CANCER EPIDEMIOLOGY AND MECHANISTIC BIOMARKERS OF CANCER: Precision Medicine Strategy

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Tapestry of Life, Transformations in Science Art, Clare O. Hagan and Denise Wylie

No Disclosures

Towards Precision Medicine and a Molecular Taxonomic Classification of Disease

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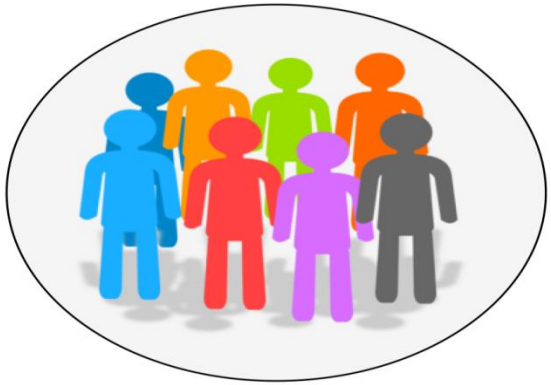
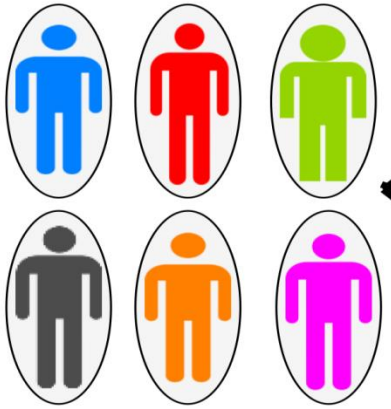
Traditional Medicine



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

Precision Medicine

- Multi-layered
- Individual-centric
- Interconnected

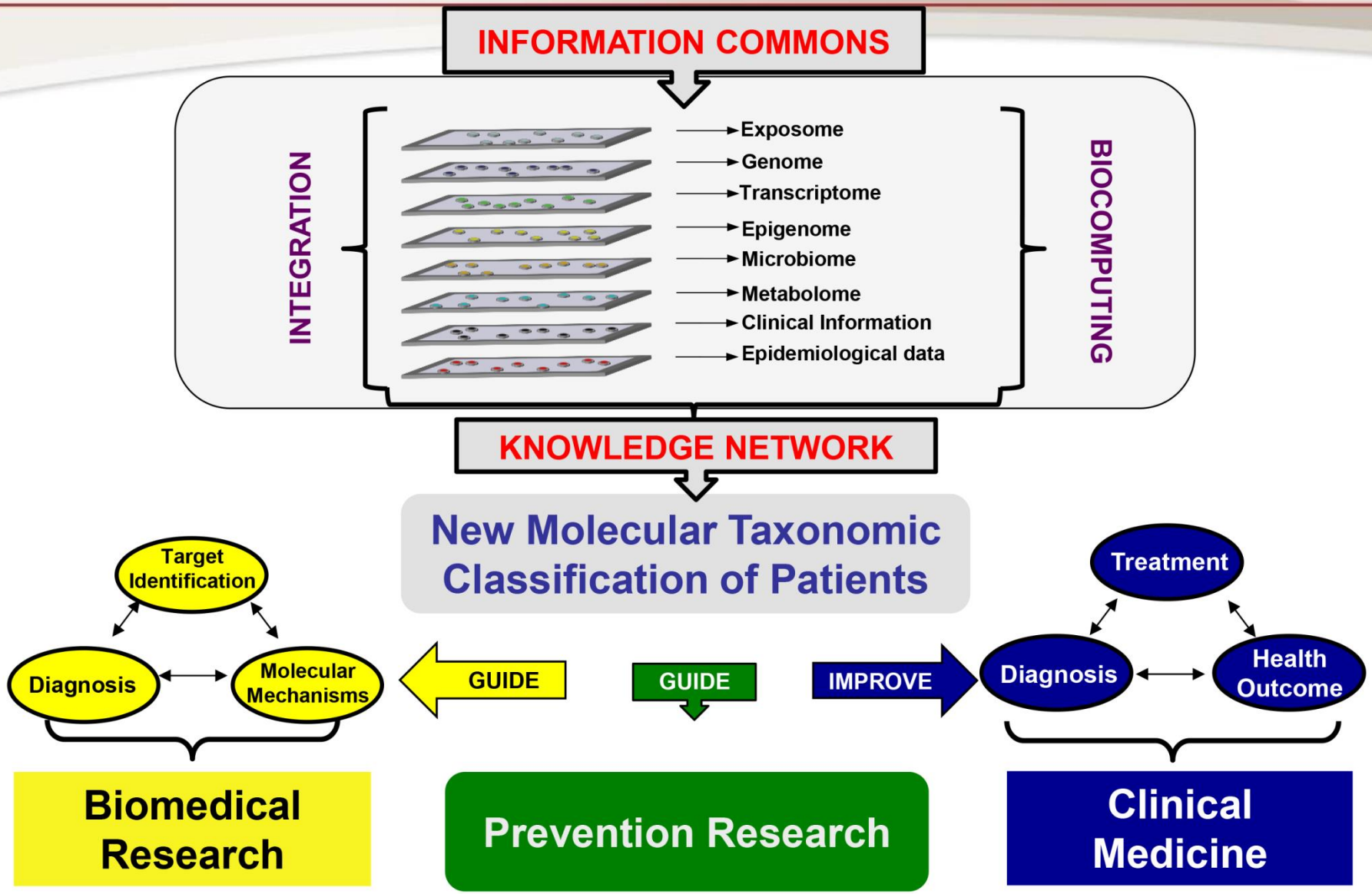


INFORMATION COMMONS

- 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]

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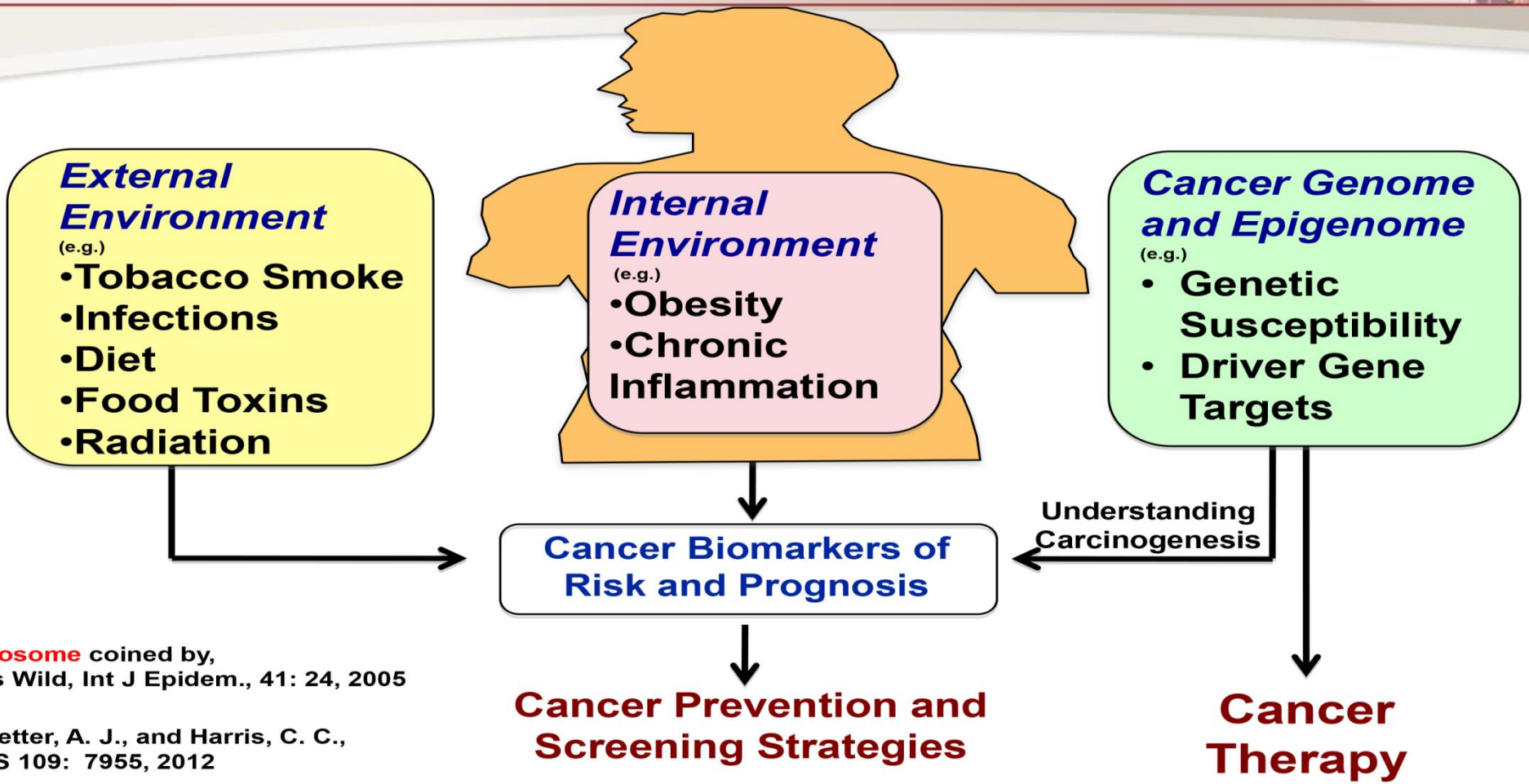

[1]Exposome coined by, Chris Wild, Int J Epidem., 41: 24, 2005

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

Examples of Chemical Agents Causing Cancer

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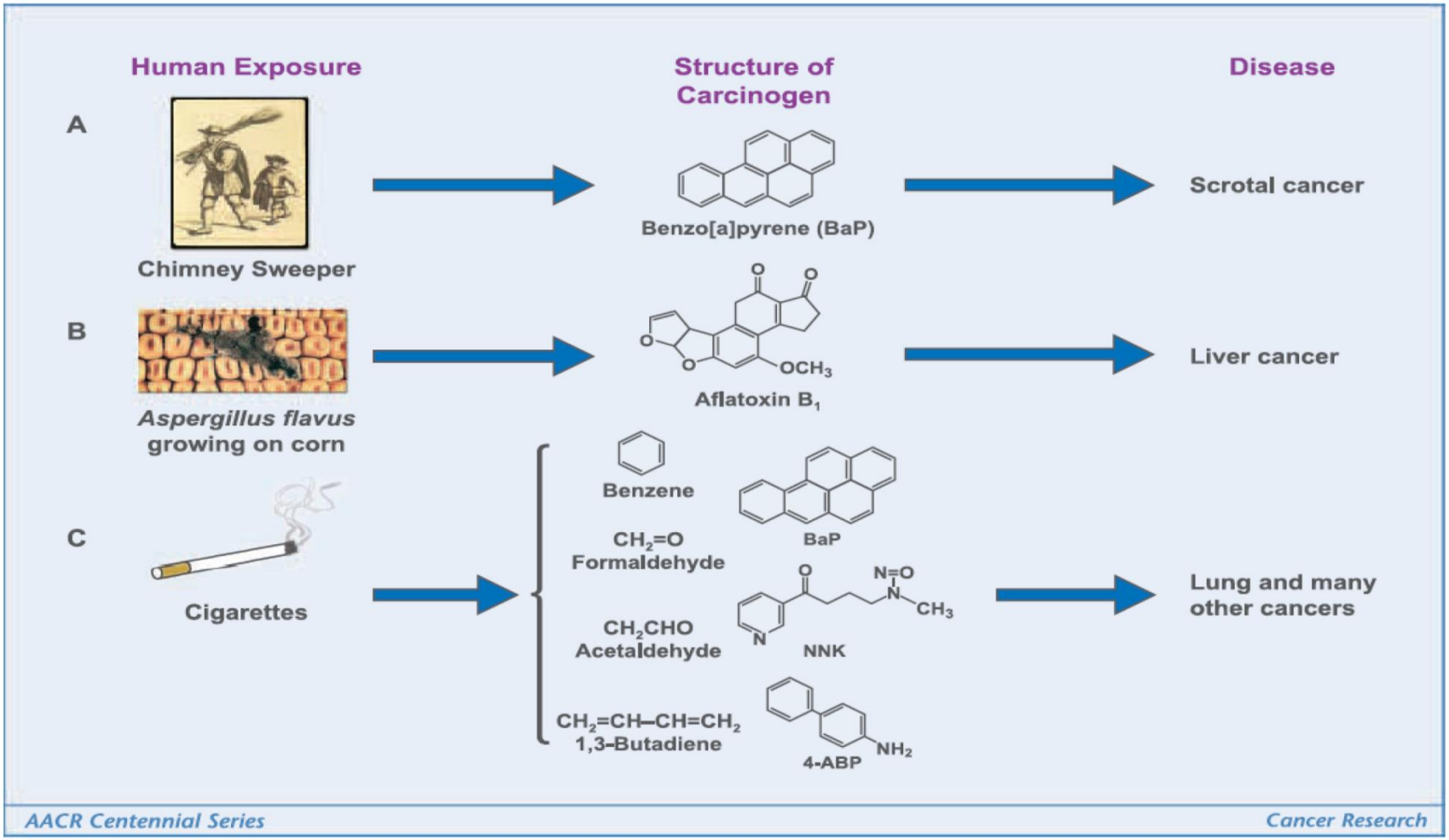
Examples of Chemical Agents Causing Cancer



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

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

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Marc Greeatt

Carcinogen/ (exposure)	Target organ	Base substitution: IARC database	Base substitution: In Vitro Human Cell Assays	Distinctive: 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

P53 and Liver Cancer

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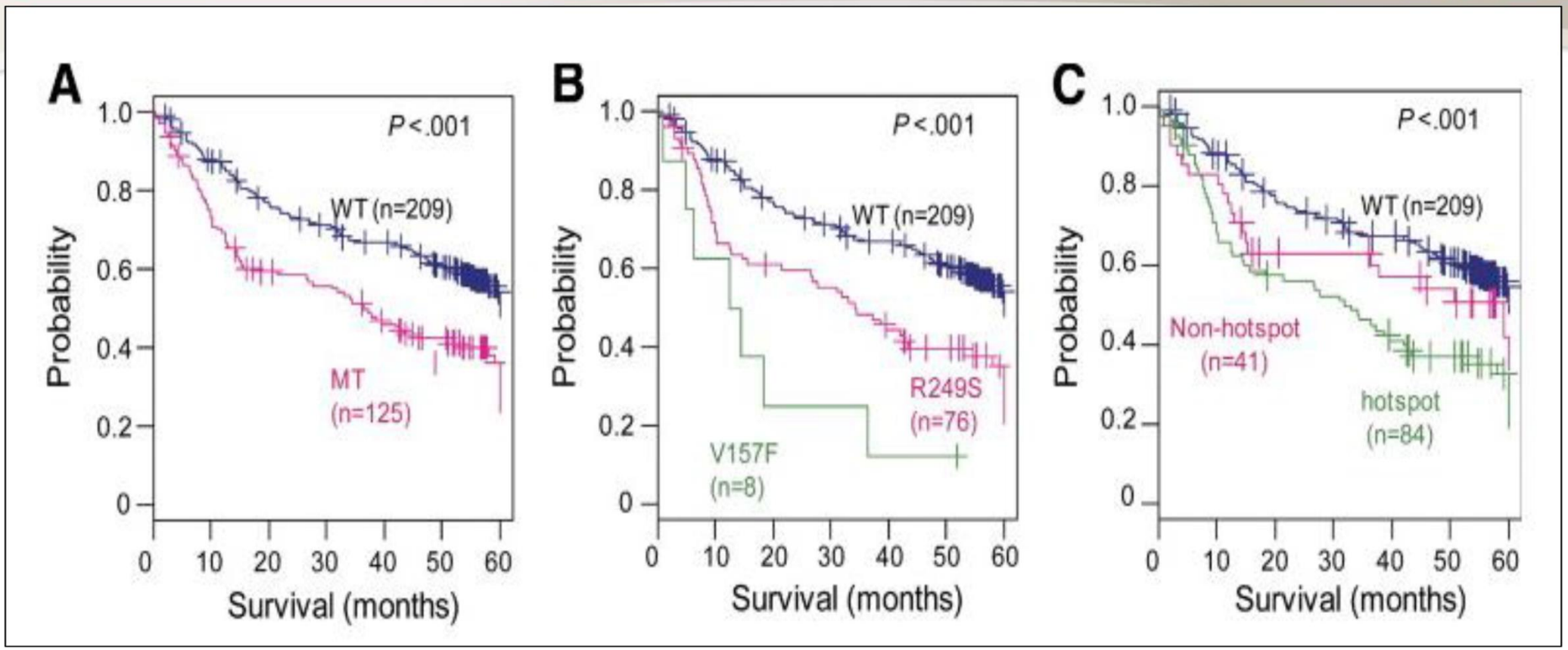
Kaplan-Meier Plots: Prognostic Values of TP53 Mutation Sites in Hepatocellular Carcinoma



(*A*) Kaplan–Meier plot for survival between the tumors of mutation-type (*MT*) and wild-type (*WT*) *TP53*. (*B*) Kaplan–Meier plot for survival between the tumors with R249S and V157F mutations. (*C*) Kaplan–Meier plot for survival between the tumors with hotspot (ie, R249S and V157F) and non-hot spot mutations. The + *symbols* in *panels* indicate censored data.

Woo, H.G., et al., Gastroenterology, 140(3): 1063-1070, 2011

Chronic Inflammation and Infection can increase Cancer Risk

Chronic Inflammation and Infection Can Increase Cancer Risk

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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
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

World Cancer Report, IARC, WHO, 2014

Obesity is a Chronic Inflammatory Disease

Obesity is a Chronic Inflammatory Disease

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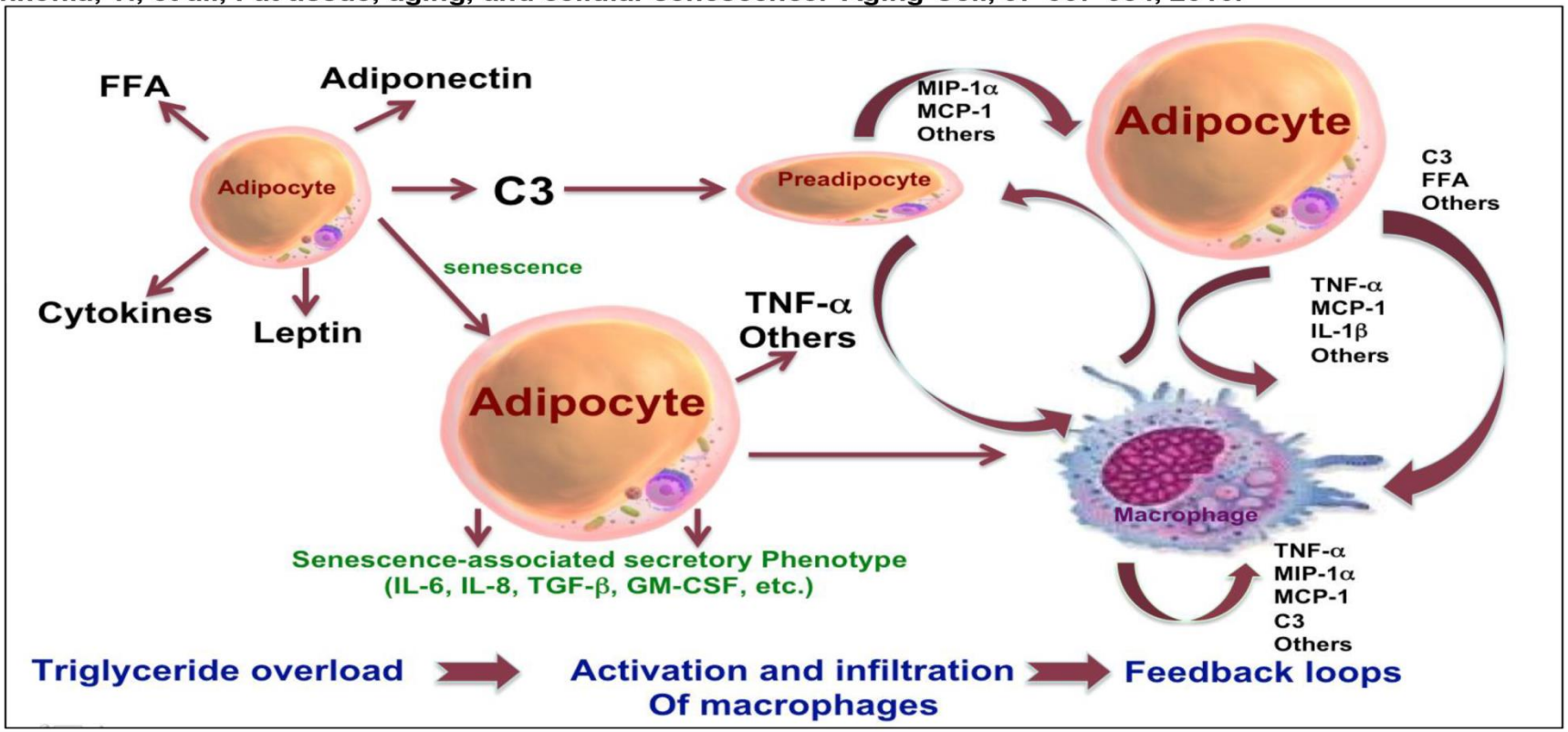
- Weisberg et al. Obesity is associated with macrophage accumulation in adipose tissue. J. Clin. Invest, 112: 1796-1808, 2003.
- Xu et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J. Clin. Invest, 112: 1821-1830, 2003.
- Minamino, T., et al., A crucial role for adipose tissue p53 in the regulation of insulin resistance. Nature Med, 15: 1082-87, 2009.
- Tchkonia, T., et al., Fat tissue, aging, and cellular senescence. Aging Cell, 9: 667-684, 2010.



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

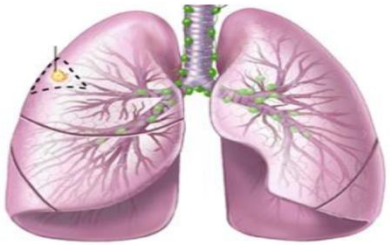
Health Disparity:
Increased Expression of Serum Pro-Inflammatory Cytokines is Associated with Lung Cancer Risk, Diagnosis and Survival

Increased Risk

↑ IL-8, ↑ CRP (EA)

JNCI 103: 1112, 2011

Diagnosis



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

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

Poor Survival

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

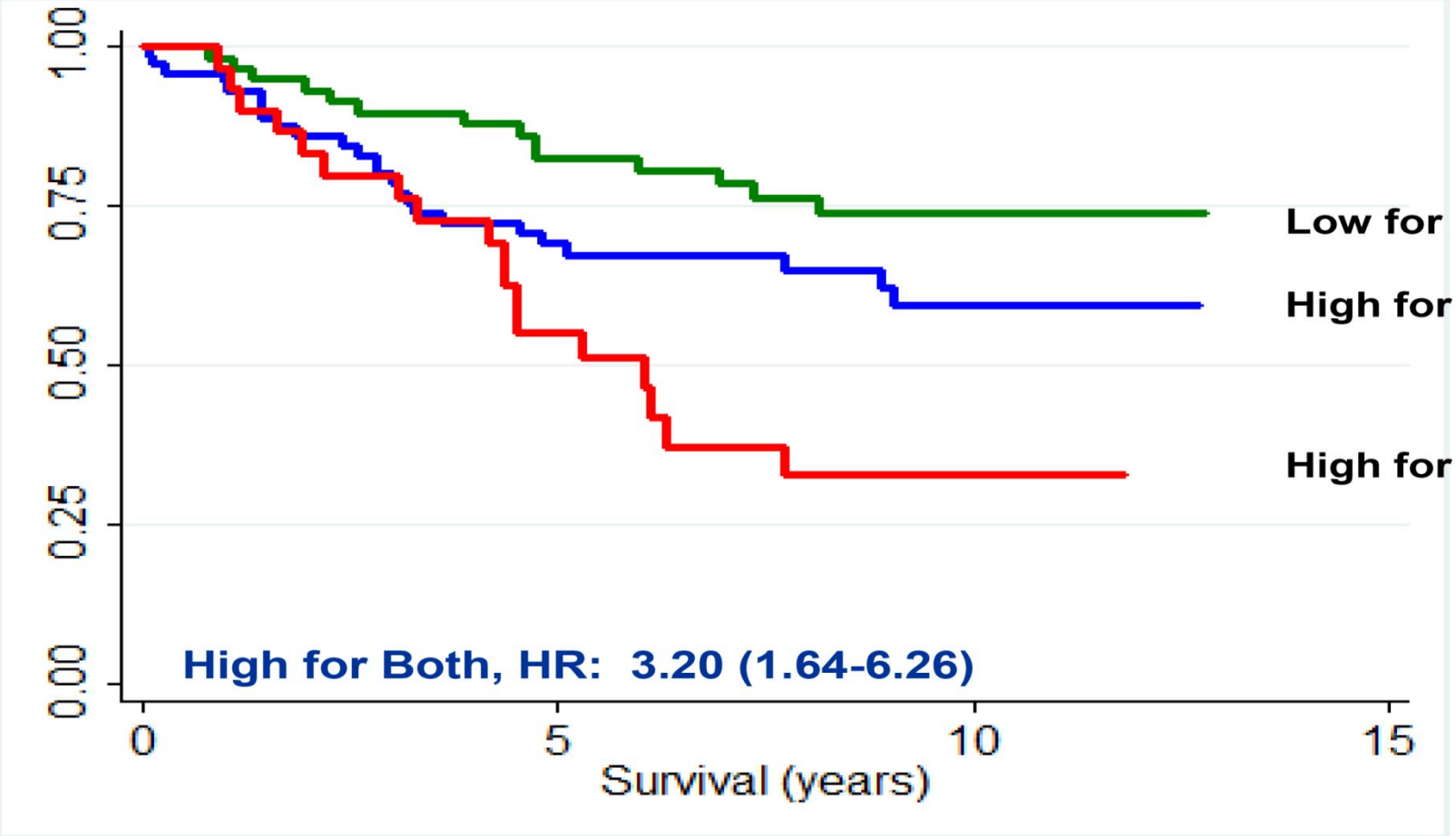
CEBP: 215, 2010
JNCI 99: 1401, 2007
J. Thoracic Oncol, 2014

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

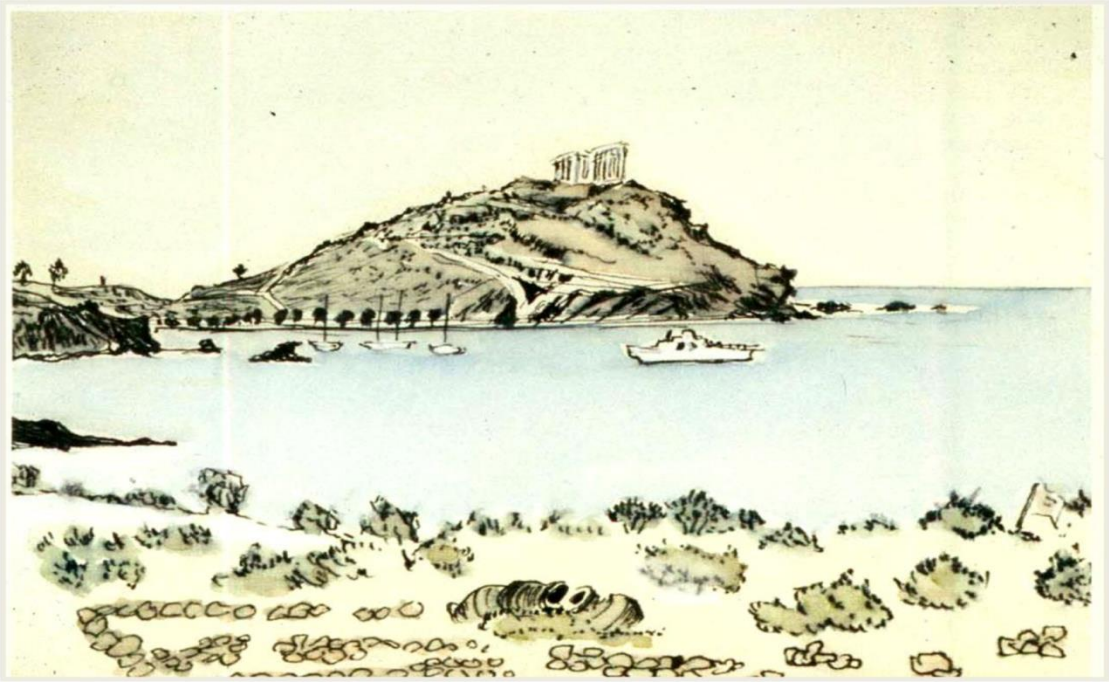
Combination of Serum IL-6 and IL-8 is a Robust Prognostic Classifier of Stage I Lung Cancer

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

Molecular Epidemiology of Lung Cancer in Never Smokers

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Molecular Epidemiology of Lung Cancer in Never Smokers

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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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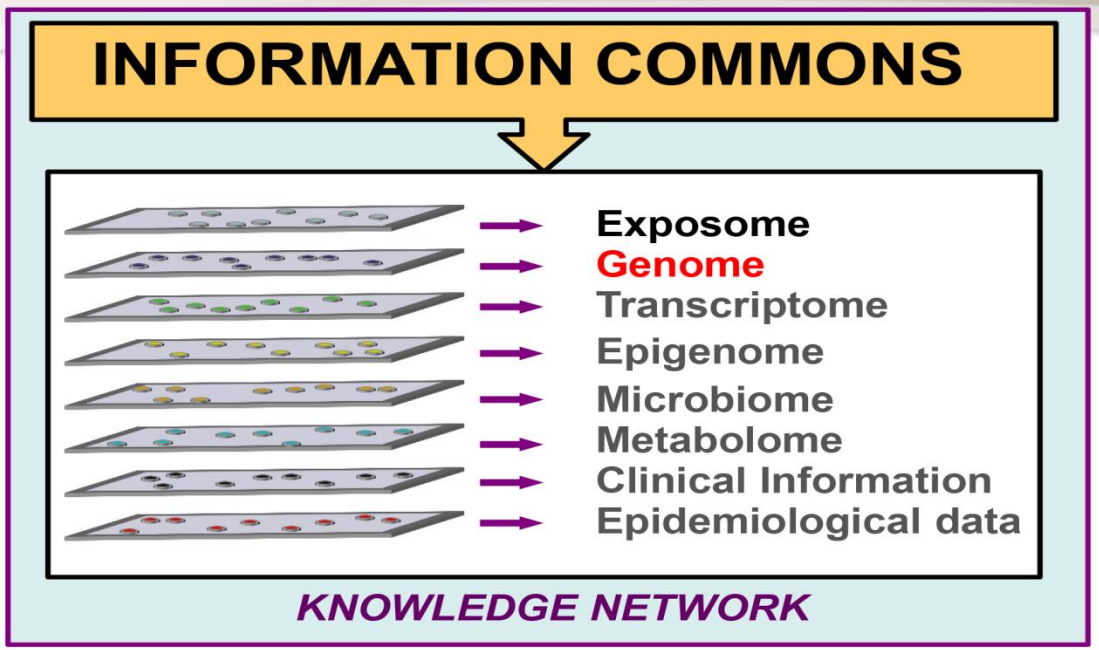
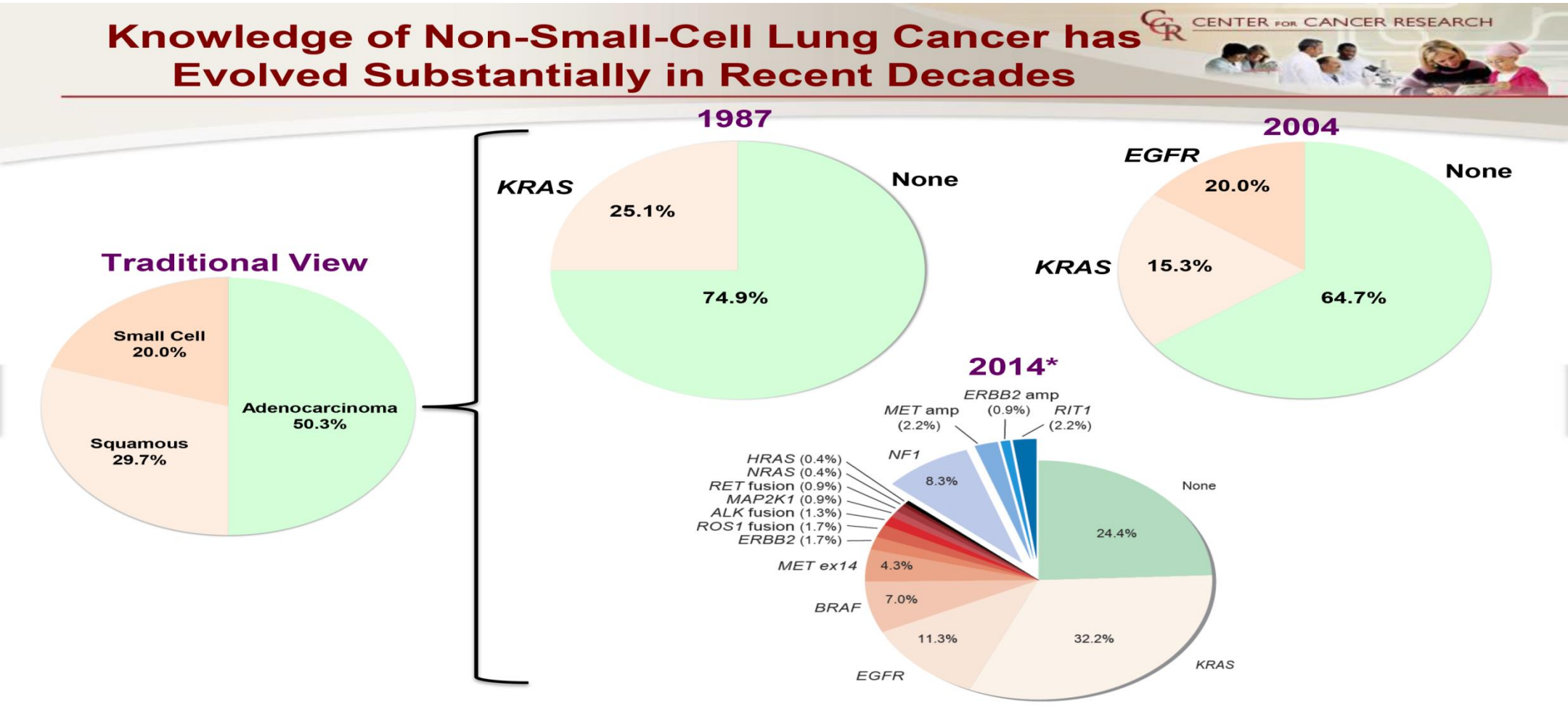
Precision Medicine



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

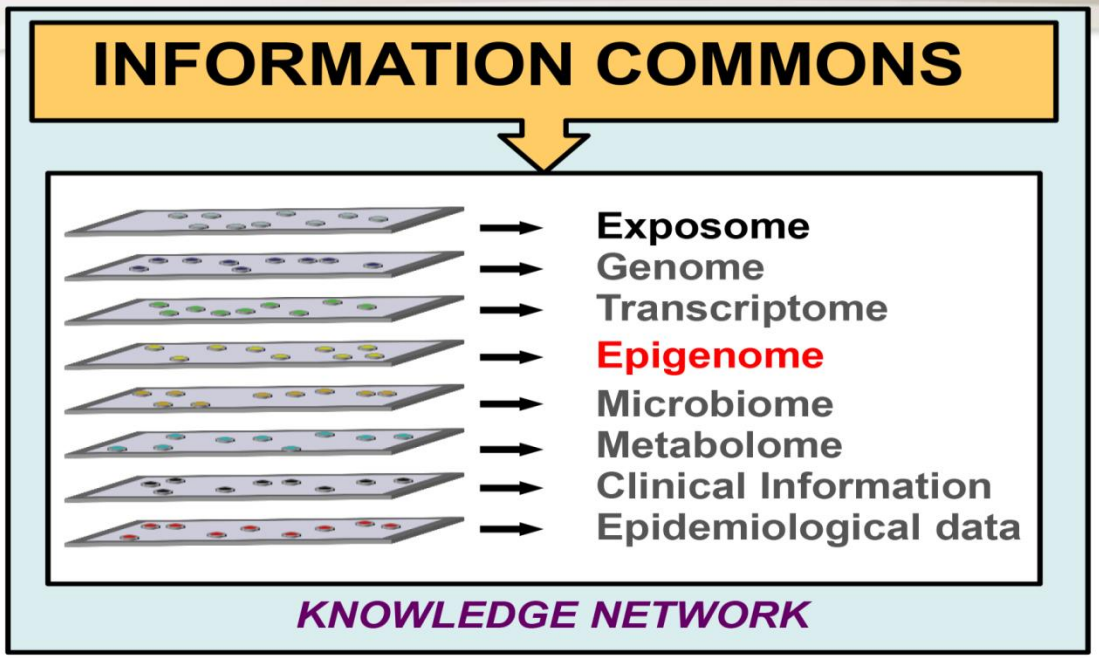
8136B-CH

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



Precision Medicine: Information Commons

Precision Medicine



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

Epigenome: Micro RNA and Cancer

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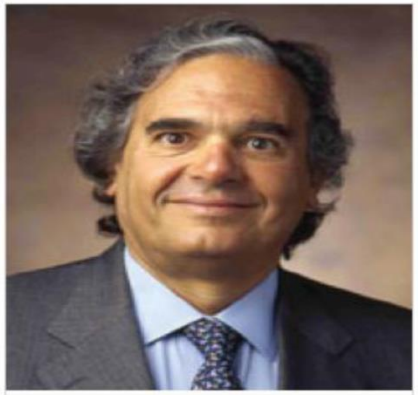
Epigenome: MicroRNA and Cancer

- **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

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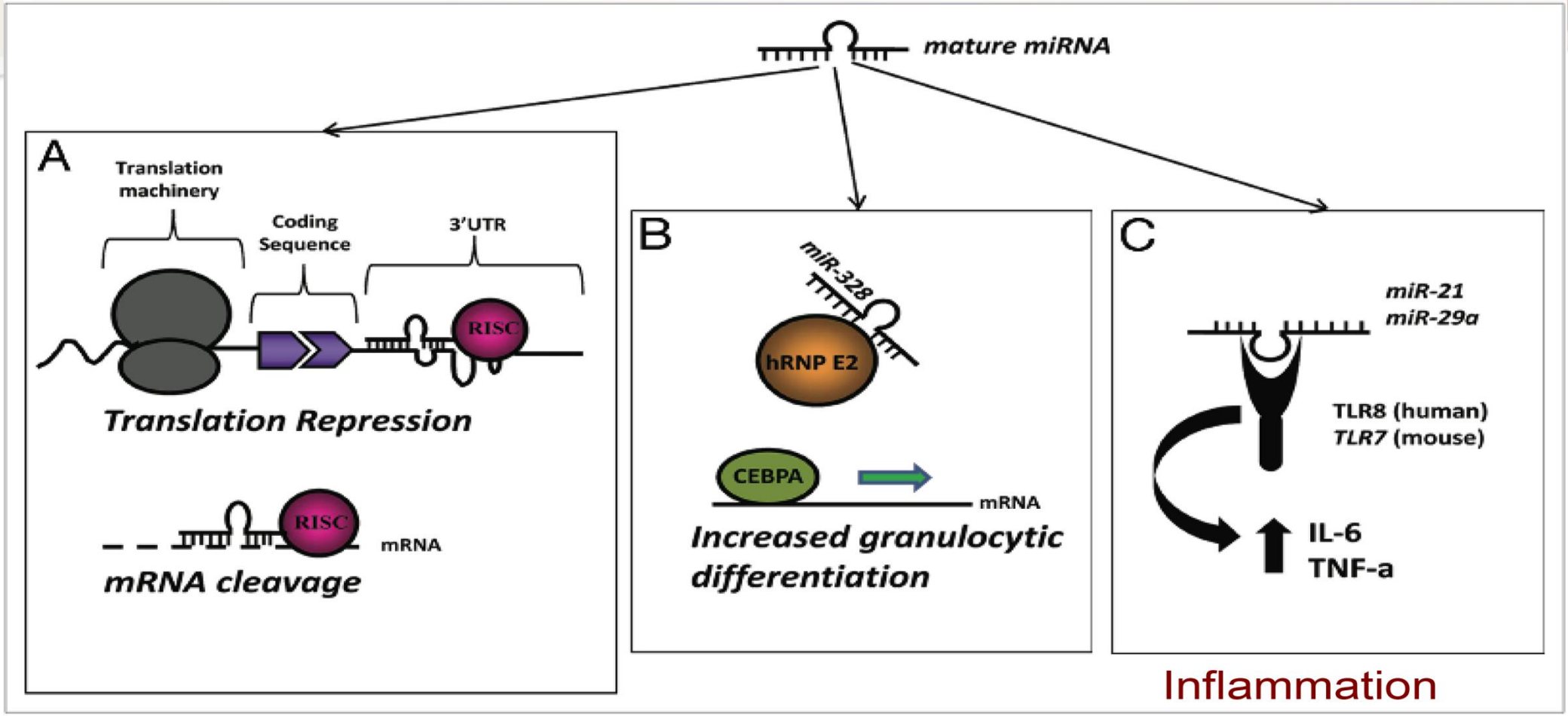

Fabbri, M., et al., RNA Biology, 10:2, 169-174, 2013

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

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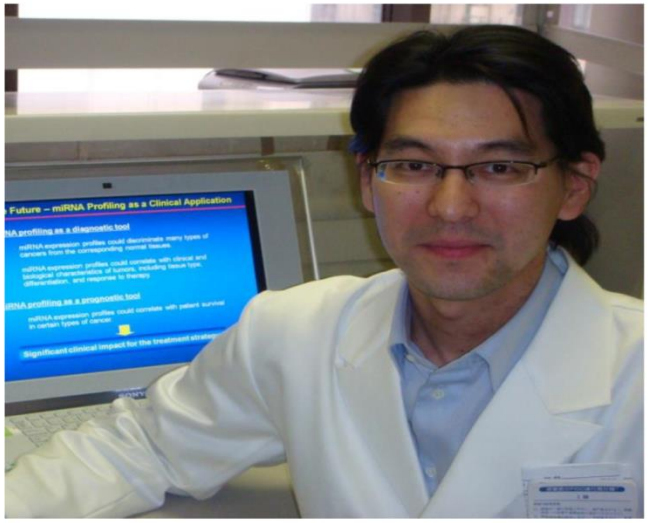
- miRNAs profiles were significantly different both between primary lung cancers and corresponding non-cancerous lung tissues and among different histological types of lung cancer.
- Increased mir-21, mir-155 and mir-106b, and decreased let-7 were each associated with diagnosis and prognosis including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

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Epigenome: Commonly Up-Regulated microRNAs in Carcinomas

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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*

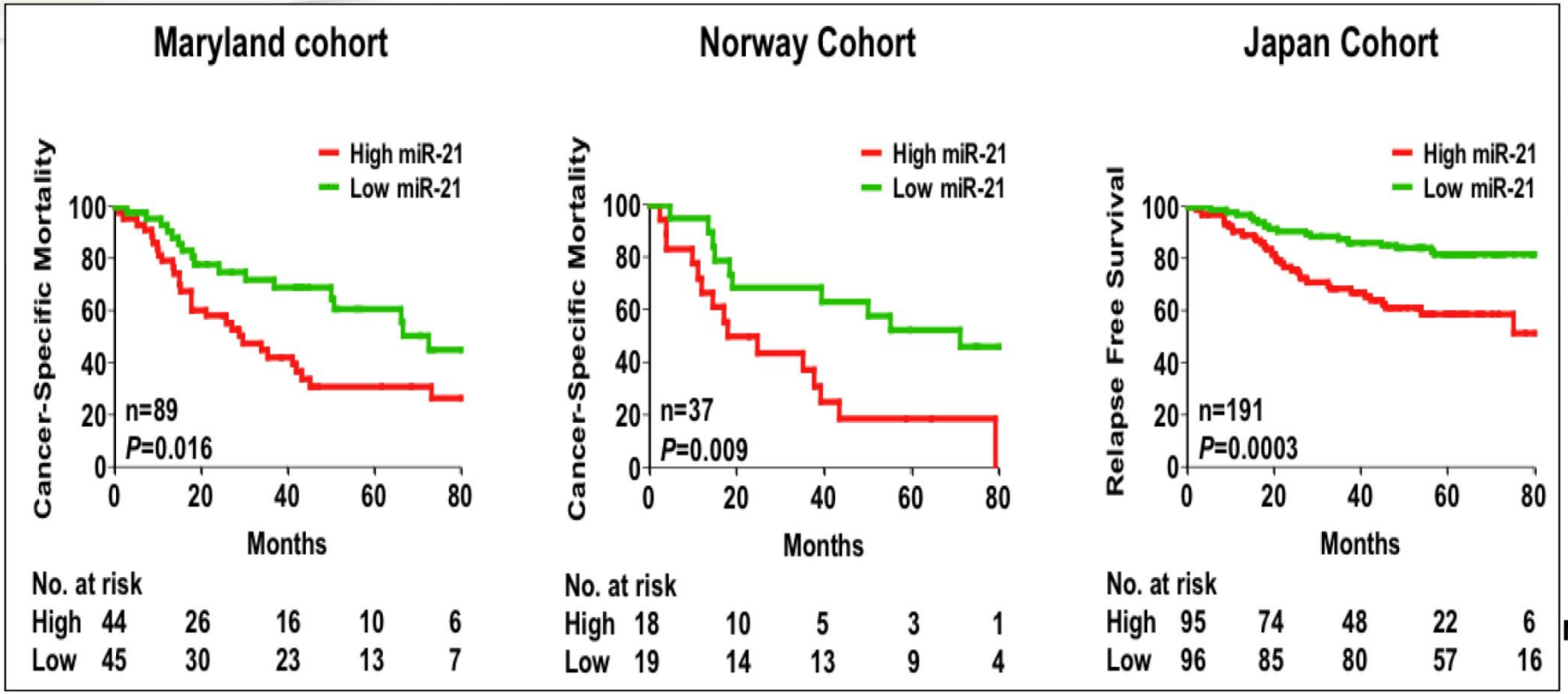
miR-21 is both up-regulated in 18 major cancers and a biomarker of poor survival in 14

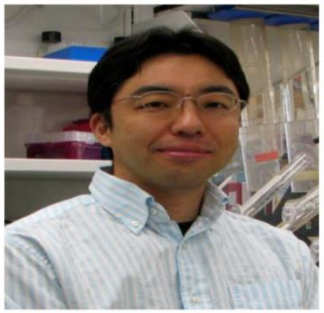
*The list includes 21 commonly up-regulated microRNAs in three or more (N) types of solid cancers (p-value=2.5×10^{-3}).

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

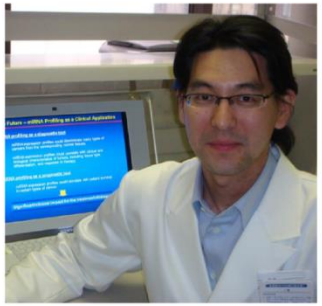
Increased miR-21 Expression in Human Lung Cancer is Associated with Poor Prognosis in Three Cohorts

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

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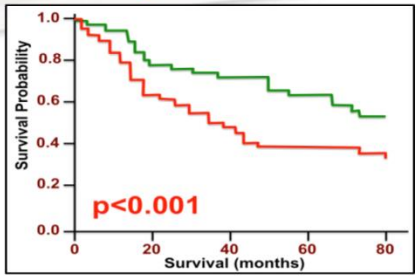
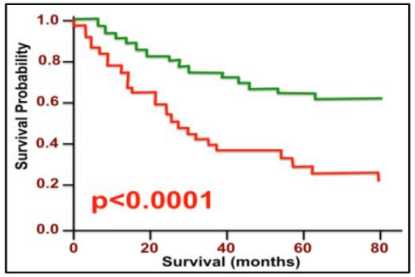
Lung Cancer



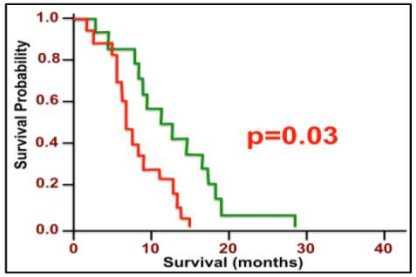
(Saito, M. et al. Clin Cancer Res., 2011)

Colon Cancer



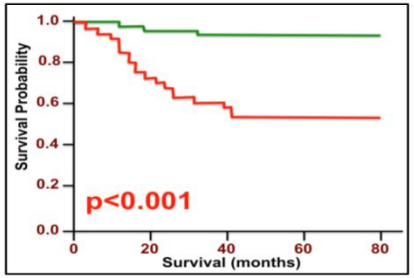
(Schetter et al. JAMA 2008)

Pancreatic Cancer



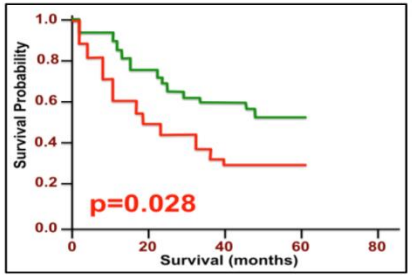
(Giovannetti, E., et al., Cancer Res. 2010)

Breast Cancer



(Yan et al, RNA 2008)

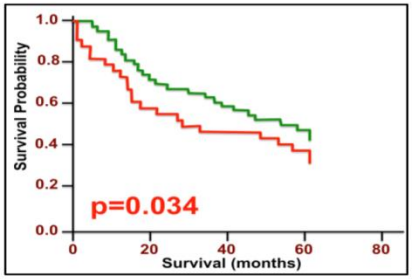
Melanoma



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

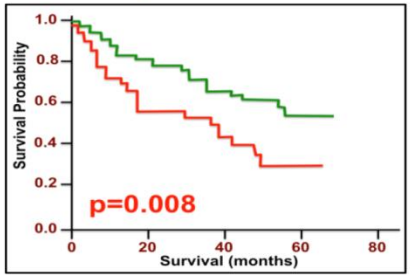
Low miR-21 Expression
High miR-21 Expression

Head & Neck Cancer



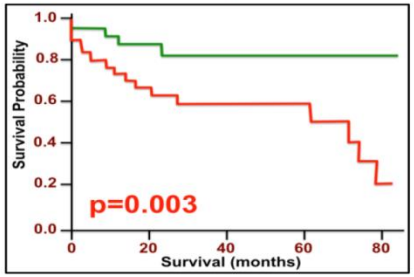
(Avissar, et al., Carcinogenesis 2009)

Tongue Cancer



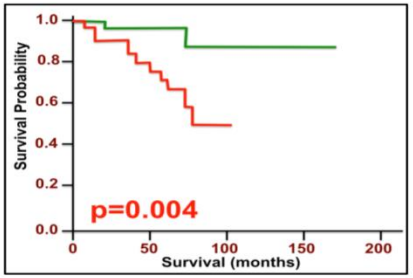
(Li, J. et al. Clin Cancer Res. 2009)

Astrocytoma



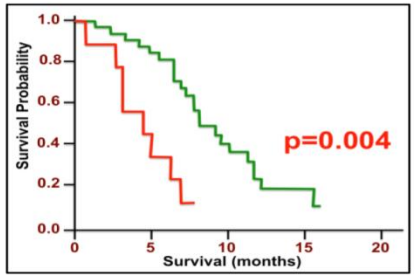
(Zhi, F. et al. Eur J Cancer 2010)

Chronic Lymphocytic Leukemia



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

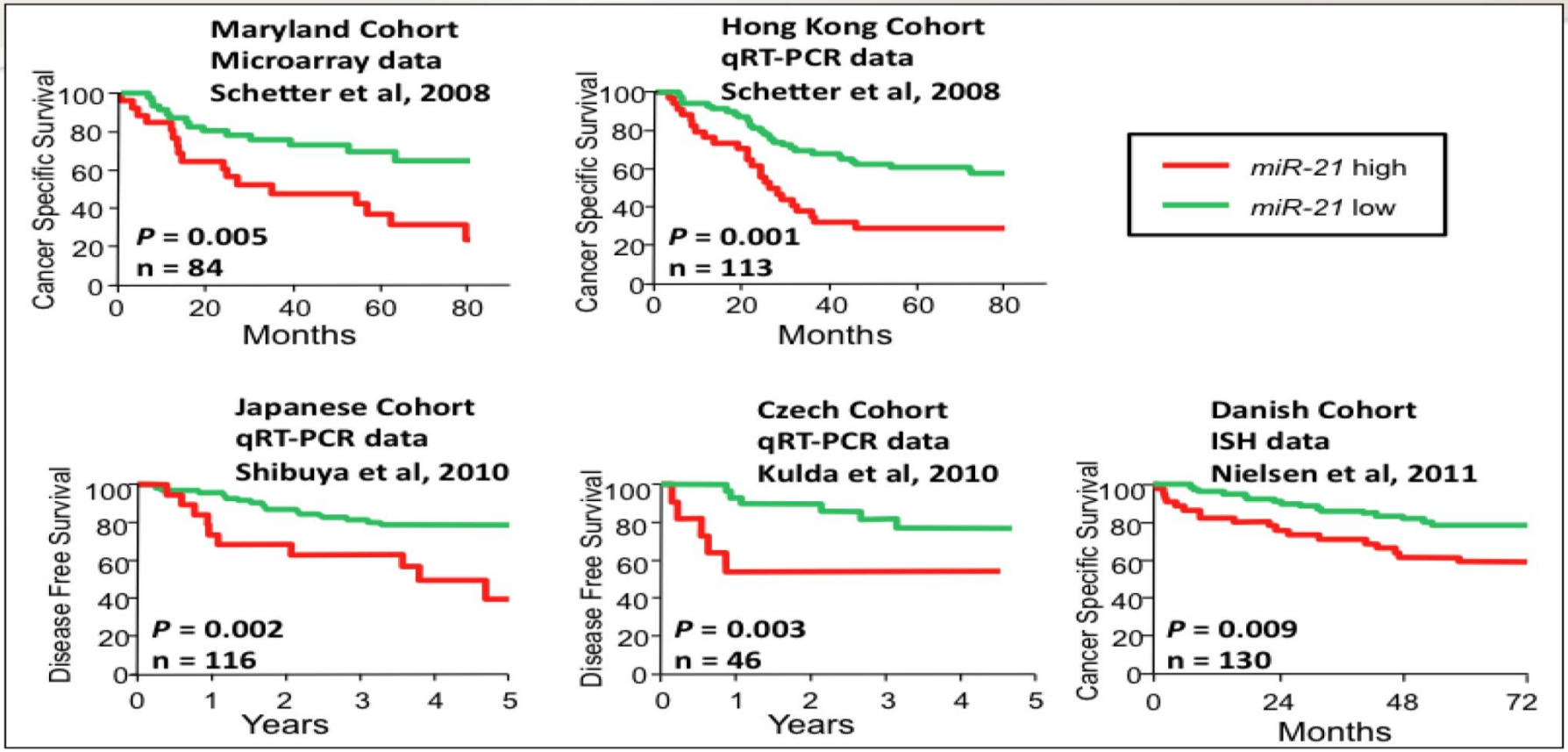
Gastric Cancer



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

High miR-21 Expression is a Prognostic Classifier in Multiple Cohorts of Colon Cancer

High *miR-21* Expression is a Prognostic Classifier in Multiple Cohorts of Colon Cancer



Aaron Schetter

Chemican Carcinogensis, Chemotherapy: Cancer's Continuing Core Challenges

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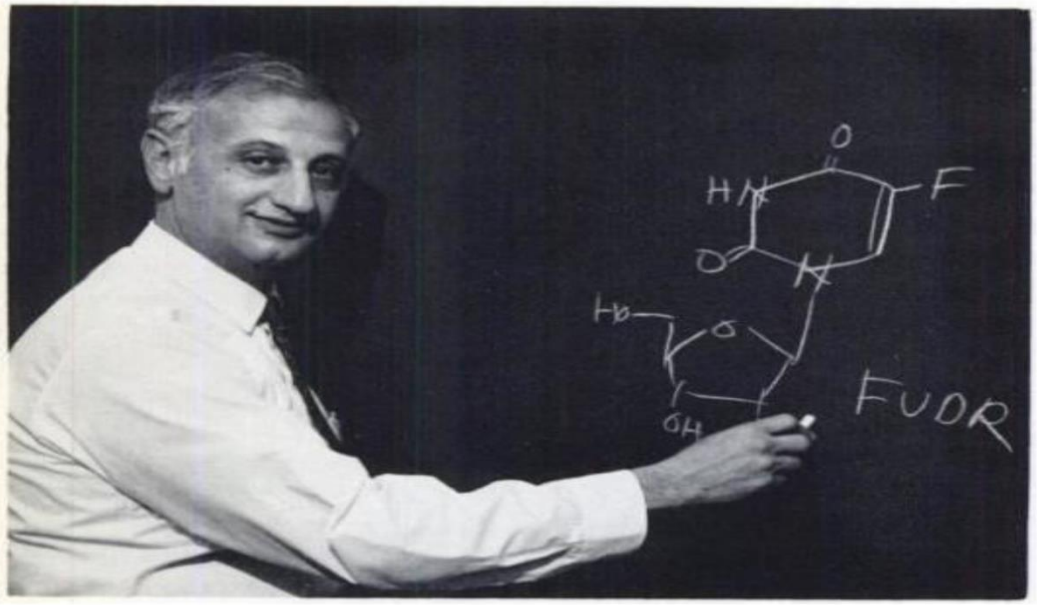
[CANCER RESEARCH 30, 1549–1569, June 1970]

Chemical Carcinogenesis, Chemotherapy: Cancer's Continuing Core Challenges—G. H. A. Clowes Memorial Lecture[1]

Charles Heidelberger[2]

McArdle Laboratory for Cancer Research, The Medical School, University of Wisconsin, Madison, Wisconsin 53706



High Expressio nof miR-21 is Associated with a worse Therapeutic Response and Survival in two Cohorts of Colon Cancer Patients treated with Adjuvant 5-FU

High Expression of miR-21 is Associated with a worse Therapeutic Response and Survival in two Cohorts of Colon Cancer Patients treated with Adjuvant 5-FU

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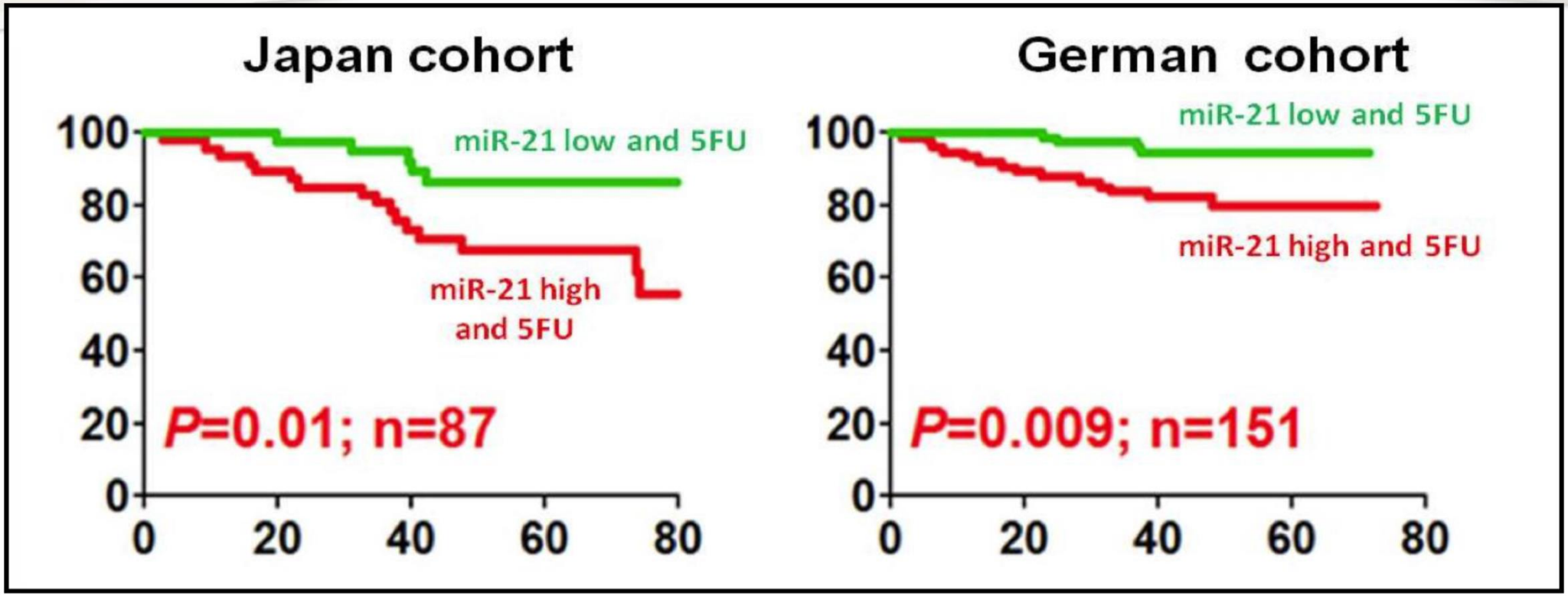

Oue, N … Harris, CC, Int J Cancer 134: 1926-34, 2014
Confirmation of: Schetter, A. … Harris, CC, JAMA, 299: 425-36, 2008

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

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

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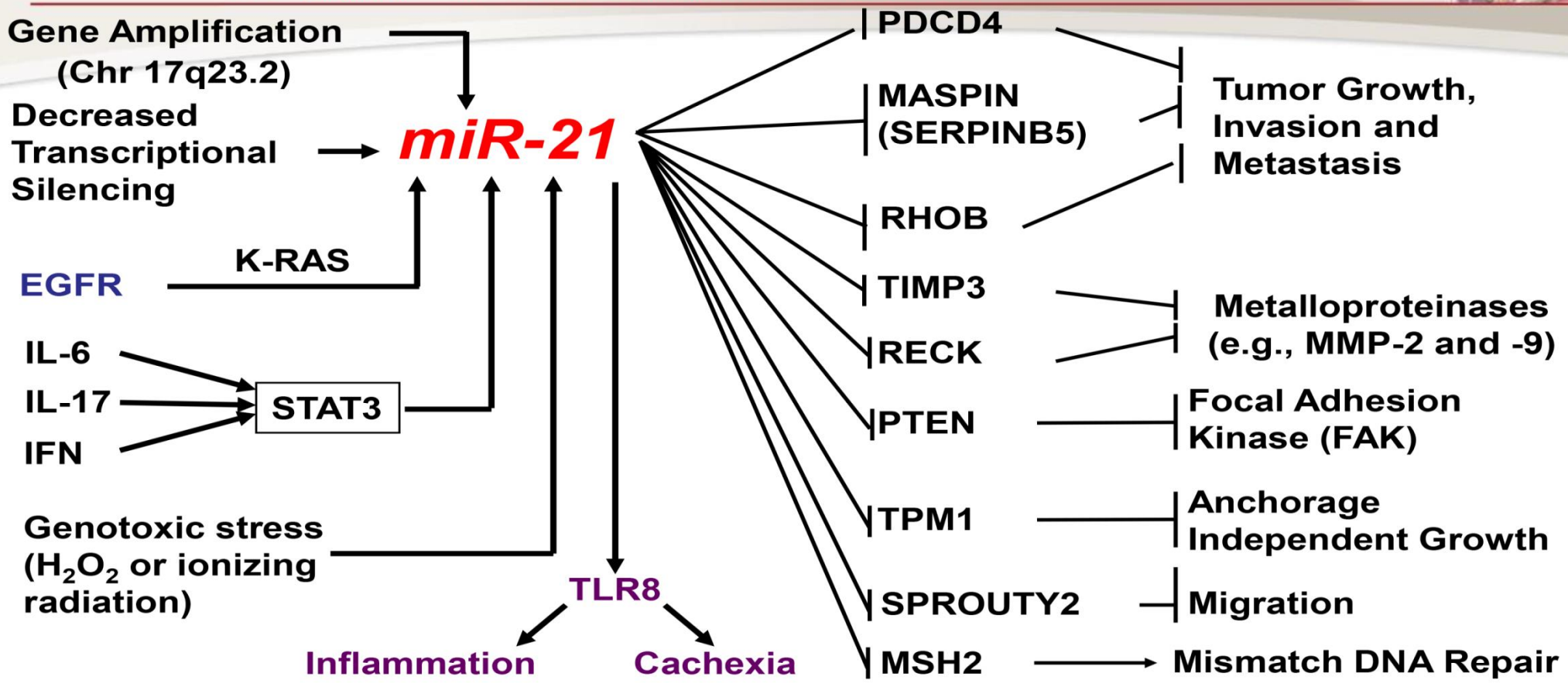

Seike ....Harris, PNAS 106: 12085-90, 2009
Schetter and Harris, Carcinogenesis 31: 37-49, 2010
Fabbri and Croce, RNA Biology 10: 169-174, 2013
He and Croce, PNAS 111: 4525-29, 2014

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

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

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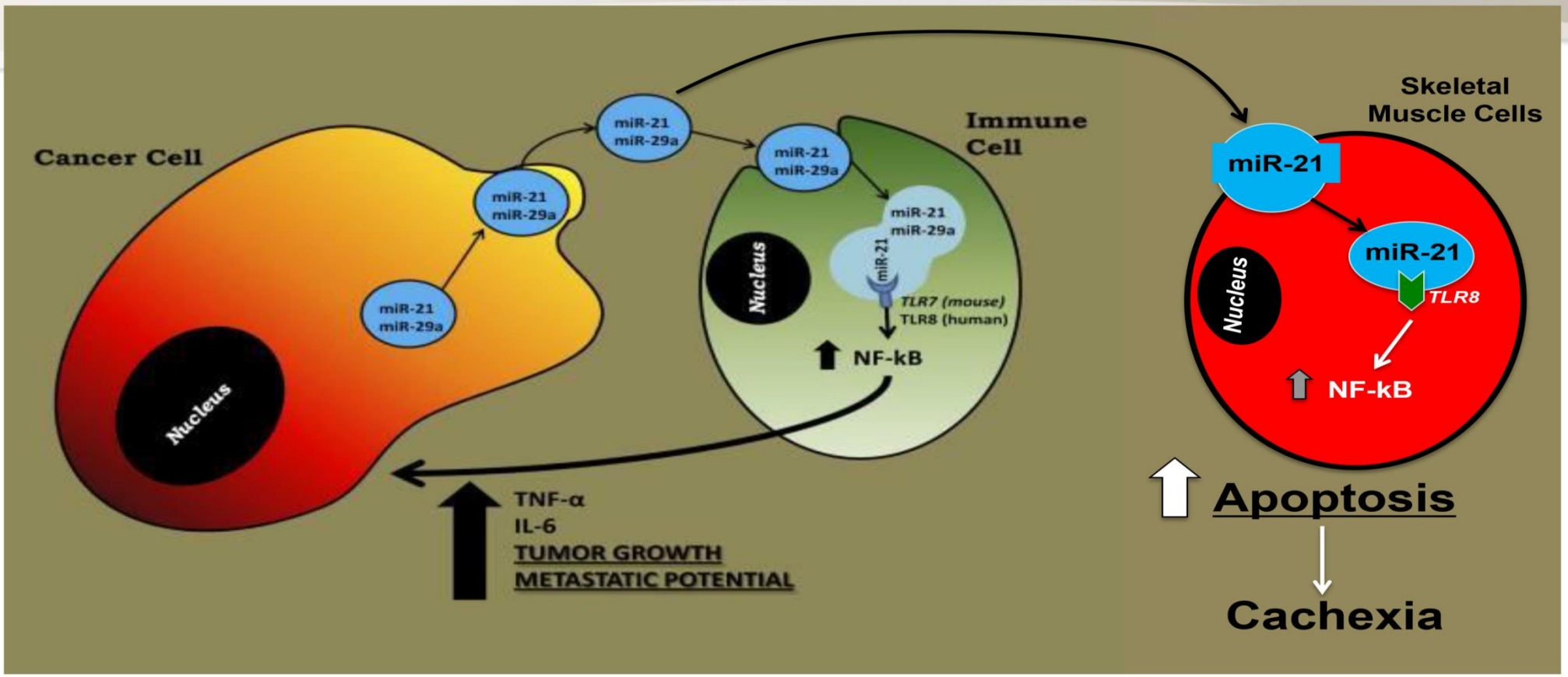

Fabbri, M., et al., PNAS, 109(31): E2110-E2116, 2012
He, W.A., et al., PNAS, 111: 4525-9, 2014

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

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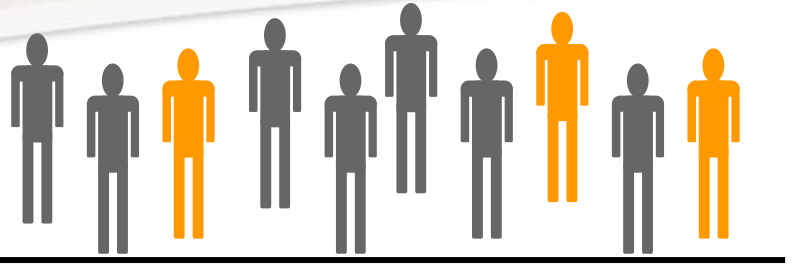
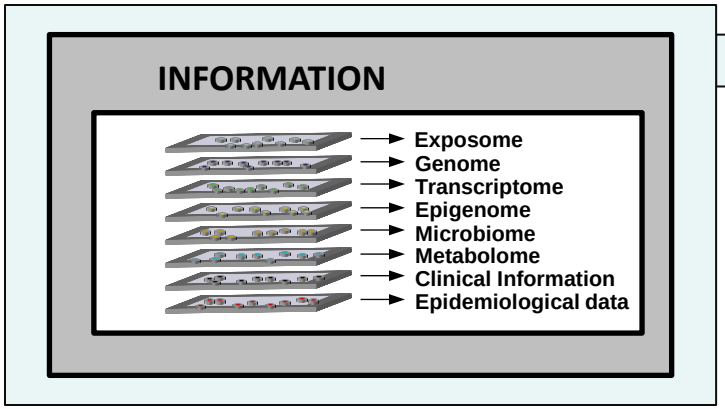
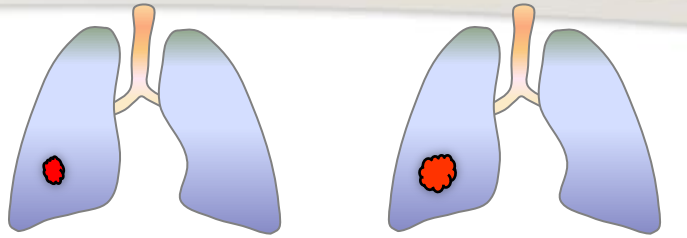


Stage I patients after curative surgery

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

Colon Cancer Biomarkers: Inflammation-Related Gene Expression

Colon Cancer Biomarkers: Inflammation-Related Gene Expression

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- **Hypothesis**: Inflammatory Risk Score (IRS) in tumor and adjacent non-tumor tissue correlates with colon cancer specific mortality independent of tumor stage.
  - Adjacent colon
    - Increased: PRG1, IL10 and CD68
    - Decreased: IL23a and IL12a
  - Colon Carcinoma
    - Increased: PRG1, ANA1, IL23a, IL17a, FOXP3 and HLA-DRA

Jane Sohn, Aaron Schetter

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HYPOTHESIS

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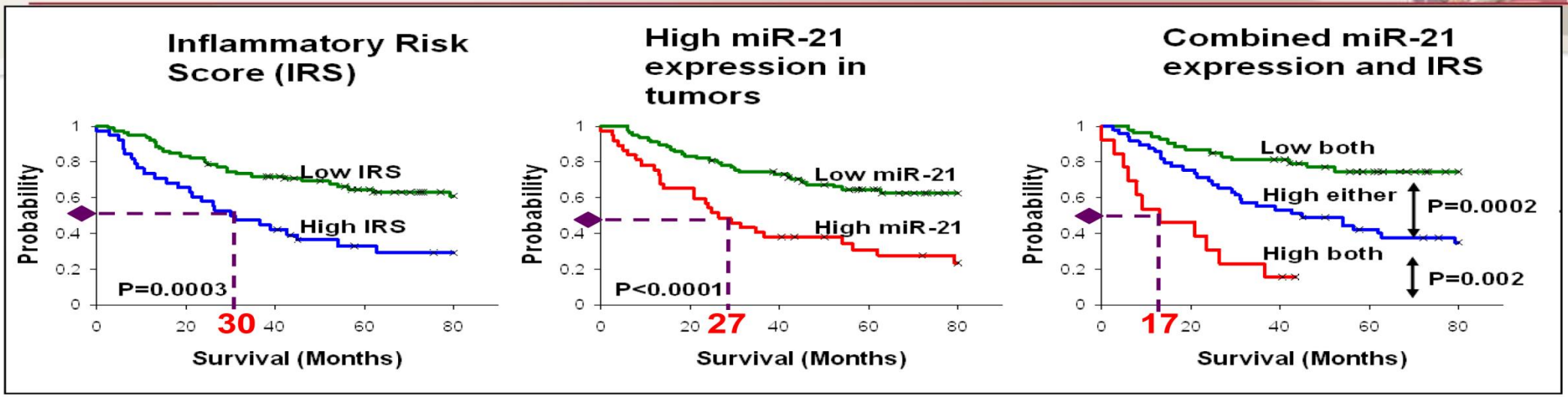
THE COMBINATION OF INFLAMMATION BIOMARKERS AND *miR-21* IS A BETTER PROGNOSTIC CLASSIFIER OF COLON CANCER THAN EITHER ALONE

Schetter A et al., JAMA 299:4251, 2008
Schetter A et al., Clin Cancer Res 15: 5878, 2009

miR-21 Expression

miR-21 Expression and Inflammatory Risk Score are Prognostic Classifiers of Colon Cancer



Variable (comparison/referent)	Univariate Analysis HR (95% CI)	Univariate Analysis P-Value	Multivariate Analysis HR (95% CI)	Multivariate Analysis P-Value
IRS (high/low)	2.4 (1.4 – 4.2)	0.001	2.2 (1.3 – 3.8)	0.005
miR-21 (High/low)	3.0 (1.7 – 5.1)	<0.0005	3.0 (1.7 – 5.2)	<0.0005
TNM Stage (III-IV/I-II)	4.7 (2.5 – 8.8)	<0.0005	4.0 (2.1 – 7.5)	<0.0005
Age (≥ 50 / < 50)	1.1 (0.6 – 2.1)	0.82		

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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

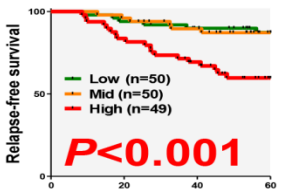
4-gene classifier

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

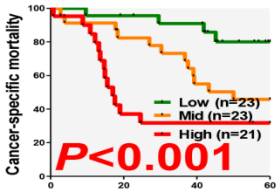
4-gene

- Lowest tertile
- Middle tertile
- Highest tertile

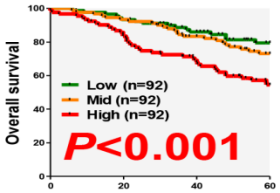
5 original cohorts of stage I adenocarcinoma



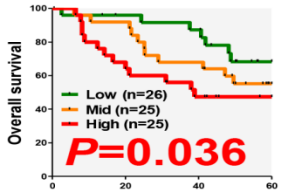
Japan (n=149)
qRT-PCR
Japan



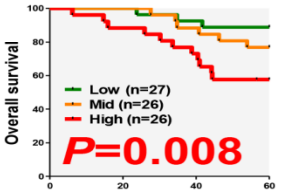
US/Norway (n=67)
qRT-PCR
UMD, Norway



Directors (n=276)
Affymetrix U133A
MSK,HLM,CAN/DF,UM



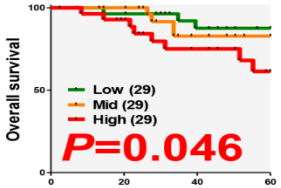
Bhattacharajee (n=76)
Affymetrix U95A
Harvard



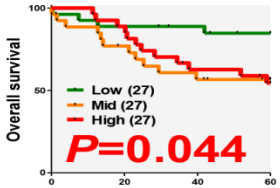
Tomida (n=79)
Agilent 44K
Japan

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

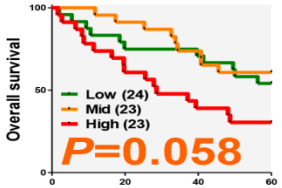
7 new cohorts of stage I adenocarcinoma



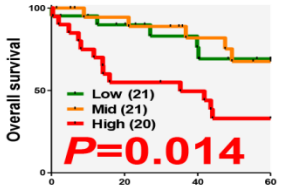
Tang (n=87)
Illumina WG6 V3
(GSE42127)
MD Anderson, 2013



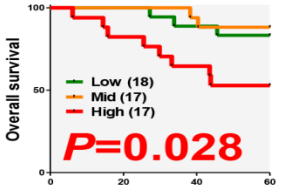
Rousseaux (n=81)
Affymetrix U133+2
(GSE30219)
France, 2013



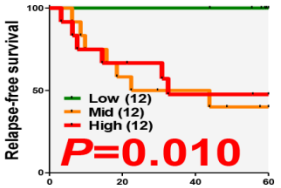
Botling (n=70)
Affymetrix U133+2
(GSE37745)
Sweden, 2013



Wilkerson (n=62)
Agilent 44K custom
(GSE26939)
UNC, 2012



Matsuyama (n=52)
Agilent 21.6K custom
(GSE11969)
Japan, 2011



Lee (n=36)
Affymetrix U133+2
(GSE8894)
South Korea, 2008

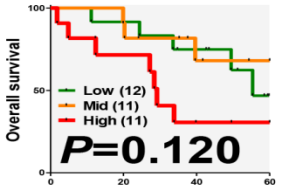


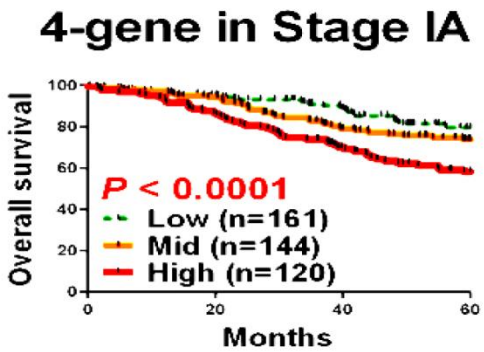
Bild (n=34)
Affymetrix U133+2
(GSE3141)
Duke, 2006

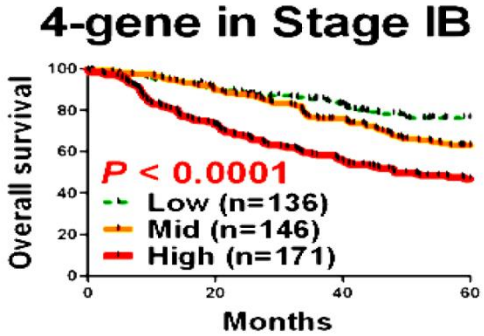
Okayama, H, Schetter, A ...Harris CC Cancer Epi Prev Biomarker 23:2884-94, 2014.

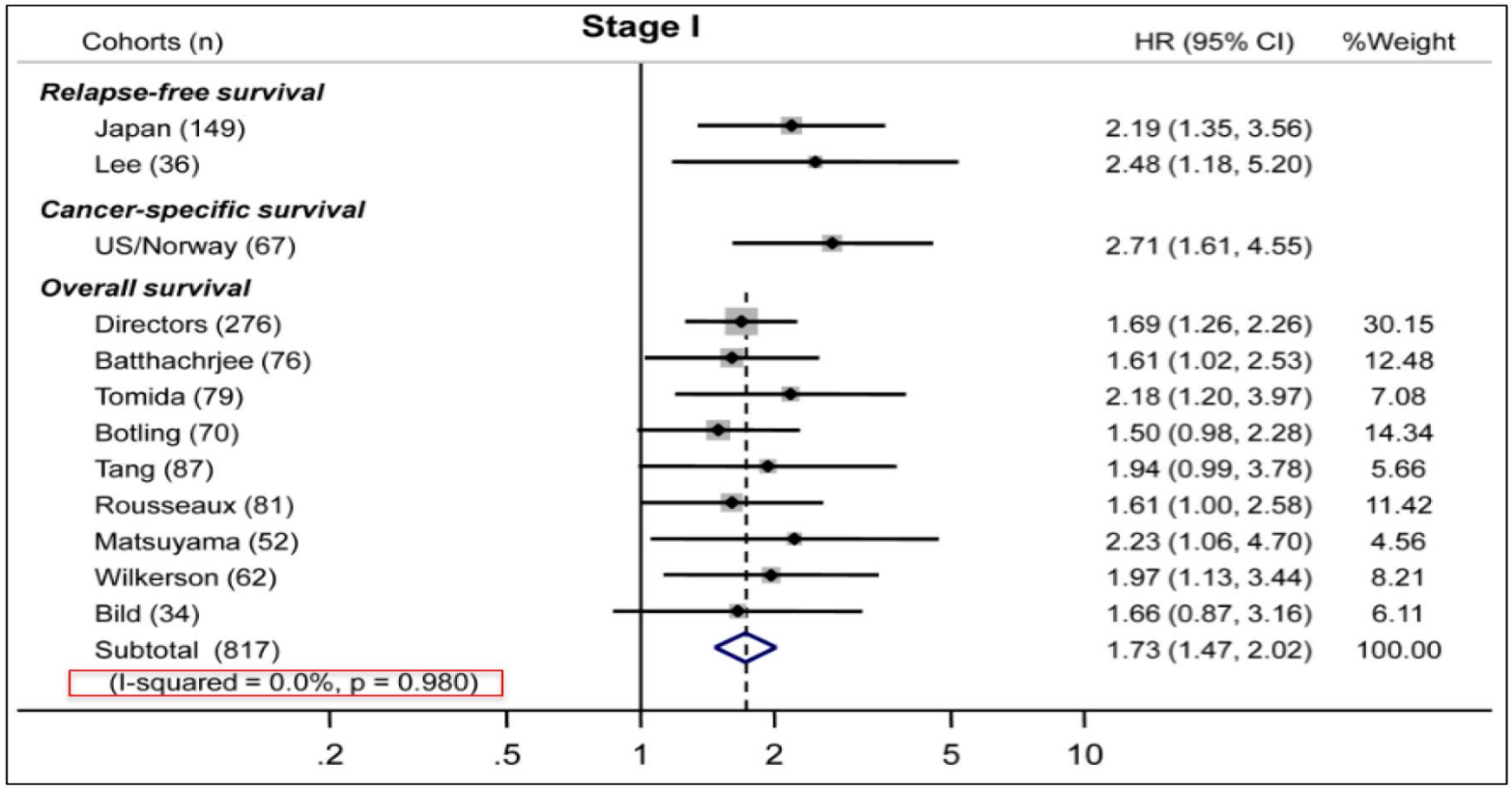
Meta-analysis

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







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

Mechanistic Cancer Biomarkers: Proof of Principle in Lung Adenocarcinoma

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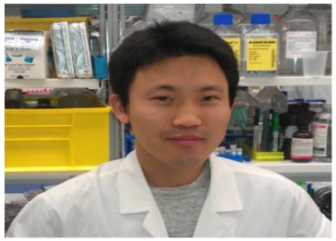
- **Hypothesis: The combination of protein-coding genes that are mechanistically related to lung cancer and the non-coding mir-21 is a better prognostic classifier than either alone**



Hiro Okayama

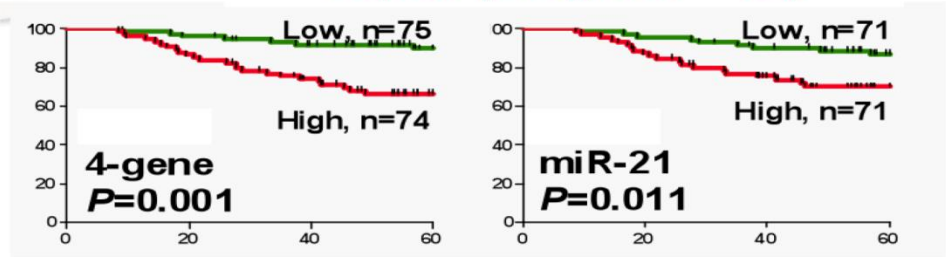
Ichiro Akagi

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

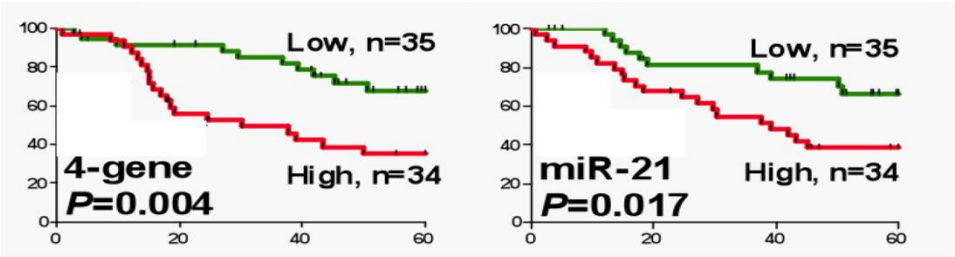
Prognosis of Stage I Lung Adenocarcinoma

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

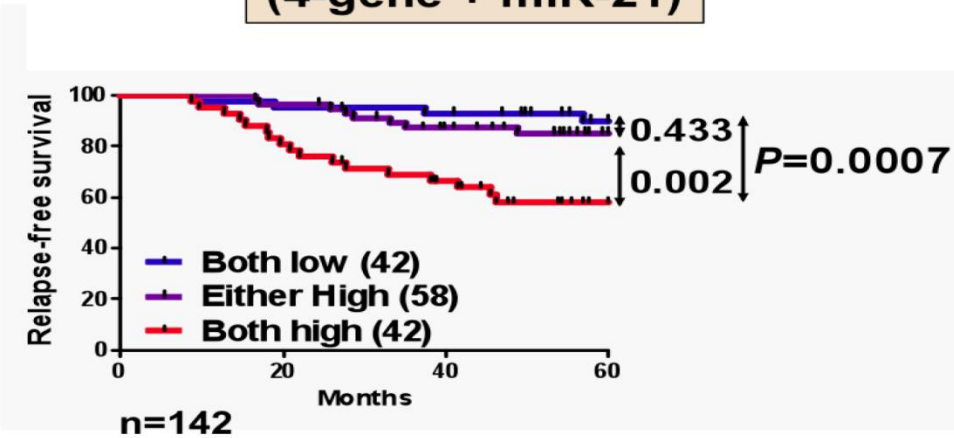
Japan (Stage IA > IB)



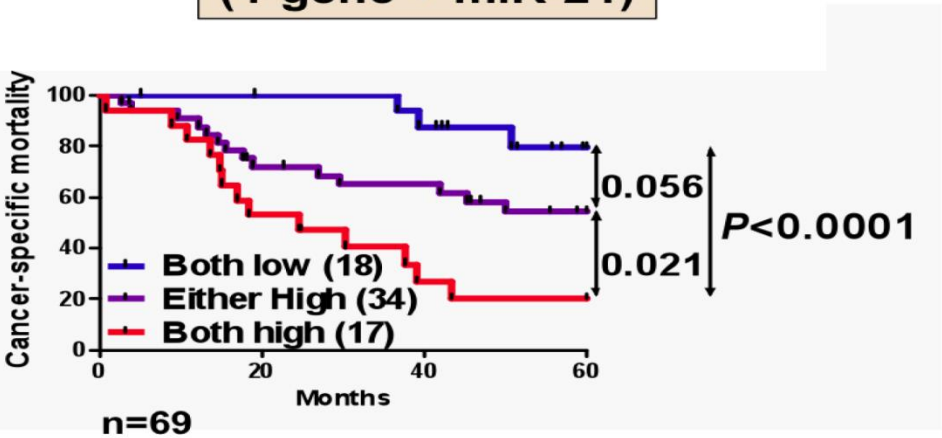
US/Norway (Stage IB > IA)



Combined (4-gene + miR-21)



Combined (4-gene + miR-21)



Early stage cancer

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

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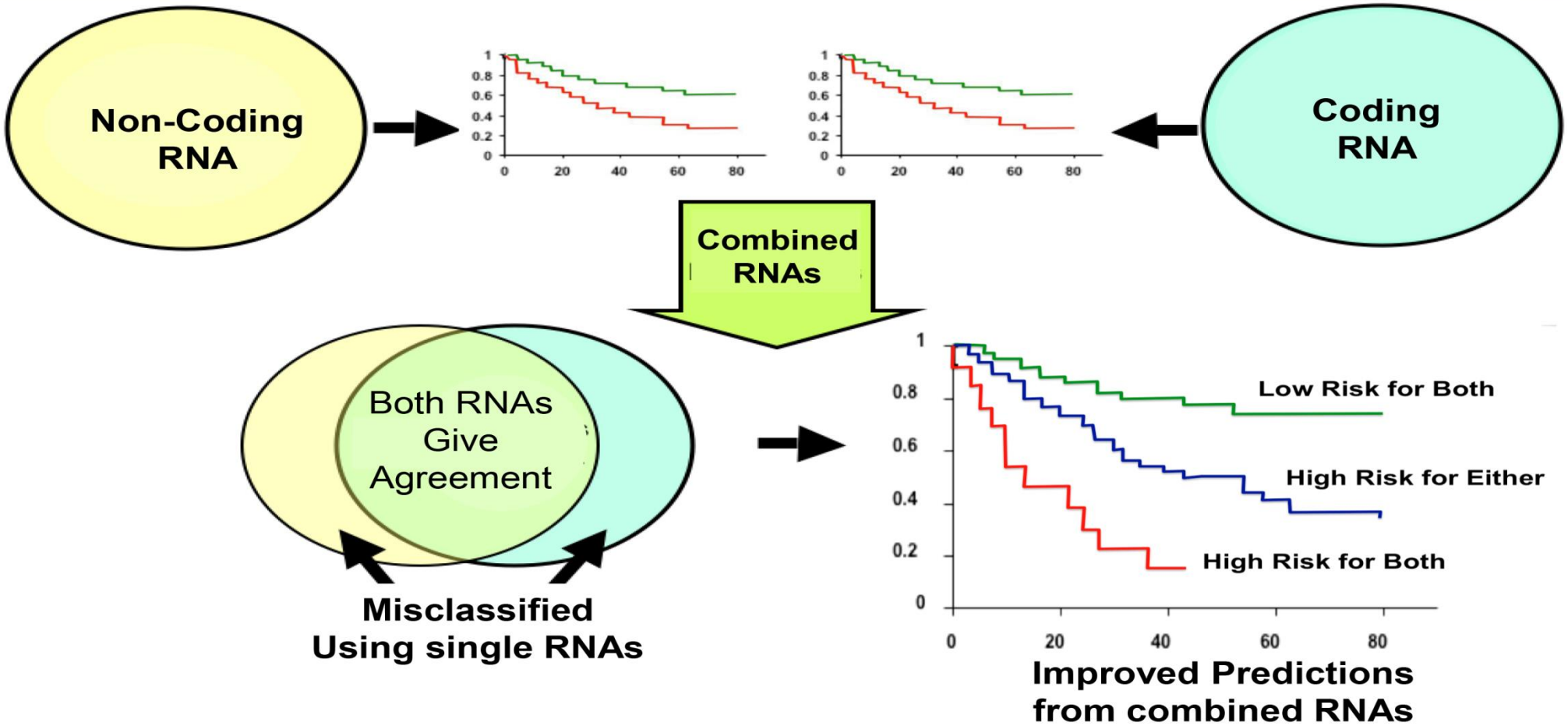
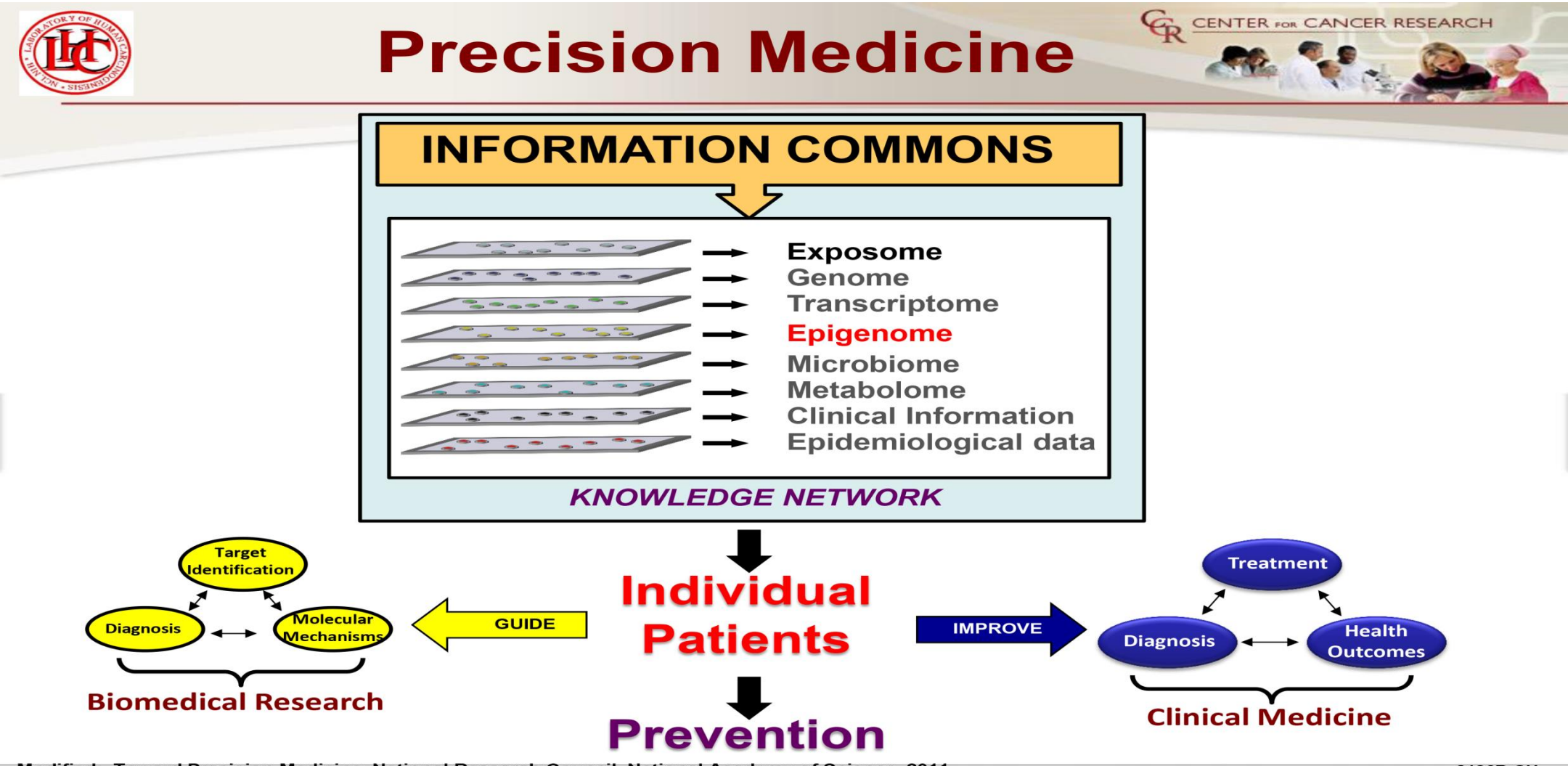


Epigenome



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

8136B-CH

EPIGENOME: DNA METHYLATION

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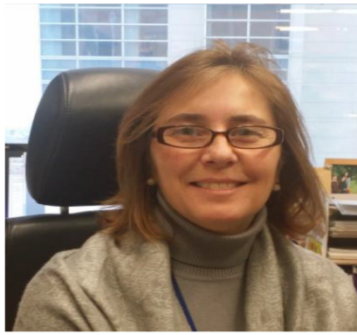
HYPOTHESIS:
An integrated biomarker classifier of stage I lung adenocarcinoma based on independent mRNA, microRNA and DNA methylation biomarkers, will further improve the prognostic classification



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

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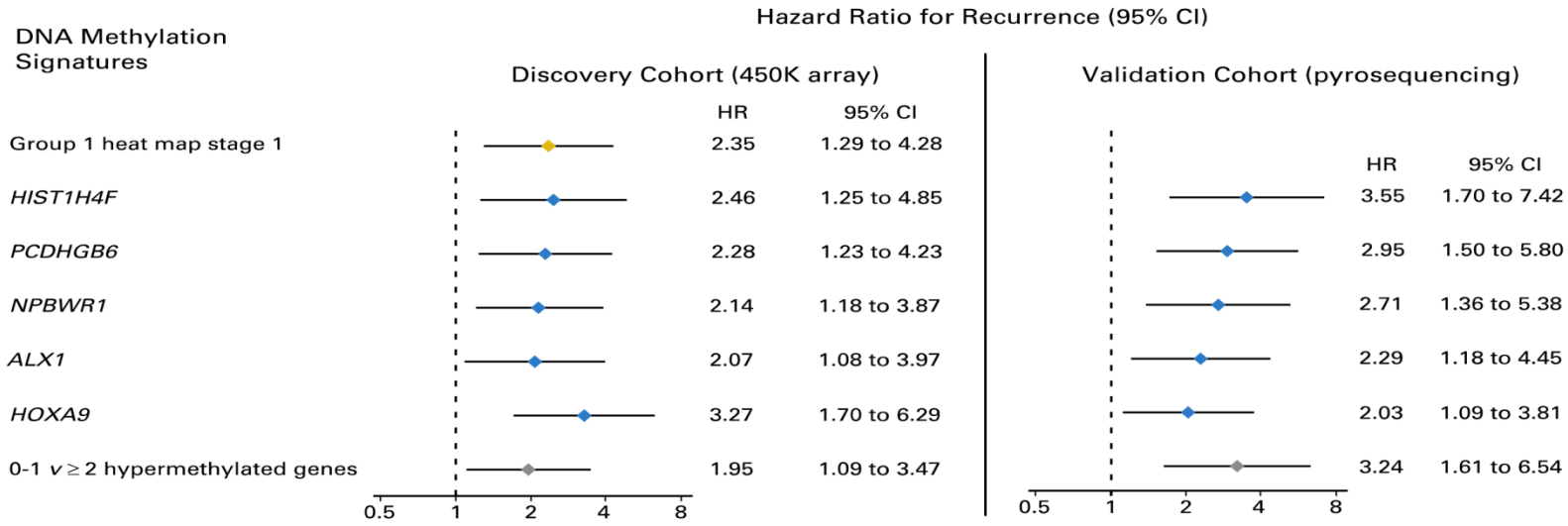
A Prognostic DNA Methylation Signature for Stage I Non–Small-Cell Lung Cancer

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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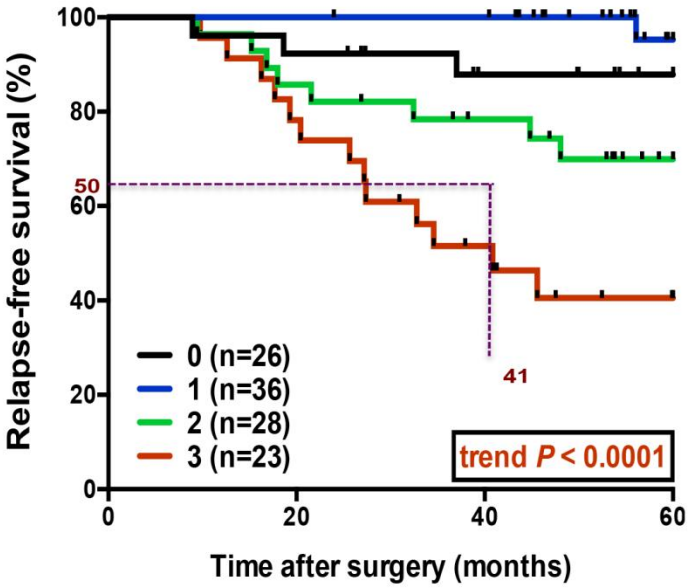
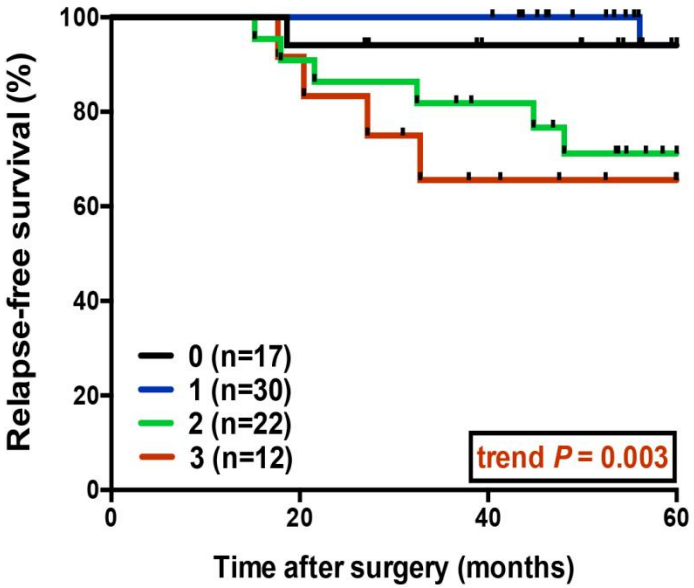
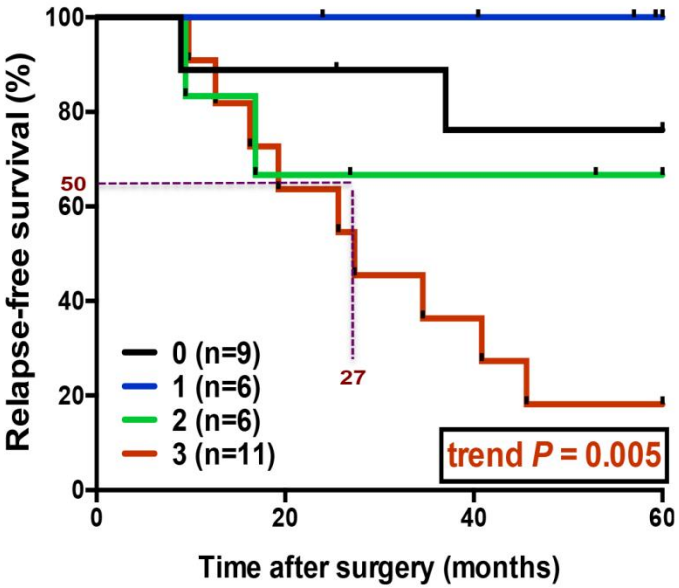
Stage 1



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

Precision Medicine

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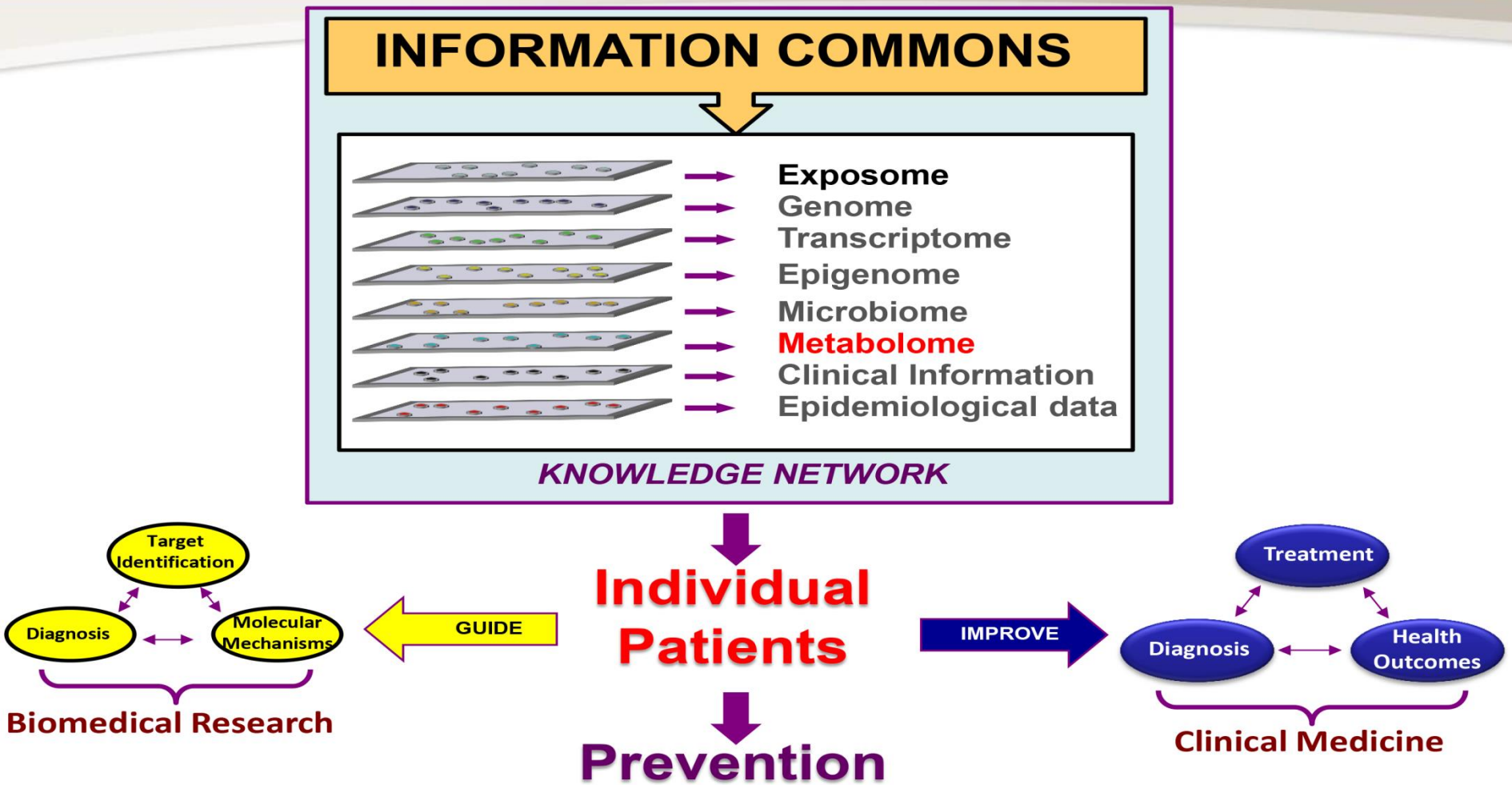

Modified: Toward Precision Medicine, National Research Council, National Academy of Science, 2011

Tumor Metabolism and Metabolome

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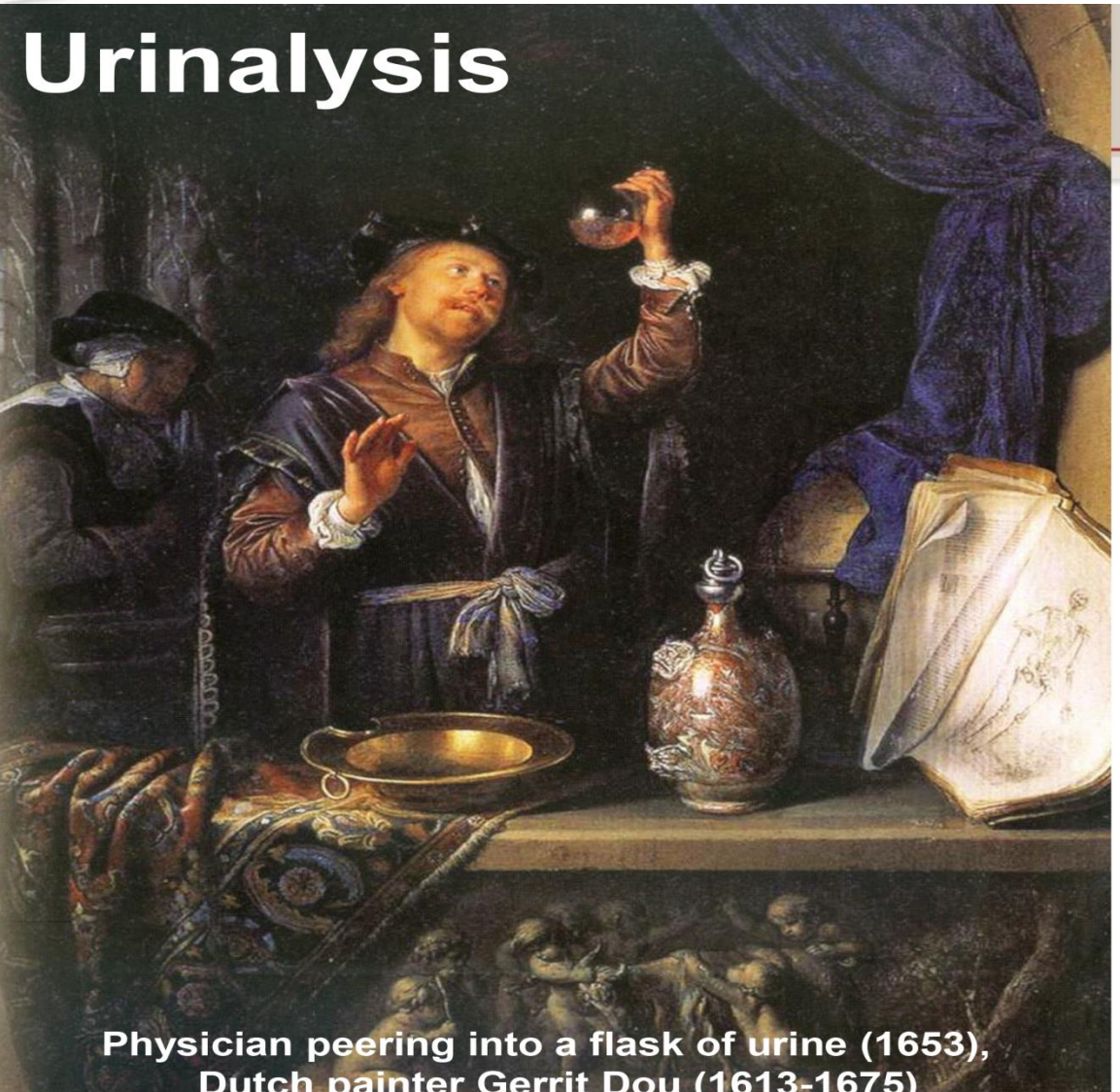
Hypothesis: Unbiased metabolomics will discover biomarkers associated with the risk, diagnosis, prognosis and therapeutic outcome of lung cancer.

Majda Haznadar

Ewy Mathe

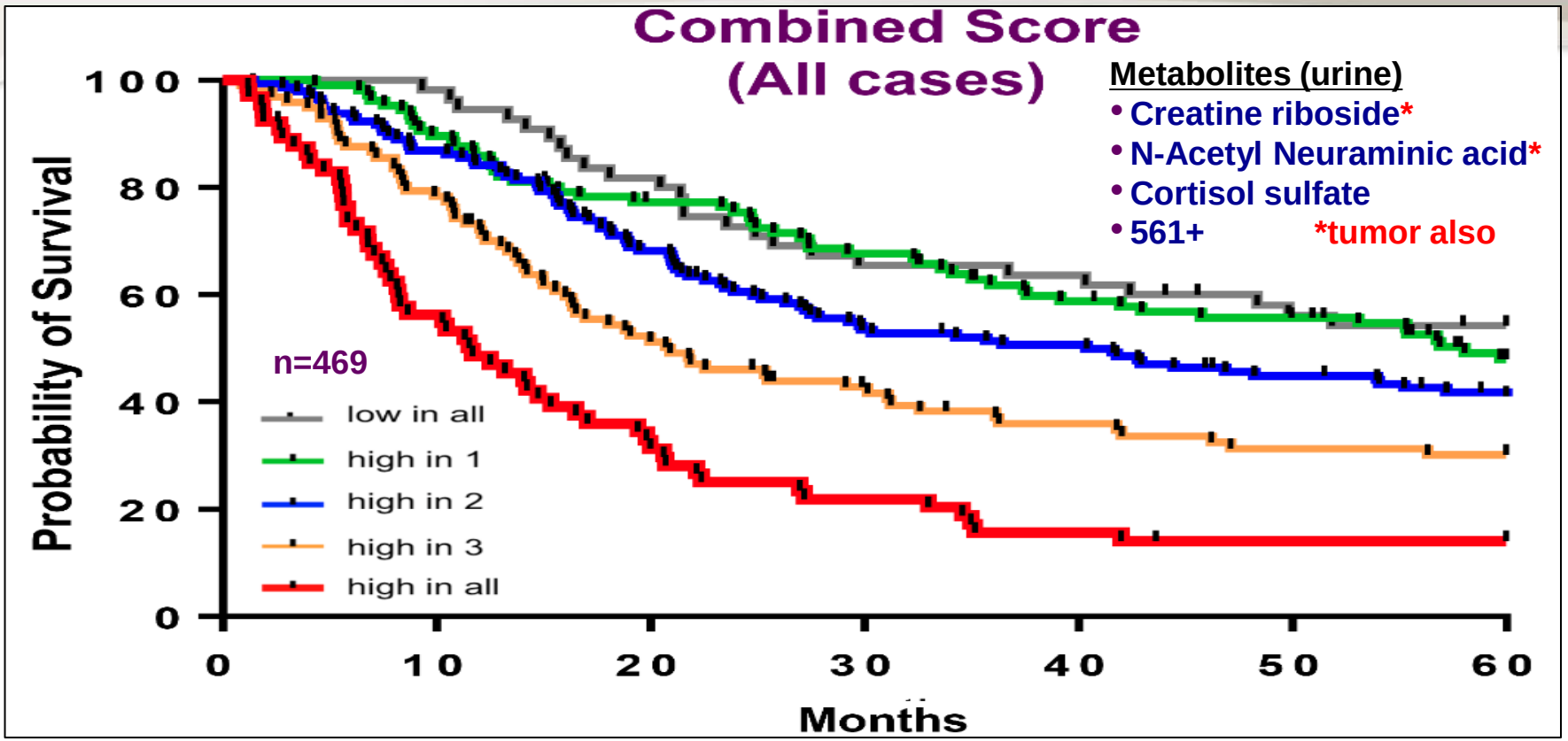
Urinalysis



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

- **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 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 is Positively Correlated in Cancer and Urine

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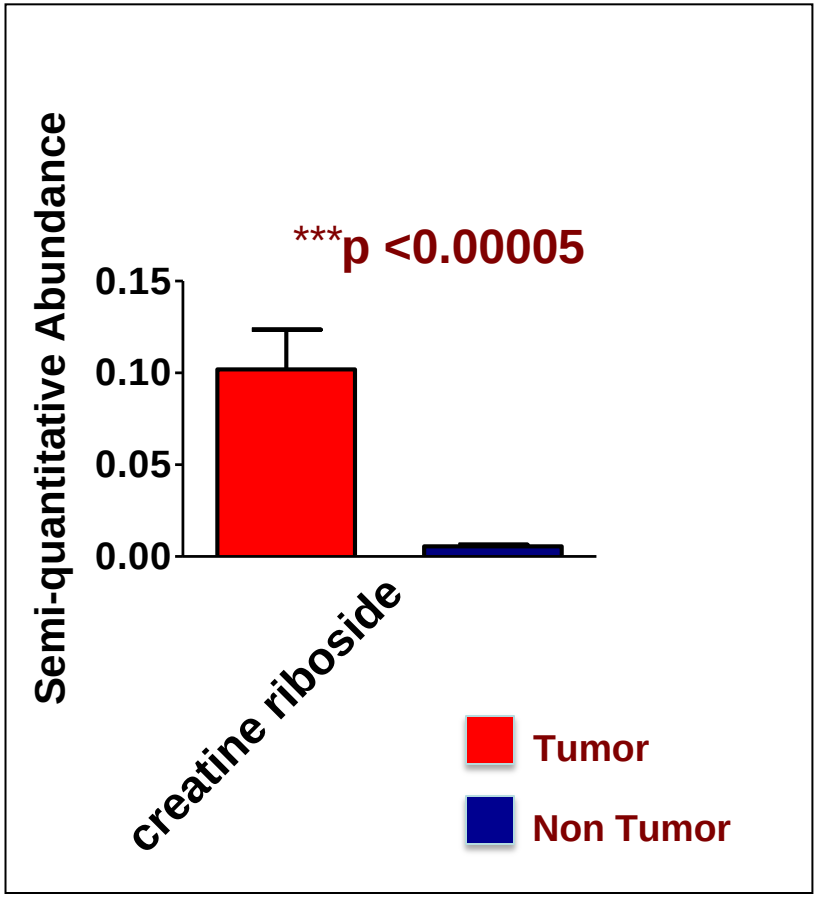
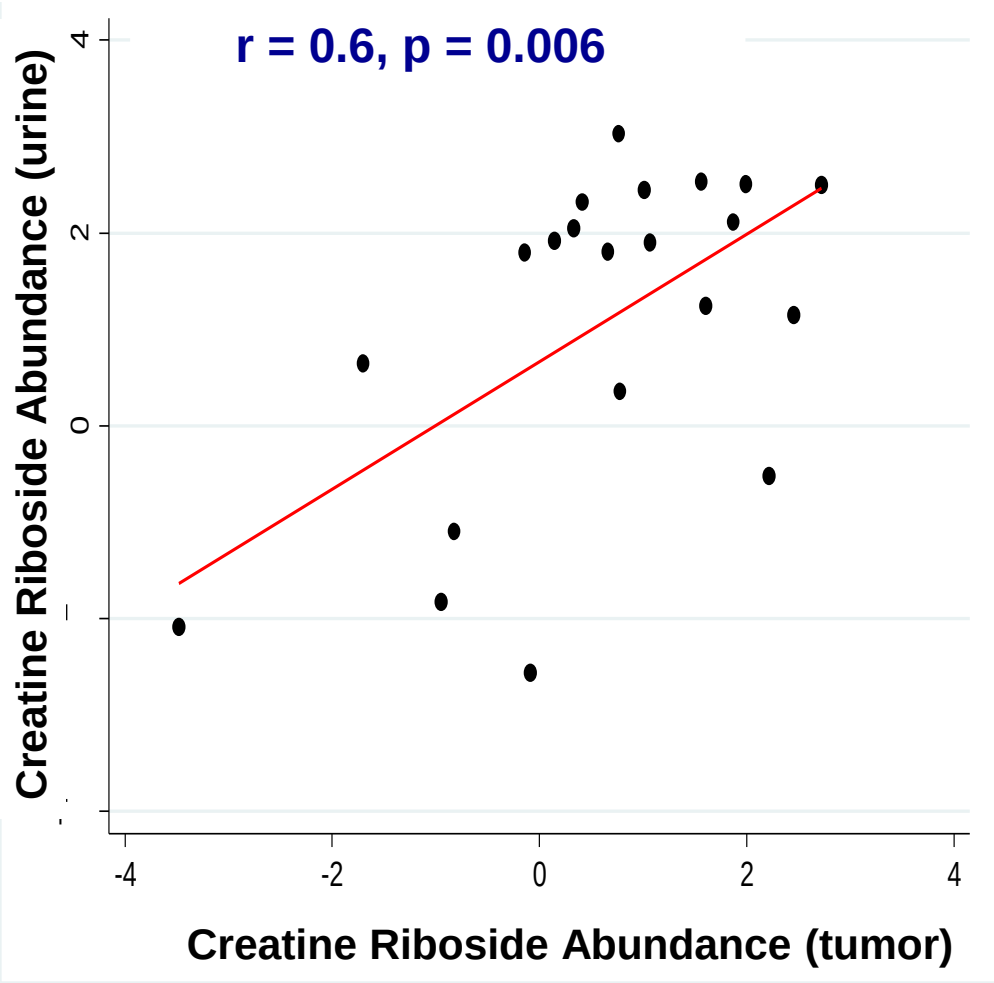
Lung Adenocarcinoma
(targeted UPLC-MS/MS)
N = 48 (Tumor), 48 (Non Tumor)





Precision Medicine: LUNG CANCER

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Report of the Surgeon General, 2014

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

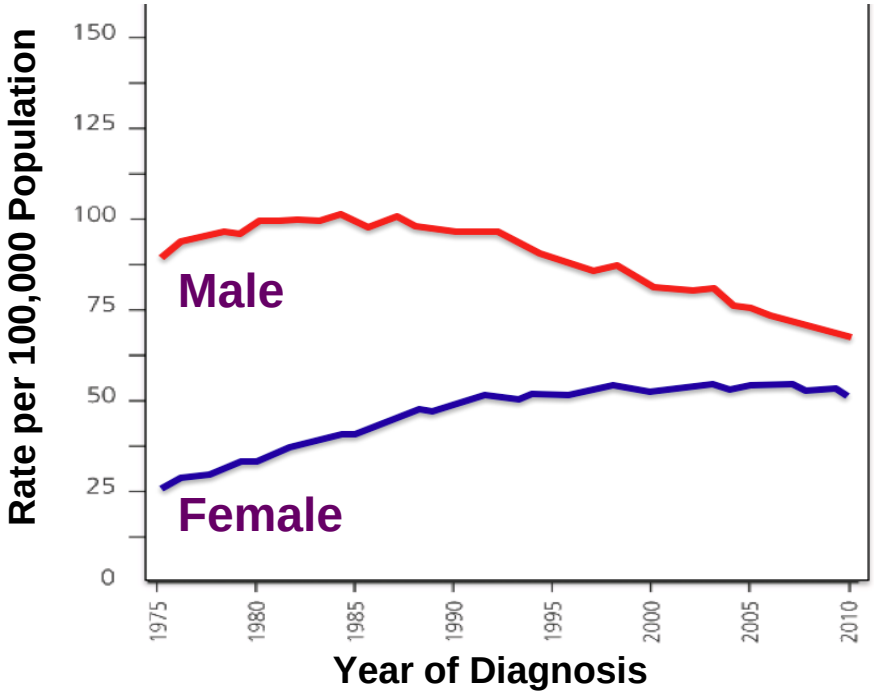
Cause of death	Total
Smoking-related cancers	6,587,000
Cardiovascular and metabolic diseases	7,787,000
Pulmonary diseases	3,804,000
Conditions related to pregnancy and birth	108,000
Residential fires	86,000
Lung cancers caused by exposure to secondhand smoke	263,000
Coronary heart disease caused by exposure 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 and Cigarette Consumption in 187 Countries, 1980-2012

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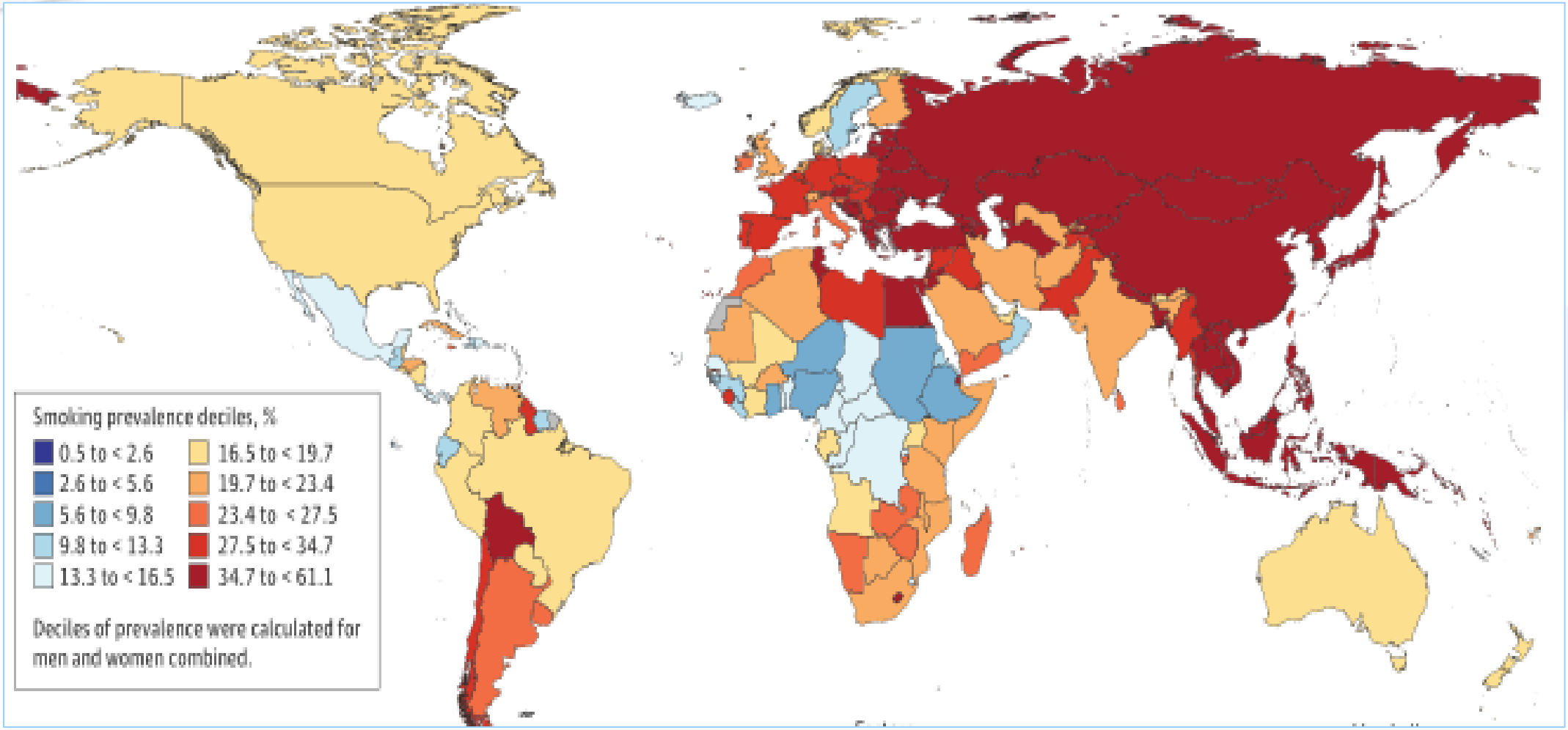
- **Estimate Age-Standardized Prevalence of Daily Smoking in 2012 among Men**



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

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

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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

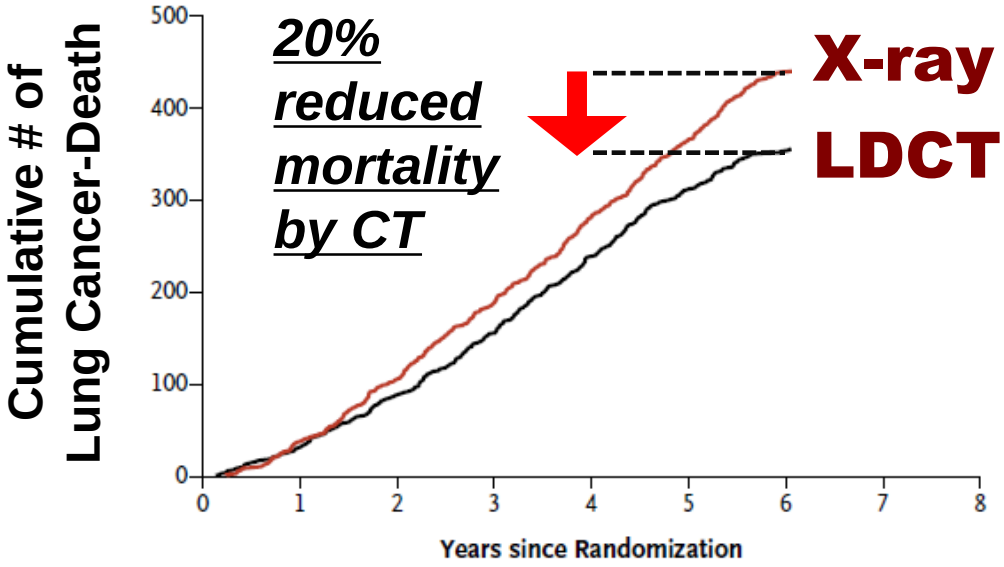
The National Lung Screening Trial Research Team*

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

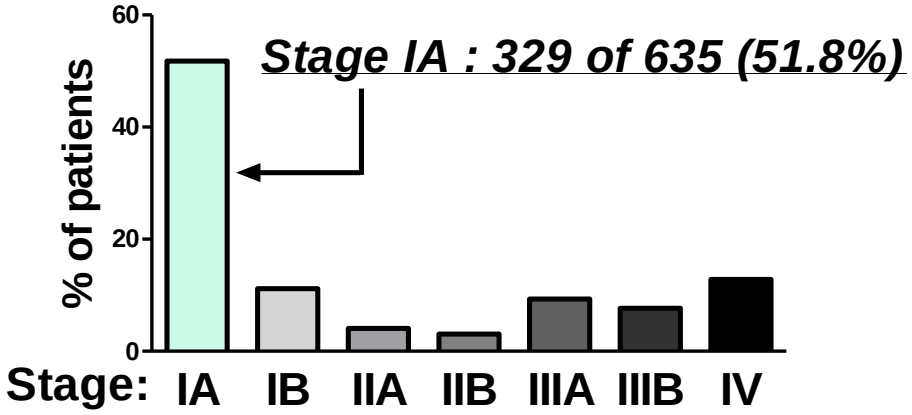
X-ray n=26732

LDCT n=26722

Low-Dose CT
- False Positive Rate = 96.4%



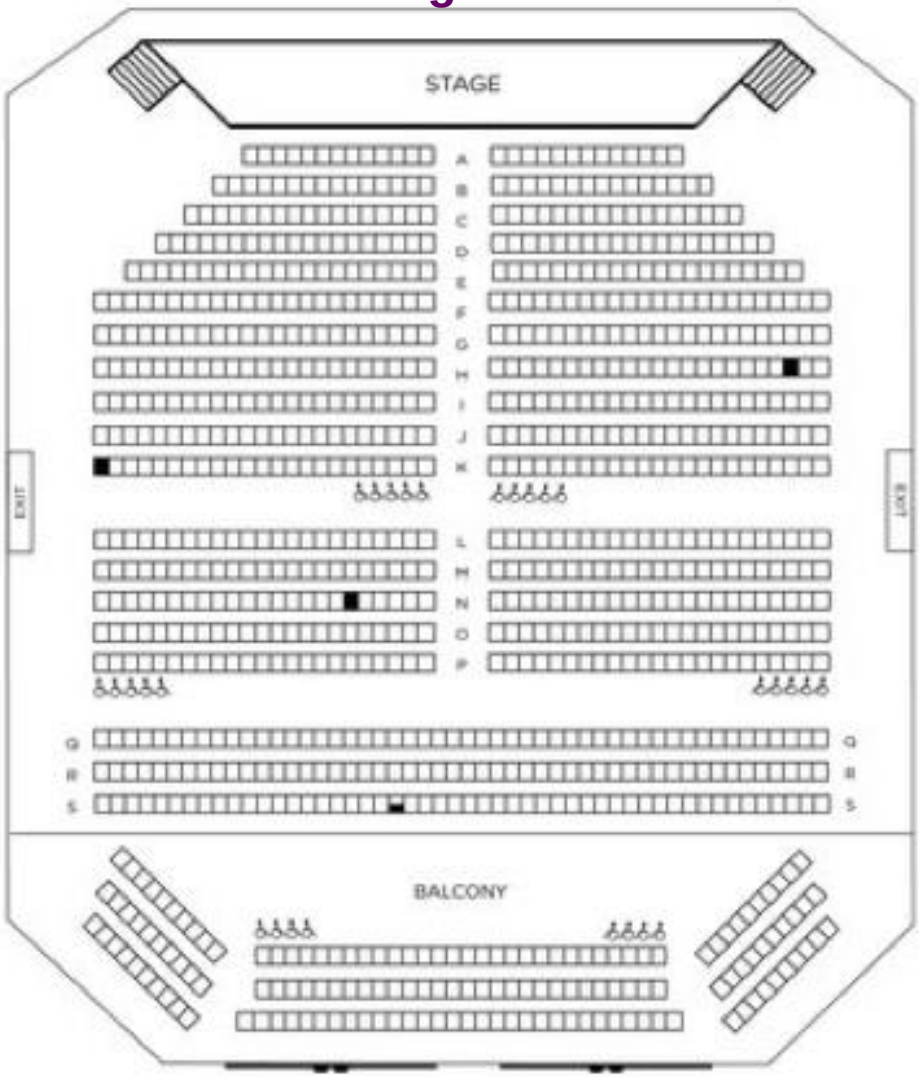
Stage of Lung Cancers Diagnosed After Positive CT Screening



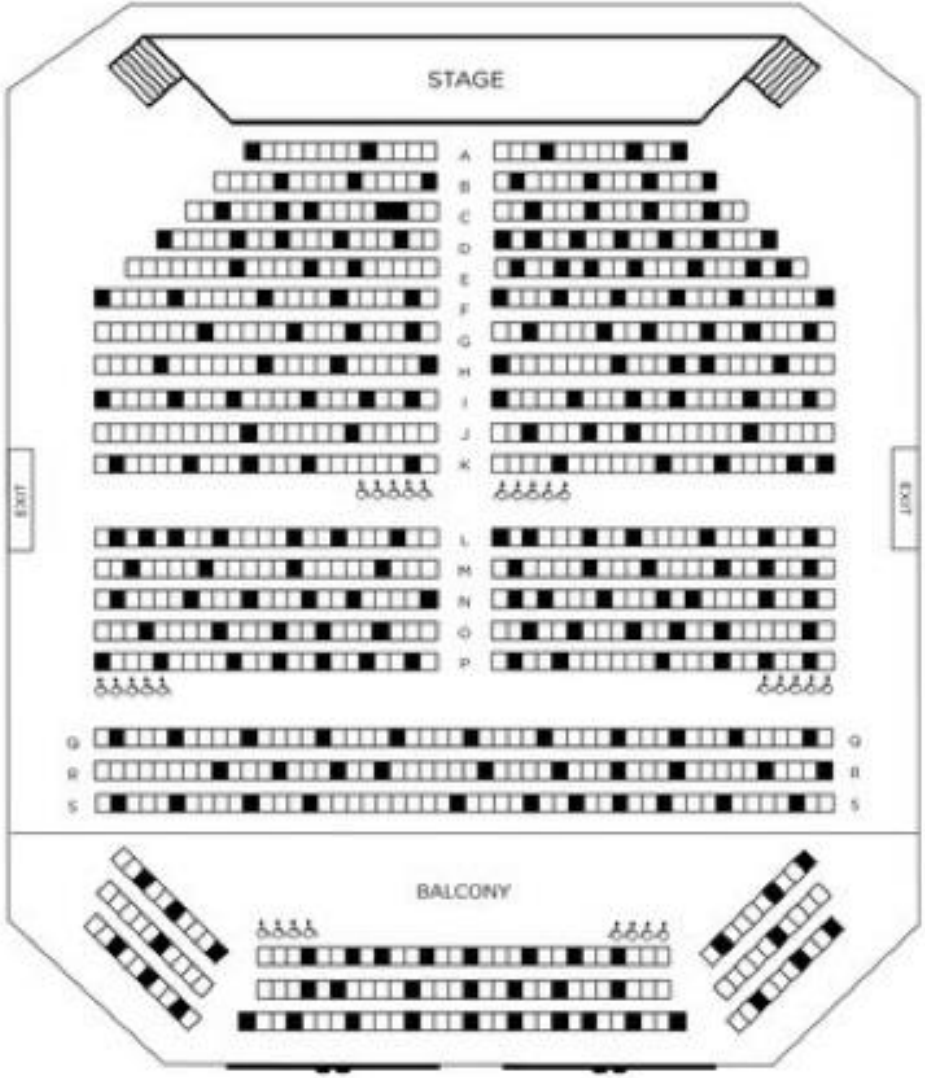
Analogy of the Number of Lung Cancer Deaths Averted with Annual Spiral CT Scans, Compared to the Total Number of Scans Done

CENTER FOR CANCER RESEARCH

Lung Cancer



False Positive



Andrew Lazris and Erik Rifkin: Interpreting Health Benefits And Risks

Low-Dose Computed Tomography (LDCT)

Individuals

NLST reports benefits for high risk individuals (2011)

USPSTF recommends LDCT (2013)

CMS announces Medicare coverage (2015)

Affordable Care Act mandates coverage (2015)

Lung Cancer Screening

- **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)**

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

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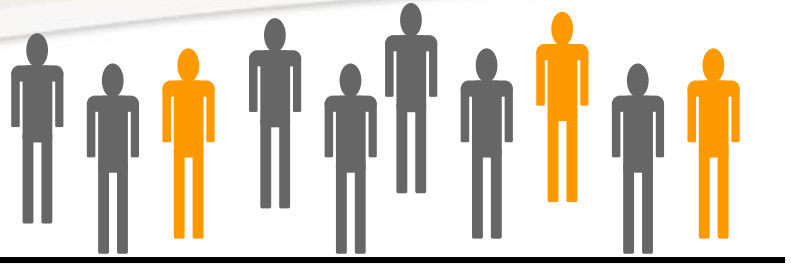
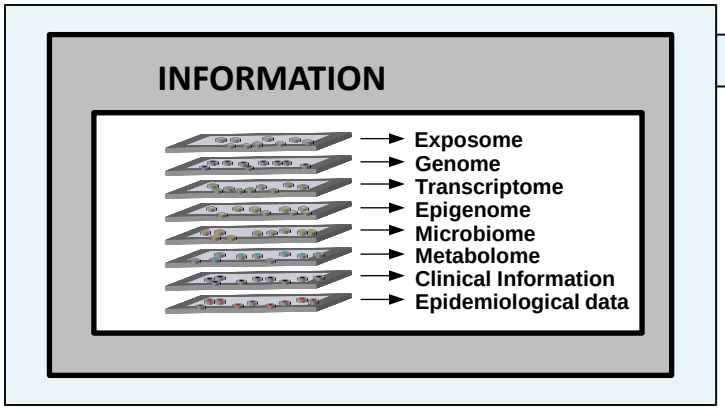
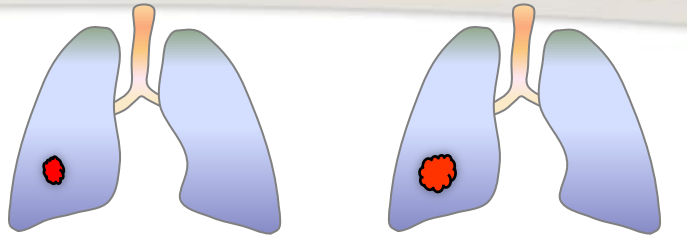


Stage I patients after curative surgery

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

COWORKERS AND COLLABORATORS

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