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Biomarker Testing
Tuesday, October 31, 2023

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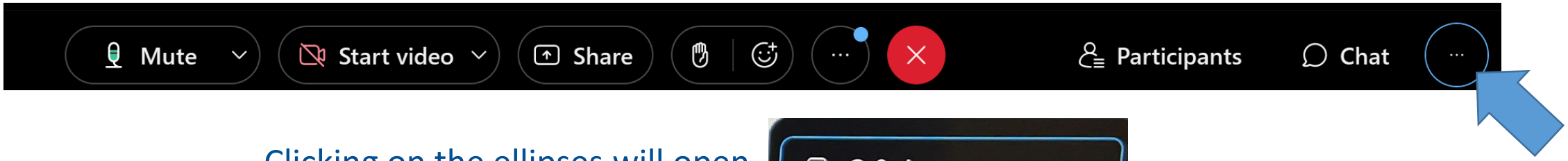
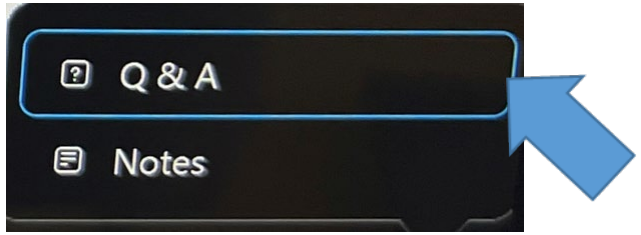
For most devices, the **Q&A function** can be found by clicking on the ellipses at the bottom of your screen on the far right.



Clicking on the ellipses will open a new menu, which will then allow you to click on **Q&A.**



- With the **Q&A** window open, type in your question and send to **HOST** or **Ashley Tait-Dinger.**
- There is a 512-character limit for questions.
- If we are unable to address your questions during the online presentation, we will try to have the remaining questions answered following the session and posted with the follow up material.
- For participants who have called in, to mute/unmute use *6
- Please reserve the **CHAT** function for technical questions to the **HOST.**

For Questions Related to Technical or Logistical Issues use the CHAT FUNCTION

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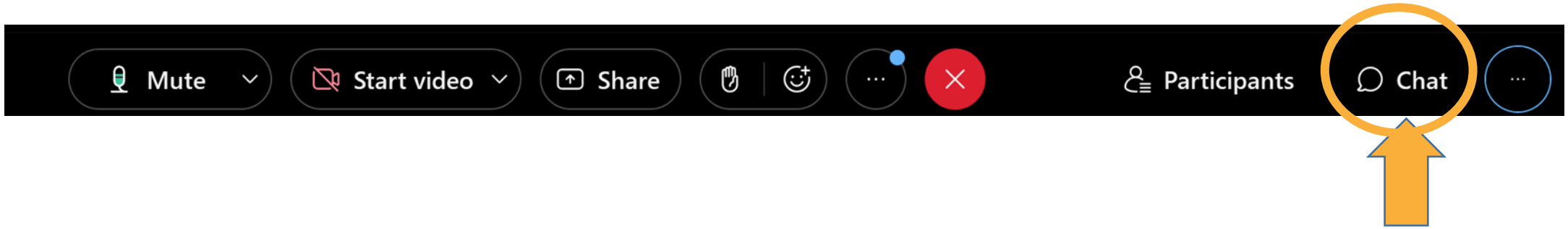
Technical Issues

We request the **Chat function** be reserved for technical or logistical issues or questions.



- With the Chat window open, type in your question and send to **Ashley Tait-Dinger (Host).**
- There is a 512-character limit for questions.
- We will address your issue as quickly as possible.

Today's Topic and its Importance

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- Biomarker testing can ensure that patients receive therapies from which they are most likely to benefit while avoiding treatments that are unlikely to be effective or could cause harm
- Biomarker testing can potentially limit costs to the patient and the plan
- On November 21, we are holding a webinar on Cell and Gene Therapies - we will explain what they are and how to manage their cost

Today's Speakers

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Our expert panelists:

Federico Monzon, MD
Executive Leader at the Association for Molecular Pathology

Susan Harbin, J.D.
American Cancer Society Cancer Action Network

Marian Birkeland, PhD
National Comprehensive Cancer Network

Biomarker Testing

Federico A. Monzon, MD

Disclaimer

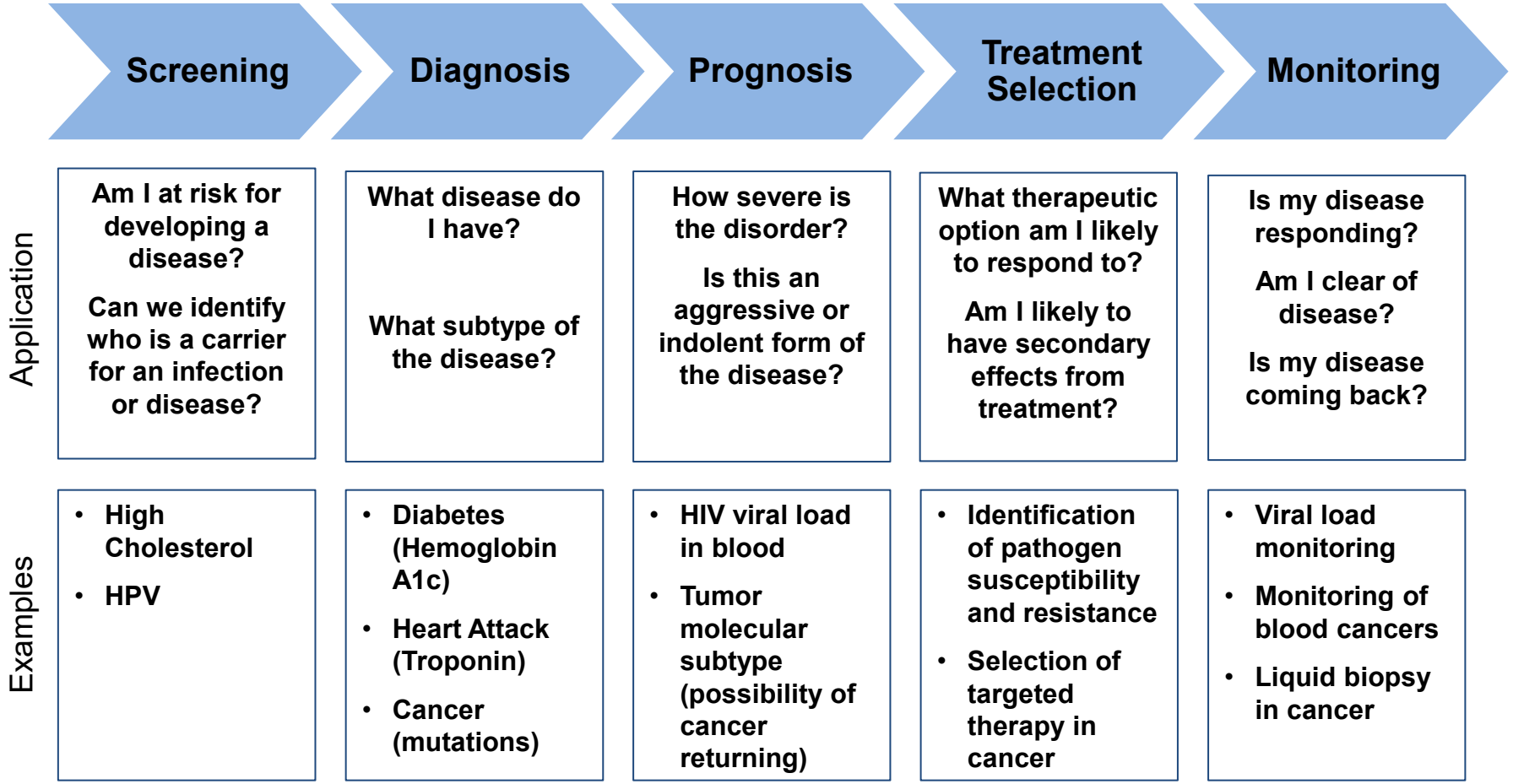
- Developing and bringing new biomarkers to patients is the focus of my professional life and my consulting business. I hold stock in biomarker companies

- Opinions in this presentation and/or in the subsequent panel discussion are mine only and do not necessarily represent the positions of the Association for Molecular Pathology or other organizations

What is a biomarker?

- A biomarker (short for biological marker) is an objective measure that captures what is happening in a cell or an organism at a given moment.
  - Many biomarkers come from simple measurements made during a routine doctor visit, like blood pressure or body weight.
  - Other biomarkers are based on laboratory tests of blood, urine, or tissues.
  - Some capture changes at the molecular and cellular level by looking at genes or proteins.
- Biomarkers are very important to medicine in general because they can tell us how the body's doing, or how it is responding to disease or treatment
- Biomarkers are at the core of what we call today "Personalized Medicine"

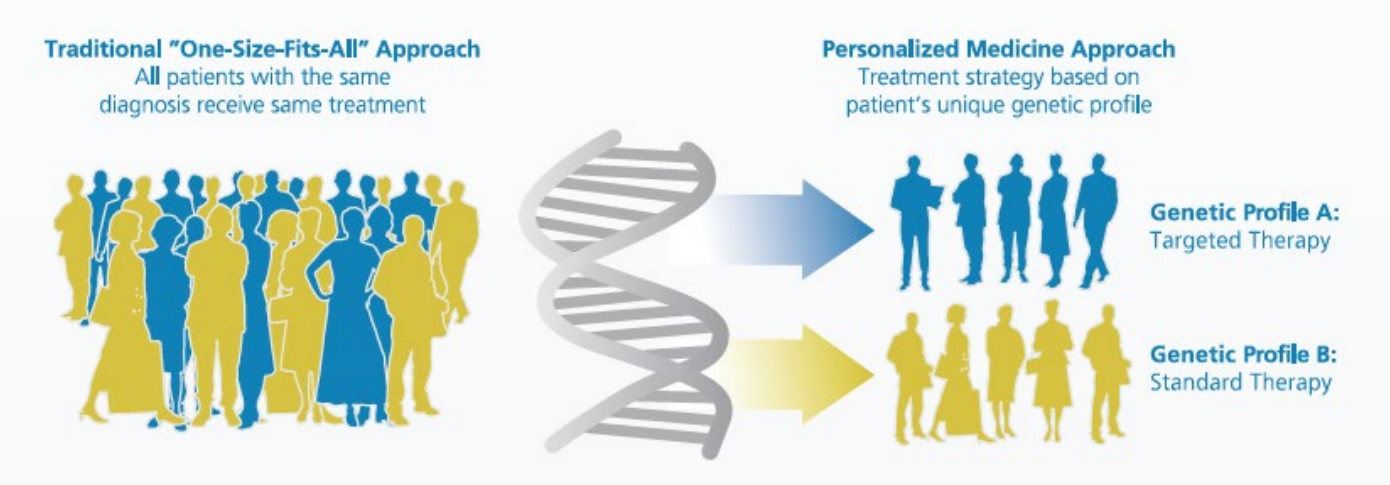
Biomarkers in the Continuum of Medical Care



AMP Association for Molecular Pathology

What is personalized medicine?

Before Now



Personalized medicine has been defined as medical treatment selection based on individual characteristics of each patient (*i.e.* **biomarkers**) to classify individuals in subpopulations that differ in their susceptibility for specific diseases or response to specific treatments.

With this, preventive or therapeutic interventions can be concentrated on those who benefit from them, leading to better utilization of resources and limiting secondary or adverse events in patients who do not benefit.

AMP Association for Molecular Pathology

Biomarkers are an essential component of modern cancer medicine

Uses of biomarkers in cancer care:

- **Help find some early-stage cancers.** Your doctor can use your biomarkers to catch things in your body that are not normal. Early detection of cancer is very important.
- **Predict how serious a cancer might be.** Biomarkers can also help your doctor understand how far along a cancer is in your body.
- **Look at how you might respond to a cancer treatment.** This can help your care team find a proper treatment for you. Biomarkers can also tell how well a treatment works for you over a period of time. Because of this, experts are looking at how biomarker testing can replace image-based tests like CT scans and MRIs.
- **Monitor how likely it is for cancer to come back.** In some cases, if you have a tumor, doctors will take cells from that tumor and look at biomarkers. They'll give a recurrence risk score. This will tell you how likely it is that your cancer could come back.

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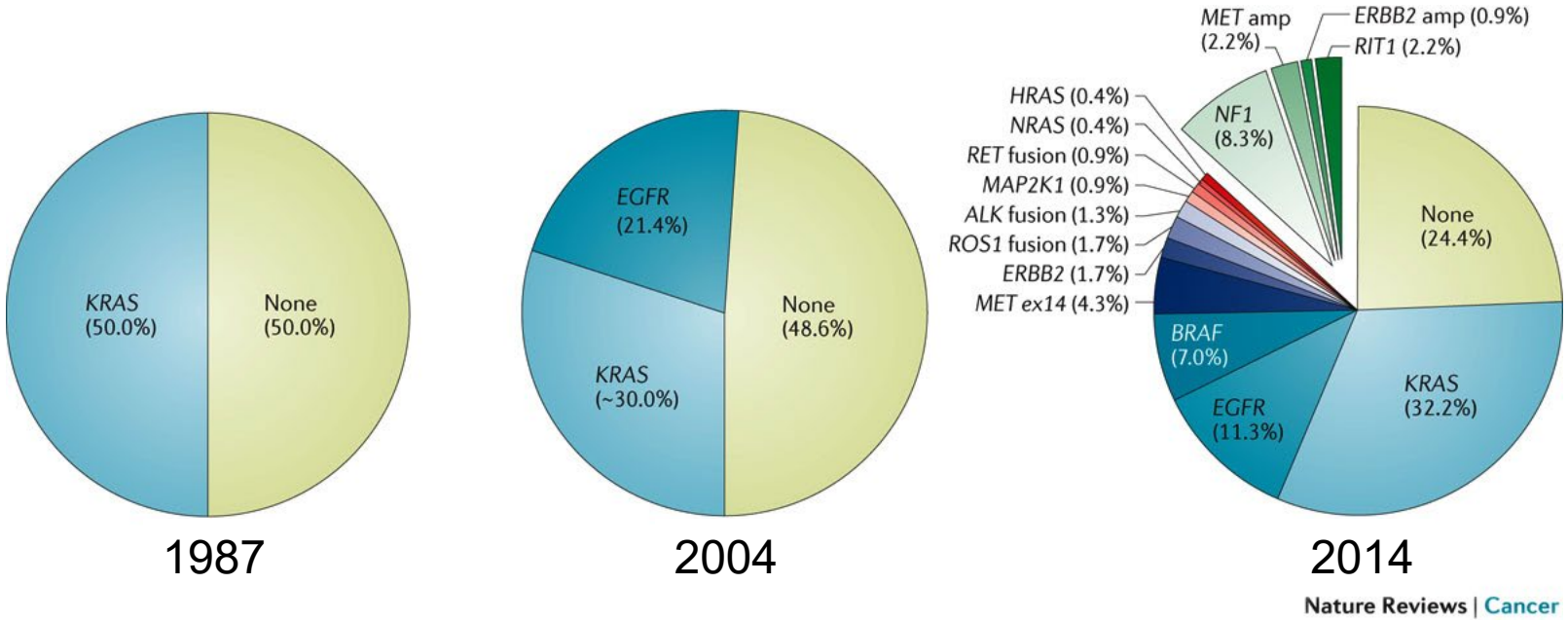
Example: Biomarkers in Lung Cancer

Advances in technology has led to better understanding of disease over time

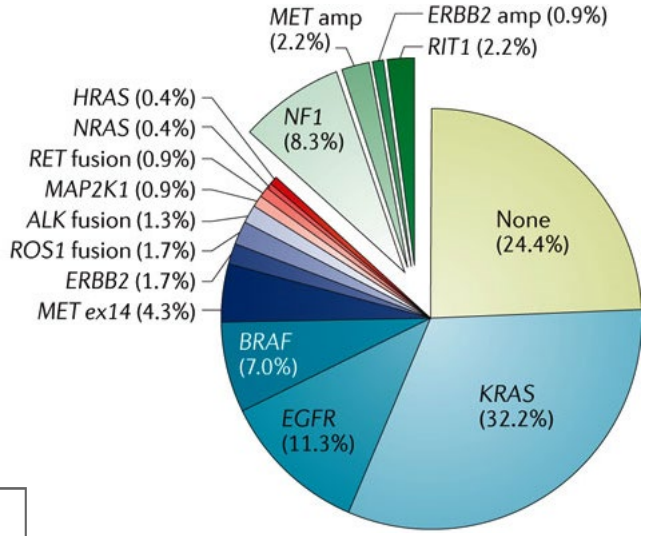


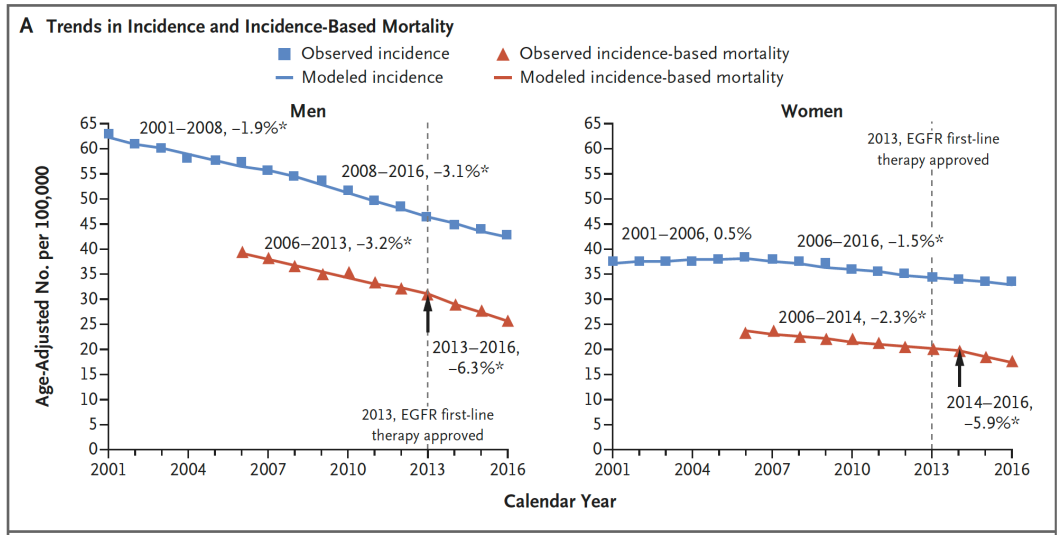
This knowledge allows us to better care for these patients

AMP Association for Molecular Pathology

Example:
Biomarkers in Lung Cancer

- *Many of these lung cancer subtypes respond to novel lung cancer targeted therapies*
- *A decrease in lung cancer mortality has been shown to occur at the time targeted therapies started being used*





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Biomarkers are an essential component of modern ~~cancer~~ medicine

Biomarkers help us:

- Identify people at risk for disease
- Diagnose disease and find it earlier
- Predict how serious a specific disease might be
- Look at how a person might respond to treatment and what treatment is better
- Monitor how the disease is responding to treatment and a new treatment is needed

AMP Association for Molecular Pathology

Thank You!

federico@genomicpath.net

Expertise that advances patient care through education, innovation, and advocacy.

www.amp.org

AMP Association for Molecular Pathology

Biomarker Testing and Targeted Therapies

American Cancer Society Cancer Action Network℠

Susan Harbin
Senior Government Relation Director
susan.harbin@cancer.org

Barriers to Cancer Biomarker Testing

Coverage of tests differs greatly across payers

- Coverage policies generally more common for single-gene tests vs. multi-gene panel tests

Plans aren't necessarily following the evidence

- A recent paper in *Personalized Medicine* highlights gaps between insurance coverage and clinical practice guidelines.
  - Although 91% of plans evaluated reference NCCN treatment guidelines in their biomarker testing policies, 71% are "more restrictive" than these guidelines for biomarker testing in breast, non-small cell lung cancer, melanoma and/or prostate cancer patients.
- **In Florida, 75% of commercial insurance plans provide coverage that is more restrictive than NCCN guidelines**. This shows that many patients in our state could be missing out on needed testing that could connect them with a targeted therapy.

Wong, W., et al. (2022) *Alignment of health plan coverage policies for somatic multigene panel testing with clinical guidelines in select solid tumors.*

What does this look like for a patient?

Kathy is a 54-year-old white woman with no history of tobacco use. After visiting her primary care physician for persistent cough and shortness of breath, she was ultimately referred to an oncologist. Her oncologist ordered a diagnostic CT scan which revealed a large mass in the left lung with lymph node involvement. A biopsy confirmed stage IV non-small cell lung cancer, and her PET/CT scan was consistent with extensive bone metastases.

Kathy, 54
Lung Cancer Patient

Without Comprehensive Biomarker Testing

JANUARY → FEBRUARY → MARCH → APRIL → MAY → JUNE → JULY → AUGUST → SEPTEMBER → OCTOBER → NOVEMBER → DECEMBER

5 cycles of chemoimmunotherapy. Causes shortness of breath.

Insurance only covers single marker testing for ALK and EGFR. No mutations found.

Starts combination chemotherapy. Must **stop working due to side effects.**

ER visit for shortness of breath. CT scan shows tumor continues to grow.

Rebiopsy to test for another single marker, **RET.** No mutation found.

Switches to another chemotherapy due to toxicity. **After 5 cycles, a CT scan shows the tumor continues to grow.**

Rebiopsy and single marker test for ROS1 **reveals ROS1 mutation.**

Starts targeted oral therapy. **Disease stabilizes.**

With Comprehensive Biomarker Testing

Comprehensive biomarker testing reveals a **ROS1 mutation**.
Starts targeted oral therapy. **Disease stabilizes.**

JANUARY → FEBRUARY → MARCH → APRIL → MAY → JUNE → JULY → AUGUST → SEPTEMBER → OCTOBER → NOVEMBER → DECEMBER

Legislation to Address Coverage Gaps

Requires state-regulated insurance plans including Medicaid to cover comprehensive biomarker testing when supported by medical and scientific evidence

Biomarker testing must be covered for the purposes of diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition when the test is supported by medical and scientific evidence, including, but not limited to:

1. Labeled indications for an FDA-approved or -cleared test
2. Indicated tests for an FDA-approved drug;
3. Warnings and precautions on FDA-approved drug labels
4. Centers for Medicare and Medicaid Services (CMS) National Coverage Determinations and Medicare Administrative Contractor (MAC) Local Coverage Determinations; or
5. Nationally recognized clinical practice guidelines and consensus statements.

Disease and stage agnostic

American Cancer Society Cancer Action Network℠

Why Disease Agnostic?

Biomarker testing applications extend beyond oncology

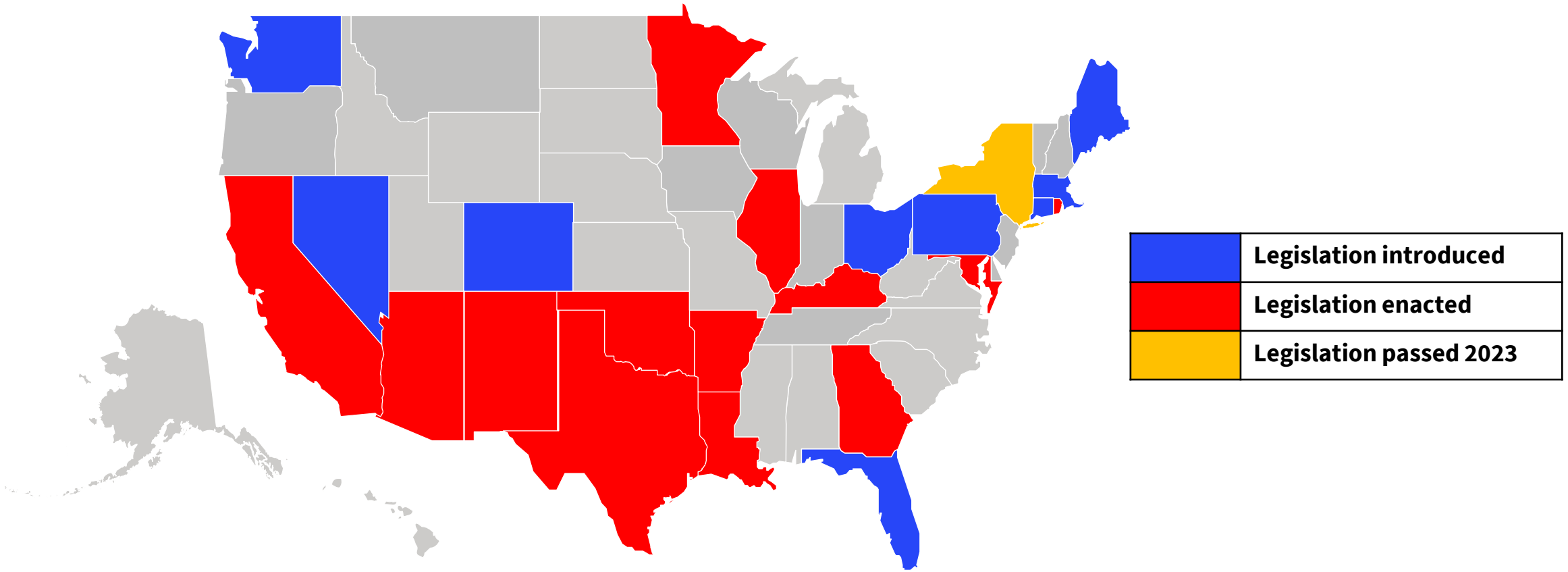
- Biomarker testing is increasingly important for the treatment of diseases including:
  - Arthritis and other autoimmune conditions
  - Rare diseases

Research is happening in many other areas including Alzheimer's, other neurological conditions, and cardiology.

Cancer patients and survivors have high rates of comorbidities

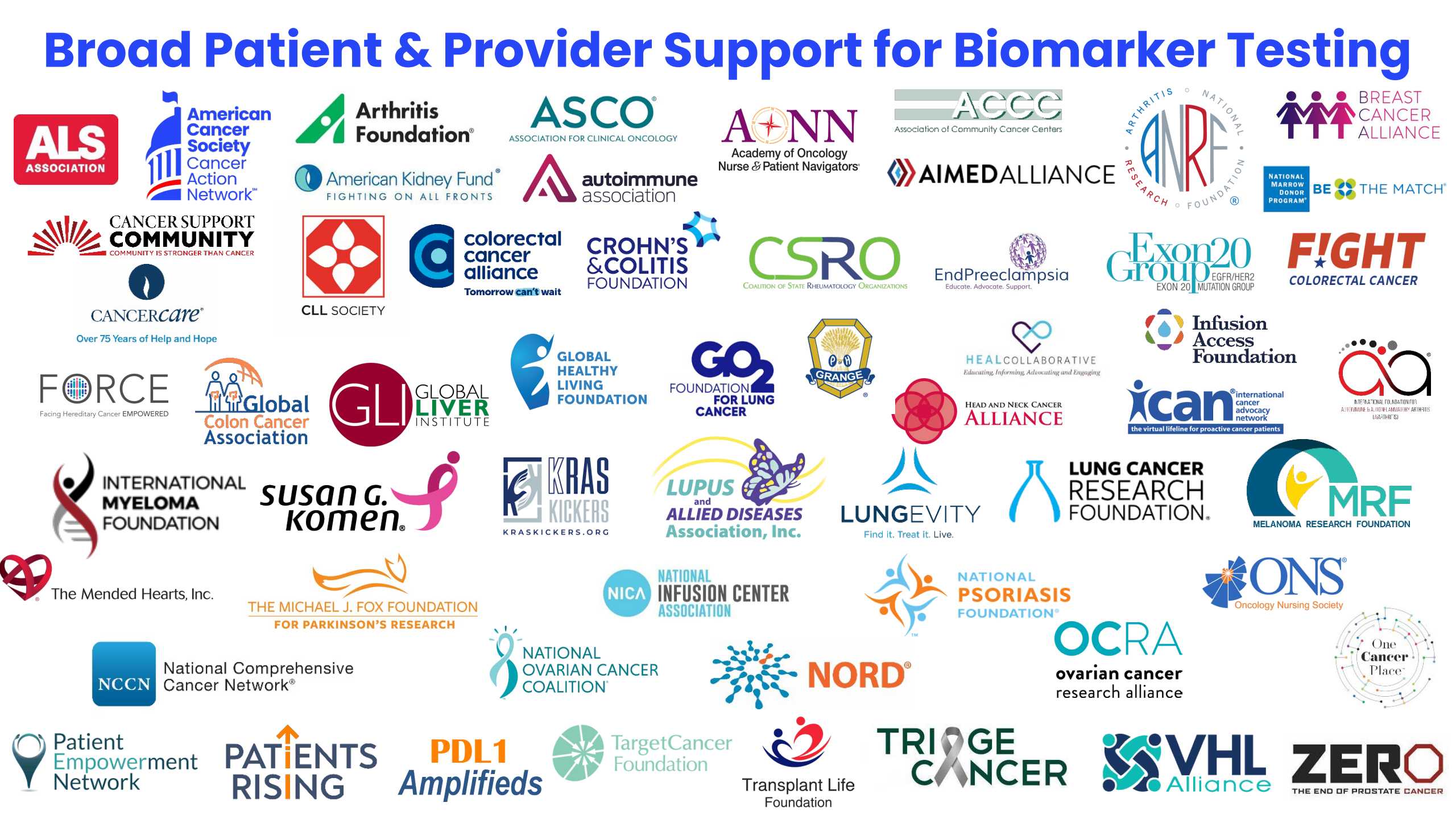
- Substantial progress has been made in the fight against cancer in recent decades, resulting in a 33% reduction in the cancer death rate since its peak in 1991.
- As patients are living longer, and some cancers become more of a chronic condition, cancer patients are often living with one or more comorbidities.
  - Most common comorbidities include diabetes, cardiac conditions (COPD, congestive heart failure, cerebrovascular disease), peripheral vascular disease), renal failure, and rheumatological conditions.
  - A recent study found that nearly two-thirds of patients diagnosed with colorectal cancer, lung cancer, or Hodgkin's lymphoma had at least one comorbidity at the time of their diagnosis, and about half of patients had multiple comorbidities.

Legislation to Expand Access to Biomarker Testing



Legislation enacted: AZ, CA, IL, LA, RI, KY, NM, AR*, GA, MD, MN, TX, OK
Legislation passed in 2023: NY
Legislation introduced: CO, CT, FL, MA, ME, NV, OH, PA, WA
*commercial coverage only

Broad Patient & Provider Support for Biomarker Testing



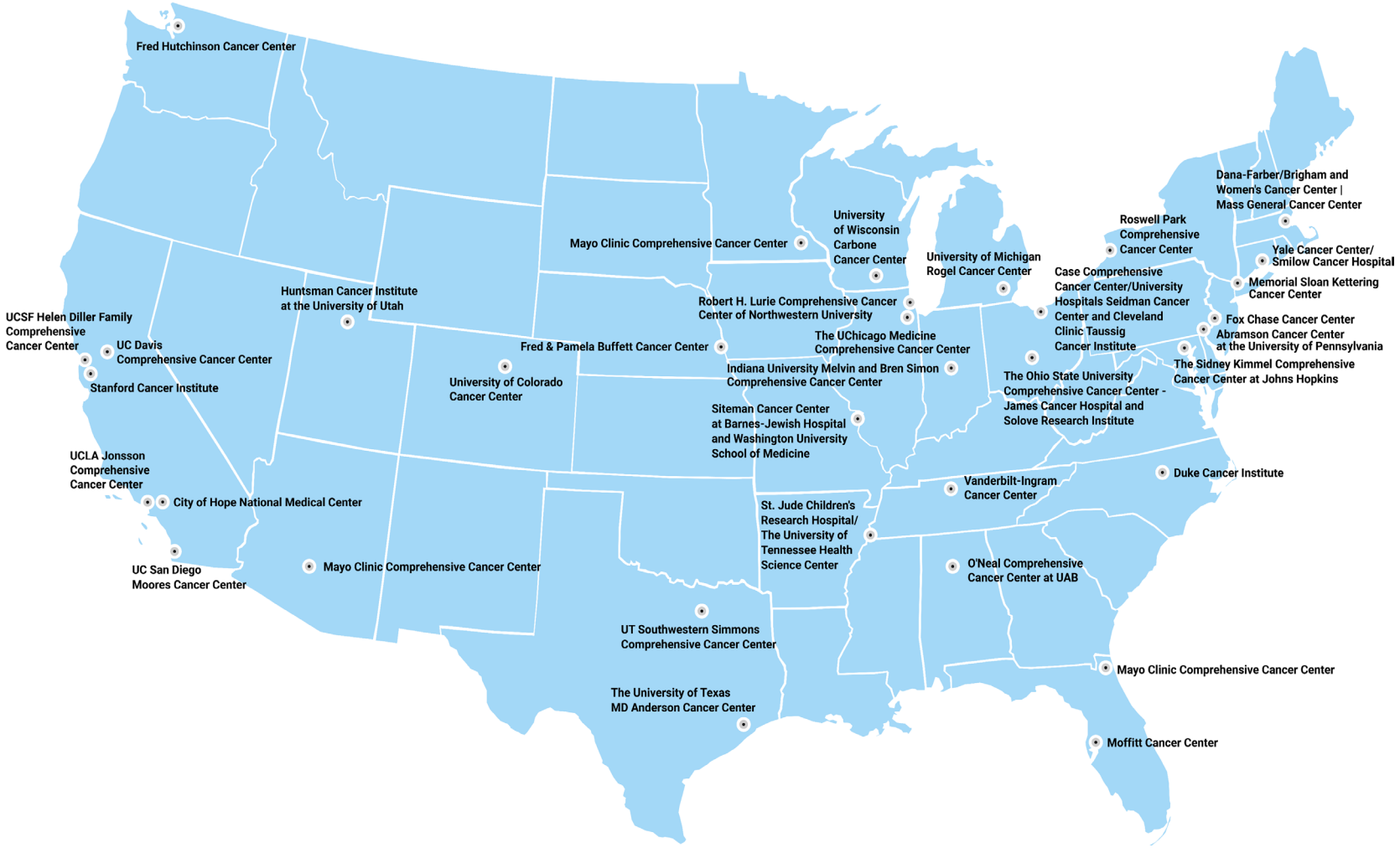
National Comprehensive Cancer Network®

NCCN and Biomarker Testing

Marian Birkeland PhD, Senior Director,
Compendia Development, NCCN

NCCN Member Institutions

NCCN is an alliance of 33 leading cancer centers devoted to patient care, research, and education.



National Comprehensive Cancer Network®

About NCCN

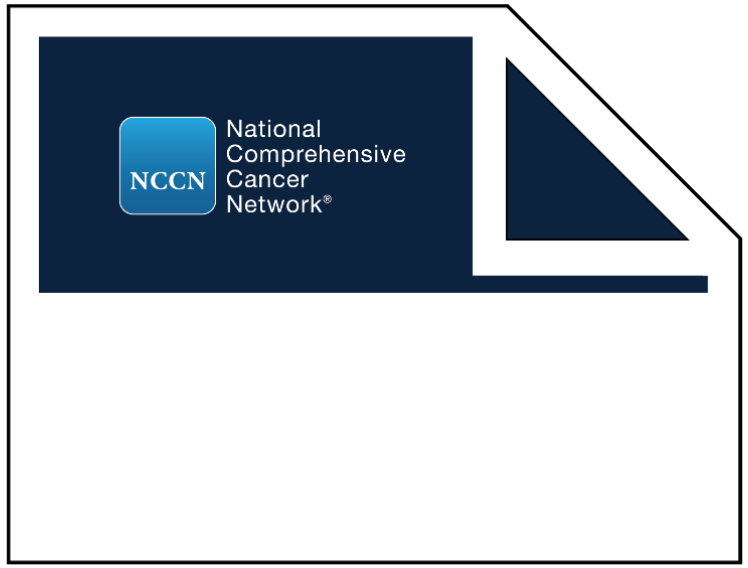
A not-for-profit alliance of 33 leading academic cancer centers in the United States

- Arbiter of high-quality cancer care
- Develops and communicates scientific, evaluative information to better inform the decision-making process between patients and physicians
- Develops and promotes national programs to facilitate the fulfillment of Member Institution missions
- Strives to improve and facilitate quality, effective, equitable, and accessible cancer care

National Comprehensive Cancer Network®

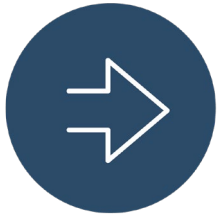
NCCN Guidelines®

85 NCCN Guidelines® feature 218 algorithms that apply to 97% of cancer cases in the United States



About the NCCN Guidelines®

The NCCN Guidelines are the most thorough and most frequently updated clinical practice guidelines available in any area of medicine



- The recognized standard for clinical policy in cancer care in the United States
- Widely available free of charge for non-commercial use
- Basis for insurance coverage policy and quality evaluation

National Comprehensive Cancer Network®

NCCN Guidelines® Expertise

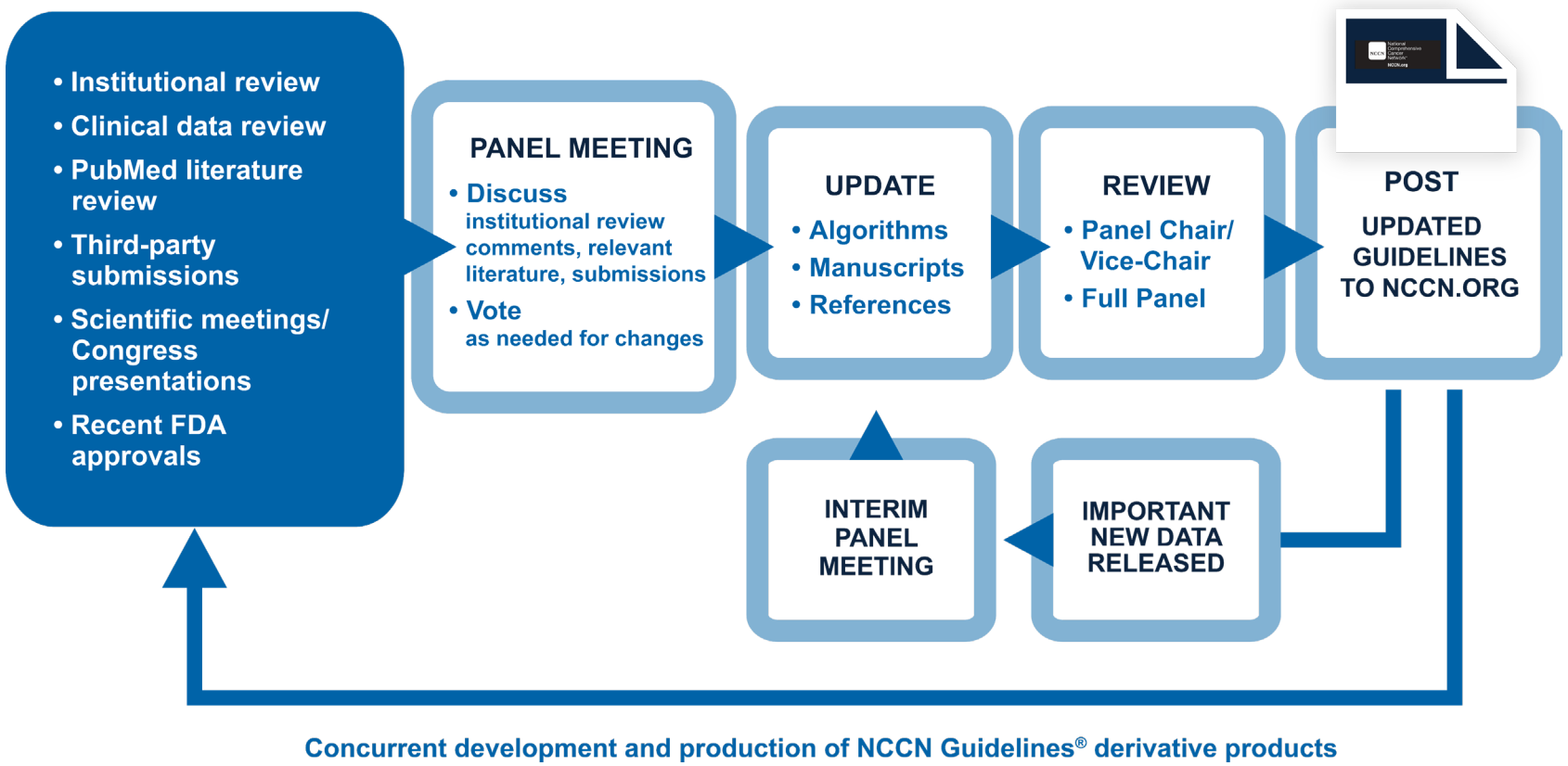
- **61 NCCN Guidelines Panels** are comprised of multidisciplinary, disease- and issue-specific subspecialists who are clinicians, researchers, and advocates.
- **More than 1,800 Panel Members** participate in developing and updating NCCN Guidelines.
- It is estimated that NCCN Guidelines **Panel Members contributed more than 44,000 hours in 2022.**

Multidisciplinary NCCN Guidelines® Panels

- Medical oncology
- Surgery/Surgical oncology
- Radiation oncology
- Hematology/Hematology oncology
- Bone Marrow Transplantation
- Urology
- Neurology/Neuro-oncology
- Gynecologic oncology
- Otolaryngology
- Orthopedics/Orthopedic oncology
- Pathology
- Dermatology
- Internal medicine
- Gastroenterology
- Endocrinology
- Diagnostic Radiology
- Interventional Radiology
- Nursing
- Cancer genetics
- Psychiatry, psychology
- Pulmonary medicine
- Pharmacology/Pharmacy
- Infectious diseases
- Allergy/Immunology
- Anesthesiology
- Cardiology
- Geriatric medicine
- Epidemiology
- Patient advocacy
- Palliative, Pain management
- Pastoral care
- Oncology social work

NCCN Guidelines® Development

The NCCN Guidelines are continuously updated and revised to reflect new data and clinical information.



Concurrent development and production of NCCN Guidelines® derivative products

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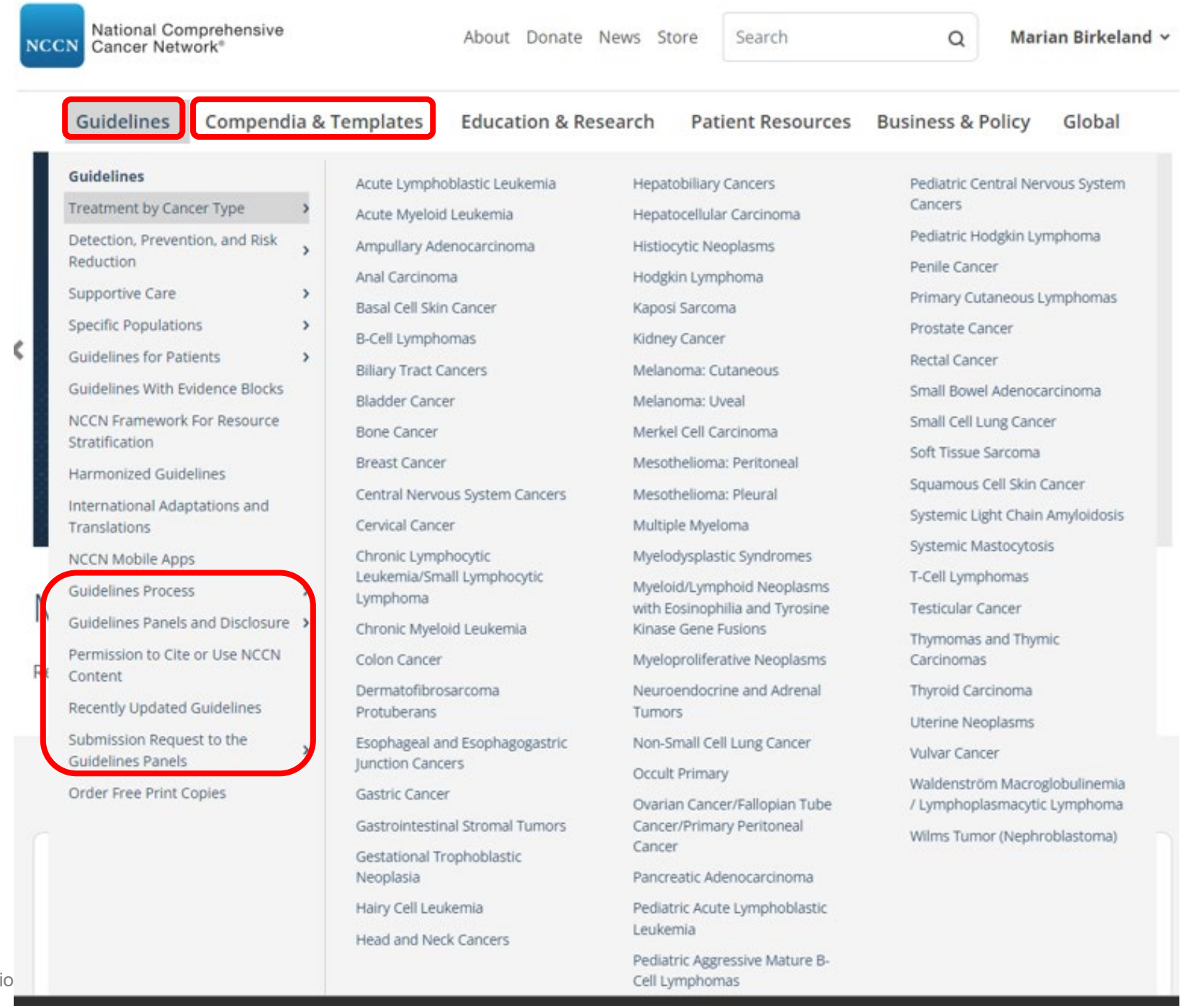
NCCN Guidelines® Firewall

NCCN imposes strict policies to shield the guidelines development processes from external influences

- The “firewall” surrounding the NCCN Guidelines processes includes:
  - financial support policies
  - panel participation and communication policies
  - guidelines disclosure policies
  - policies regarding relationships to NCCN’s other business development activities
- NCCN does not accept any form of industry or other external financial support for the guidelines development program.
- The guidelines development is supported exclusively by the Member Institutions’ dues.

Where to find it on NCCN.org

- Links to guidelines
- Links to more information about process and panels
- Links to Compendia



NCCN Library of Compendia

Based directly on the NCCN Guidelines

NCCN Drugs & Biologics Compendium (NCCN Compendium®)

- Lists both FDA-approved uses and appropriate uses beyond the FDA-approved label
- Recognized as an authoritative reference for oncology coverage policy by CMS and for at least 85% of covered lives through insurers

NCCN Biomarkers Compendium®

- Contains more than 1,350 biomarker recommendations

NCCN Radiation Therapy Compendium™

- Includes more than 1,007 radiation therapy recommendations

NCCN Imaging Appropriate Use Criteria (NCCN Imaging AUC™)

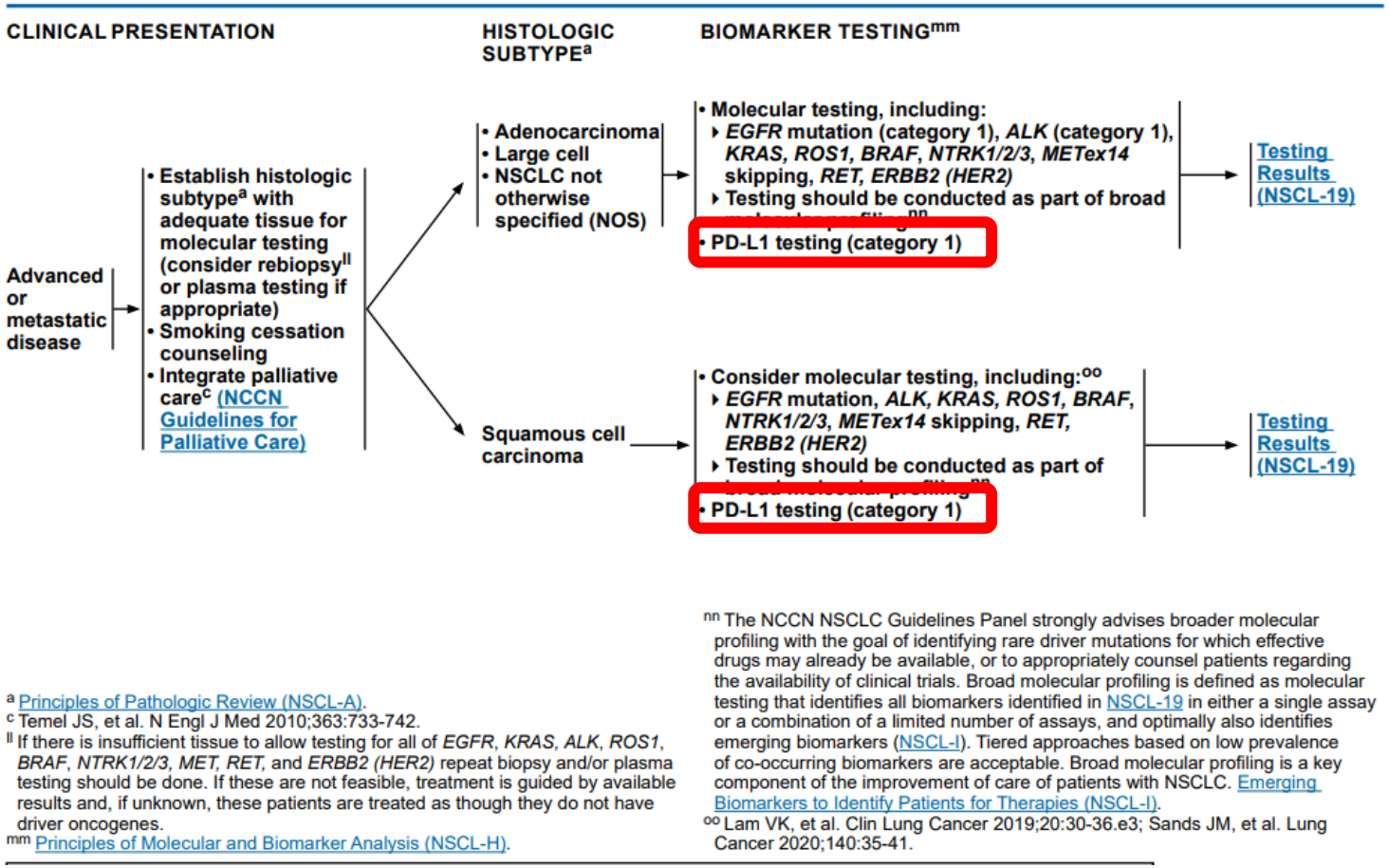
- Available for more than 10 cancer types to guide use of imaging in patients with cancer
- NCCN is a CMS-approved Provider-Led Entity

National Comprehensive Cancer Network®

Development of NCCN Biomarkers Compendium

- The Biomarkers Compendium provides essential details for those tests which are included in NCCN Guidelines
- Diagnostic, screening, monitoring, surveillance, predictive or prognostic tests are included
- Methodologic information is provided, focusing on the biology or molecular abnormality rather than on commercially available tests or test kits

Biomarker testing in NCCN Guidelines



[a] Principles of Pathologic Review (NSCL-A).
[c] Temel JS, et al. N Engl J Med 2010;363:733-742.
[ll] If there is insufficient tissue to allow testing for all of *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*, *RET*, and *ERBB2 (HER2)* repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.
[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[nn] The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is defined as molecular testing that identifies all biomarkers identified in NSCL-19 in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers (NSCL-I). Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. Emerging Biomarkers to Identify Patients for Therapies (NSCL-I).
[oo] Lam VK, et al. Clin Lung Cancer 2019;20:30-36.e3; Sands JM, et al. Lung Cancer 2020;140:35-41.

- Biomarker testing recommendations can be found within the guideline algorithm pages

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Additional Biomarker testing information in Principles sections of the guideline

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NCCN Guidelines Version 4.2023
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

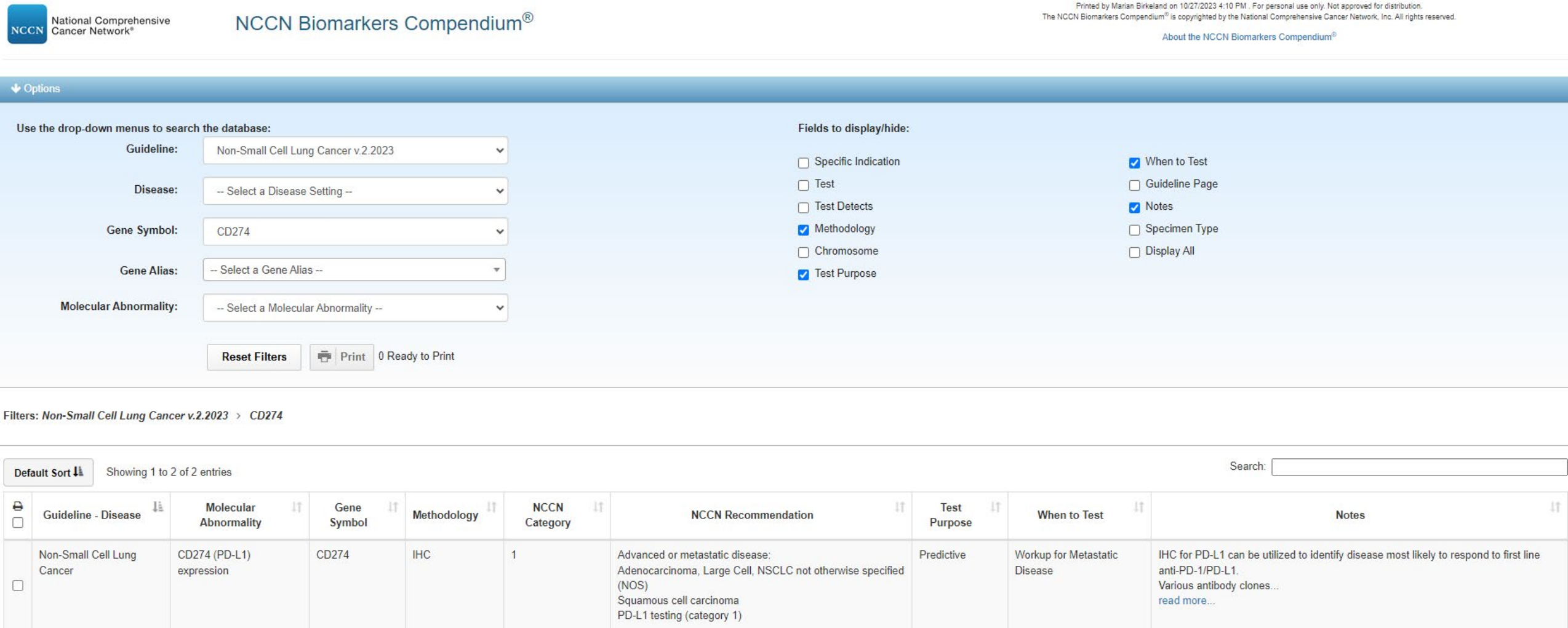
PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **PD-L1 (programmed death ligand 1): PD-L1 is a co-regulatory molecule that can be expressed on tumor cells and inhibit T-cell–mediated cell death. T-cells express PD-1, a negative regulator, which binds to ligands including PD-L1 (CD274) or PD-L2 (CD273). In the presence of PD-L1, T-cell activity is suppressed.**
  - **Checkpoint inhibitor antibodies block the PD-1 and PD-L1 interaction, thereby improving the antitumor effects of endogenous T cells.**
  - **IHC for PD-L1 can be utilized to identify disease most likely to respond to first-line anti PD-1/PD-L1.**
    - **Various antibody clones have been developed for IHC analysis of PD-L1 expression, and while several are comparable regarding intensity and proportion of cells stained, some are not.**
      - **The definition of positive and negative testing is dependent on the individual antibody, clone, and platform deployed, which may be unique to each checkpoint inhibitor therapy. The approval of multiple different assays for PD-L1 has raised concern among both pathologists and oncologists.**
      - **While some clones for PD-L1 IHC are FDA-approved for specific indications, use of multiple IHC tests is not necessary, provided any individual IHC test has been internally validated for comparability for categorical results against the FDA-approved clone.**
      - **Interpretation of PD-L1 IHC in NSCLC is typically focused on the proportion of tumor cells expressing membranous staining at any level and therefore is a linear variable; scoring systems may be different in other tumor types.**
    - **Although PD-L1 expression can be elevated in patients with an oncogenic driver, targeted therapy for the oncogenic driver should take precedence over treatment with an immune checkpoint inhibitor.**

Plasma Cell-Free/Circulating Tumor DNA Testing:

- **Cell-free/circulating tumor DNA testing should not be used in lieu of a histologic tissue diagnosis.**
- **Some laboratories offer testing for molecular alterations examining nucleic acids in peripheral circulation, most commonly in processed plasma (sometimes referred to as "liquid biopsy").**
- **Studies have demonstrated cell-free tumor DNA testing to generally have very high specificity, but significantly compromised sensitivity, with up to a 30% false-negative rate; however, data support complementary testing to reduce turnaround time and increase yield of targetable alteration detection.**
- **Published guidelines elaborating standards for analytical performance characteristics of cell-free tumor DNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing.**
- **Cell-free tumor DNA testing can identify alterations that are unrelated to a lesion of interest, for example, clonal hematopoiesis of indeterminate potential (CHIP).**
- **The use of cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, most notably:**
  - **If a patient is medically unfit for invasive tissue sampling**
  - **In the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA can be used; however, follow-up tissue-based analysis for all patients in which an oncogenic driver is not identified should be planned (see NSCL-18 for oncogenic drivers with available targeted therapy options).**
  - **In the initial diagnostic setting, if tissue-based testing does not completely assess all recommended biomarkers owing to tissue quantity or testing methodologies available, consider repeat biopsy and/or cell-free/circulating tumor DNA testing.**
  - **In the initial diagnostic setting, if the feasibility of timely tissue-based testing is uncertain, concurrent cfDNA testing may aid in biomarker evaluation for treatment selection, provided negative results are considered per above limitations.**

Biomarker testing as found in the NCCN Biomarkers Compendium



National Comprehensive Cancer Network®

NCCN Biomarkers Compendium®

About the NCCN Biomarkers Compendium®

Options

Use the drop-down menus to search the database:

Guideline: Non-Small Cell Lung Cancer v.2.2023

Disease: -- Select a Disease Setting --

Gene Symbol: CD274

Gene Alias: -- Select a Gene Alias --

Molecular Abnormality: -- Select a Molecular Abnormality --

Reset Filters | Print | 0 Ready to Print

Fields to display/hide:

- [ ] Specific Indication
- [ ] Test
- [ ] Test Detects
- [x] Methodology
- [ ] Chromosome
- [x] Test Purpose
- [x] When to Test
- [ ] Guideline Page
- [x] Notes
- [ ] Specimen Type
- [ ] Display All

Filters: *Non-Small Cell Lung Cancer v.2.2023* › *CD274*

Default Sort | Showing 1 to 2 of 2 entries | Search:

Guideline - Disease	Molecular Abnormality	Gene Symbol	Methodology	NCCN Category	NCCN Recommendation	Test Purpose	When to Test	Notes
Non-Small Cell Lung Cancer	CD274 (PD-L1) expression	CD274	IHC	1	Advanced or metastatic disease: Adenocarcinoma, Large Cell, NSCLC not otherwise specified (NOS) Squamous cell carcinoma PD-L1 testing (category 1)	Predictive	Workup for Metastatic Disease	IHC for PD-L1 can be utilized to identify disease most likely to respond to first line anti-PD-1/PD-L1. Various antibody clones... read more...

Print view of Biomarkers Compendium entry

National Comprehensive Cancer Network®

NCCN Biomarkers Compendium®

Disease Information	
Guideline Name:	Non-Small Cell Lung Cancer 2.2023
Disease:	Non-Small Cell Lung Cancer
Molecular Abnormality:	CD274 (PD-L1) expression
Test:	PD-L1 expression
Test Detects:	Protein expression
Methodology:	IHC
Category of Evidence:	1
When To Test:	Workup for Metastatic Disease
GuidelinePage:	NSCL-H 7 of 7, NSCL-18
Recommended:	Advanced or metastatic disease: Adenocarcinoma, Large Cell, NSCLC not otherwise specified (NOS) Squamous cell carcinoma PD-L1 testing (category 1)
Test Purpose:	Predictive
Notes:	IHC for PD-L1 can be utilized to identify disease most likely to respond to first line anti-PD-1/PD-L1. Various antibody clones have been developed for IHC analysis of PD-L1 expression, and while several are comparable regarding intensity and proportion of cells stained, some are not. • The definition of positive and negative testing is dependent on the individual antibody, clone and platform deployed, which may be unique to each checkpoint inhibitor therapy. The approval of potential for multiple different assays for PD-L1 has raised concern among both pathologists and oncologists. • While some clones for PD-L1 IHC are FDA-approved for specific indications, use of multiple IHC tests is not necessary, provided any individual IHC test has been internally validated for comparability for categorical results against the FDA-approved clone. • Interpretation of PD-L1 IHC in NSCLC is typically focused on the proportion of tumor cells expressing membranous staining at any level and therefore is a linear variable; scoring systems may be different in other tumor types.
Disease Indication:	Adenocarcinoma| Large cell| NSCLC NOS| Squamous cell carcinoma

NCCN Biomarker testing recommendations

- NCCN builds clinical practice guidelines that are current, evidence based and cover 97% of cancer cases in the United States
- Recommendations within the guidelines are voted on and assigned an NCCN category of evidence (1, 2A, 2B, 3)
- NCCN Biomarkers Compendium entries are based directly on clinical practice guidelines information
- Compendium entries are reviewed by panel experts prior to publication on the NCCN website
- Biomarkers compendium provides a searchable interface to allow quick access to NCCN recommended testing information

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