Precision Oncology for Veterans with Lung Cancer: Real-world Evidence with Nationwide Data

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HSRD CDA Cyberseminar
November 2022

Outline

- **Why turn real-world VA data into real-world evidence: Case studies in vaccines** + precision oncology

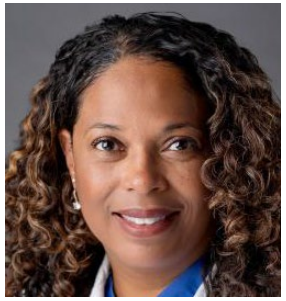
- Implementing in clinical practice
  Case study in screening for second primary lung cancer

- Diversity Supplement and funding opportunities

Amazing scientific collaborators

Leading oncology, precision medicine, and data science

Summer Han, Ph.D.



Leah Backhus, M.D.

Shipra Arya, M.D.

Michael Kelley, M.D.

Nathanael Fillmore, Ph.D.

Albert Lin, M.D.

Westyn Branch-Elliman, M.D.

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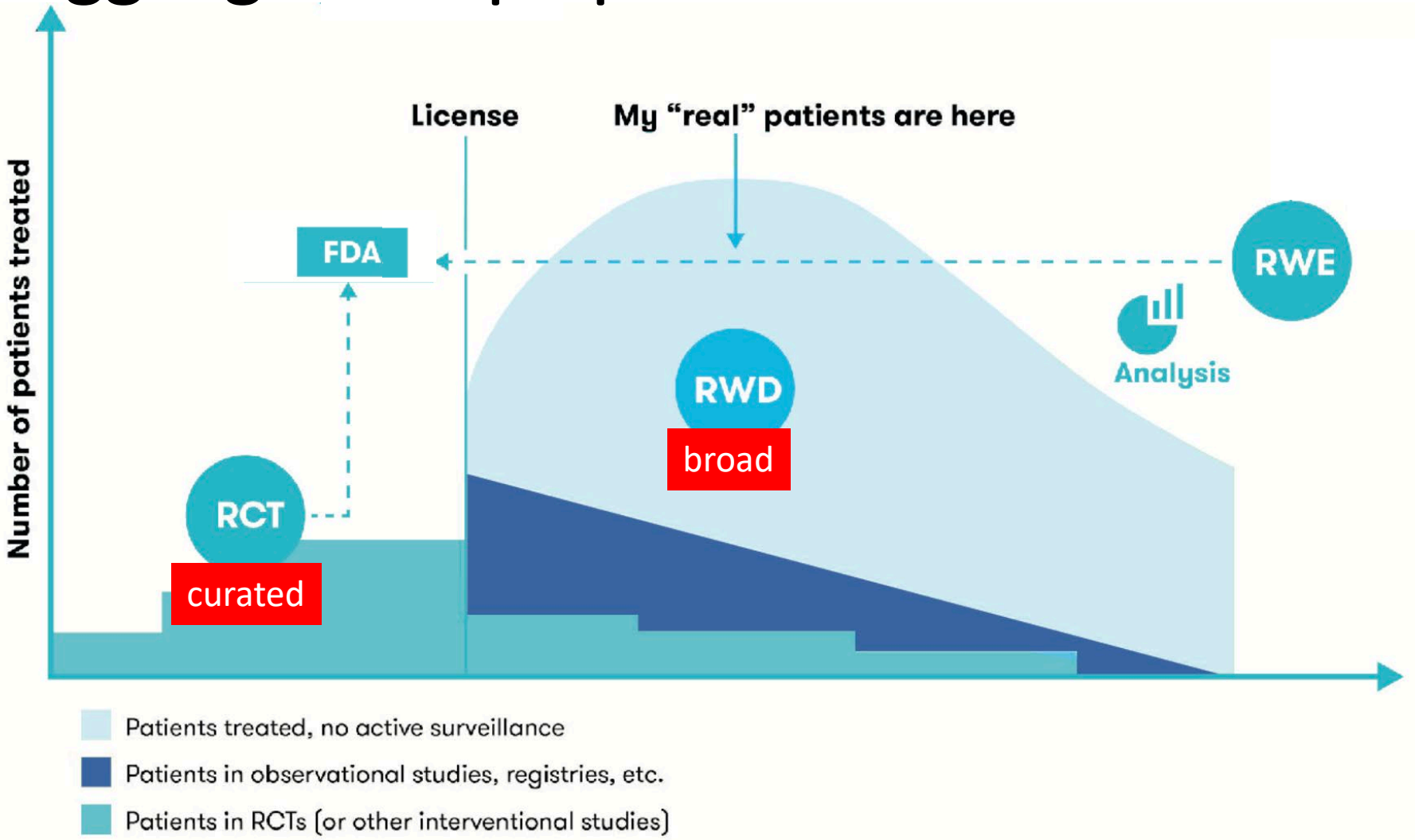
Clinical trials revolutionized medicine (1940s) but struggling to keep up with the real world…



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Theme 1: Trial patients are not real-world patients, so real-world data is needed

Randomized controlled trials

- Controlled environment
- Interventional
- Limited population
- Academic centers

Real-world data

- Collected from clinical practice
- Observational
- Broader population
- Academic and non-academic

Zuidgeest et. al. *Journal of Clinical Epidemiology* (2017).

Theme 2: Transforming real-world data into real-world evidence that can benefit patients

Real-world data
- Collected from clinical practice
- Observational
- Broader population
- Academic and non-academic

Real-world evidence

Implementation

Zuidgeest et. al. *Journal of Clinical Epidemiology* (2017).

Case study 1: COVID-19 vaccination for patients with cancer

1. **How does cancer treatment affect vaccine effectiveness?**
2. Effect by cancer type?
3. Risk factors for severe breakthrough?

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371

JAMA Oncology

AMERICAN SOCIETY OF HEMATOLOGY

Top 10 JAMA Oncology Attention score of the year

2021 ESMO congress

AMERICAN SOCIETY OF HEMATOLOGY blood®

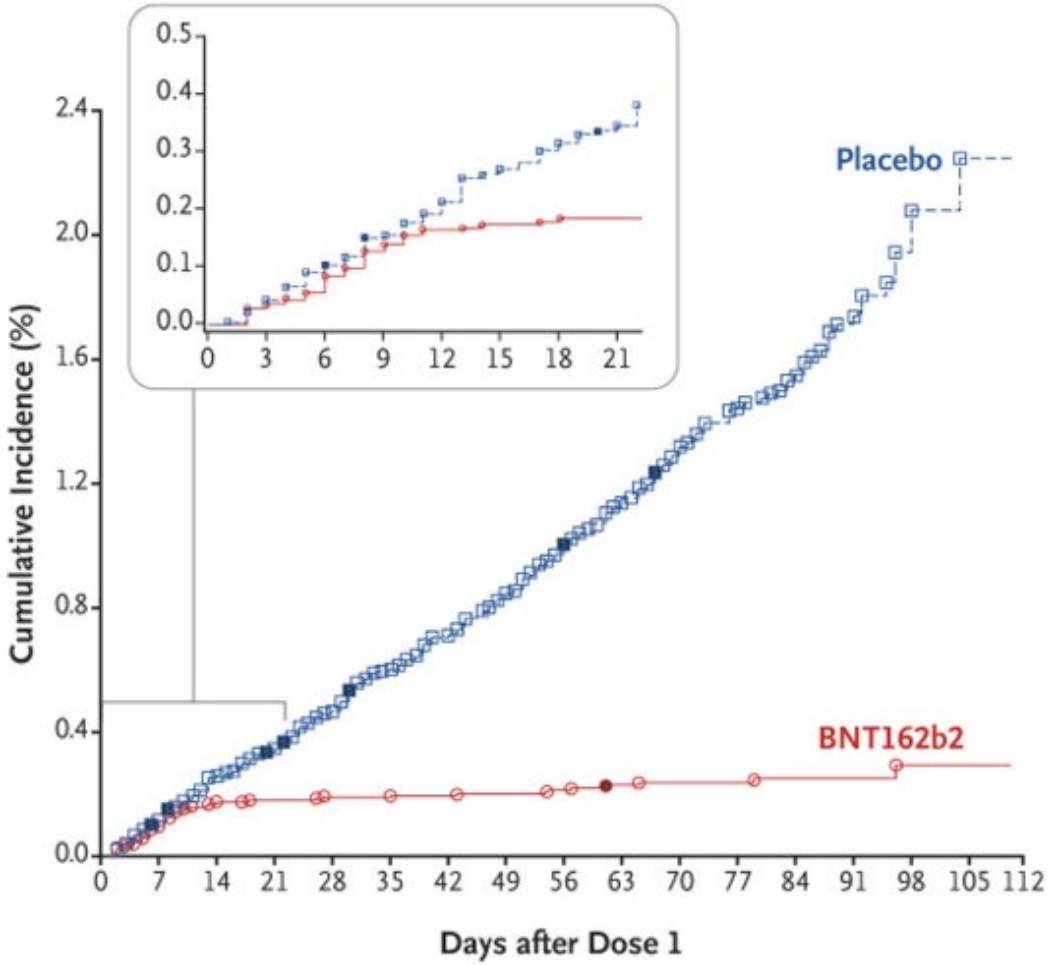
Refresher: Vaccination trials showed 95% efficacy

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

F.P. Polack, et al. DOI: 10.1056/NEJMoa2034577



Vaccine efficacy of 95% (95% credible interval, 90.3 –97.6%)

December 31, 2020

N Engl J Med 2020; 383:2603-2615

Vaccination trials did not include unhealthy patients

Study to Describe the Safety, Tolerability, I[illegible]nd Efficacy of RNA Vaccine Candidates Against COVID-1[illegible] in Healthy Individuals

ClinicalTrials.gov Identifier: NCT04368728

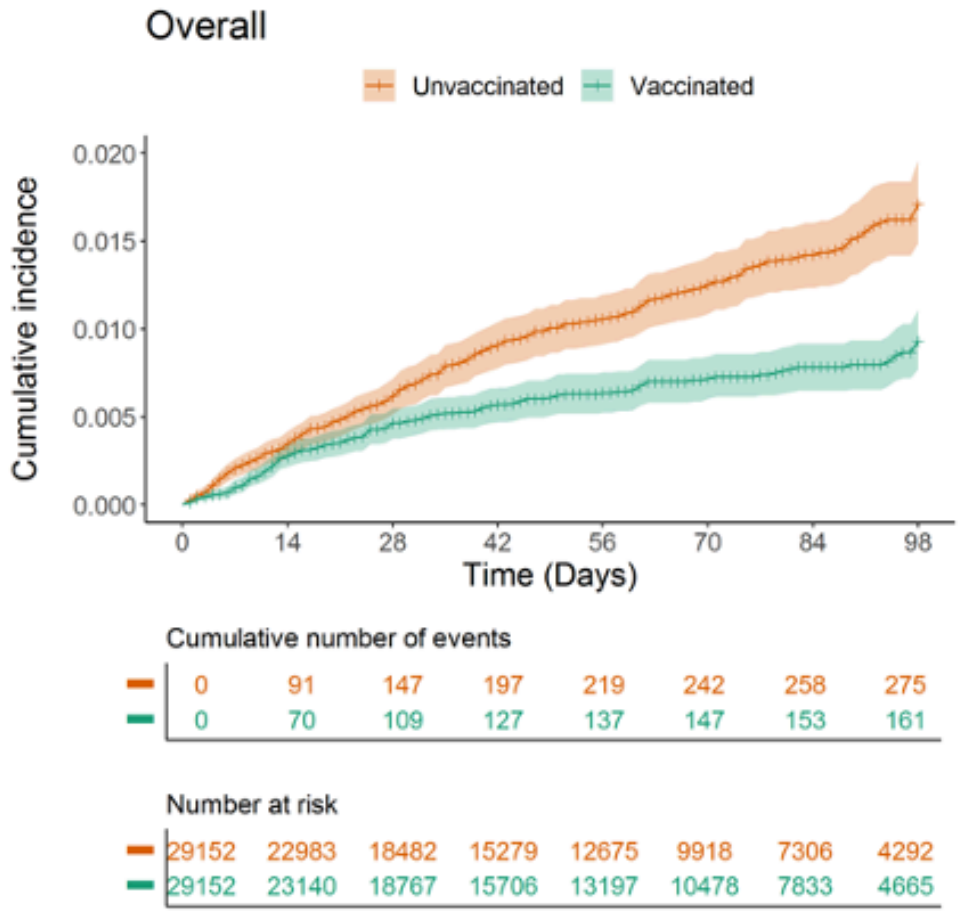
Exclusion Criteria:

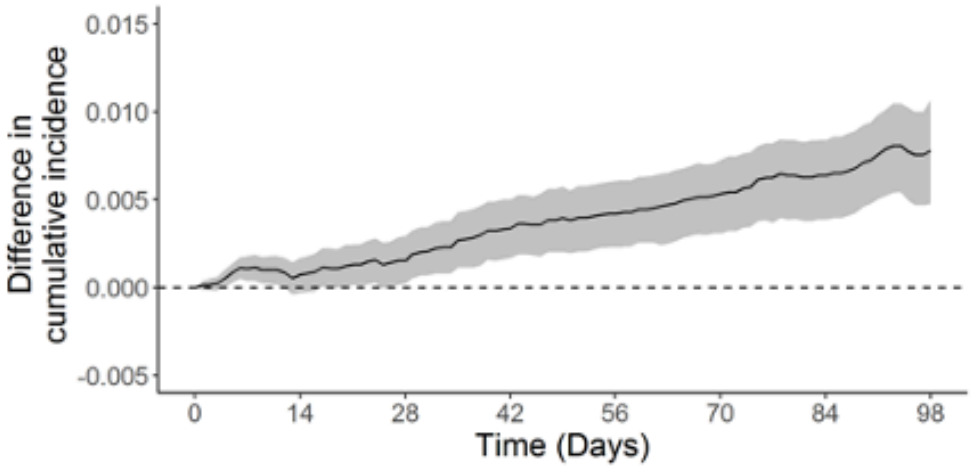
- Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study.

Problem: How cancer treatment will affect vaccination is unknown.

Solution: Use nationwide EHR data to estimate vaccine effectiveness.

Overall vaccination is effective against COVID infection





Median follow-up 47 days

Overall effectiveness 14 days post-second dose = **58%** (95% CI 39% to 73%)

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COVID-19 vaccine for patients with cancer: takeaways

- How does cancer treatment affect vaccine effectiveness?
  - Vaccination is effective in patients with cancer
    - **First** study to demonstrate vaccination effectiveness against **infection**
    - **Largest** cohort of cancer patients on topic
- Trial emulation can transform real-world data into real-world evidence

Westyn Branch-Elliman, M.D.

For our most recent work, check out

Original Investigation | Infectious Diseases

October 20, 2022

Factors Associated With Severe COVID-19 Among Vaccinated Adults Treated in US Veterans Affairs Hospitals

Austin D. Vo, BS[1]; Jennifer La, PhD[1]; Julie T.-Y. Wu, MD[2,3]; et al

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2797495

Outline

- **Why turn real-world VA data into real-world evidence:**
  Case studies in vaccines + **precision oncology**

- Implementing in clinical practice
  Case study in screening for second primary lung cancer

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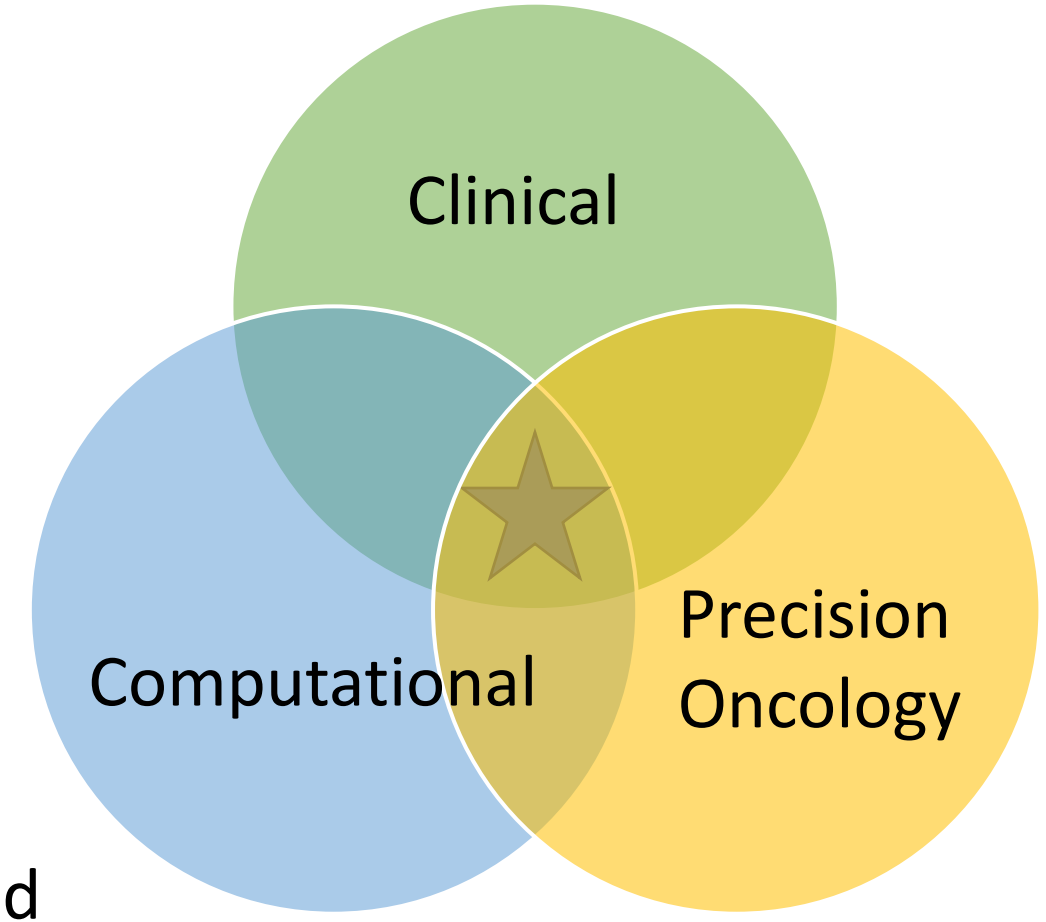
Why real-world precision oncology is big and is getting bigger

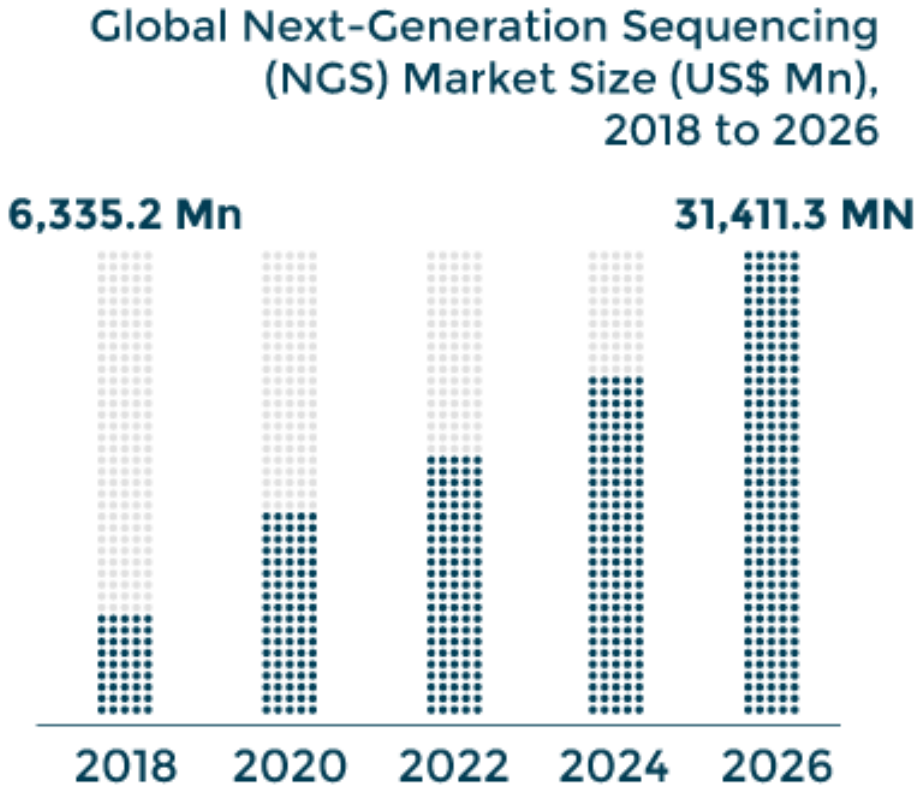
Electronic medical record



Analysis and interpretation algorithms

Cancer “-omic” data

Population-level molecular testing is a key emerging science



AACR American Association for Cancer Research
FINDING CURES TOGETHER™

PROJECT GENIE
Genomics Evidence Neoplasia Information Exchange

Wu J, et al. JCO Precision Oncology 2020

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2021
Non-Small Cell Lung Cancer

Advanced or metastatic disease

- **Establish histologic subtype[a] with adequate tissue for molecular testing (consider rebiopsy[kk] if appropriate)**
- **Smoking cessation counseling**
- **Integrate palliative care[c] (See NCCN Guidelines for Palliative Care)**

Stanford Cancer Institute

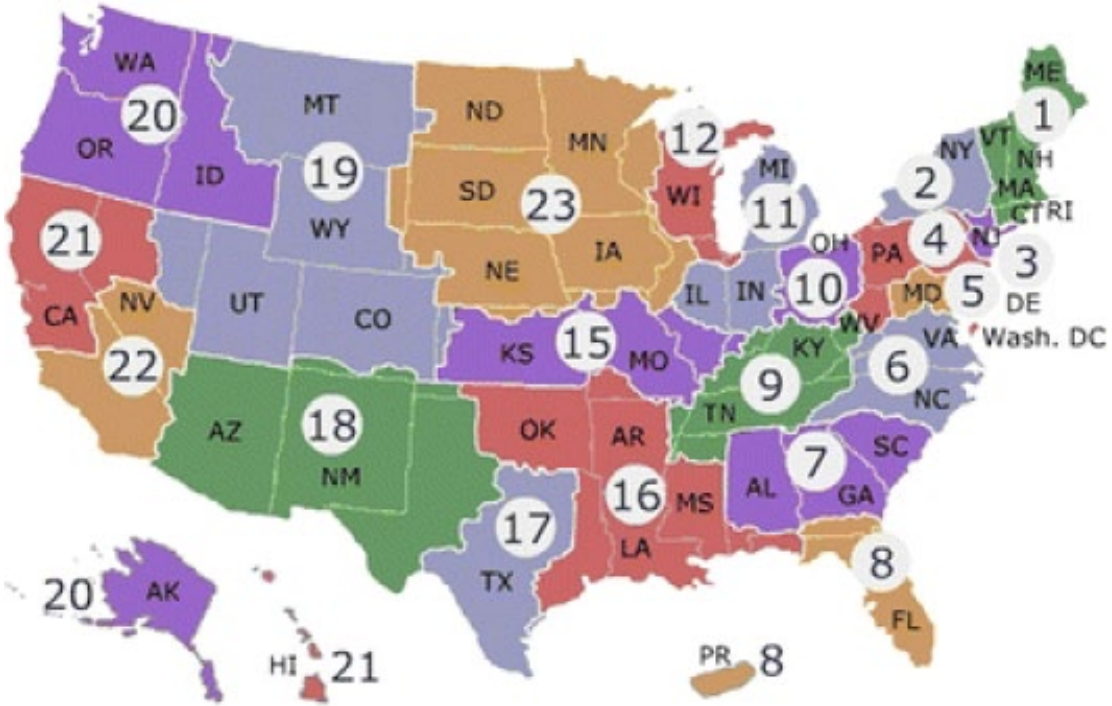
Wu J, et al. JCO Precision Oncology 2022

Case study 2: Immunotherapy efficacy in lung cancer

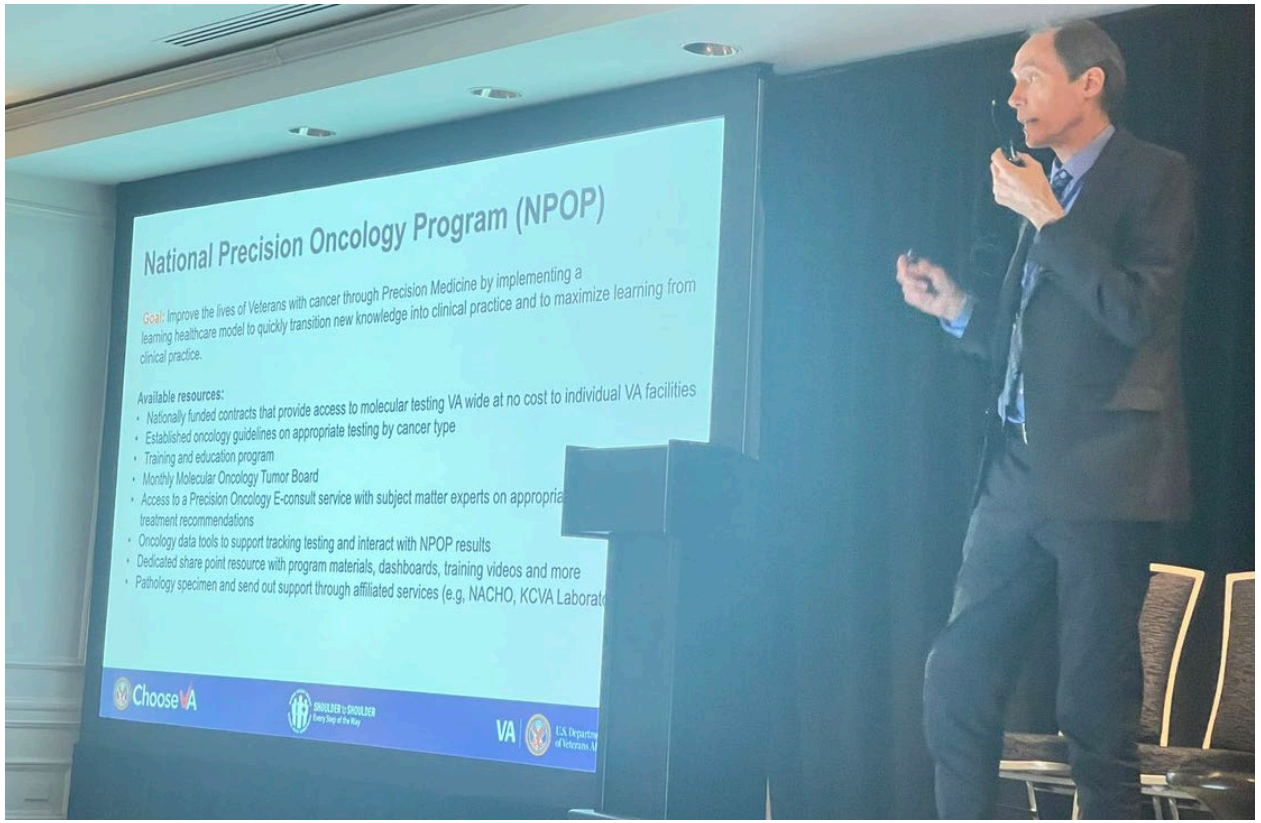
- Immunotherapy has revolutionized lung cancer, enabling long term responses that approximate cure
- However, immunotherapy doesn't work for everyone and can have lethal side effects → biomarkers of response are needed
- Key immunotherapy biomarker trials excluded patients with poor performance status… who are the ones who need it!
  - Performance status = comorbidities + tumor burden

Question: What immunotherapy biomarkers can guide therapy in patients with poor performance status?

Nationwide clinicogenomic data can guide precision medicine



Map of Veterans Integrated Service Networks. J Gen Intern Med. 2007 Nov; 22(11): 1560–1565.



Dr. Michael Kelley (VA Oncology Program Director) at the National Lung Cancer Roundtable

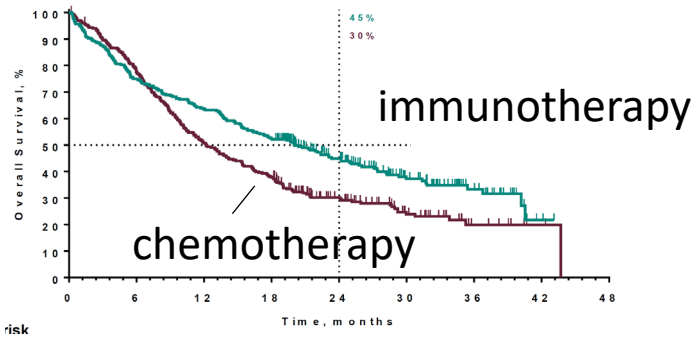
Photo credit: Jack West

NATIONAL LUNG CANCER ROUNDTABLE

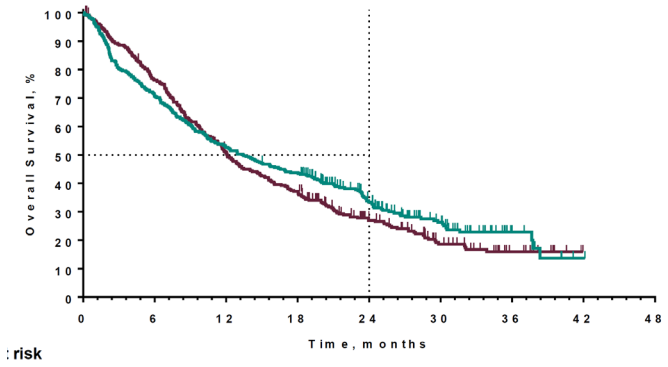
Biomarkers behave differently in patients with poor performance status

Trial:

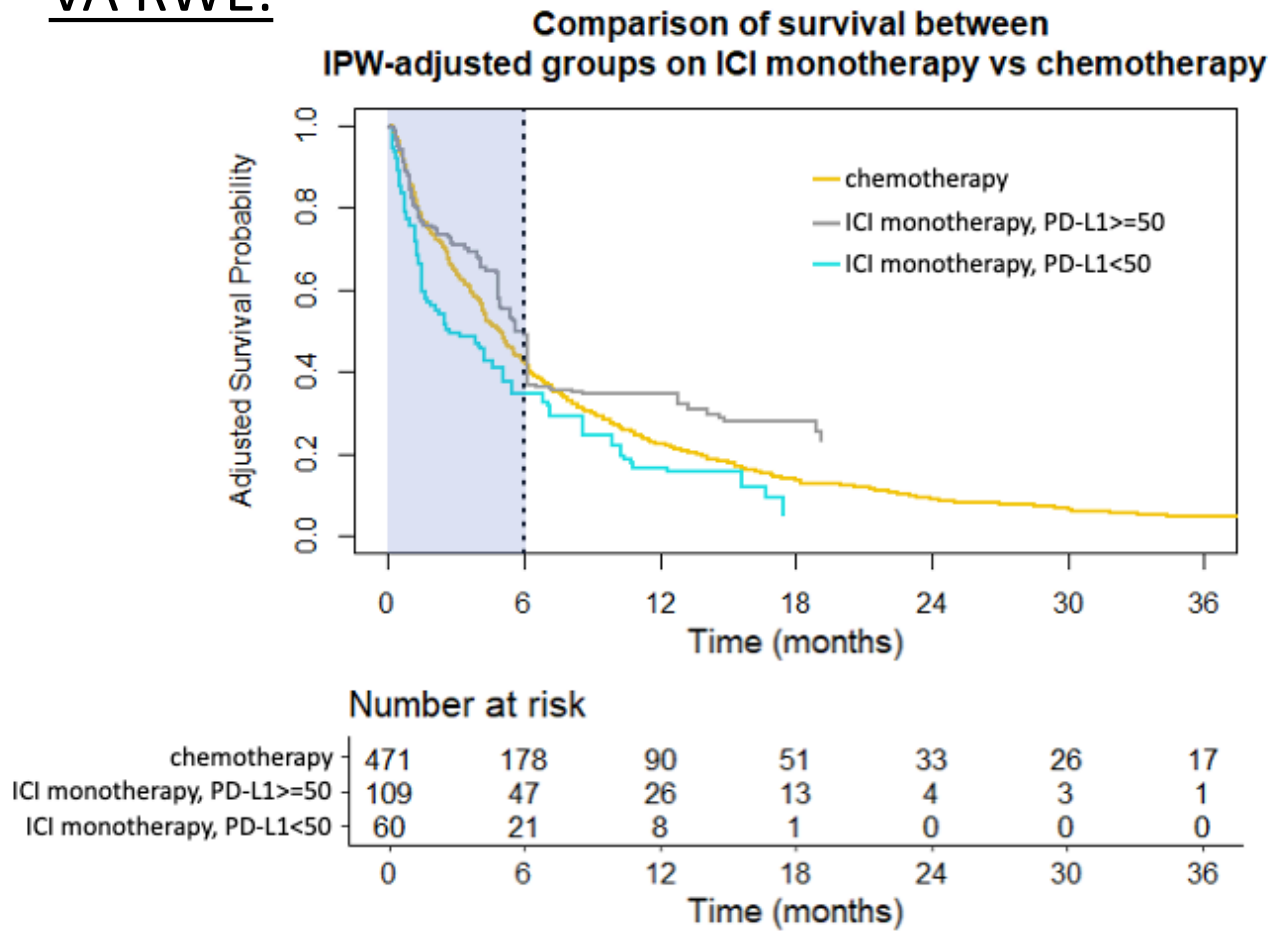
PD-L1 >=50



PD-L1 <50



VA RWE:



Unpublished data

Let’s collaborate!

Michael Kelley, M.D.

Nathanael Fillmore, Ph.D.

- How do immunotherapy biomarkers translate to trial-ineligible patients?
  - Although the PD-L1 low group has similar outcomes in trials, the PD-L1 low group has **worse survival** on immunotherapy compared to chemotherapy in patients with poor performance status
  - Immunotherapy is currently given preferentially over chemotherapy for patients with poor performance status – maybe we shouldn’t?

- Talk to us about lung cancer and biomarker testing!

Outline

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  Case studies in vaccines + precision oncology

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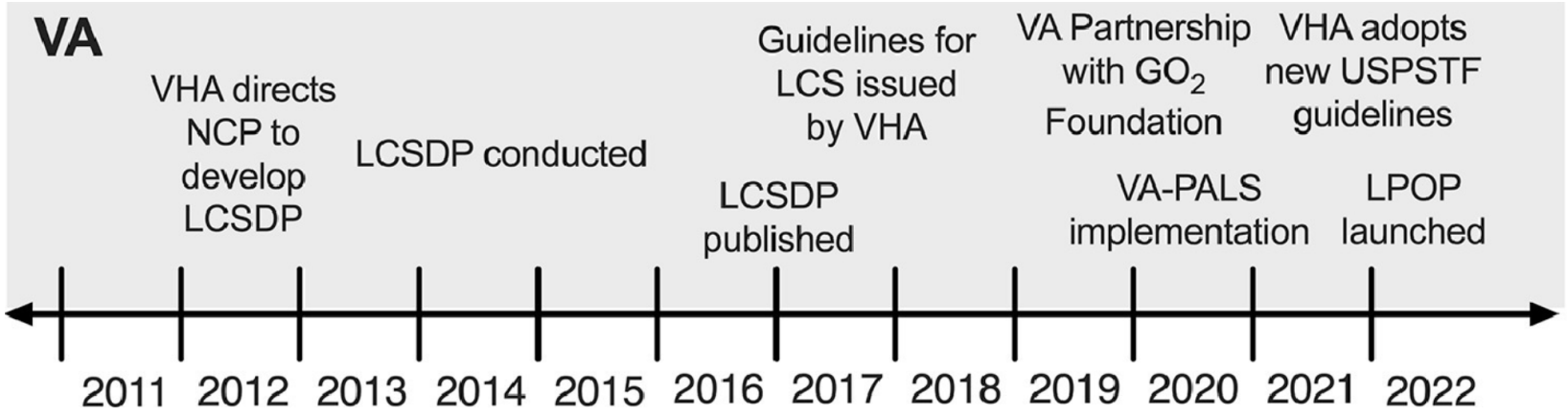
Lung cancer screening is a VA priority

- Lung cancer is the leading cause of cancer-related death among Veterans
- Lung cancer burden among Veterans is almost double that of general population due to high smoking prevalence
- Lung cancer screening through annual chest CT has proven effectiveness in reducing lung cancer mortality

National VA initiatives to improve lung cancer screening



Maurice and Tanner, *Seminars in Oncology* 2022

The dark lining of cancer care breakthroughs

Good News

400K US LC survivors

# of lung cancer survivors projected to grow by 33% over the next ten years

Bad news

Survivors of initial primary lung cancer are at increased risk of developing a second primary lung cancer

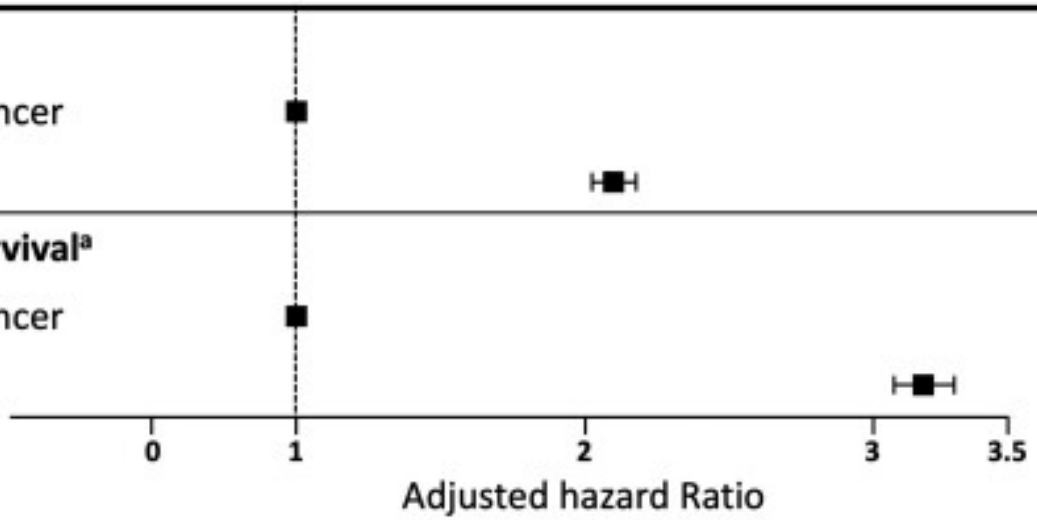
Second primary lung cancer increases survivor mortality 2x+

Summer Han, Ph.D.

Eunji Choi, Ph.D.

A

SEER	HR (95% CI)	*P* value
Overall survival[a]		
Single primary lung cancer	Referent	
SPLC[b]	2.12 (2.06 to 2.17)	<.001
Lung cancer-specific survival[a]		
Single primary lung cancer	Referent	
SPLC[b]	3.20 (3.10 to 3.30)	<.001



Choi et al, *JNCI* 2022

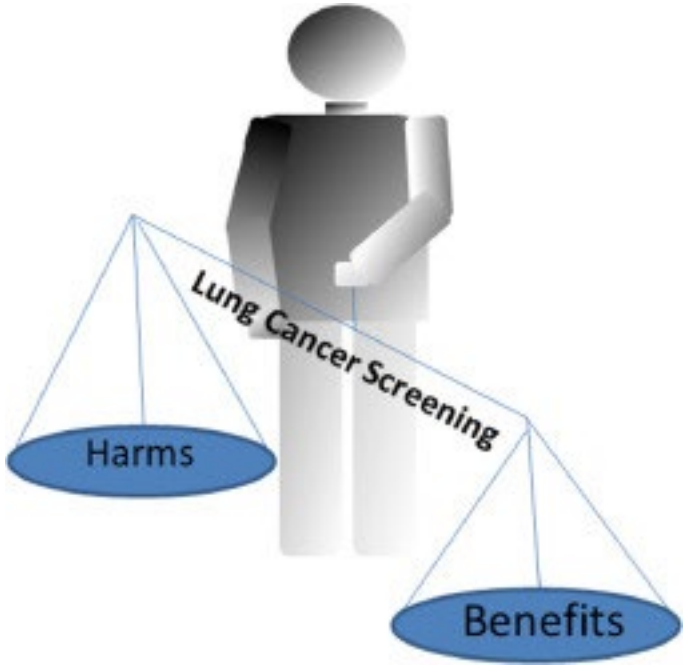
At-risk patients not being screened, yet dangerous to screen everyone

Anxiety

Unnecessary procedures for false positives

Costs of unnecessary scans

Cost of unnecessary treatment

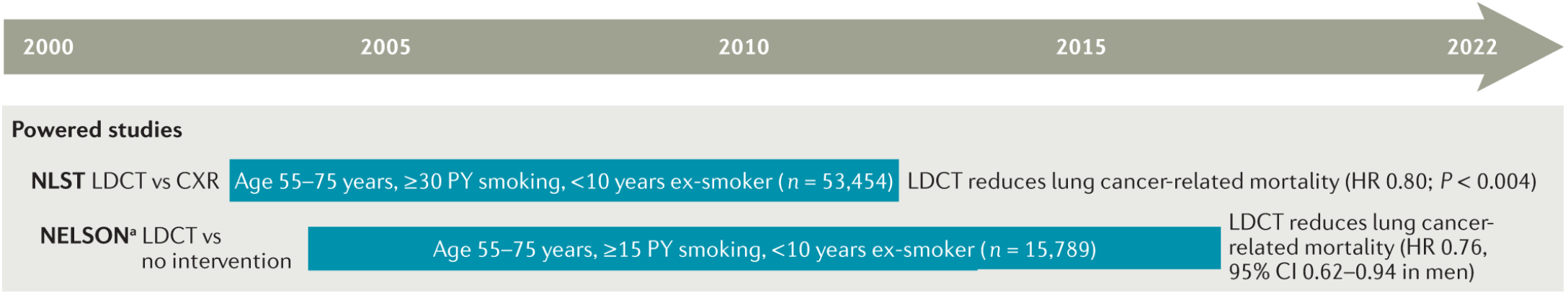


Saving cost of advanced stage cancer therapy

Detecting cancer early

Preventing lung cancer death

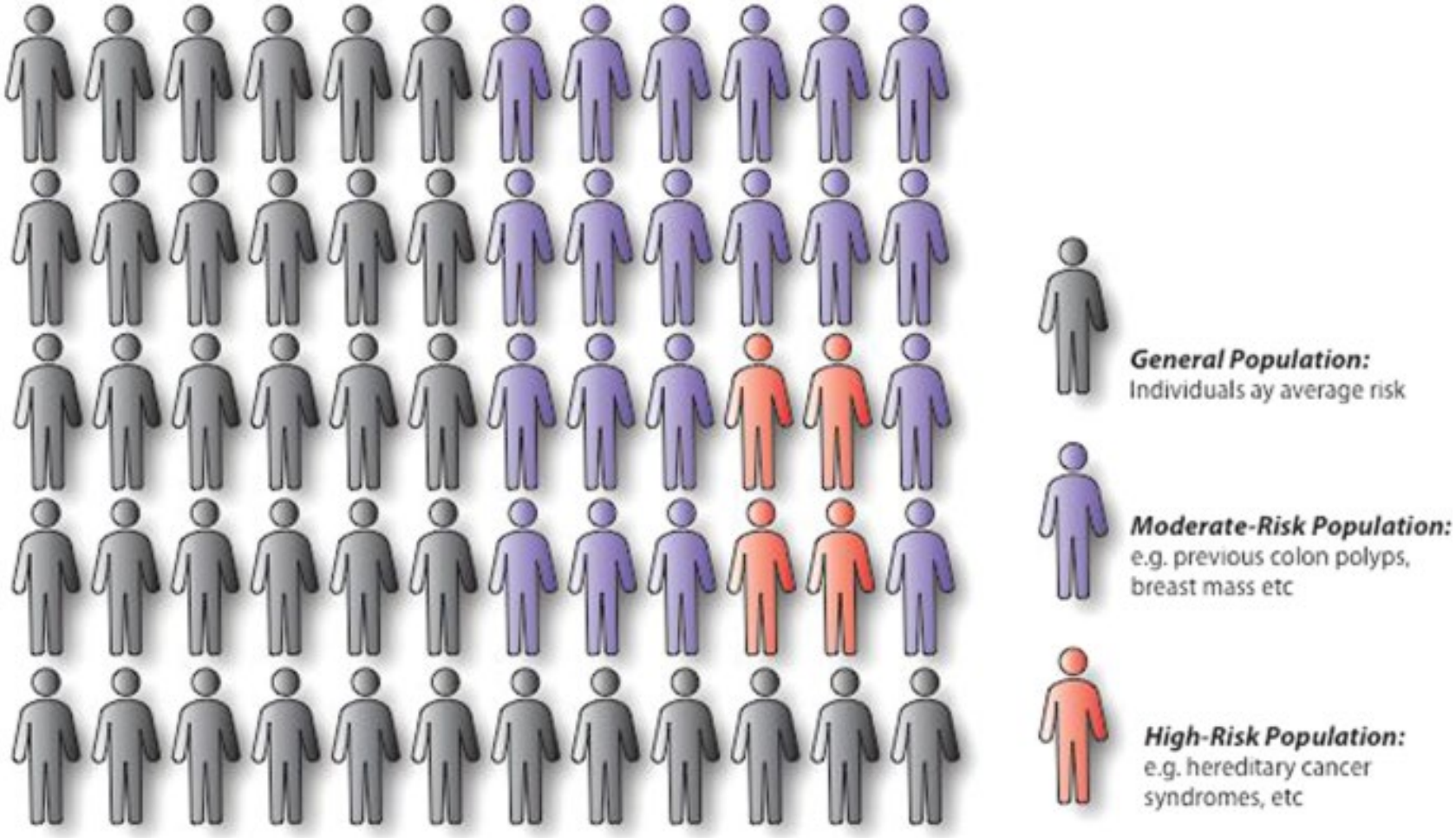
Why clinical trials aren’t enough for lung cancer screening



NIH NATIONAL CANCER INSTITUTE
Cancer Intervention and Surveillance Modeling Network

Oudkerk et. al. *Nature Reviews Clinical Oncology* (2020).

Insight: Risk stratification is an effective strategy for **primary** lung cancer screening



Loomans-Kropp and Umar. *NPJ Precision Oncology* 2019.

Model to predict risk of second primary lung cancer

Summer Han, Ph.D.

Eunji Choi, Ph.D.

Variables included:

- Prior hx of cancer
- Met 2013 USPTF criteria (smoking hx)
- Histology of initial lung cancer
- Stage of initial lung cancer
- Treatment with surgery

Competing risk regression

Predict 10-year risk of second primary lung cancer

Choi et. al. JNCI 2022
Han et al. JCO 2017

Developed in the Multiethnic Cohort dataset, validated in Prostate, Lung, Colorectal and Ovarian Screening Trial and National Lung Screening Trial datasets

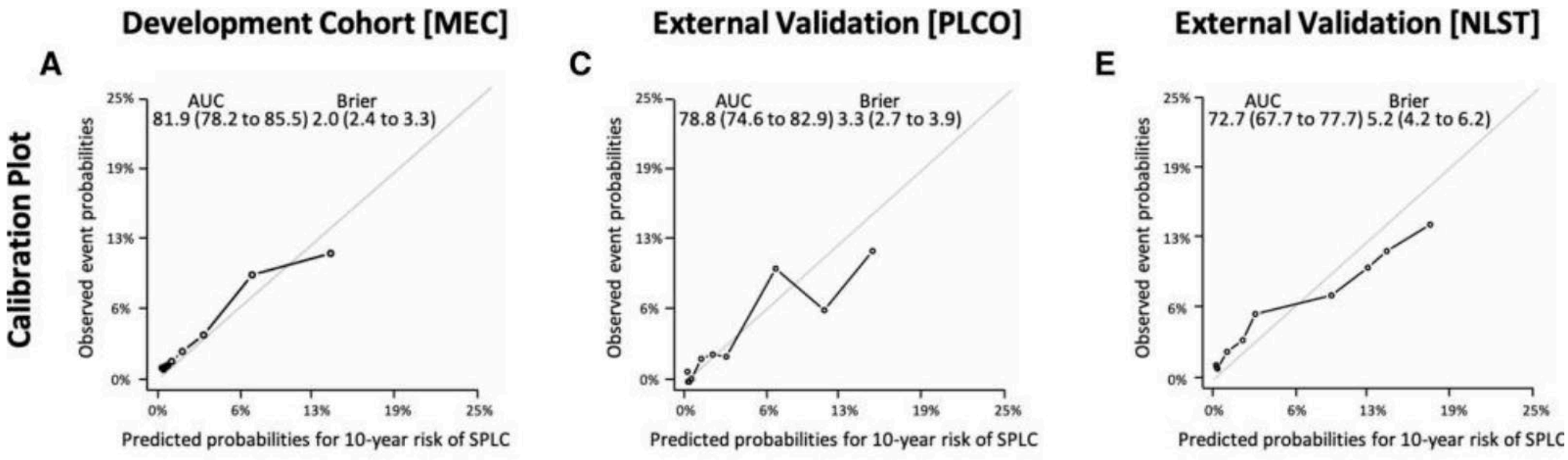
The baseline demographics are diverse

Variables	Total	Outcome
		SPLC
Total events, No. (%)	6325 (100.0)	145 (2.3)
Follow-up time, y		
Mean (IQR)	2.2 (0.2-2.6)	4.6 (1.0-6.8)
Demographic information		
Age at IPLC diagnosis		
Mean (SD), y	74.2 (8.2)	72.1(8.2)
Sex, No. (%)		
Female	2529 (40.0)	66 (45.5)
Male	3796 (60.0)	79 (54.5)
Race, No. (%)		
White	1591 (25.2)	43 (29.7)
Japanese American	1357 (21.5)	34 (23.4)
African American	1736 (27.4)	38 (26.2)
Latino	824 (13.0)	15 (10.3)
Native Hawaiian	533 (8.4)	11 (7.6)
Others	284 (4.5)	4 (2.8)

Risk factors in the final model

Factors	No.	Cause-specific Cox hazards model	
		HR (95% CI)	P
Histology of IPLC			
Squamous cell	1185	Referent	
Large cell	2053	2.01 (0.88 to 4.57)	.01
Adenocarcinoma	163	1.15 (0.76 to 1.75)	.51
Small cell	624	0.79 (0.23 to 2.66)	.70
Non–small cell carcinoma, NOS	473	0.88 (0.30 to 2.57)	.82
Other[c]	856	0.99 (0.52 to 1.89)	.97
Prior history of cancer[d]			
No	3949	Referent	
Yes	1405	1.44 (1.00 to 2.06)	.047
Met the 2013 USPSTF criteria[e]			
No	3539	Referent	
Yes	1815	1.74 (1.15 to 2.63)	.008
Smoking intensity, cigarettes per day	5354	1.01 (0.99 to 1.04)	.25
Surgery for IPLC			
No	2525	Ref	
Yes	3414	2.10 (1.23 to 3.59)	.007
Stage of IPLC			
Early stage[f]	2254	Referent	
Advanced stage	3100	0.48 (0.21 to 1.07)	.07
Stage of IPLC × Met the 2013 USPSTF Criteria[e]		0.28 (0.06 to 1.36)	.11

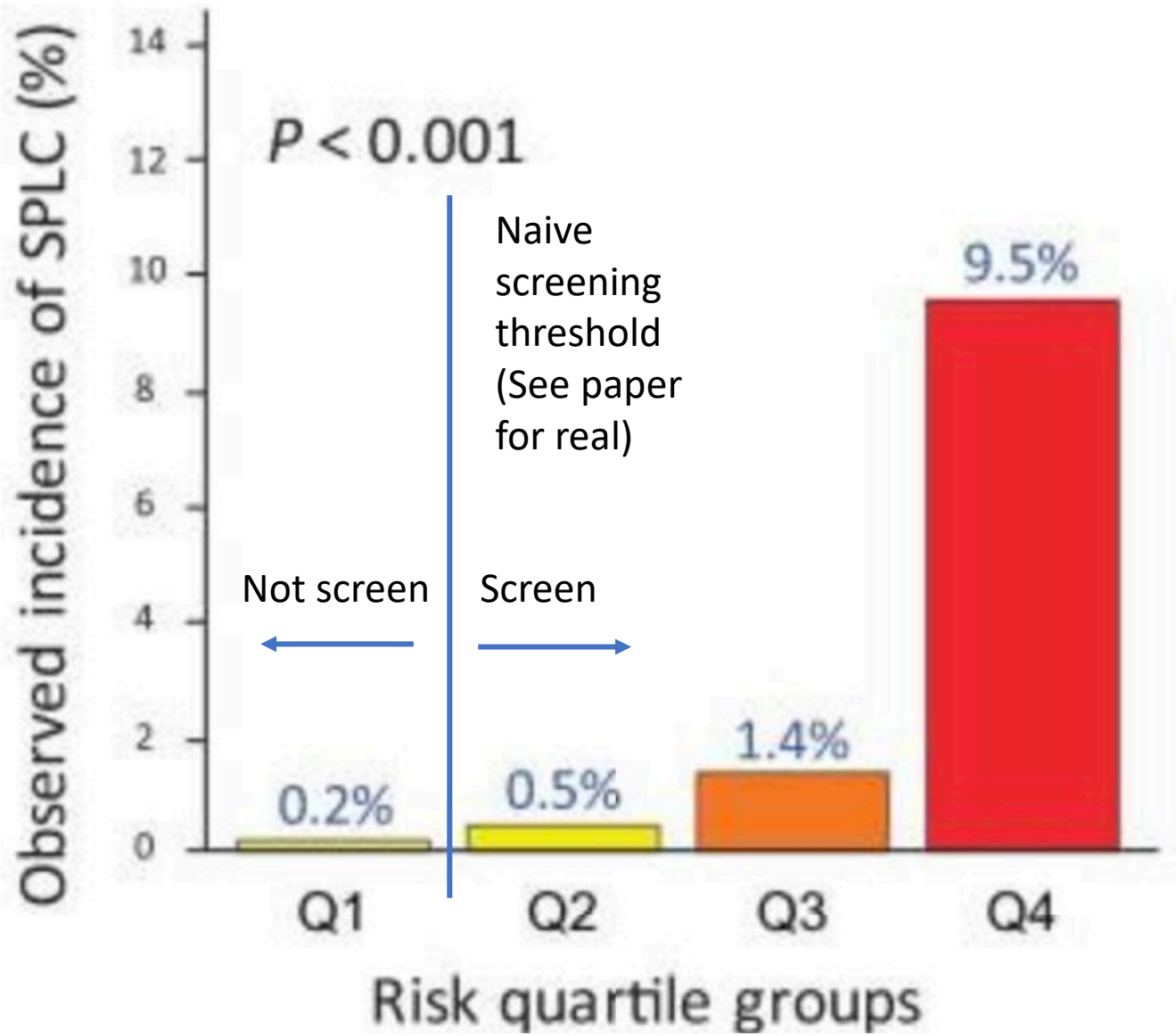
Our model is externally validated in multiple datasets



Evaluation of model on validation cohort

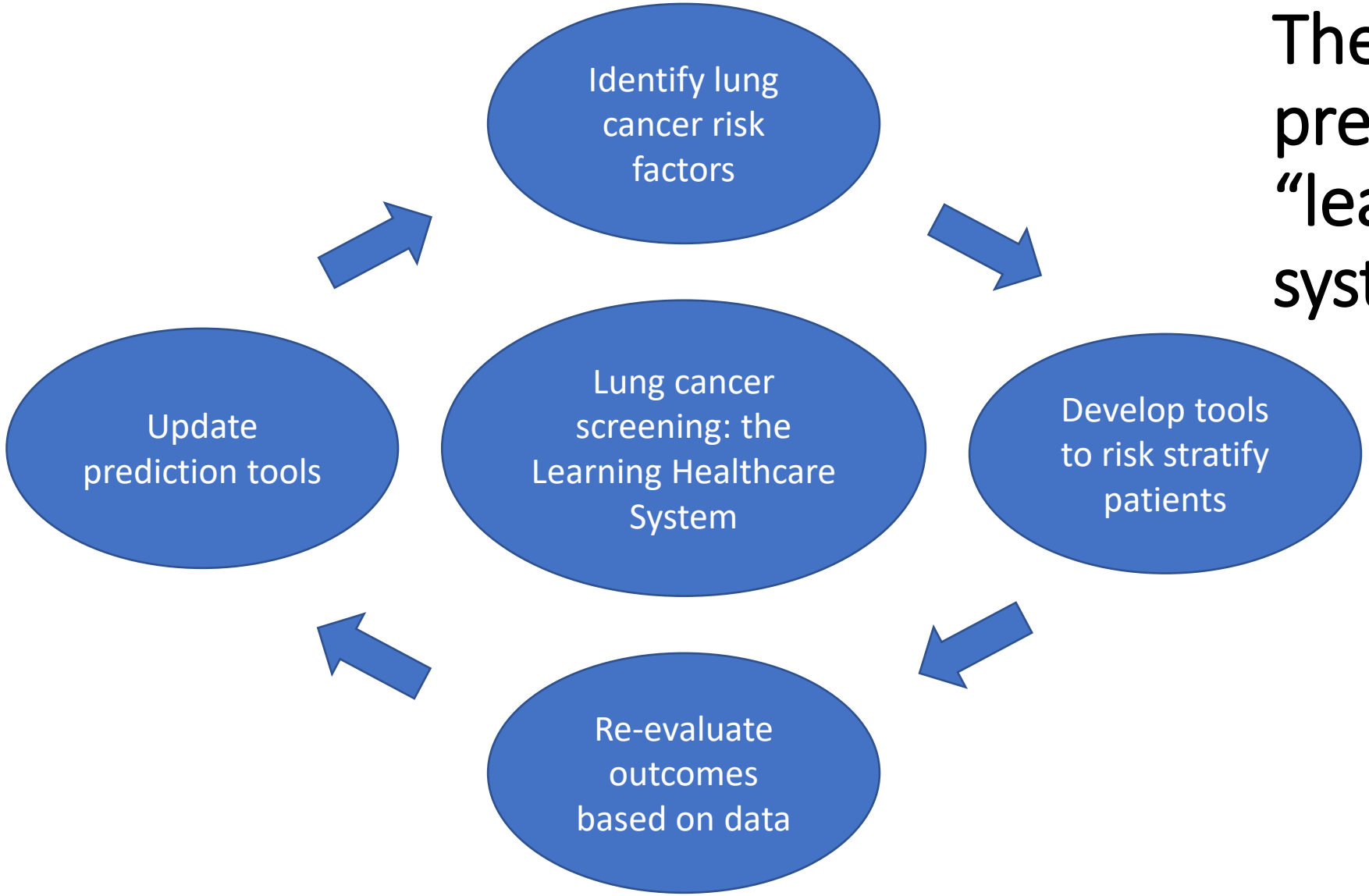
- ✓ Predicted 98% of SPLC
- ✓ Foregoing 25% of screenings misses only 2% of SPLC

See paper for smarter decision process



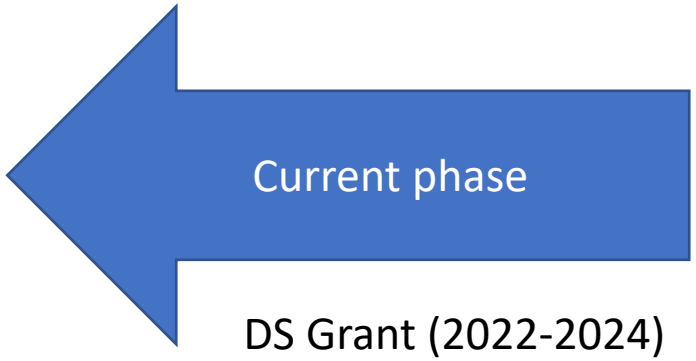
Choi et. al. JNCI 2022

The future of precision oncology: a “learning healthcare system”



Next steps

- ✓ Stanford patient model
- **VA patient model**
- **Implementing in clinical practice**
- Regional & national trials
- Policy change



DS Grant (2022-2024)

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- Diversity Supplement and funding opportunities

Mentored diversity supplement (RD-22-029)

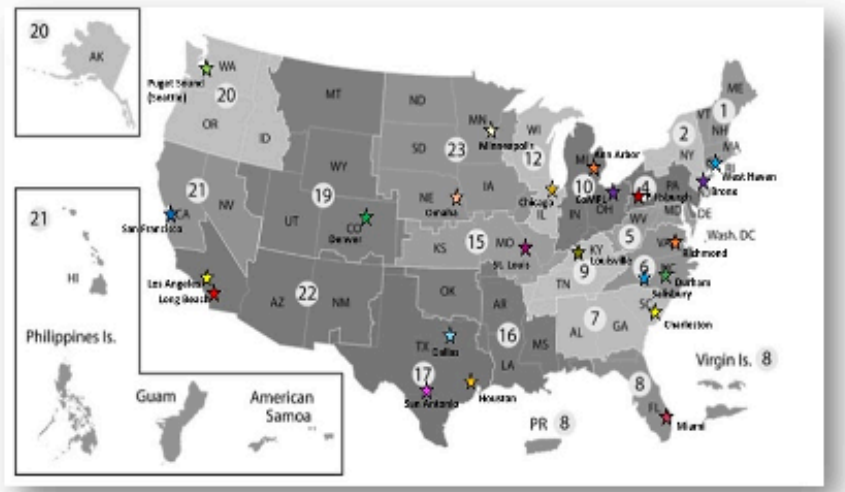
- Goal: “Designed to provide support for mentored VA research experiences for early career scientists from diverse backgrounds (see definitions below) to ultimately develop an application for a VA-ORD CDA award”
- Requirements: VA Merit funded PI as mentor
- Funding deadline: August 1 2022
- Biggest advice: VA grant checkboxes -- Find someone who has previously reviewed for DS or CDA

Website: https://www.research.va.gov/funding/diversity.cfm

VA Precision Oncology Funding priorities and opportunities (from ORD)

The Lung Precision Oncology Program (LPOP) demonstrates the incredible work VA Research can perform by working together

Nationwide network of lung cancer sites.
Hub in every VISN, 85 total hub + spoke sites.



- LPOP is a national network in lung cancer research and clinical care, including: lung cancer screening, smoking cessation, genomic testing, and clinical trials
- Strong clinical and operations support
- Clinicians and researchers working side-by-side to improve Veterans well-being
- Coordinating center at West Haven Cooperative Studies Program
- Serving as a model for additional research-clinical collaborations

Takeaways

- Real-world data can be used to generate real-world evidence (RWE) to complement clinical trials
- Precision oncology is expanding at a rapid pace and RWE is needed to keep up
- VA funding strongly supports RWE and implementation of precision oncology

- Interested in lung cancer, genomics, screening, or clinical trials? Talk to us!

Thank you!

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- **Summer Han**
- **Shipra Arya**
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- **Leah Backhus**
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- Millie Das
- Joel Neal
- Allison Kurian
- Keith Humphreys

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- Ted Thomas

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C-19

Washington University in St. Louis

The COVID-19 & Cancer Consortium

Appendix

Estimated vaccine effectiveness in cancer patient subgroups

Group	1-RR (95% CI)
Overall	58 (39 to 73)
Cancer category	
Solid malignancy	66 (48 to 79)
Hematologic malignancy	19 (-68 to 65)
Treatment timing[a]	
Distant treatment (>6 months)	85 (29 to 100)
Recent treatment (3-6 months)	63 (23 to 87)
Current treatment (0-3 months)	54 (28 to 72)
Treatment after vaccine	49 (-110 to 100)
Treatment type (0-3 months)[b]	
Current chemotherapy-containing	57 (-23 to 91)
Current targeted	29 (-84 to 75)
Current endocrine	76 (50 to 91)