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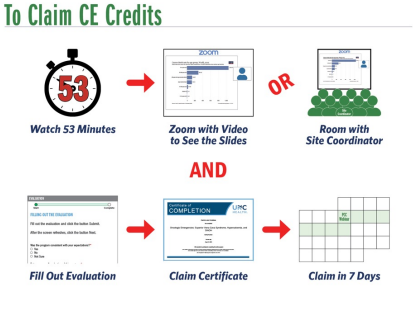

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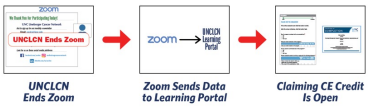

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From Discovery to the Clinic

May 21 - May 22

unclineberger.org/symposium

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Our Presenter

Lori Ramkissoon, PhD

Lori Ramkissoon, Ph.D., is a Clinical Assistant Professor of Pathology and Laboratory Medicine at the University of North Carolina Medical Center, where she leads the Cytogenetics Laboratory. This laboratory specializes in advanced genetic testing methodologies, including karyotyping, chromosomal microarray, and fluorescence in situ hybridization, to detect structural genetic variations in a broad spectrum of specimens ranging from prenatal and constitutional to oncological. These diagnostic services are crucial for identifying genetic disorders and pinpointing specific genetic markers that help classify various tumor types, thereby enhancing patient care through precise diagnoses.

Dr. Ramkissoon received a BA in Biochemistry from Baylor University and a Ph.D. from Weill Cornell Graduate School of Medical Sciences. Her postdoctoral tenure at the Dana-Farber Cancer Institute, under the mentorship of Dr. Keith Ligon, was pivotal in shaping her research focus on the genomic underpinnings of pediatric brain tumors. This experience motivated her to complete a clinical fellowship in Molecular and Clinical Cytogenetics at UNC, culminating in her board certification in Laboratory Genetics and Genomics. Additionally, Dr. Ramkissoon contributes her expertise to the UNC Precision Oncology Program, facilitating the incorporation of genomic insights into personalized treatment strategies for oncology patients.

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Our Presenter

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Our Presenter

4. Lori Ramkissoon, PhD is Director of the Cytogenetics laboratory at the University of North Carolina Medical Center

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3. She earned her PhD from Weill Cornell Graduate School of Medical Sciences and did a postdoctoral fellowship at Dana-Farber Cancer Institute
2. Prior to graduate school, she was a pre-doctoral fellow in the laboratory of Dr. Neal Young at the National Heart, Lung and Blood Institute in Bethesda, MD

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2. Prior to graduate school, she was a pre-doctoral fellow in the laboratory of Dr. Neal Young at the National Heart, Lung and Blood Institute in Bethesda, MD
1. She worked for a year as a staff assistant in the United States Senate.

14

Sample Poll Everywhere Question

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ACCME Disclosure

This activity has been planned and implemented under the sole supervision of the Course Director, Stephanie Wheeler, PhD, MPH, in association with the UNC Office of Continuing Professional Development (CPD). The course director received research support from AstraZeneca (ended June 2023) and Pfizer Medical Foundation (ended December 2023). These financial relationships have been mitigated. CPD staff have no relevant financial relationships with ineligible companies as defined by the ACCME.

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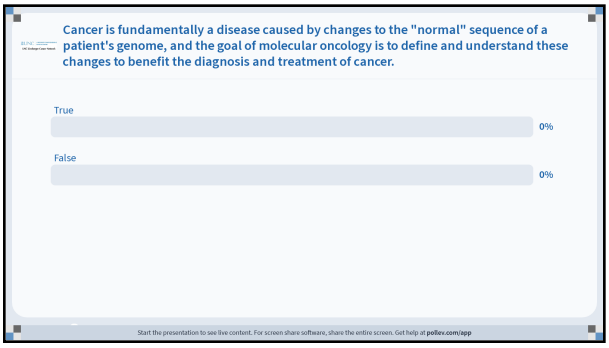

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From Bench to Bedside: Molecular Oncology's Role in Personalized Cancer Diagnosis and Treatment

Lori Ramkissoon, PhD
Lori.Ramkissoon@unchealth.unc.edu
May 8, 2024

UNC SCHOOL OF MEDICINE

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Learning Objectives

- Review advancements in the laboratory methods used to detect molecular biomarkers in oncology specimens
- Illustrate how molecular biomarkers have been integrated into diagnostic algorithms for certain cancer types
- Discuss the contributions of molecular oncology in treatment strategies

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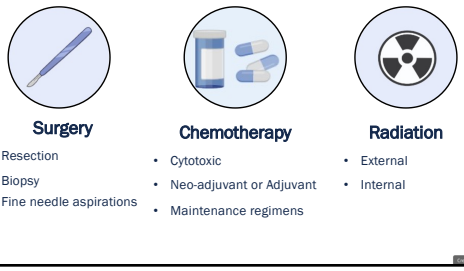
Conventional treatment options for cancer patients



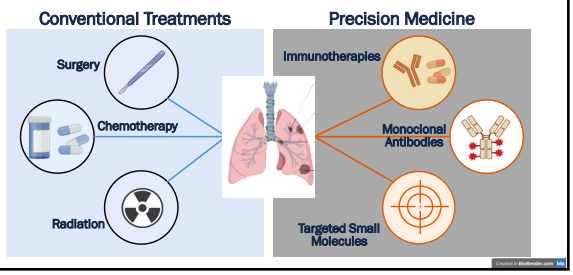
Surgery
- Resection
- Biopsy
- Fine needle aspirations

Chemotherapy
- Cytotoxic
- Neo-adjuvant or Adjuvant
- Maintenance regimens

Radiation
- External
- Internal

22

Advancement in treatment options



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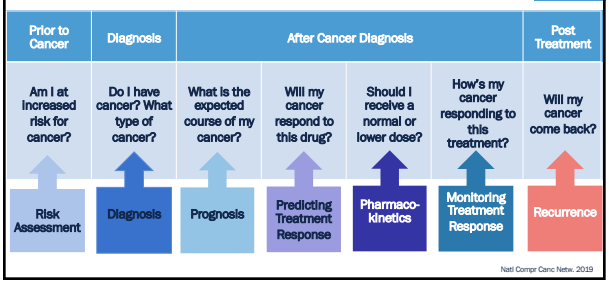
Biomarkers guiding cancer care



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Molecular biomarkers in cancer

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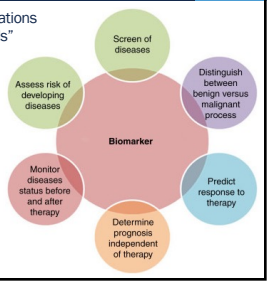
What are biomarkers?

Biomarker: "cellular, biochemical or molecular alterations that are measurable in human tissues, cells, or fluids"

Biomarker	Example
Physiological biomarker	Blood pressure
Inflammatory biomarker	C-reactive protein
Prostate cancer biomarker	PSA
Molecular biomarker	*EGFR*
Somatic mutational biomarker	*KRAS* G12D
Germline mutational biomarker	*BRCA1*
Tumor agnostic biomarker	TMB, MSI, NTRK
Immune biomarker	PDL1



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How are molecular biomarkers used in oncology?

Diagnostic
- Assist with establishing diagnosis or classification
- Example: *BCR::ABL1* gene fusion in chronic myeloid leukemia (CML)

Prognostic
- Assist with determining the likely aggressiveness or course of disease
- Example: *TP53* mutations are an adverse prognostic factor in chronic lymphocytic leukemia (CLL)

Therapeutic
- Assist with prediction of response or resistance to a given drug, biologic, or regimen
- Example: *EGFR* activating mutations are associated with response to EGFR tyrosine kinase inhibitor (TKI) therapy in Non-Small Cell Lung Cancer

Clinical Trial Eligibility

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NCCN Guidelines and biomarkers

- Currently more than 800 biomarker recommendations are included in NCCN Guidelines
  - Determine risk of disease (BRCA-1/BRCA-2)
  - Screening (PSA for prostate)
  - Diagnostic (BCR/ABL in CML)
  - Prognostic (CA 19-9 in pancreas)
  - Predictive (ER/PR status in breast)
  - Risk of toxicity (UGT1A1*28 allele for irinotecan)
  - Response/disease monitoring (AFP; HCG in testicular)

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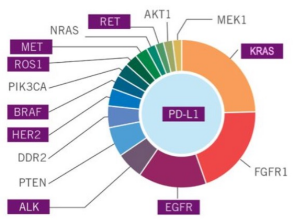
NCCN recommendations for biomarker testing in non-small cell lung cancer



Adapted from genetechnology.com and NCCN guidelines.

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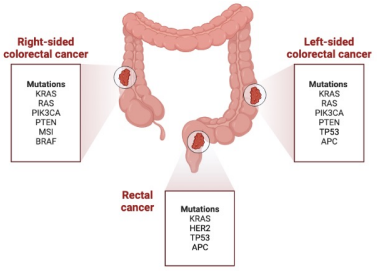
NCCN biomarkers in colorectal cancer



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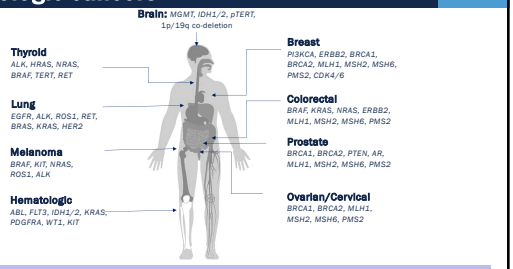
Biomarker landscape in solid & hematologic cancers



Tumor agnostic biomarkers in solid tumors: Fusions (NTRK), TMB, MSI

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ASCO Guidelines

SOMATIC GENOMIC TESTING IN PATIENTS WITH METASTATIC OR ADVANCED CANCER
PROVISIONAL CLINICAL OPINION

WHICH METASTATIC OR ADVANCED SOLID TUMORS SHOULD UNDERGO GENOMIC SEQUENCING?

- Patients with metastatic or advanced solid tumors if there are genomic biomarker–linked therapies for that disease approved by the relevant regulatory agency (FDA)
- Patients with metastatic or advanced solid tumors if there are clearly defined resistance markers for a treatment being considered.

Chakravarty D et al. J Clin Oncol (2022) 40:1231-1258.

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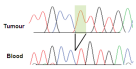
Detecting molecular biomarkers in cancer

33

Types of genomic alterations that define cancer biomarkers

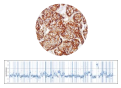
Base Pair Substitutions

- Limited to a single base pair/region within a single gene
- Examples: *EGFR* L858R, T790M; *BRAF* V600E, *IDH1* R132H



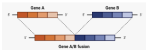
Insertions/deletions

- Limited to single genes and small changes in DNA sequence
- Examples: *EGFR* exon 19 deletions, *MET* exon 14



Copy Number Alterations

- Overexpression/amplification
- Examples: *HER2* amplification, *PDGFRA* amplification



Gene Rearrangements (Fusions)

- Detected via DNA and RNA (ASCO recommends RNA)
- Examples: *ALK* fusions, *NTRK* fusions

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Driver versus passenger alterations

Driver mutations (driving the bus)

- Mutations that give a cancer cell a competitive advantage
  - Increased rate of proliferation
  - Decreased apoptosis
  - Resistance to therapy
  - Etc.
- Contribute to oncogenesis ("oncogenic")

Passenger mutations (along for the ride)

- Mutations that arise in cancer cells but don't improve the "fitness" of the cancer cell
- Do not contribute to cancer development/progression

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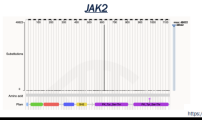
Gain-of-function versus Loss-of-function alterations

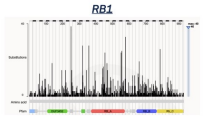
- **Targetable mutations are typically GAIN OF FUNCTION mutations in oncogenes that encode for SIGNALING MOLECULES**
  - **GAIN OF FUNCTION mutations are frequently heterozygous (only one copy needs activated to drive the pathway)**
  - **There is generally a very limited number of mutations that can activate a protein**
  - **GAIN OF FUNCTION mutations tend to be recurrent among individuals**

JAK2



- **LOSS OF FUNCTION mutations typically occur in TUMOR SUPPRESSOR GENES**
  - **Mutations tend to be LOSS OF FUNCTION, which requires BIALLELIC mutation**
    - **You need to lose BOTH copies to eliminate normal protein function**
  - **Because many different mutations can result in loss of function, there is typically a much broader spectrum of clinically significant mutations in tumor suppressor gene**

RB1



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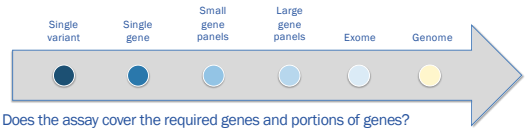
Finding the right assay



- Does the assay cover the required genes and portions of genes?
- What variant types can the assay detect?
  - Does the assay detect variant types required given the clinical indication for testing (single nucleotide variants, insertion-deletion, copy number gain/loss, gene rearrangements)?
- What are sample requirements?
- What is the expected turnaround time and cost?

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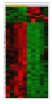
Methodologies to detect cancer biomarkers

Fluorescence in situ hybridization (FISH)
Detect specific genomic translocations, copy number deletions/gains

Chromosome Analysis
Detects changes in chromosome number, translocations, large deletions/insertions

SNP microarrays
Used for genotyping and copy number determination



Gene expression arrays
Can provide subtype classification for certain tumors and/or prognostic information

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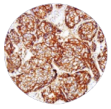
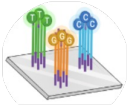
Methodologies to detect cancer biomarkers

Single Gene Assays
Evaluate alterations in a single gene

Hotspot Panels
Sequencing of select hotspot codons, and not the entire coding region, of the genes included on the panel.



Immunohistochemistry
Determines protein expression within tissue sample



Broad Panel (Comprehensive Genomic Profiling)
An NGS test that sequences a defined list of genes with at least 50 genes in total. May also include RNA testing

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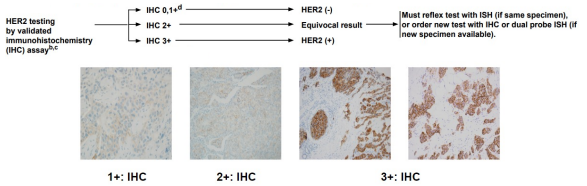
Methodologies are often combined to identify biomarkers

HER2 biomarker testing in invasive breast cancers



1+: IHC 2+: IHC 3+: IHC

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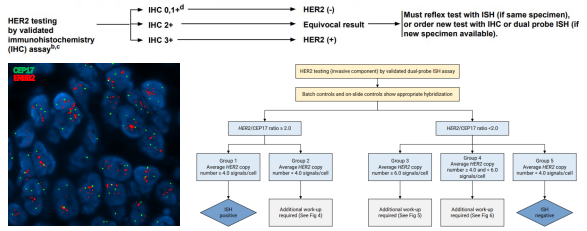
Methodologies are often combined to identify biomarkers

HER2 biomarker testing in invasive breast cancers



NCCN Guidelines Version 2.2024 Invasive Breast Cancer; Wolff AC et al. *J Clin Oncol* 2018;36:2105-2122

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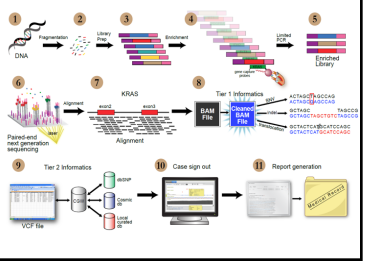
Overview of comprehensive genomic profiling

Goals

- High throughput, cost effective multiplexed sequencing assay with deep coverage
- Target clinically actionable regions important for all tumor types

Challenges

- Huge infrastructure costs
- Bioinformatic barriers
- Longer turnaround times



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Comparison of single gene testing versus comprehensive genomic profiling

Single gene testing (SGT)	Comprehensive Genomic Profiling
One or more tests ordered individually or simultaneously, but performed separately • **PCR** – defined regions for a limited number of mutations in *EGFR, KRAS or BRAF* • **FISH** – known rearrangements in *ALK, RET, ROS1 or MET* amplification • **IHC –** known expression patterns or percentage of positive cells; loss of protein expression	One test ordered following negative SGT results or instead of SGT • **DNA sequencing** – simultaneously evaluate all major genomic variant types (mutations, copy number alterations, rearrangements) in oncogenes recommended for testing that have FDA-approved targeted therapies, as well those with emerging and potential clinical significance • **RNA sequencing** – for known and novel rearrangements • **Microsatellite status and Tumor mutation burden** – immunotherapy biomarkers

Nesline et al. *Oncol Ther* 2024 Mar 19.

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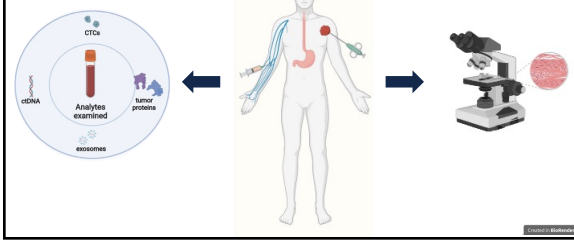
Cancer biomarker testing can be performed on a liquid or tissue biopsy



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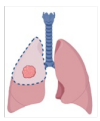
Tissue acquisition: What material is available for testing?



Tissue Resection

- Obtained for diagnosis and symptomatic relief
- Tumor cell percentage may be an issue
- CGP and multiple assays typically not a problem for tumor-rich samples

Biopsy

- Obtained for a diagnosis
- Testing options may be limited but depends on tumor content not necessarily tissue size

Endobronchial Ultrasound (EBUS)/ Fine Needle Aspiration (FNA)

- Diagnosis can be made from very few cells
- Considered a cytology specimen
- May have significant limitations for testing

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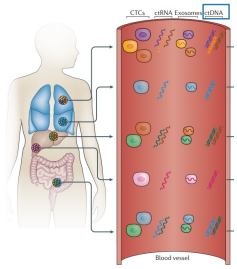
Liquid biopsy: source of circulating tumor DNA (ctDNA)



- **ctDNA:** component of cell-free DNA which is tumor related
- **Cell-Free DNA Blood Collection Tubes:** specialized tubes required allow for isolation of plasma DNA up to 14 days after sample collection

Nat Rev Clin Oncol. 2017 Sep;14(9):531-548

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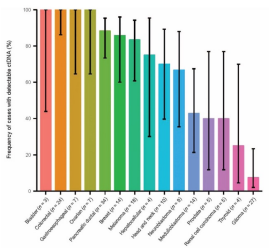
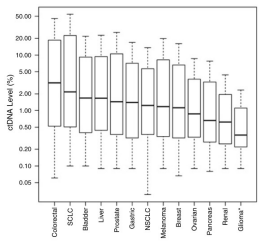
ctDNA varies among tumor types





Bettegowda C et al. Sci Transl Med. 2014 Feb 19; 6(224): 224.
Zill OA et al. Clin Cancer Res. 2018 Aug 1;24(15):3528-3538.

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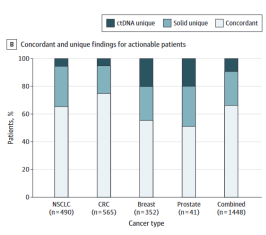
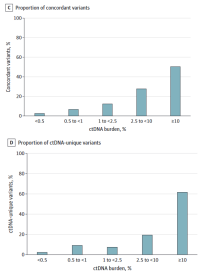
Liquid biopsy and tumor tissue concordance





Isms WT et al. JAMA Netw Open. 2024 Jan 2;7(1):e2351700.

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Advantages and disadvantages of tumor versus liquid biopsy

Tumor Biopsy

Histological evaluation

Tumor microenvironment analysis

Clinical gold standard

- Surgery/needle biopsy
- Risk of complications
- Difficult to repeat & expensive
- Possible sampling bias
- Highly sensitive
- Longer TAT

- Blood draw
- Minimal complications
- Easy & repeatable
- Quick & cost-efficient
- Less sampling bias
- Rapid TAT
- False negatives
- Detection of CHIP

Liquid Biopsy

Non-invasive

Short half-life (<2 h)

Compatible with longitudinal monitoring

Representative of tumor heterogeneity

Adapted from Corcoran et al Nature Medicine 2020

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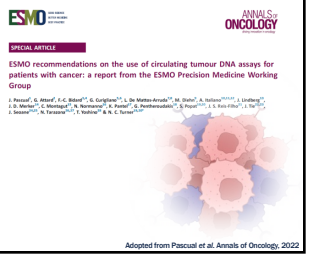
ESMO Guidelines: Advanced cancer genotyping recommendations

Liquid Biopsy Best Practice

- ✓ May be used in clinical practice when results impact treatment.
  - ✓ May be used in clinical scenarios first where time to result is clinically important
  - ✓ Aggressive tumor type
  - ✓ No available tissue or biopsy not feasible
- ✓ Collect when tumor progressing (not regressing)
- ✓ Confirm testing if pathogenic variants of cancer susceptibility genes identified
- ✓ Negative tests should prompt tissue testing



Adopted from Pascual *et al.* Annals of Oncology, 2022

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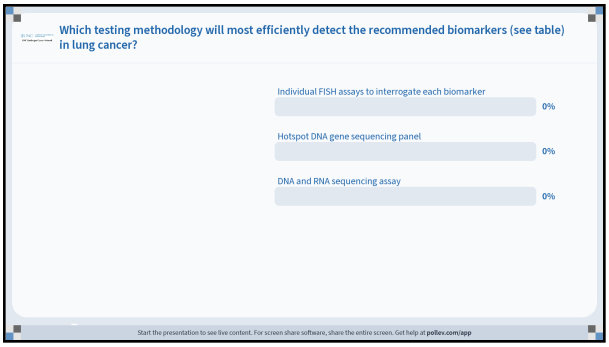
Poll everywhere question #2:

- Which testing methodology will most efficiently detect the recommended biomarkers (see table) in lung cancer?

1. Individual FISH assays to interrogate each biomarker
2. Hotspot DNA gene sequencing panel
3. DNA and RNA sequencing assay

Recommended Testing
ALK rearrangements
BRAF mutations
EGFR mutations
ERBB2 (HER2) mutations
KRAS mutations
MET exon 14 skipping mutations
MET amplification
NTRK 1/2/3 rearrangements
RET rearrangements
ROS1 rearrangements

51



52

Poll everywhere question #2: Answer

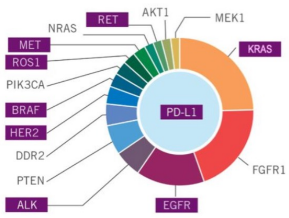
- Which testing methodology will most efficiently detect the recommended biomarkers (see table) in lung cancer?

1. Individual FISH assays to interrogate each biomarker
2. Hotspot DNA gene sequencing panel
3. DNA and RNA sequencing assay

Recommended Testing
ALK rearrangements
BRAF mutations
EGFR mutations
ERBB2 (HER2) mutations
KRAS mutations
MET exon 14 skipping mutations
MET amplification
NTRK 1/2/3 rearrangements
RET rearrangements
ROS1 rearrangements

53

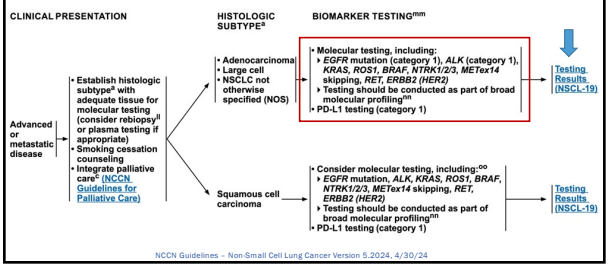
NCCN recommendations for biomarker testing in non-small cell lung cancer



Adapted from genetechnology.com and NCCN guidelines.

54

Guidelines and other resources assist with biomarker and test interpretation



NCCN Guidelines – Non-Small Cell Lung Cancer Version 5.2024, 4/30/24

55

Guidelines and other resources assist with biomarker and test interpretation

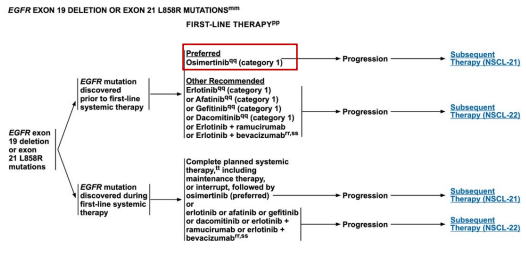
TESTING RESULTS[ll,mm]

EGFR exon 19 deletion or exon 21 L858R mutation positive	NSCL-20
EGFR S768I, L861Q, and/or G719X mutation positive	NSCL-23
EGFR exon 20 insertion mutation positive	NSCL-24
KRAS G12C mutation positive	NSCL-25
ALK rearrangement positive	NSCL-26
ROS1 rearrangement positive	NSCL-29
BRAF V600E mutation positive	NSCL-31
NTRK1/2/3 gene fusion positive	NSCL-32
METex14 skipping mutation positive	NSCL-33
RET rearrangement positive	NSCL-34
ERBB2 (HER2) mutation positive	NSCL-35
PD-L1 ≥1% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37

NCCN Guidelines – Non-Small Cell Lung Cancer Version 5.2024, 4/30/24

56

Biomarker approved therapies for NSCLC

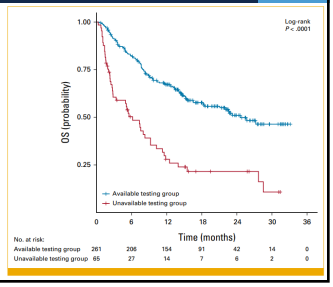


NCCN Guidelines – Non-Small Cell Lung Cancer Version 5.2024, 4/30/24

57

Availability of molecular biomarker testing in NSCLC impacts overall survival

- 326 consecutive treatment naïve patient with a new diagnosis of metastatic NSCLC
- Patients with molecular test results available before first line therapy (available group) had significantly longer overall survival



Aggarwal C et al. JCO Precis Oncol 2023 Jul;7:e2300191

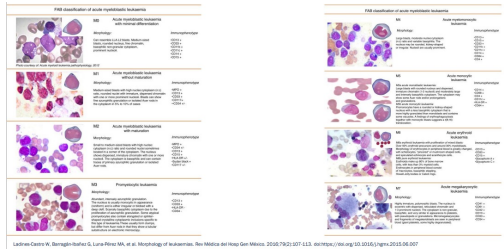
58

Molecular biomarkers are refining classification of tumors

59

Evolution of hematologic malignancy classification

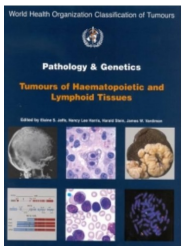
French-American-British (FAB) Classification System



Ladines-Castro W, Borrego-Ibañez G, Luna-Pérez MA, et al. Morphology of leukaemias. Rev Médica del Hosp Gen México. 2016;79(2):107-113. doi:https://doi.org/10.1016/j.hgmx.2015.06.007

60

Evolution of hematologic malignancy classification



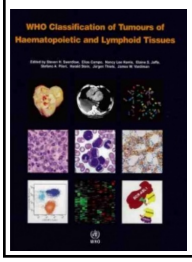
2001

I. Acute myeloid leukaemias with recurrent cytogenetic translocations

- AML with t(8;21)(q22;q22),AML1(CBFa)/ETO
- Acute promyelocytic leukaemia (AML with t(15;17)(q22;q11-12) and variants, PML/RARa)
- AML with abnormal bone marrow eosinophils (inv(16)(p13q22) or t(16;16)(p13;q11), CBFb/MYH11X)
- AML with 11q23 (MLL) abnormalities.

61

Evolution of hematologic malignancy classification



2008

I. Acute myeloid leukemia with recurrent genetic abnormalities

- AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
- APL with t(15;17)(q22;q12); PML-RARA
- AML with t(9;11)(p22;q23); MLLT3-MLL
- AML with t(6;9)(p23;q34); DEK-NUP214
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
- AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1

II. Provisional entities:

- AML with mutated NPM1
- AML with mutated CEBPA

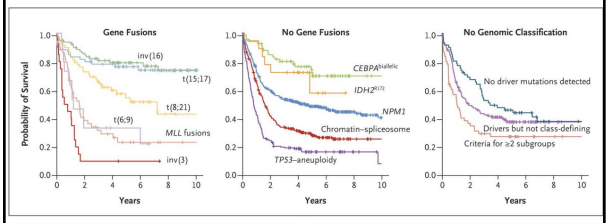
62

Evolution of hematologic malignancy classification

WHO 2017	WHO 2022	ICC 2022
AML with recurrent genetic abnormalities	AML with defining genetic abnormalities (no blast % cut-off, except*)	AML with recurrent genetic abnormalities (requiring equal or greater than 10% blasts, except *)
AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1	AML with RUNX1::RUNX1T1 fusion	AML with t(8;21)(q22;q22.1)/RUNX1::RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11	AML with CBFB::MYH11 fusion	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11
APL with PML-RARA	Acute promyelocytic leukaemia with PML::RARA fusion	Acute promyelocytic leukaemia (APL) with t(15;17)(q24.1;q21.2)/ PML::RARA; APL with other RARA rearrangements
AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A	AML with KMT2A rearrangement	AML with t(9;11)(p21.3;q23.3)/MLLT3::KMT2A; AML with other KMT2A rearrangements
AML with t(6;9)(p23;q34.1);DEK-NUP214	AML with DEK::NUP214 fusion	AML with t(6;9)(p22.3;q34.1)/DEK::NUP214
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2-MECOM	AML with MECOM rearrangement	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2::MECOM(EVI1); AML with other MECOM rearrangements
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1	AML with RBM15::MRTFA fusion	
Provisional entity: AML with BCR-ABL1	AML with BCR::ABL1 fusion*	AML with BCR::ABL1 fusion*
	AML with NUP98 rearrangement	
	AML with other (rare) defined genetic alterations*	AML with other rare recurring translocations

63

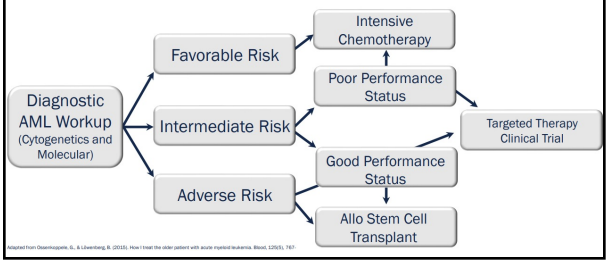
Impact of molecular testing in myeloid malignancy classification



Papaemmanuil E et al. N Engl J Med. 374:2209-2221

64

Impact of molecular testing in myeloid malignancy classification



Adapted from Ossenkoppele, G., & Löwenberg, B. (2015). How I treat the older patient with acute myeloid leukemia. Blood, 125(5), 767.

65

Molecular biomarkers are increasingly incorporated into neuro-oncology

66

Evolution of molecularly classified CNS tumors

WHO 2016 GLIOMAS

Diffuse Astrocytic and Oligodendroglial Tumours

Classification
Diffuse Astrocytoma, IDH-mutant
• Gemistocytic astrocytoma, IDH-mutant
Diffuse astrocytoma, IDH-wildtype
Diffuse astrocytoma, NOS
Anaplastic astrocytoma, IDH-mutant
Anaplastic astrocytoma, IDH – wildtype
Anaplastic astrocytoma, NOS
Glioblastoma, IDH-wildtype • Giant cell glioblastoma • Gliosarcoma • Epithelioid glioblastoma
Glioblastoma, IDH-mutant
Glioblastoma, NOS
Diffuse midline glioma, H3 K27M mutant
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
Oligodendroglioma, NOS
Anaplastic, oligodendroglioma, IDH-mutant and 1p/19q-codeleted
Anaplastic oligodendroglioma, NOS
Oligoastrocytoma, NOS
Anaplastic oligoastrocytoma, NOS

WHO 2021 GLIOMAS

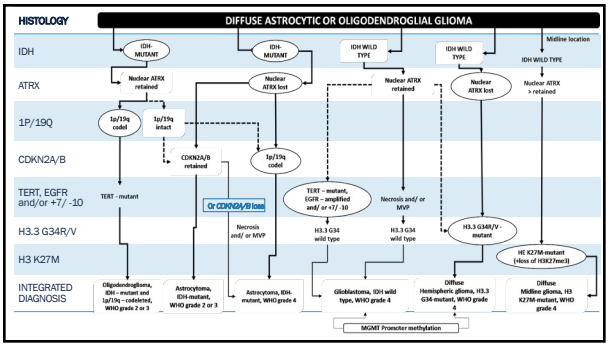
Gliomas, Glioneural and Neuronal Tumours

Adult-type diffuse gliomas
- Astrocytoma, IDH-mutant
- Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- Glioblastoma, IDH-wildtype

Paediatric-type diffuse low-grade gliomas
- Diffuse astrocytoma, MYB or MYBL1 – altered
- Angiocentric glioma
- Polymorphous low-grade neuroepithelial tumour of the young
- Diffuse low-grad glioma, MAPK pathway-altered.

Paediatric-type diffuse high-grade gliomas
- Diffuse midline glioma, H3 K27- altered
- Diffuse hemispheric glioma, H3 G34-mutant
- Diffuse paediatric-type high-grade glioma, H3 wild-type and IDH wild type
- Infant-type hemispheric glioma

67

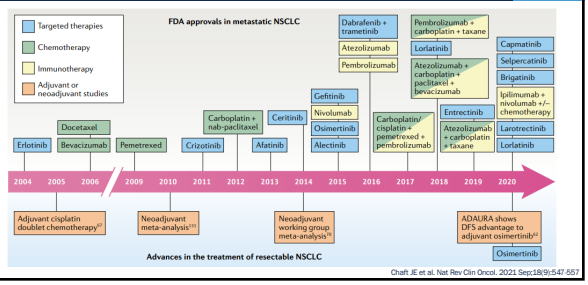


68

Molecular biomarkers guide treatment decisions

69

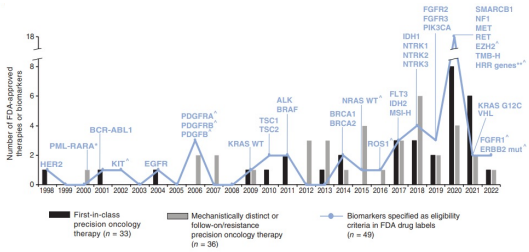
Biomarker approved therapies for metastatic NSCLC



Chaft JE et al. Nat Rev Clin Oncol. 2021 Sep;18(9):547-557

70

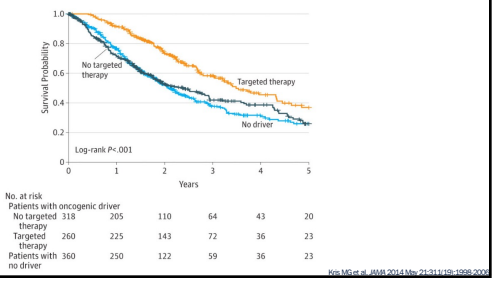
Precision oncology approvals by FDA continues to expand



Suehnholz SP et al. Cancer Discov. 2024 Jan 12;14(1):49-65.

71

Why are Matched Therapies Important?



Kris MG et al. JAMA 2014 May 21;311(19):1998-2006

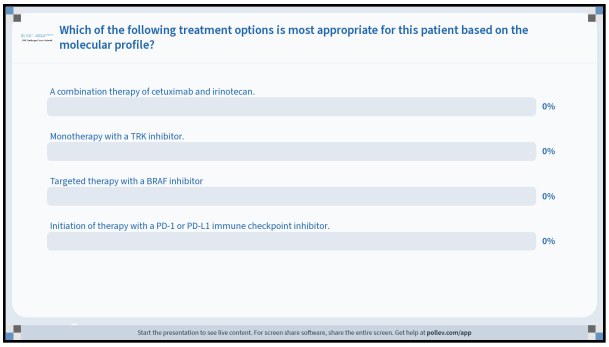
72

Poll everywhere question #3:

In a patient with newly diagnosed colon cancer, testing determined that the tumor had microsatellite instability (MSI) or was MSI-high. Which of the following treatment strategies is indicated for MSI-high status?

1. A combination therapy of cetuximab and irinotecan.
2. Monotherapy with a TRK inhibitor.
3. Targeted therapy with a BRAF inhibitor
4. Initiation of therapy with a PD-1 or PD-L1 immune checkpoint inhibitor.

73



74

Poll everywhere question #3:

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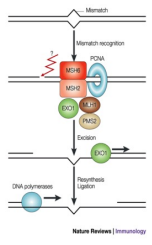
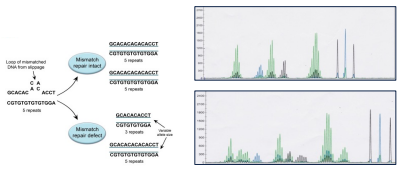
1. A combination therapy of cetuximab and irinotecan.
2. Monotherapy with a TRK inhibitor.
3. Targeted therapy with a BRAF inhibitor
4. Initiation of therapy with a PD-1 or PD-L1 immune checkpoint inhibitor.

75

DNA Mismatch Repair and Microsatellite Instability



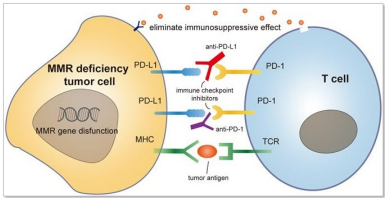
- During DNA replication, errors occur in microsatellite regions
  - Short repetitive DNA sequences (1-6 base pairs) or tandem repeats
- Multi-protein complex corrects these single base pair mismatches and small insertion-deletion errors
- Failures to repair these errors during replication leads to expansion of repeats and genomic instability = **microsatellite instability**



76

Anti-PD-1/L1 therapies reactivate T cell activity

- MSI-High/dMMR tumors generate neoantigens which are recognized by the immune system
- Tumor cells also express PD-L1 to inhibit T-cell activity
- Immune checkpoint inhibitors reactive T-cell activity



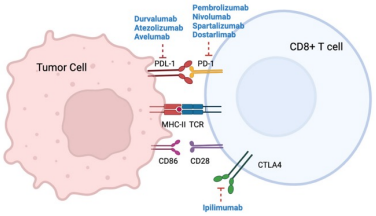
He Y et al. *Int J Biol Sci* 2022; 18(7):2821-2832

77

Tumor agnostic immune checkpoint inhibitor approval

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

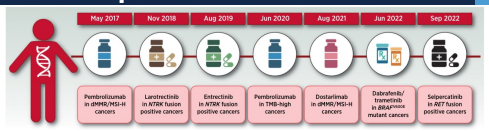
- 2017 approval for adult and pediatric patients with unresectable or metastatic solid tumors
  - microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
  - progressed following prior treatment



Ros J et al. Cancers (Basel). 2023 Aug 24;15(17):4245.

78

Additional FDA-approved tumor agnostic targeted therapies



- ***NTRK1, NTRK2, NTRK3*** transmembrane tyrosine kinases that are important for neuronal development
  - Fusions detected in 1.6% of profiled cases
  - *NTRK* fusions can be targeted using Larotrectinib and Entrectinib
- **Tumor mutation burden (TMB)** reflects the number of genetic alterations in the genome of cancer cells
  - Calculated using data from NGS of either tissue or plasma, mutations per megabase (mut/MB)
  - 10 mut/mb as for defining indication of pembrolizumab
- ***BRAF* V600E** can be targeted by using inhibitors of BRAF and MEK
  - Detected in 3% of AACR Project GENIE (version 13) pan-cancer cohort
  - Dabrafenib and Trametinib received FDA approval for BRAFV600E-positive solid tumors
- ***RET* fusion-positive** samples were identified in 1.5% of 25,972 tumors profiled for structural variants
  - Selpercatinib, ATP-dependent selective RET inhibitor, approved by FDA for solid tumors with *RET* fusions

Gouda MA et al. *Clin Cancer Res*. 2023 Aug 1;29(15):2753-2760

79

Targeted therapy success story

Chronic Myeloid Leukemia

80

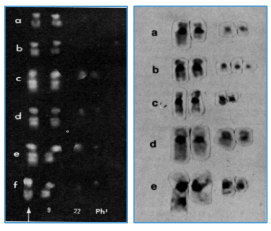
Visualization of first chromosome translocation

A New Consistent Chromosomal Abnormality in Chronic Myelogenous Leukaemia identified by Quinacrine Fluorescence and Giemsa Staining

JANET D. ROWLEY

Department of Medicine, University of Chicago and Franklin McLean Memorial Research Institute, Chicago, Illinois 60637

Received January 8; revised February 8, 1973.

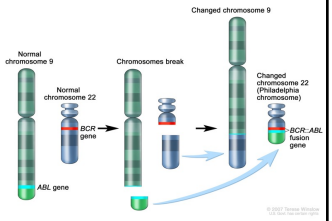


Nature volume 243, pages290–293 (1973)

81

Genomic rearrangement results in oncogenic fusion gene

- Exchange of genetic material between chromosome 9 and chromosome 22 produces novel oncogenic fusion gene
  - *BCR::ABL1* creates a constitutively active tyrosine kinase



https://www.cancer.gov/publications/dictionaries/cancer-terms/def/bcr-abl-fusion-gene

82

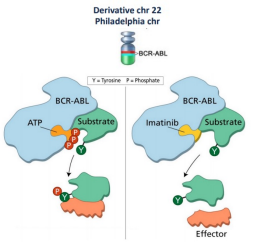
Understanding mechanism of *BCR::ABL1* transforms care for CML patients

The NEW ENGLAND JOURNAL of MEDICINE

Efficacy and Safety of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia

Authors: Brian J. Druker, M.D., Moshe Talpaz, M.D., Debra J. Resta, R.N., Bin Peng, Ph.D., Elisabeth Buchdunger, Ph.D., John M. Ford, M.D., Nicholas B. Lydon, Ph.D., Hagop Kantarjian, M.D., Renaud Capdeville, M.D., Sayuri Ohno-Jones, B.S., and Charles L. Sawyers, M.D. Author Info & Affiliations

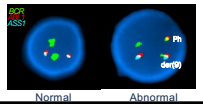
- 2001 Phase I clinical trial
  - 98% had complete hematologic response
  - 54% had cytogenetic response
- Imatinib is the first FDA approved drug to counteract molecular defect = targeted therapy



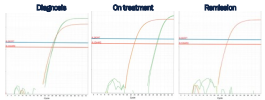
Mughal TI & Goldman JM. *Front Biosci.* 2006. 11:209-220.

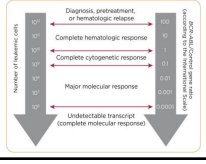
83

Combining molecular methods to diagnosis and monitor CML



Normal Abnormal





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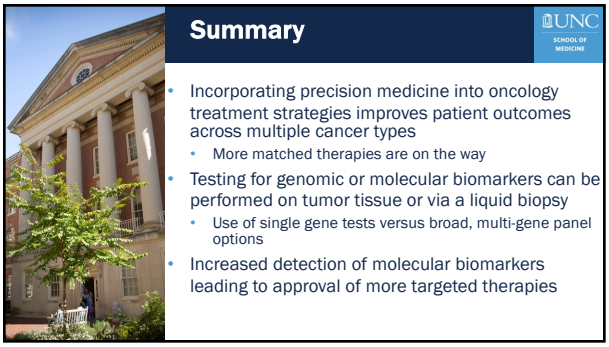

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87

Thank You . . .

University Cancer Research Fund

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

UNC Lineberger Cancer Network

The Telehealth Team

Tim Poe – Director

Veneranda Obure – Technology Support Specialist
Jon Powell, PhD – Continuing Education Specialist
Oliver Marth – Technology Support Technician
Andrew Dodgson, DPT – Continuing Education Specialist
Patrick Muscarella – Technology Support Technician
Lindsey Reich, MA – Public Communication Specialist
Barbara Walsh, DNP, MPH, MSN, RN – Nurse Planner

The song *Back Rhodes* written and performed by **Don Poe**

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Upcoming Live Webinars

learn.unclcn.org

ADVANCED PRACTICE PROVIDER

May 15
4:00 PM

Using Acceptance and Commitment Therapy to Help Cancer Survivors Move Forward After Treatment
Melissa Holt, DNP, PMHNP-BC **Lisa Kanser,** PsyD

RESEARCH TO PRACTICE

May 22
12:00 PM

The Selective Use of Radiation in Solid Malignancies
Kevin Pearlstein, MD

PATIENT-CENTERED CARE

June 12
12:00 PM

Medication-Related Osteonecrosis of the Jaw
Ricardo Padilla, DDS

89

Self-Paced, Online Courses

learn.unclcn.org/spoc

ADVANCED PRACTICE PROVIDER

Physical Therapy Approaches to Oncology Care: Beyond Lymphedema
Sarah Richardson, PT, DPT, CLT, WCS

RESEARCH TO PRACTICE

Immune (check point) Related Adverse Events
Frances Collichio, MD

PATIENT-CENTERED CARE

Oncologic Emergencies
Jake Stein, MD

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