St. Elizabeth HEALTHCARE

BIOMARKER OVERVIEW - ONCOLOGY
KY HOUSE PRESENTATION

Michael Gieske, MD

October 26, 2022 11:00 am

St. Elizabeth PHYSICIANS

BIOMARKERS

Cancer Predilection - Prediction, Risk Modeling

Genetic Markers
Proteomics
Proteins/Genes – genetic predeterminants

Cancer Detection – Determine Presence of Disease

Cf (cell-free) DNA and RNA
Proteins shed into blood
MCED – Multi-Cancer Early Detection, SCED – Single-Cancer Early Detection

Cancer Direction - Treatment

Liquid Biopsies (blood test)
Tissue biopsies (pathology)

- To determine treatments – Driver Gene Mutations - Precision Medicine - targeted therapies
- Tracking therapy – cancers change and evolve – keeping ahead – determine aggressiveness
- Monitoring success of treatment – predict how the patient will respond

Development and validation of a protein biomarker panel in the Lung Cancer Cohort Consortium

Hilary A. Robbins, PhD MHS MSPH
International Agency for Research on Cancer | RobbinsH@iarc.fr | @hilaryarobbins

Mattias Johansson

Hilary Robbins

Paul Brennan

Florence Guida

Karl Smith Byrne

Hana Zahed

Andreea Spanu

Karine Alcala

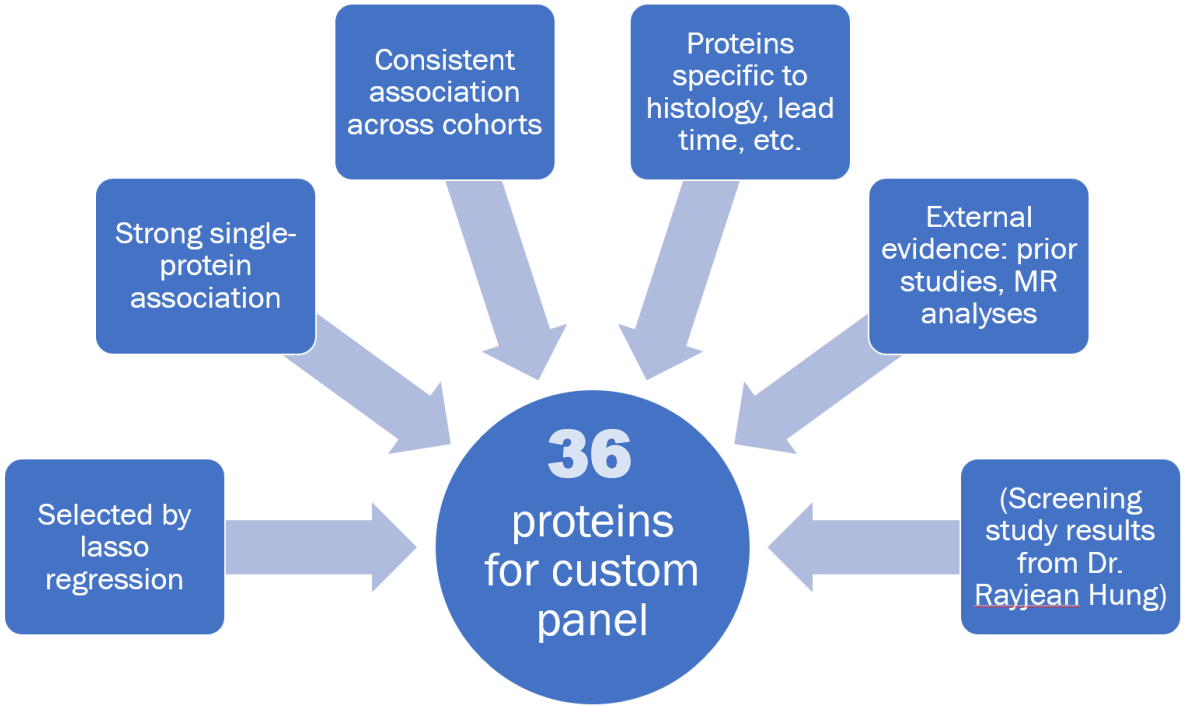
The INTEGRAL (Integrative Analysis of Lung Cancer Etiology and Risk) U19 Program

- Project 1: Genetics
  - Dr Chris Amos, Baylor College of Medicine, Texas, USA
- **Project 2: Pre-diagnostic biomarkers**
  - **Dr Mattias Johansson, Dr Hilary Robbins, & Dr Paul Brennan, IARC, France**
- Project 3: Screening biomarkers & radiomics
  - Dr Rayjean Hung, Lunenfeld-Tanenbaum Research Institute, Toronto

Initial studies indicated that protein markers can improve lung cancer risk models

SEHC will participate with the IARC/WHO to be a R01 subsite for this international study

Expected outcome



Robust answers to a few questions:

Can circulating proteins improve the discrimination of standard lung cancer risk prediction models? By how much?

How does this affect who is classified as screening-eligible?

How does the performance of lung cancer risk models vary across geography and ethnicity?

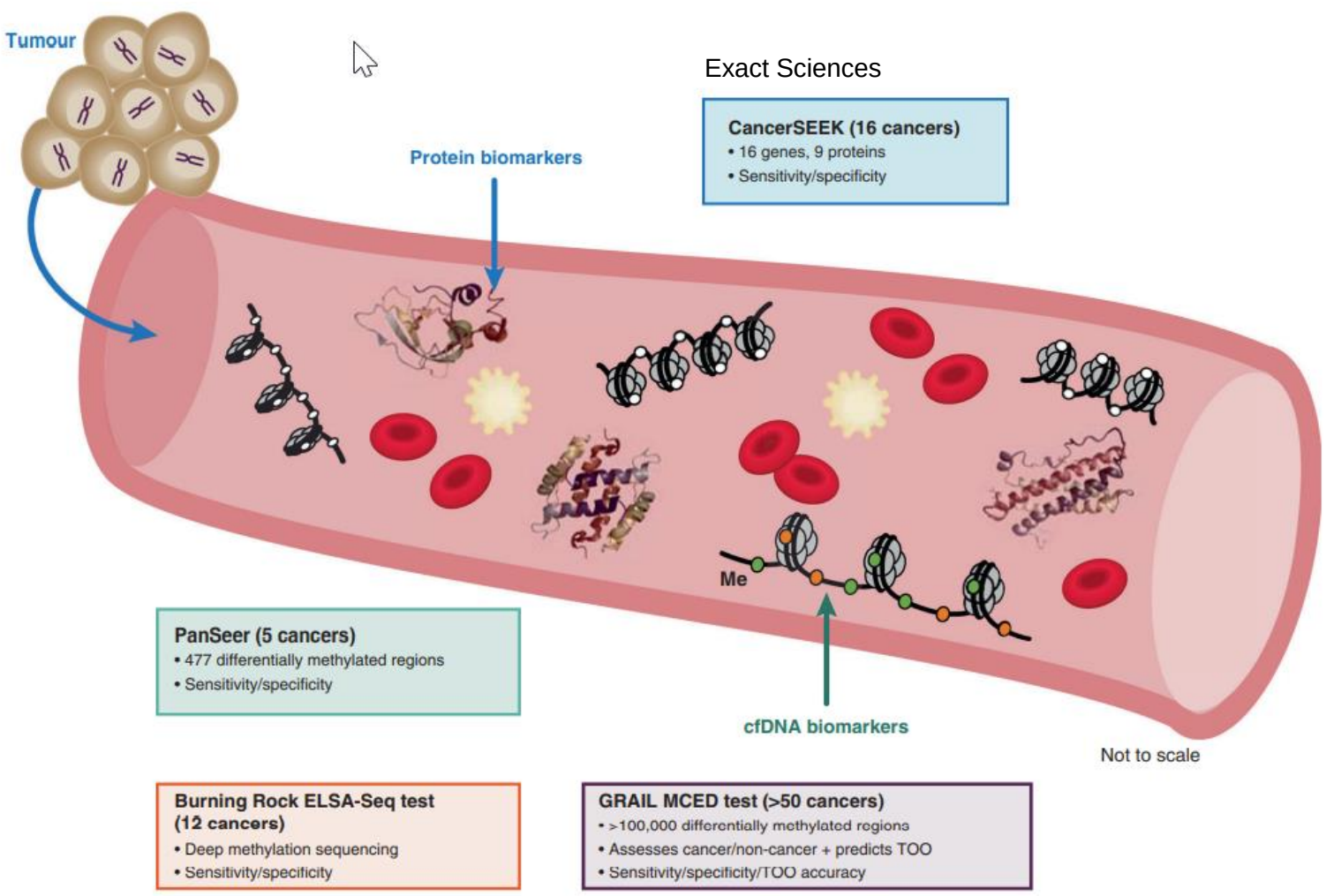
DETECTION - MCED – MULTI-CANCER EARLY DETECTION

- We've proven that early detection reduces mortality for 6 cancers: cervix, lung, breast, colon/rectal, prostate
- Some MCEDs can detect over 50 cancers
- Will this expanded testing reduce mortality for the other cancers detected?
- We need to harness regional, state, national, and international registries and real-world data

DETECTION - MCED – MULTI-CANCER EARLY DETECTION

- Circulating DNA, RNA can detect and indicate deadly cancers in asymptomatic people
- The Public will embrace the concept of a blood test that can find cancer
- Can increase screening rates, even for cancers for which we already have screening tests
- These tests are coming; they are here!

DETECTION - MCED – MULTI-CANCER EARLY DETECTION



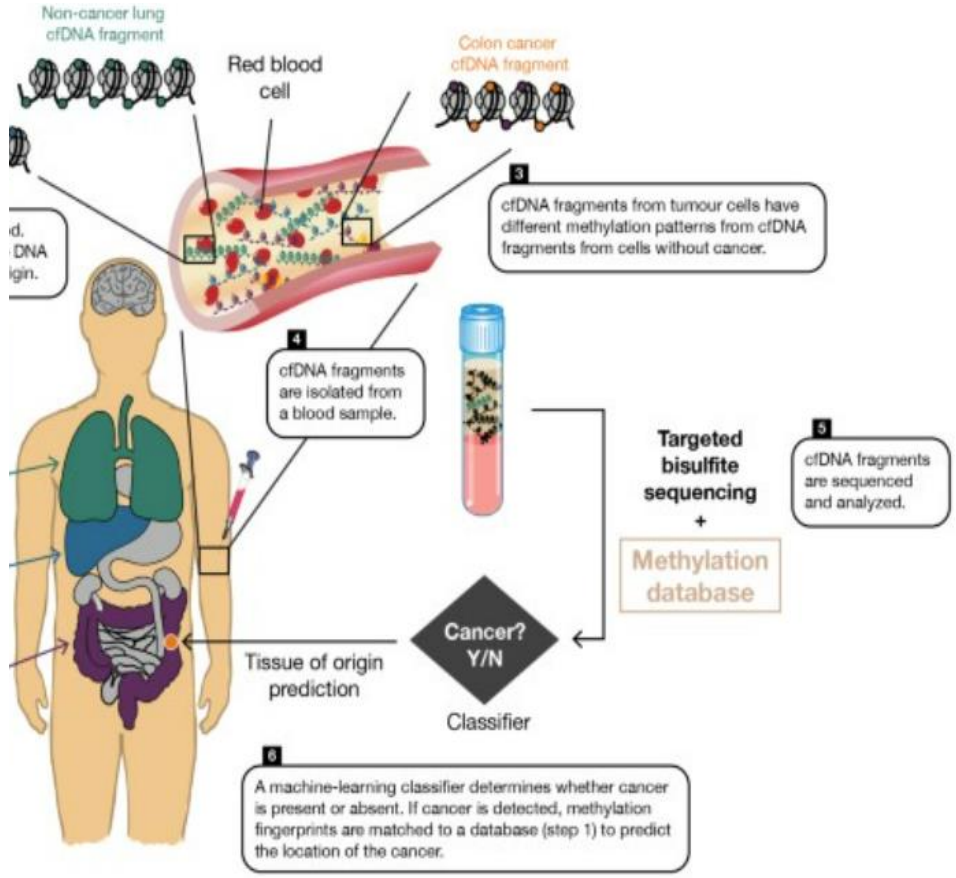


Fig. 1 Attributes of multi-cancer detection methods. MCED multi-cancer early detection, TOO tumour of origin.

British Journal of Cancer (2021) 124:1475–1477; https://doi.org/10.1038/s41416-020-01223-7

g DNA methylation patterns in blood. A targeted methylation-
can recognize differences in DNA methylation patterns in cell-free
DNA (cfDNA) fragments in a blood sample. These patterns are characteristic of different cell types and
abnormally methylated cfDNA can be used to detect cancer and map its location in the body.

Joshua J. Ofman, MD, MSHS; Megan P. Hall, PhD; Alexander M. Aravanis, MD, PhD GRAIL, Inc., 1525 O'Brien Dr., Menlo Park, CA 94025

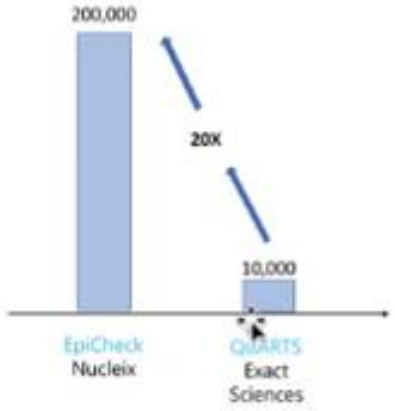
DETECTION - HIGH SENSITIVITY DETECTION METHYLATED CF-DNA, SCED

CANCER SCREENING REQUIRES FOUR KEY ELEMENTS

Nucleix is differentiated on all key elements required for early cancer detection

Best Performance

EpiCheck® has 20X analytical sensitivity



Patient-Friendly

EpiCheck® is a convenient blood or urine test, ideal for broad adoption

Simple, Flexible

EpiCheck® can leverage local labs for speed and ease of use, by running on standard lab equipment (qPCR)

Affordable

EpiCheck® CoGS <$30, allows for reasonable pricing — crucial for early screening & monitoring

Currently there are no liquid biopsy early detection tests for lung cancer. Large market opportunity for early detection of lung cancer patients

A SIMPLE BLOOD TEST COULD BE USED AS AN ADJUNCT TO LOW DOSE CT

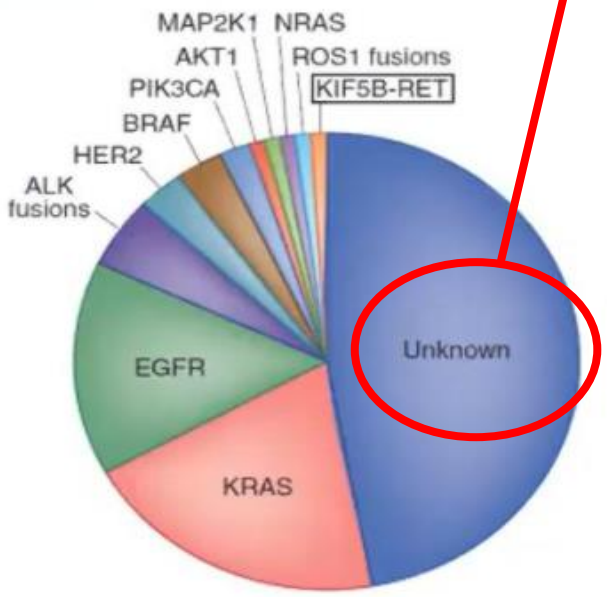
DETECTION - MCED – MULTI-CANCER EARLY DETECTION

- These tests are:
  - Expensive
  - Not included in present screening guidelines
  - Not covered by insurance, not FDA approved
  - Will generate the need for expensive and sometimes hard to access follow-up testing
  - Will they contribute to existing healthcare disparity and inequities?

DIRECTION – CONFRONTING NIHILISM – THE NEW FRONTIER

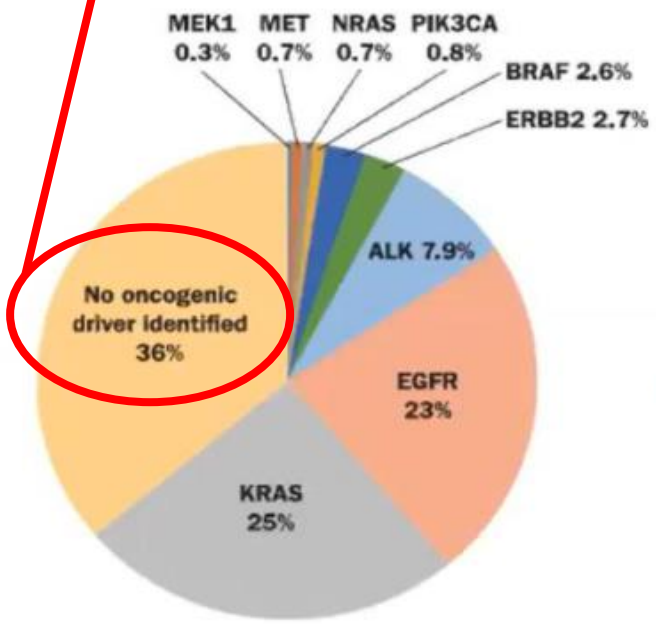
Non-Squamous Non-Small Cell Lung Cancer Biomarkers

~50%



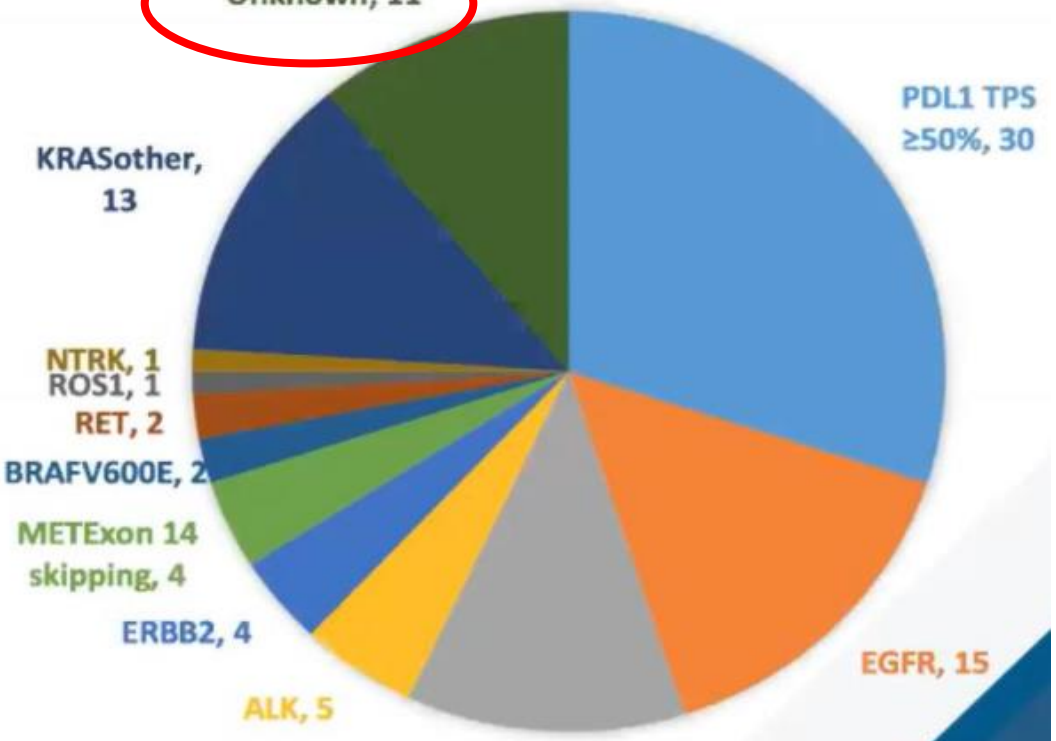
Pao and Hutchinson 'Chipping away at the lung cancer genome'
Nature Medicine. **March 2012**

36%



Scholl et al. Lung Cancer Mutation Consortium
J Thorac Oncol. **May 2015**

11%



2020: biomarkers with drug targets

There is a targeted therapy revolution, being led by lung cancer

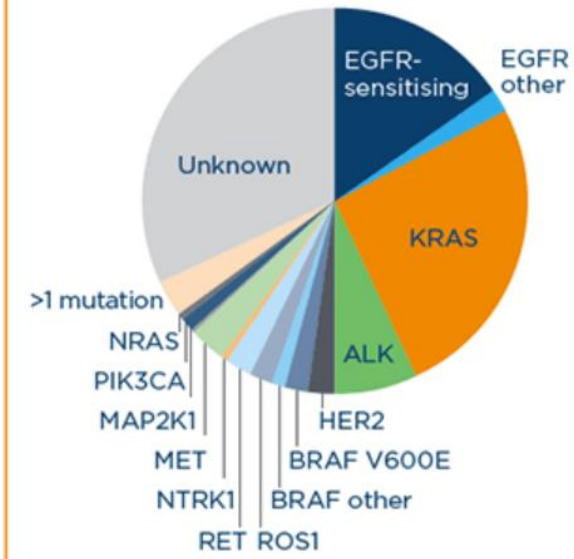
BIOMARKERS – CANCER TREATMENT

Targeted Therapies- for mutations; genetic abnormalities(variants) in cancer cells

Nine (9) Genes with driver mutations for which there are FDA-approved targeted therapies for the treatment of lung cancer:

- **ALK** – Xalkori/crizotinib, Alecensa/alectinib, Alunbri/brigatinib, Zykadia/certinib, Lobrena/loratinib
- **BRAF V600E** - combined Tafinlar/dabrafenib and Mekinist/tremetinib
- **EGFR** – Tarceva/erlotinib, Gilotnif/afatinib, Iressa/gefitinib, Tagrisso/osimirtinib (AZ, 2015), Rybrevant/amivantamab, Portrazza/necitumab, Excivity/mobocertinib (9/15/21)
- **KRAS G12C** – Lumakras/sotorasib
- **MET exon 14 skipping** – Xalkori/crizotinib, Cometriq/cabozantinib
- **NTRK**– Vitrakvi/larotrecinib, Rozlytrek/entrectinib
- **RET**– Gavreto/pralsetinib, Cometriz/carbozantinib
- **ROS1**– Xalkori/crizotinib, Rozlytrek/entrectinib, Lobrena/lorlatinib
- **HER2 /not amplifications**– Herceptin/trastuzumab, TDM-1 ado-trastuzumab ematansine

DRIVER MUTATIONS IN LUNG ADENOCARCINOMA



Driver mutations in lung adenocarcinoma	
EGFR-sensitizing	15%
EGFR other	2%
KRAS	25%
ALK	7%
HER2	2%
BRAF V600E	2%
BRAF other	1%
ROS1	2%
RET	2%
NTRK1	0–5%
MET	3%
MAP2K1	0–5%
PIK3CA	1%
NRAS	0–5%
>1 mutation	3%
Unknown	31%

All current FDA-approved targeted therapies treat non-small cell lung cancer (NSCLC). There are as yet no approved targeted therapies for small cell lung cancer

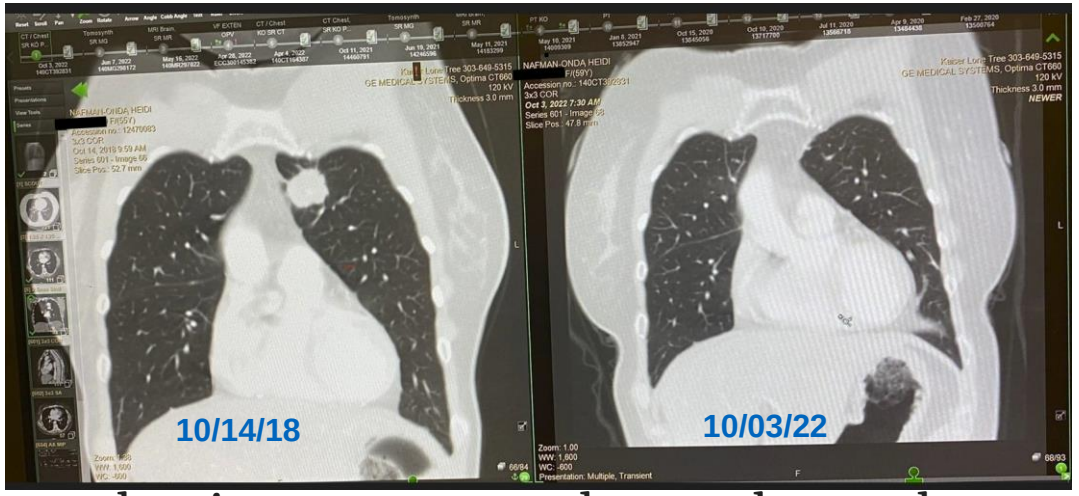
IMMUNOTHERAPY – THE OTHER FRONTIER

Immunotherapy drugs are treatments that work by essentially boosting the ability of the immune system to fight cancer.

One category of immunotherapy drugs is checkpoint inhibitors, of which five drugs are currently available for treating non-small cell lung cancer (with different indications):

American Cancer Society, Immunotherapy for non-small cell lung cancer. Updated April 18, 2019.

- Opdivo (nivolumab)
- Keytruda (pembrolizumab)
- Tecentriq (atezolizumab)
- Imfinzi (durvalumab)
- Yervoy (Ipilimumab)



Not everyone responds to immunotherapy, but in some cases, the results can be very dramatic with long-term control of the disease. Unfortunately, there is not yet a tool in place to predict who will respond to these drugs.

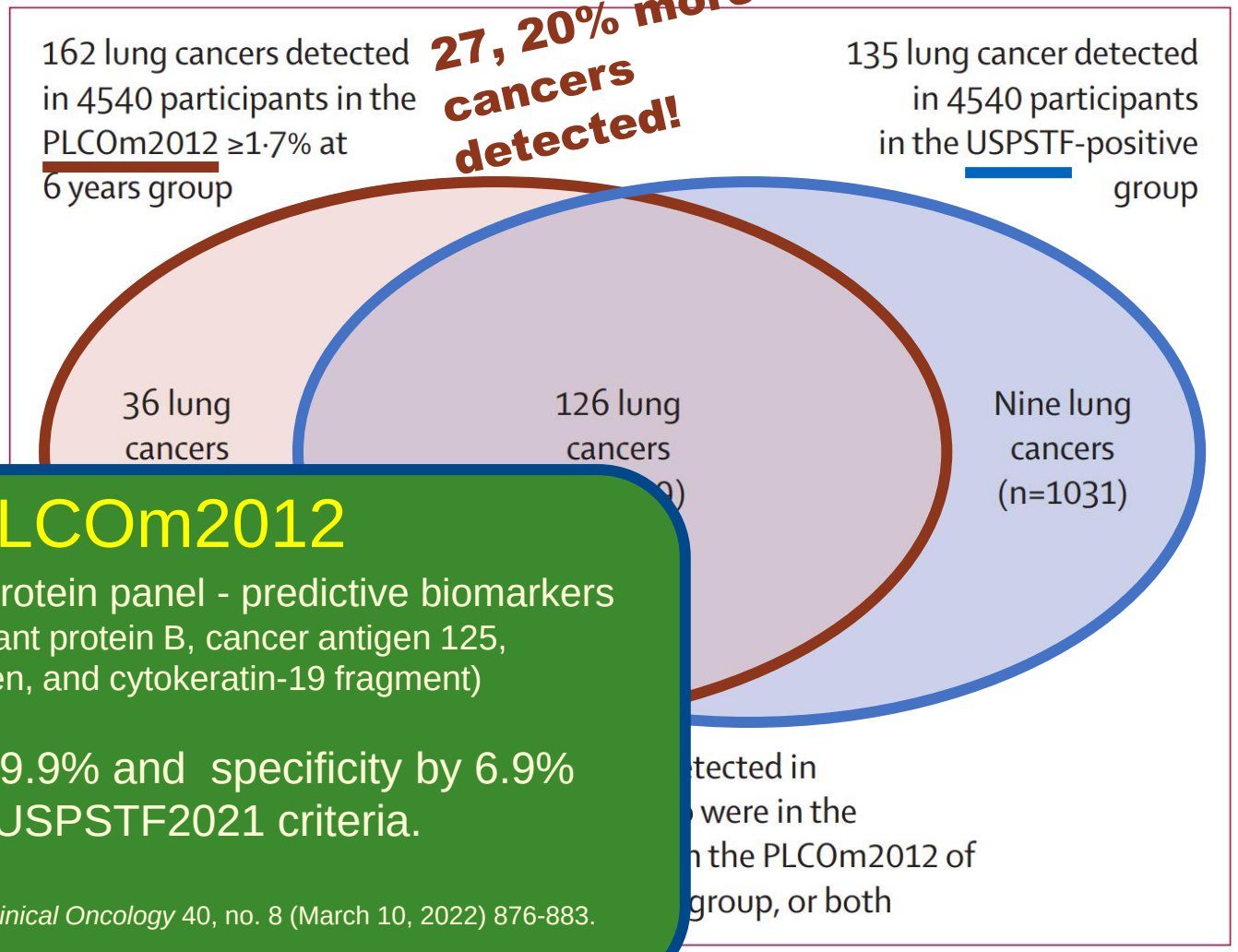
ONGOING RESEARCH, THERAPEUTIC TRIALS

- Unfortunately, even when cancers respond favorably and succumb to treatment, they eventually outsmart the treatments and develop resistance to the targeted therapies.
- Previously, we did not know this to be the case as lung cancer patients did not outlive their first lines of treatment.
- Now we are discovering that we need to be nimble and correct course as cancers outsmart the targeted therapies. Biomarker testing will guide this course adjustment. We need new replacement therapies or combined therapies that are less likely to succumb to resistance.

RISK PREDICTION MODELS

PLCOm2012

We have implemented and utilized the PLCOm2012 risk prediction model to calculate risk; use ≥1.3% chance of lung cancer in 6 years. Incorporates 11 predictors: (1) age; (2) highest level of education obtained; (3) body mass index (BMI); (4) chronic obstructive pulmonary disease (C… history of cancer; (6) … cancer; (7) race and … status (former or cur… of cigarettes smoked … smoked (y); and (1) y…



4MP+PLCOm2012

Incorporates a 4 marker protein panel - predictive biomarkers
(precursor form of surfactant protein B, cancer antigen 125, carcinoembryonic antigen, and cytokeratin-19 fragment)

Improved sensitivity by 9.9% and specificity by 6.9% compared with USPSTF2021 criteria.

DOI: 10.1200/JCO.21.01460 *Journal of Clinical Oncology* 40, no. 8 (March 10, 2022) 876-883.

USPSTF2013 versus PLCOm… eligibility criteria (Internati… interim analysis of a prospective …

Martin C Tammemägi, Mamta Ruparel, Alain Tremblay, Renelle Myers, John Mayo, John Yee, Sukhinder Atkar-Khattra, Ren Yuan, Sonya Cressman, John English, Eric Bedard, Paul MacEachern, Paul Burrowes, Samantha L Quaife, Henry Marshall, Ian Yang, Rayleen Bowman, Linda Passmore, Annette McWilliams, Fraser Brims, Kuan Pin Lim, Lin Mo, Stephen Melsom, Bann Saffar, Mark Teh, Ramon Sheehan, Yijin Kuok, Renee Manser, Louis Irving, Daniel Steinfort, Mark McCusker, Diane Pascoe, Paul Fogarty, Emily Stone, David C L Lam, Mina-Yen Na, Varut Vardhanabhuti, Christine D Berg†, Rayjean J Hung, Samuel M Janes, Kwun Fong*, Stephen Lam *Lancet Oncol* 2022; 23: 138–48

…igure: Venn diagram describing the distribution of individuals and lung cancer cases by criteria (USPSTF2013 positivity and PLCOm2012 ≥1·7% at 6 years status)

WE NEED A BETTER RISK PREDICTION MODEL/ALGORITHM

- 20% Lung Cancers in the United States occur in individuals without a history of smoking
- SEHC – 55.2% lung cancers not within CMS 2015 criteria, 2015 - 2021
- Radon is considered to be a major risk factor for non-smoking related Lung Cancers
- In Asia and Africa, cooking oils and open wood burning without ventilation is a major risk factor
- Family history is a substantial risk factor and increases with the number of relatives affected
- Air pollution is a major risk factor in many areas of the world
- In Taiwan, 53% of Lung Cancer occurs in individuals with no smoking history

AS WE MAKE PROGRESS,

- Cancer Care is entering an extraordinary era
- Lung Cancer has been increasingly at the forefront of many emerging technologies and treatments
- We can not tolerate progress for some but not for others
- Achieving equitable cancer care and outcomes is going to become increasingly difficult

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HEALTHCARE

THANK YOU!