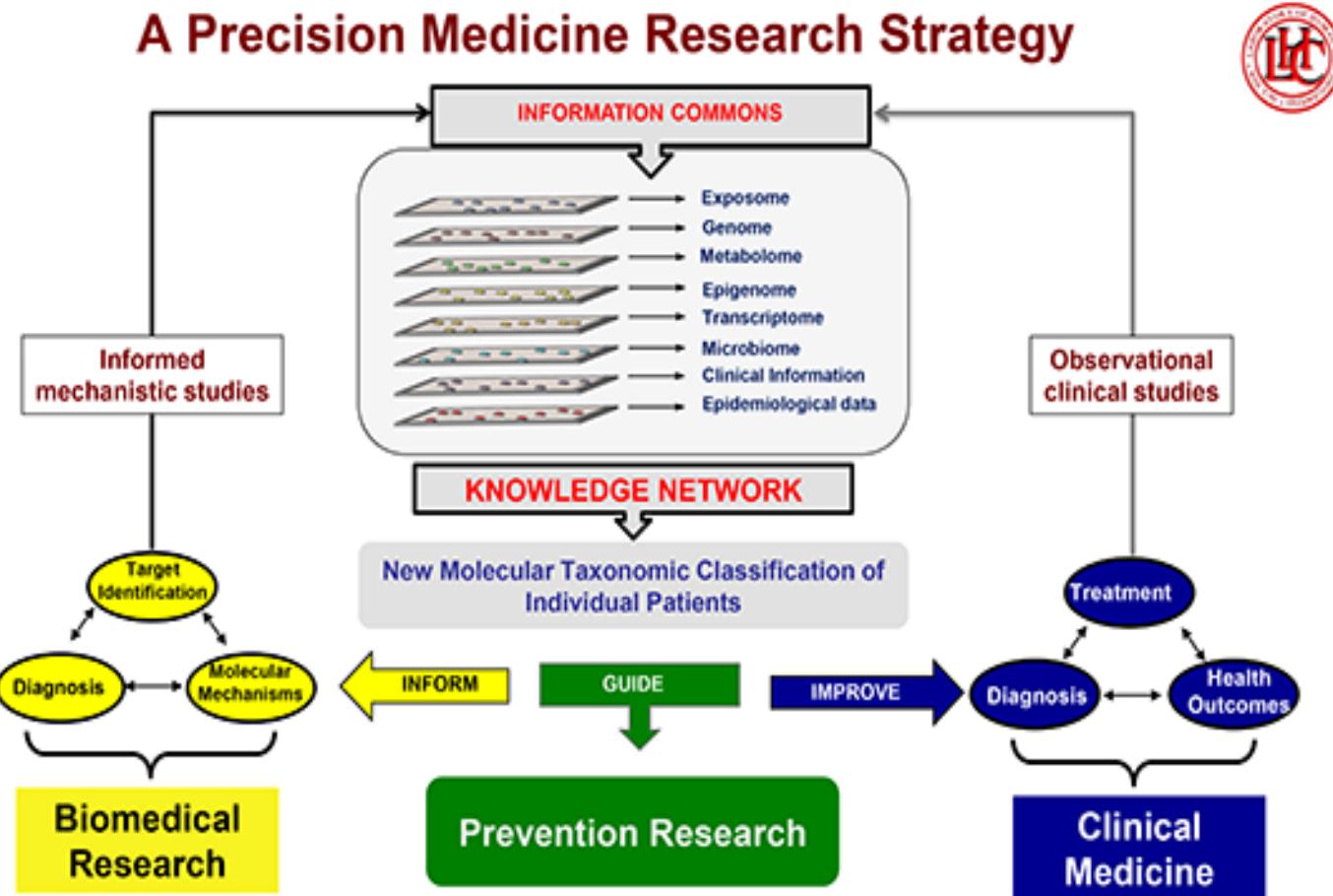
Collins F and Varmus H. NEJM 372: 793-5, 2015

Disease classification

Towards Precision Medicine and a Molecular Taxonomic Classification of Disease



Research strategy

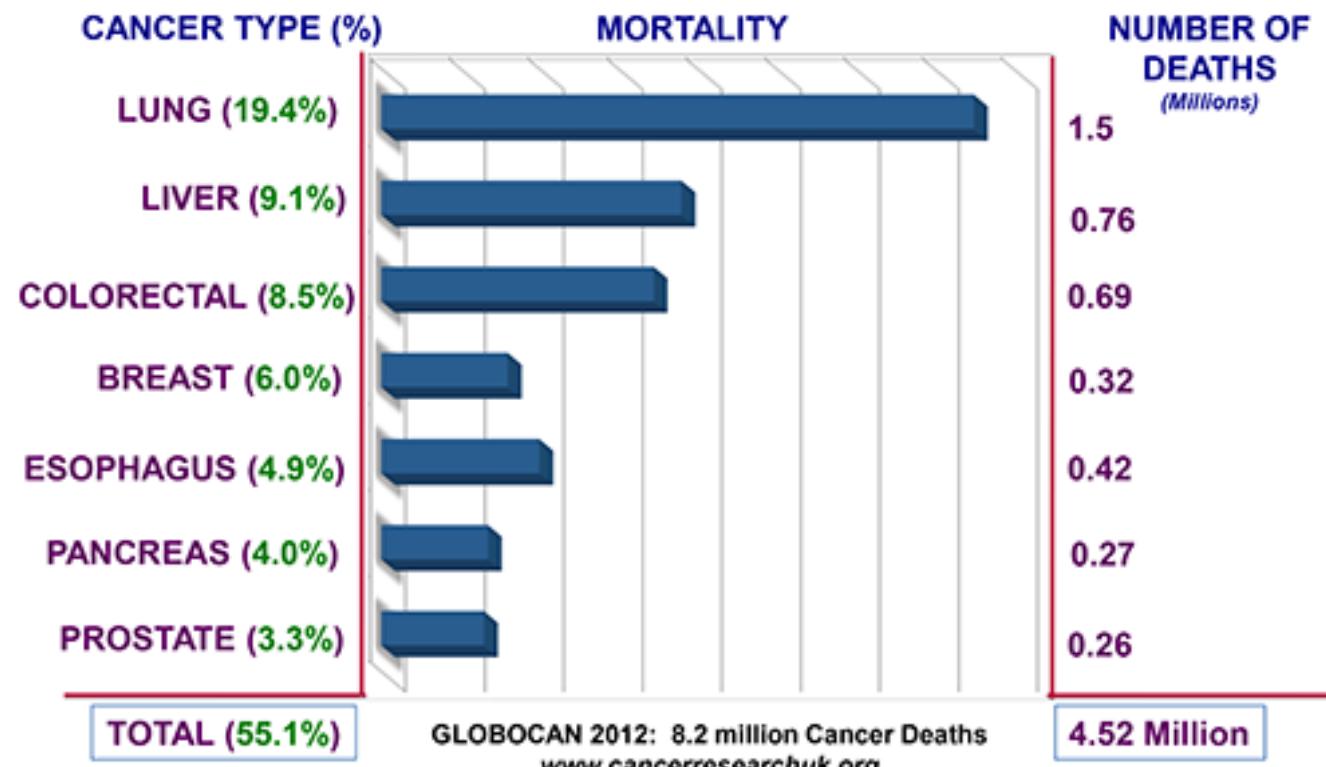


- Modified: "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease" (National Research Council 2011)
- Vargas, A. and Harris, CC, "Precision Medicine of Cancer", *Nature Review Cancer*, 18:525-33, 2016

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Worldwide cancers

Major Worldwide Lethal Types of Human Cancer



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

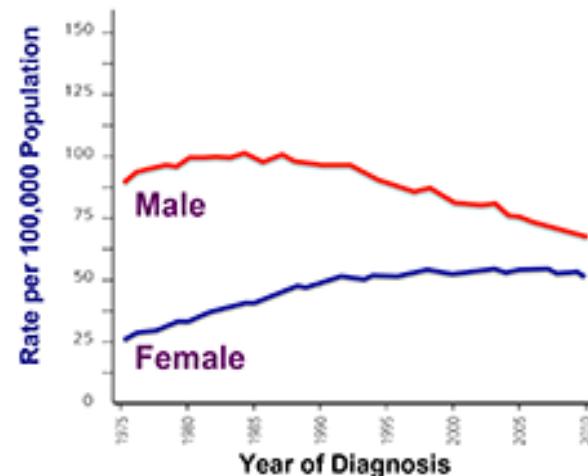
Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

Report of Surgeon General, Executive Summary, 2014

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Cancer Statistics (ACS), 2014

Lung & Bronchus



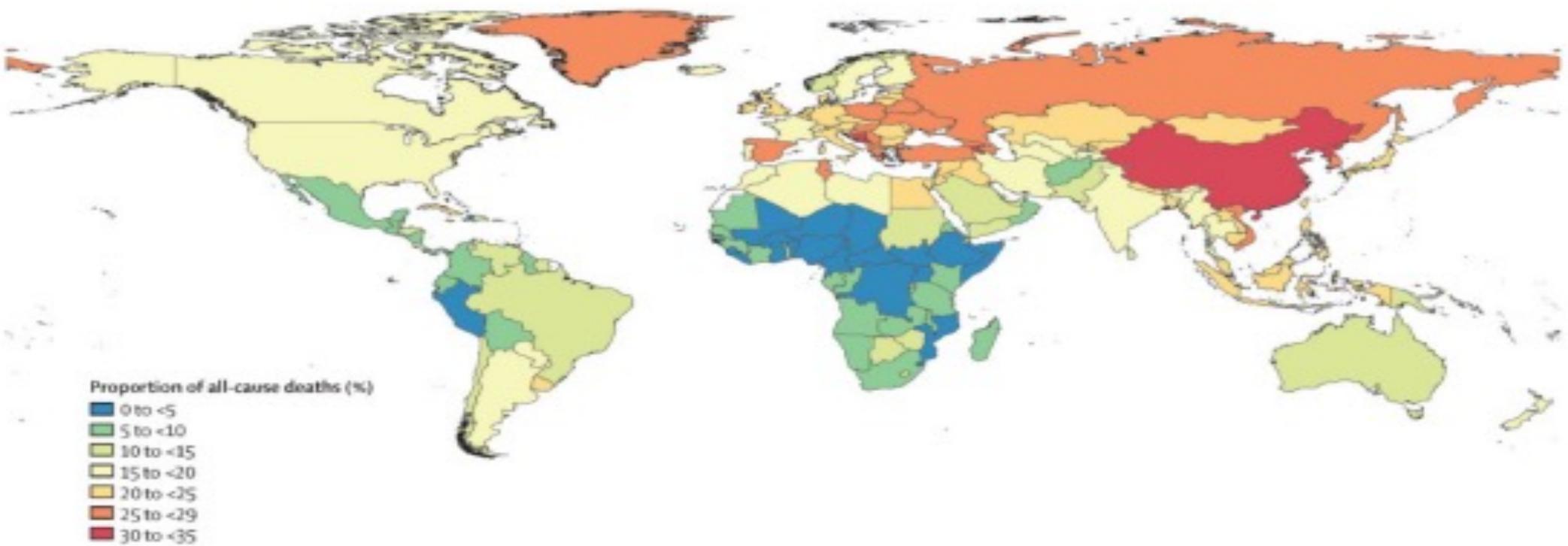
Siegel, R., et al., CA Cancer J Clin, 64: 9-29, 2014

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Male smoking deaths



PROPORTION OF ALL-CAUSE DEATHS ATTRIBUTABLE TO
SMOKING TOBACCO USE AMONG MALES OF ALL AGES IN 2019



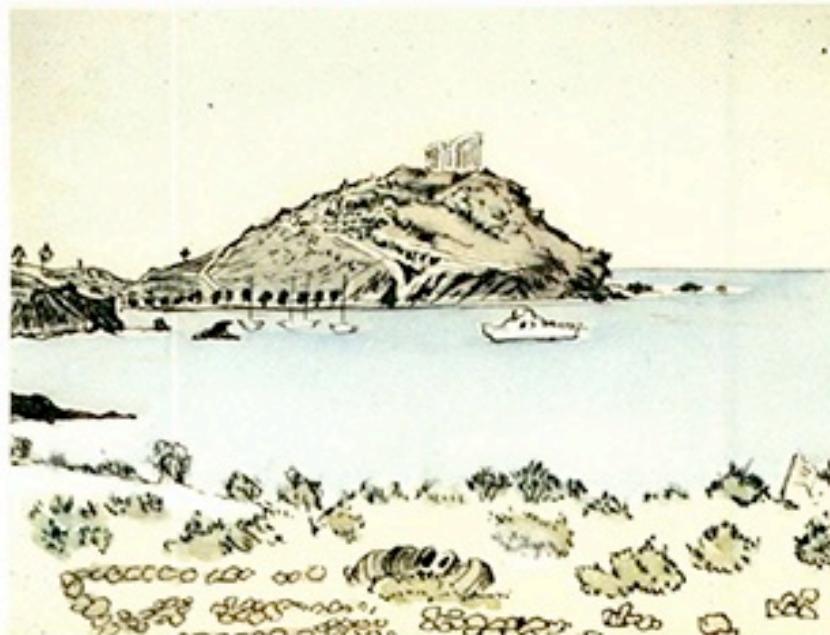
The Lancet 2021; 397:2337-2360 DOI: 10.1016/S0140-6736(21)01169-7
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Smoke exposure

**"EXPOSURE TO SECONDHAND OR 'ENVIRONMENTAL
TOBACCO SMOKE IS CARCINOGENIC TO HUMANS"**



(Host Factors in Human Carcinogenesis, IARC MONOGRAPH 183)



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

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

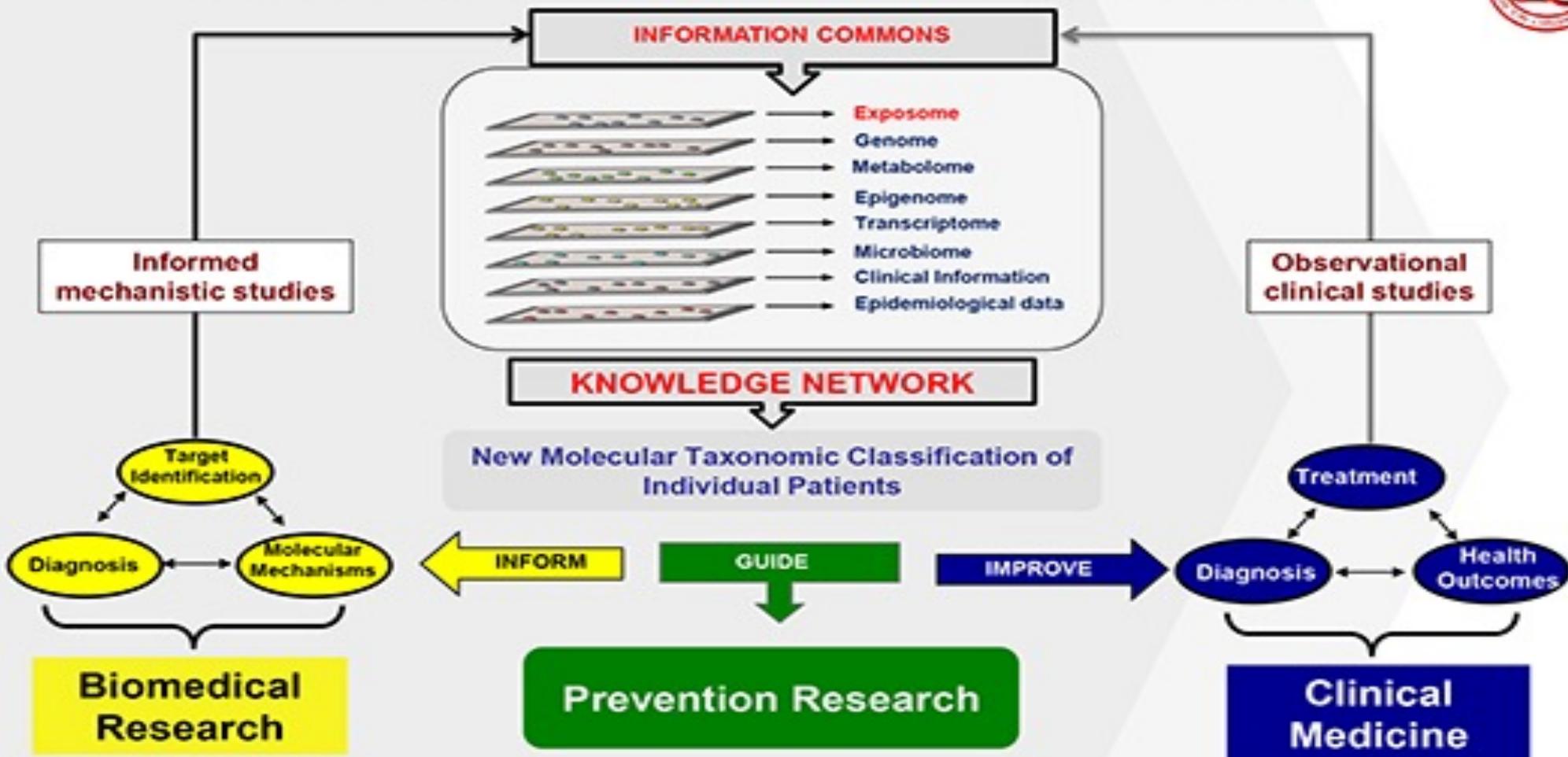
Cancer Epi Bio Prev.,
18: 3375-83, 2009

Collaboration with Jen Jin
and Ping Yang, Mayo Clinic

Exposome

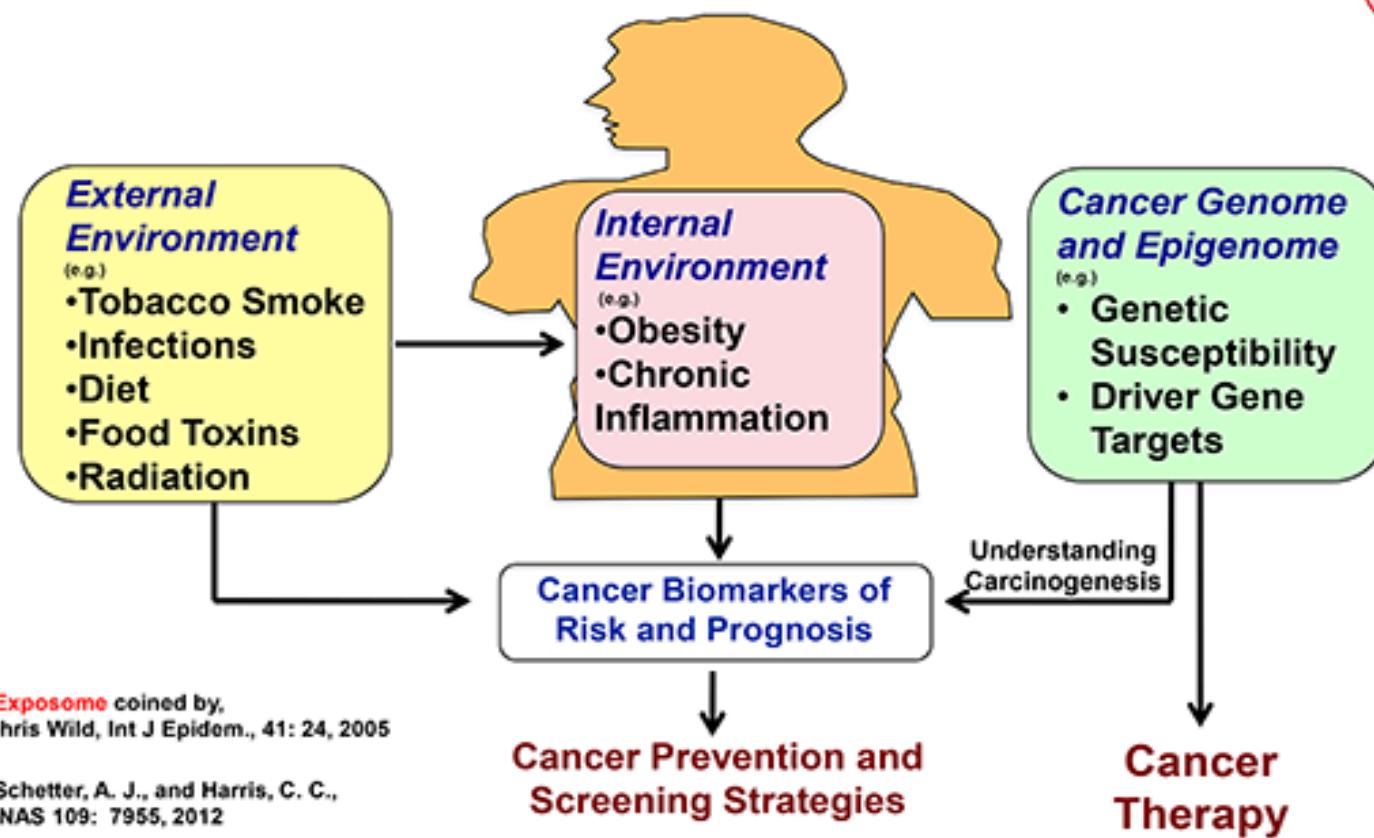


A Precision Medicine Research Strategy



Modified: "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease" (National Research Council 2011)

Exposome¹: p53 Tumor Suppressor is at the Crossroads of the Exposome and Cancer Genome²



¹Exposome coined by,
Chris Wild, Int J Epidemiol., 41: 24, 2005

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

Chronic inflammation and infection

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)

Acquired > Inherited

Disease Agent	Tumor Site
<u>Viral</u>	
Hepatitis B	Liver
Hepatitis C	Liver
<u>Bacterial</u>	
<i>Helicobacter Pylori</i>	Gastric
PID	Ovary
<u>Parasitic</u>	
<i>S. hematobium</i>	Urinary Bladder
<i>Japonicum</i>	Colon
Liver Fluke	Liver

Chemical, Physical, and Metabolic Examples

Acid reflux	Esophagus
Obesity	Multiple sites & Liver
Smoking	Multiple sites

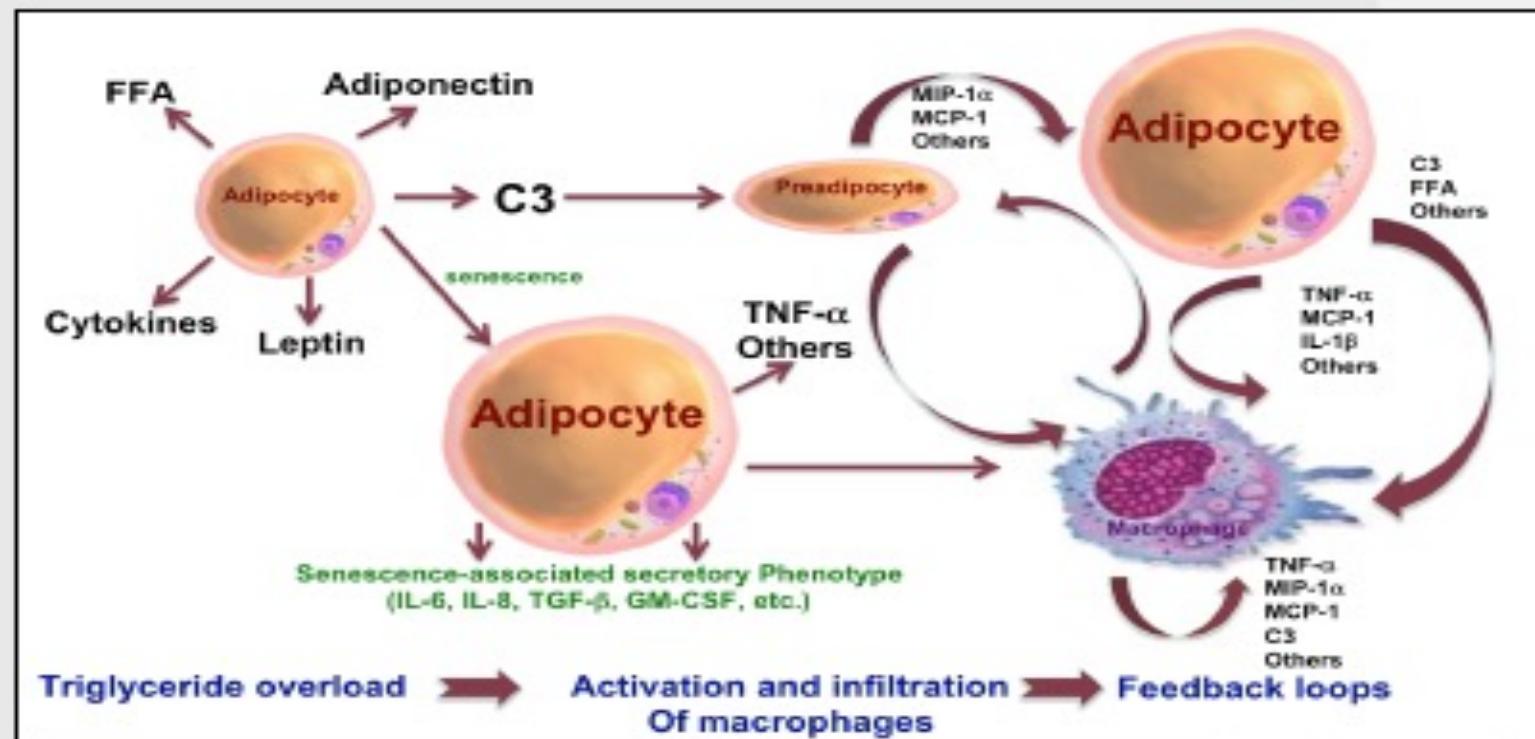
World Cancer Report, IARC, WHO, 2014

Obesity is a chronic inflammatory disease



Obesity is a Chronic Inflammatory Disease

- Weisberg et al. Obesity is associated with macrophage accumulation in adipose tissue. *J. Clin. Invest.* 112: 1790-1808, 2003.
- Xu et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J. Clin. Invest.* 112: 1821-1830, 2003.
- Minamino, T., et al. A crucial role for adipose tissue p53 in the regulation of insulin resistance. *Nature Med.* 15: 1082-87, 2009.
- Tahirovic, T., et al. Fattissue, aging, and cellular senescence. *Aging Cell.* 9: 687-684, 2010.

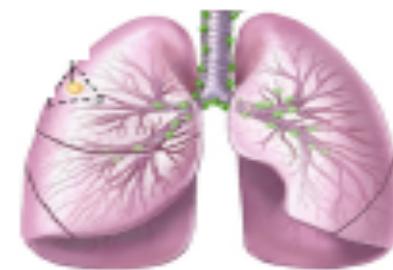


Cytokines

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)

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

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

JNCI 103: 1112, 2011

JNCI 103: 1112, 2011

CEBP: 215, 2010

J. Thoracic Oncol, 1494, 2014

JNCI 99: 1401, 2007

Health Disparity:

EA, European-American

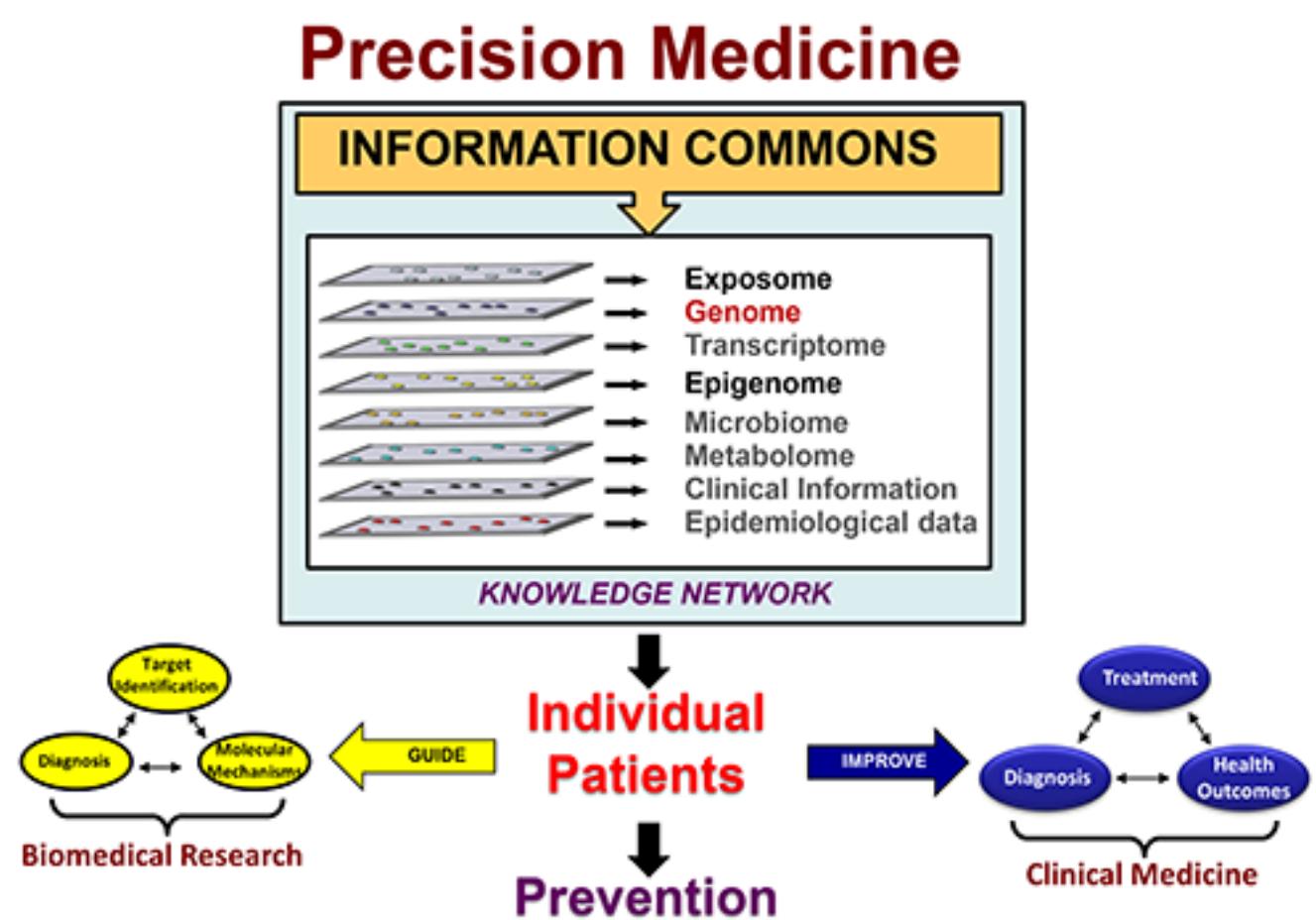
AA, African-American

Collaboration: Ann Schwartz

J. Thoracic Oncol, 1494, 2014

CEBP: 488, 2016

Genome



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

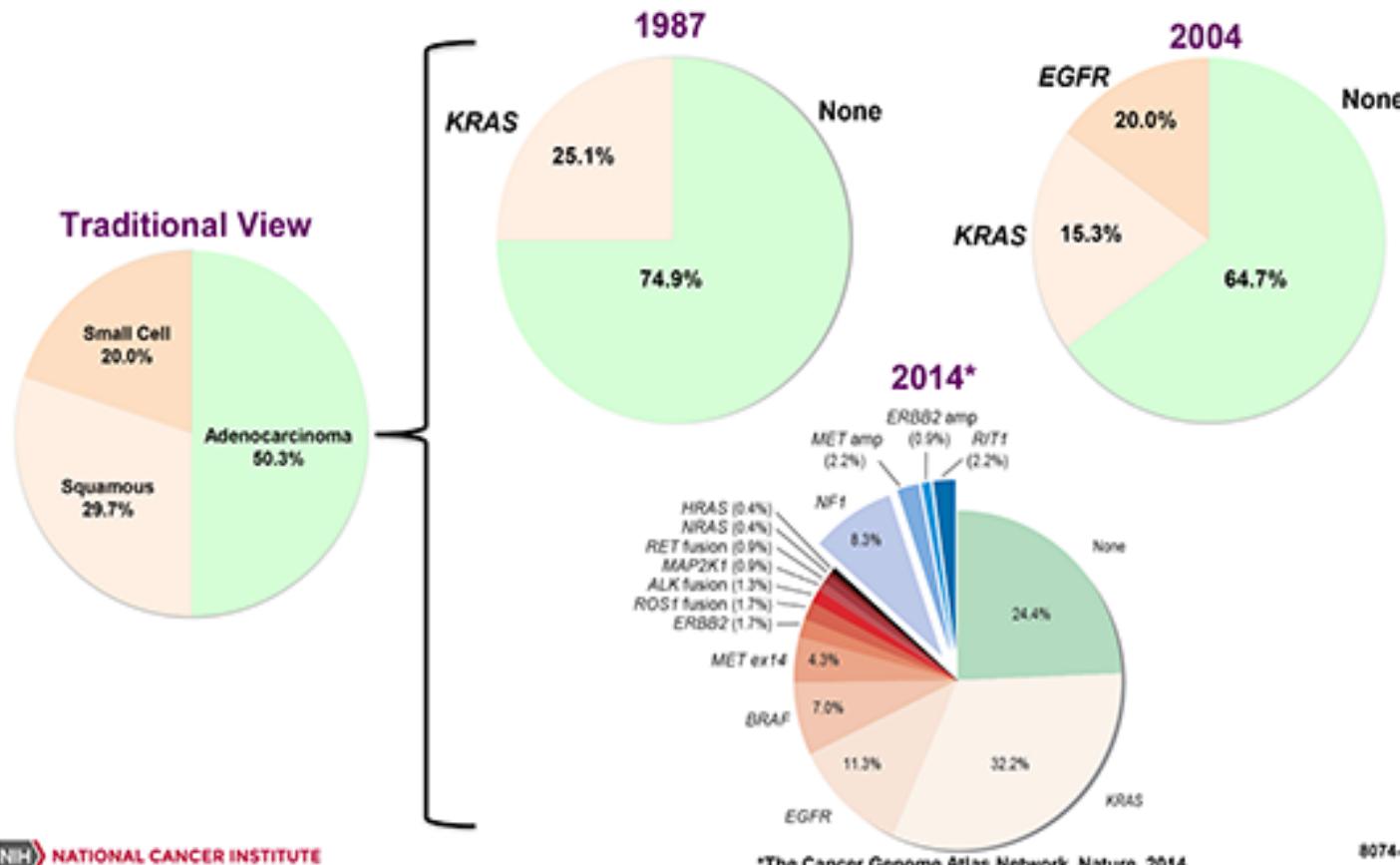


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NSCLC evolution



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



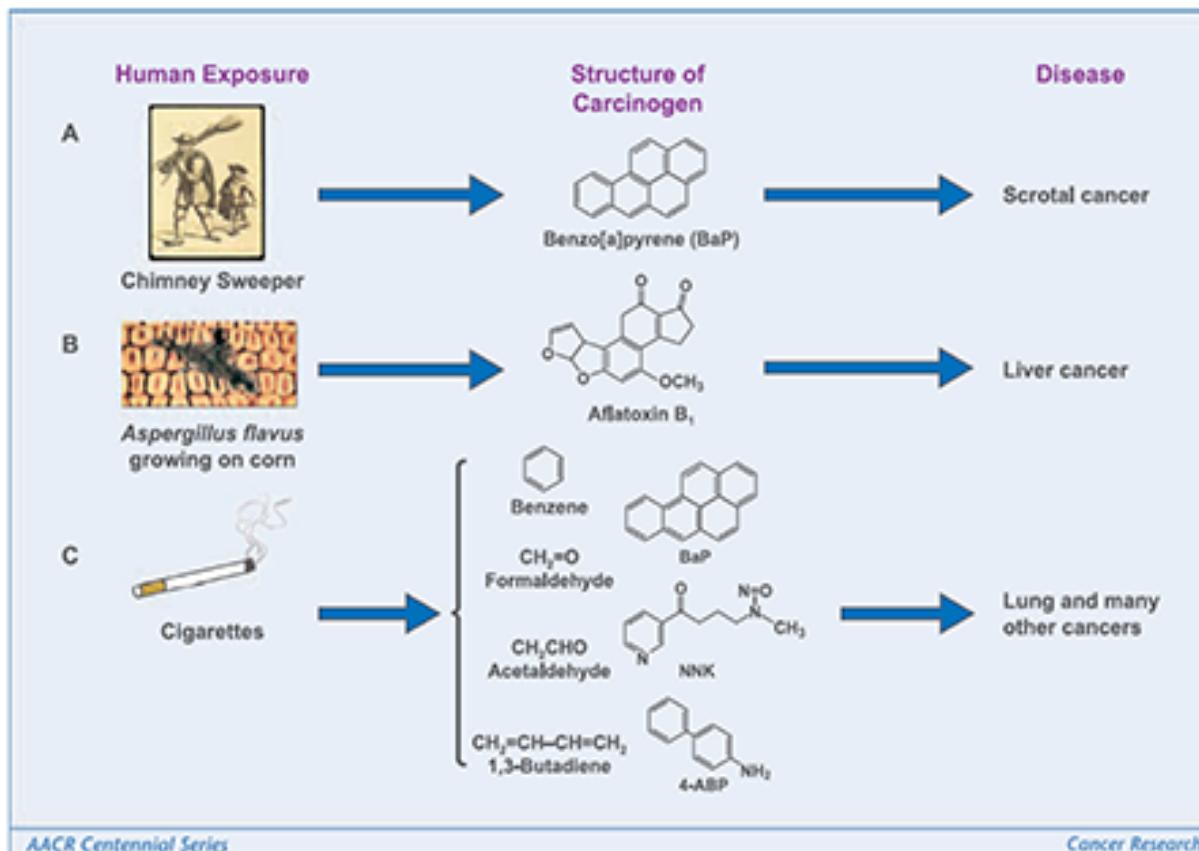
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Chemical agents



Examples of Chemical Agents Causing Cancer



AACR Centennial Series

Cancer Research

Three decades

Three Decades(1970s, 1990s and 2010s) of Examples of Initial Seminal Advances in Exposure of Environmental Carcinogens Being Molecularly Linked to Mutagenesis



- Development of a Rapid Mutagenicity Testing of Chemical Carcinogens and Metabolic Activation of Chemical Carcinogens
 - McCann J Ames BN; Detection of Carcinogens as Mutagens in the Salmonella/Microsome Test: Assay of 300 Chemicals. P.N.A.S 72:5135-39, **1975**
 - Heidelberger, C. **Chemical Carcinogenesis**, Annual Rev Biochemistry 44:79-121, **1975**
 - Harris CC et al., Human Bronchus-Mediated Mutagenesis of Mammalian Cells by Carcinogenic Polynuclear Aromatic Hydrocarbons. PNAS 75:2003-7, **1978**.
- **Discovery of TP53 Mutations Linked to Environmental Carcinogen Exposure**
 - Hsu IC Harris CC. p53 Mutational Hotspot in Hepatocellular Carcinoma from Qidong, China. Nature 350: 427-8, **1991**
 - Bressac B Ozturk M. Selective G to T mutations of p53 gene in Hepatocellular Carcinoma from Southern Africa. Nature 350:429-31, **1991**.
 - Holstein M, Sidransky D, Vogelstein B and Harris CC: p53 Mutations in Human Cancer. Science 253: 49-53, **1991**
- Computational Analysis of Genome-Wide DNA Sequencing Data Identifies Exogenous and Endogenous Induced Mutations including those Caused by Chemical and Physical Carcinogens, Inflammation, DNA Repair Defects and Aging
 - Alexandrov LB.....Stratton MR. Signatures of Mutational Processes in Human Cancer. Nature 500:415-421, **2013**

TP53 mutations

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

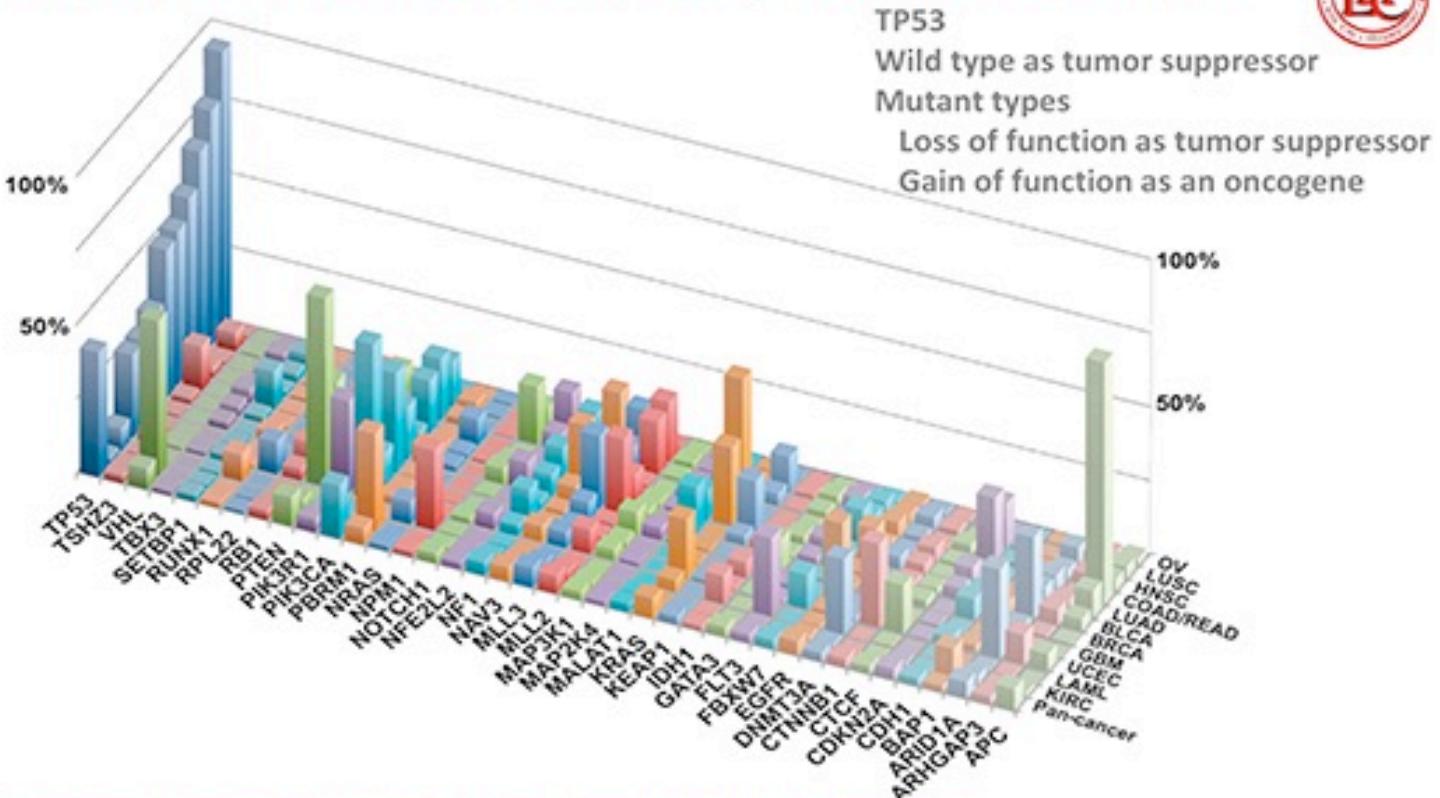


Carcinogen/ (exposure)	Target organ	IARC database	Base substitution	Distinctive
			In Vitro Human Cell Assays	Hotspots (codons)
Aflatoxin B1 (dietary contam.)	Liver	G to T	G to T	249 (3 rd base)
PAH (B[a]P) (smoking)	Lung	G to T with Strand bias	G to T with Strand bias	157, 158, 273
UV radiation (sunlight)	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., Vogelstein, B., and Harris, C.C., Harris, Science, 253: 49-53,1991
- Greenblatt, M.....Harris, C.C., Cancer Res., 54: 4855-78, 1994

TP53 mutations

TP53 is the Gene most frequently Mutated in Cancer



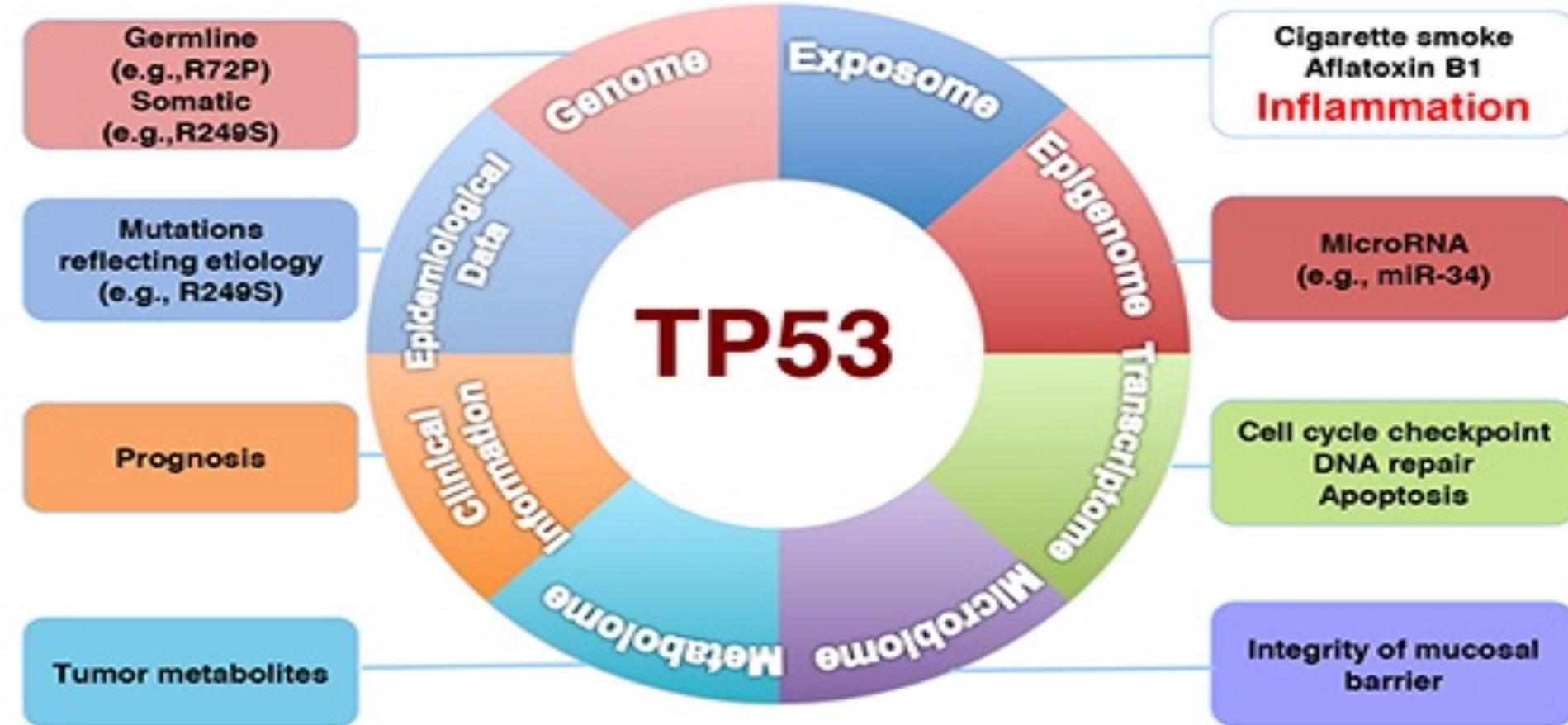
Genes most frequently mutated in various types of cancer in the TCGA Pan-Cancer study.
Data were generated by analysis of the mutations released by Kandoth et al. Nature 2013.

Soussi & Wiman, 2015

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TP53 functions

TP53 and its Functions Affect Multiple Layers of “-OMICS” Data in the Precision Medicine Paradigm



Three decades

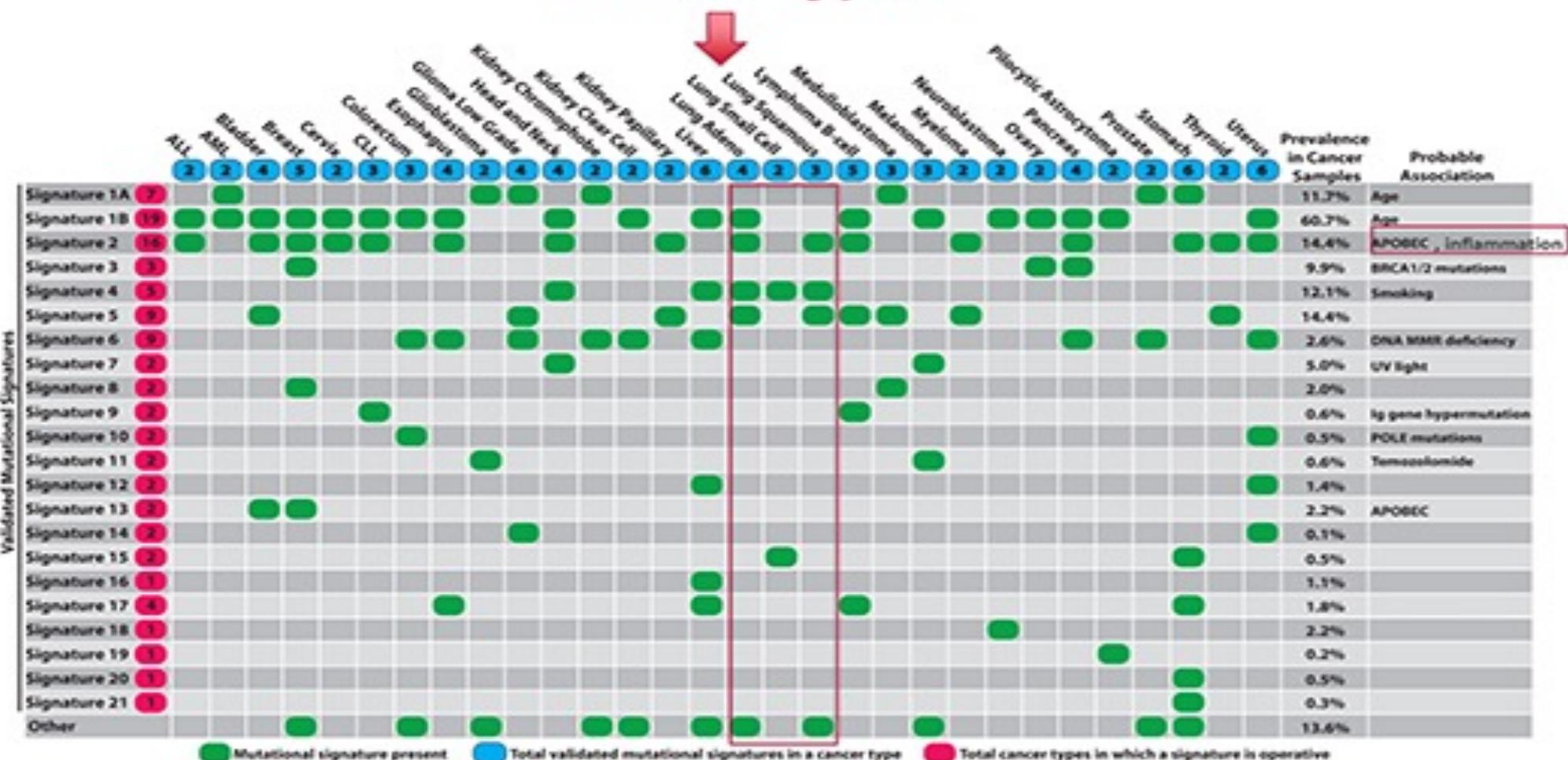
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 - McCann J Ames BN; Detection of Carcinogens as Mutagens in the Salmonella/Microsome Test: Assay of 300 Chemicals. P.N.A.S 72:5135-39, **1975**
 - Heidelberger, C. **Chemical Carcinogenesis**, Annual Rev Biochemistry 44:79-121, **1975**
 - Harris CC et al., **Human Bronchus-Mediated Mutagenesis of Mammalian Cells by Carcinogenic Polynuclear Aromatic Hydrocarbons**. PNAS 75:2003-7, **1978**.
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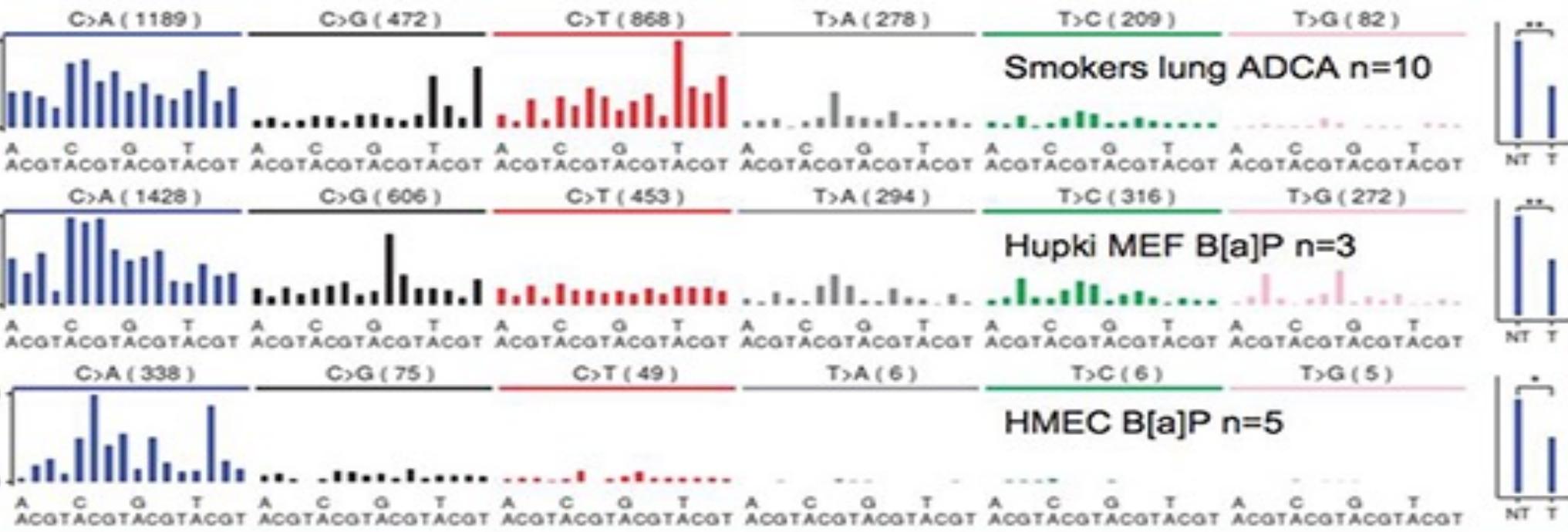
Somatic mutations

The Prevalence of Somatic Mutations Across Human Cancer Types



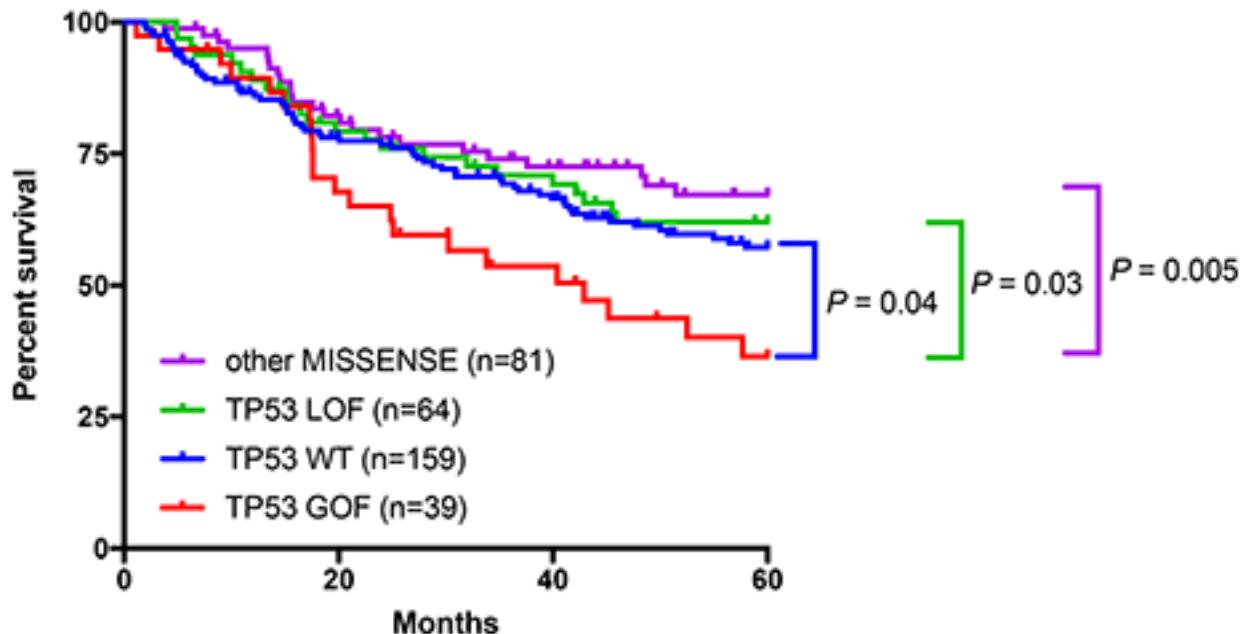
Carcinogens fingerprint

A Carcinogen's Fingerprint in Human Lung Cancer DNA Can be Reproduced in Experimental Systems: Benzo(a)pyrene



Patient prognosis

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



$HR_{GOF\text{vs}all\text{others}}: 1.8; CI, 1.0-3.0; P= 0.034$

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

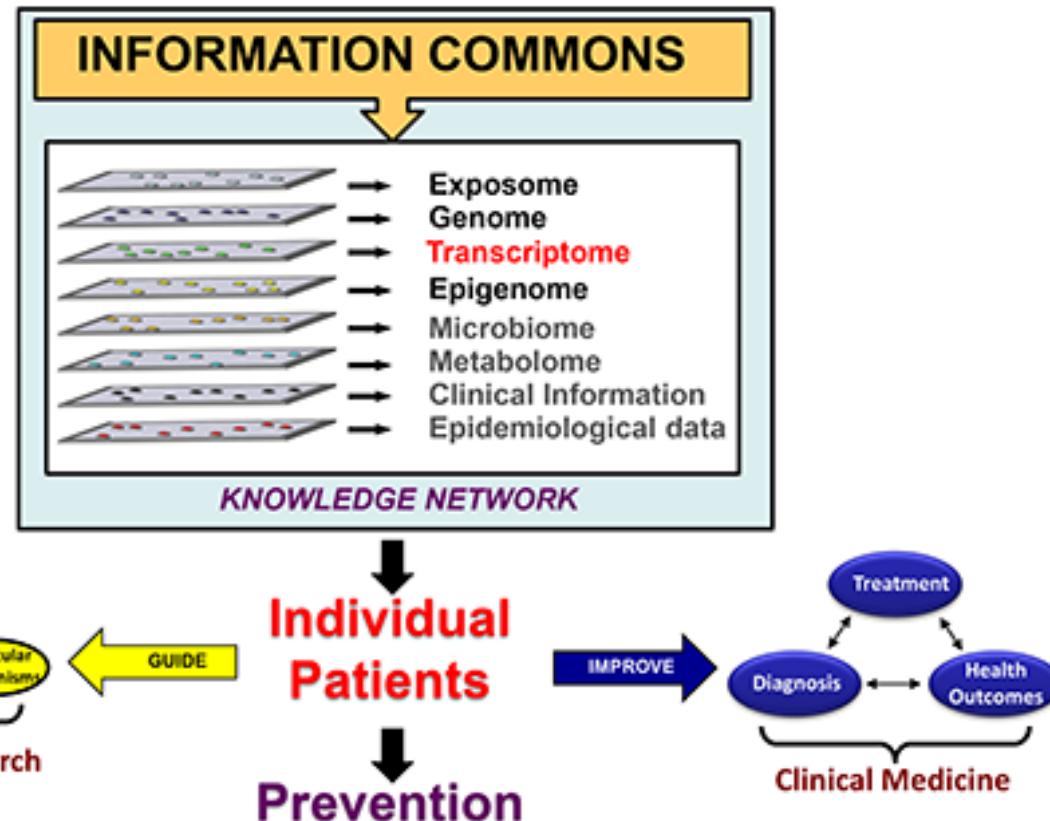
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Robles A and Harris CC, NCI-MD Case Control Study

Transcriptome



Precision Medicine



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

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MicroRNA

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.

- **Human Cancer**

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



Victor Ambros



Gary Ruvkun

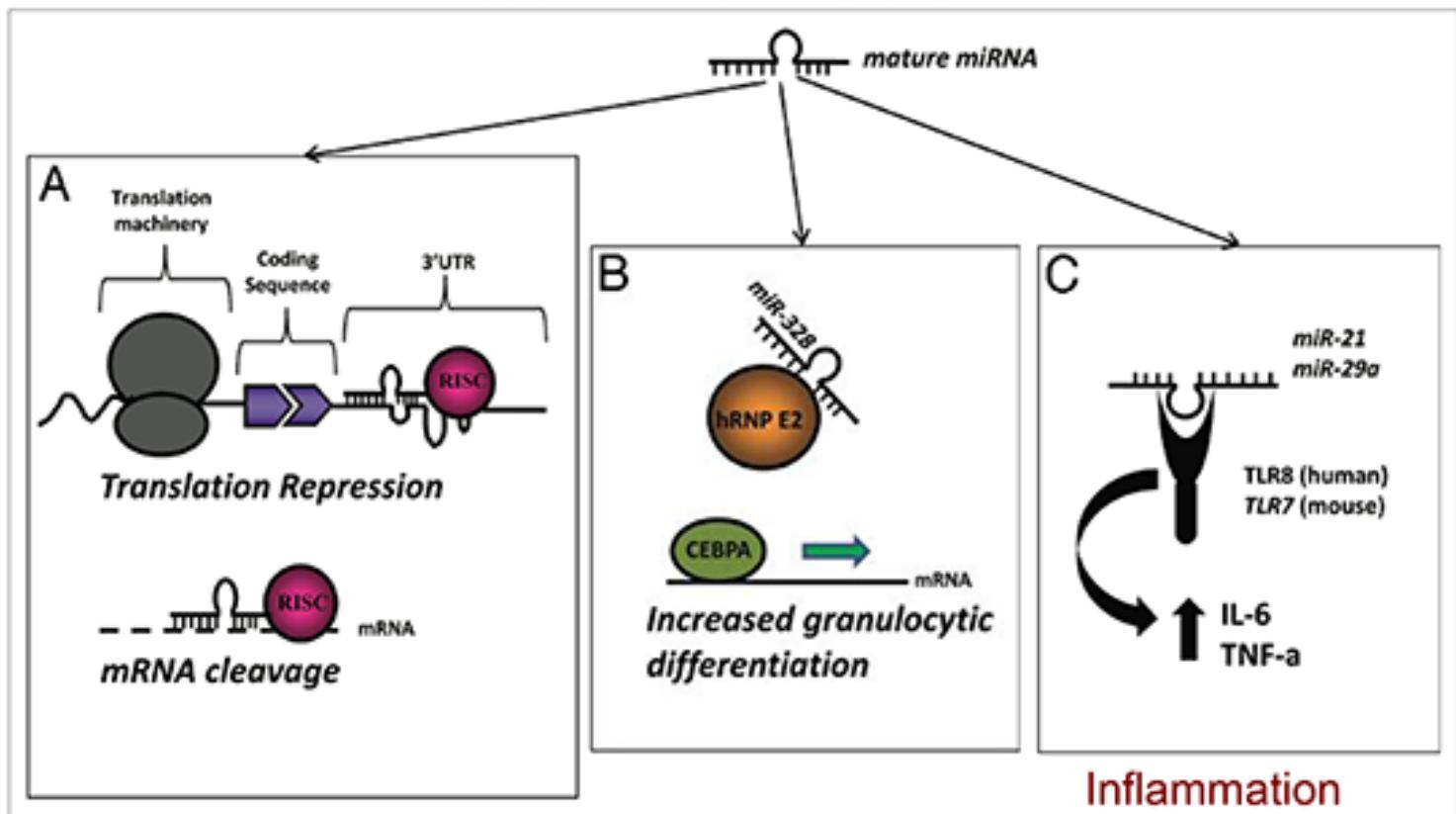


Carlo Croce

3690°-CH

microRNA mechanisms

Different Mechanisms of Action of Mature microRNAs



Hypothesis

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.**



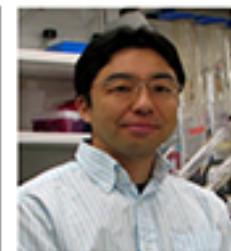
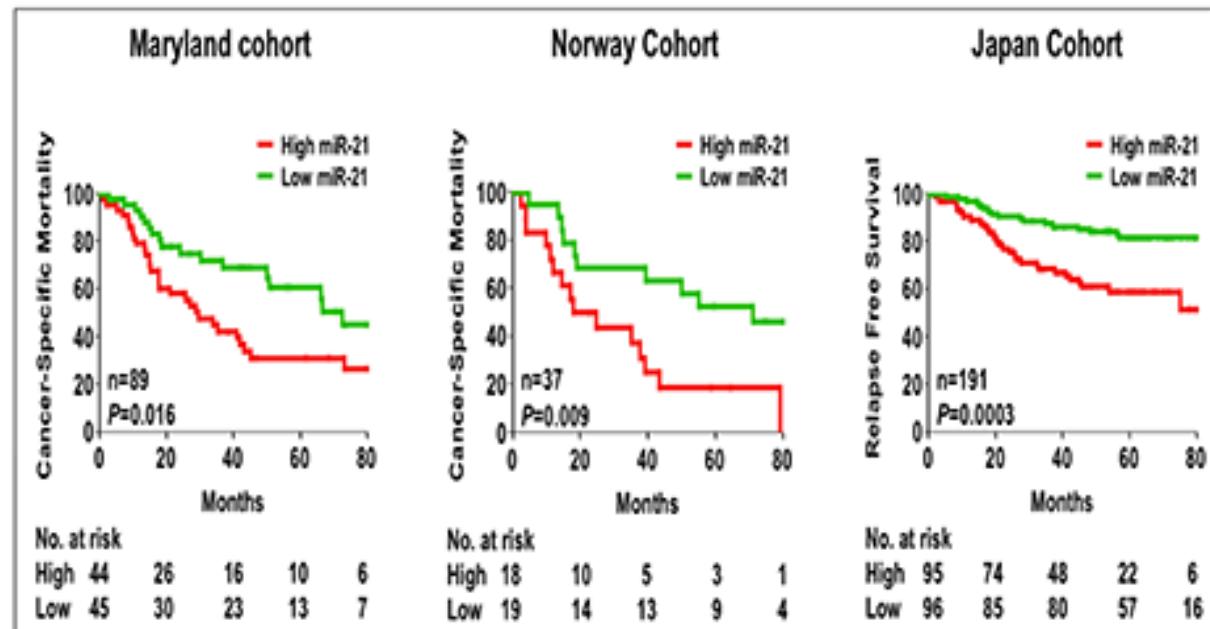
Nozumu Yanaihara

let-7: confirmed studies by Takahashi and Slack

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

Increased miR-21 expression

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



Motonobu Saito



Nozumu Yanaihara

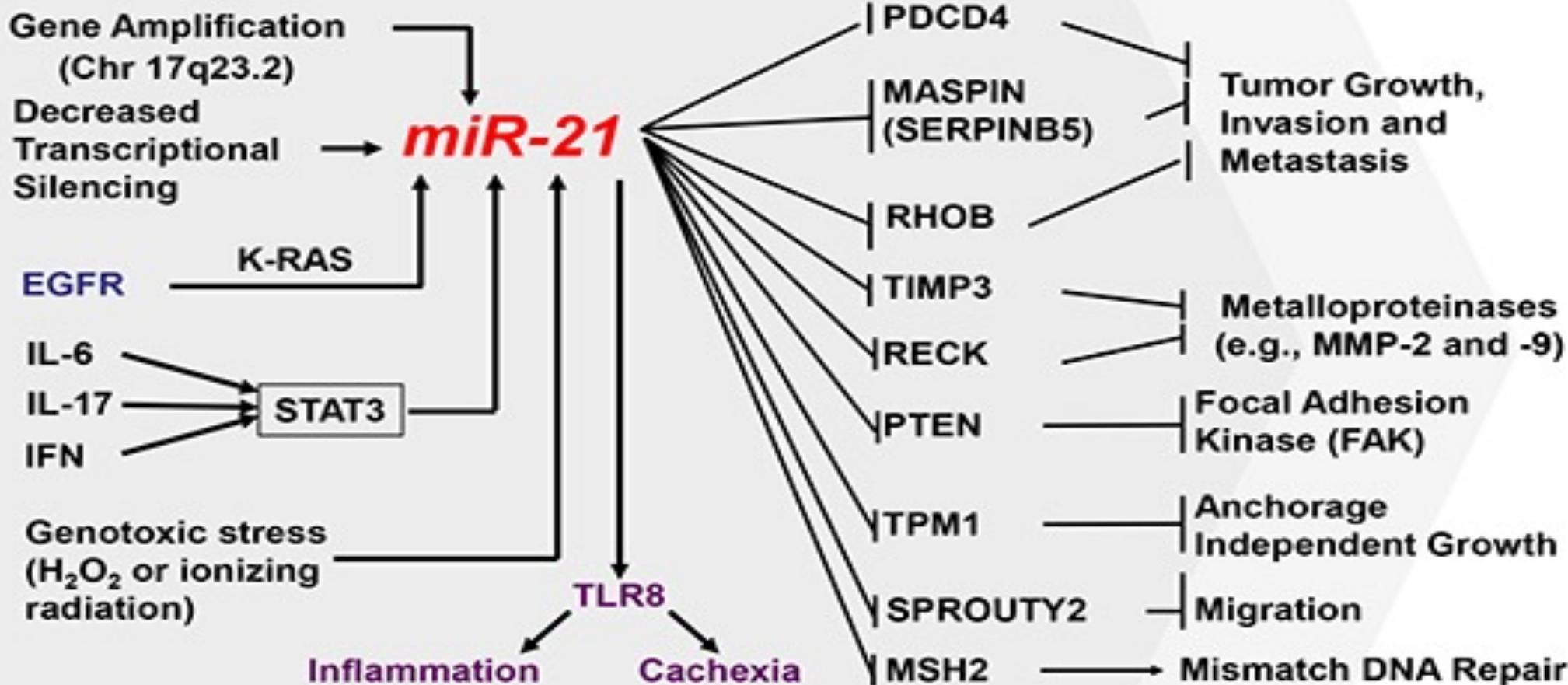
Yanaihara et al. *Cancer Cell* 9:189, 2006

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

miR-21



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

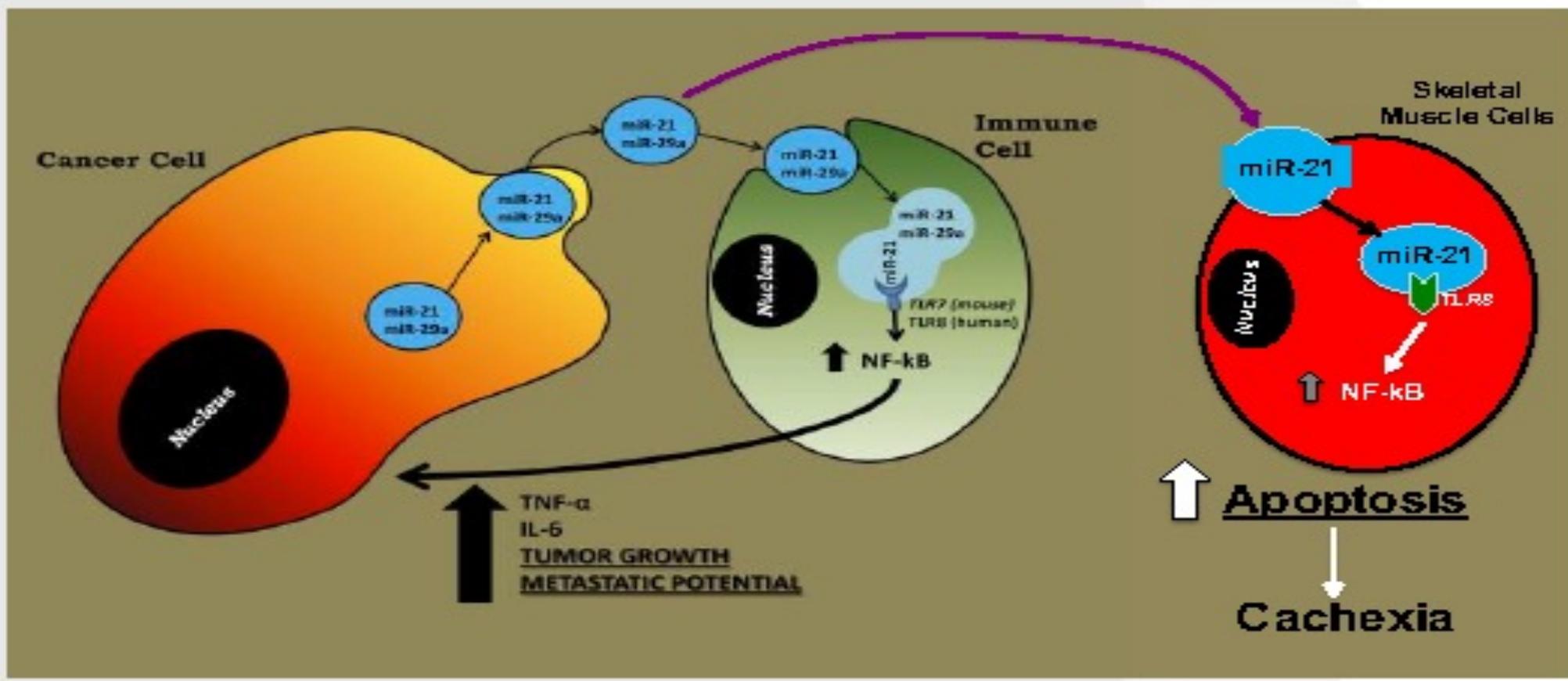
Fabbri and Croce, RNA Biology 10: 169-174, 2013

He and Croce, PNAS 111: 4525-29, 2014

MiRNAs



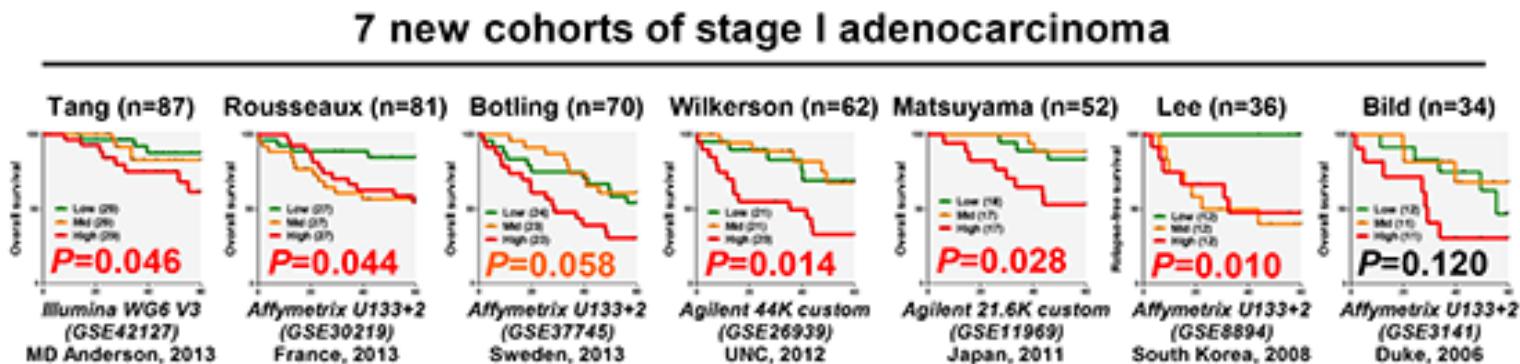
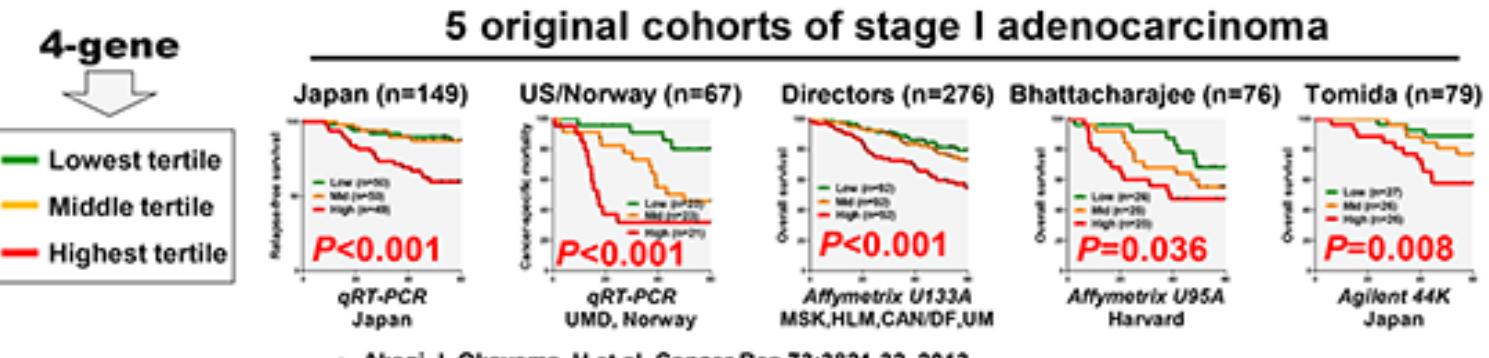
MiRNAs are Secreted by Cancer Cells in Exosomes and can Reach and Bind TLR8 Receptors in the Endosomes of Surrounding Immune and Muscle Cells



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

4-gene classifier

The Performance of the 4-gene Classifier (Increased XPO1, BRCA1 and HIF1a and Decreased DLC1) in 12 Independent Cohorts of Stage I ADC



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

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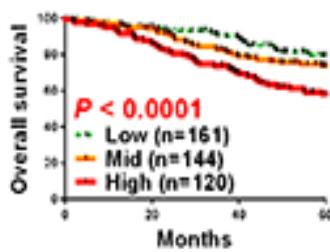
Meta-Analysis

Meta-Analysis of the 4-gene Classifier (\uparrow XPO1, BRCA1, HIF1a, \downarrow DLC1) in 12 Independent Cohorts of Stage I ADC

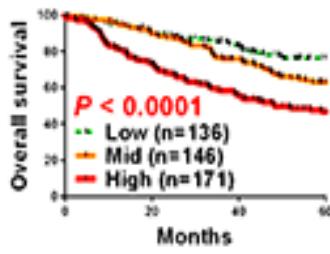


- 883 Stage I Patients

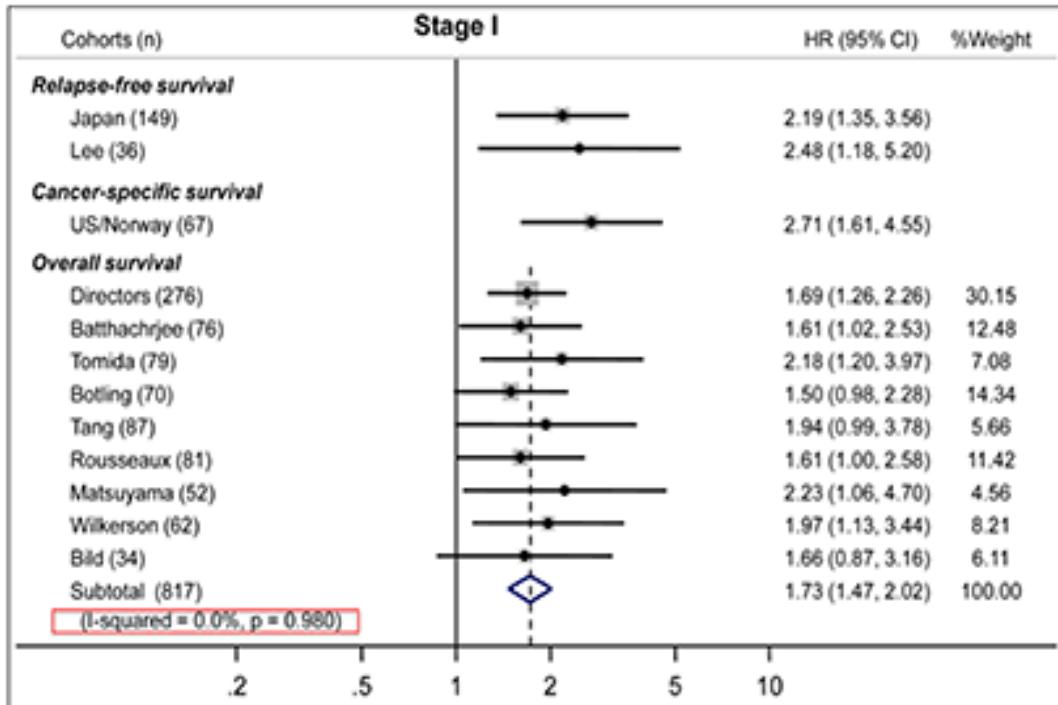
4-gene in Stage IA



4-gene in Stage IB



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



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

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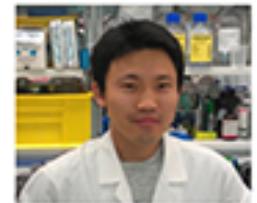


Mechanistic cancer biomarkers

Mechanistic Cancer Biomarkers: Proof of Principle in Lung Adenocarcinoma



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



Hiro Okayama



Ichiro Akagi

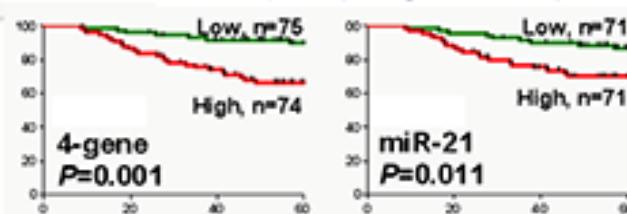
Akagi et al, Cancer Res. 73: 3821-32, 2013

miR-21 and 4 coding genes

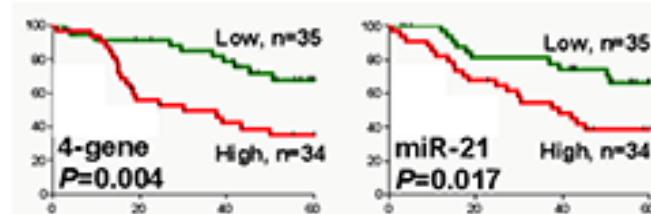


Hypothesis: The Combination of miR-21 and Four Coding Genes (Increased XPO1, BRCA1 and HIF1a and Decreased DLC1) Predicts Prognosis of Stage I Lung Adenocarcinoma

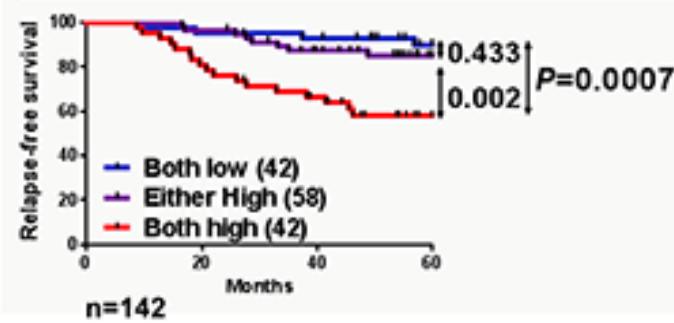
Japan (Stage IA > IB)



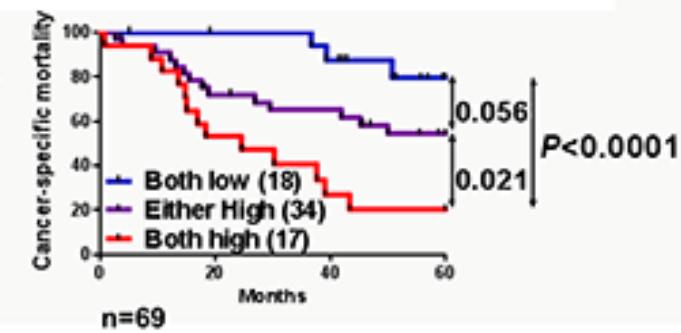
US/Norway (Stage IB > IA)



Combined
(4-gene + miR-21)



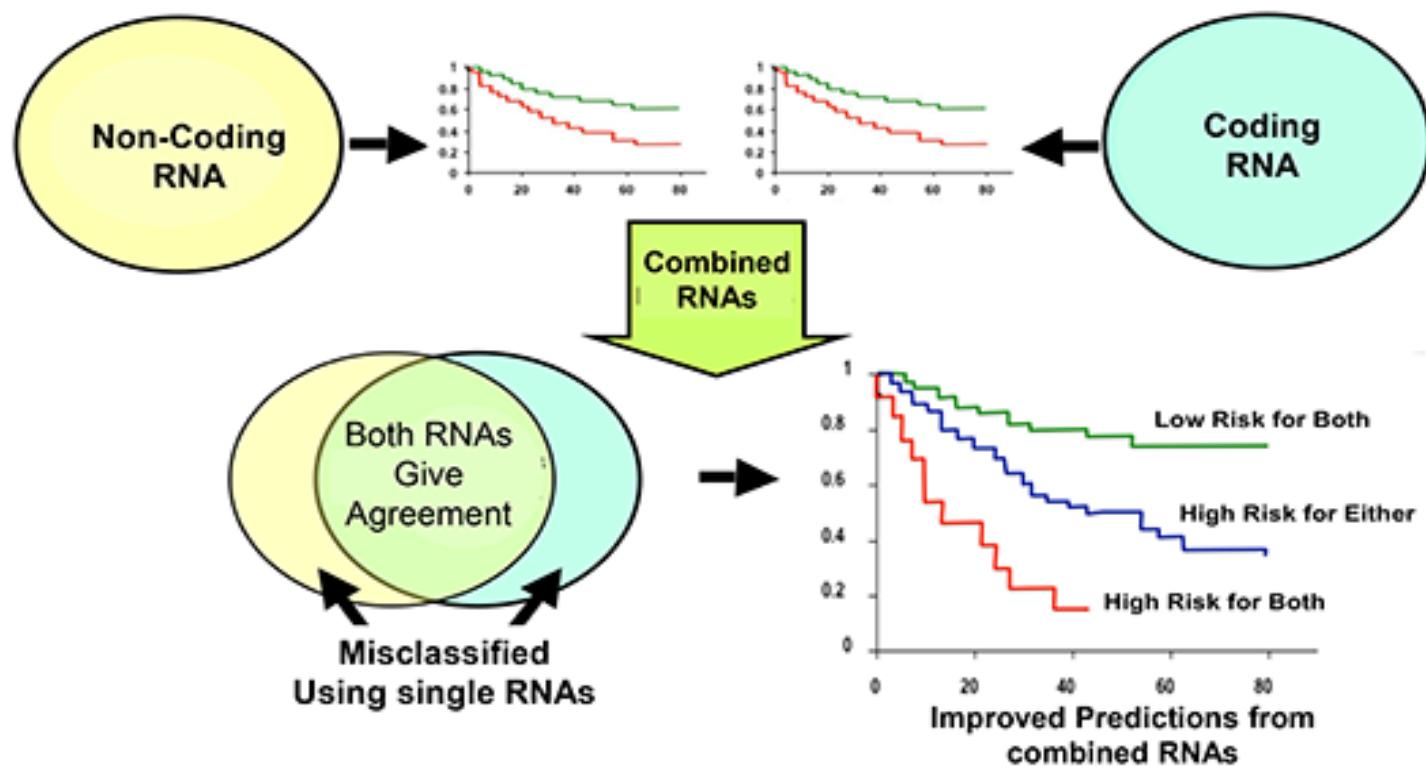
Combined
(4-gene + miR-21)



Non-coding RNA

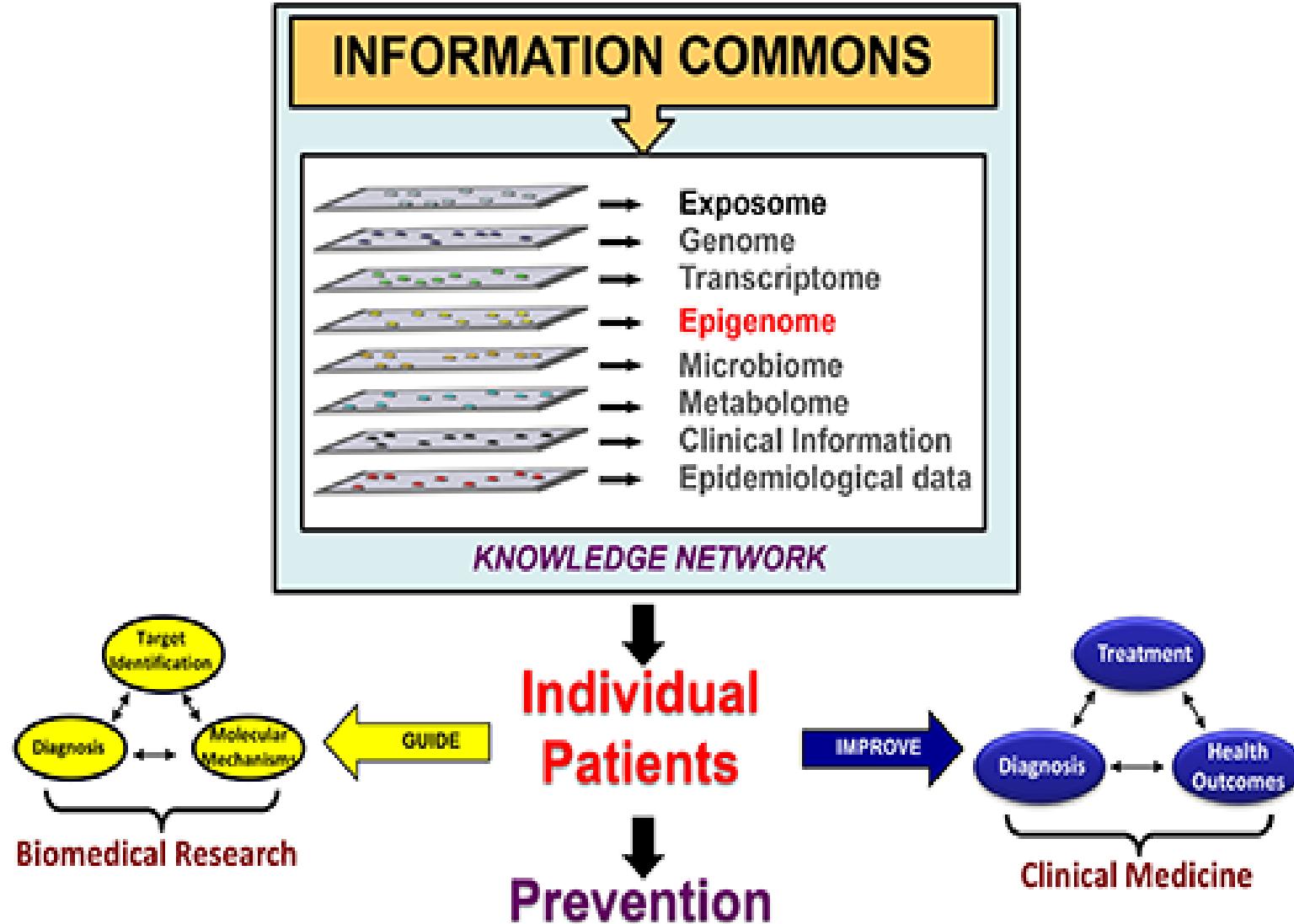


Principle: The Combination of Protein Coding and Non-Coding Gene Expression is a more Robust Prognostic Classifier of Early Stage Cancer



Epigenome

Precision Medicine



DNA methylation

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

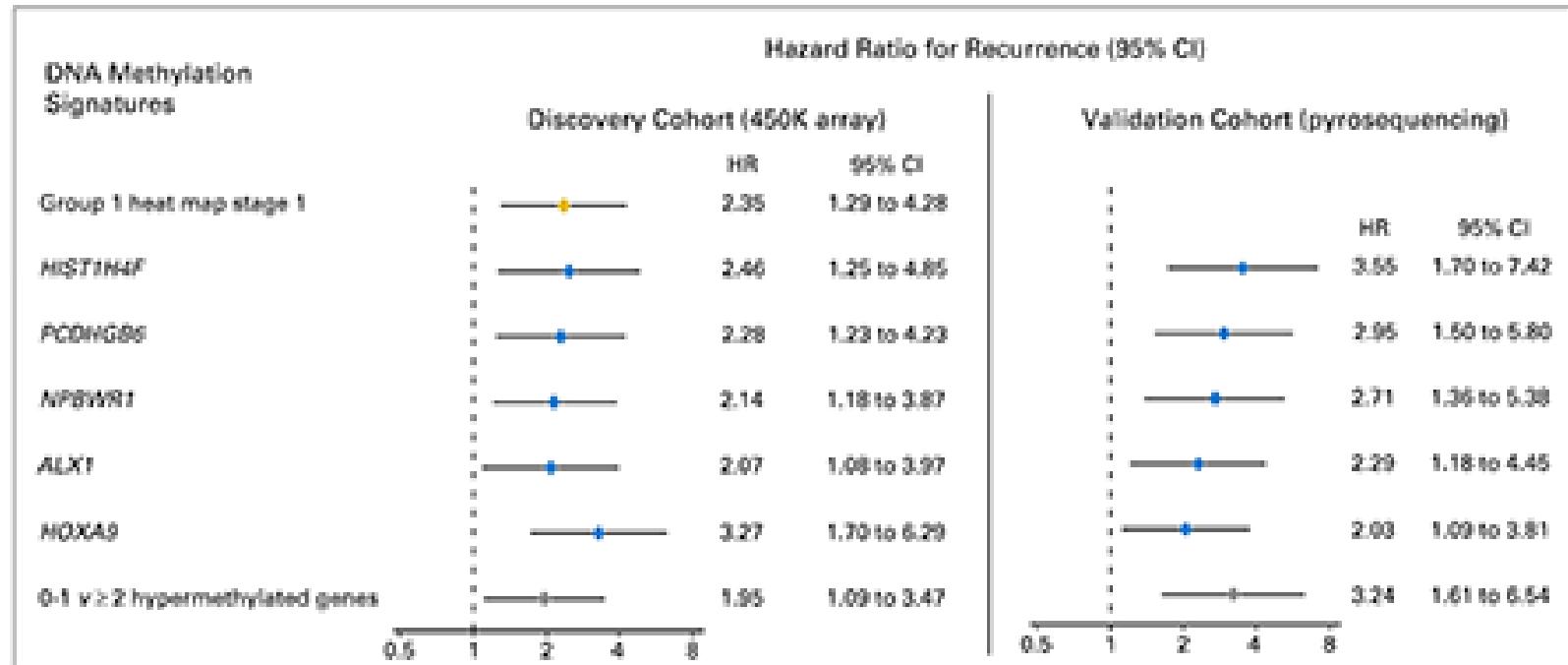
Prognostic epigenetic signature

DNA Methylation in NSCLC is a Prognostic Epigenetic Signature

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

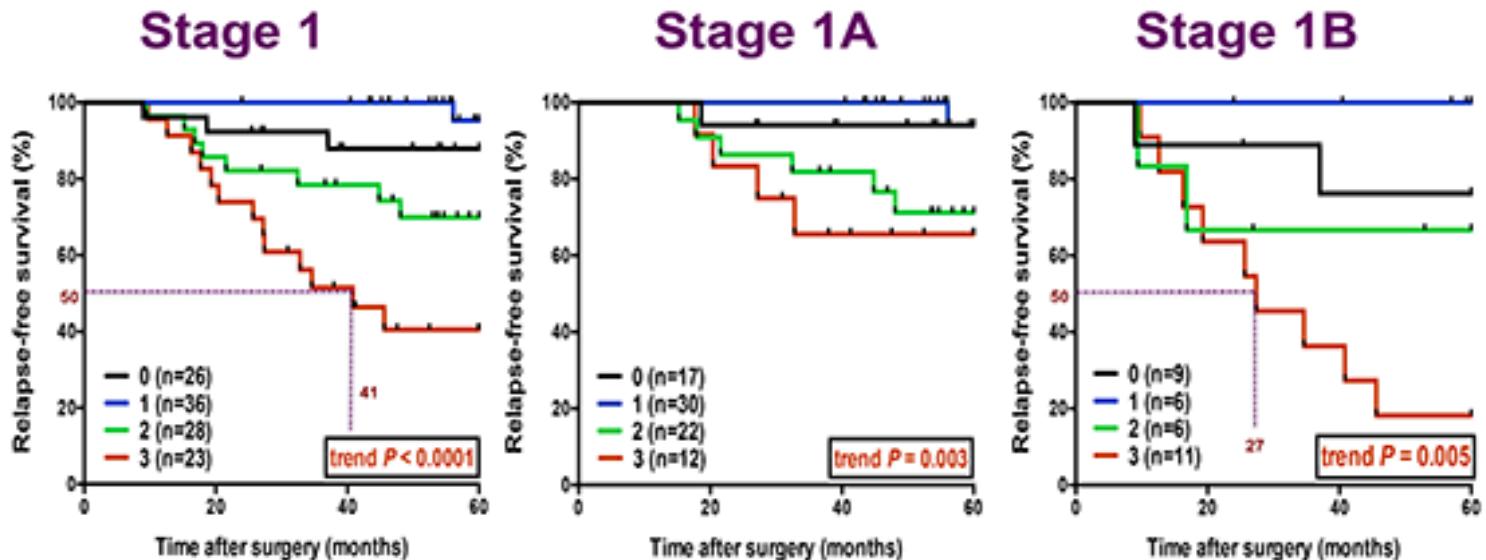
Juan Sandrinal, Jesus Mendez-Gonzalez, Ernest Nadal, Guoan Chen, P. Javier Carmona, Sergi Sayols,
Sebastian Moran, Holger Heyn, Miguel Vizoso, Antonio Gomez, Montse Sanchez-Carpodeto, Yassine Asselme,
Fabian Müller, Christoph Beck, Miguel Taron, Josefina Mora, Lucia A. Moccarella, Triantafyllos Lileoglou,
Michael Davies, Marina Pollan, Maria J. Pajares, Wenceslao Torre, Luis M. Montaraga, Elisabeth Brumbilla,
John K. Field, Luca Roc, Mario Lo Iacono, Giorgio V. Scagliotti, Rafael Rosell, David G. Beir,
and Manel Esteller

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



Survival curve

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

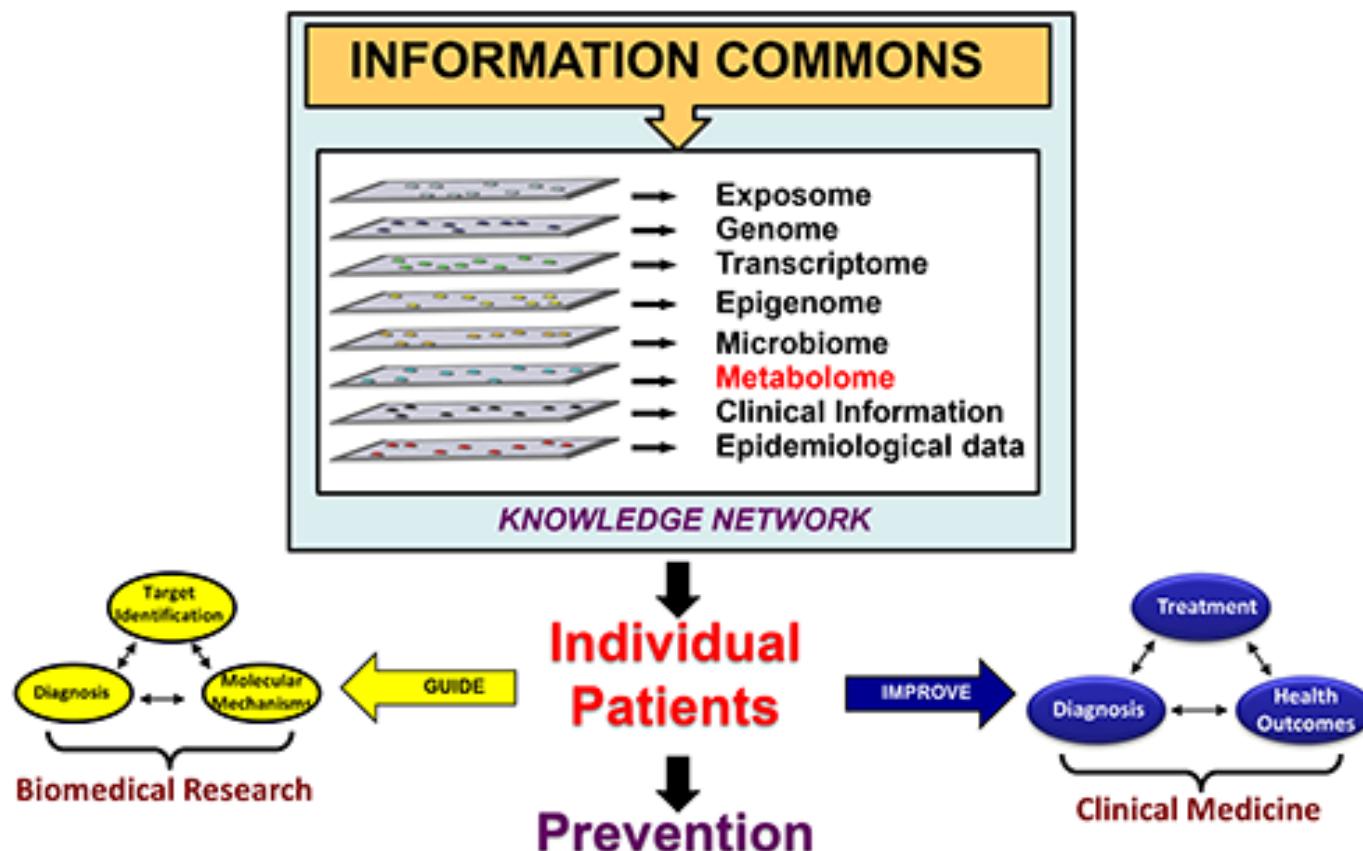


- Cases were categorized according to the combined number of high values for HOXA9 methylation, miR-21 (Clin. Cancer Res. 2011;17:1875-82) and 4-gene signature (Cancer Res. 2013;73:3821-32) and HOXA9 promoter methylation (J. Thoracic Oncology 10: 1037-48, 2015).
- P values calculated by log-rank test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

Microbiome



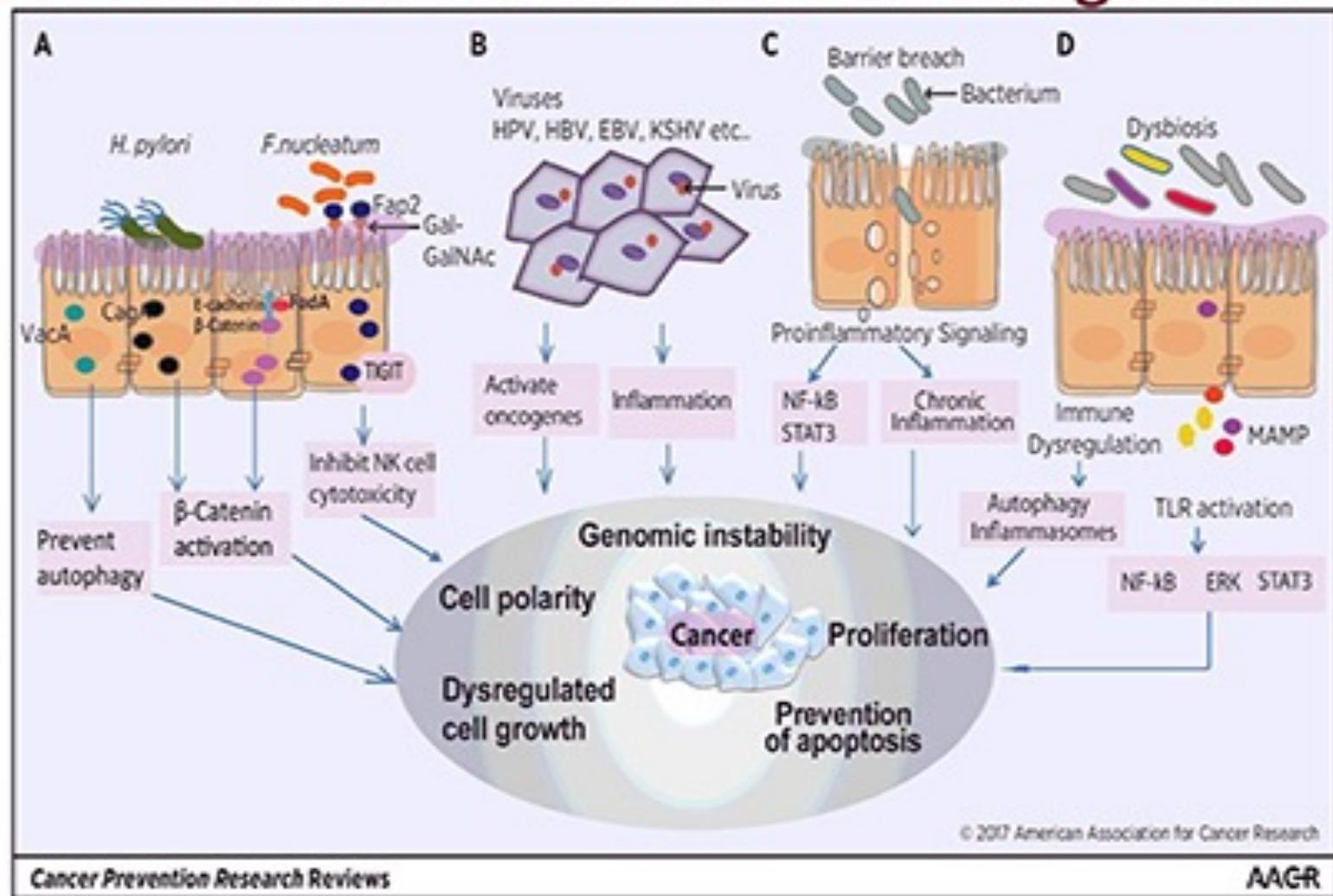
Precision Medicine



Microbiome and carcinogenesis

Bacterial and Viral Microbiome Promotes Carcinogenesis

- H. pylori***
Gastric cancer
- F. nucleatum***
Colon Cancer
- Dysbiosis**
Multiple Cancers
Cancer Therapy
- HPV**
Cervical and Head and Neck Cancer



Microbiome, TP53 and lung cancer

Interaction between the Microbiome, Smoking and TP53 in Human Lung Cancer

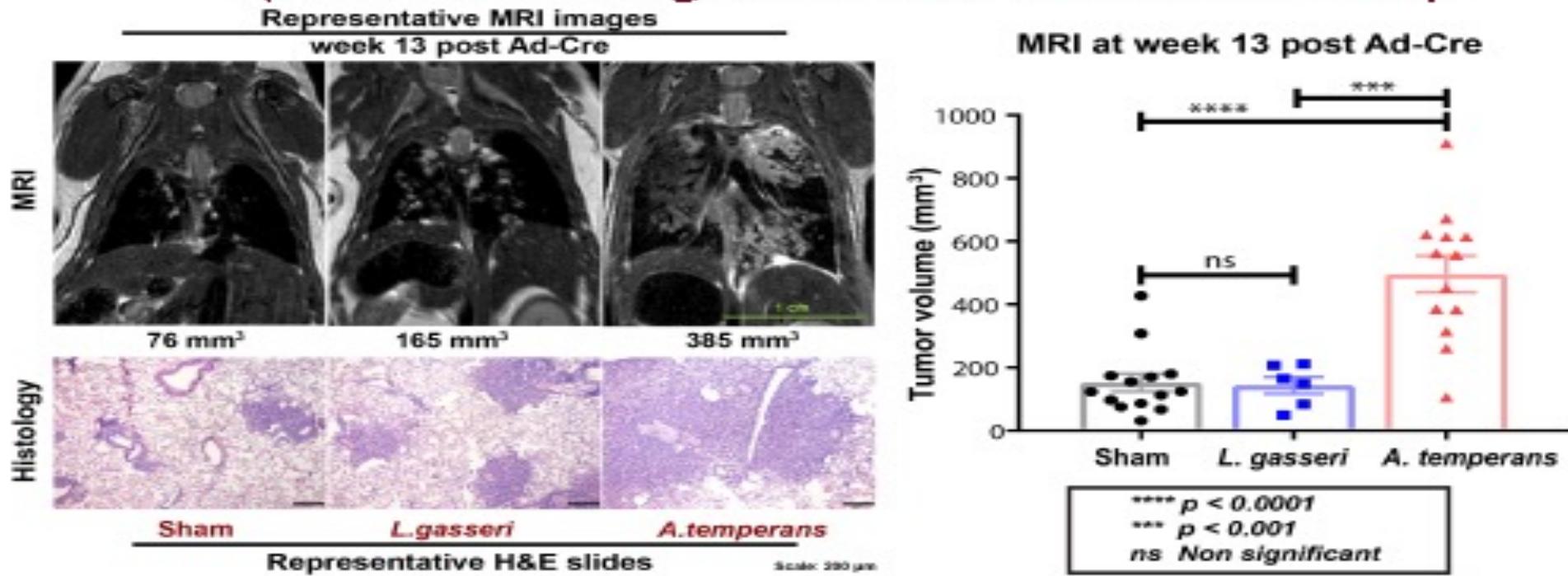


- Certain taxa including *Acidovorax* were higher in both adenocarcinoma and squamous carcinoma (SCC) in smokers and former smokers than in non-smokers.
- A group of taxa were significantly associated with SCC, of which *Acidovorax* was enriched in smokers
- SCC cases with *TP53* mutations had a higher abundance of the SCC-associated taxa, including *Acidovorax*

SCC-associated taxa are enriched in tumors with *TP53* mutations, which establishes a microbiome-gene interaction in lung cancer tissue

Temperans challenge

A. *temperans* Challenge Accelerates Lung Tumorigenesis (Chenran Zhang and Natalia von Muhlinen)

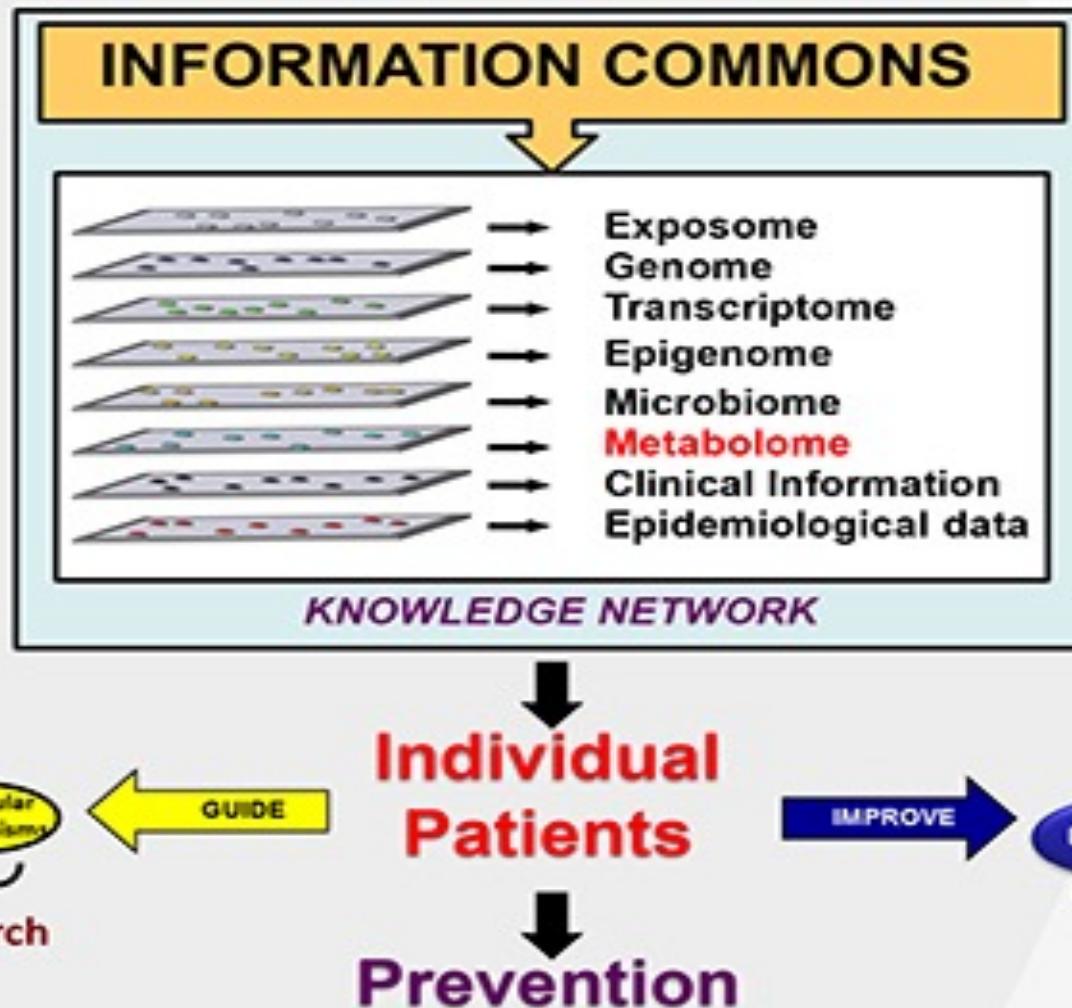


- Mice challenged with *A. temperans* exhibit significantly larger tumors at week 13 post AdCre compared to *L. gasseri* or PBS.

Metabolome



Precision Medicine



Tumor metabolism

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



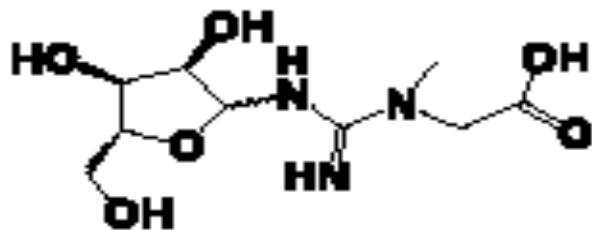
- Hippocrates tasted urine in the diagnosis of disease in his patients. (460-370, BC)
- Physiologist J. A. Armstrong writes, “From a liquid window through which physicians felt they could view the body’s inner workings, urine led to the beginnings of laboratory medicine...”

Novel cancer metabolites

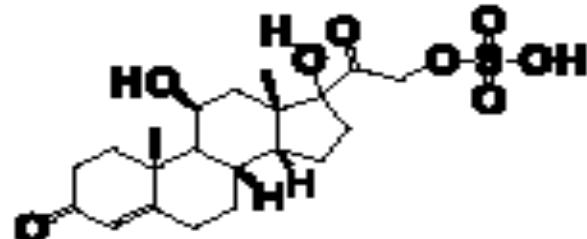
CR and NCP are Novel Metabolites of Cancer Metabolome Imbalance



Creatine Riboside
(CR)

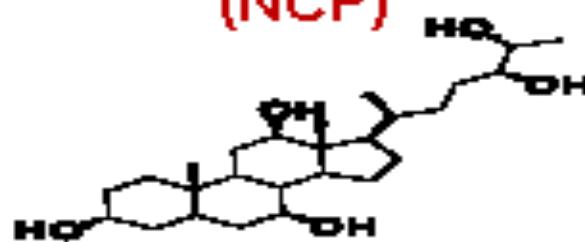


Cortisol Sulfate
(CS)

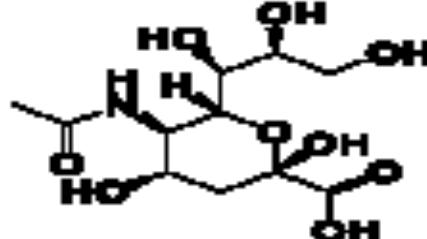


Creatine riboside Synthesis and Biomedical Analysis:
Patel, DP et al., Pharmaceutical and Biomedical Analysis:
191:113596, 2020. CUA ready

27-nor-5 β -cholestane-
3 α ,7 α ,12 α ,24,25 pentol
(NCP)



N-acetylneurameric acid
(NANA)



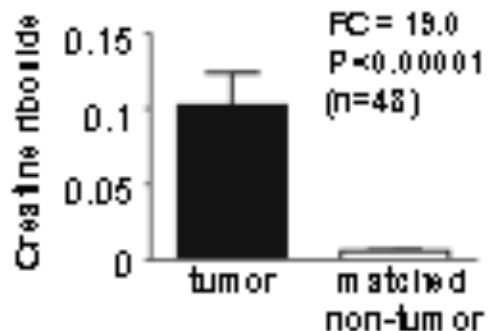
NCP manuscript describing its metabolic pathway
and biological activity is in preparation.

Creatine riboside



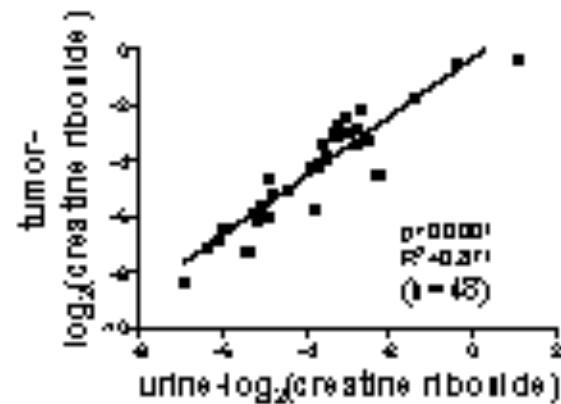
Creatine Riboside is Increased in Lung Cancer Tissue: Correlation Studies with Liquid Biopsy

Enrichment in tumor vs matched non-tumor

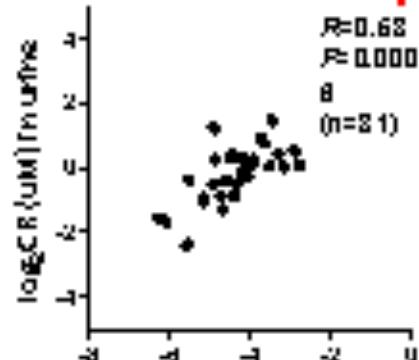
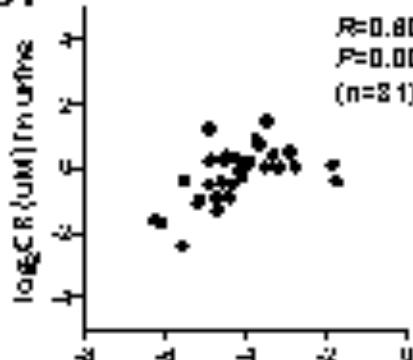


Mathe et al. Cancer Res 2014;74(12): 3259-70.

Strong positive correlation between tumor and urine



Strong positive correlation between urine and serum or plasma



Four urinary metabolites



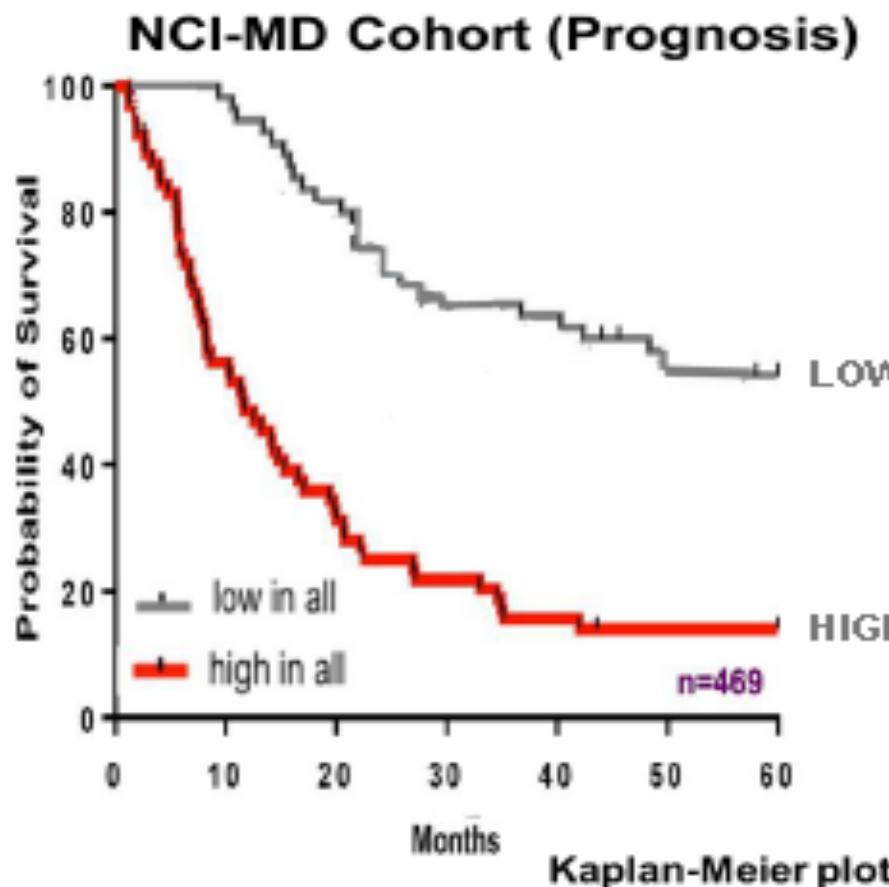
Urinary Metabolomic Profiling Identifies Four Metabolites Associated with Lung Cancer Diagnosis and Prognosis

NCI-MD Lung Cancer Case-Control Study¹

- 469 NSCLC patients
- 536 population controls
- Untargeted Mass Spectrometry
 - RP Chromatography-qTOF MS Analysis
 - Random Forest Analysis for feature identification
 - associated with diagnosis and prognosis
- Four Metabolites
 - Creatine Riboside
 - N-Acetyl Neuramino Acid
 - Cortisol Sulfate
 - 561.3 (NPC)

Lung Cancer Diagnosis		
Metabolite	All Cancers OR (95%CI)	Stage I-IV OR (95%CI)
Creatine Riboside	6.06 (2.67-7.14)	3.84(2.07-6.28)
N-Acetyl Neuramino Acid	2.68 (1.22-2.62)	1.84(1.14-2.88)
Cortisol Sulfate	2.12(1.62-2.82)	1.72(1.06-2.1)
561.3 NPC	1.88 (1.24-2.87)	1.8(0.8-2.12)

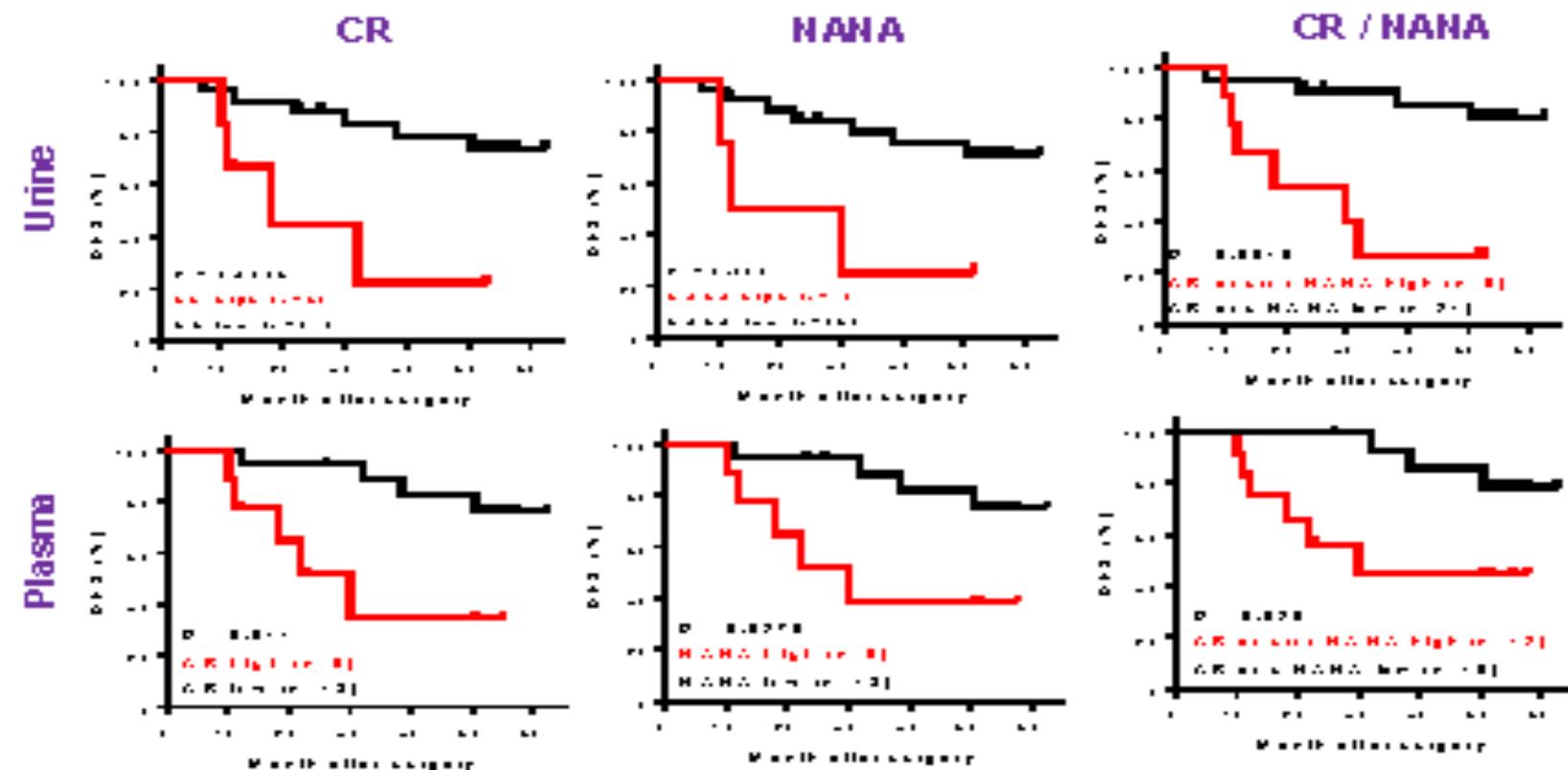
Two-tailed Odds Ratio, p<0.05



Liquid biopsy



Creatine Riboside in Liquid Biopsy is Associated with Recurrence of Early Stage Lung Cancer

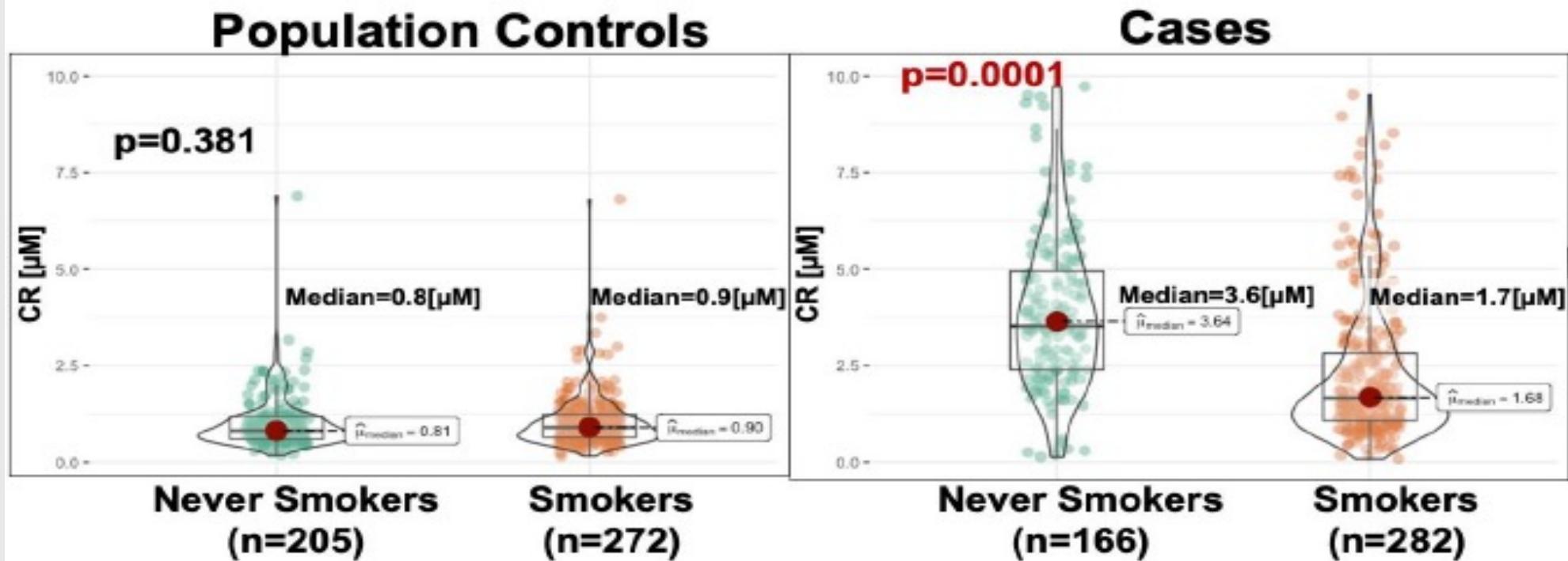


unpublished

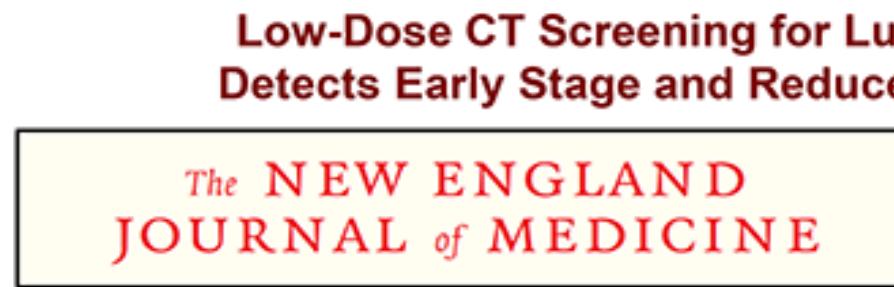
Violin plot



NCI-MD Cohort in Lung Cancer from Never Smoker vs. Smokers: Violin Plot Analysis of Creatine Riboside

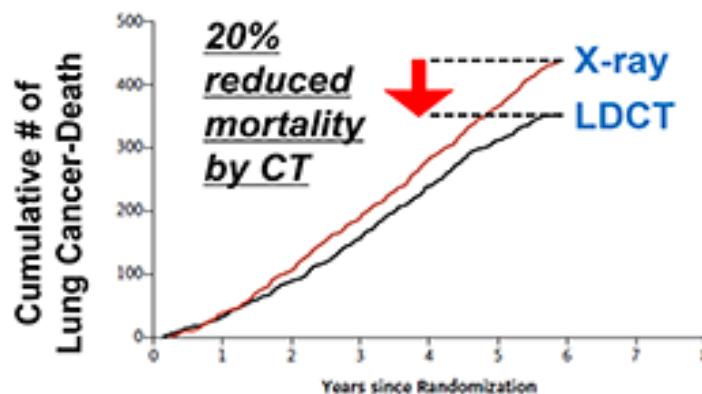


Low dose CT screening

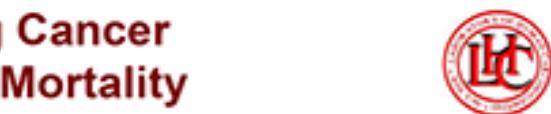


Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*



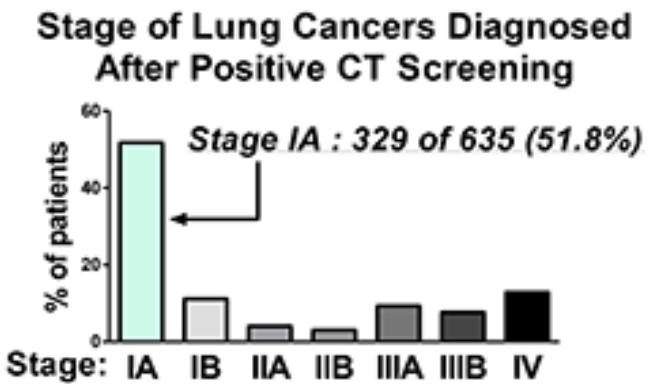
NIH NATIONAL CANCER INSTITUTE



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

X-ray
n=26732 LDCT
n=26722

Low-Dose CT
• False Positive Rate = 96.4%



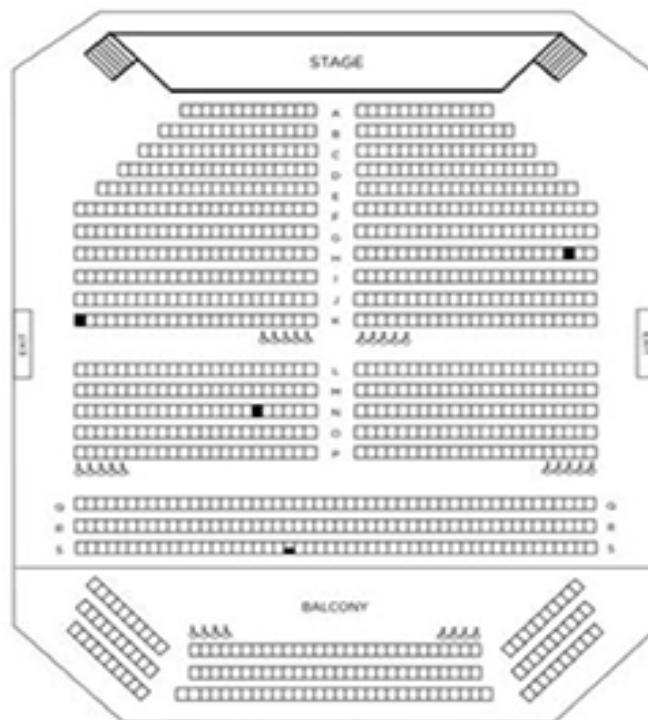
8167-CH

Spiral CT scans

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



NATIONAL CANCER INSTITUTE

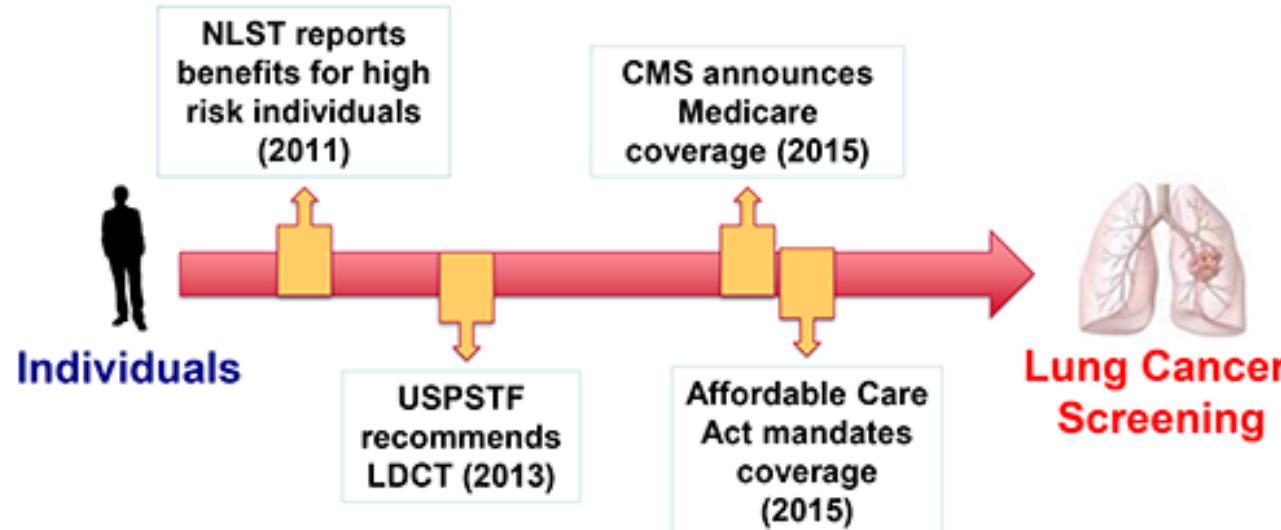
Andrew Lazris and Erik Rifkin: Interpreting Health Benefits And Risks

8817-CH

Low dose CT



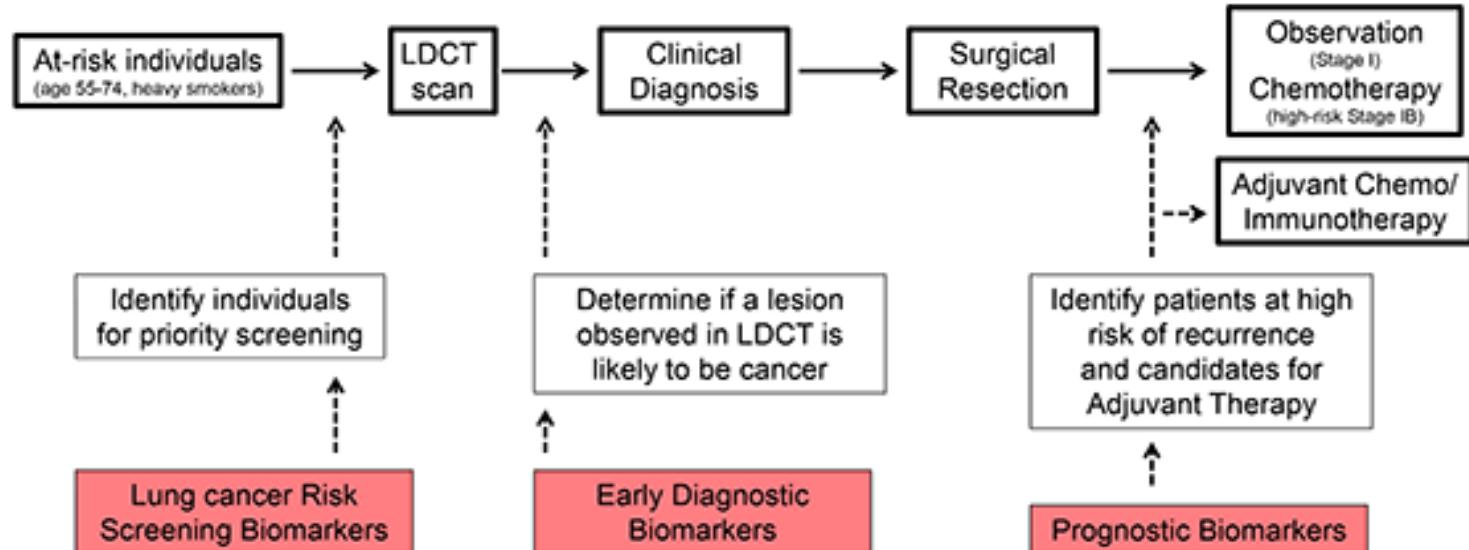
Low-Dose Computed Tomography (LDCT)



- 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)

Unmet needs

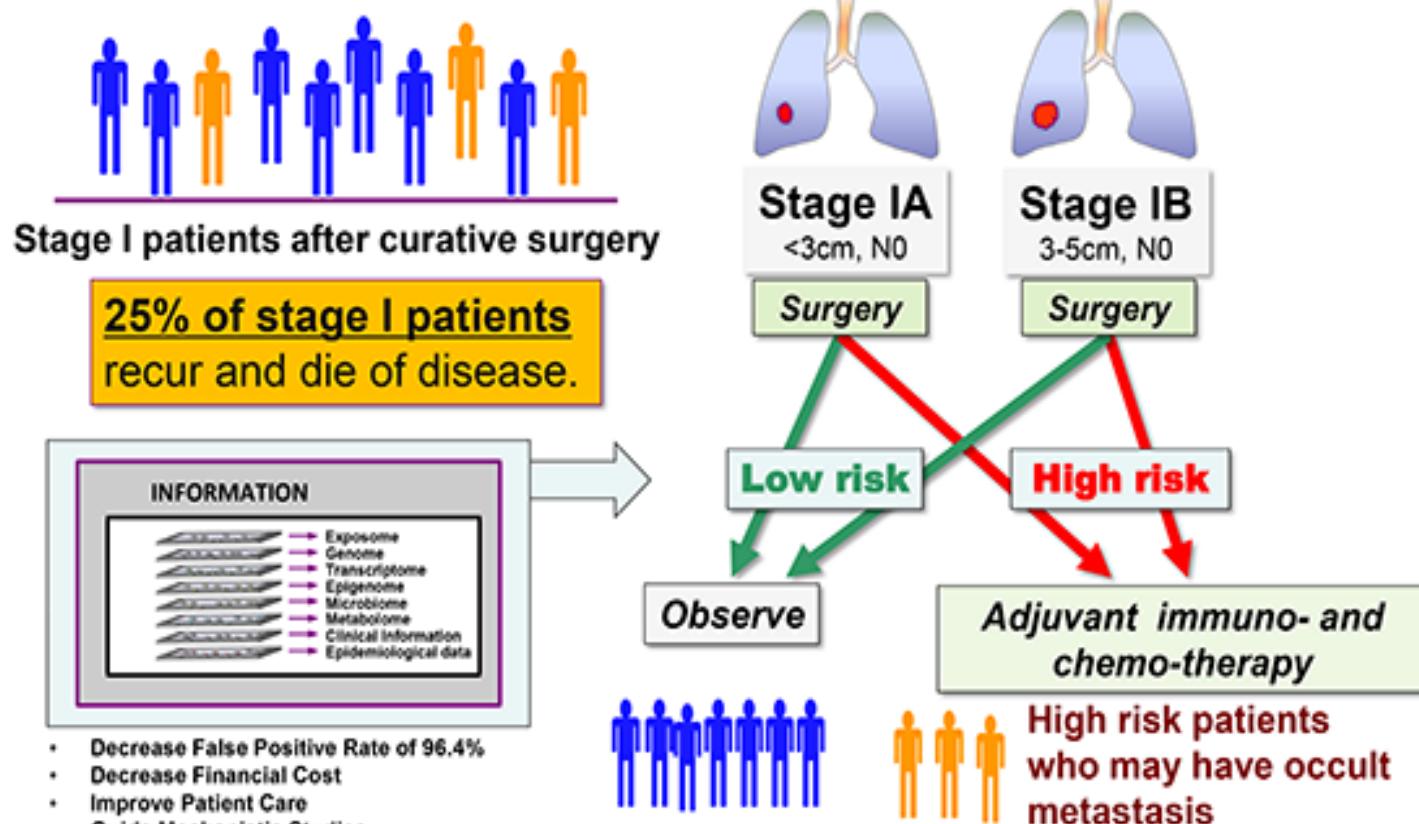
Early Stage Lung Cancer: Unmet needs



Precision medicine goals



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



Collaborators

COWORKERS AND COLLABORATORS



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- Takashi Kohno
- Sharon Pine
- Ann Schwartz
- Masahiro Seike
- Peter Shields
- Kouya Shiraishi
- Jun Yokota

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