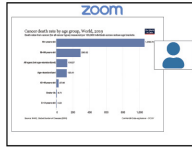1

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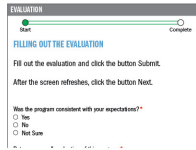
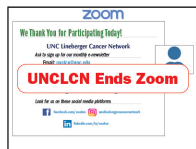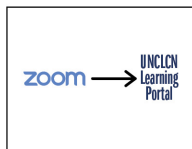**Fill Out Evaluation**   **Claim Certificate**   **Claim in 7 Days**
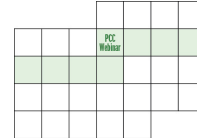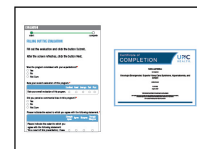
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May 21 - May 22

unclineberger.org/symposium

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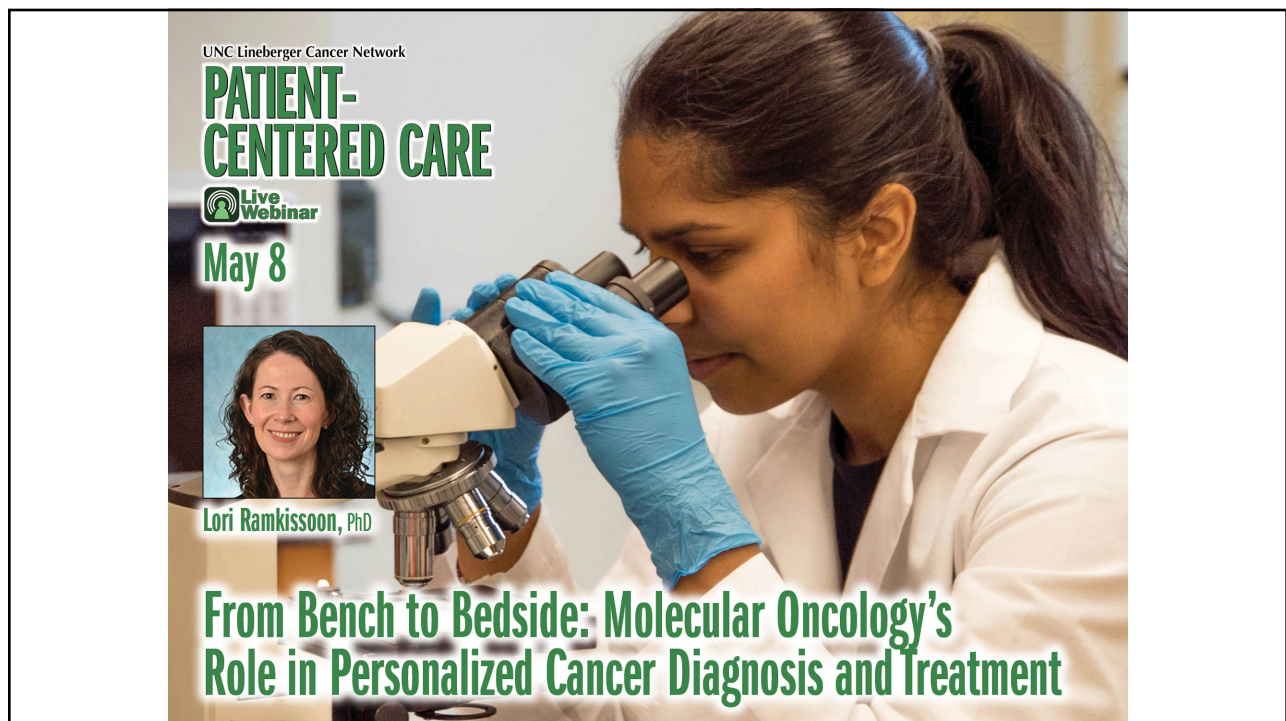unclcn.org/promoter

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7

UNC Lineberger Cancer Network

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Live Webinar

May 8

Lori Ramkissoon, PhD

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

8

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.

9

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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13

Our Presenter

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

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

1. She worked for a year as a staff assistant in the United States Senate.

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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.

A potential conflict of interest occurs when an individual has an opportunity to affect educational content about health-care products or services of a commercial interest with which he/she has a financial relationship. The speakers and planners of this learning activity have not disclosed any relevant financial relationships with any commercial interests pertaining to this activity.

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ANCC Disclosure

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Criteria for successful completion requires attendance at the NCPD activity and submission of an evaluation within 30 days.

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17

Cancer is fundamentally a disease caused by changes to the "normal" sequence of a patient's genome, and the goal of molecular oncology is to define and understand these changes to benefit the diagnosis and treatment of cancer.

True

0%

False

0%

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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

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19

Molecular biomarkers are only used in the research setting and are not part of current standard of care clinical paradigms?

True   0%

False   0%

Start the presentation to see live content. For screen share software, share the entire screen. Get help at **pollev.com/app**

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Learning Objectives
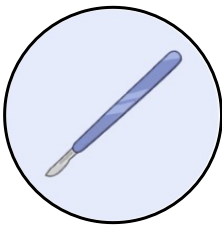
- Review advancements in the laboratory methods used to detect molecular biomarkers in oncology specimens

- 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

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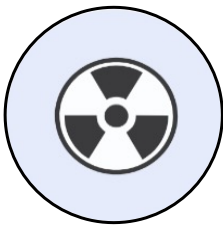
Surgery

- Resection
- Biopsy
- Fine needle aspirations

Chemotherapy

- Cytotoxic
- Neo-adjuvant or Adjuvant
- Maintenance regimens

Radiation

- External
- Internal

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22

Advancement in treatment options

Conventional Treatments — Surgery, Chemotherapy, Radiation

Precision Medicine — Immunotherapies, Monoclonal Antibodies, Targeted Small Molecules

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23

Biomarkers guiding cancer care

Prior to Cancer	Diagnosis	After Cancer Diagnosis				Post Treatment
Am I at increased risk for cancer?	Do I have cancer? What type of cancer?	What is the expected course of my cancer?	Will my cancer respond to this drug?	Should I receive a normal or lower dose?	How's my cancer responding to this treatment?	Will my cancer come back?
Risk Assessment	Diagnosis	Prognosis	Predicting Treatment Response	Pharmaco-kinetics	Monitoring Treatment Response	Recurrence

Natl Compr Canc Netw. 2019

24

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?

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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

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- 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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Biomarker landscape in solid & hematologic cancers

Brain: *MGMT, IDH1/2, pTERT, 1p/19q co-deletion*

Thyroid
ALK, HRAS, NRAS, BRAF, TERT, RET

Lung
EGFR, ALK, ROS1, RET, BRAS, KRAS, HER2

Melanoma
BRAF, KIT, NRAS, ROS1, ALK

Hematologic
ABL, FLT3, IDH1/2, KRAS, PDGFRA, WT1, KIT

Breast
PI3KCA, ERBB2, BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, CDK4/6

Colorectal
BRAF, KRAS, NRAS, ERBB2, MLH1, MSH2, MSH6, PMS2

Prostate
BRCA1, BRCA2, PTEN, AR, MLH1, MSH2, MSH6, PMS2

Ovarian/Cervical
BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2

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

31
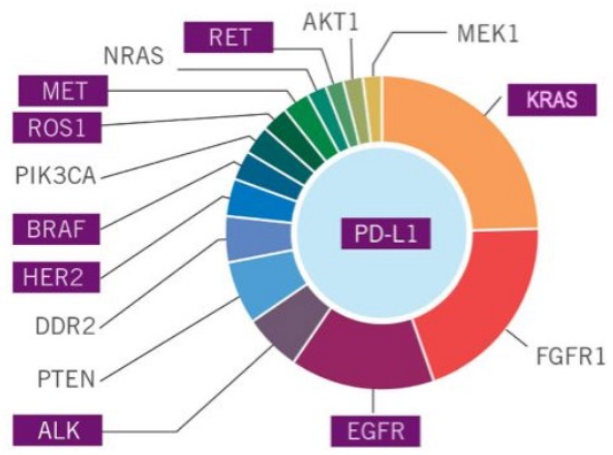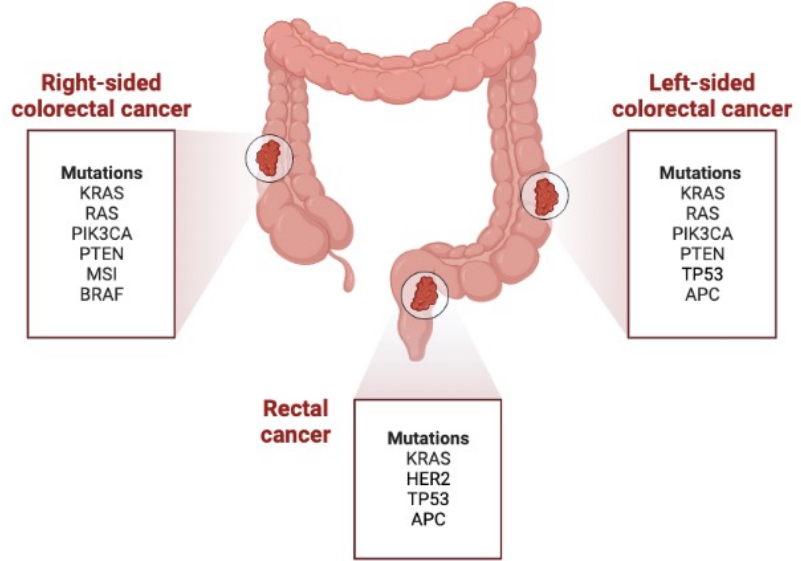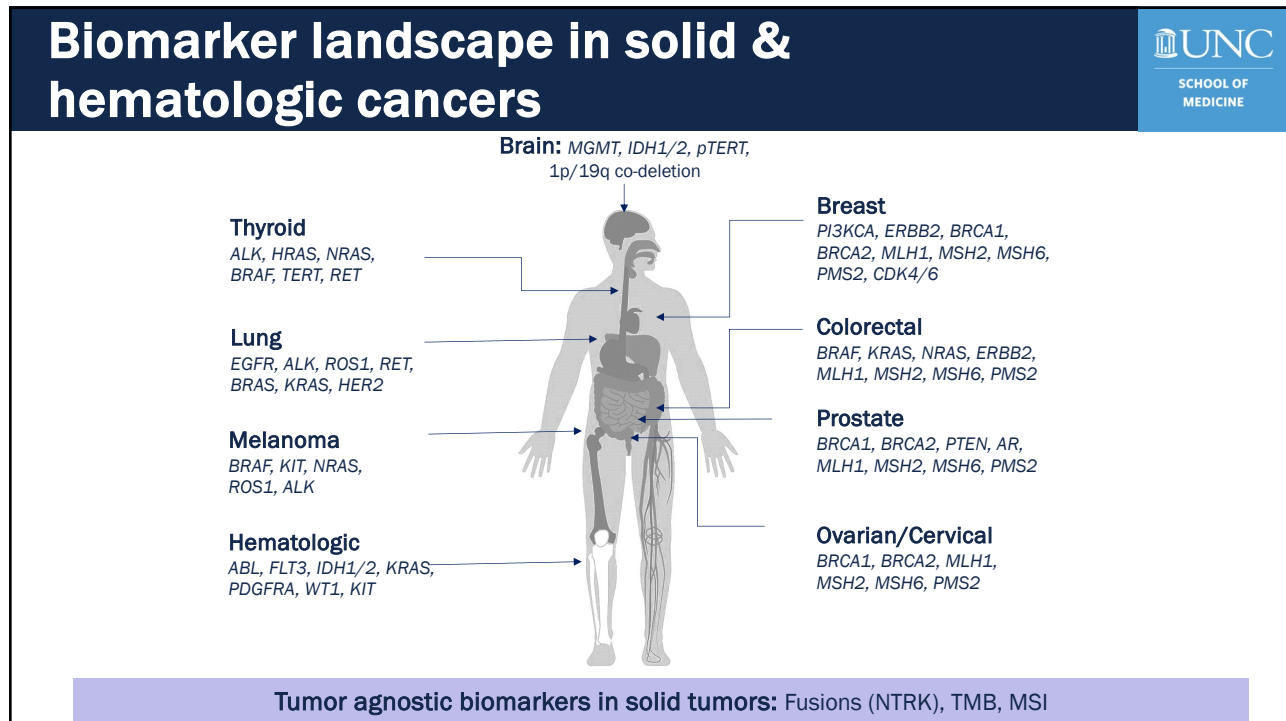
SOMATIC GENOMIC TESTING IN PATIENTS WITH METASTATIC OR ADVANCED CANCER
PROVISIONAL CLINICAL OPINION

ASCO Guidelines

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.

32
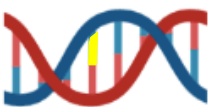
Detecting molecular biomarkers in cancer

33
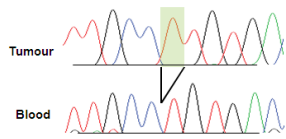
Types of genomic alterations that define cancer biomarkers
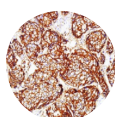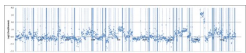
Base Pair Substitutions

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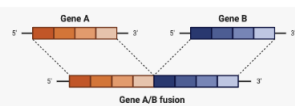
Insertions/deletions

- 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

35
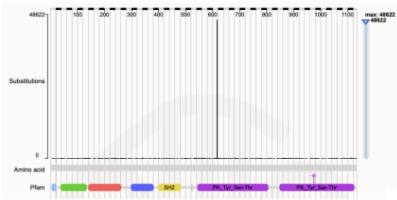
Gain-of-function versus Loss-of-function alterations

- 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
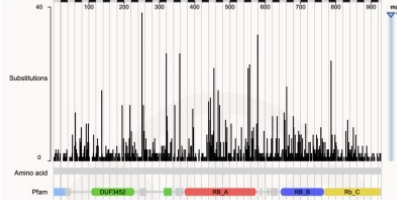
- LOSS OF FUNCTION mutations typically occur in TUMOR SUPPRESSOR GENES

  - 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

JAK2

https://cancer.sanger.ac.uk/cosmic/
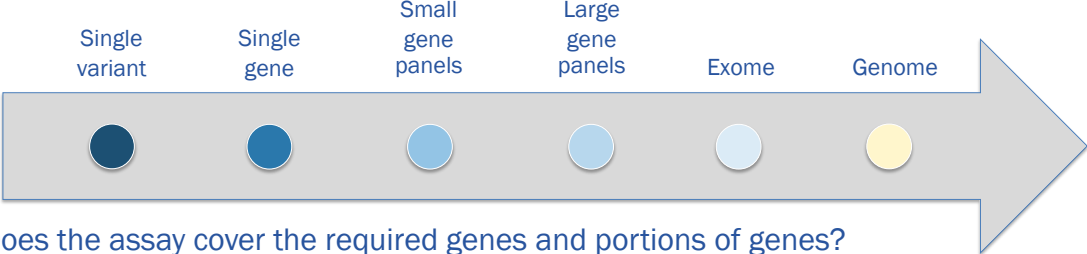
RB1

36

Finding the right assay

Single variant | Single gene | Small gene panels | Large gene panels | Exome | Genome
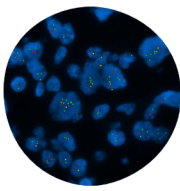
- Does the assay cover the required genes and portions of genes?

- 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?
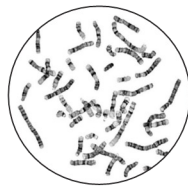
37

Methodologies to detect cancer biomarkers
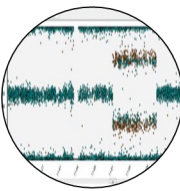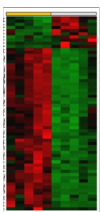
Fluorescence in situ hybridization (FISH)
Detect specific genomic translocations, copy number deletions/gains

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.
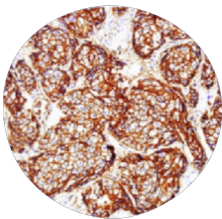
Immunohistochemistry

Determines protein expression within tissue sample
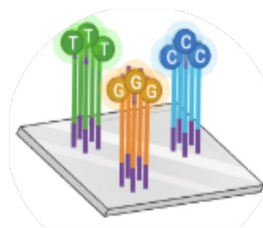
Broad Panel (Comprehensive Genomic Profiling)

An NGS test that sequences a defined list of genes with at least 50 genes in total. May also include RNA testing

39

Methodologies are often combined to identify biomarkers
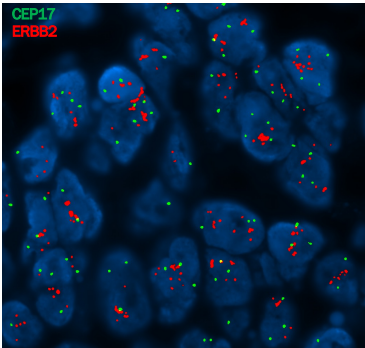
HER2 biomarker testing in invasive breast cancers

HER2 testing by validated immunohistochemistry (IHC) assay[b,c]

→ IHC 0,1+[d] ——————→ HER2 (-)

→ IHC 2+ ——————→ Equivocal result

→ IHC 3+ ——————→ HER2 (+)

Must reflex test with ISH (if same specimen), or order new test with IHC or dual probe ISH (if new specimen available).
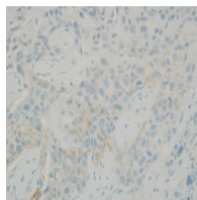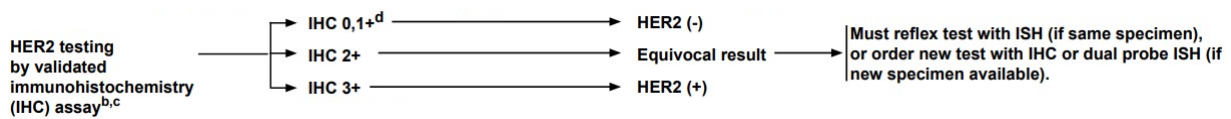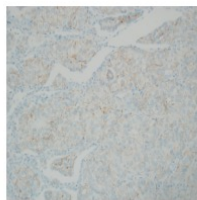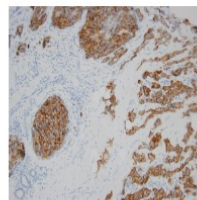
1+: IHC   **2+: IHC**   **3+: IHC**

40

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

41
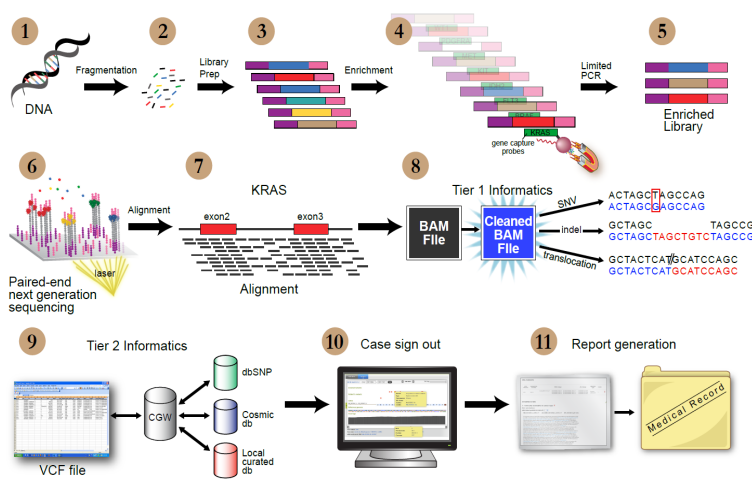
Overview of comprehensive genomic profiling

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
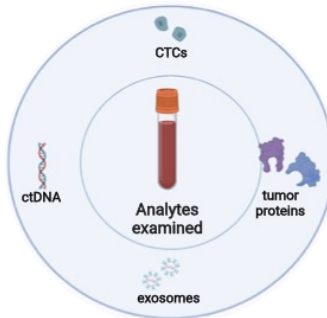
Single gene testing (SGT)	Comprehensive Genomic Profiling
One or more tests ordered individually or simultaneously, but performed separately • **PCR** – defined regions for a limited number of mutations in *EGFR, KRAS or BRAF* • **FISH** – known rearrangements in *ALK, RET, ROS1 or MET* amplification • **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
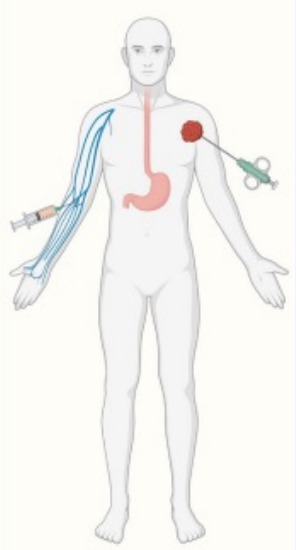
Nesline et al. *Oncol Ther* 2024 Mar 19.

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Cancer biomarker testing can be performed on a liquid or tissue biopsy
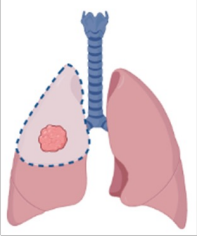
44

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

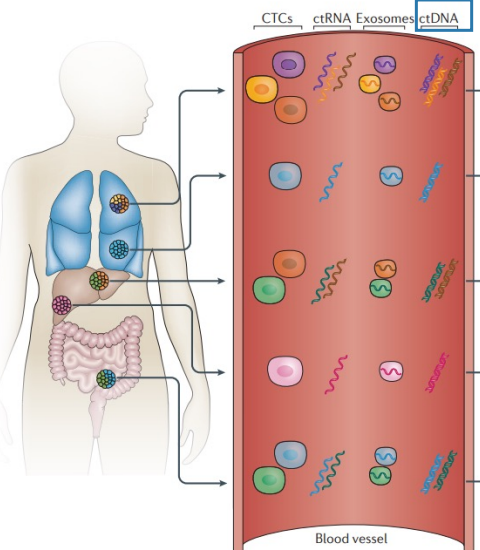**Endobronchial Ultrasound (EBUS)/ Fine Needle Aspiration (FNA)**

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

Created in BioRender.com

45

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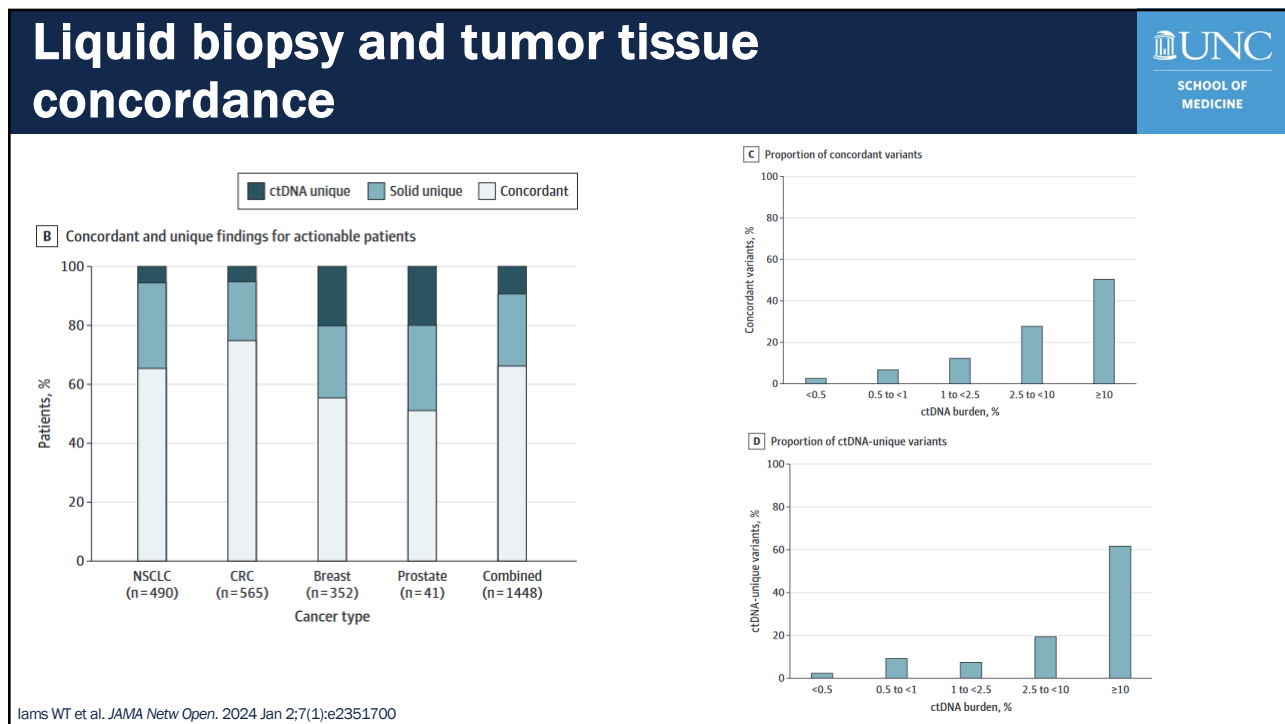
Nat Rev Clin Oncol. 2017 Sep;14(9):531-548

46

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.

47

Iams WT et al. *JAMA Netw Open*. 2024 Jan 2;7(1):e2351700
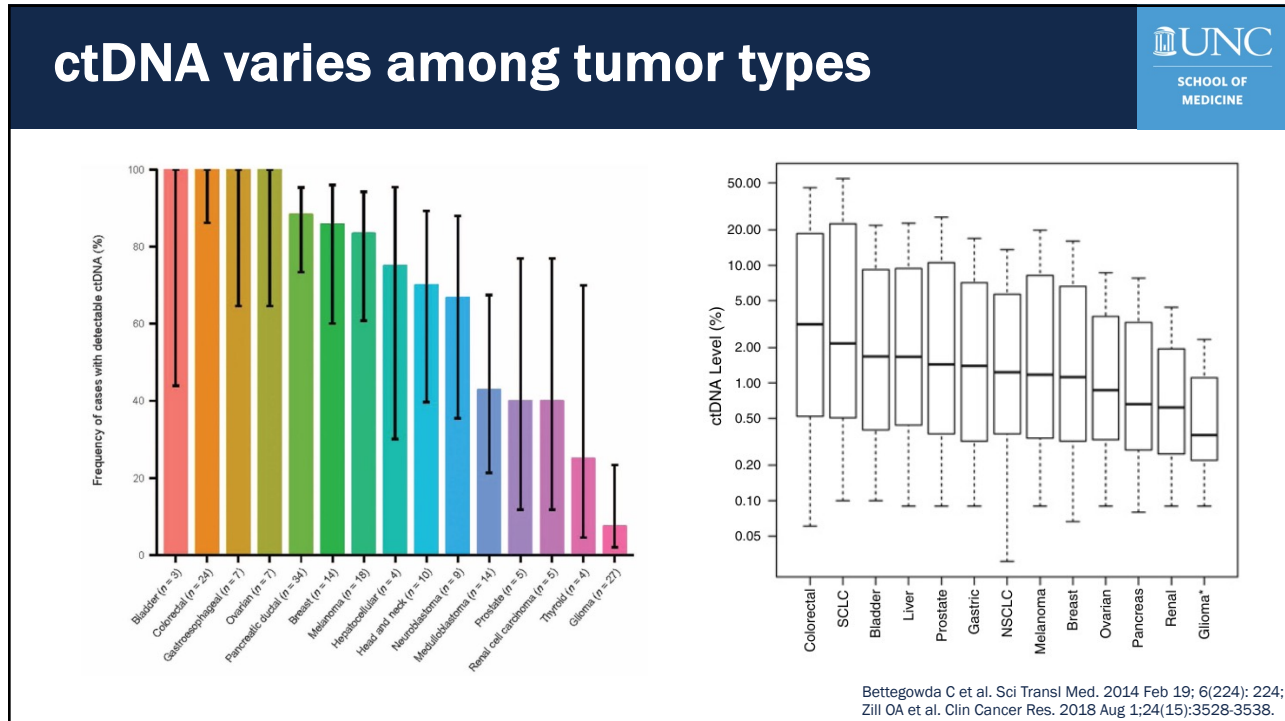
48

Advantages and disadvantages of tumor versus liquid biopsy

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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

49

ESMO Guidelines: Advanced cancer genotyping recommendations

UNC
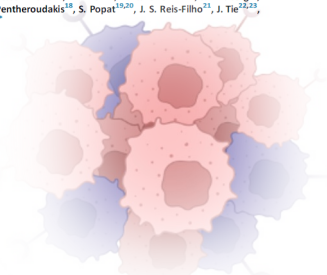**SCHOOL OF MEDICINE**

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

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY

SPECIAL ARTICLE

ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group

J. Pascual[1], G. Attard[2], F.-C. Bidard[3,4], G. Curigliano[5,6], L. De Mattos-Arruda[7,8], M. Diehn[9], A. Italiano[10,11,12], J. Lindberg[13], J. D. Merker[14], C. Montagut[15], N. Normanno[16], K. Pantel[17], G. Pentheroudakis[18], S. Popat[19,20], J. S. Reis-Filho[21], J. Tie[22,23], J. Seoane[24,25], N. Tarazona[26,27], T. Yoshino[28] & N. C. Turner[19,20]*

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

50

Poll everywhere question #2:

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- 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

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

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Individual FISH assays to interrogate each biomarker

0%

Hotspot DNA gene sequencing panel

0%

DNA and RNA sequencing assay

0%

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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
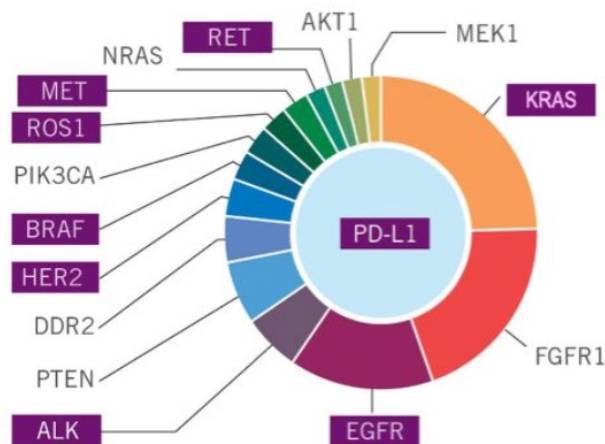
Adapted from genetechnologycom and NCCN guidelines.

54

Guidelines and other resources assist with biomarker and test interpretation

NCCN Guidelines – Non-Small Cell Lung Cancer Version 5.2024, 4/30/24
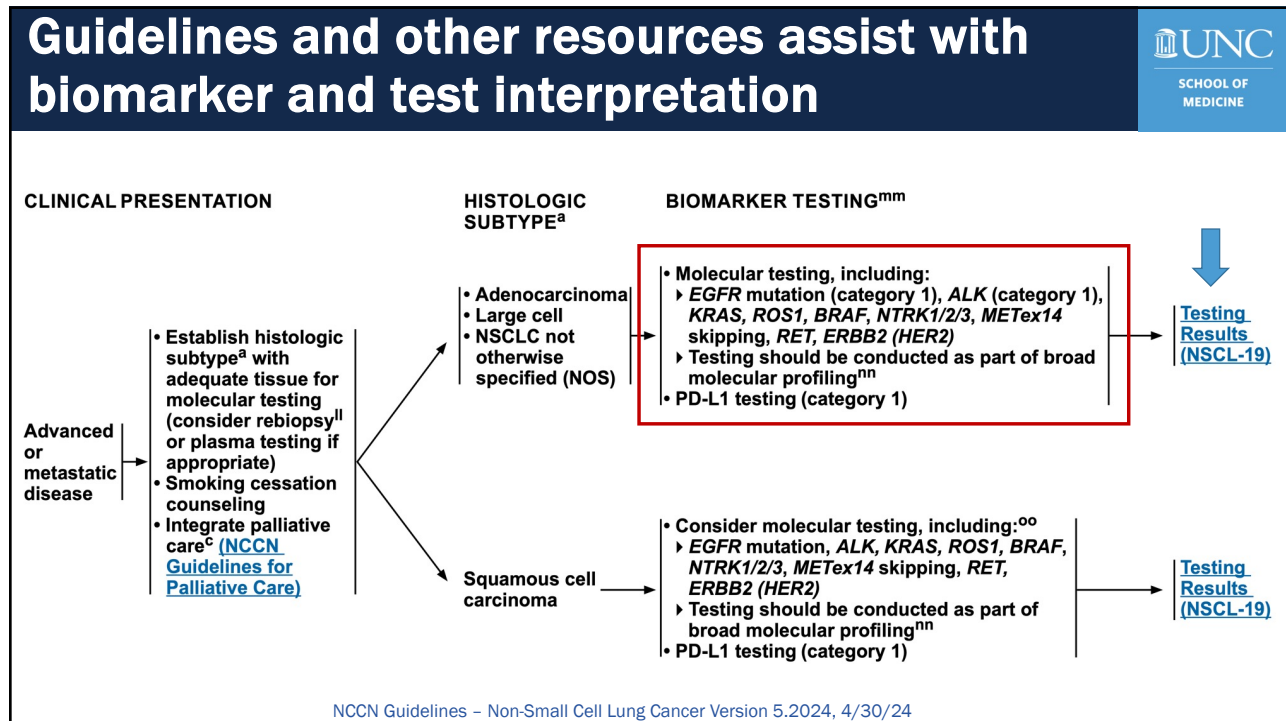
55

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

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Biomarker approved therapies for NSCLC

EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS[mm]

FIRST-LINE THERAPY[pp]

EGFR exon 19 deletion or exon 21 L858R mutations

EGFR mutation discovered prior to first-line systemic therapy

Preferred
Osimertinib[qq] (category 1) → Progression → Subsequent Therapy (NSCL-21)

Other Recommended
Erlotinib[qq] (category 1)
or Afatinib[qq] (category 1)
or Gefitinib[qq] (category 1)
or Dacomitinib[qq] (category 1)
or Erlotinib + ramucirumab
or Erlotinib + bevacizumab[rr,ss] → Progression → Subsequent Therapy (NSCL-22)

EGFR mutation discovered during first-line systemic therapy

Complete planned systemic therapy,[tt] including maintenance therapy, or interrupt, followed by osimertinib (preferred) or → Progression → Subsequent Therapy (NSCL-21)

erlotinib or afatinib or gefitinib or dacomitinib or erlotinib + ramucirumab or erlotinib + bevacizumab[rr,ss] → Progression → Subsequent Therapy (NSCL-22)

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

Log-rank $P < .0001$

+ Available testing group
+ Unavailable testing group

No. at risk:	0	6	12	18	24	30	36
Available testing group	261	206	154	91	42	14	0
Unavailable testing group	65	27	14	7	6	2	0

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, Barragán-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
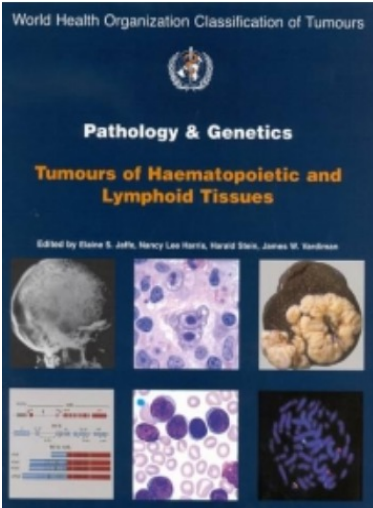
2001

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
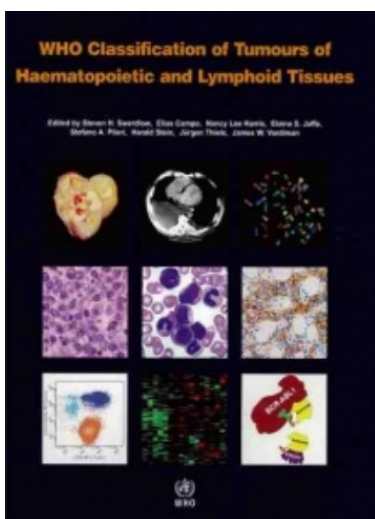
2008

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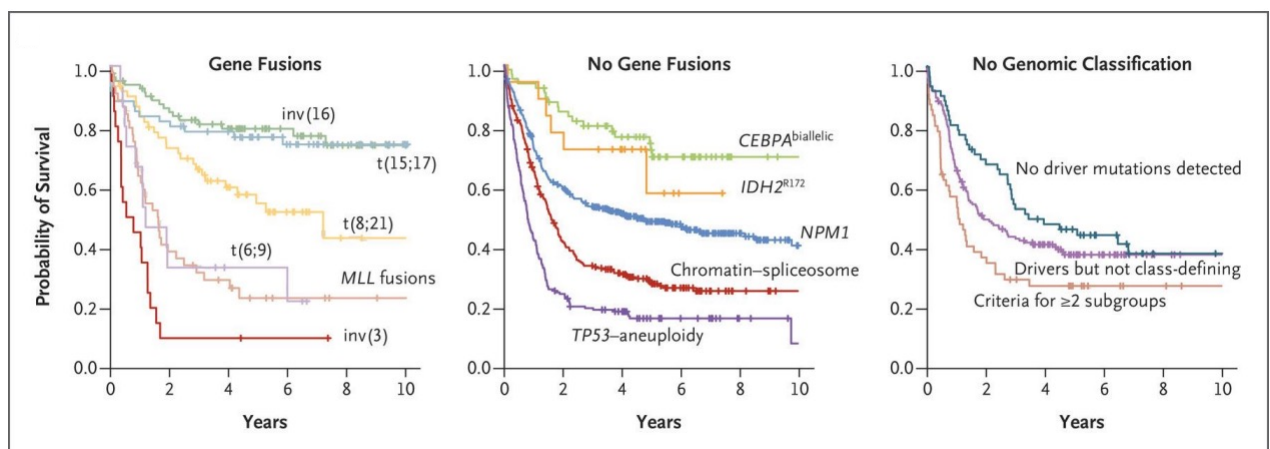
Papaemmanuil E et al. N Engl J Med ;374:2209-2221

64

Impact of molecular testing in myeloid malignancy classification
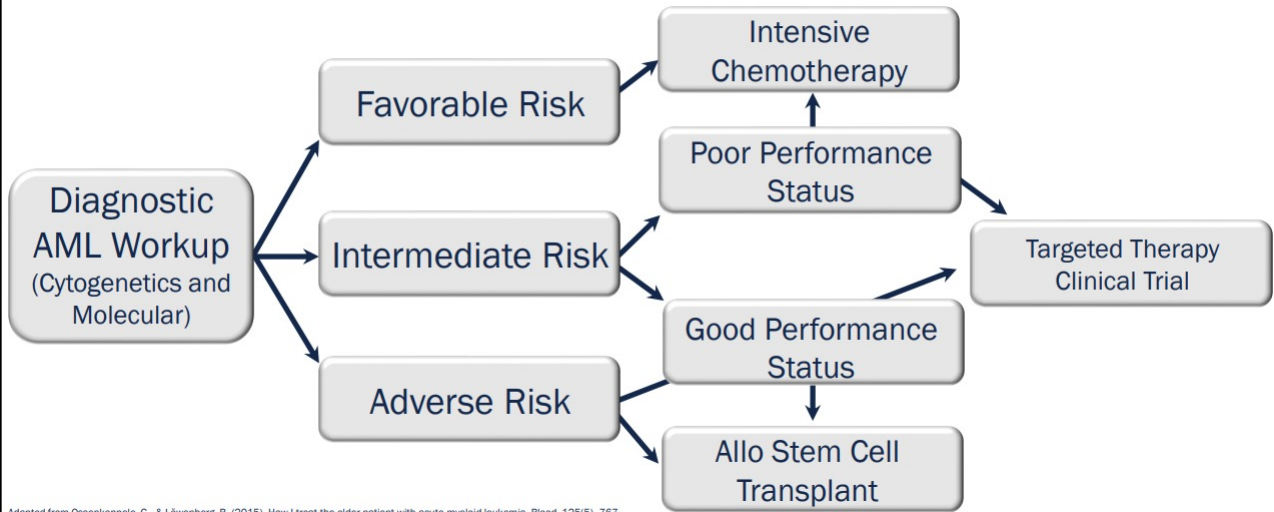
Adapted from Ossenkoppele, G., & Löwenberg, B. (2015). How I treat the older patient with acute myeloid leukemia. Blood, 125(5), 767-

65

Molecular biomarkers are increasingly incorporated into neuro-oncology

66

67
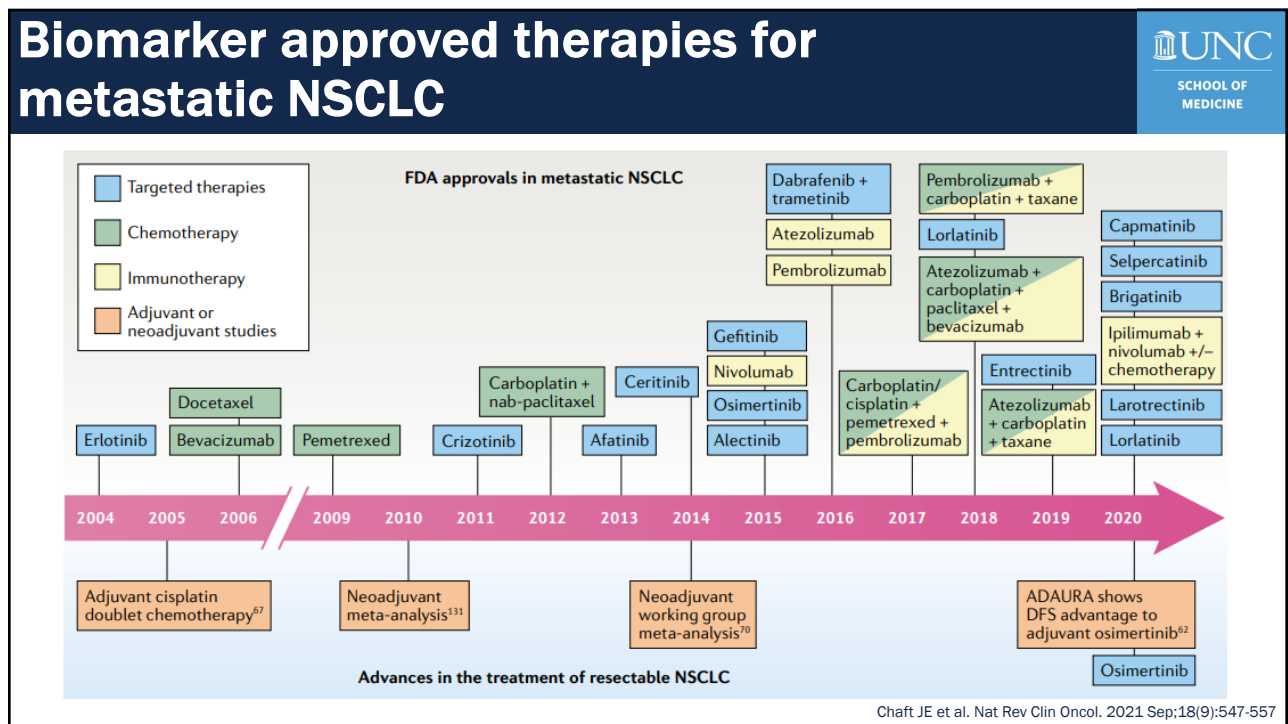

68

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.
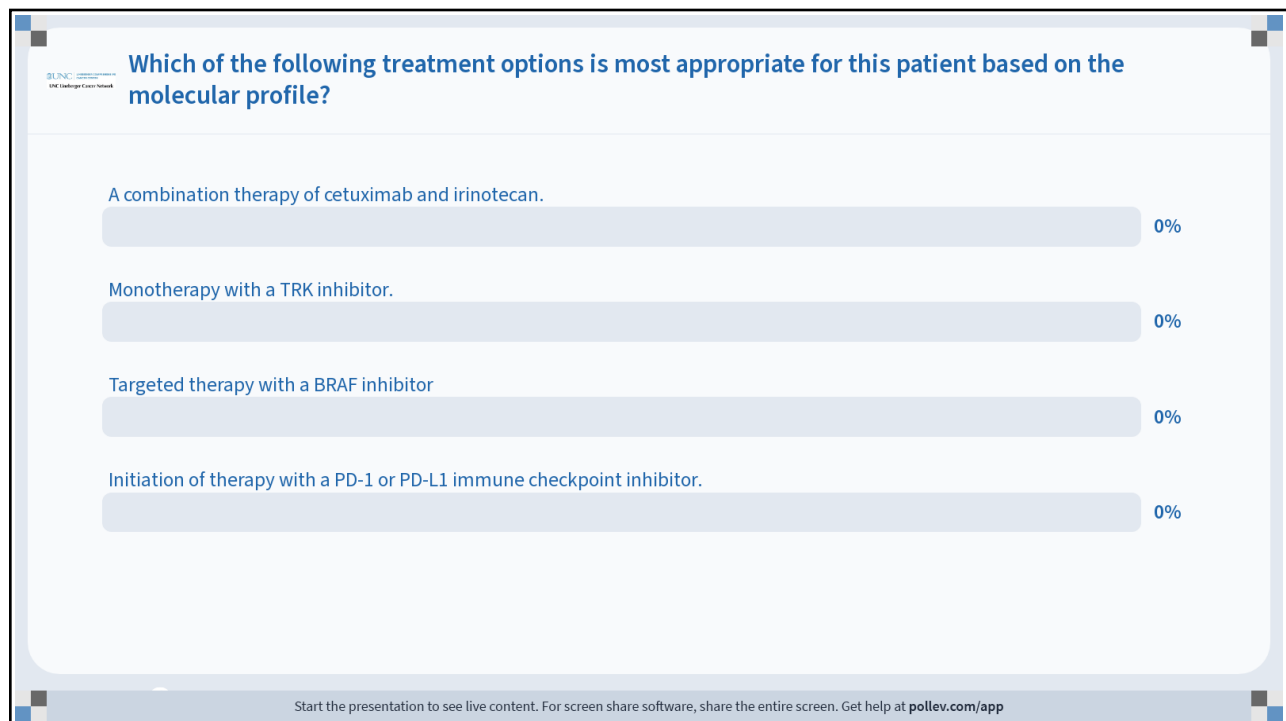
72

Poll everywhere question #3:

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MEDICINE

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

UNC Lineberger Cancer Network

Which of the following treatment options is most appropriate for this patient based on the molecular profile?

A combination therapy of cetuximab and irinotecan.

0%

Monotherapy with a TRK inhibitor.

0%

Targeted therapy with a BRAF inhibitor

0%

Initiation of therapy with a PD-1 or PD-L1 immune checkpoint inhibitor.

0%

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74

Poll everywhere question #3:

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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
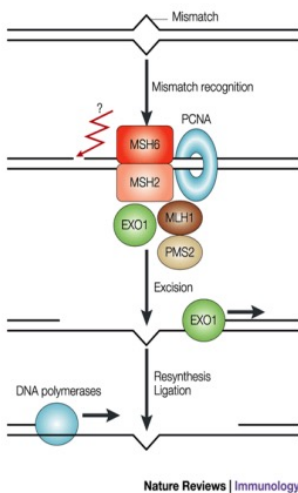
- During DNA replication, errors occur in microsatellite regions
  - Short repetitive DNA sequences (1-6 base pairs) or tandem repeats
- Multi-protein complex corrects these single base pair mismatches and small insertion-deletion errors
- Failures to repair these errors during replication leads to expansion of repeats and genomic instability = **microsatellite instability**
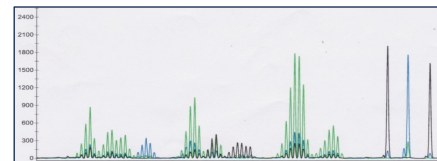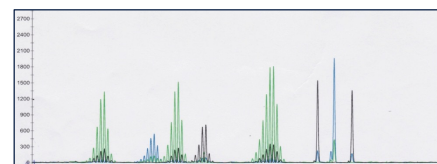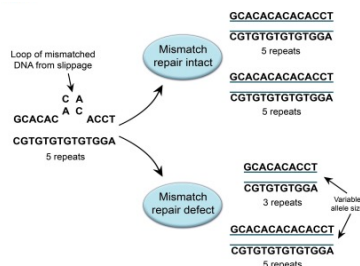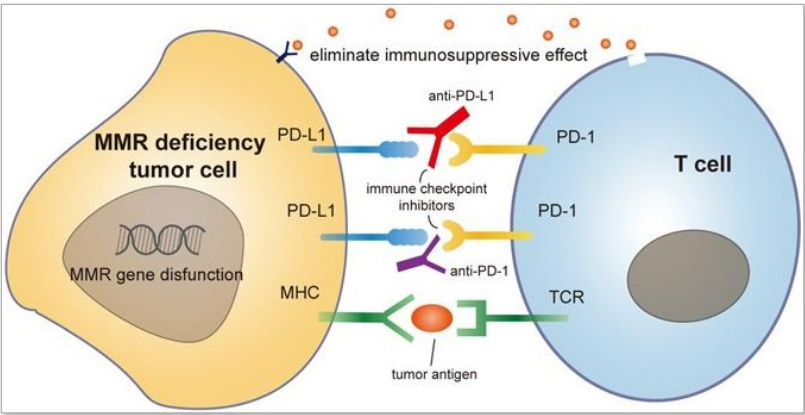
76

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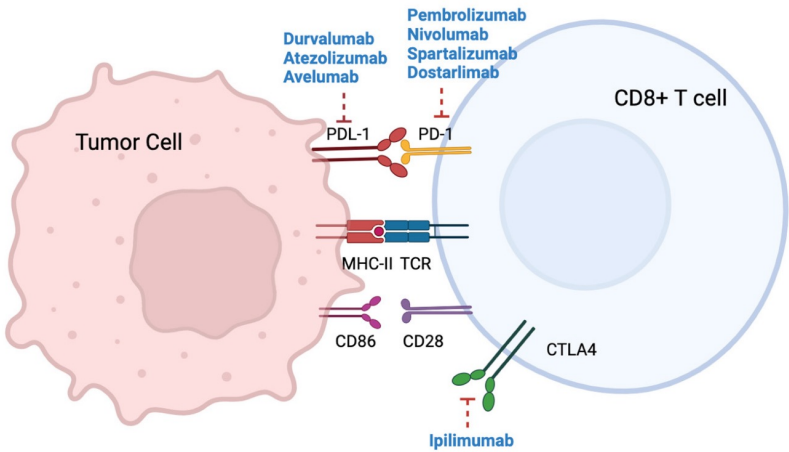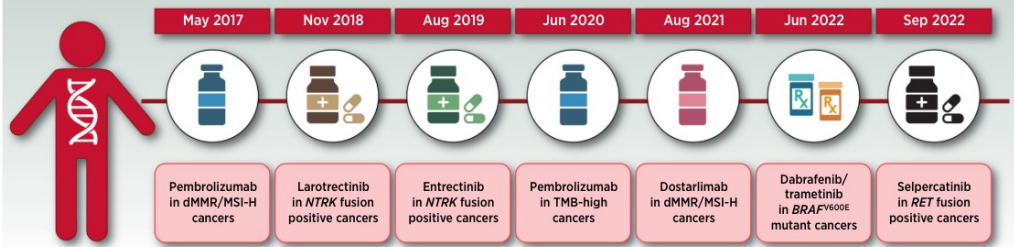
Ros J et al. Cancers (Basel). 2023 Aug 24;15(17):4245.

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

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Targeted therapy success story

Chronic Myeloid Leukemia

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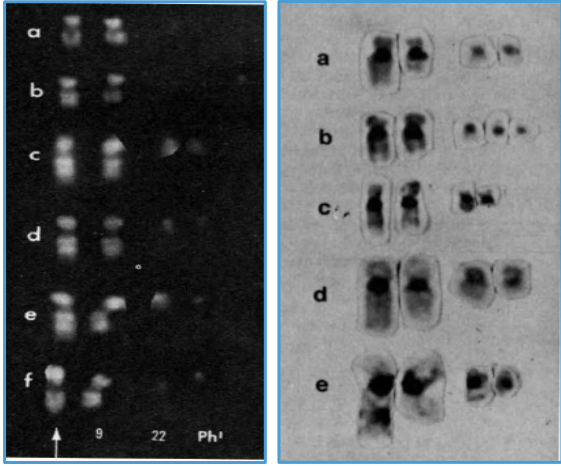## Visualization of first chromosome translocation

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,
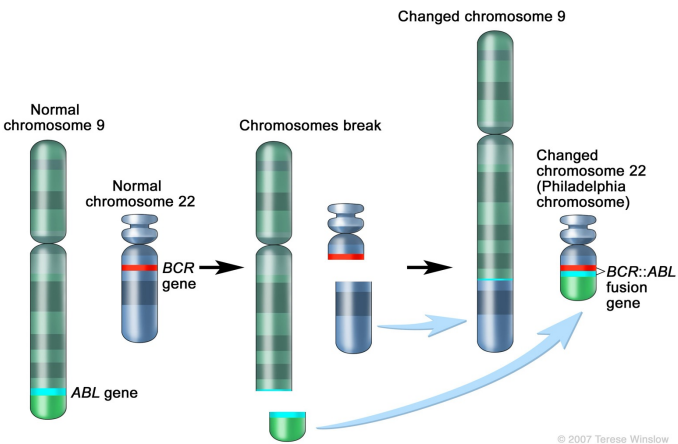Chicago, Illinois 60637
Received January 8; revised February 8, 1973.

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

Slide 83: Understanding mechanism of *BCR::ABL1* transforms care for CML patients

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Slide 84: Combining molecular methods to diagnosis and monitor CML

84

Summary

- Incorporating precision medicine into oncology treatment strategies improves patient outcomes across multiple cancer types
  - More matched therapies are on the way
- Testing for genomic or molecular biomarkers can be performed on tumor tissue or via a liquid biopsy
  - Use of single gene tests versus broad, multi-gene panel options
- Increased detection of molecular biomarkers leading to approval of more targeted therapies

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Questions?

86

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Upcoming Live Webinars
learn.unclcn.org

ADVANCED PRACTICE PROVIDER — Live Webinar — *May 15* / *4:00 PM*

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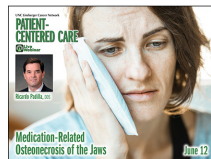**Melissa Holt,** DNP, PMHNP-BC   **Lisa Kanser,** PsyD

RESEARCH TO PRACTICE — Live Webinar — *May 22* / *12:00 PM*

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

PATIENT-CENTERED CARE — Live Webinar — *June 12* / *12:00 PM*

Medication-Related Osteonecrosis of the Jaw
Ricardo Padilla, DDS

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ADVANCED PRACTICE PROVIDER — Self-Paced, Online Course

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

RESEARCH TO PRACTICE — Self-Paced, Online Course

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

PATIENT-CENTERED CARE — Self-Paced, Online Course

Oncologic Emergencies
Jake Stein, MD

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