

Pathophysiology of Tobacco Induced Cancers

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February 27, 2014



Goals of this presentation

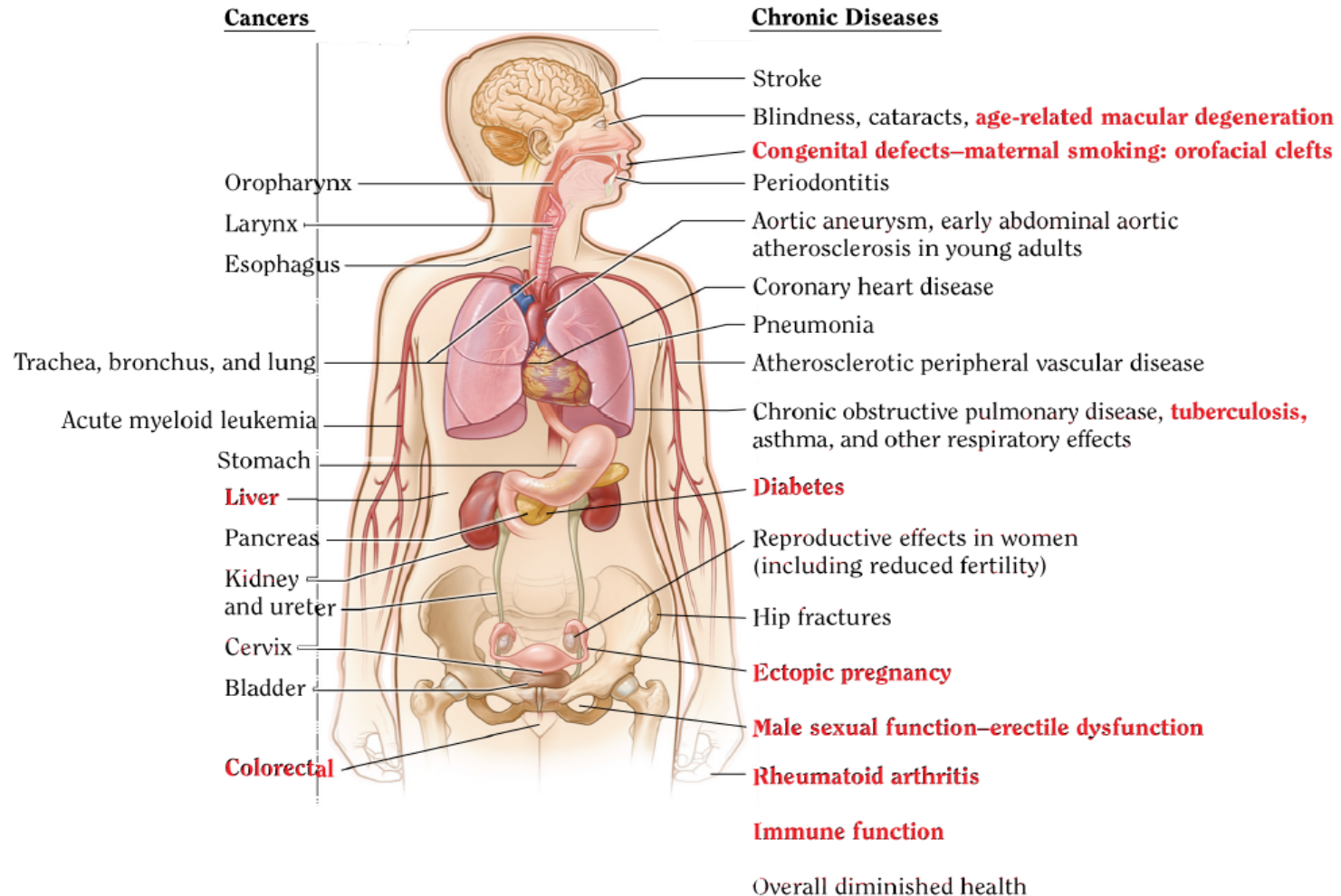
- Pathogenesis of tobacco induced cancer
 - Epidemiology and mechanism
 - Focus on lung and head and neck cancer
- Joint AACR/NCI efforts related to tobacco control
 - Tobacco use in patient's receiving treatment for cancer
 - Clinical trials
- New Approaches to treatment of tobacco induced disease- the lung cancer master protocol

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The Health consequences causally linked to smoking

Figure 1.1A The health consequences causally linked to smoking



Source: USDHHS 2004, 2006, 2012.

Note: The condition in red is a new disease that has been causally linked to smoking in this report.

Tobacco is the Single Largest Cause of Cancer in the World

- Tobacco use causes cancer in no less than 18 organ sites.
- Smoking causes more than 85% of lung cancers.
- One in three cancer deaths in the U.S. is directly linked to tobacco.
- The 2014 Surgeon Generals Report added the association of tobacco with hepatocellular and colorectal cancer

Tobacco causes cancer at 18 different organ sites

oral cavity,
oropharynx,
nasopharynx,
hypopharynx,
esophagus,
stomach,
colorectum,
liver,
pancreas,
nasal cavity and
paranasal sinuses,
larynx, lung,
uterine cervix,
ovary,
urinary bladder,
kidney, ureter,
and bone marrow
(myeloid leukemia)

Epidemiology of Tobacco-Related Cancers in the US, Estimated in 2012

Cancer type	# cases	# deaths
Lung	226,160	160,340
Head and neck*	52,610	11,500
Esophageal	17,460	15,070
Stomach	21,320	10,540
Pancreas	43,920	37,390
Kidney	64,770	13,570
Bladder	73,510	14,880
Uterus	47,130	8,010
Cervix	12,170	4,220
Colon/rectum	143,460	51,690
Ovary	22,280	15,500
AML	13,780	10,200

* larynx, oral cavity, nasopharynx, pharynx

Epidemiology of Tobacco-Related Cancers Worldwide in 2008

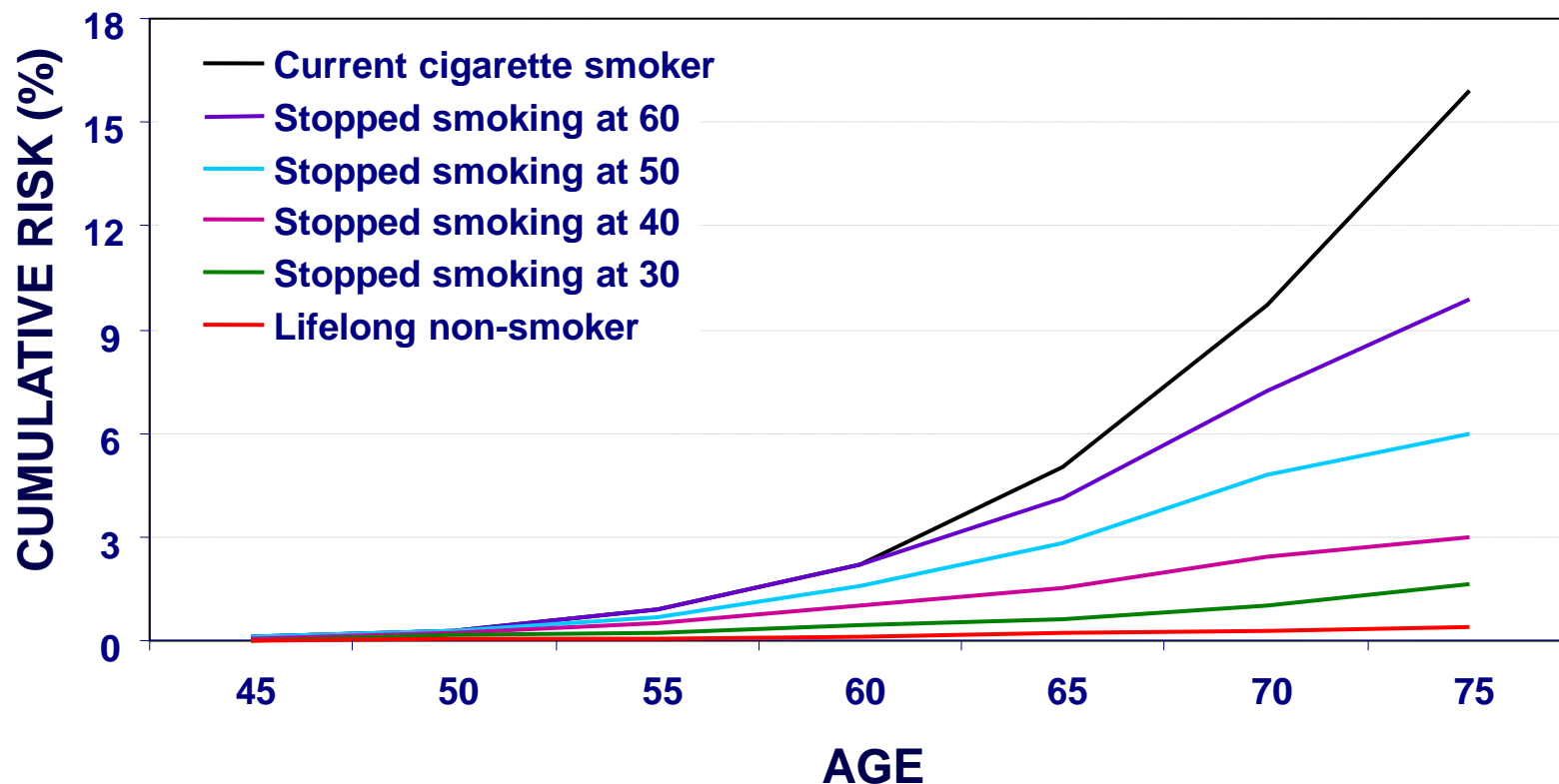
Cancer type	# cases	# deaths
Lung	1,606,911	1,375,919
Head and neck*	631,786	355,217
Esophageal	481,645	406,198
Stomach	987,904	736,976
Pancreas	278,470	266,543
Kidney	264,146	110,824
Bladder	382,130	150,143
Uterus	288,265	73,818
Cervix	529,601	274,668
Colon/rectum	570,795	288,323
Ovary	222,613	139,472

* larynx, oral cavity, nasopharynx, pharynx

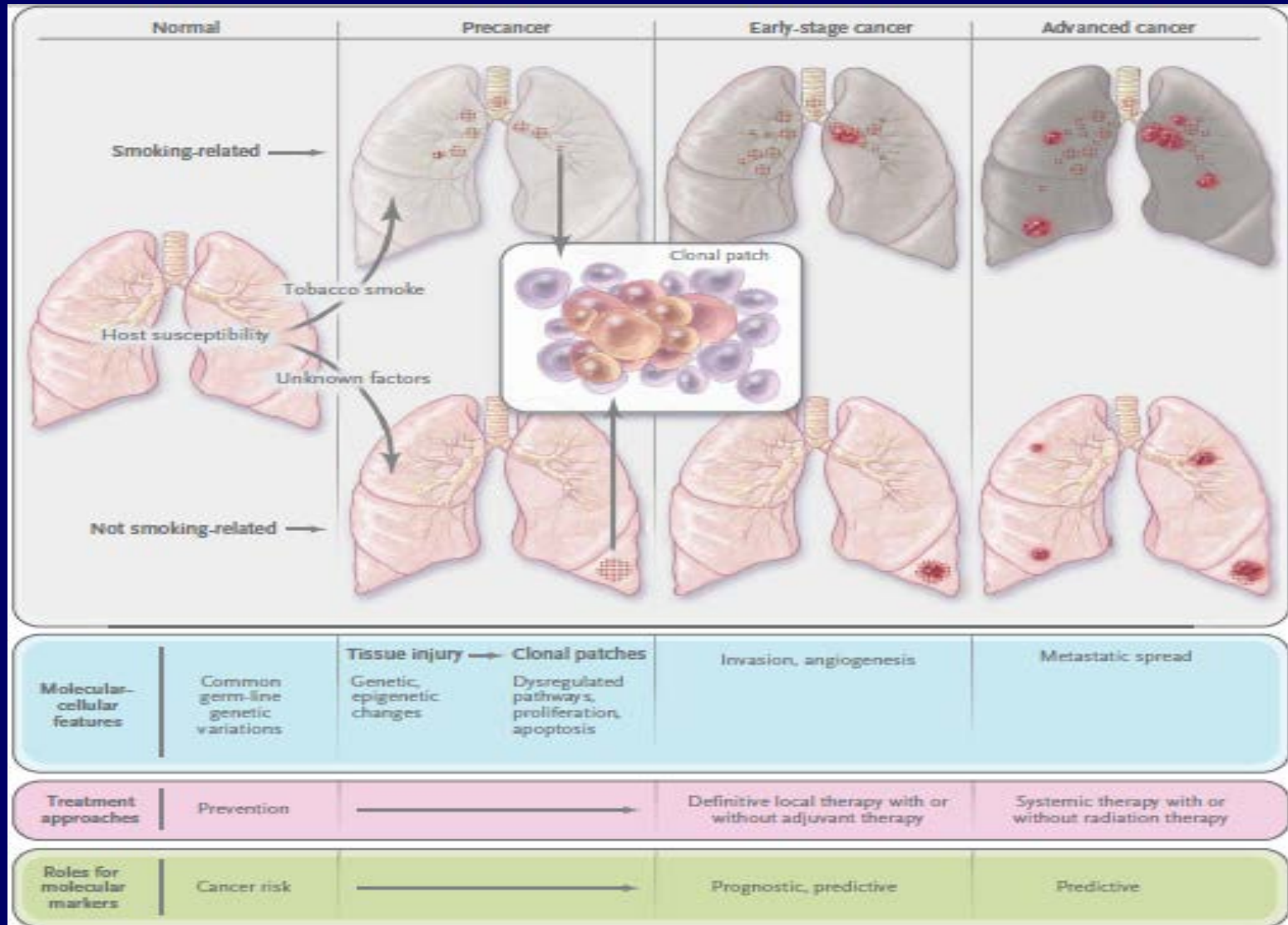
How Smoking Causes Cancer

- Cigarette smoke contains more than 7,000 compounds of which >60 are known carcinogens (600 added to enhance flavor/nicotine absorption)
- Inhaling this mix of chemicals induces tissue injury and changes in the cellular environment fostering the proliferation and transformation into cancer
- Mutations result in loss of normal growth control, silencing of tumor progression genes, and promotion of cancer
- Field effects, second (or more) primary cancers are common

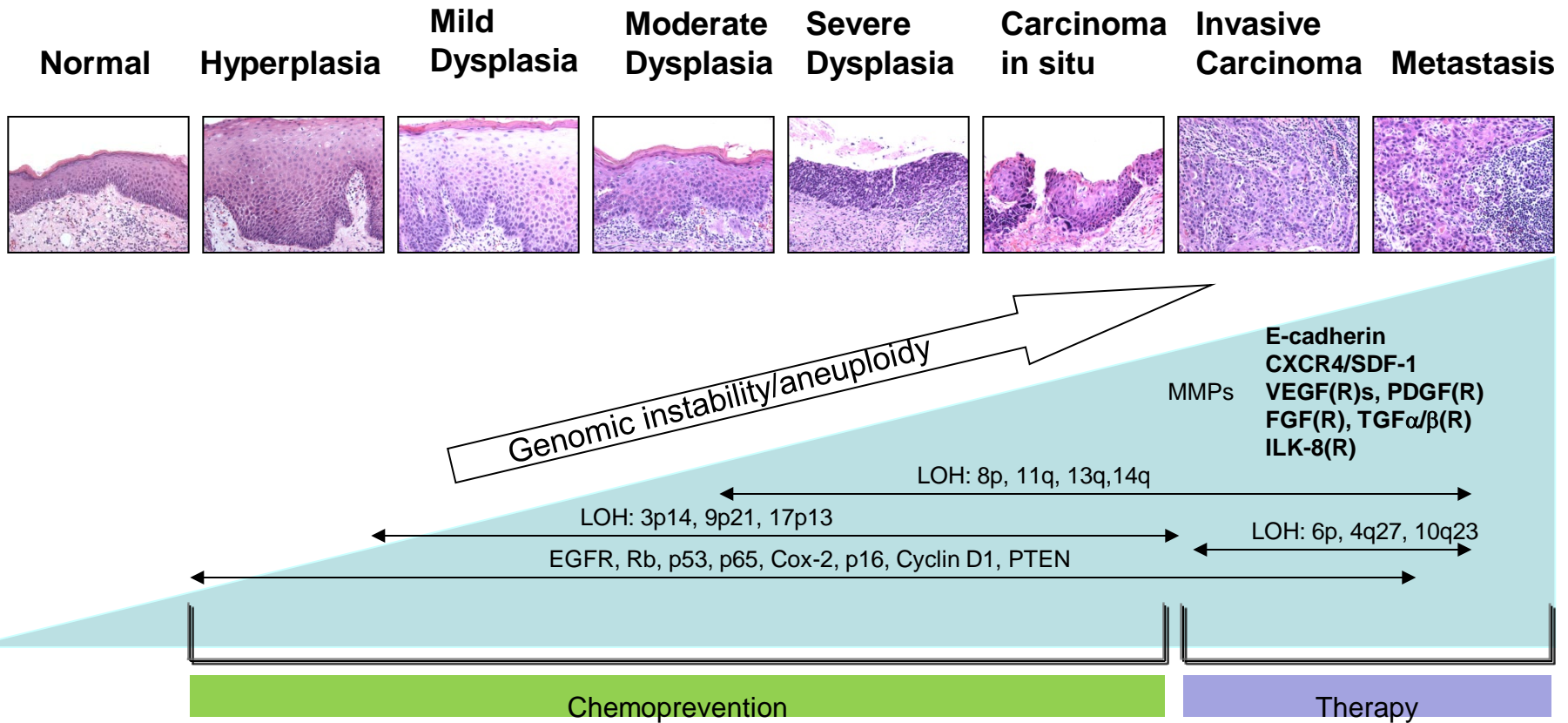
Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer by age 75 for men



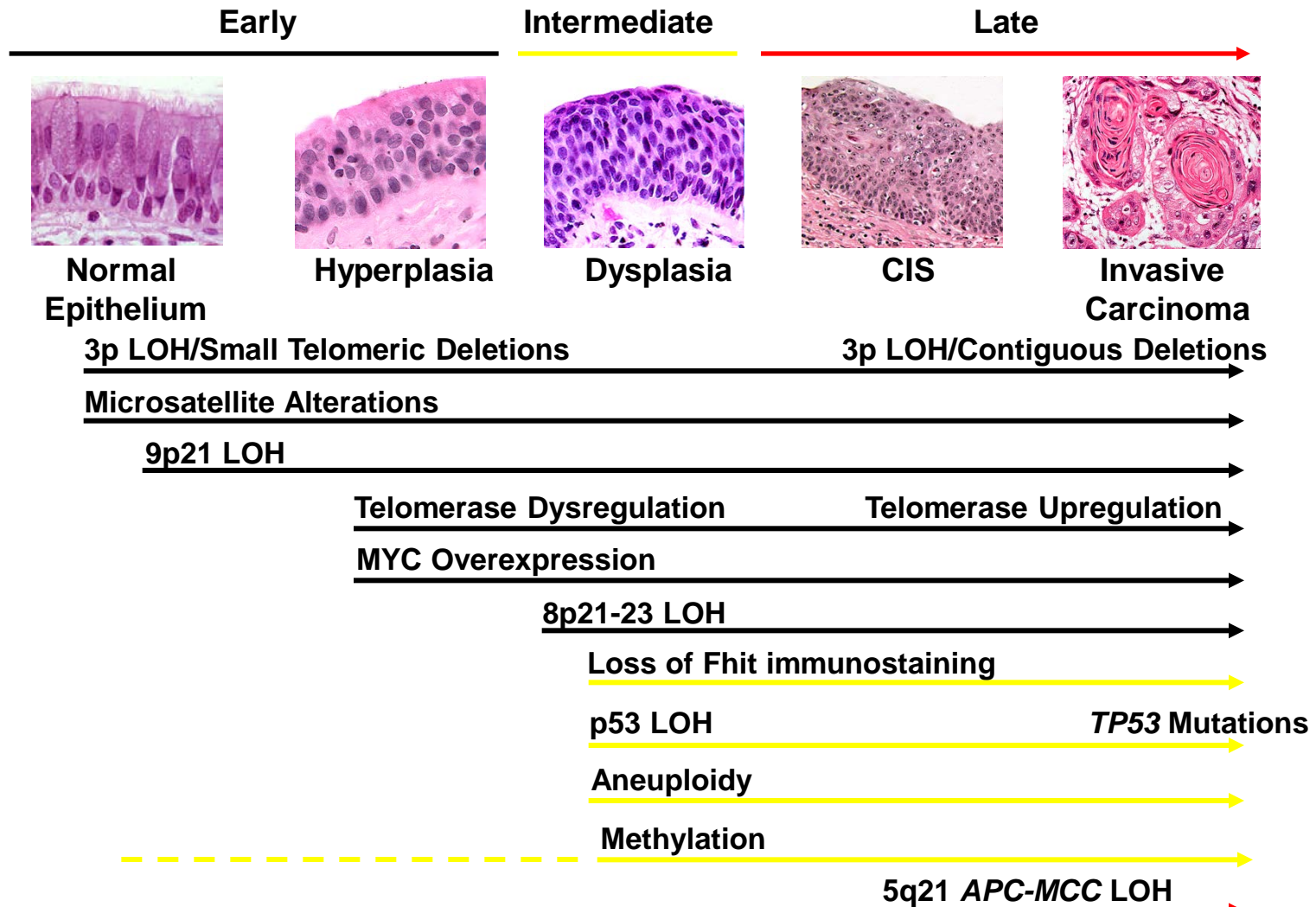
Molecular Carcinogenesis of Lung Cancer



Molecular Carcinogenesis of Head and Neck Cancer

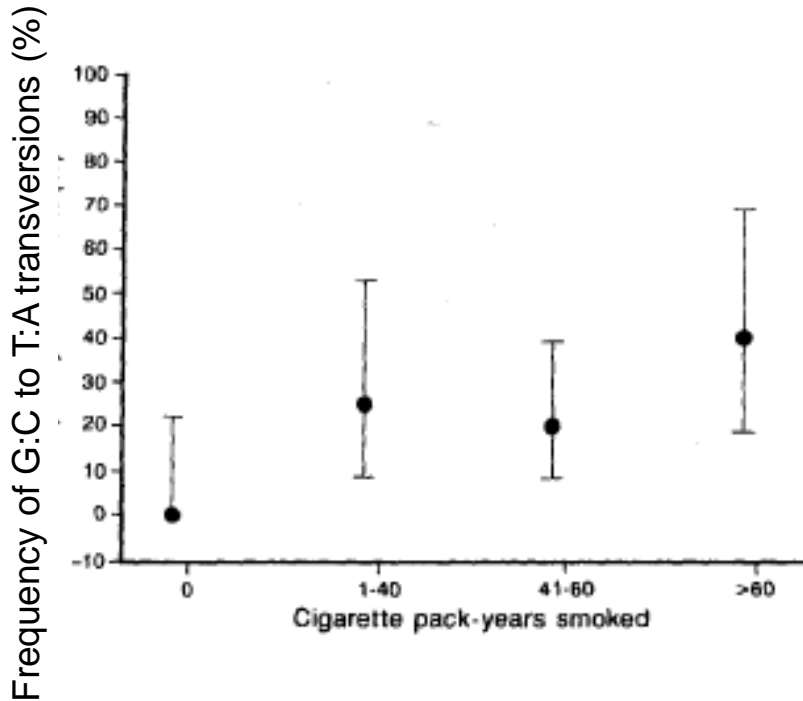


Complexity of Tobacco-Related Carcinogenesis



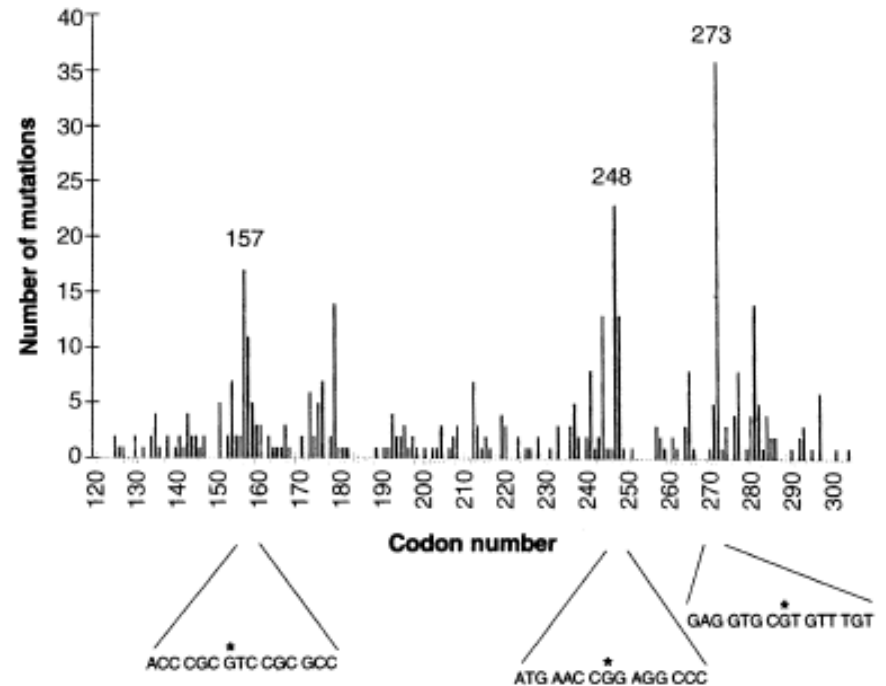
Cigarette Smoke Carcinogen Adducts at Lung Cancer Mutational Hotspots in P53

- Identification of p53 G:C to T:A mutations in lung cancer smokers



Takeshima et al. Lancet 1993; 342:1520-21

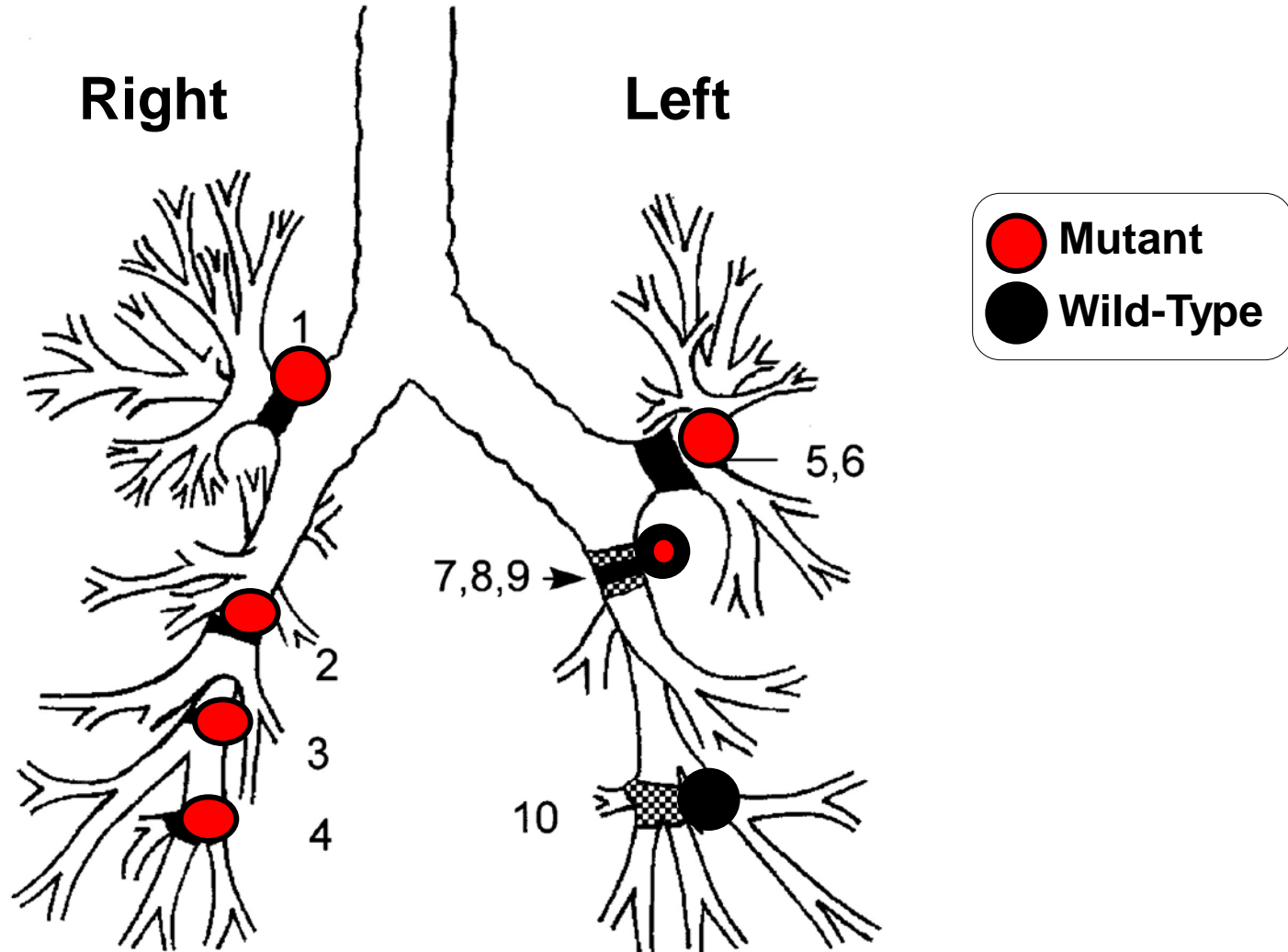
- Cigarette smoke carcinogen BPDE adducts in p53 mapped to guanines in codons 157, 248, and 273 - major mutational hotspots in human lung cancer



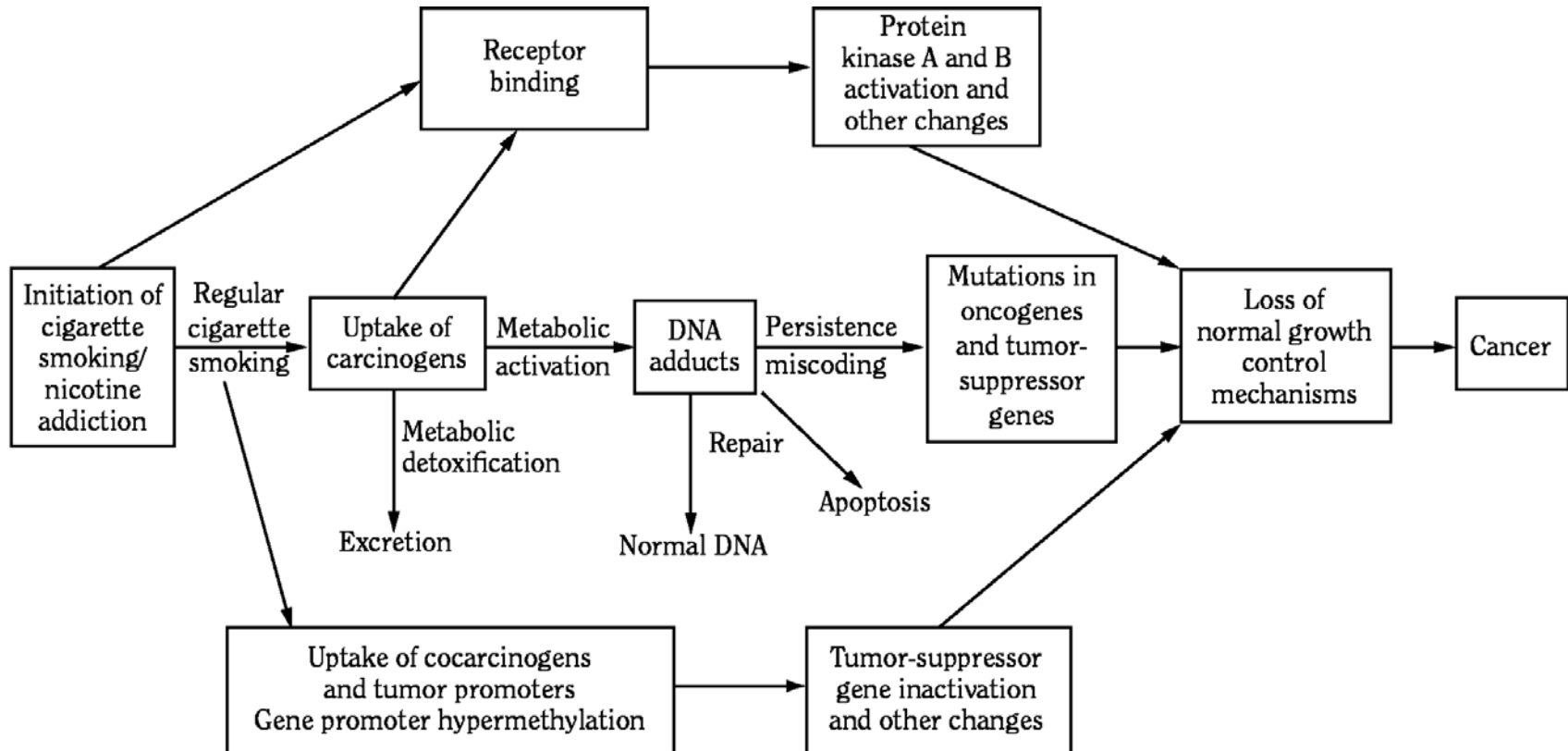
Dennisenko et al. Science 1996;274:430-432.

Widespread Dispersed p53 Mutation in Respiratory Epithelium of a Smoker

66-yr-old
Smoker – Male
TP53 Mutation
Codon 245
(G:C to T:A)



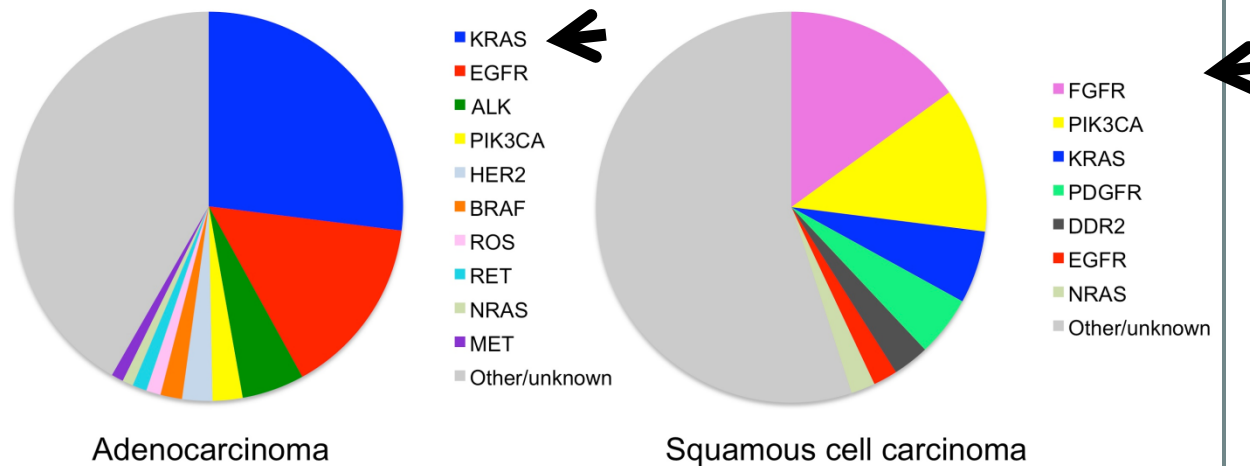
Link between Cigarette Smoking and Cancer through Carcinogens in Tobacco Smoke



Lung Cancer Mutation Consortium: Squamous Cell Cancers also have driver mutations

Genetic Profiles by Histologic Subtype

Oncogenic drivers differ between adenocarcinomas and squamous cell carcinomas



Sequist et al., Ann Oncol 22:2616, 2011; Bergethon et al., JCO Jan 3, 2012; Weiss et al., Sci Transl Med 2:62ra93, 2010; Kris et al., WCLC 2011; Hammerman et al., Cancer Discovery 1:78, 2011; AJ lafrate, personal communication

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- Pathogenesis of tobacco induced cancer
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Tobacco and Cancer: An AACR Policy Statement

- Includes research and policy recommendations for:
 - Preventing tobacco use
 - Treating tobacco addiction and fostering cessation
 - Reducing exposure to second hand smoke
 - Addressing tobacco-related cancer

Published OnlineFirst April 13, 2010; DOI: 10.1158/0008-5472.CAN-10-1087

Cancer Research

AACR American Association
for Cancer Research

**Tobacco and Cancer: An American Association
for Cancer Research Policy Statement**

Kasisomayajula Viswanath, Roy S. Herbst, Stephanie R. Land, Scott J. Leischow, and
Peter G. Shields; Writing Committee for the AACR Task Force on Tobacco and Cancer

Executive Summary

The evidence against tobacco use is clear, incontrovertible, and convincing; so is the need for urgent and immediate action to stem the global tide of tobacco-related death and suffering and to improve public health.

The American Association for Cancer Research makes an unequivocal call to all who are concerned about public health to take the following immediate steps:

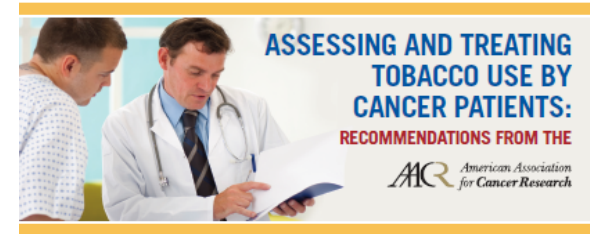
- Increase the investment in tobacco-related research, commensurate with the enormous toll that tobacco use takes on human health, to provide the scientific evidence to drive the development of effective policies and treatments necessary to dramatically reduce tobacco use and attendant disease.
- Develop new evidence-based strategies to more effectively prevent the initiation of tobacco use, especially for youth and young adults.
- Promote the further development of evidence-based treatments for tobacco cessation, including individualized therapies, and ensure coverage of and access to evidence-based behavioral and pharmacological treatments.
- Develop evidence-based strategies for more effective public communication to prevent, reduce, and eliminate tobacco use and to guide health policies and clinical practice.
- Develop effective, evidence-based policies to reduce disparities across the tobacco continuum among social groups and developed and developing nations.
- Implement to the fullest extent existing evidence-based, systems-wide tobacco control programs to prevent initiation and foster cessation. Adapt and implement appropriate approaches to reduce the growing burden of tobacco use in the developing world.
- Enhance and coordinate surveillance efforts, both in the United States and globally, to monitor tobacco products, tobacco use, and tobacco-related disease, including tobacco use in oncology clinical trials.
- Establish a comprehensive, science-based regulatory framework to evaluate tobacco products and manufacturers' claims.
- Promote research that addresses the following: the potential harms of current and new tobacco products; the impact of altering the levels of addictive components in tobacco products; the identification of risk and risk-reduction measures for current and former tobacco users; enhanced early detection methods for tobacco-related cancers; and effective treatments against tobacco-related cancers tailored to the unique effects of tobacco on cancer.
- Pursue domestic and international economic policies that support tobacco control.
- Urge the United States to ratify the World Health Organization Framework Convention on Tobacco Control. Foster global scientific efforts to support the Framework.
- Work together with stakeholders worldwide, including federal agencies, to develop and implement effective tobacco control strategies and to deter counter-tobacco control efforts by the tobacco industry.

Only such concerted global actions by scientists, policymakers, and advocates together can prevent the invidious impact of tobacco, the use of which is cutting wide swathes of death and disease around the world.
Cancer Res 70(9): 3419-30. ©2010 AACR.

www.aacrjournals.org **AACR** American Association for Cancer Research 3419

Assessing Tobacco Use by Cancer Patients and Facilitating Cessation: An AACR Policy Statement

- Primary recommendations:
 - Provide patients in all clinical cancer settings, including clinical trials, with evidence-based tobacco cessation assistance
 - Evaluate the confounding effects of tobacco on cancer treatment, disease progression, comorbid events, and survival in all oncology clinical trials from registration to survival endpoints.



It is never too late to quit. When diagnosed with cancer, patients can immediately make a meaningful positive impact on their health by stopping their tobacco use. The evidence is clear that tobacco use by patients with cancer decreases the effectiveness and safety of cancer treatments, decreases survival, decreases quality of life, increases treatment-related toxicity and increases risk of cancer recurrence and second primary tumors.

Evidence-based tobacco cessation interventions are infrequently offered in oncology settings despite data suggesting that tobacco cessation can improve outcomes and survival in patients with cancer.

Therefore, the American Association for Cancer Research suggests the following:

RECOMMENDATIONS

- 1 Patients with cancer from all clinical settings, including clinical trial participants and cancer screening patients, who use tobacco or have recently quit should be provided with evidence-based tobacco cessation assistance.**
 - Assistance should be provided to current users and recent quitters (past 30 days)
 - Assistance should be provided within or associated with the oncology practice
 - The oncology service provider should assume responsibility for ensuring that the patient receives appropriate care
 - Oncology provider assistance can be supplemented with telephone quitline care by having patients call 1-800-QUIT-NOW
- 2 Researchers should evaluate the confounding effects of tobacco on cancer treatment, disease progression, comorbid events and survival in all oncology clinical trials, from registration to survival endpoints.**

- Implementation of these recommendations will require:**
- Universal assessment and documentation of tobacco use by cancer patients in all clinical settings, including cancer clinical trials, and cancer screening patients
 - Development of universal standards for measurement of tobacco use and exposure in clinical and research settings
 - Incorporation of evidence-based tobacco interventions into review criteria used by research and health care quality and accreditation bodies
 - Recognition and support of the value of tobacco cessation interventions by health systems, payers and research funders through provision of appropriate incentives for infrastructure development and intervention delivery

The full AACR policy statement can be accessed at:
tiny.cc/AACR2013Tobacco

Problem (Clinical)

Cancer patients and survivors who smoke cigarettes have worse health outcomes (including higher all-cause and cancer-specific mortality, and risk of tobacco-related second primary cancer).

Smokers may have higher risk of recurrence, poorer response to treatment, and increased toxicity.

Clinical significance of smoking by cancer patients

- Relative risk of all-cause mortality*
 - Current smokers 1.5 (relative to never smokers)
 - Former smokers 1.3
- Relative risk of cancer-specific mortality**
 - Current smokers 1.6 (relative to never smokers)
 - Former smokers 1.05

Problem

There are many scientific questions related to tobacco use in the cancer patient population.

Current approaches to data collection:

- Not widely assessed in trials or practice
- Inconsistent tobacco use assessment methods
- Little follow-up during/after treatment

Current practice

- NCI-Designated Cancer Centers
 - < 50% include tobacco use as a vital sign in the medical record
- NCI-funded phase III Cooperative Group trials
 - 22% record cigarette smoking status at enrollment, and
 - 4% during follow-up.

Goldstein, NTR, 2012; Warren, IJC, 2012

NCI-AACR Cancer Patient Tobacco Use Assessment Task Force

- History
 - Formed March, 2013
 - Conference calls, writing groups, and in-person meeting September 2013 (Bethesda)
- Goal
 - Develop recommendations for assessing and documenting tobacco use in clinical trials
 - Identify research priorities
- Progress
 - Drafted two tiers of measurement items and protocol for the timing and conduct of the assessment in cancer clinical trials.
 - Tier 1: minimum set of baseline and follow-up items recommended for clinical trials in any cancer patient or survivor study.
 - Tier 2: longer menu of curated items for use when more comprehensive assessment is feasible.
 - Items focus on tobacco use history, status, and intensity
 - Recommended assessment items for specific NCTN trials in development

Draft recommended measures

Tier 1 (minimal) paraphrased

Baseline:

- Ever smoked 100+ cigarettes in lifetime?
- How long since smoked?
- How many years smoked?
- Average number of cigarettes per day?

Follow-up:

- How long since smoked?

Task Force Roster

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Nancy Rigotti, MD

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Robert A. Schnoll, PhD

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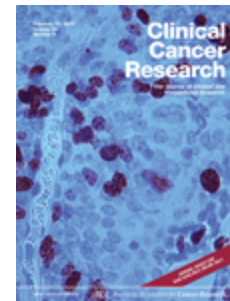
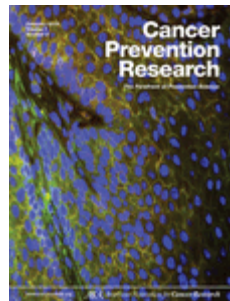
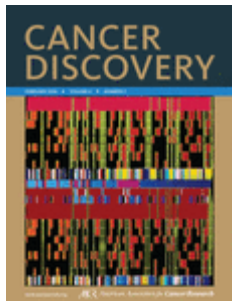
Benjamin Toll, PhD

K. (Vish) Viswanath, PhD

Graham Warren, MD, PhD



- Research and review articles published in AACR journals
- Editorial Overview: *AACR Celebrates 50 Years of Tobacco Research and Policy*
- Commentary from Howard Koh
- Q&As with Howard Koh and Mitchell Zeller



Tobacco Science and Policy at AACR Annual Meeting 2014

- Honoring the 50th Anniversary Surgeon General's Report—*The Health Consequences of Smoking: 50 Years of Progress*
Speakers: Roy S. Herbst, Jonathan Samet, Graham Warren, Robert Croyle, Mitchell Zeller
- Advancing Tobacco Regulatory Science: Meet Experts in FDA CTP
Speakers: Carolyn M. Dresler, Cathy L. Backinger, Dana M. van Bemmelen, Nicolette Borek



AACR-ASCO Policy Statement on Electronic Cigarettes

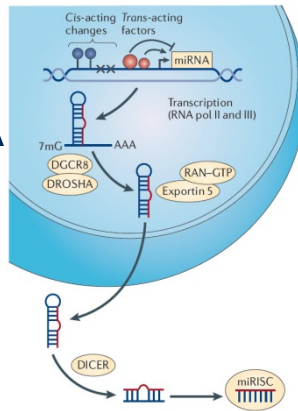
- Subcommittee of AACR and ASCO members
- Statement will include recommendations for
 - Research
 - Clinical practice
 - Regulation



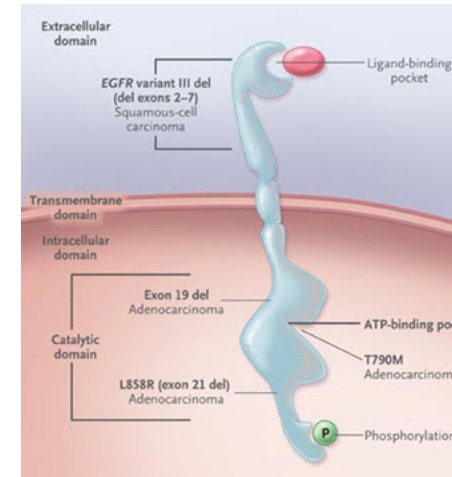
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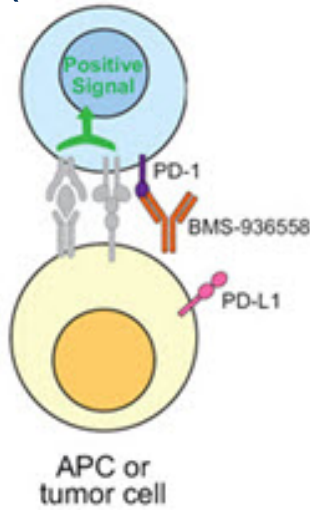
Targeting microRNA



Targeting EGFR Resistance

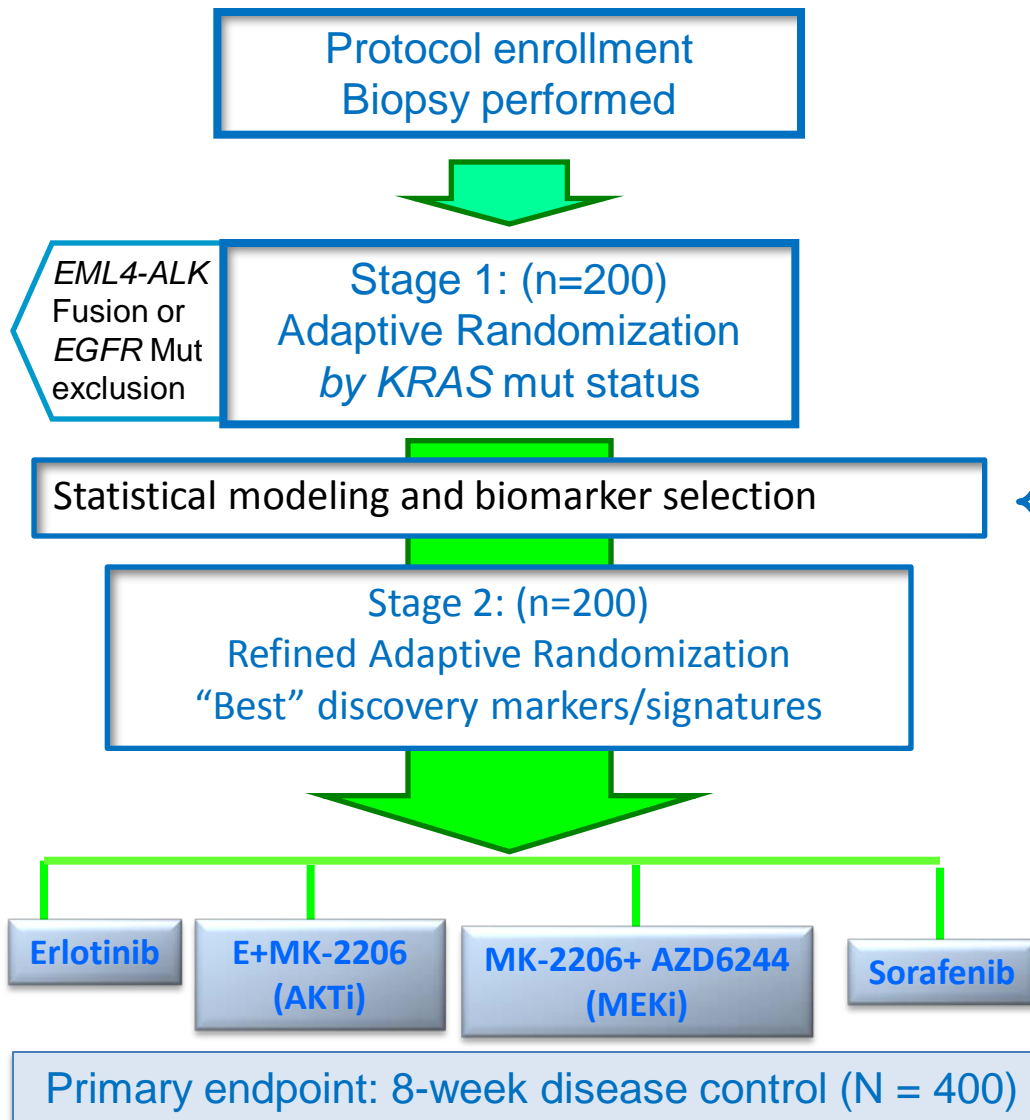


Targeting PD-1/B7-H1 (PD-L1)



Targeting lung cancer risk characteristics for personalized prevention by smoking cessation

BATTLE-2 – Targeting Kras

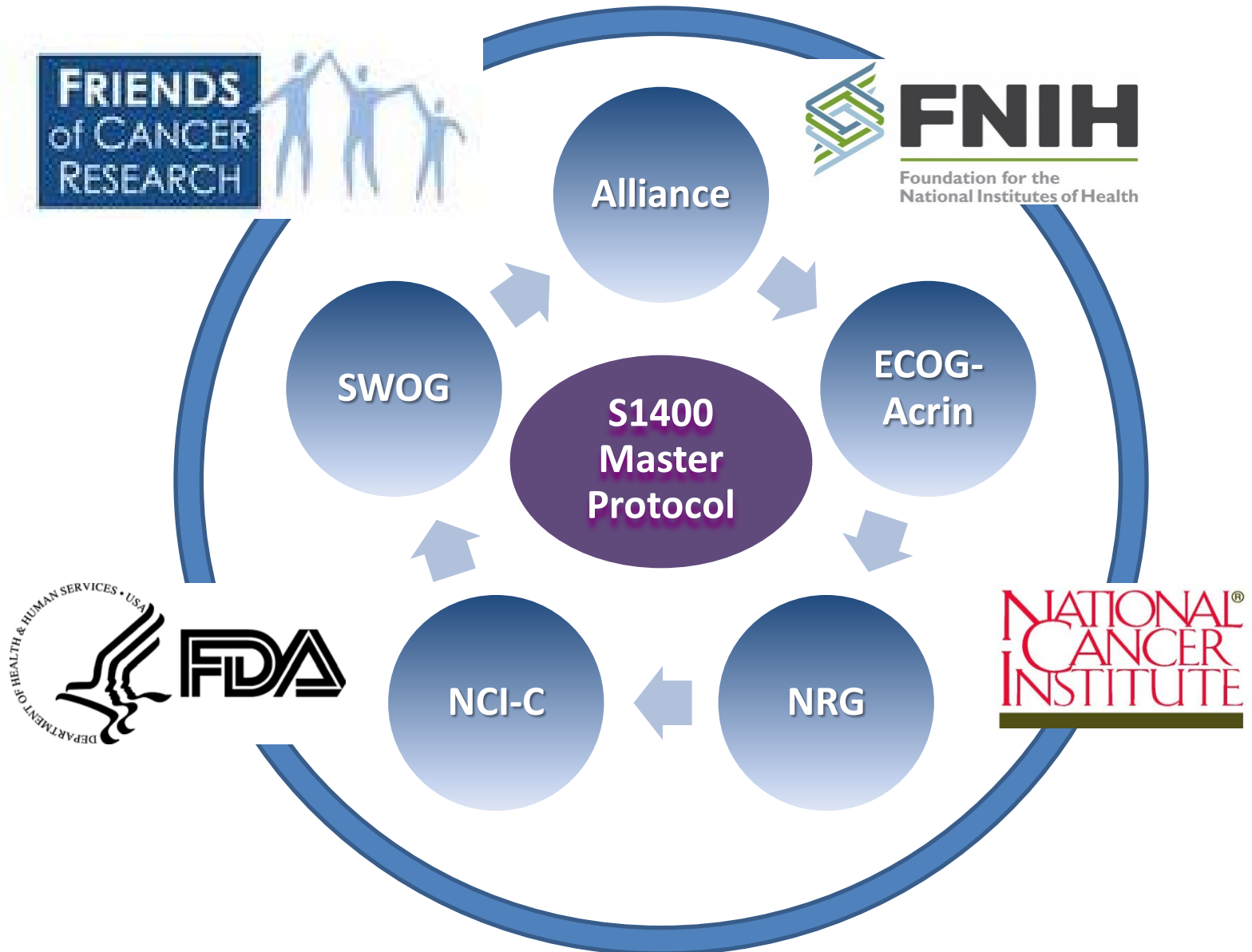


Discovery Markers:

- Protein expression (IHC): p-AKT (Ser473), PTEN, HIF-1 α , LKB1
- Mutation analysis (Sequenom): *PI3KCA*, *BRAF*, *AKT1*, *HRAS*, *NRAS*, *MAP2K1* (MEK1), *MET*, *CTNNB1*, *STK11* (LKB1)
- mRNA pathways activation signatures: Affymetrix®
 - BATTLE-1: WT-*EGFR*- Erlotinib, EMT, and Sorafenib
 - BATTLE-2: new “discovery” signatures
- Protein profiling – RPPA (n=174)
- NGS-Foundation Medicine
- RNA sequencing

S1400 Master Protocol

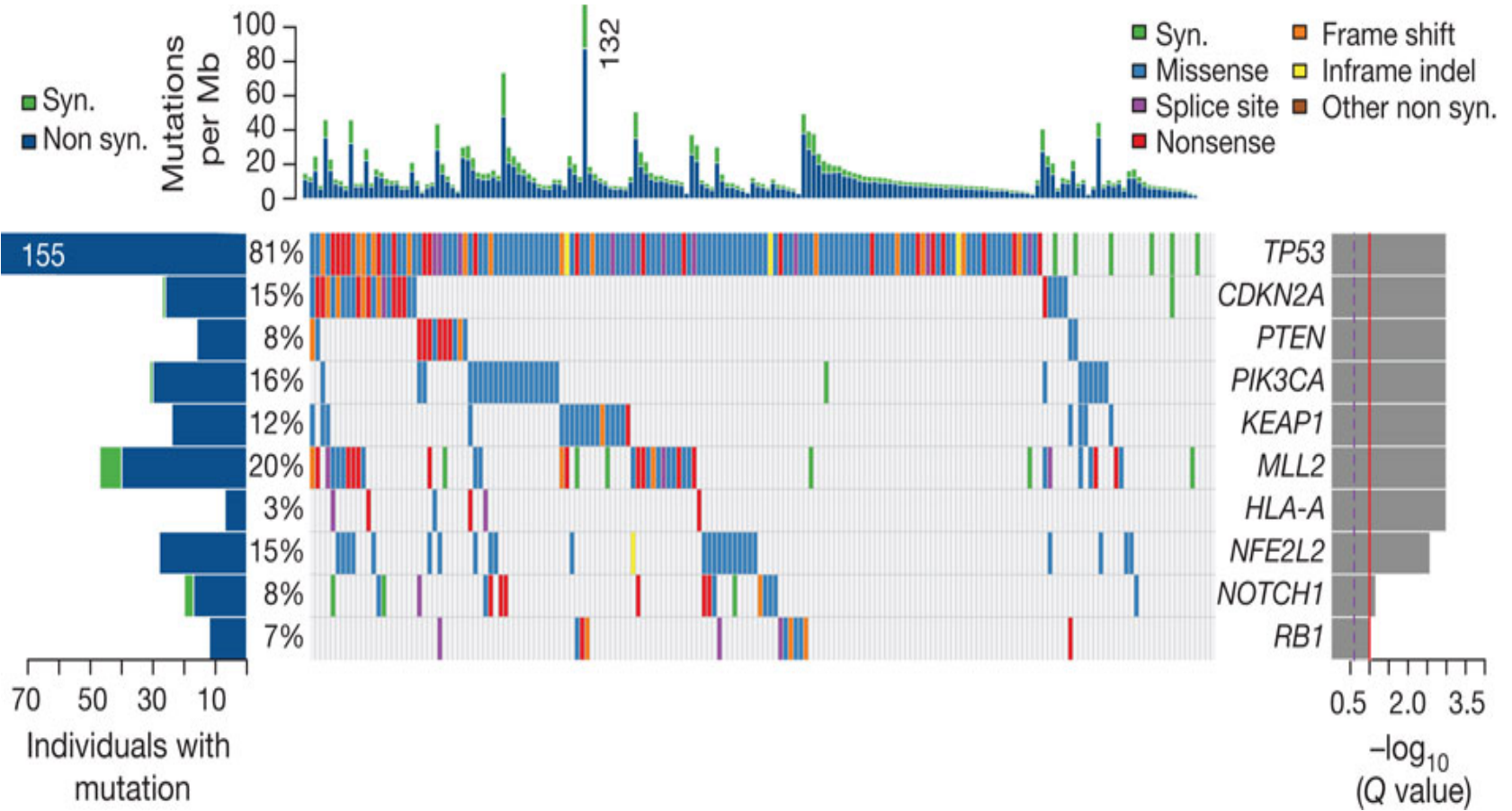
Unique Private-Public Partnerships with the NCTN



Rationale for Master Protocol Design

- **Multi-arm Master Protocol**
 - Homogeneous patient populations & consistent eligibility from arm to arm
 - Each arm independent of the others
 - Infrastructure facilitates opening new arms faster
 - **Phase II-III design** allows rapid drug/biomarker testing for detection of “large effects”
- **Screening** large numbers of patients for multiple targets by a broad-based NGS platform reduces the screen failure rate
- Provides a **sufficient “hit rate”** to engage patients & physicians
- **Bring safe & effective drugs to patients faster**
- Designed to facilitate **FDA approval** of new drugs

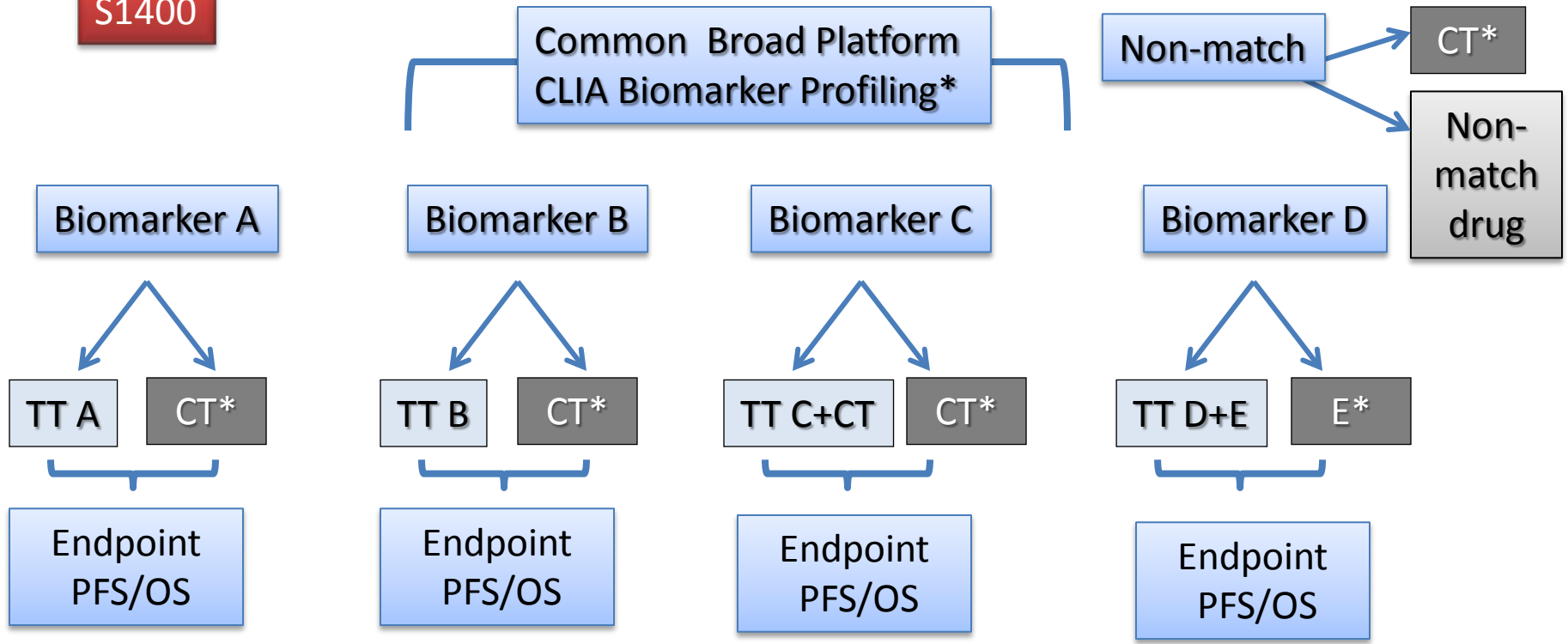
Significantly mutated genes in lung SQCC.



PS Hammerman *et al. Nature* **000**, 1-7 (2012) doi:10.1038/nature11404

MASTER PROTOCOL

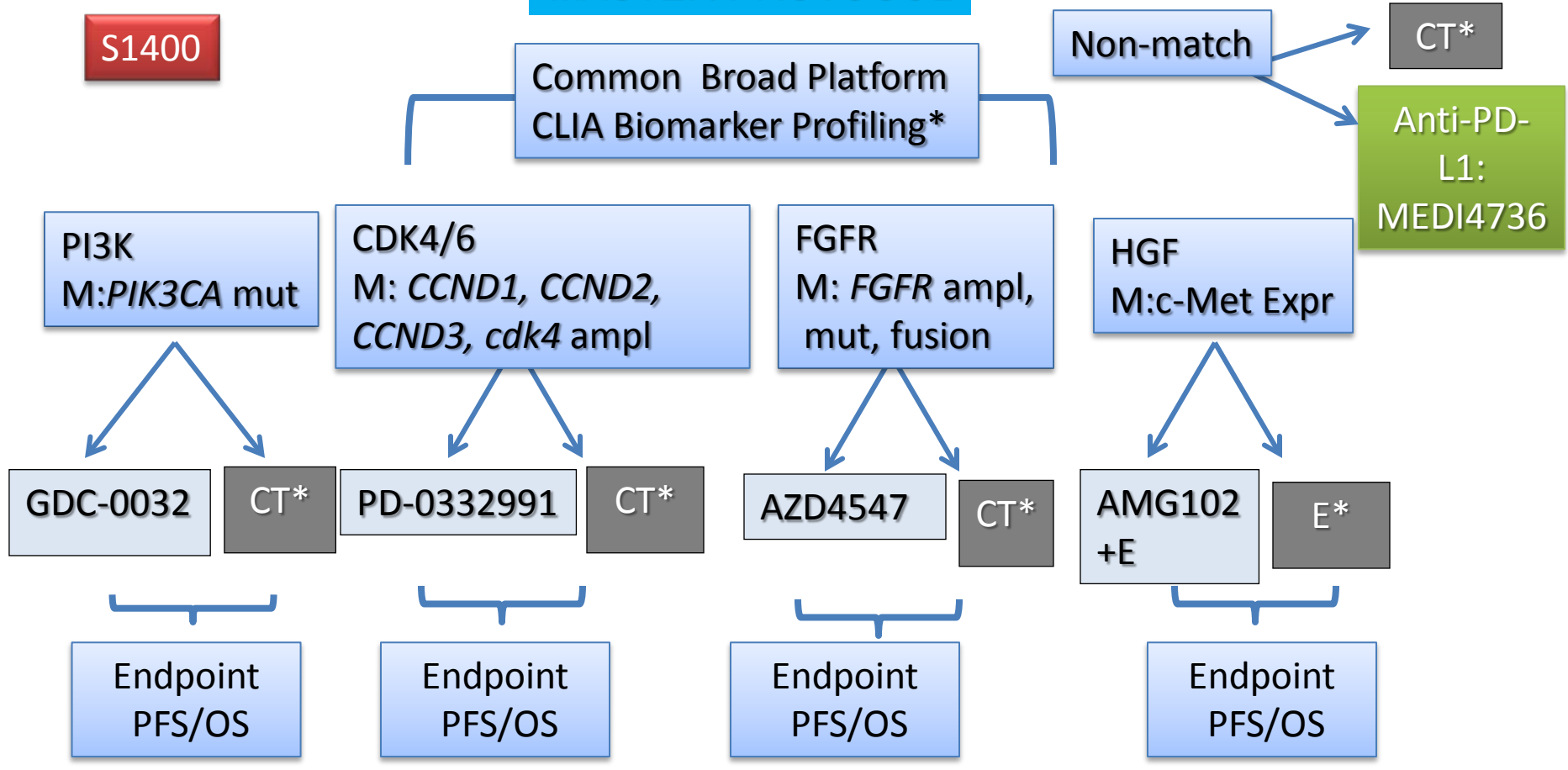
S1400



Phase II/III Biomarker-Driven Master Protocol for Second Line Therapy of Squamous Cell Lung Cancer

MASTER PROTOCOL

S1400

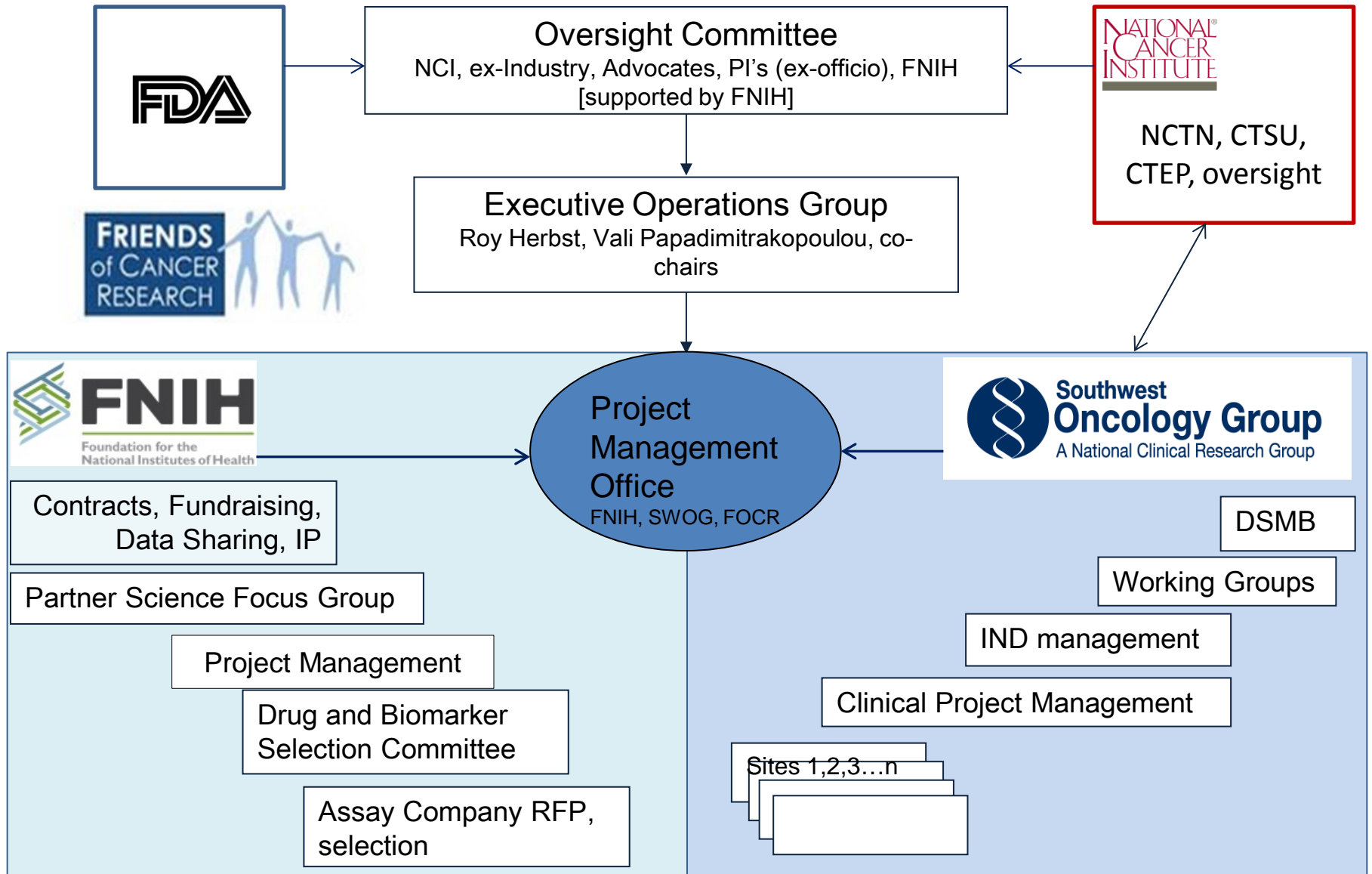


TT=Targeted therapy, CT=chemotherapy (docetaxel), E=erlotinib

*Archival FFPE tumor, fresh CNB if needed

Target/M: Drug target and biomarker

The Lung Master Protocol trial will be managed with multiple partners



Conclusions

- Association of tobacco with cancer is well documented
- Unique concerns in patient's getting therapy for cancer- issues being addressed
- While primary and secondary prevention is of course critical- better therapeutic options/trial designs for smoking related cancers are underway

THANK YOU!

