Lung Cancer, Radon and New Strategies

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Oct 24, 2022

Outline

- Dramatic Evolution of Lung Cancer Understanding
  - Precision Medicine, Genetics and Immunology
  - New Diagnosis and Treatment (many types of lung cancer)
  - Smoker and non-smoker
- Radon-induced Lung Cancer
  - What we do and don't understand
- Strategies to merge and extend new diagnostics
  - Clinically identify Radon Induced Lung Cancer

Radon-induced Lung Cancer

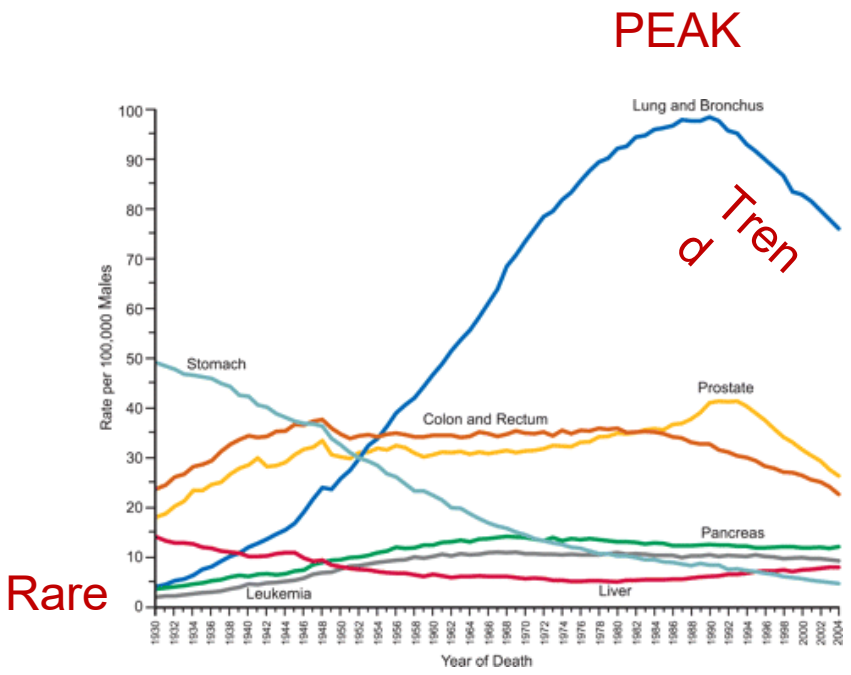
- Radon is Radiation
- Lung cancer is the reason we identify + mitigate radon
  - Smoking
  - Avoid asbestos, radiation, heavy metals, etc
- Statistics are real people
- Those involved in Awareness/Mitigation save lives

Invisible Ribbon

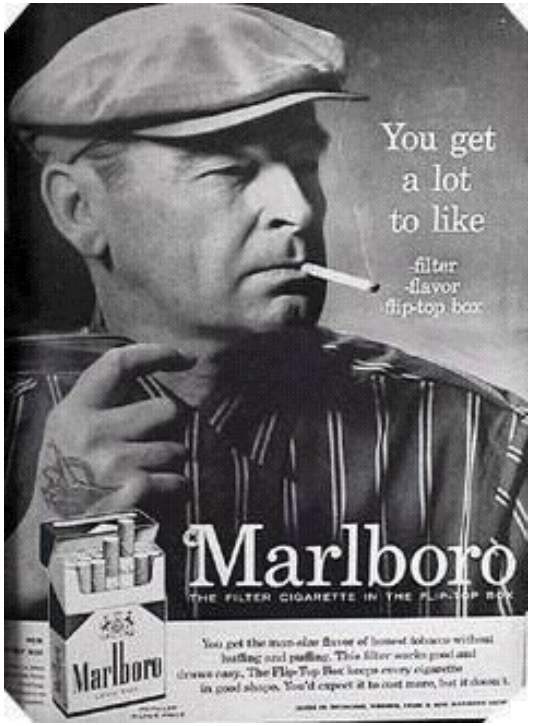
- Lung Cancer – Unrecognized
- Invisible Killer
- Number 1 Cancer Mortality in the USA
- Lacks Advocacy (lethality)
- Guilt (Tobacco)

A L C A S E

USA Cancer Mortality



– #1 Cause of cancer death (nationally and Utah)
– Improving Mortality Trend
– Has the potential to be a rare cancer again



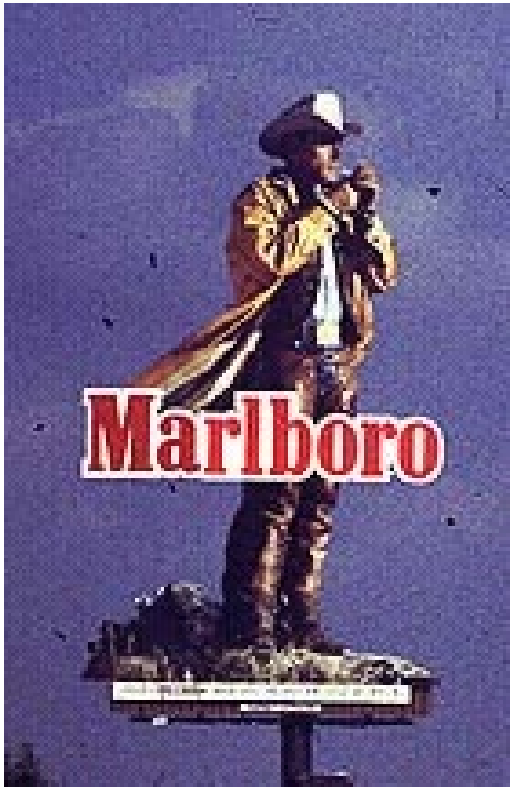
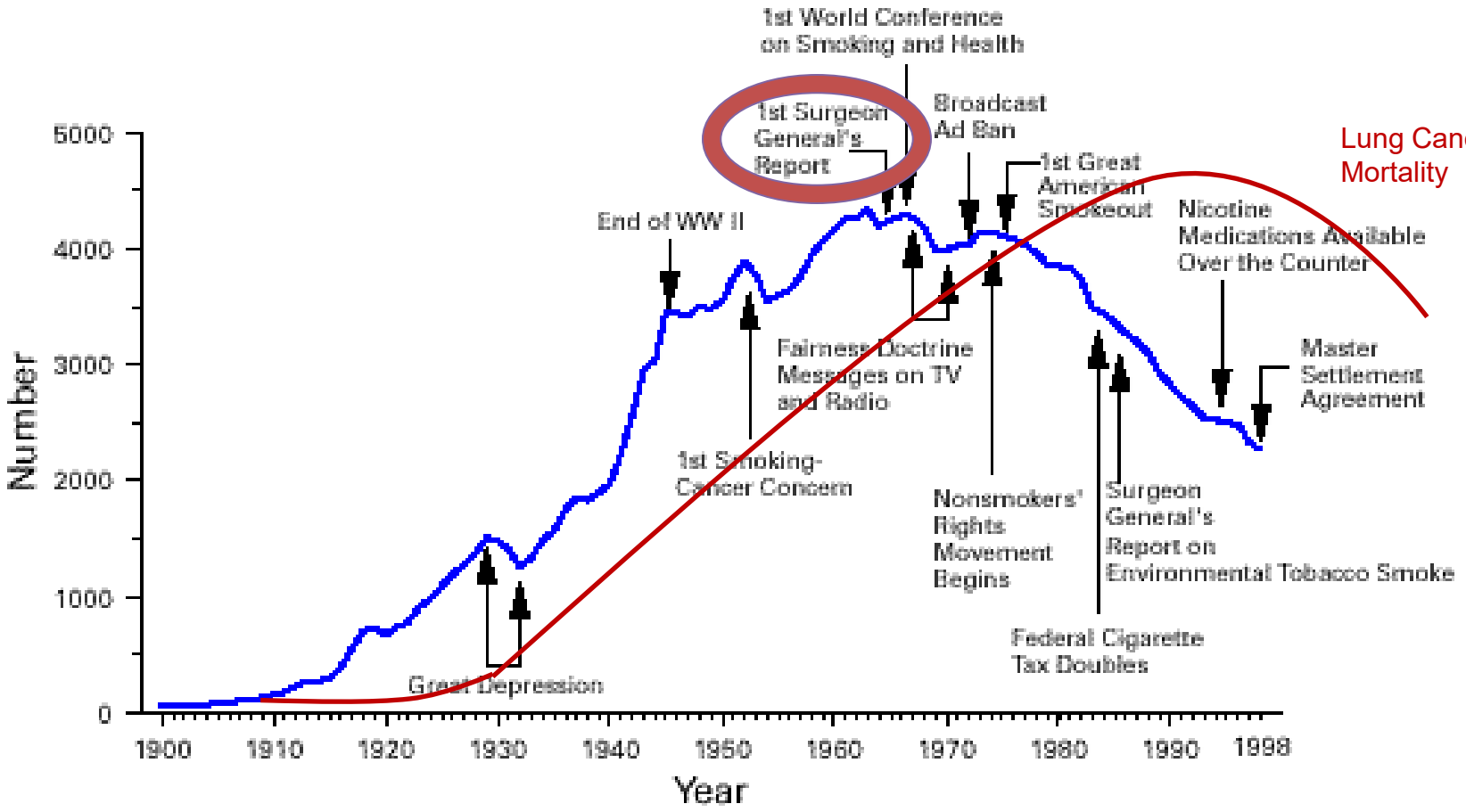


FIGURE 1. Annual adult per capita cigarette consumption and major smoking and health events — United States, 1900–1998



Sources: United States Department of Agriculture; 1986 Surgeon General's Report.

Lung Cancer

Smoking

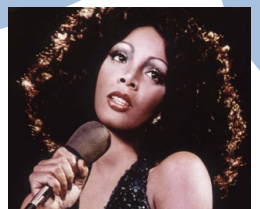
Radon

Non-Smoker

JOAN'S LEGACY

CanSAR™

Cancer Survivors Against Radon



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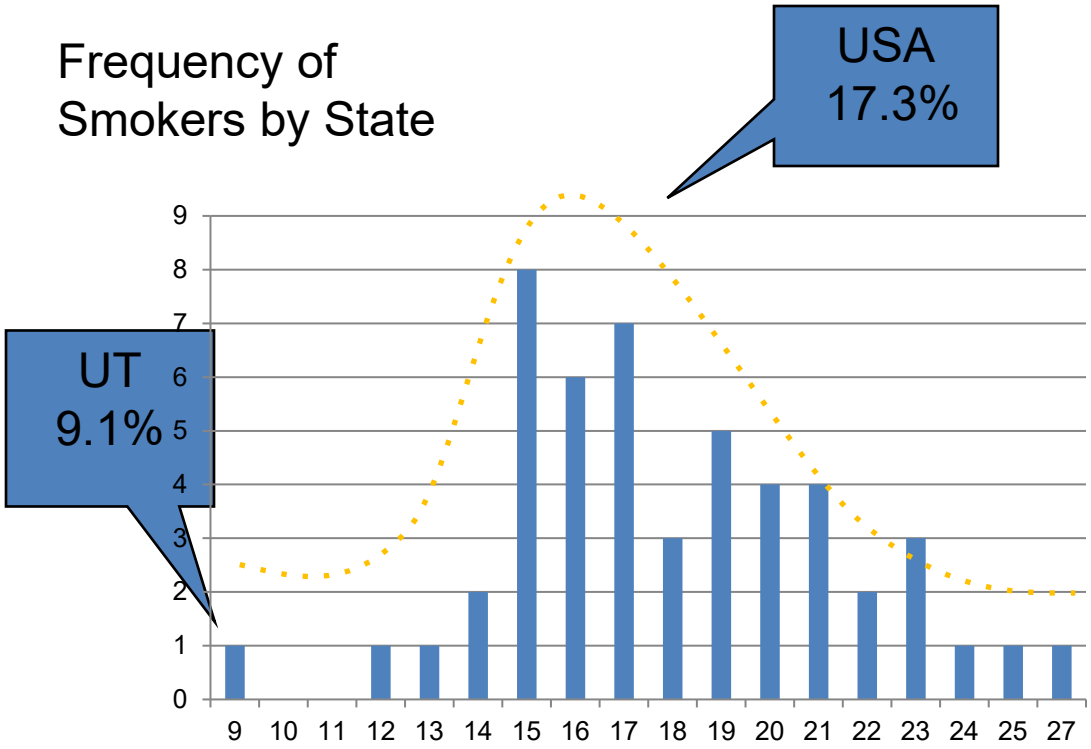
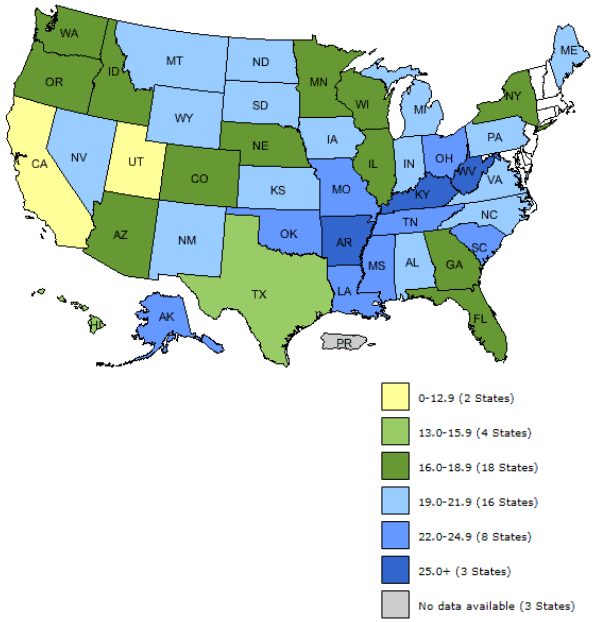
Example of Low Smoke State (Utah)

Frequency of Smokers by State



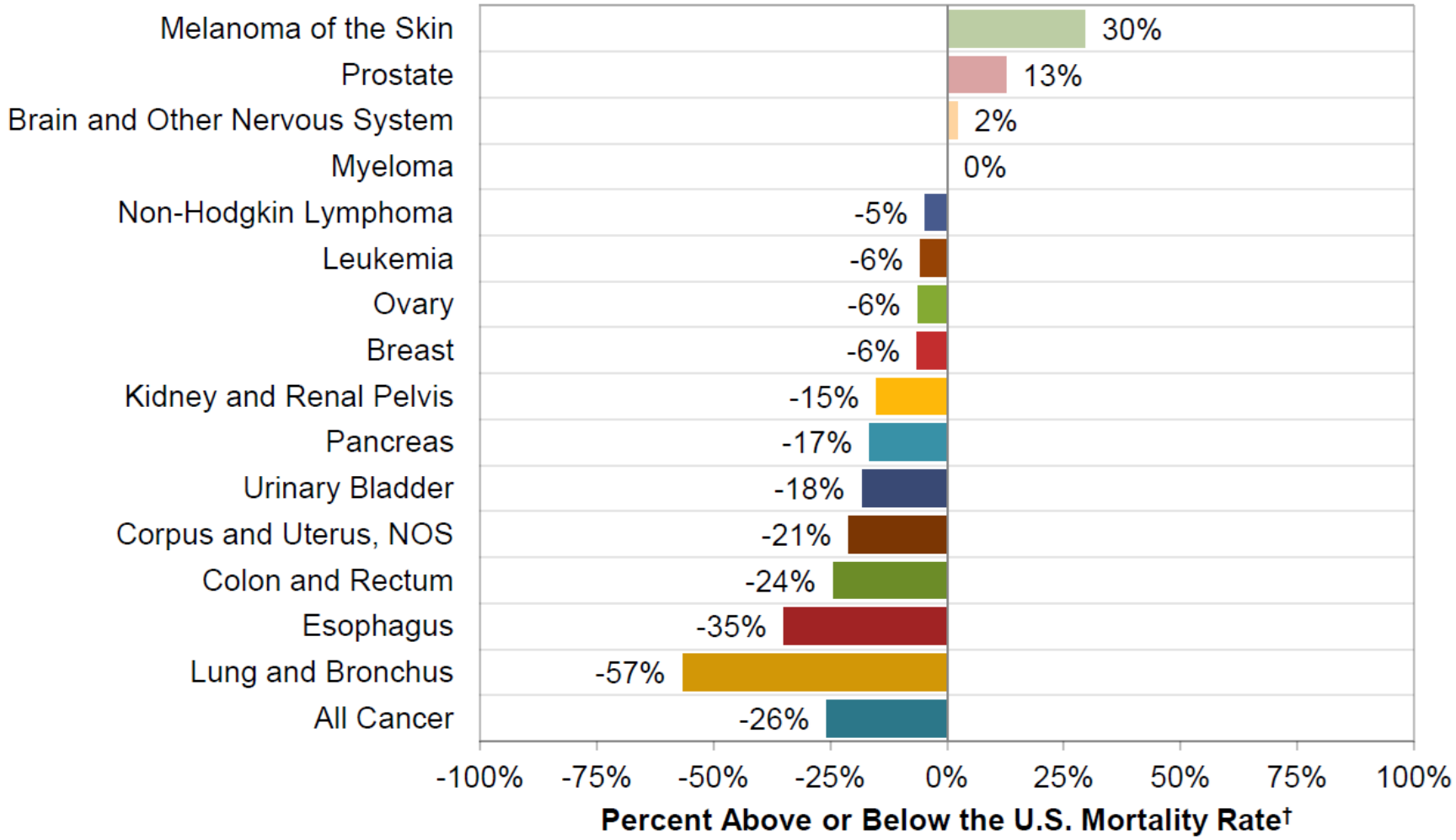


5.8% in Provo-Orem

CDC: BRFSS 2010

MMWR / May 31, 2013 / Vol. 62

Utah Lung Cancer Mortality compared to USA



Harrell et al. Utah Cancer Registry, 2014.

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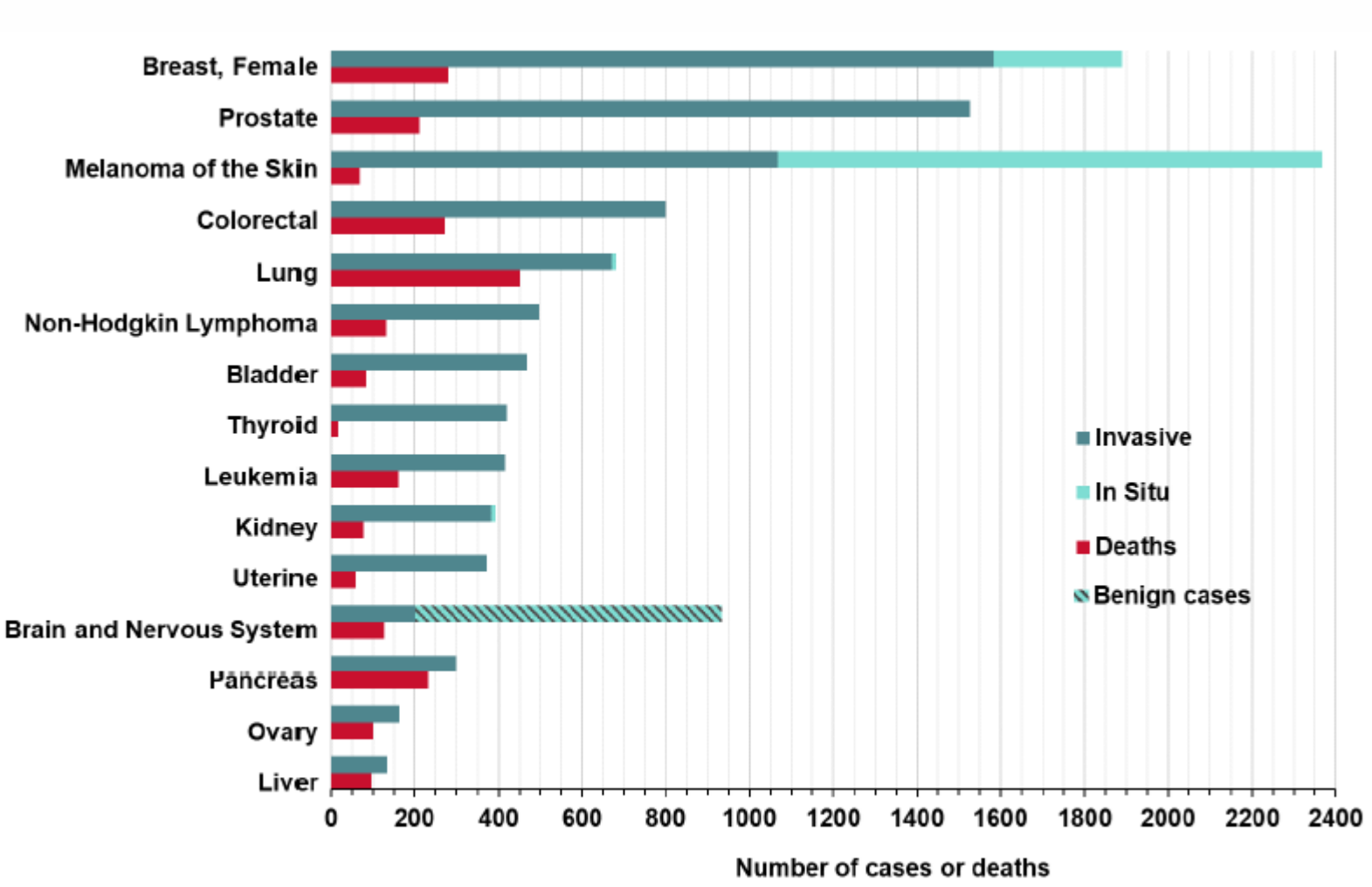
Utah Cancer Incidence and Mortality



Millar et al. Utah Cancer Registry, 2019.

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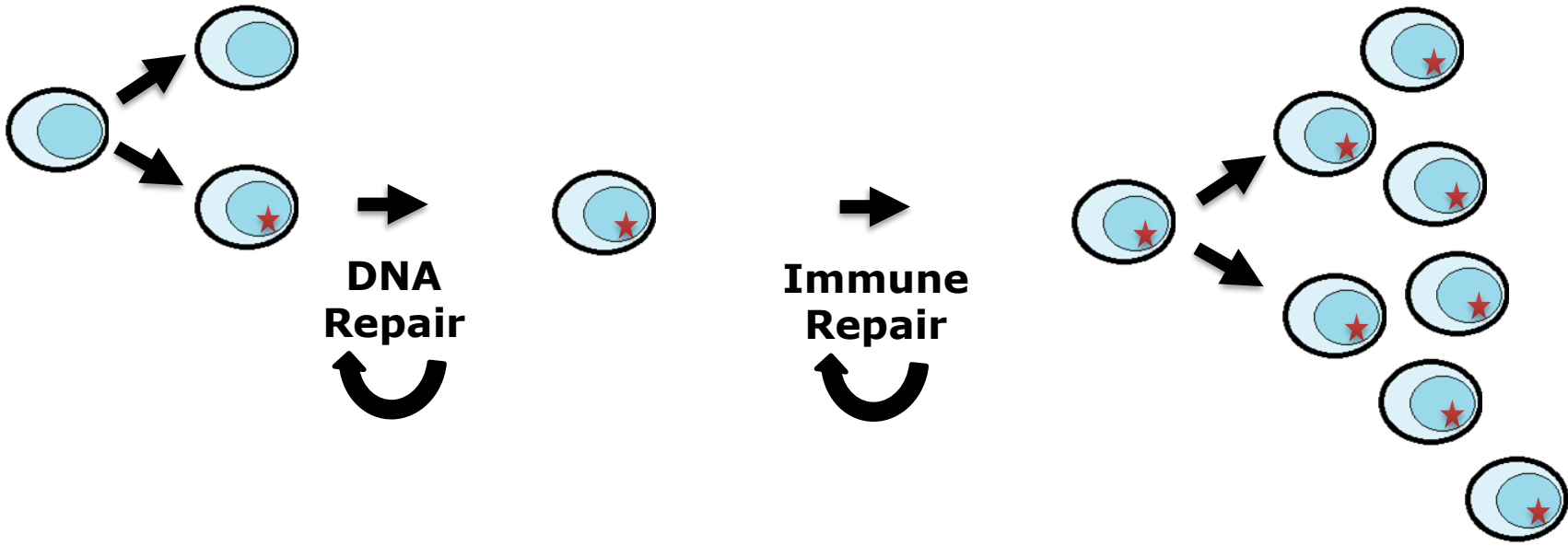
Clinical Carcinogenesis-

What are the failings that let cancer happen?



DNA
Panel

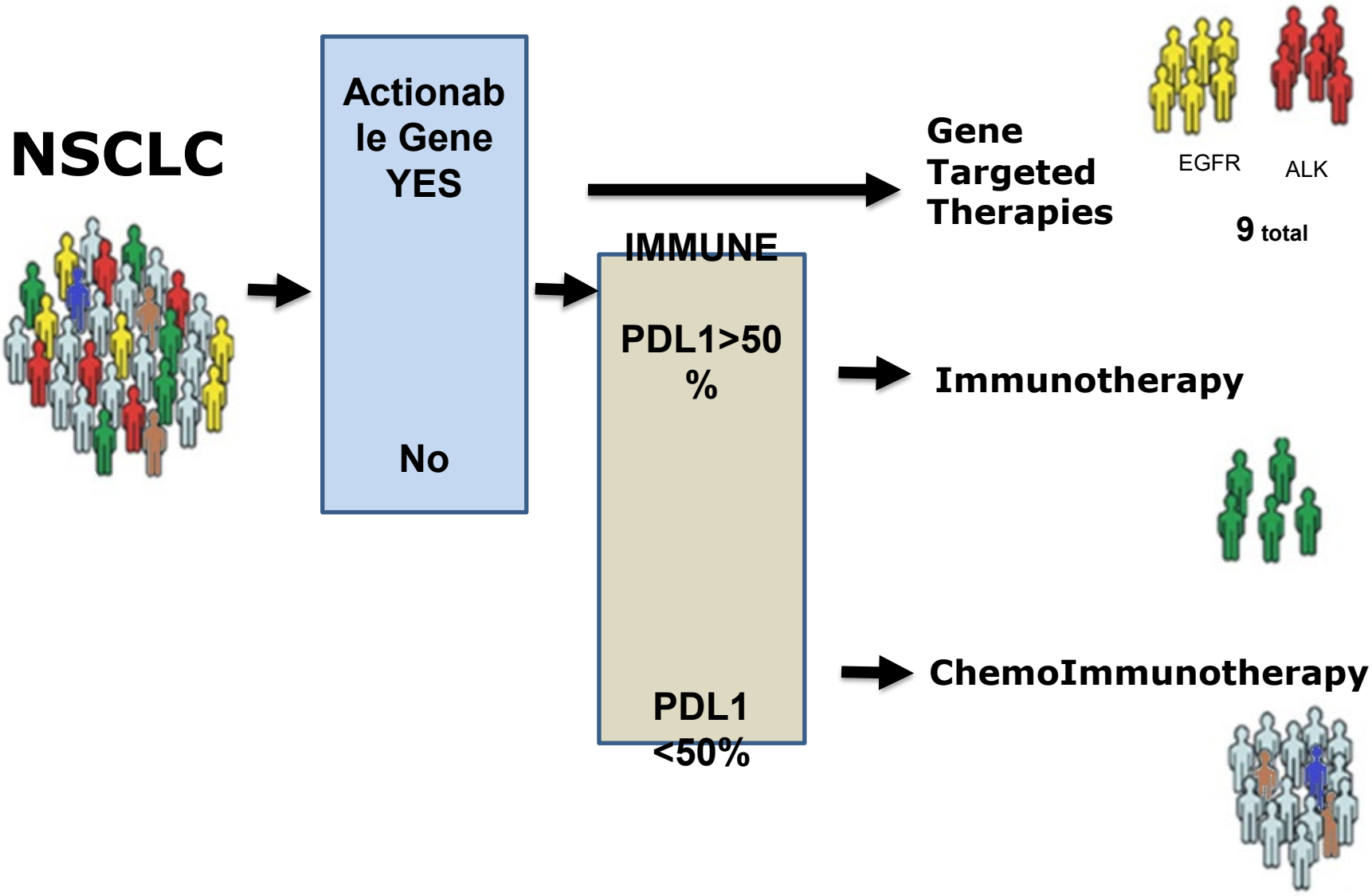
Immune
Panel

Cancer Treatment Revolution

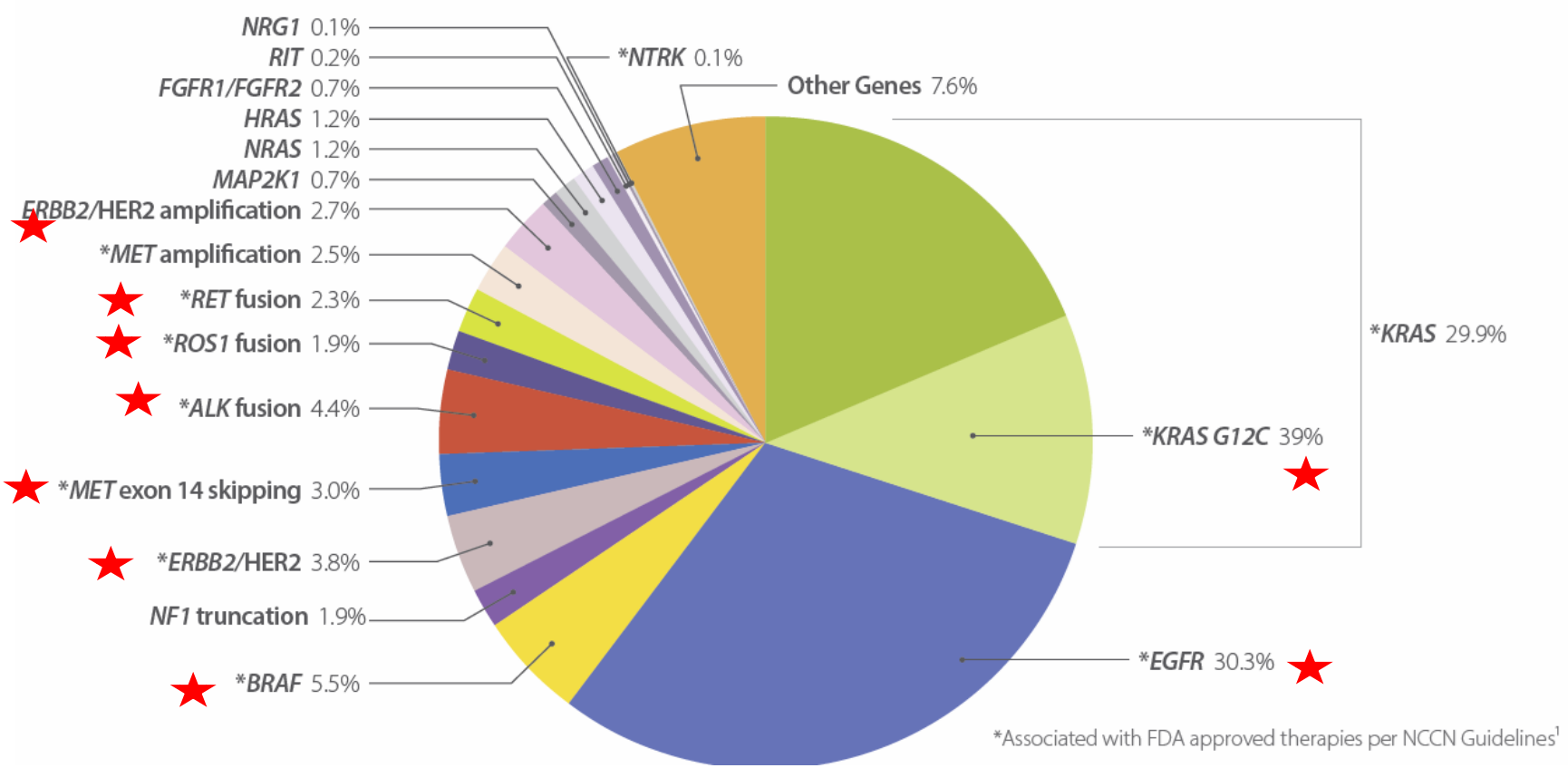
Past
- Non-small Cell Lung Cancer – One Group
- Organ based Therapy (chemotherapy)

Present (PRECISION MEDICINE)
- NSCLC - Many types
- Defined by Histology, Genetics and Immune Profiles
  - Tissue and Blood Profiling
- Precision Medicine (treat based on cancer weakness)
  - Gene Targeted therapy (EGFR, ALK, BRAF, HER2, ROS, RET, MET, NTREK,KRAS)
  - Plasticity - Serial Biopsy
- Immunotherapy
  - Biomarker (PD1, PD-L1, Mutational Burden)

NSCLC Treatment



Frequency of Potential Actionable Driver Mutations in NSCLC



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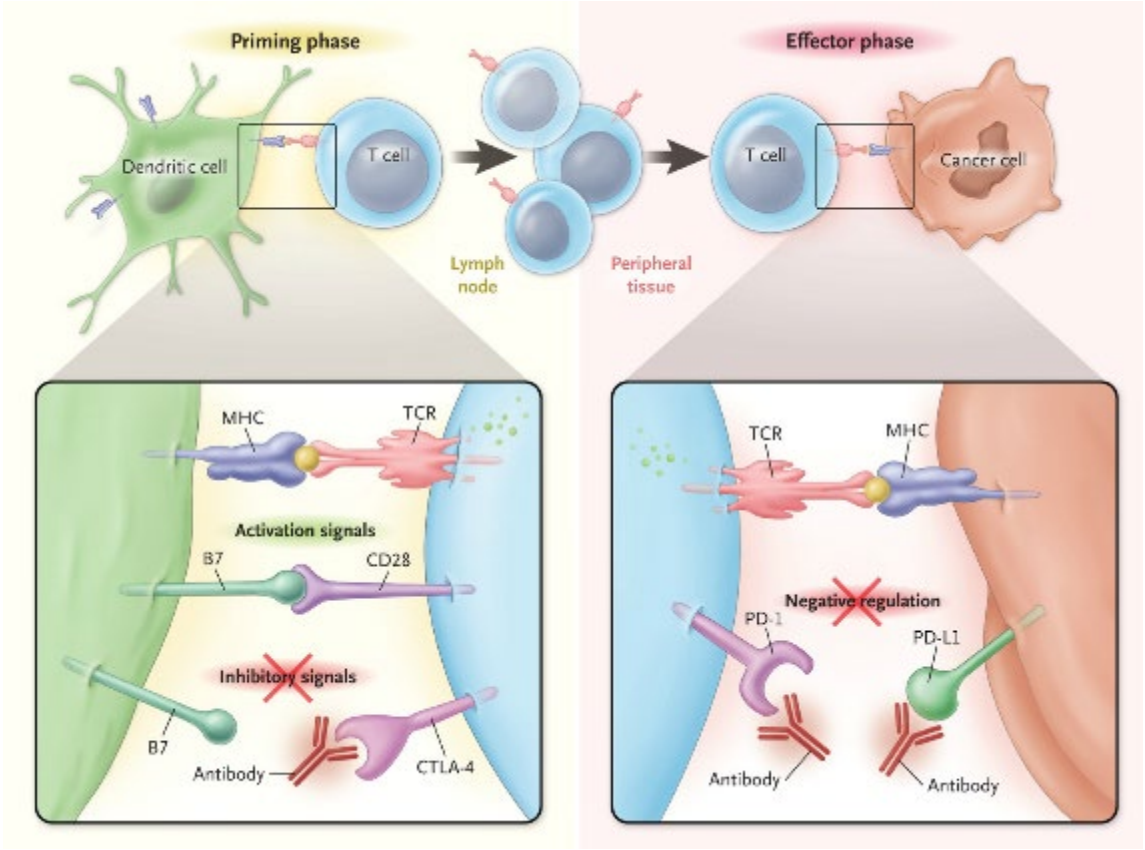
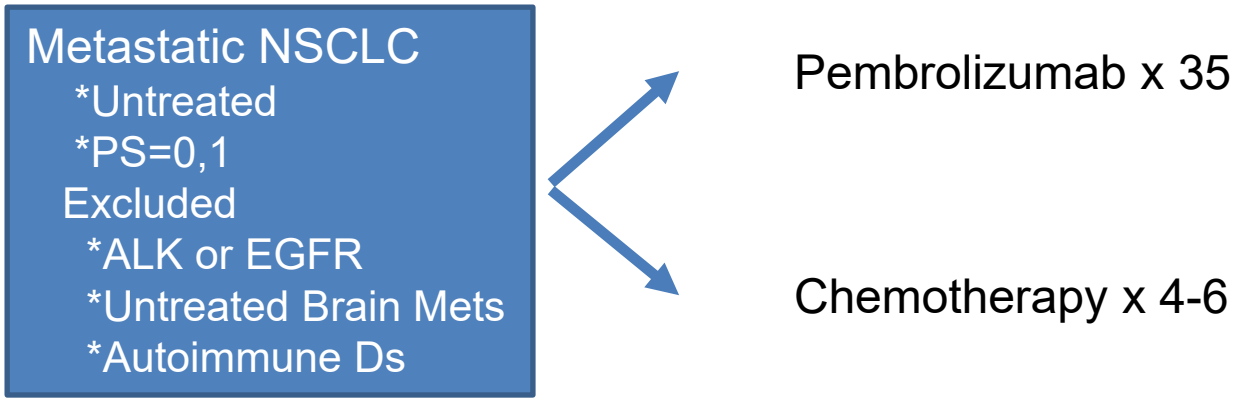
Immune checkpoint Regulation



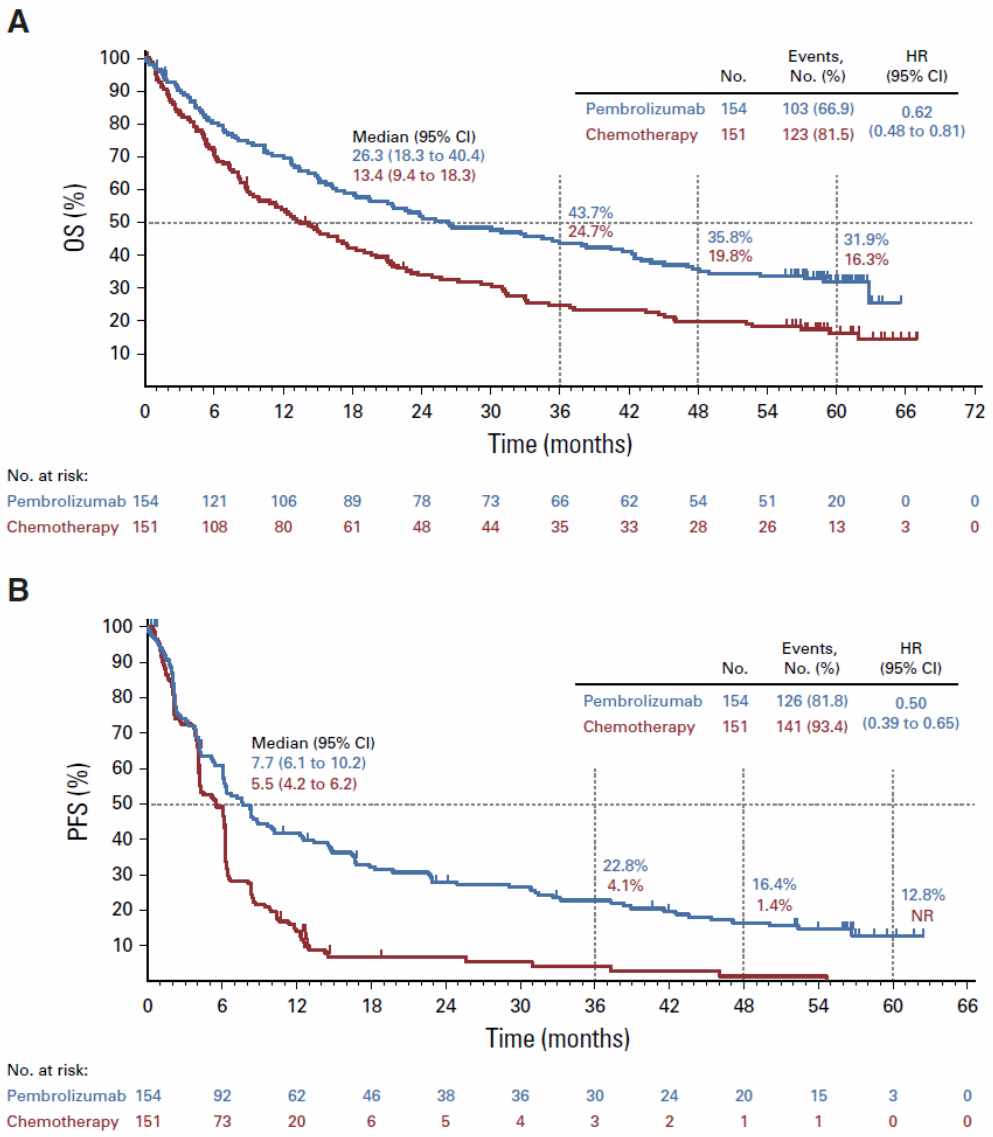
Keynote 024- Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic NSCLC and PD-L1 >50%.



Stratified by PS(0 or 1), histology (squamous or nonsquamous), and region (East Asian or non–East Asian enrollment).
Crossover allowed
Powered for RR, PFS and OS
BICR and Investigator Review

Reck et al. J Clin Oncol 39:2339, 2021

Keynote 024- Immuno versus Chemotherapy Five-Year Outcomes



Reck et al. J Clin Oncol 39:2339, 2021

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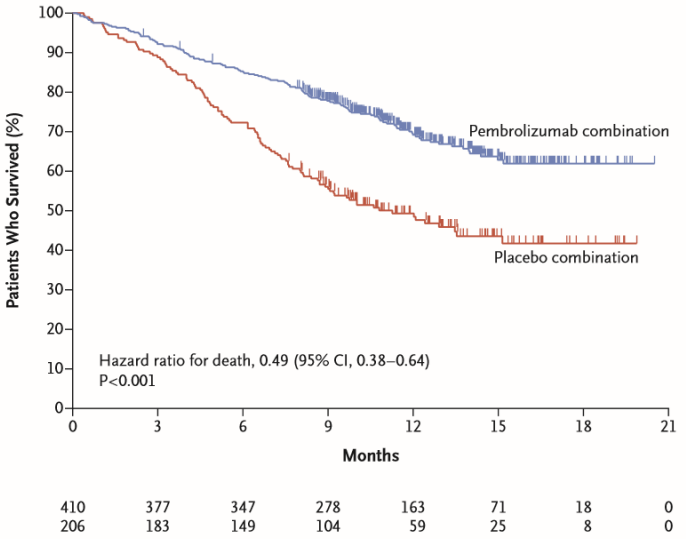
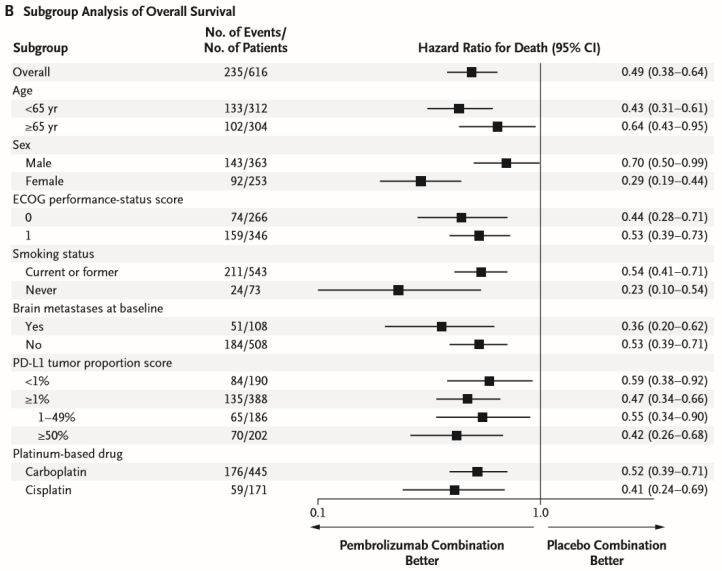
ChemoImmunotherapy versus Chemotherapy

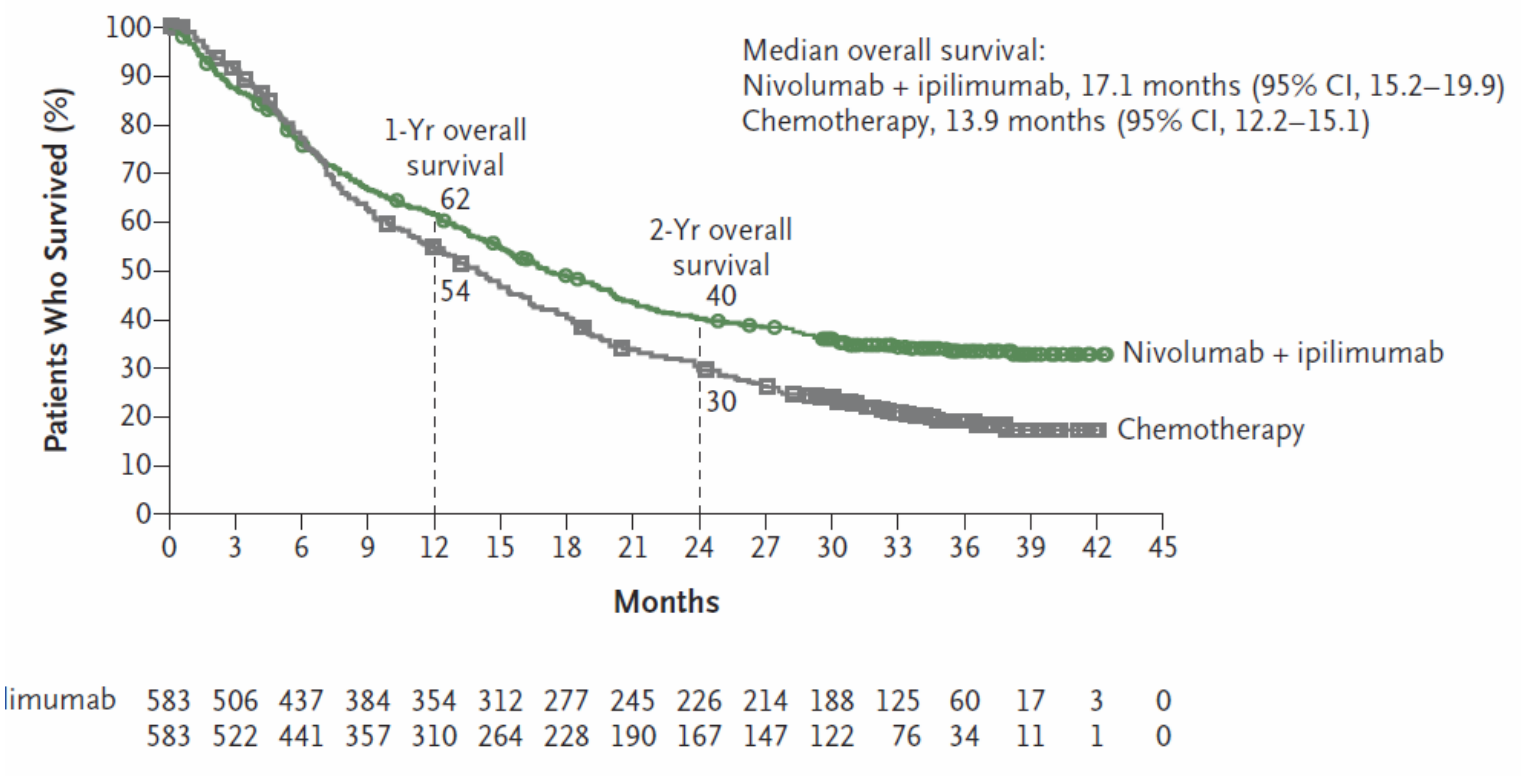




N=616 in 2:1 randomization
ORR 47% versus 19%.

Gandhi et al. N Engl J Med 2018;378:2078-92.

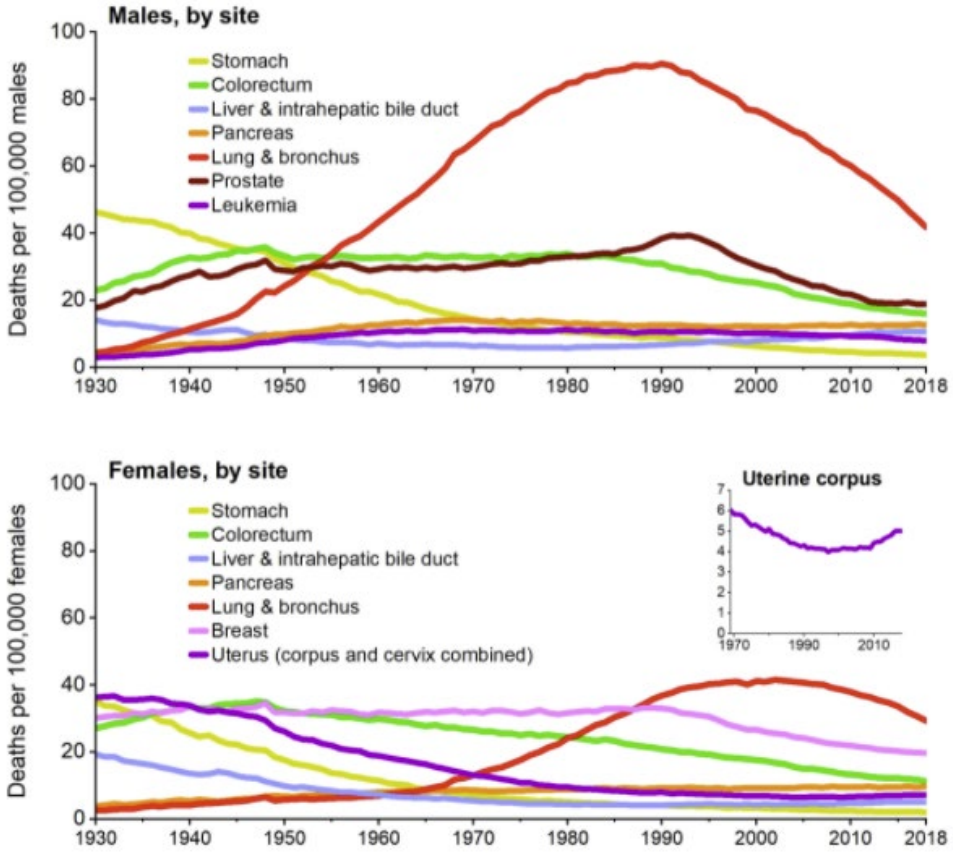
Dual Immuno versus Chemotherapy Nivolumab/Ipilimumab



BMS 227 6-arm randomization
NivIpi=583, included 30% Sq
RR35.9%

Hellman et al. N Engl J Med 381;21 11/21/19.

USA Cancer Mortality over Time



1965- Surgeon General Smoking
1991-2018- 31%decline USA Mortality
Lung CA is half of decline 2014-18

Siegel et al. CA CANCER J CLIN 2021;71:7

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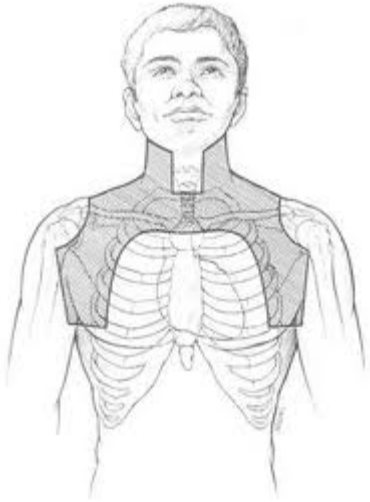
Radon-Induced Lung Cancer

- Radon is a noble gas naturally produced environmentally through uranium decay that releases ***alpha***, beta, and gamma radiation.
- Models of Chronic exposure of inhaled radon support radon as the #2 cause of lung cancer
- Currently, there is no clinical way to identify patients with radon-induced lung cancer.

EPA/CDC

Radiation and Cancer



Radon Occupational Studies

- BEIR VI (Biologic Effects of Ionizing Radiation)
  - 11 studies of miners and lung cancer
    - 68,000 miners, 1.2 million person-years
    - 2700 cancer deaths
  - Lung cancer proportional to radon exposure
    - Cigarette smoking interaction
    - Subset @ EPA level = 4 pCi/l - same result

National Research Council. Health effects of exposure to Radon : BEIR VI. National Academy Press 1999.
Lubin. Environmental factors in cancer: radon. Rev Envir Health 2010

Radon Residential Studies

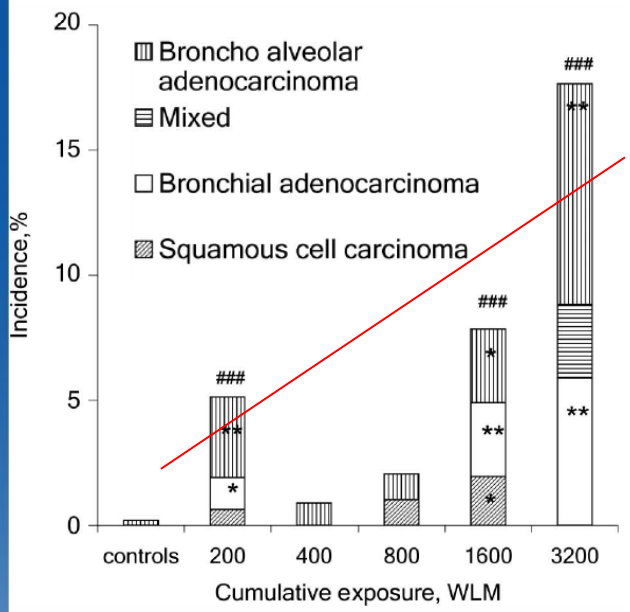
- 22 case control studies
  - China (2), Europe (13), North America (7)
- 19/22 increase lung cancer risk at 2.7pCi/l
  - China 1.13, EU 1.08, No America 1.11

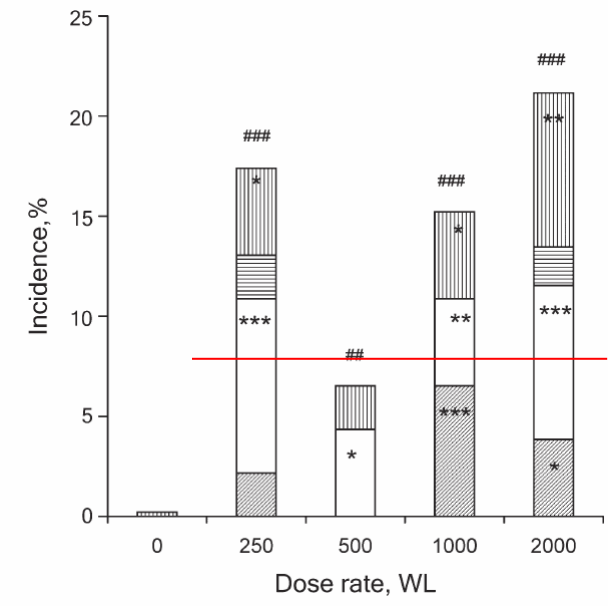
- If effect is seen at 2.7, then risk is underestimated!

Darby. Residential radon and lung cancer-detailed result of a collaborative analysis of 7148 persons with lung cancer and 14208 without lung cancer from 13 epidemiological studies in Europe.

Scand J Work Environ Health 32:1-84, 2006

Radon Rat Model of Lung Cancer





1574 rats exposed to radon through rebreathing system.
WLM (working level months)

Cumulative exposure more important than dose rate

Collier et al. Int. J. Radiat. Biol., 81:631, 2005.

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What molecular type of Lung Cancer is Associated with Radon

- Studies in Never smokers

• Rauvina	Spain	2016	Inc radon in ALK	(NS)
• Mezquita	France	2019	Inc radon with mutation	(NS)
• Taga	USA	2012	No association	

Taga et. al. Cancer Epidemiol Biomarkers Prev; 21: 988. 2012

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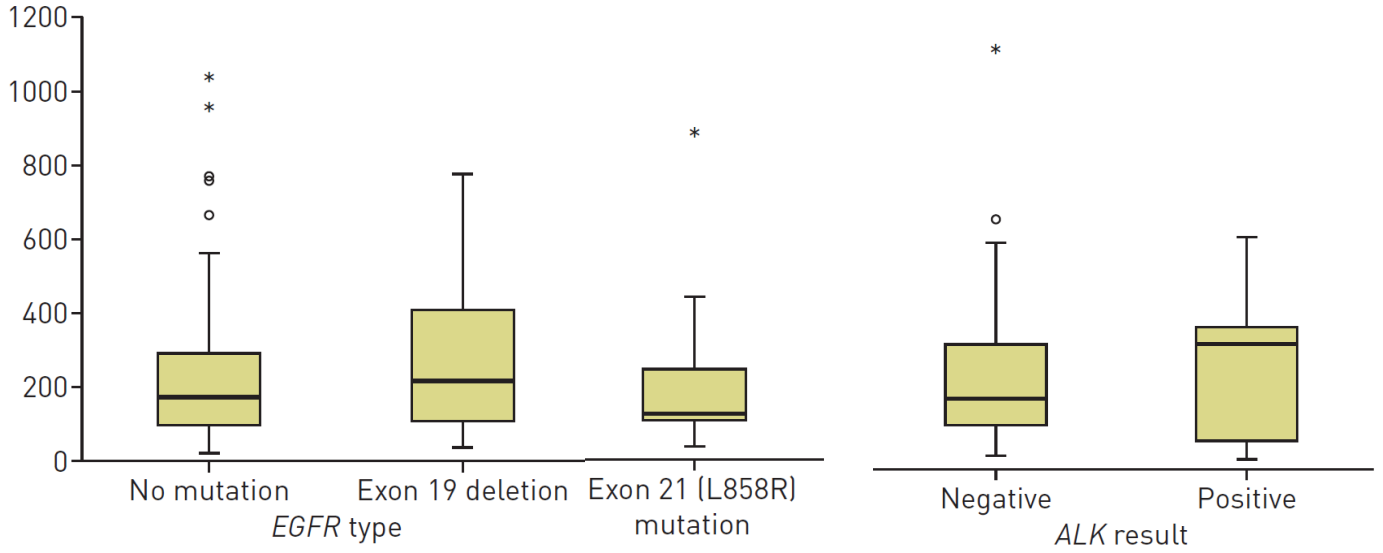
Residential radon, EGFR mutations and ALK alterations in never-smoking lung cancer cases



Ruano-Ravina et al. Eur Respir J 2016; 48: 1462

Molecular Alterations, Indoor Radon in lung cancer from the French National Cancer Registry

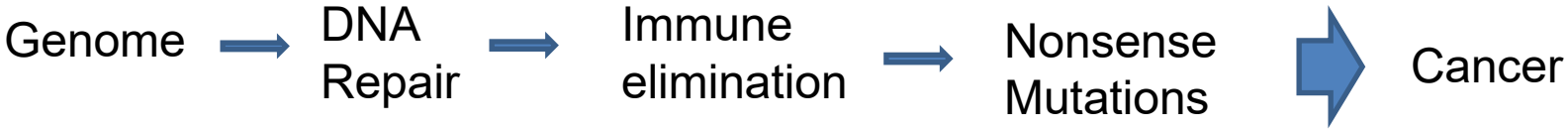
	Low risk	Intermediate	High	P
EGFR mutation	1962 (10%)	4338 (11%)	**4176 (11.4%)**	**<0.0001**
ALK rearrangement	577 (3.3%)	1019 (3%)	896 (3%)	0.35
BRAF mutation	327 (1.8%)	**830 (2.4%)**	**692 (2.4%)**	**0.0001**
HER2 mutation	109 (0.6%)	**266 (0.9%)**	**252 (0.8%)**	**0.01**
ROS1 rearrangement	61 (0.9%)	133 (0.9%)	**126 (1.3%)**	**0.005**
KRAS mutation	**4717 (29.8%)**	9215 (28.2%)	7895 (27%)	**<0.0001**
Molecular drivers*	3037 (3.9%)	**6587 (4.4%)**	**6142 (4.4%)**	**<0.0001**
* *EGFR, BRAF & HER2* mutations, *ALK & ROS1* rearrangements; *KRAS* mutation excluded.				

Table 2: Prevalence of molecular alteration by radon risk area in France.

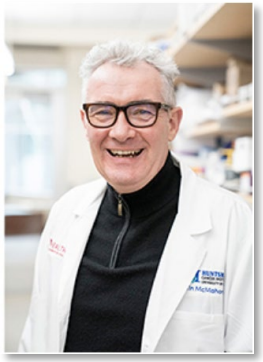
Mezquita et al. WLCC JTO Abstract 2019

What Kind of Lung Cancer is Associated with Radon

- My Bias-
- Radon is associated with all forms of Lung cancer and will show a large variety of mutations and have a gene signature that mimics radiation or smoking



Team ~~Radon~~



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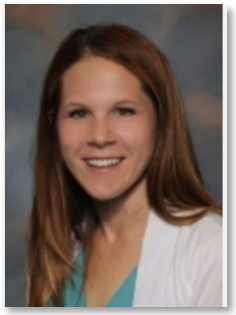
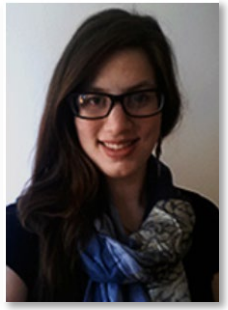


Heidi Hanson, PhD



Joemy Ramsay, PhD

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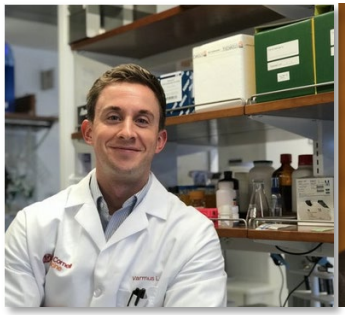


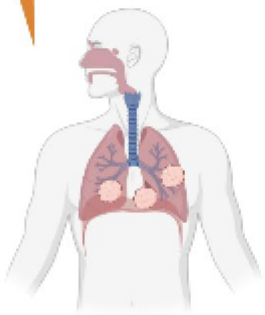
Eric Gardner, PhD, PharmD

Harold Varmus, PhD

Weill Cornell Medicine

HCI Lung DOT Pilot Grant Workflow

Radon
α-
emission



LCINS patient

UPDB

1B. Quantify Utah residential radon exposure for LCINS patients

1A. Isolate LCINS tumors

2. Sequence LCINS tumors with exposure to high radon

3. Establish bank of LCINS PDXs

Projected Timeline

100 initiated *PTC* mice are shipped to Flinders University in Adelaide Australia from Huntsman Cancer Institute (Begin Aim 1)

3 months

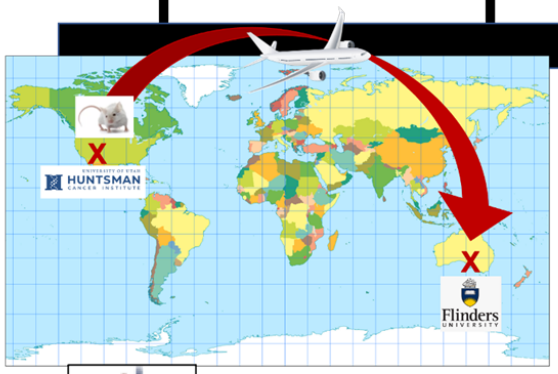
Post-shipping, quarantine, and travel de-stress/adjustment period (Aim 1)

6 months

6 months tx (Aim1)
1000 Bq/m^3 [^{222}Ra] PTC mice

9-12 months

Year 1
December 2021-November 2022



5 new LCINS PDX mice establishing and expanding at HCI following radon exposure metrics of patient samples. 5 existing models expand and prepare for analysis (Aim 2)

1 month

Pathological analysis, DNA and RNA isolation (Aim 3)

4-10 months

Sequencing analysis and informatics, additional IHC/IF (Aim 3)

Year 2
December 2022-November 2023

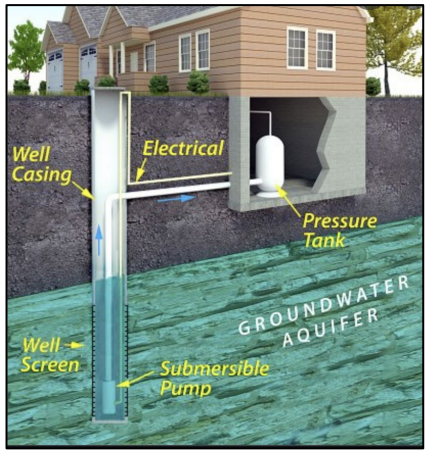
Euthanize PTC mice, ship fixed lung tissue back to HCI (end Aim 1)

2-3 months

Sequencing, IHC, DSB molecular analysis (Aim 3)

6-12 months

UPDB:National Database
HCI is one of the best places in the world to study LCINS



Zillow

UTAH DEPARTMENT of ENVIRONMENTAL QUALITY

EPA

UTAH DNR UTAH GEOLOGICAL SURVEY

Lung Cancer Summary

- Lung cancer is defined by
  - Microscope
  - DNA mutations panel,
  - Immune panel,

- Lung Cancer is many types of cancer
  - Smoker versus non-smoker
  - Few Actionable mutation versus Many

- Radon
  - Cause of lung cancer in smokers and never-smokers
  - Most important natural cause of cancer (preventable)
  - Awareness, Mitigation saves lives
  - We hope to define a radon signature