Precision Medicine

LUNG CANCER:
Precision Medicine Strategy

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NIH
Bethesda, Maryland
USA

Vargas A and Harris CC Nature Review Cancer 16: 525-37, 2016
Robles S and Harris CC Lung Cancer 107:50-58, 2017

Precision medicine

PRECISION MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

A New Initiative on Precision Medicine

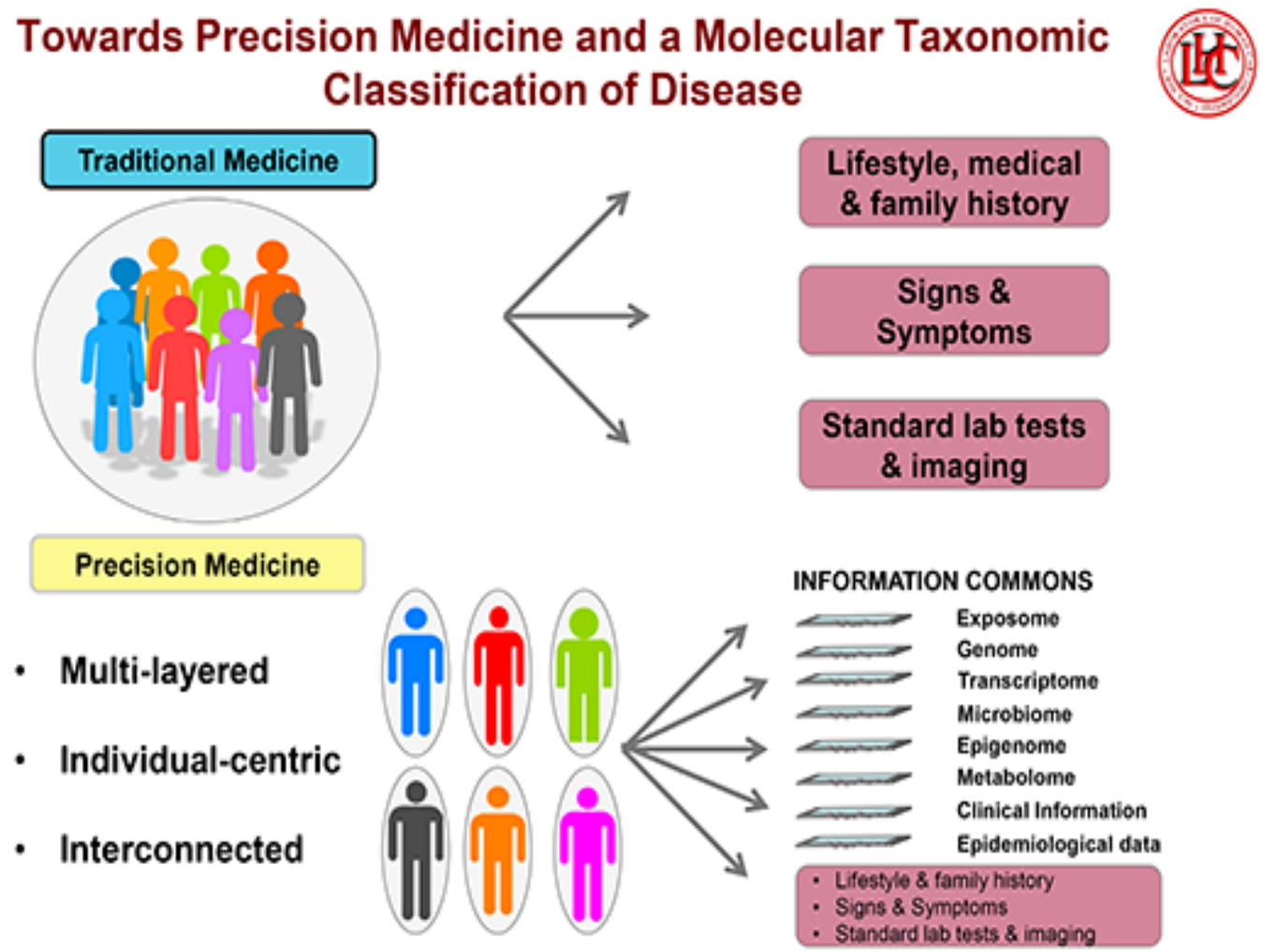
Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

"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."

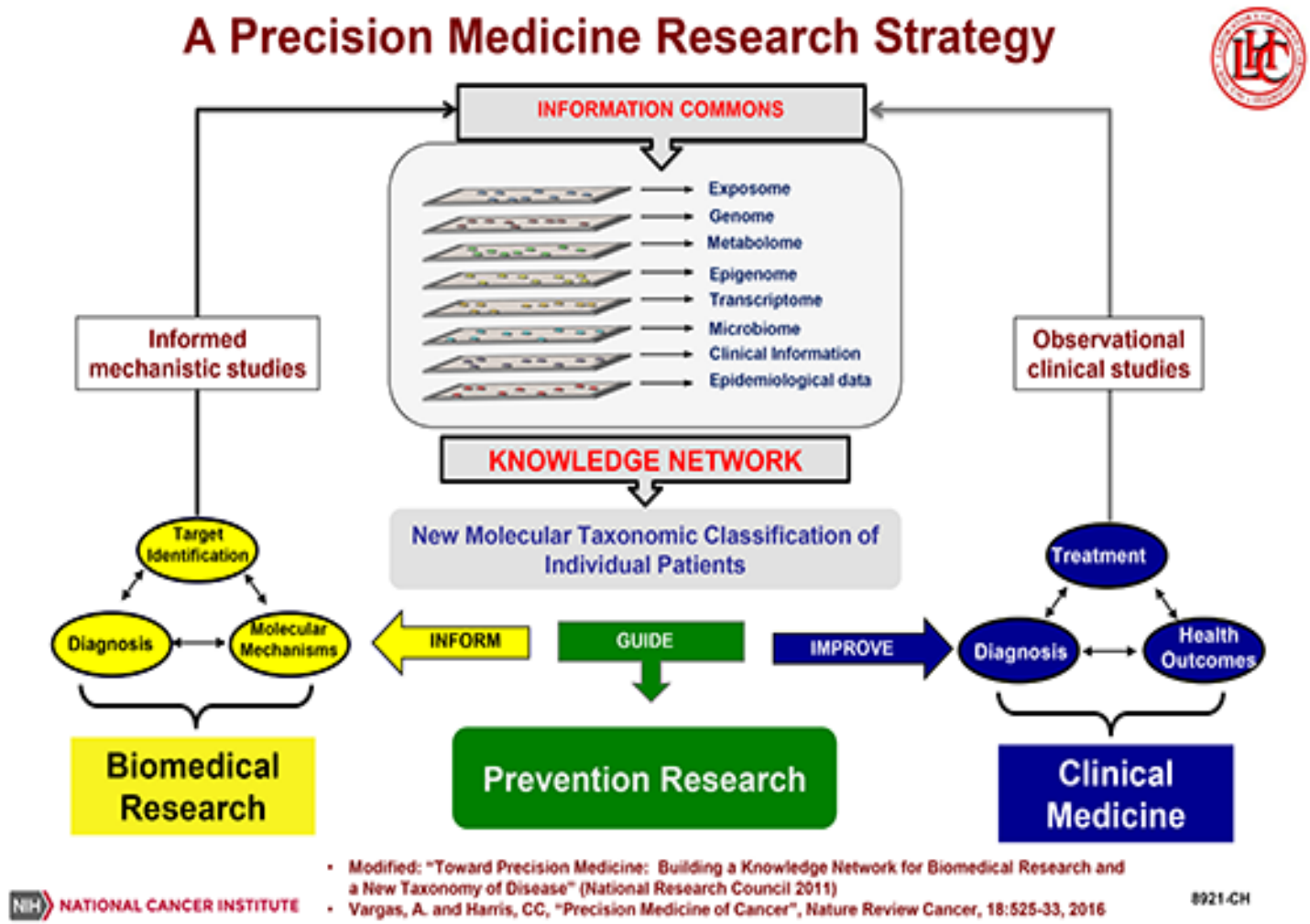
— President Barack Obama, State of the Union Address, January 20, 2015

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

Disease classification



Research strategy



Lung cancer

Precision Medicine: LUNG CANCER

Report of the Surgeon General, 2014

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

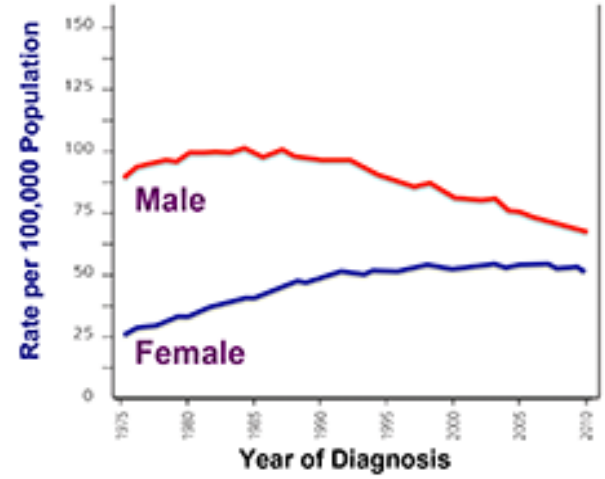
Cause of death	Total
Smoking-related cancers	6,587,000
Cardiovascular and metabolic diseases	7,787,000
Pulmonary diseases	3,804,000
Conditions related to pregnancy and birth	108,000
Residential fires	86,000
Lung cancers caused by exposure to secondhand smoke	263,000
Coronary heart disease caused by exposure 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and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.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

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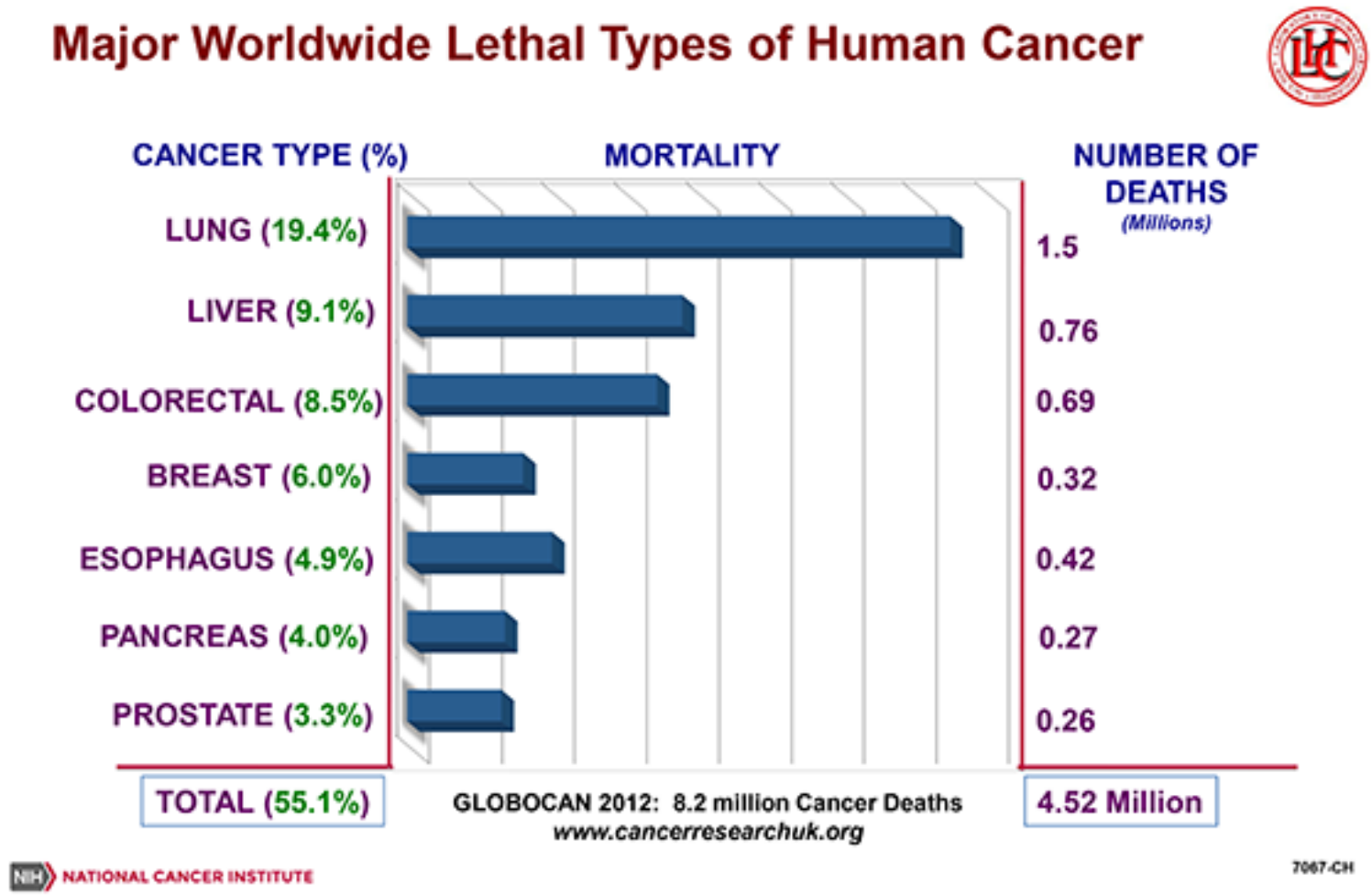
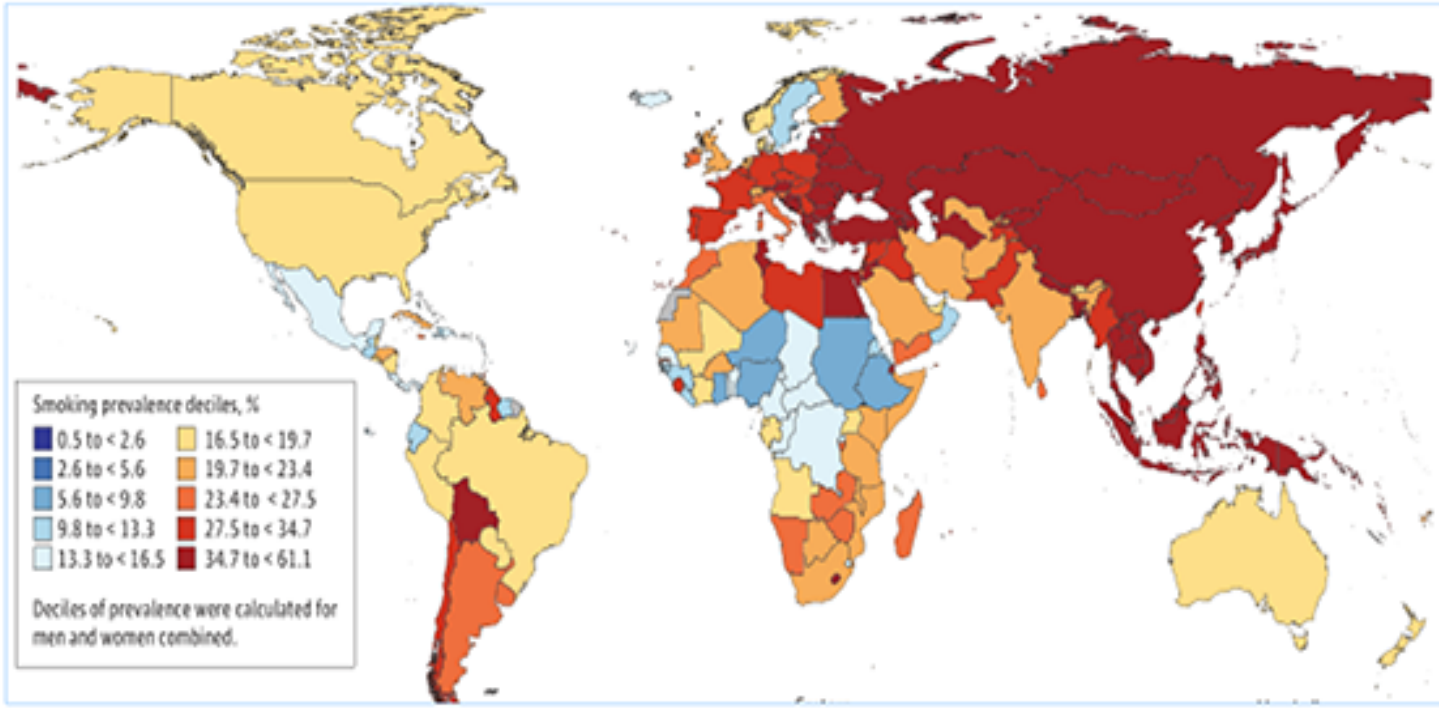
Worldwide cancers



Geographical map

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

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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

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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

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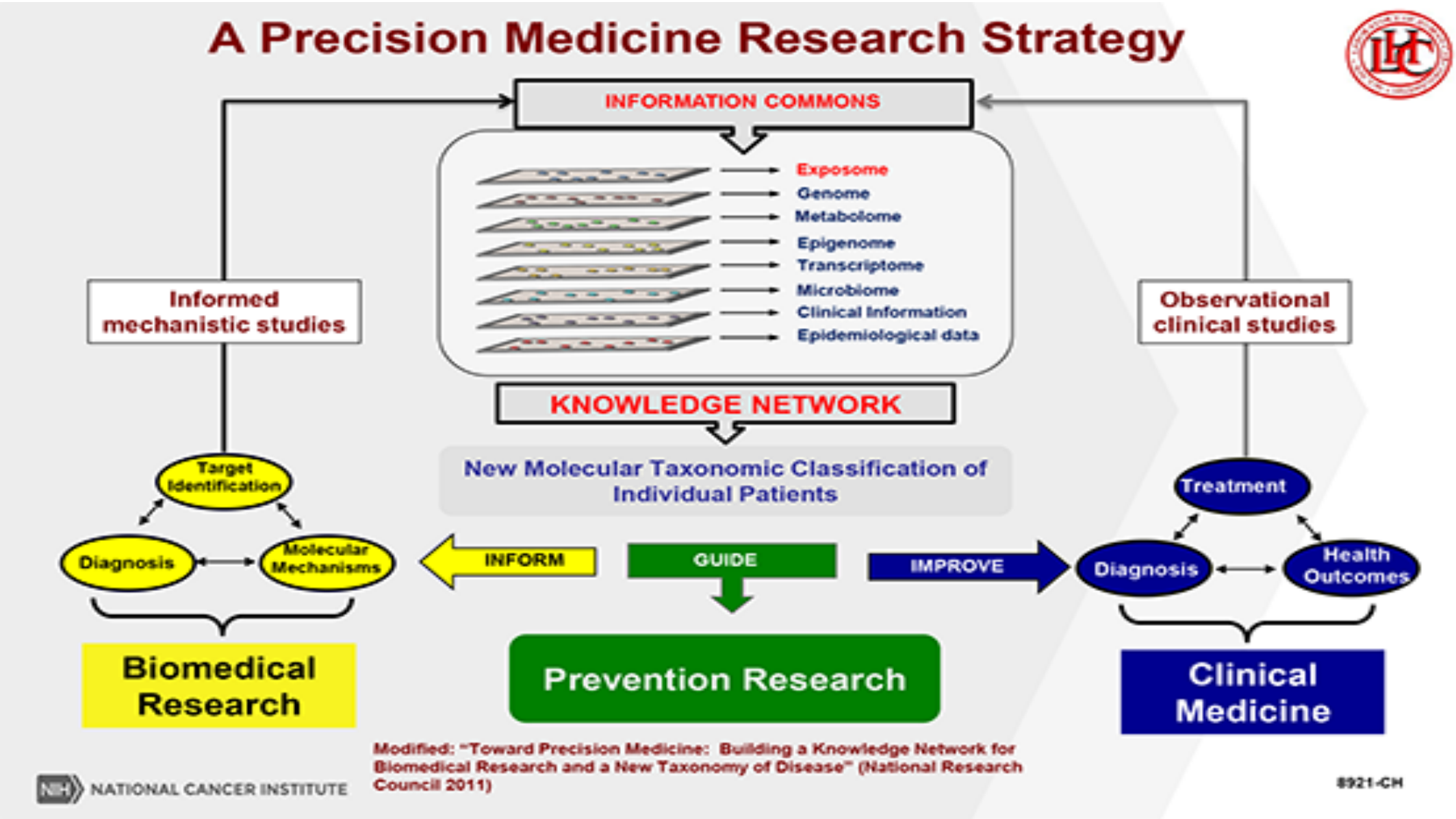
Exposome


A Precision Medicine Research Strategy
INFORMATION COMMONS
Exposome
Genome
Metabolome
Epigenome
Transcriptome
Microbiome
Clinical Information
Epidemiological data
Informed mechanistic studies
Observational clinical studies
KNOWLEDGE NETWORK
New Molecular Taxonomic Classification of Individual Patients
Target Identification
Diagnosis
Molecular Mechanisms
INFORM
GUIDE
IMPROVE
Treatment
Diagnosis
Health Outcomes
Biomedical Research
Prevention Research
Clinical Medicine
Modified: "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease" (National Research Council 2011)
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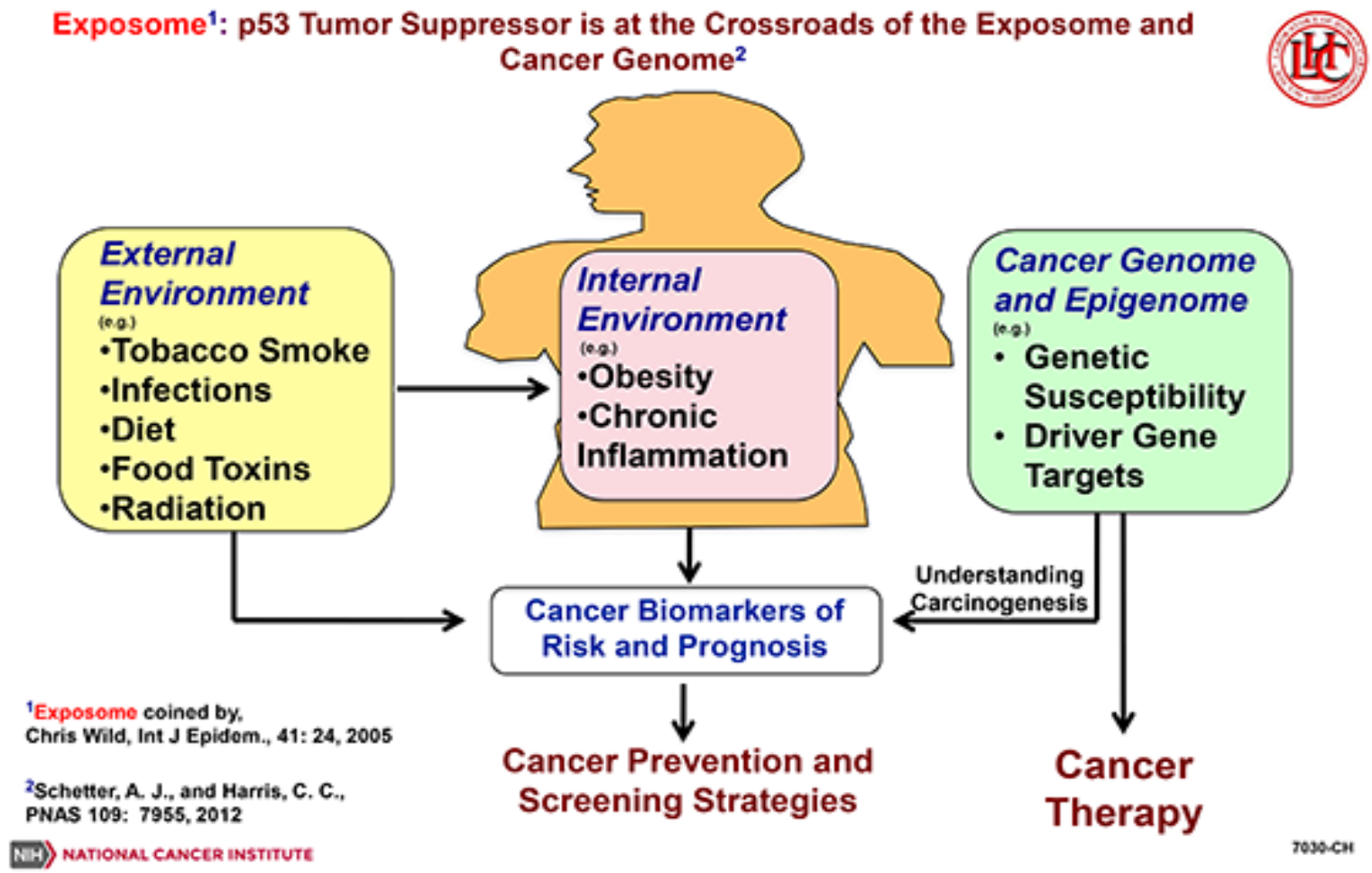
p53


Exposome[1]: p53 Tumor Suppressor is at the Crossroads of the Exposome and Cancer Genome[2]
External Environment
(e.g.)
•Tobacco Smoke
•Infections
•Diet
•Food Toxins
•Radiation
Internal Environment
(e.g.)
•Obesity
•Chronic Inflammation
Cancer Genome and Epigenome
(e.g.)
• Genetic Susceptibility
• Driver Gene Targets
Understanding Carcinogenesis
Cancer Biomarkers of Risk and Prognosis
Cancer Prevention and Screening Strategies
Cancer Therapy
[1]Exposome coined by, Chris Wild, Int J Epidem., 41: 24, 2005
[2]Schetter, A. J., and Harris, C. C., PNAS 109: 7955, 2012
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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
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 & Liver
Smoking	Multiple sites

World Cancer Report, IARC, WHO, 2014

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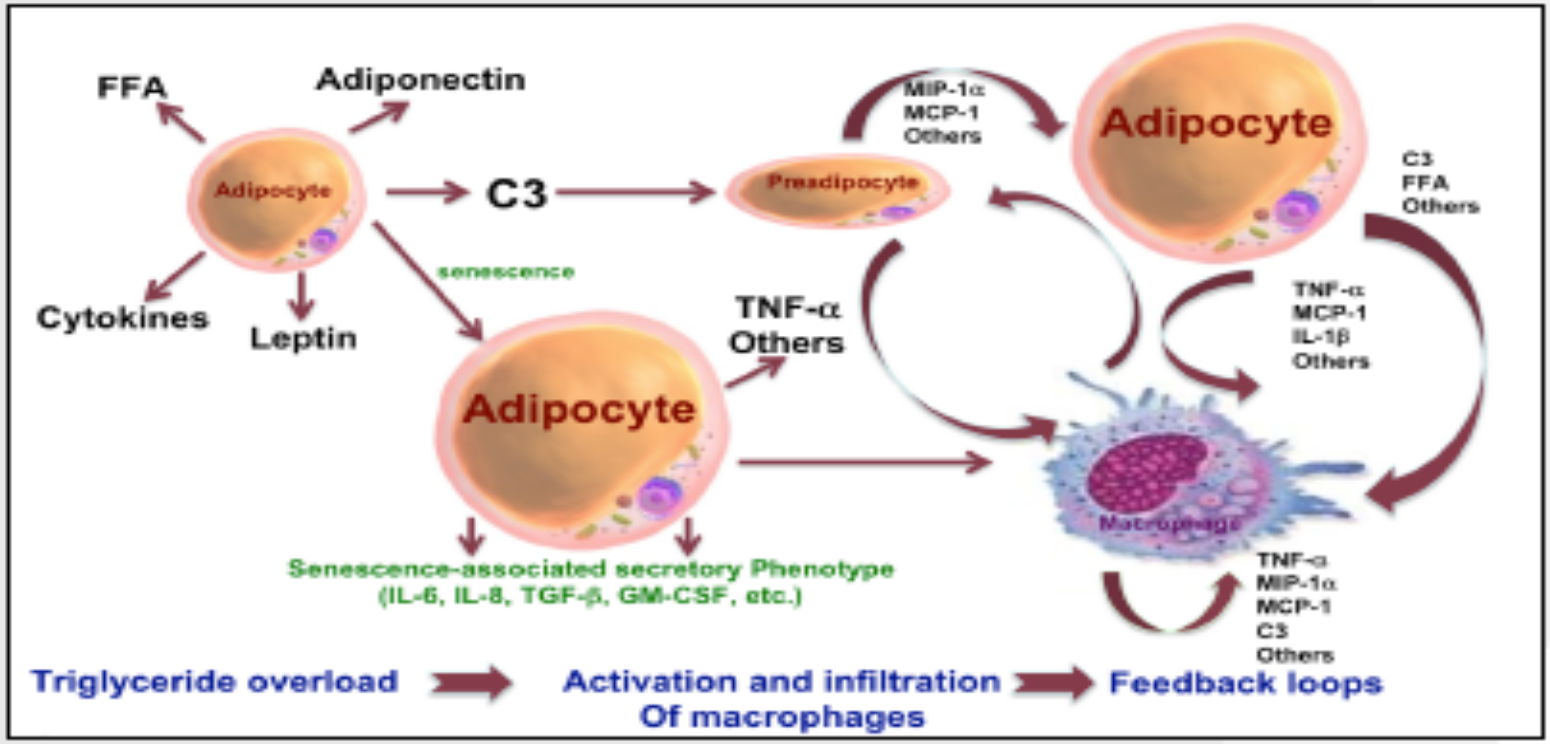
Obesity is a chronic inflammatory disease

Obesity is a Chronic Inflammatory Disease

- Weisberg et al. Obesity is associated with macrophage accumulation in adipose tissue. J. Clin. Invest, 112: 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.



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)

JNCI 103: 1112, 2011

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

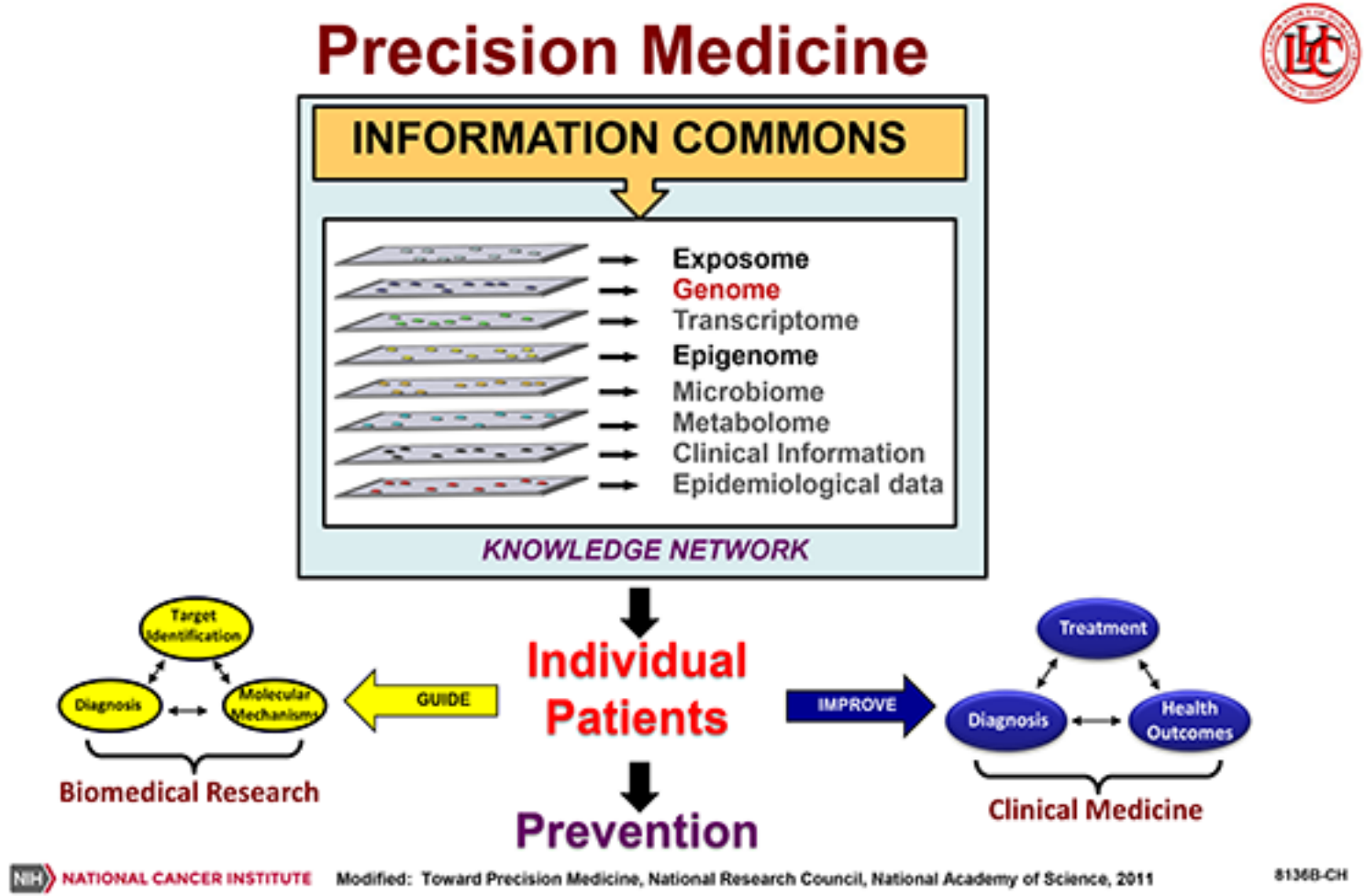
JNCI 103: 1112, 2011
J. Thoracic Oncol, 1494, 2014

↑ 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, 1494, 2014
CEBP: 488, 2016

Health Disparity:
EA, European-American
AA, African-American
Collaboration: Ann Schwartz

Genome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INFORMATION COMMONS
Exposome
Genome
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KNOWLEDGE NETWORK
Target Identification
Diagnosis
Molecular Mechanisms
Biomedical Research
GUIDE
Individual Patients
Prevention
IMPROVE
Treatment
Diagnosis
Health Outcomes
Clinical Medicine
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Modified: Toward Precision Medicine, National Research Council, National Academy of Science, 2011
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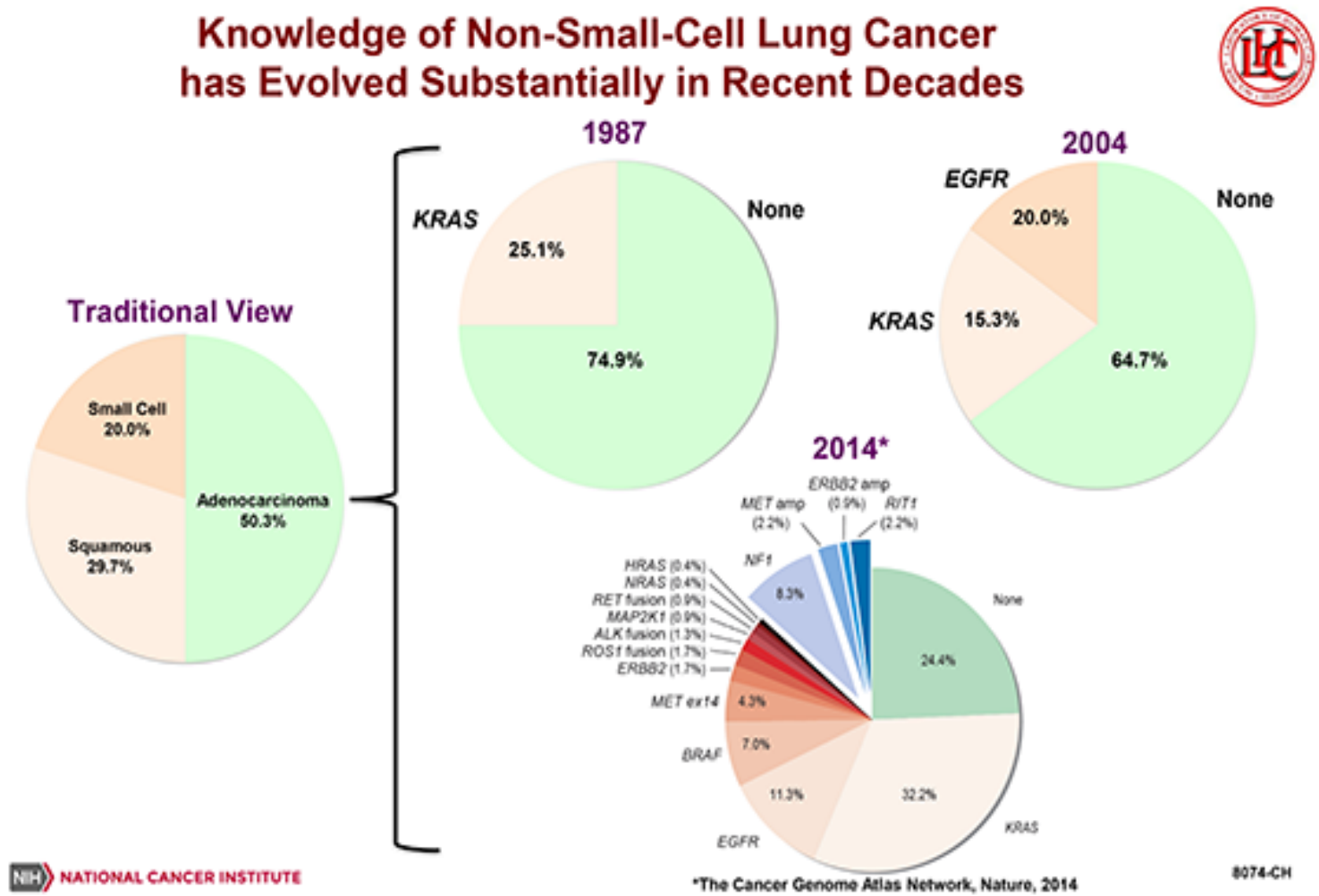
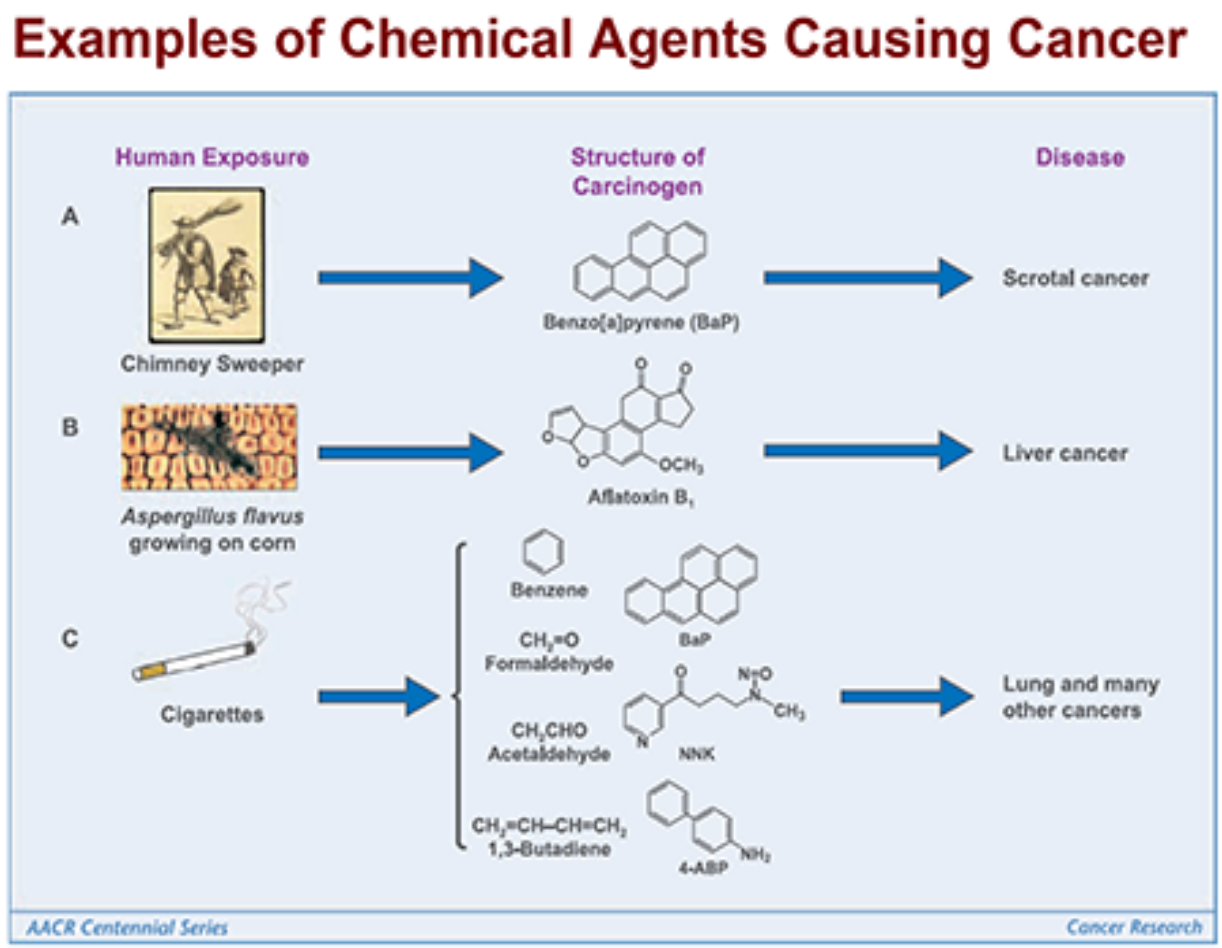
NSCLC evolution



Chemical agents



Loeb, L. and Harris, C.C., Cancer Res, 68: 6863-6872, 2008

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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	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

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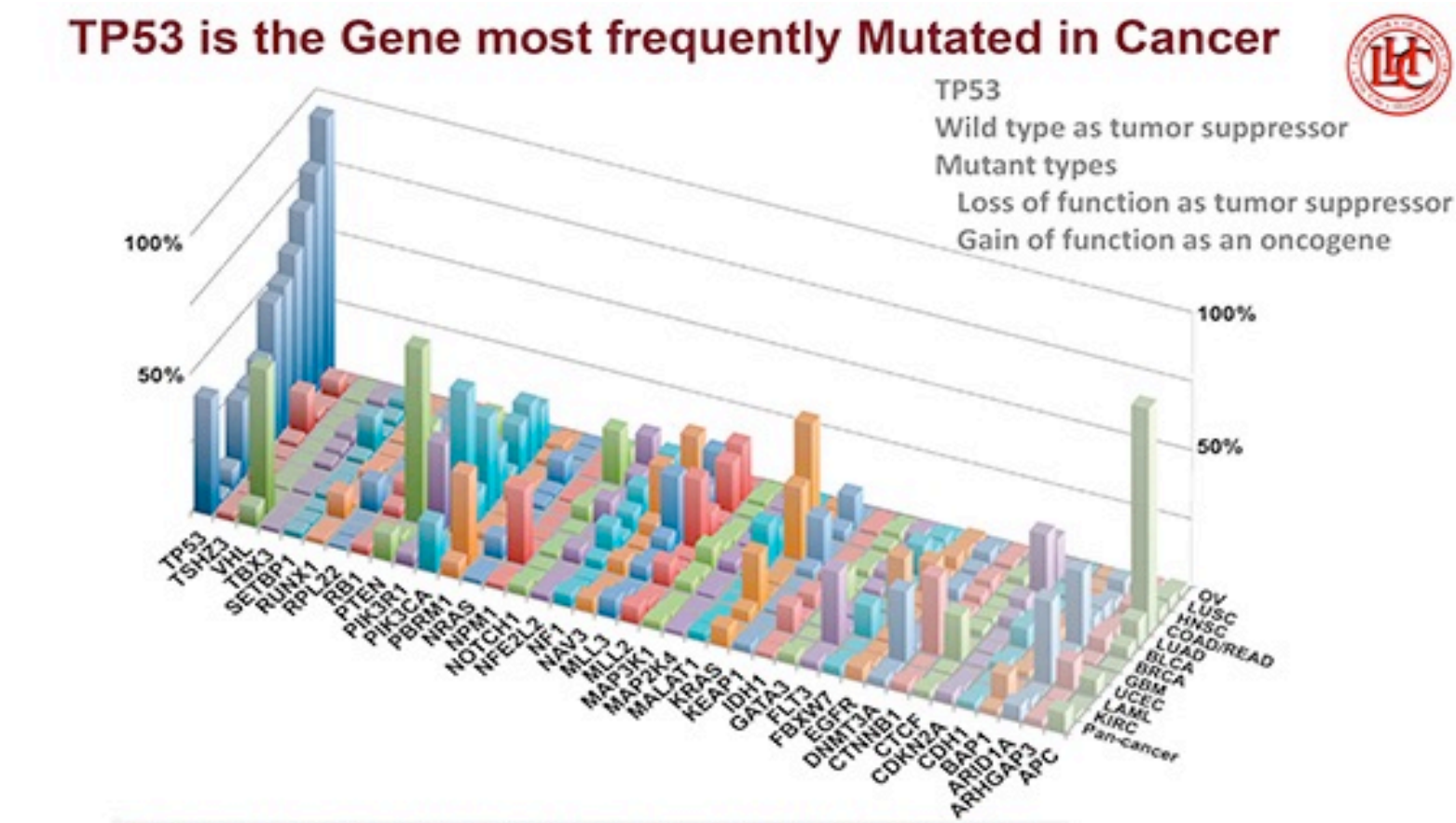
TP53 mutations



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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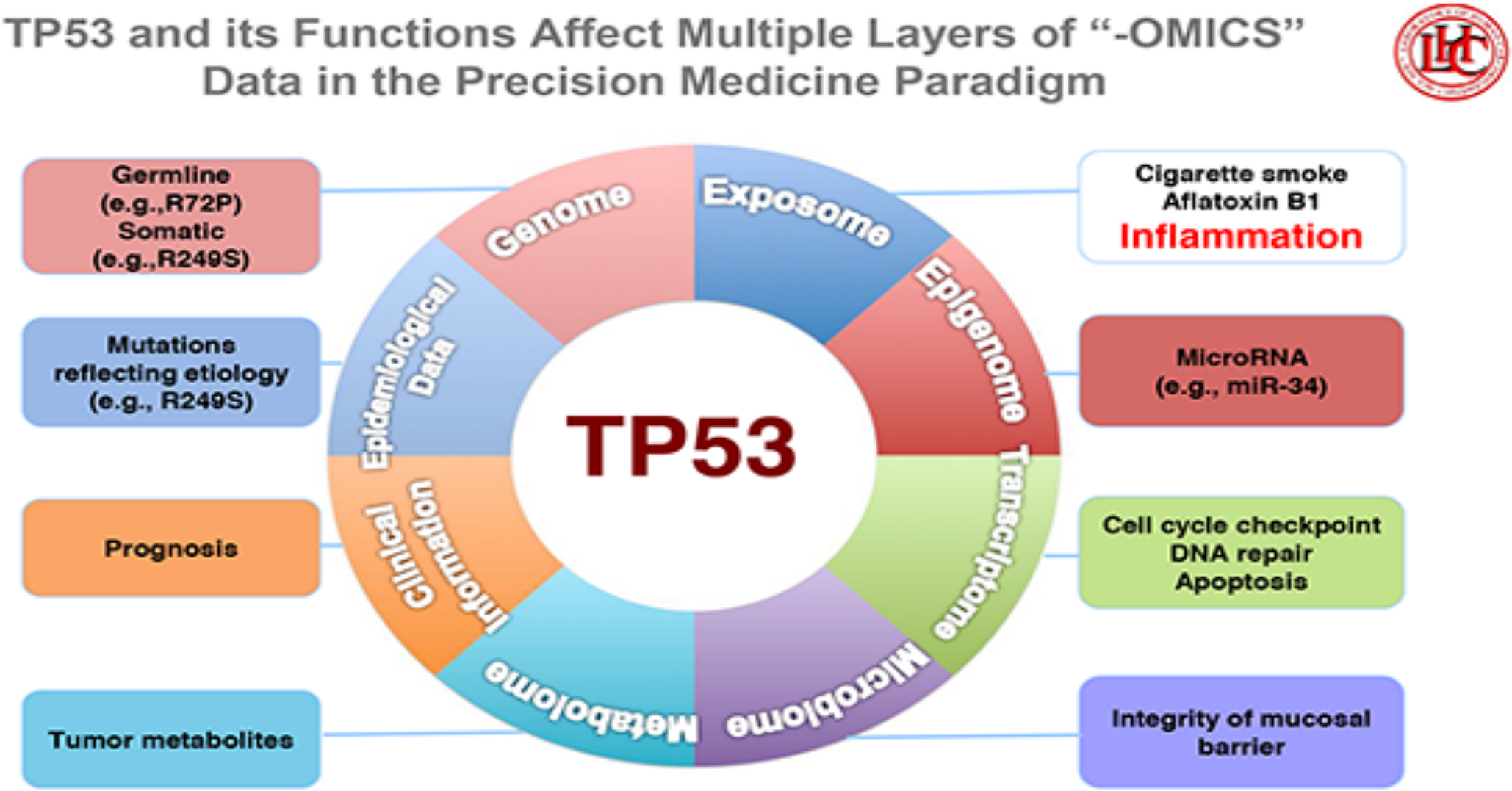
TP53 functions



Robles, A.I., .. Harris, C.C., Cold Spring Harb Perspect Med: 10.1101, 2016

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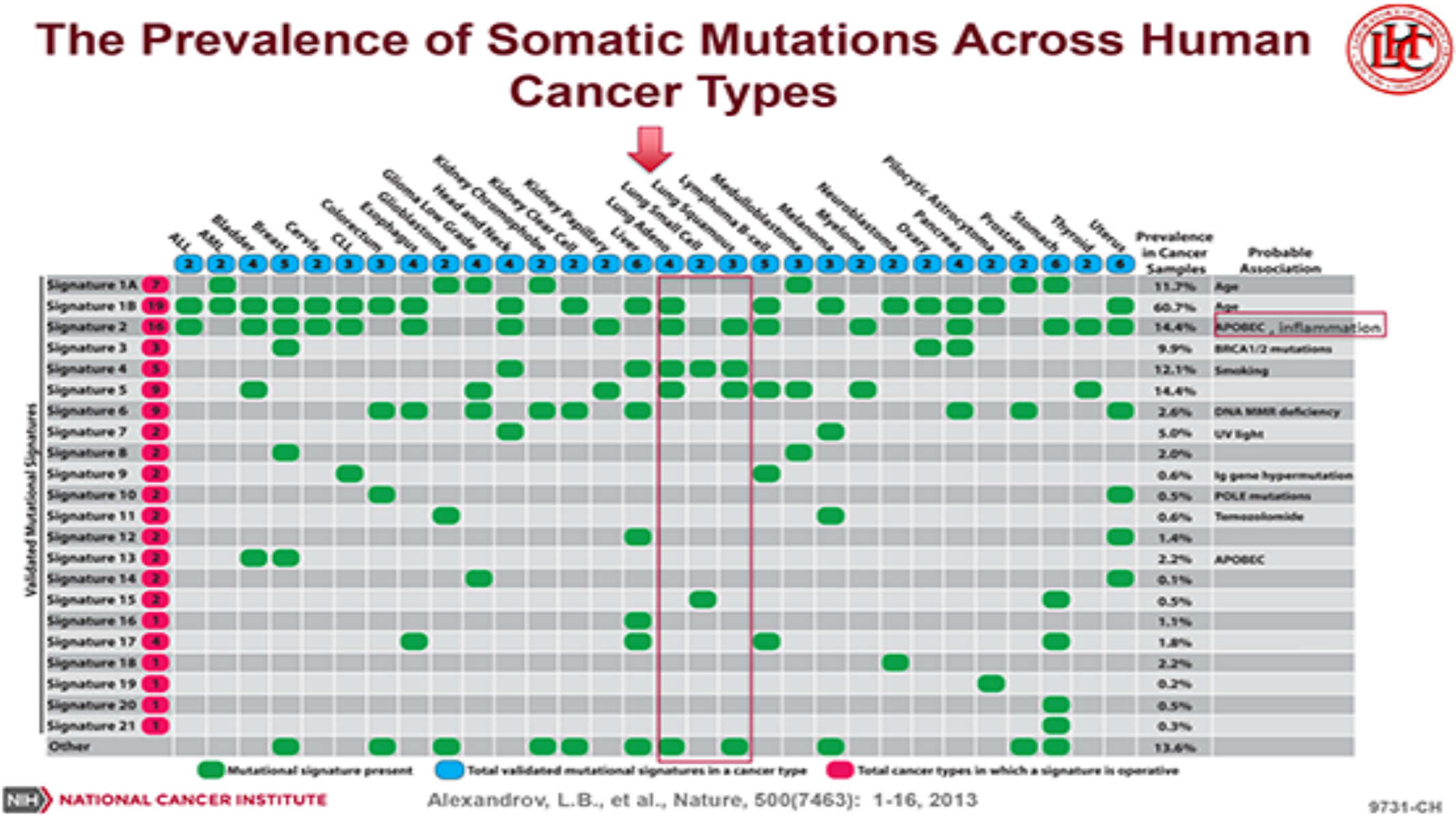
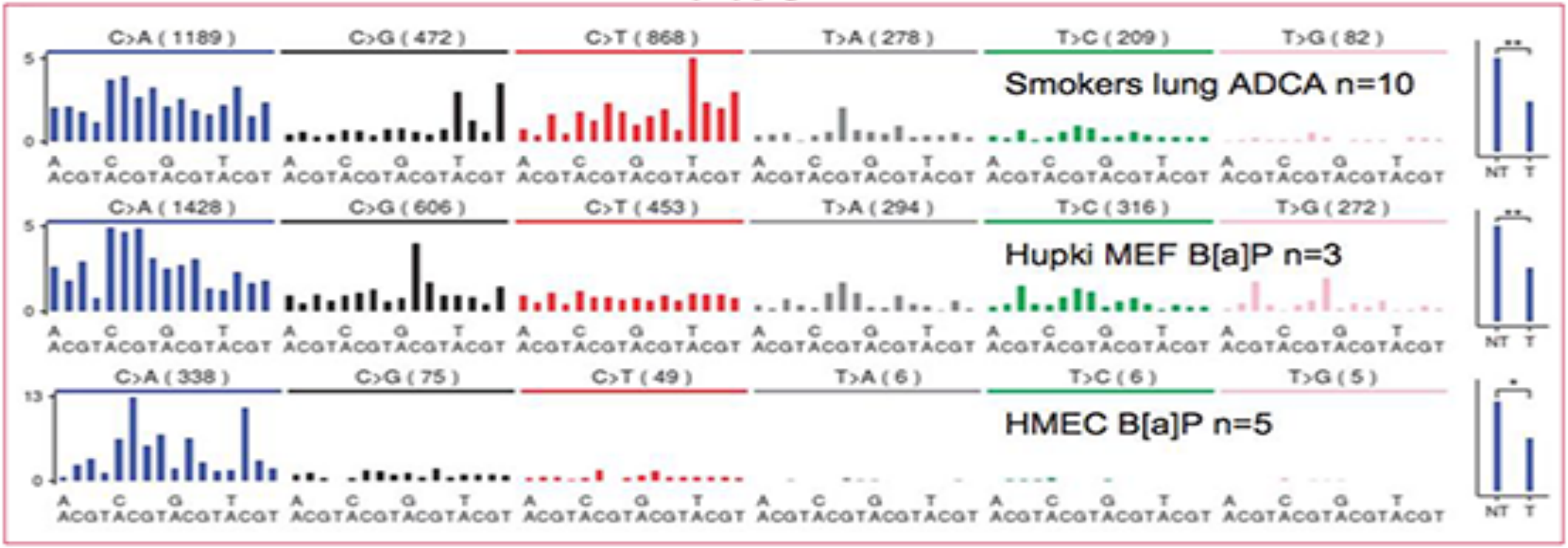
  - Alexandrov LB.....Stratton MR. Signatures of Mutational Processes in Human Cancer. Nature 500:415-421, 2013

Somatic mutations



Carcinogens fingerprint

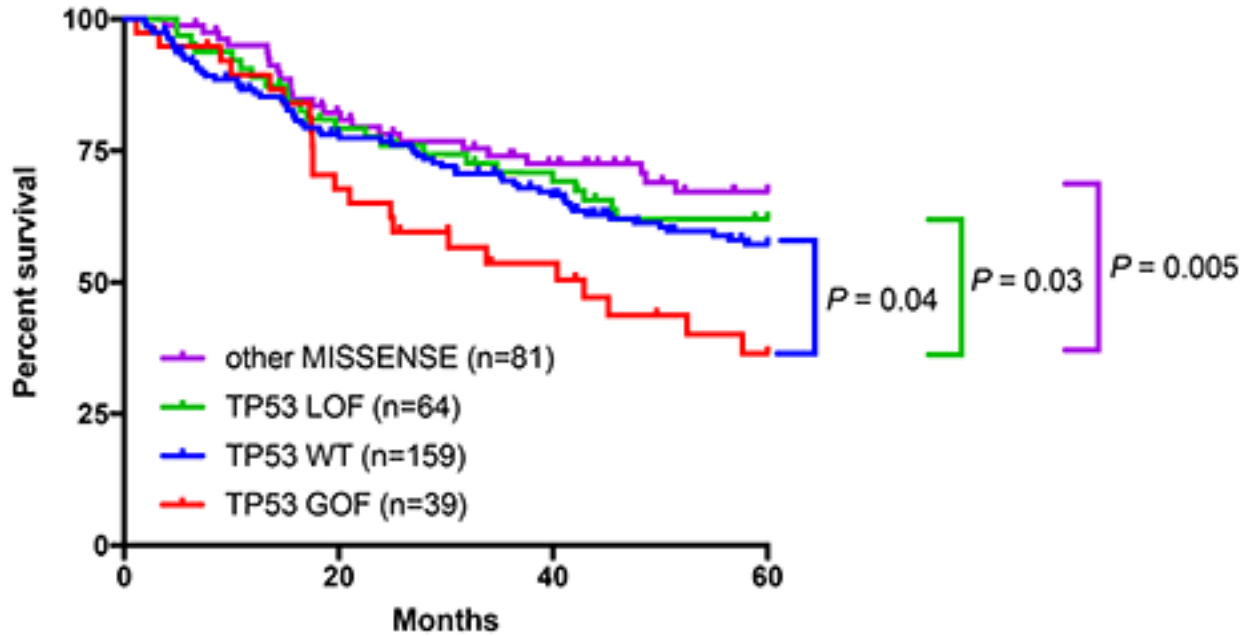
A Carcinogen's Fingerprint in Human Lung Cancer DNA Can be Reproduced in Experimental Systems: Benzo(a)pyrene



Hollstein, M., et al., Oncogene, 36: 158-167, 2017

Patient prognosis

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

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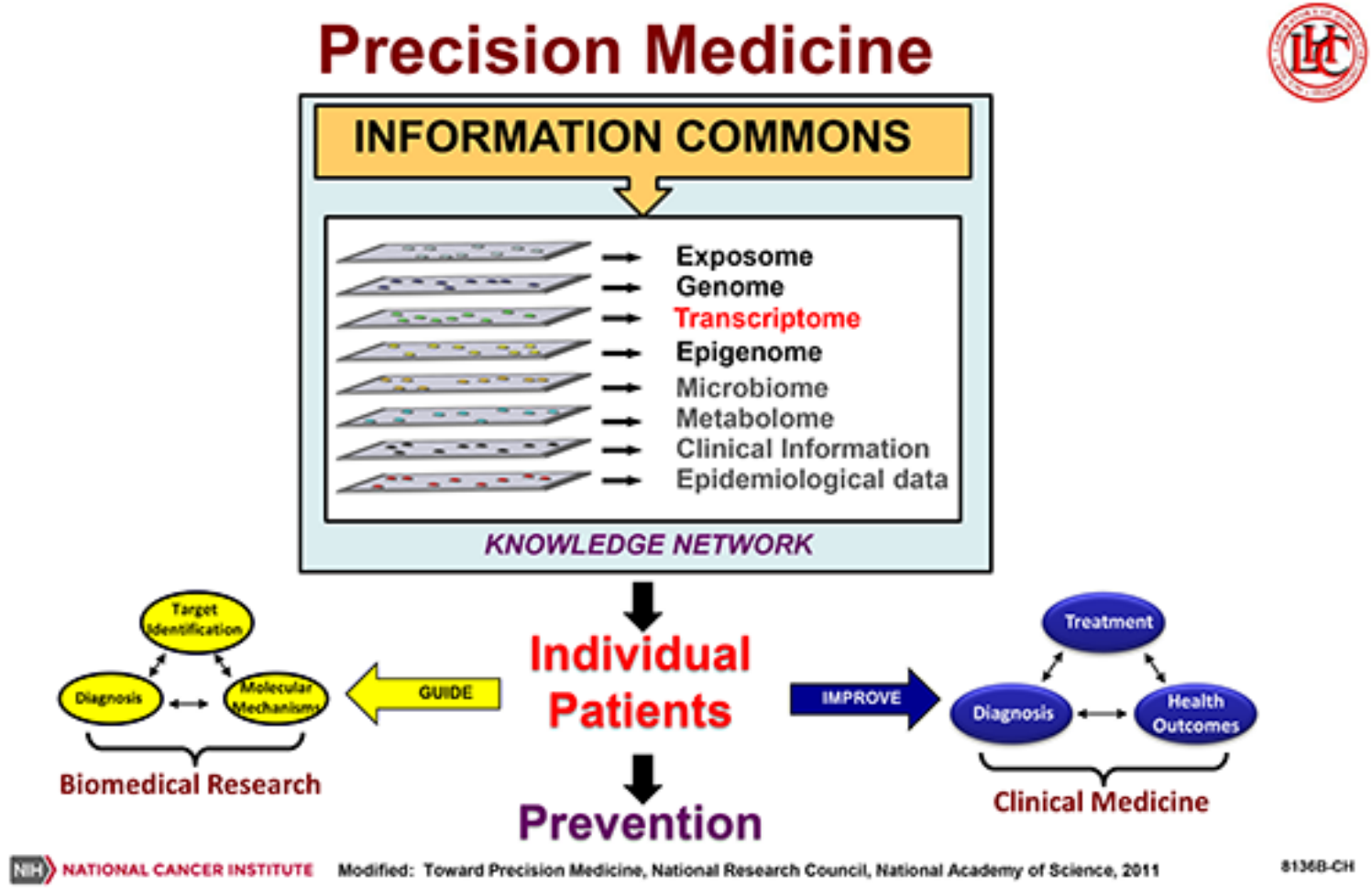
Robles A and Harris CC, NCI-MD Case Control Study

Transcriptome



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

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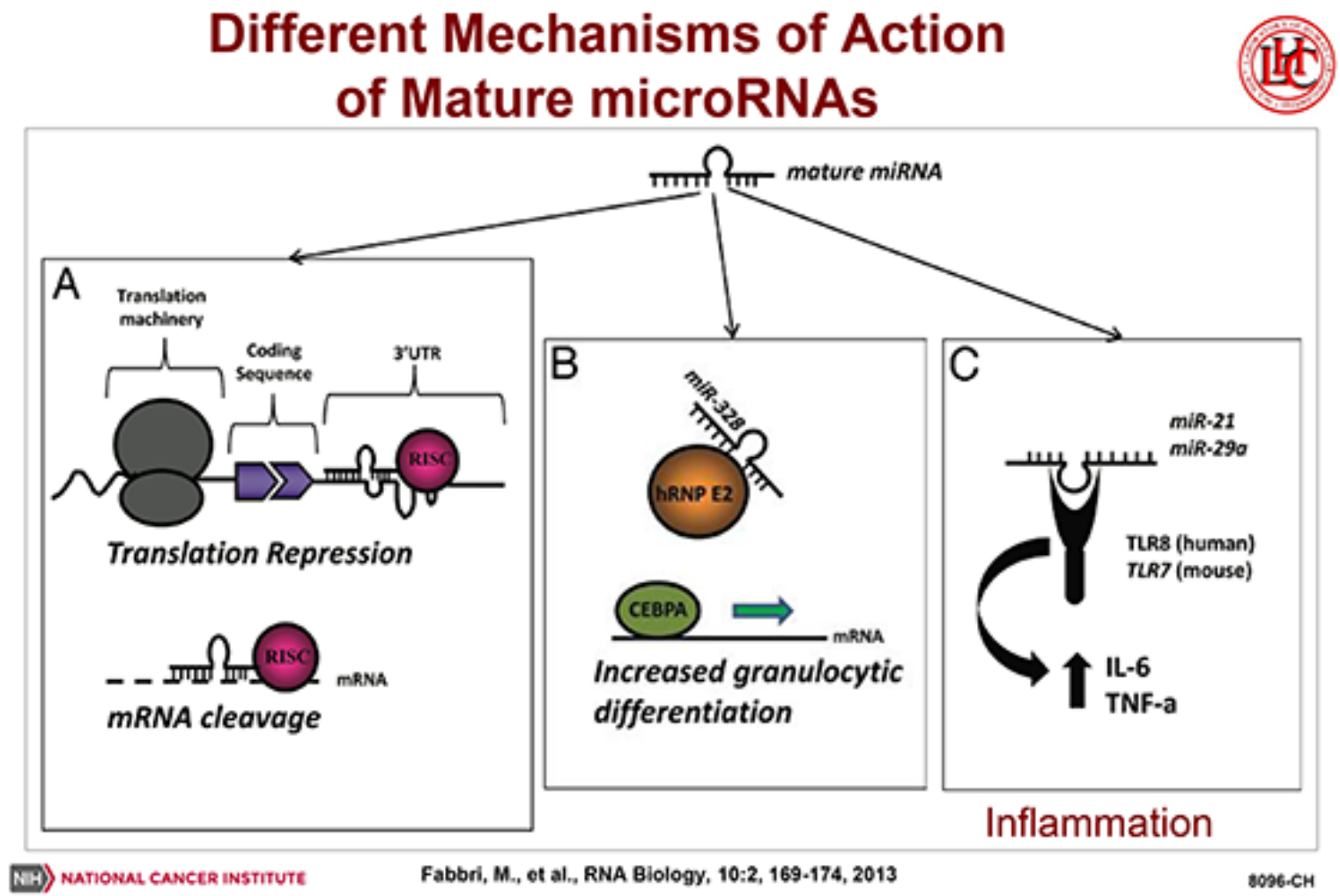
microRNA mechanisms



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.

let-7: confirmed studies by Takahashi and Slack

Nozumu Yanaihara

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

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Upregulated microRNA

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

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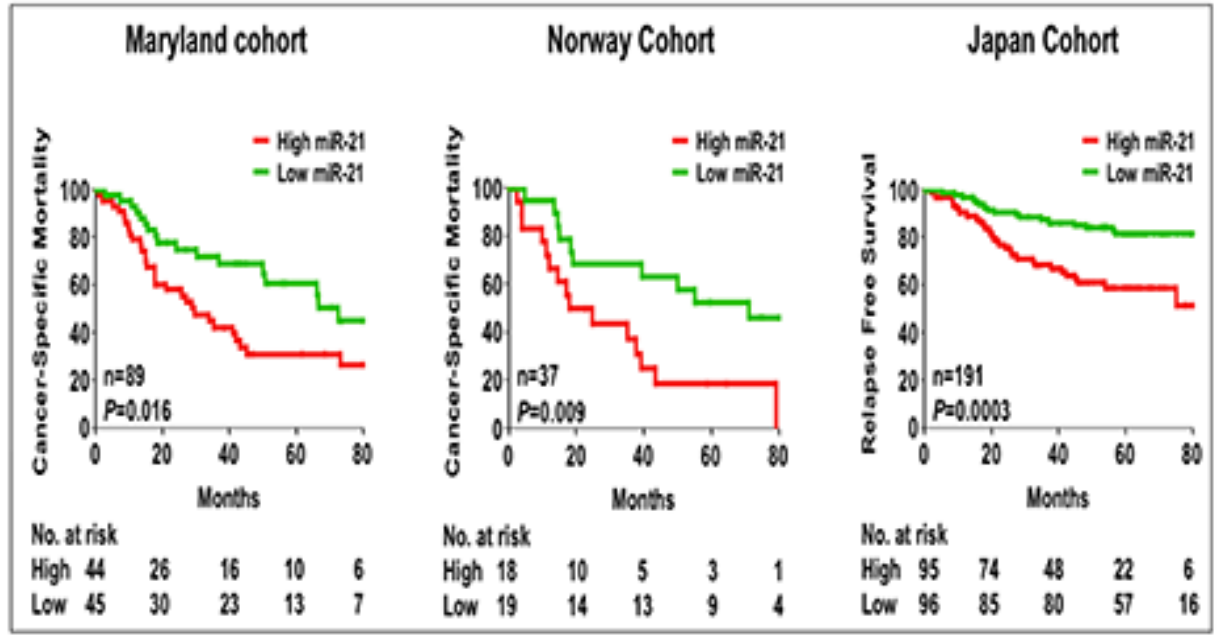
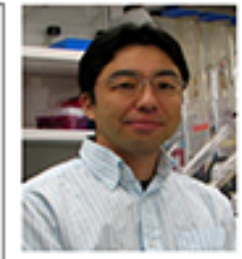
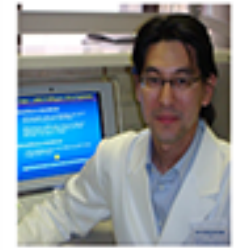
Increased miR-21 expression

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

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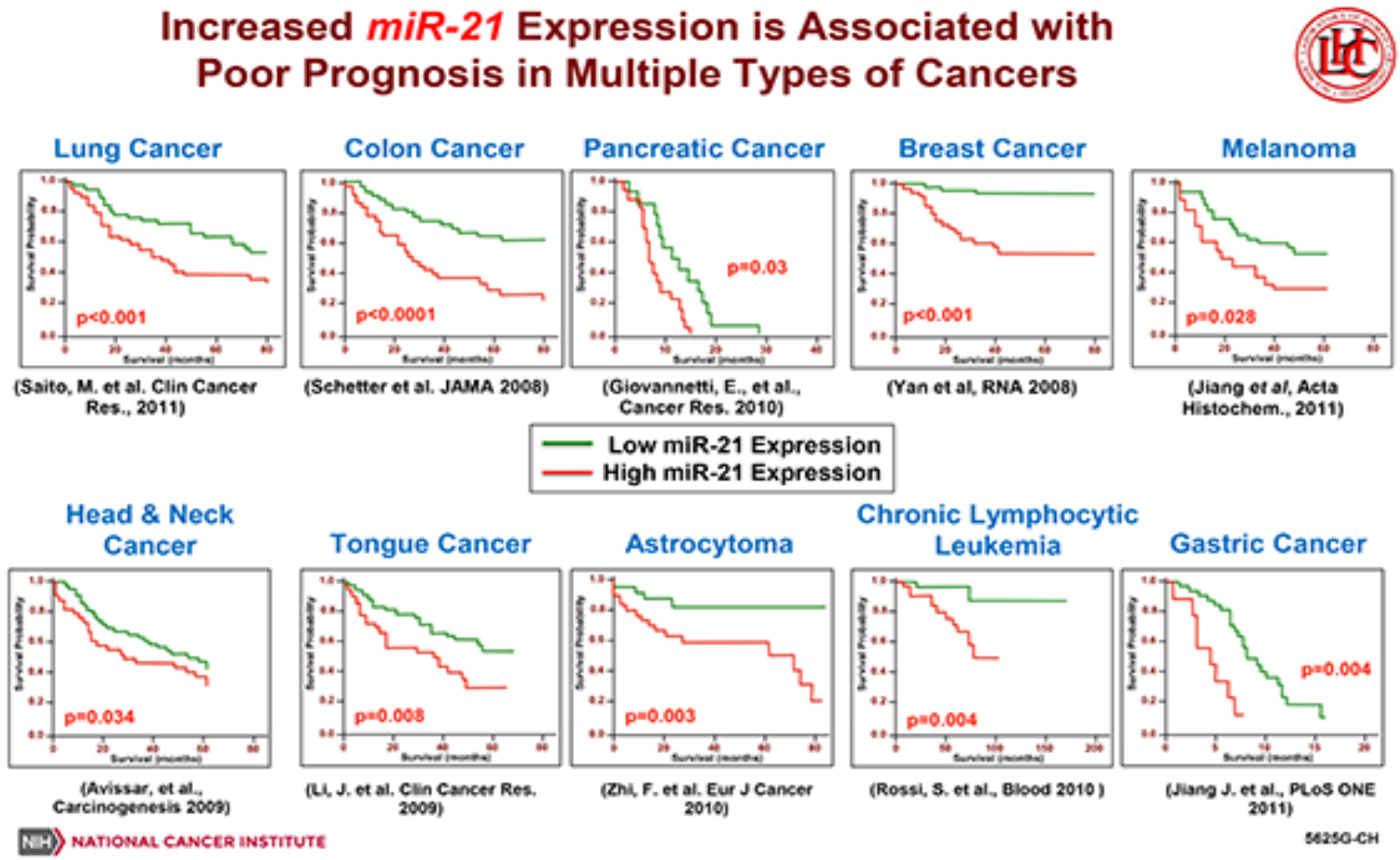
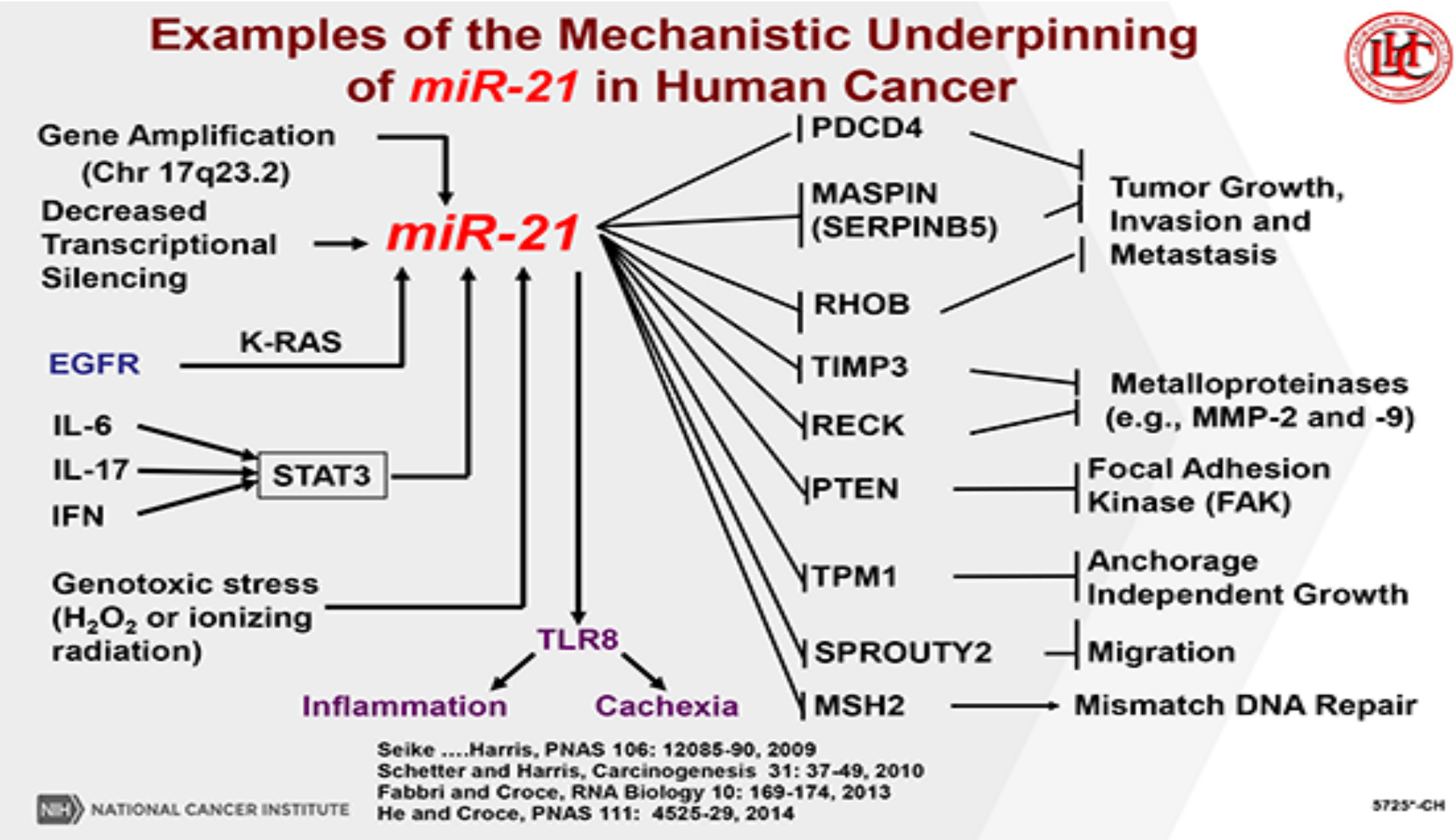
miR-21 expression



miR-21


Examples of the Mechanistic Underpinning of miR-21 in Human Cancer
Gene Amplification (Chr 17q23.2)
Decreased Transcriptional Silencing
miR-21
K-RAS
EGFR
IL-6
IL-17
IFN
STAT3
Genotoxic stress (H_2O_2 or ionizing radiation)
TLR8
Inflammation
Cachexia
PDCD4
MASPIN (SERPINB5)
RHOB
Tumor Growth, Invasion and Metastasis
TIMP3
RECK
Metalloproteinases (e.g., MMP-2 and -9)
PTEN
Focal Adhesion Kinase (FAK)
TPM1
Anchorage Independent Growth
SPROUTY2
Migration
MSH2
Mismatch DNA Repair
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
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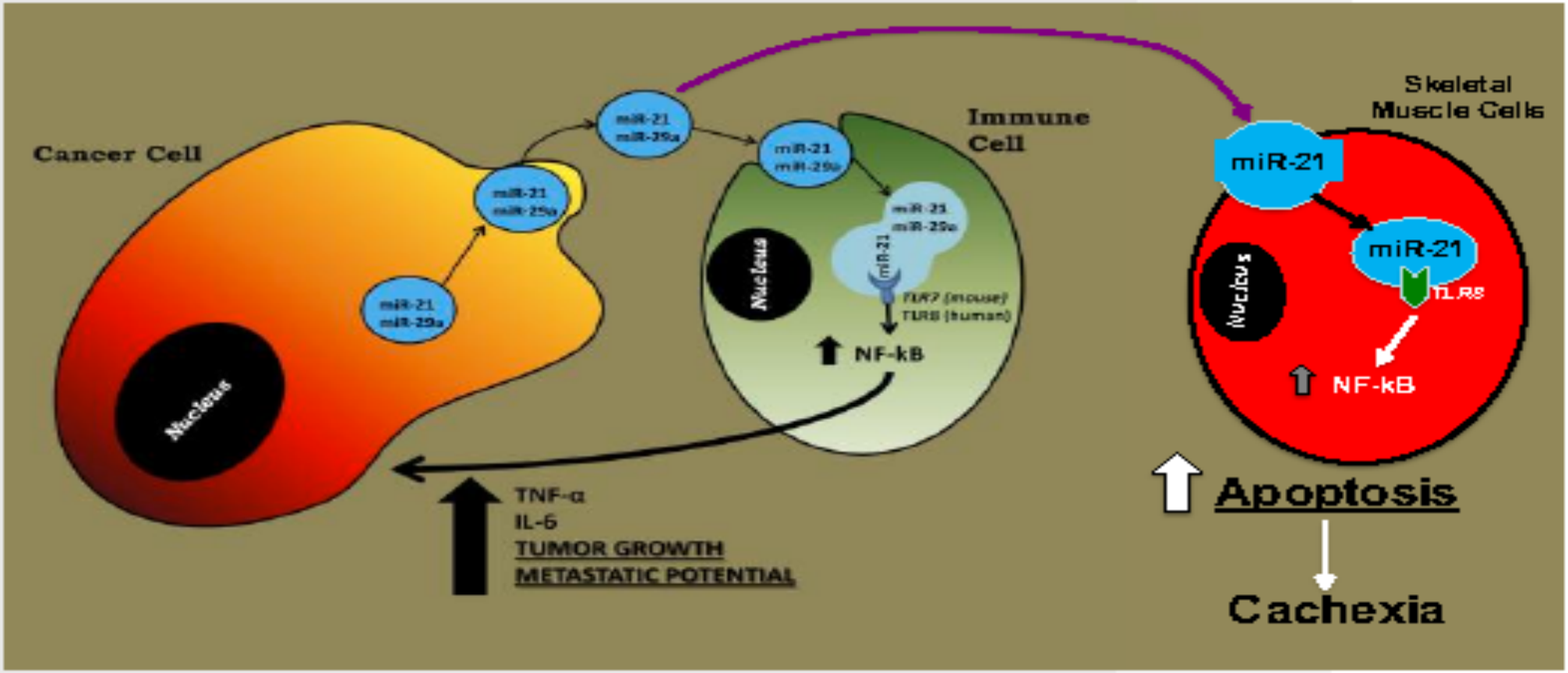
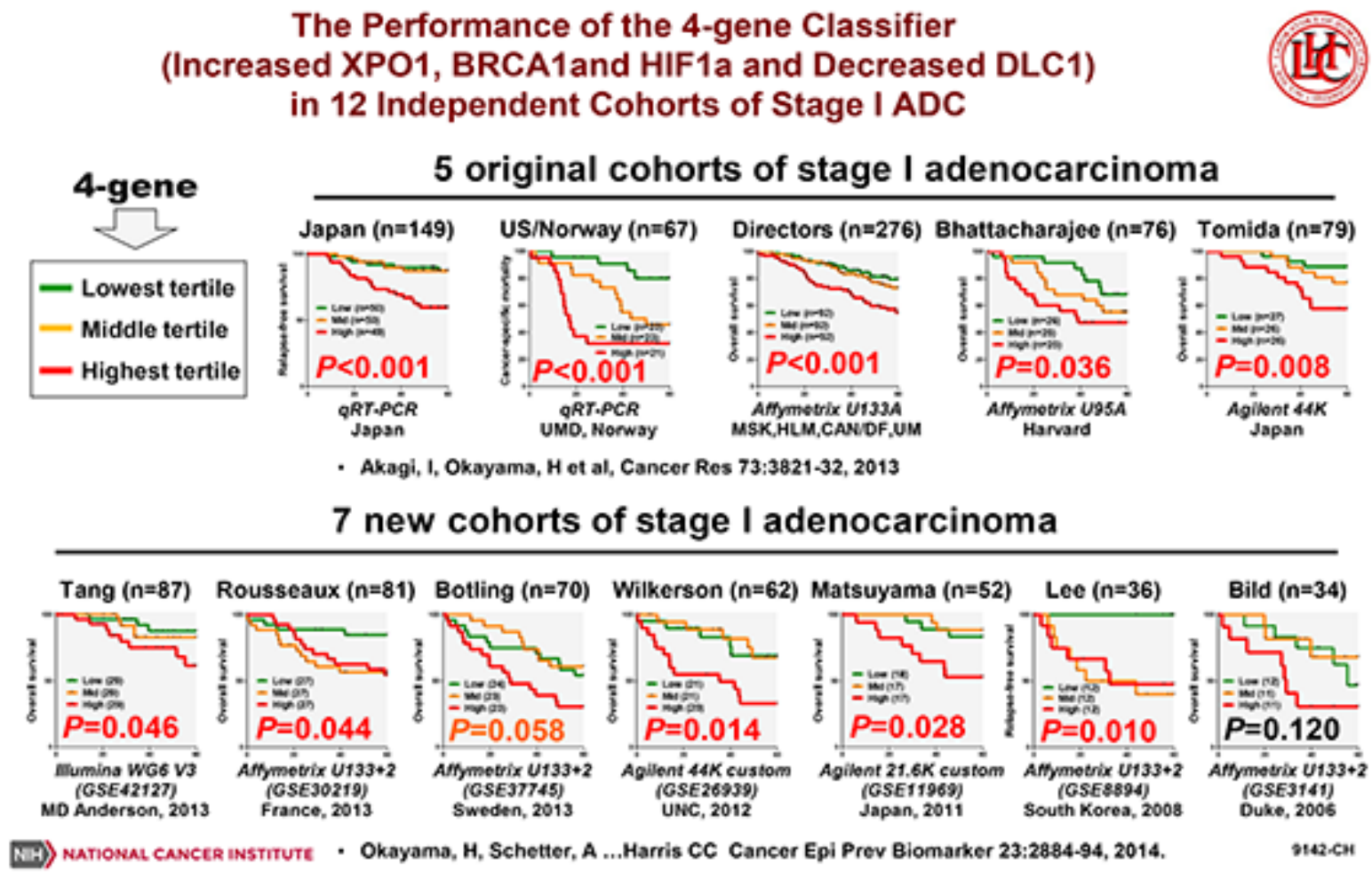
MiRNAs

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
He, W.A., et al., PNAS, 111: 4525-9, 2014

4-gene classifier

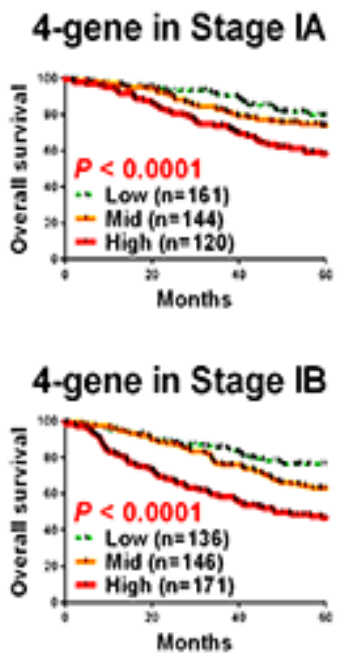


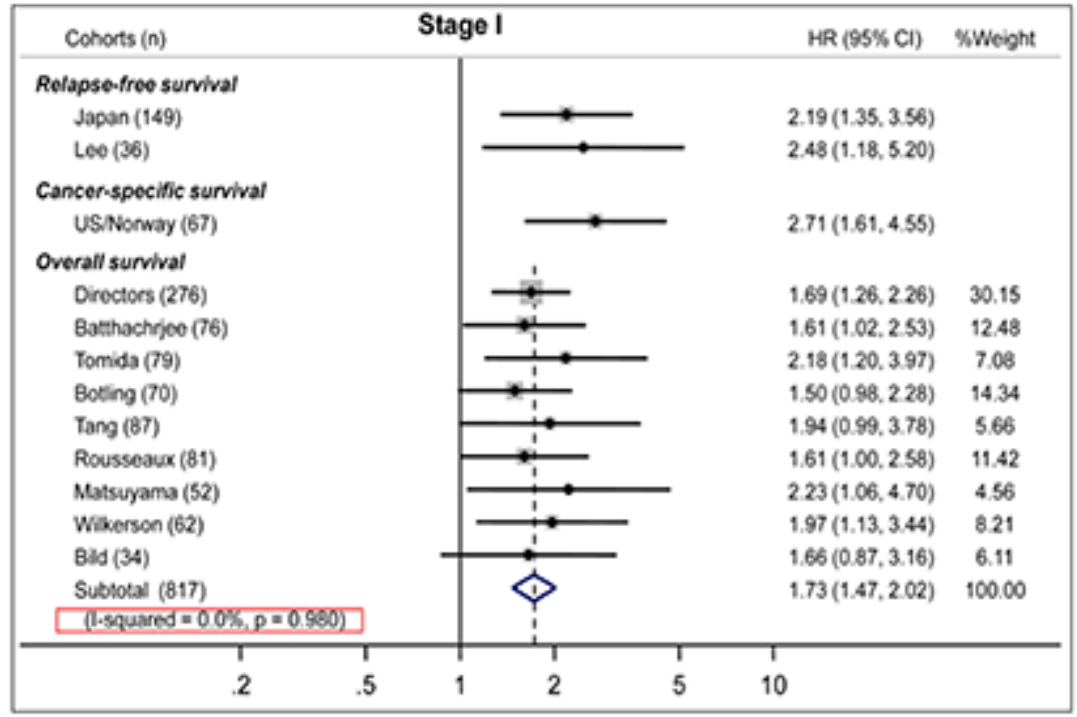
Meta-Analysis

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

- 883 Stage I Patients

- 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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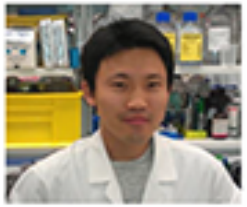
Mechanistic cancer biomarkers

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

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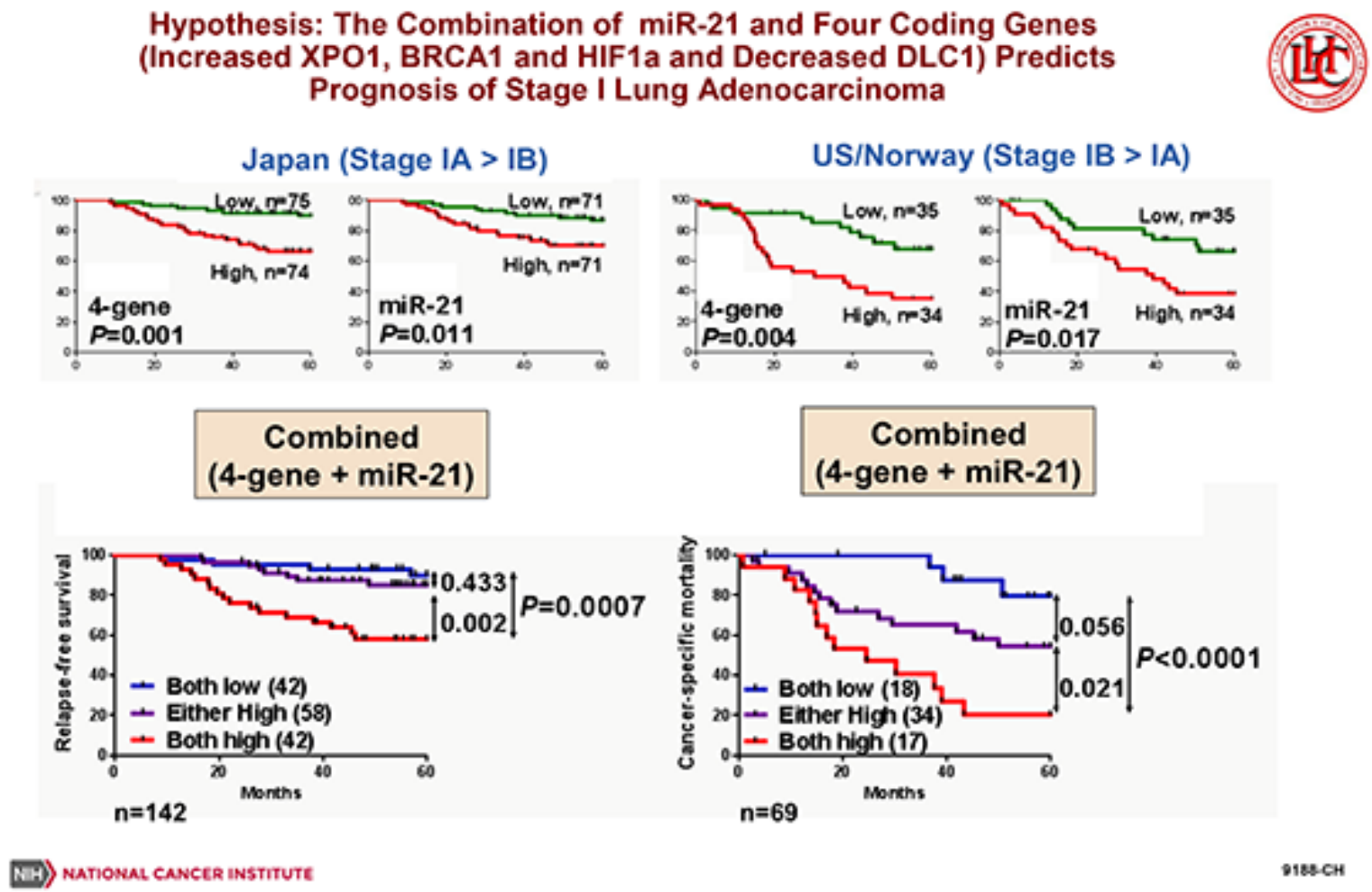
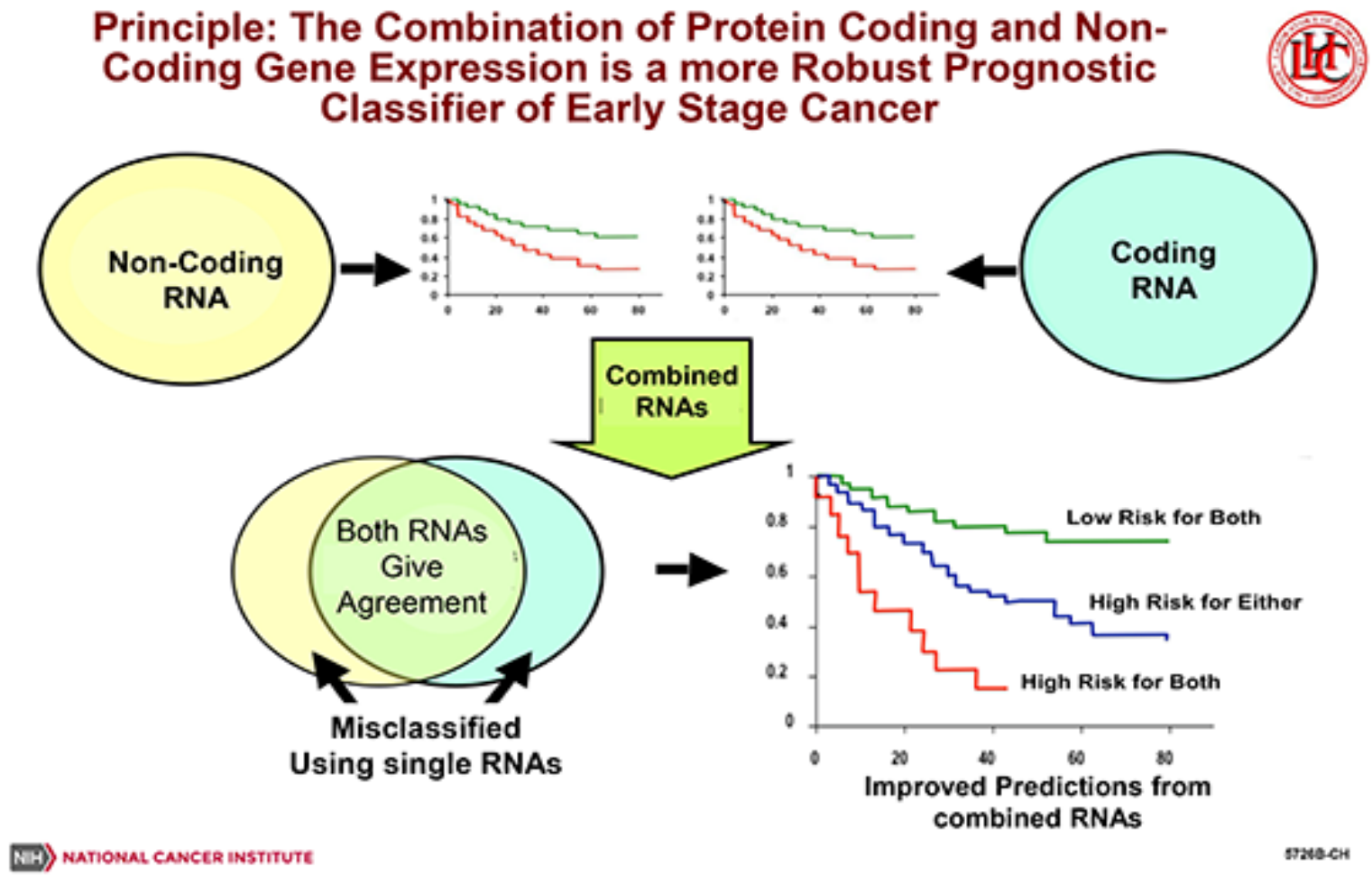
miR-21 and 4 coding genes



Non-coding RNA



Proof of Principle

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

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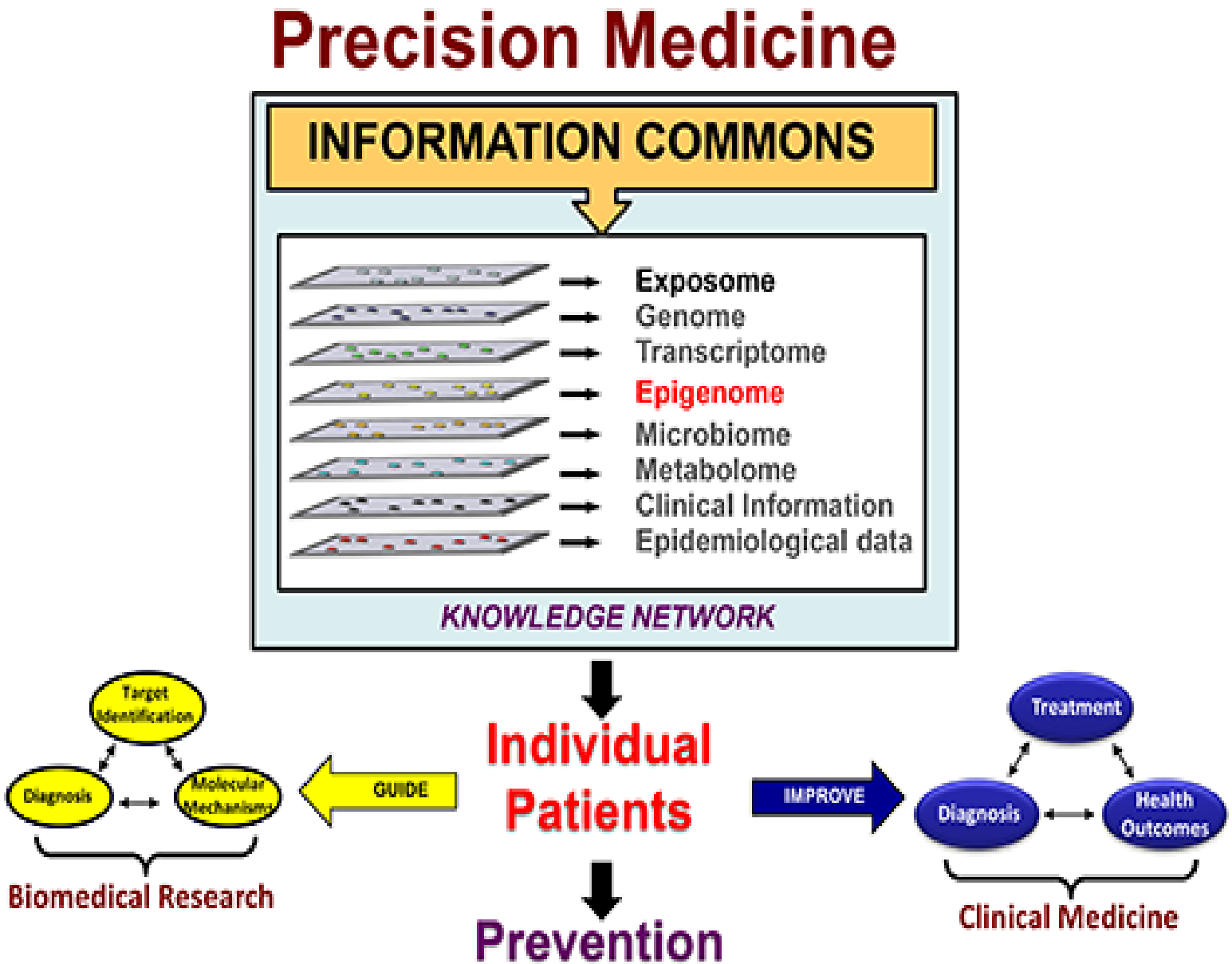
Epigenome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Transcriptome
Epigenome
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Epidemiological data
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Diagnosis
Molecular Mechanisms
GUIDE
Biomedical Research
Individual Patients
Prevention
IMPROVE
Treatment
Diagnosis
Health Outcomes
Clinical 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

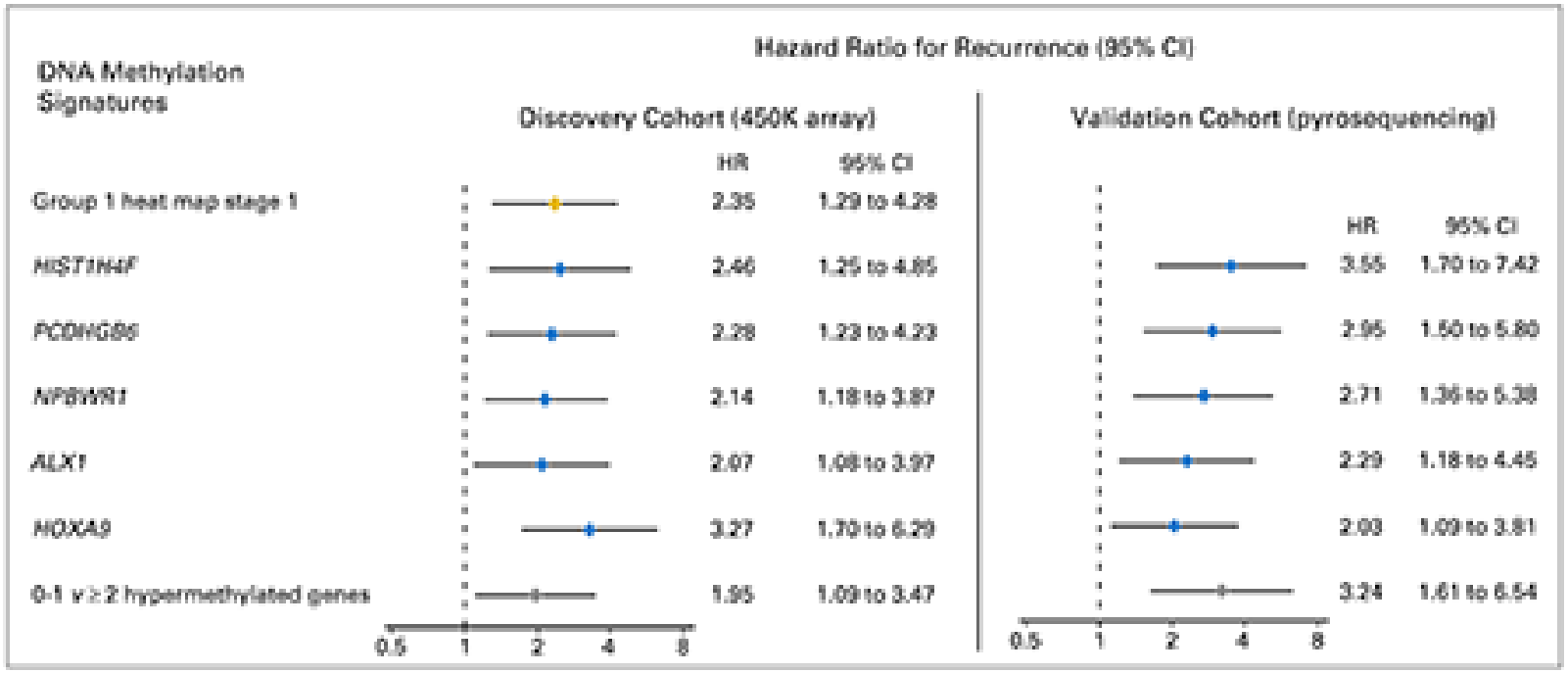
Prognostic epigenetic signature

DNA Methylation in NSCLC is a Prognostic Epigenetic Signature

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

Juan 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, Miguel 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)

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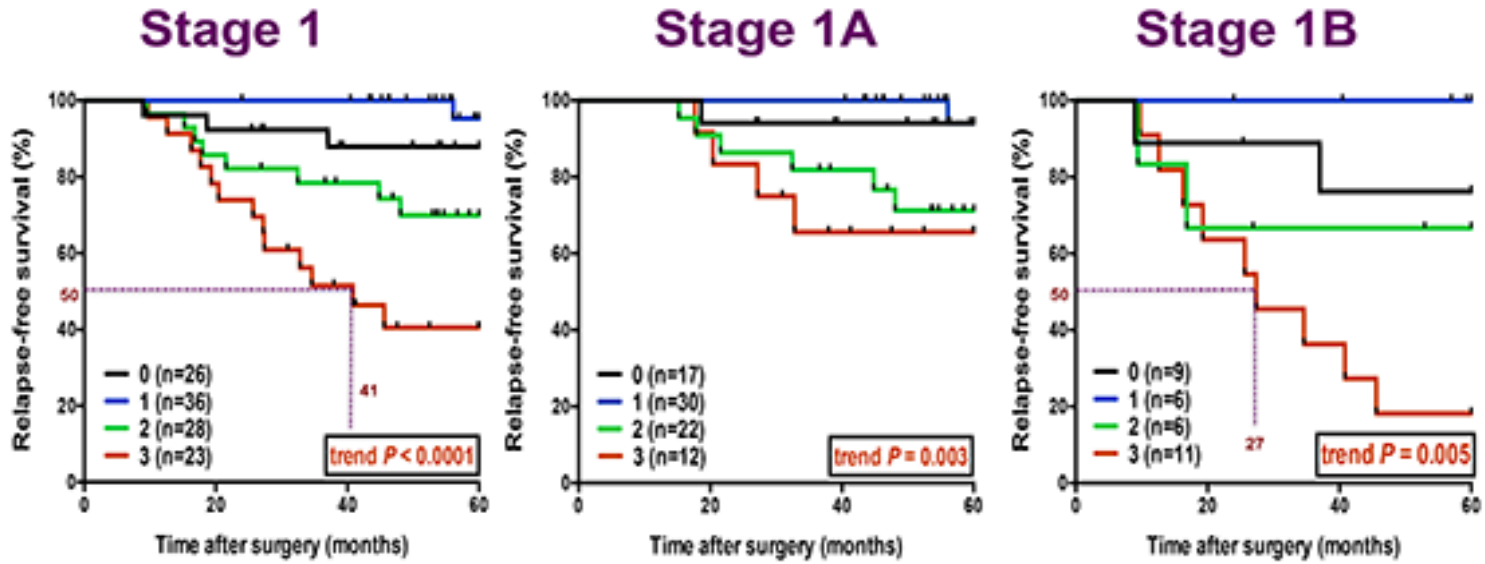
Survival curve

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.

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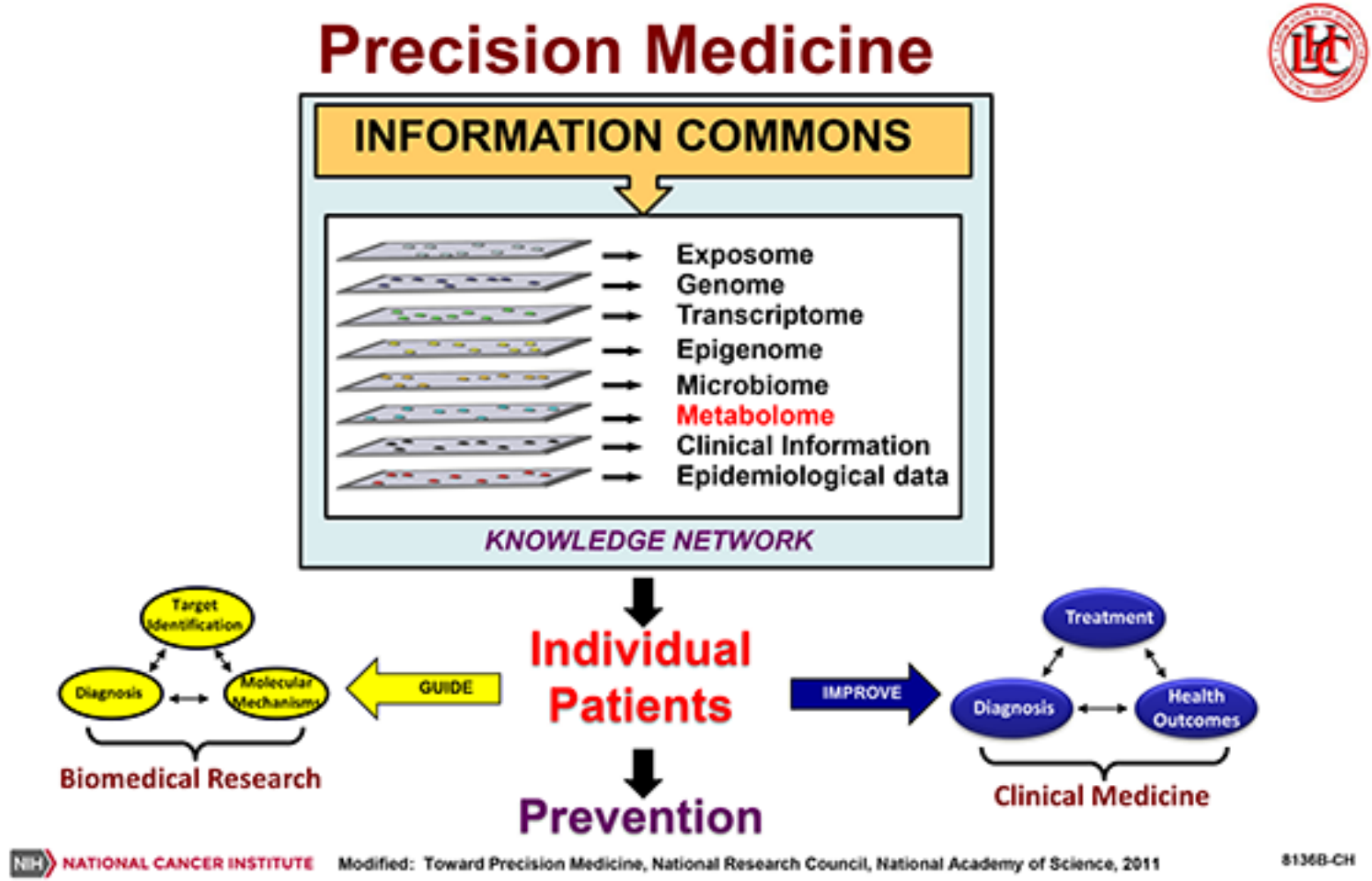
Microbiome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Clinical Medicine
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Modified: Toward Precision Medicine, National Research Council, National Academy of Science, 2011
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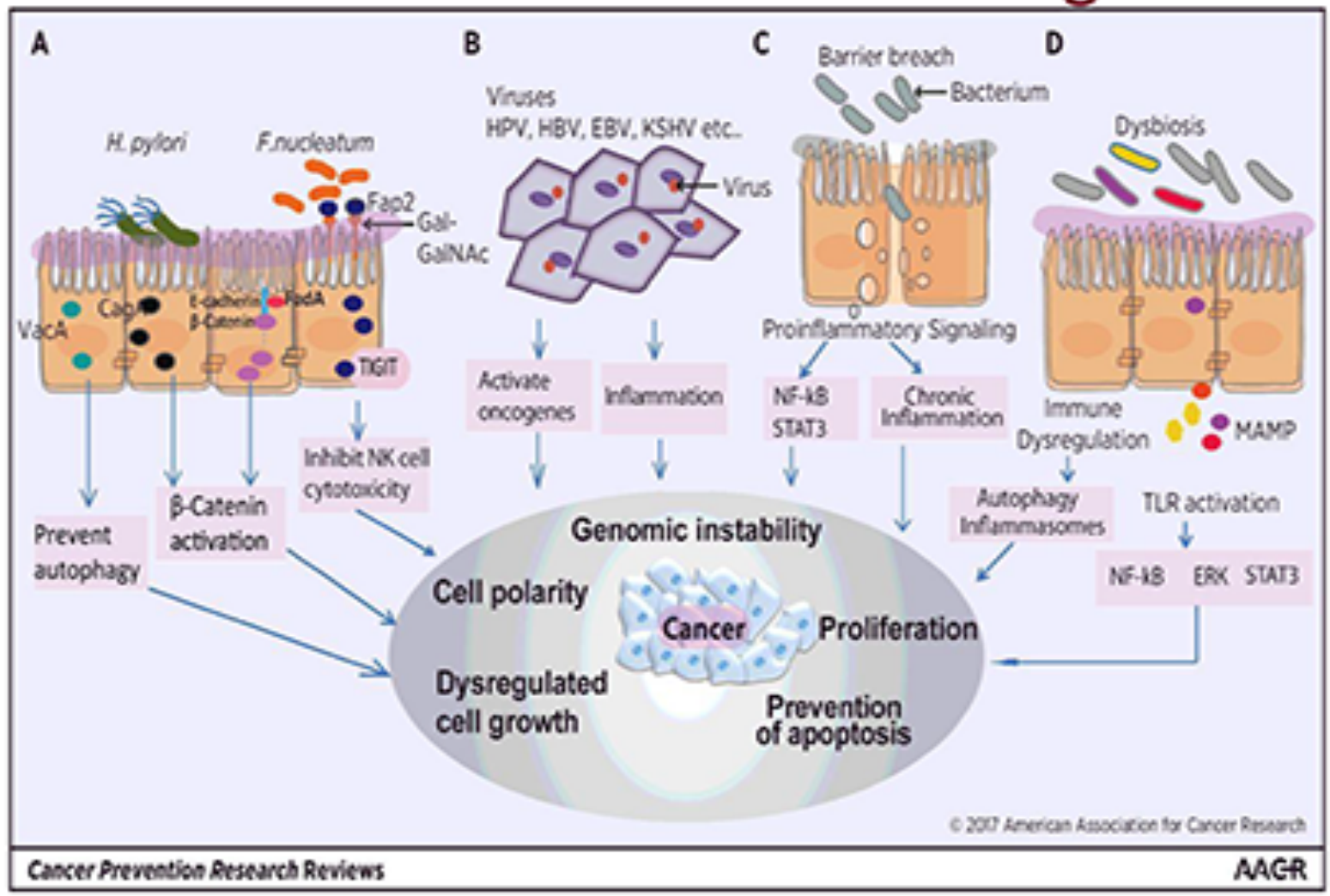
Microbiome and carcinogenesis

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



Rajagopala SV et al. Cancer Prev Res 2017;10:226-234

Microbiome, TP53 and lung cancer

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

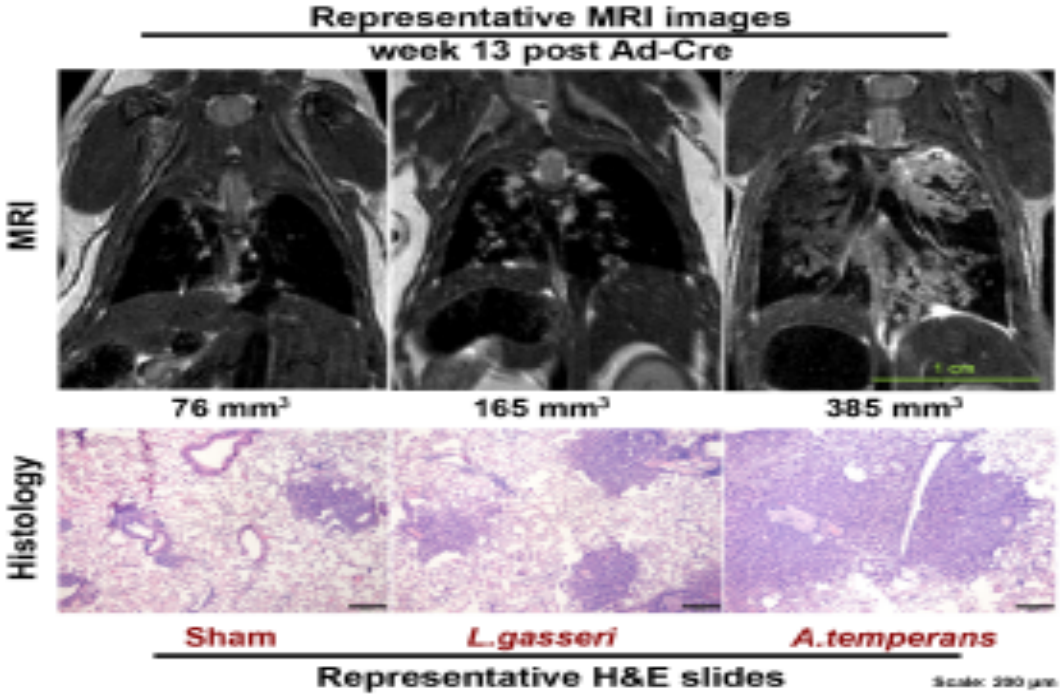
- Certain taxa including Acidovorax were higher in both adenocarcinoma and squamous carcinoma (SCC) in smokers and former smokers than in non-smokers.
- A group of taxa were significantly associated with SCC, of which *Acidovorax was* enriched in smokers
- SCC cases with *TP53* mutations had a higher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

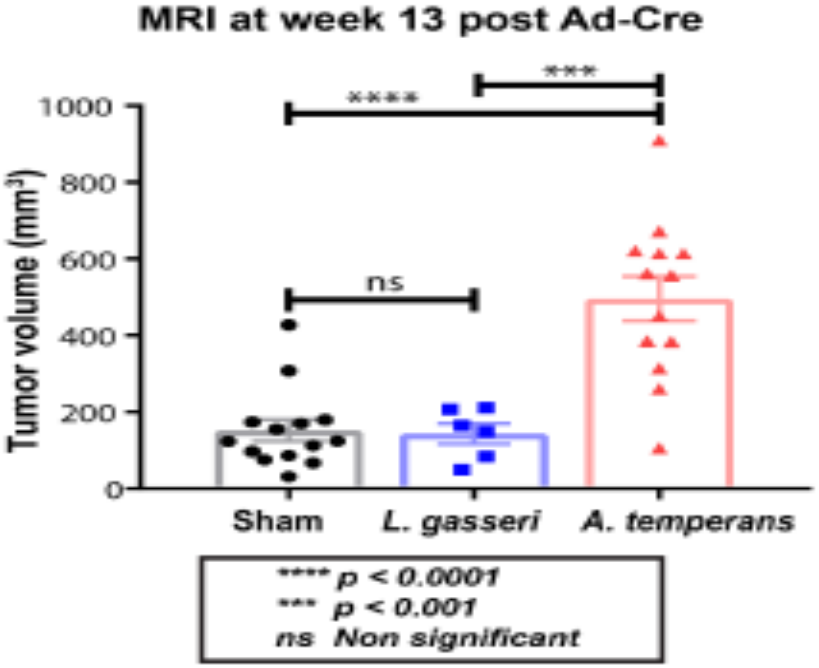
SCC-associated taxa are enriched in tumors with *TP53* mutations, which establishes a microbiome-gene interaction in lung cancer tissue

Greathouse I .....Harris CC Genome Biology, 2018, August 24:19(1):123

Temperans challenge

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

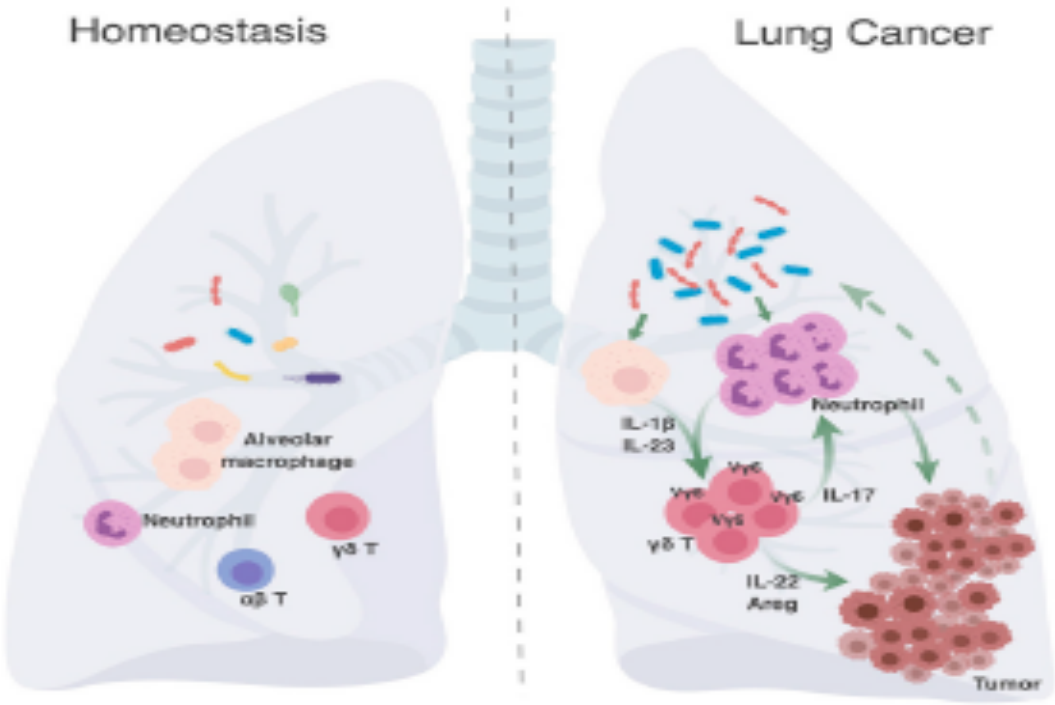




- Mice challenged with ***A. temperans* exhibit significantly larger tumors** at week 13 post AdCre compared to *L. gasseri* or PBS.

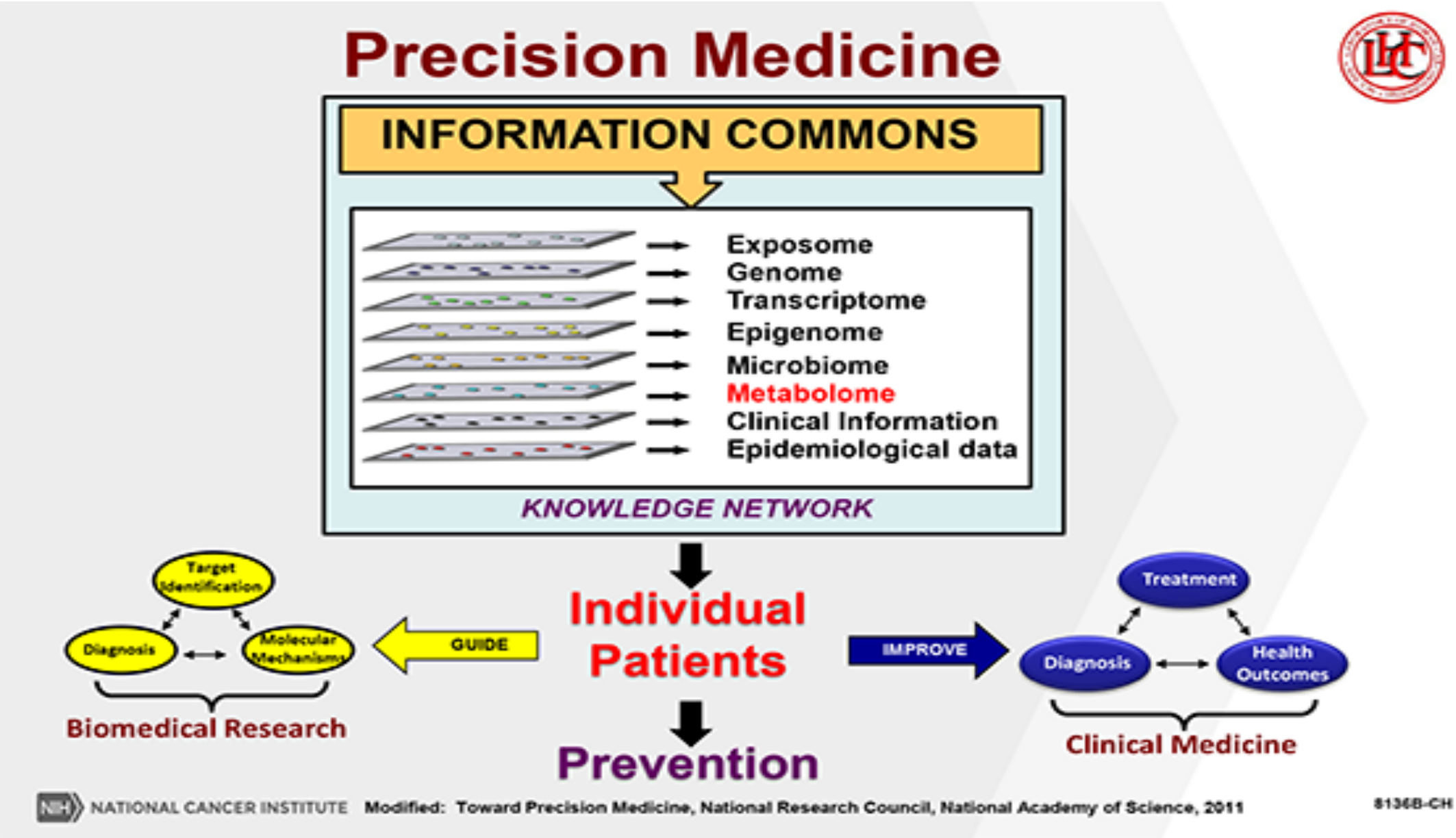
Microbiome and immune modulation

Microbiome and immune modulation



- Various commensal micro-organisms influence the local immunity.
- Intact commensal microbiota **promotes lung cancer development** through **modulation of innate immune response** and **expression of cytokines** such as IL17.

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

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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…"

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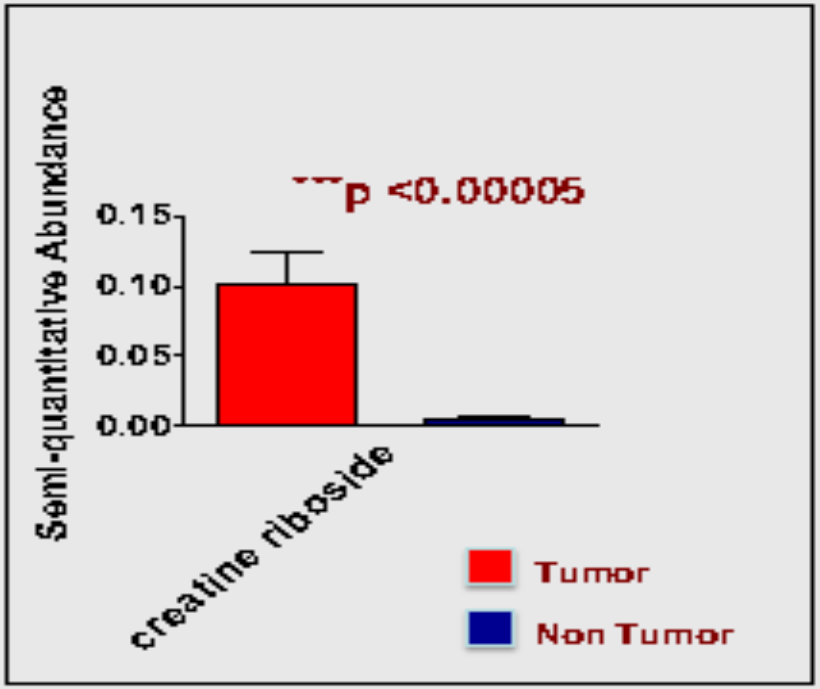
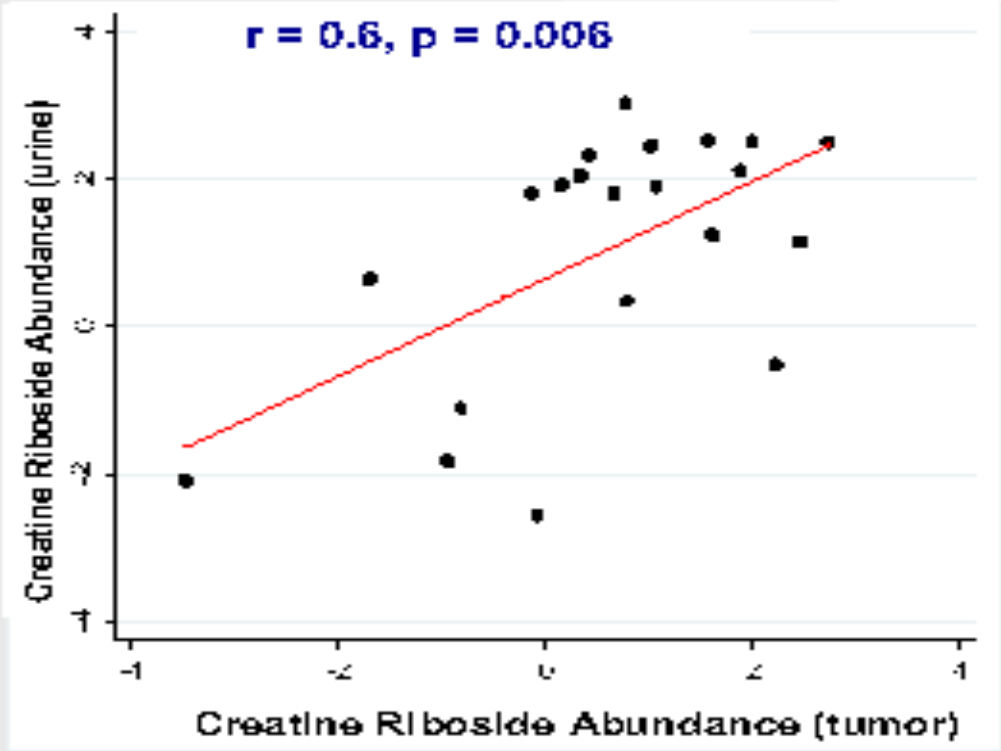
Creatine ribose

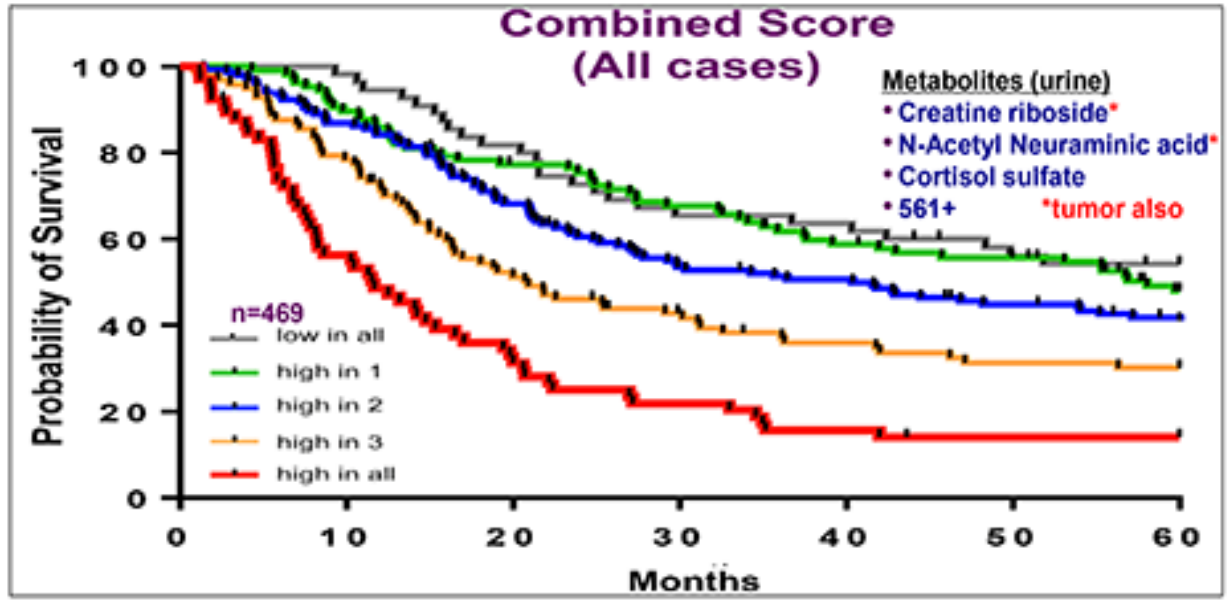
Creatine Ribose is Positively Correlated in Cancer and Urine





Survival curve

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

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

7162B-CH

Low dose CT screening

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

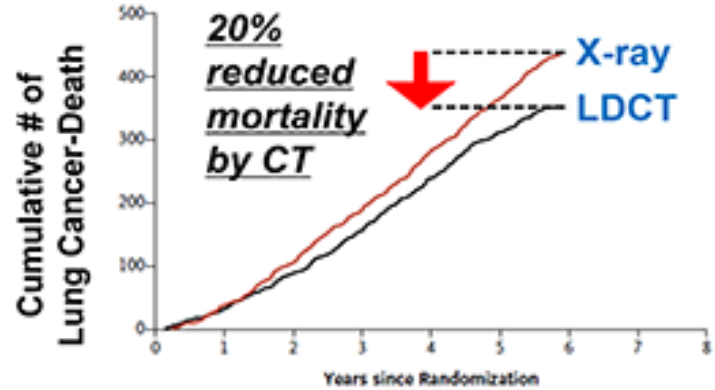
The National Lung Screening Trial Research Team*

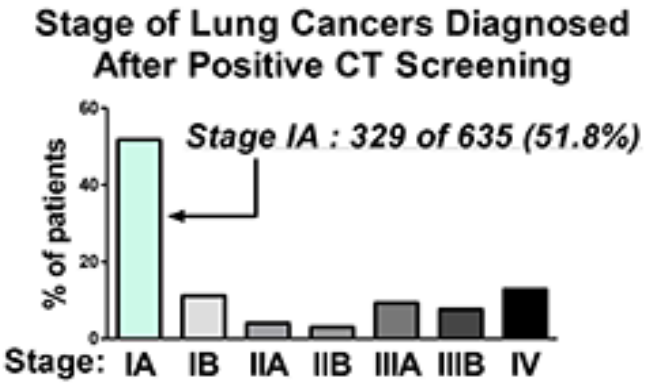
n=53,454 participants
Current/former heavy smokers, 55-77 y.o.

X-ray n=26732

LDCT n=26722

Low-Dose CT
- False Positive Rate = 96.4%





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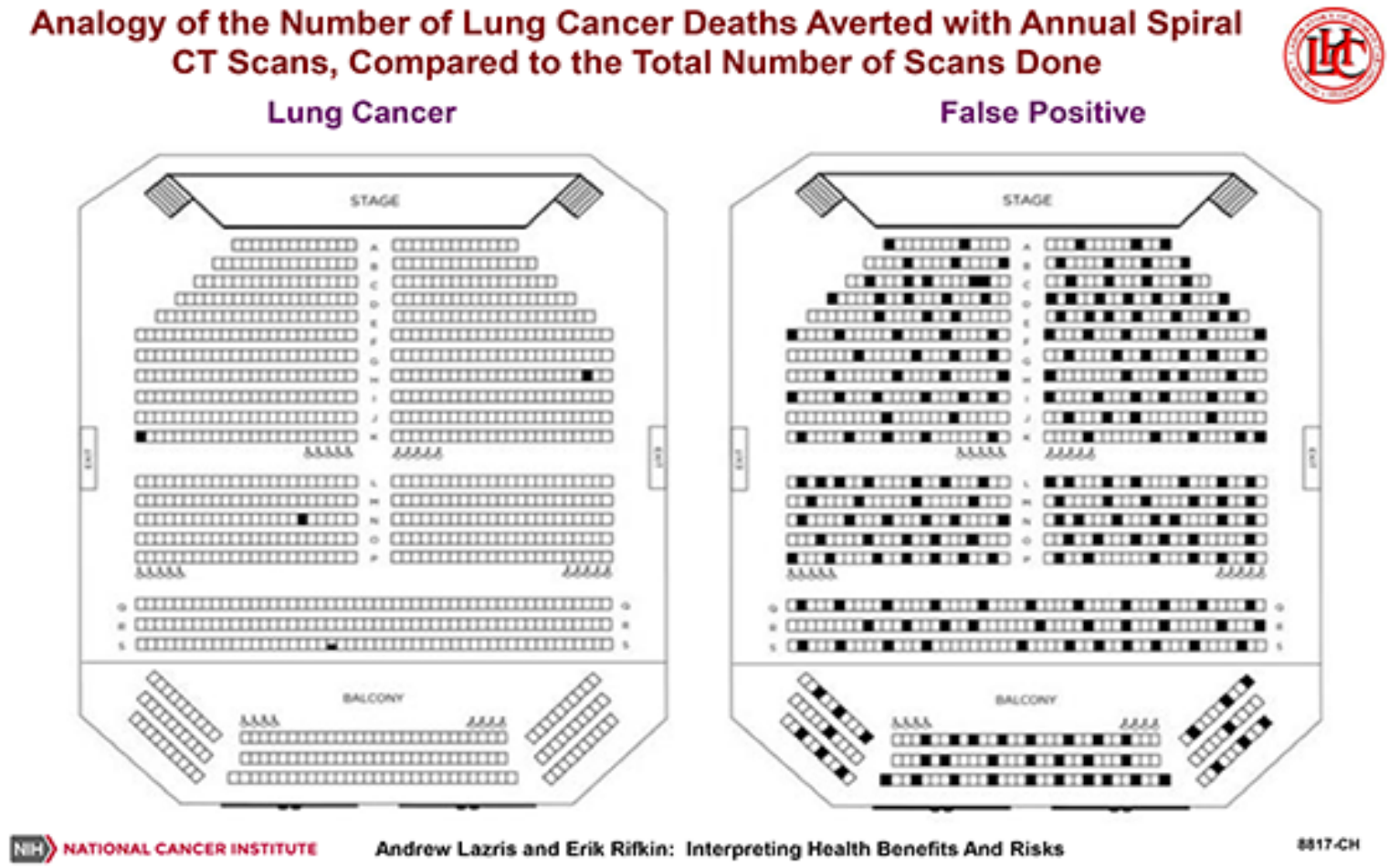
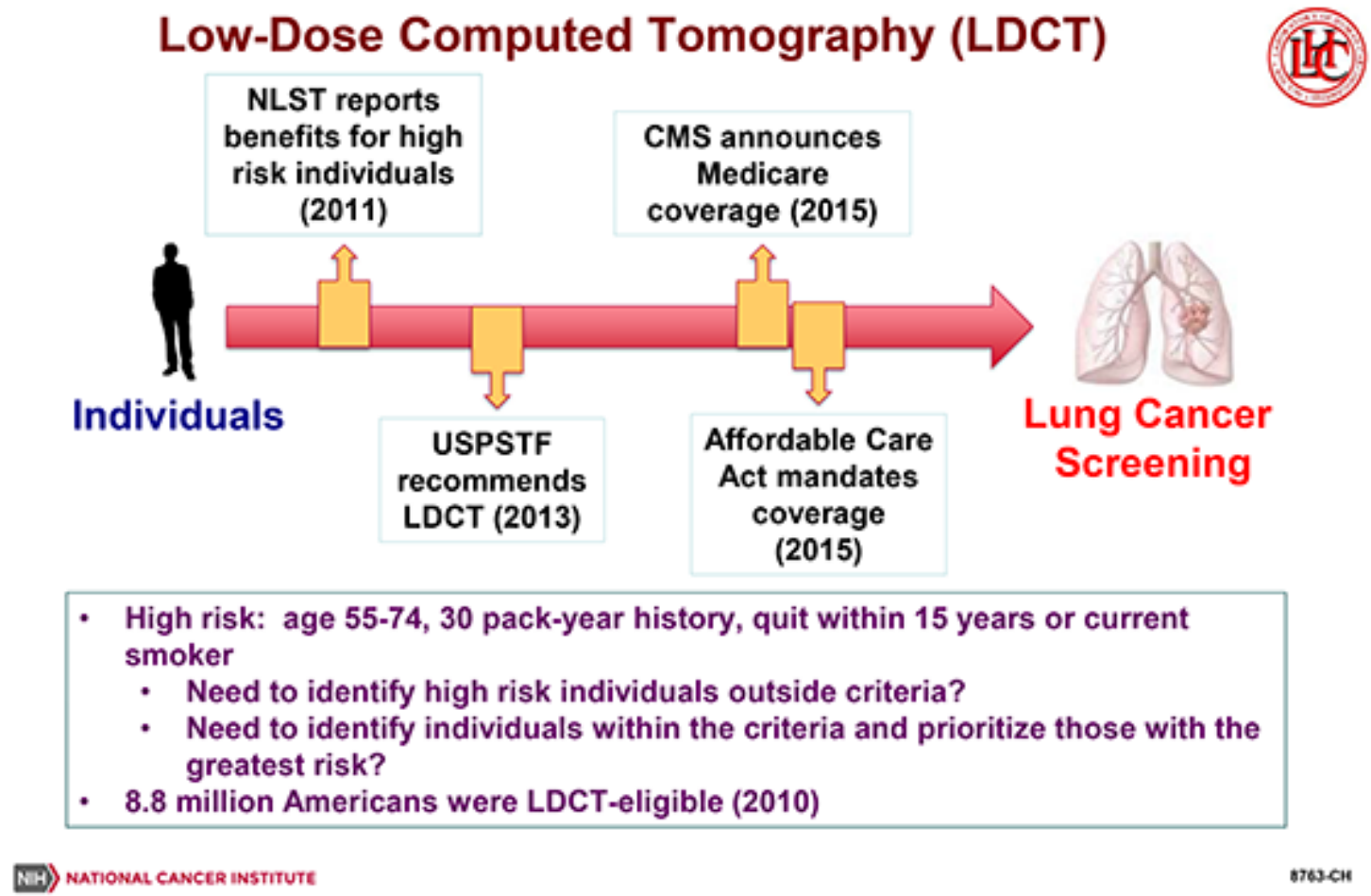
Spiral CT scans



Low dose CT


Low-Dose Computed Tomography (LDCT)
NLST reports benefits for high risk individuals (2011)
CMS announces Medicare coverage (2015)
Individuals
USPSTF recommends LDCT (2013)
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)
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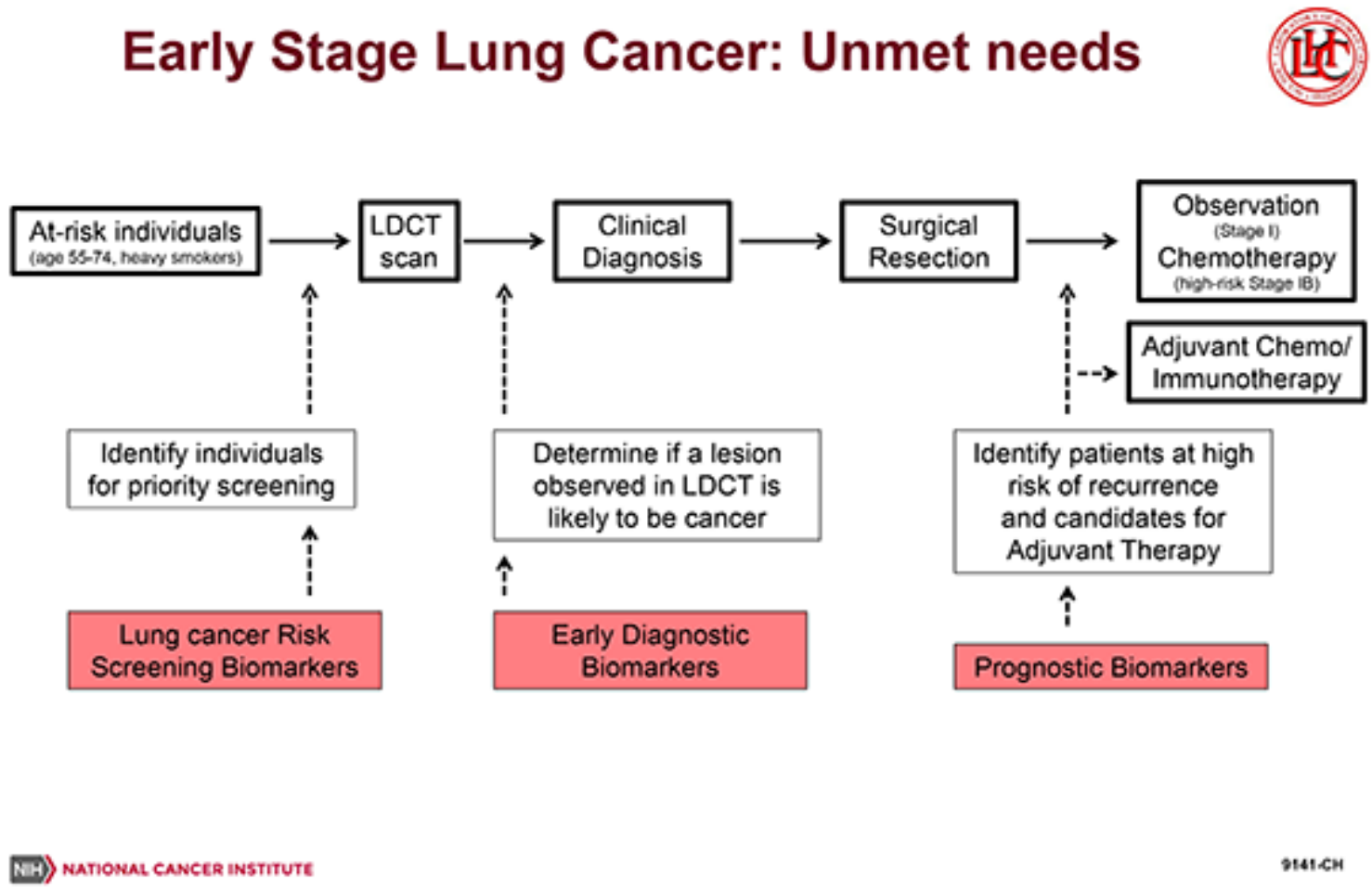
Unmet needs


Early Stage Lung Cancer: Unmet needs
At-risk individuals
(age 55-74, heavy smokers)
LDCT scan
Clinical Diagnosis
Surgical Resection
Observation
(Stage I)
Chemotherapy
(high-risk Stage IB)
Adjuvant Chemo/ Immunotherapy
Identify individuals for priority screening
Determine if a lesion observed in LDCT is likely to be cancer
Identify patients at high risk of recurrence and candidates for Adjuvant Therapy
Lung cancer Risk Screening Biomarkers
Early Diagnostic Biomarkers
Prognostic Biomarkers
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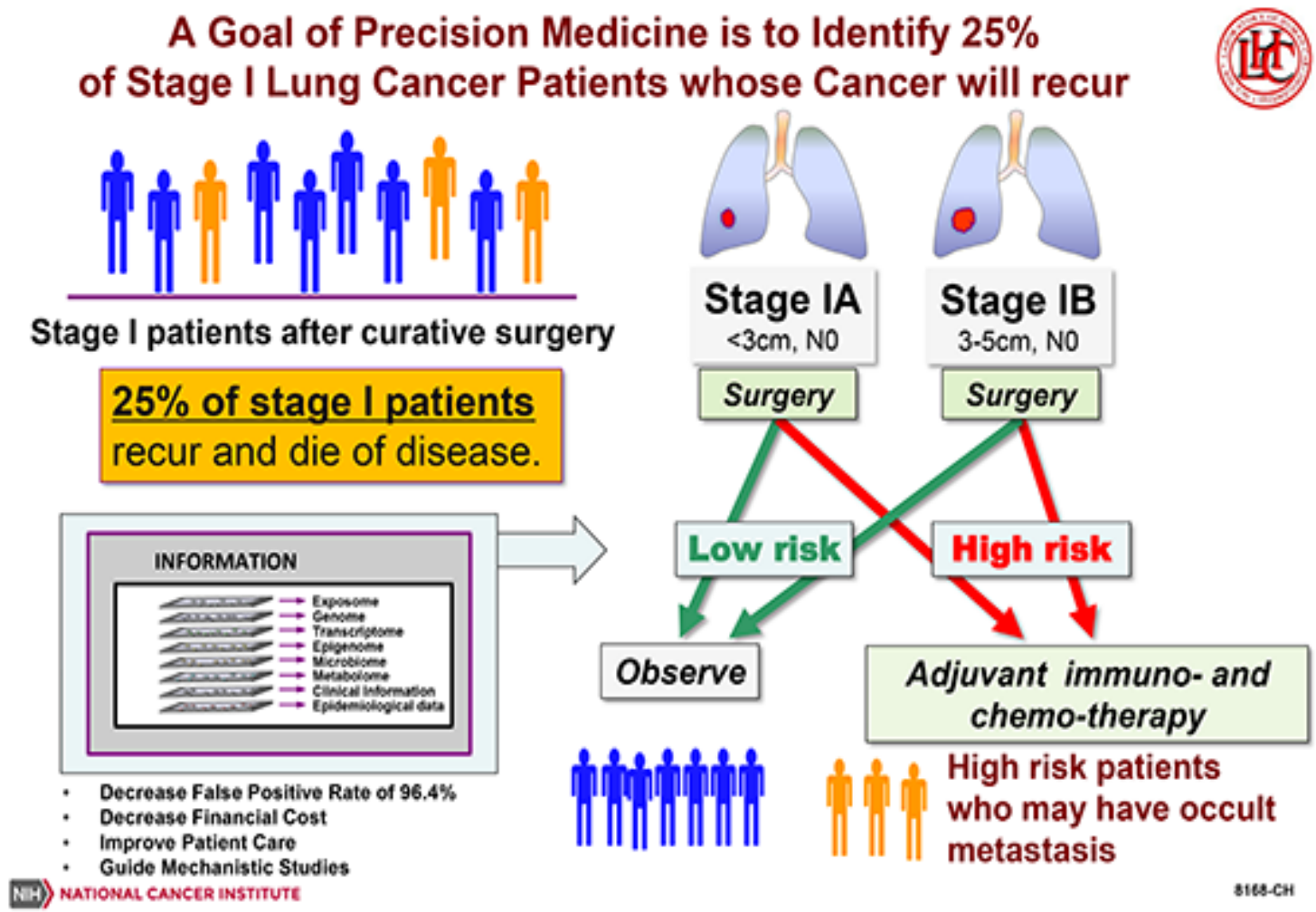
Precision medicine goals



Collaborators

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