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Genetic Testing in Cancer Patients: A Case Illustration

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1

Learning Objectives

- **Define somatic and germline genetic testing and describe their role in cancer care**
- **Discuss best ways to communicate genetic information to help bridge the language gap between providers and patients**
- **Explain the process of utilizing genetic testing to select optimal cancer treatment**

2

Case Study

- 46 y.o. never-smoking African American male presents to the ED with hemoptysis, dyspnea & syncope
- CT scan shows bilateral pulmonary nodules and osseous metastases
- Undergoes same day video-assisted thoracoscopic surgery (VATS):
  - Pathology confirms lung adenocarcinoma, PD-L1 5%
  - Staging MRI shows innumerable brain metastases
- Starts carboplatin and pemetrexed while inpatient
- Family CA History: Father esophageal cancer age 58

3

Poll question #1

What kind of genetic testing would be ordered for this patient?

A. None, based on patient's age, NSCLC diagnosis, stage, and family cancer history
B. Somatic testing based on NSCLC diagnosis and stage
C. Germline testing based on patient's age, NSCLC diagnosis, stage, and family cancer history
D. Both somatic and germline testing based on age, NSCLC diagnosis, stage and family cancer history

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4

Answer

- Stay tuned!

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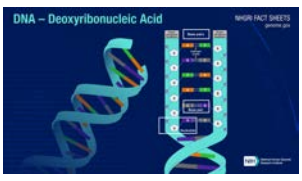
Refresher: DNA

- DNA: Molecules inside cells that carry genetic information
- Made up of four building blocks called nucleotides: adenine (A), thymine (T), guanine (G), and cytosine (C)
- The sequence of A, T, C, G creates "gene sentences" and a story that instructs cells:
  - Small changes in the order of letters can change the meaning of the sentences
  - These changes could result in gene mutation, amplification or translocation
- Tumors have *their own unique DNA profile*



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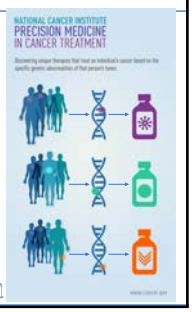
Precision Oncology

- As we learn more about cancer growth and behavior, there are new ways each person's disease can be defined: "every patient's cancer is rare"
- Traditionally, treatment was based upon where in the body the cancer started
- Precision oncology enables us to detect unique genetic changes in a patient's cancer and target them with specific treatments
- Over the past two decades, the use of "targeted" therapies has increased exponentially
- Targeted therapy is the foundation of precision oncology



7

Targeted therapy

- Treatments which interfere with specific cellular processes used by cancer to grow and spread-- as opposed to chemotherapy, which interferes with all rapidly dividing cells
- Some examples include: monoclonal antibodies, small molecule inhibitors, antibody drug conjugates, hormonal therapies
- Breast cancer and chronic myelogenous leukemia had some of the first drugs to "target" specific tumor cell characteristics:
  - *HER2* positivity in Breast (trastuzumab 1998)
  - *BCR-ABL* fusion gene in CML (imatinib, 2001)

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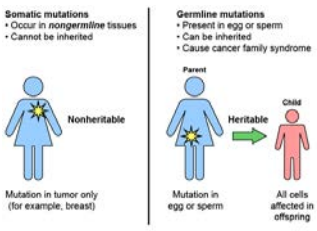
Genetic Testing: Somatic and Germline Mutations



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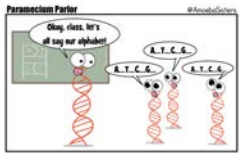
Somatic testing: Next Generation Sequencing (NGS)

- Utilizes DNA sequencing technologies that processes multiple DNA sequences in parallel, to find genetic abnormalities (cancer.gov)
- Think of it as a very fancy spell-checker for tumor DNA!



Some of the NGS labs/tests used by UNC & its affiliates:

Platform	Sample Type	# of Genes
Foundation CDx	Tumor tissue	324
Foundation CDx Liquid	Blood	311
Guardant	Blood	73
Neogenomics	Tumor tissue	Varies by disease
Tempus xT	Tumor tissue/blood	648


Image courtesy Illumina.com

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10

When is genetic testing appropriate?

Somatic Testing	Germline Testing
To guide treatment in cancers with common genetic variants (i.e. osimertinib for *EGFR*m in NSCLC)	Young age at diagnosis and/or strong family history of certain cancers
When a patient is out of standard options, or cannot tolerate standard options	Cancer type (i.e. epithelial ovarian) and/or advanced stage at diagnosis (i.e. newly diagnosed Stage IV prostate cancer)
May be required as part of eligibility requirements for clinical trial participation	Ancestry associated with certain genetic mutations and cancers (i.e. Ashkenazi Jewish heritage and BRCA1/2)
To confirm a cancer diagnosis (i.e. mandatory in sarcoma due to their rarity and histologic overlap)	Possible pathogenic variant found by somatic testing

Both somatic and germline testing are referenced in NCCN guidelines
The treating medical oncologist will most often be the one to order somatic testing
If an inherited predisposition to cancer is suspected based on age, ancestry or other features, the patient should be referred to genetic counseling to understand the purpose and potential impact of germline testing

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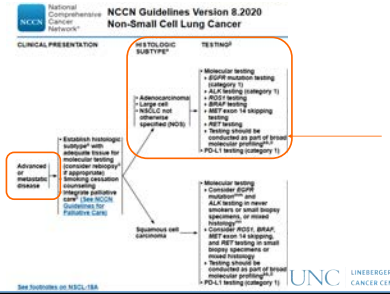
11

Back to our case study: 46 yo, Stage 4 NSCLC, limited family cancer history



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12

Answer to poll question #1:

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13

Approaching patients about genetic testing

- Your doctor can order tests on your tumor tissue or blood, to look for "targets" or "traits" that may be causing your cancer to grow
- Testing may find targets your doctor can treat with a drug
- Treatment options may include drugs only available on research studies
- Sometimes testing finds targets in your cancer cells that do not yet have a drug to treat them, because we are still learning about them
- In some cases, testing is not able to find any targets to treat with a drug
- Once your doctor has your test results, you will work together to find a treatment that is best for you

14

Results: Foundation Medicine CDx Lung Cancer

NO REPORTABLE ALTERATIONS WITH COMPANION DIAGNOSTIC (CDx) CLAIMS
See professional services section for additional information

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED
Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See professional services section for additional information.

Microsatellite status MS-Stable§
Tumor Mutational Burden 5 Muts/Mb§
BRCA1 splice site 213-11T>G
EGFR A763_Y764insFQEA
MAP2K4 MAP2K4(NM_003010) rearrangement intron 1§
RAD21 amplification§
RB1 Q257*
TP53 R273H

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result in this section.
Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

15

Patient referred to UNC's Molecular Tumor Board (MTB) for further analysis of Foundation CDx results

- After preliminarily reviewing the testing report, MTB recognized the *BRCA1* splice site 213-11T>G mutation as a *known pathogenic germline mutation*

- MTB reached out to Foundation Medicine to gather more information about the testing they performed:
  - *BRCA1* splice site 213-11T>G, Variant Allele Frequency (VAF) = 77.42%
  - The VAF % is used to infer whether a variant comes from somatic cells or may be inherited from parents when a matched normal sample is not provided; a variant is *potentially* a germline mutation if the VAF is ~50% -100% (*Genome Med. 2019 Aug 23;11(1):53*)
- With this information, the decision was made to refer patient for genetic counseling and testing

16

Genetic Evaluation for Inherited Cancer Risk

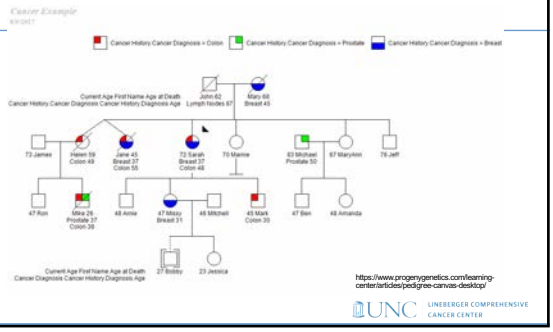
Family History | Personal Cancer Features | Other Risk Factors

→ Determine suspicion for hereditary cancer syndrome

→ Discuss:
- Genetic testing options
- Types of results
- Cancer risks
- Insurance implications
- Reproductive implications

→ **Patient makes informed decision regarding proceeding with genetic testing**

17



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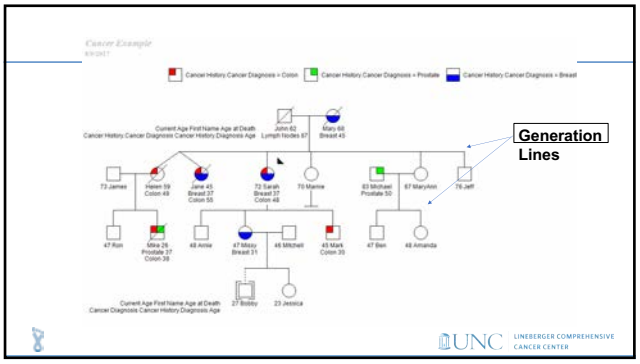
Generation Lines

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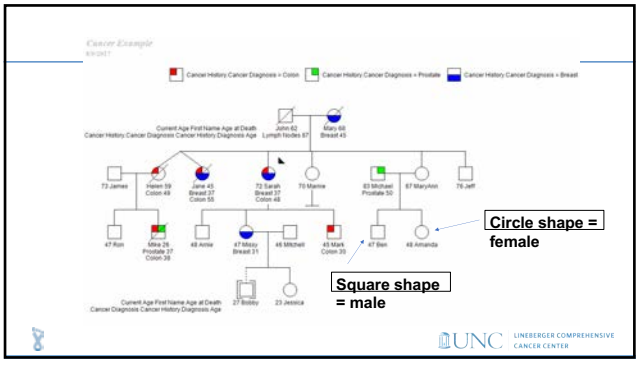
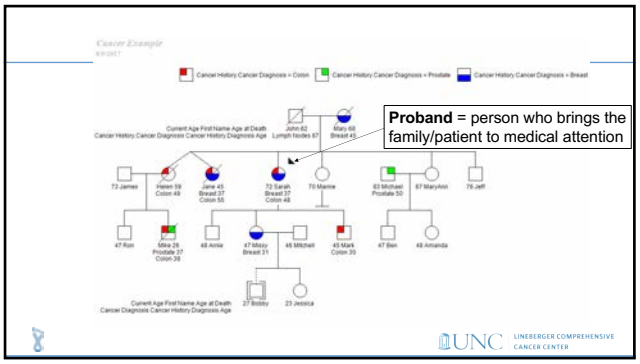

Circle shape = female
Square shape = male

20


Proband = person who brings the family/patient to medical attention

21

Knudson's Two-hit hypothesis

- Loss of heterozygosity aka second hit
- Mutations that inactivate tumor suppressor genes, called loss-of-function mutations, are often point mutations or small deletions that disrupt the function of the protein that is encoded by the gene

Landmark Study: https://www.nature.com/scitable/topicpage/tumor-suppressor-ts-genes-and-the-two-887/ (2008)

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Possible Results of Genetic Testing

Pathogenic Variant Detected or Positive Result	• Increased Cancer Risks • Apply Management Guidelines if available • Test other family members if actionable
No Pathogenic Variant Detected or Negative Result	• Assess result based on family history • ***Cancer risks may still be increased based on personal and family history*** • Typically no genetic testing for unaffected family members
Variant of Uncertain Significance (VUS)	• Subtle DNA change • Unknown if benign variant (normal) or disease causing • Follow based on family history • More info may become available

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23

Examples of Results

ATM c.486delA (p.Gln162Hisfs*4)

BRCA2 c.120C>T (p.Ser40Ser)

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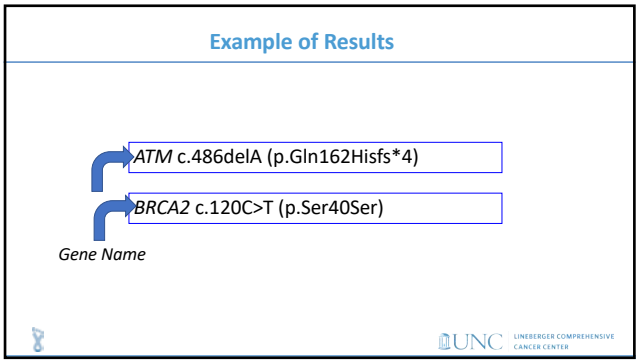
24


Example of Results
ATM c.486delA (p.Gln162Hisfs*4)
BRCA2 c.120C>T (p.Ser40Ser)
Gene Name
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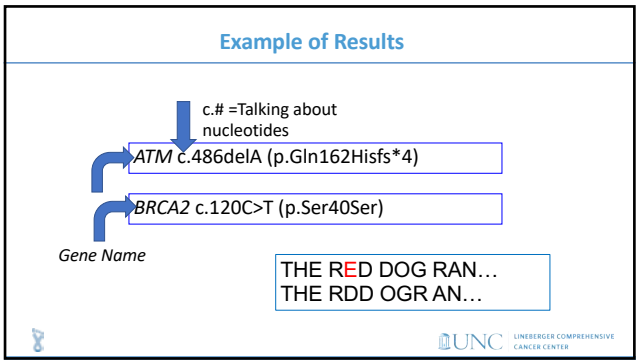
25


Example of Results
c.# =Talking about nucleotides
ATM c.486delA (p.Gln162Hisfs*4)
BRCA2 c.120C>T (p.Ser40Ser)
Gene Name
THE RED DOG RAN…
THE RDD OGR AN…
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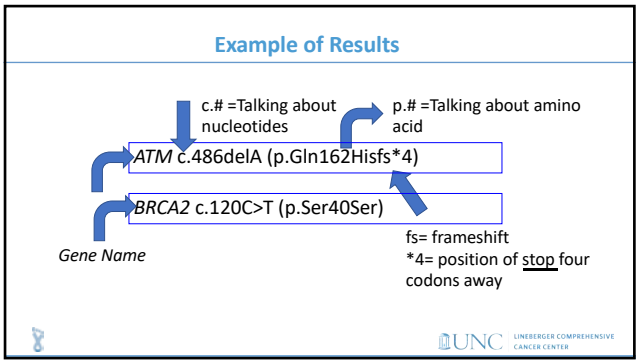
26


Example of Results
c.# =Talking about nucleotides
p.# =Talking about amino acid
ATM c.486delA (p.Gln162Hisfs*4)
BRCA2 c.120C>T (p.Ser40Ser)
Gene Name
fs= frameshift
*4= position of stop four codons away
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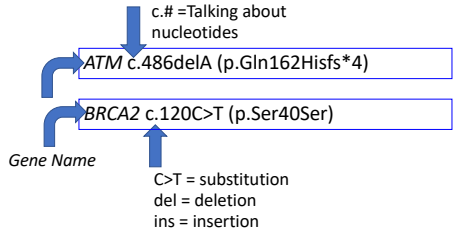
27

Example of Results



28

Poll Question

- Which of the following correctly denotes the variant described below?

A patient was identified to have a G to T substitution in the ATM gene at nucleotide position 210 resulting in an amino acid substitution of valine to glycine.

- A) *ATM* c.70T>G (p.Val210Gly)
- B) *ATM* c.210G>T (p.Val70Gly)
- C) *ATM* c.210G>T (p.Gly70Val)
- D) *ATM* c.210Gly>Val (p.G70T)
- E) *ATM* c.210Gly>Val (p.T70G)

29

Germline Result

BRCA1 c.213-11T>G

- This sequence change falls in intron 4 of the *BRCA1* mRNA
- This is expected to result in a frameshift in the *BRCA1* mRNA and an absent or truncated protein
- Cascade testing is now available for family members

30


National Society of Genetic Counselors
Celebrating 40 Years 1979 - 2019
www.nsgc.org
ABOUT US EVENTS PUBLICATIONS NEWSROOM EDUCATION CAREERS BECOME A MEMBER
Find a Genetic Counselor
This directory has been developed to assist physicians, patients and genetic counselors in accessing genetic counseling services.
DISCLAIMER
SEARCH TIPS
MEET BY PHONE
MEET IN PERSON
ABOUT GENETIC COUNSELORS
PATIENT RESOURCE SITE
MEMBER DIRECTORY
FIND A GENETIC COUNSELOR
The Find a Genetic Counselor directory offers access to over 3,300 genetic counselors (US and Canada).
Check with your insurance company to verify coverage of genetic counseling, testing and authorized providers. For more information, visit aboutgeneticcounselors.com.
To start your search, tell us how you would prefer to meet with a genetic counselor.
Searches of the "In Person" directory will show genetic counselors who meet patients in a designated location and in person. Searches can be limited to a given location.
Searches of the "By Phone" directory will show genetic counselors who meet with patients via phone, video conferencing and other virtual methods.
In Person
By Phone
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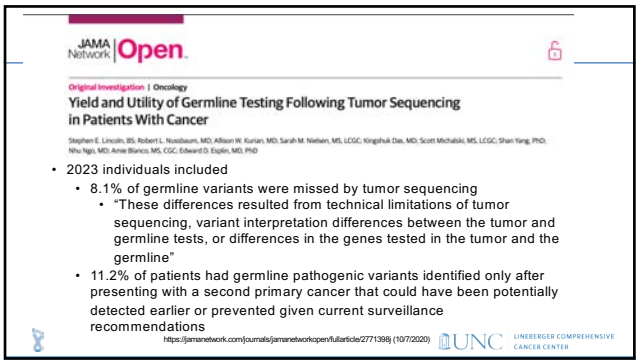
31


JAMA Network Open.
Original Investigation | Oncology
Yield and Utility of Germline Testing Following Tumor Sequencing in Patients With Cancer
Stephen E. Lincoln, BS; Robert L. Nussbaum, MD; Allison W. Kurian, MD; Sarah M. Nielsen, MS, LCGC; Kingshuk Das, MD; Scott Michalski, MS, LCGC; Shan Yang, PhD; Nhu Ngo, MD; Amie Blanco, MS, CGC; Edward D. Esplin, MD, PhD
2023 individuals included
8.1% of germline variants were missed by tumor sequencing
"These differences resulted from technical limitations of tumor sequencing, variant interpretation differences between the tumor and germline tests, or differences in the genes tested in the tumor and the germline"
11.2% of patients had germline pathogenic variants identified only after presenting with a second primary cancer that could have been potentially detected earlier or prevented given current surveillance recommendations
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2771398 (10/7/2020)
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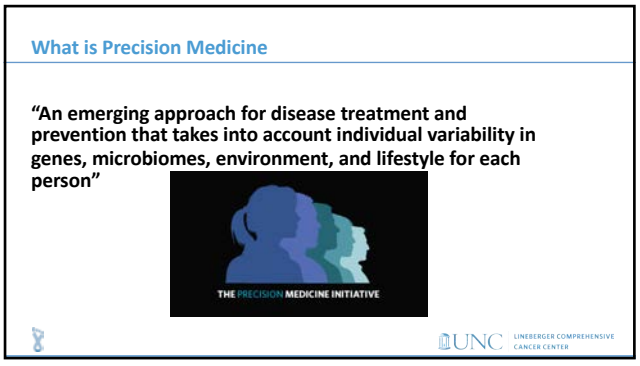
32


What is Precision Medicine
"An emerging approach for disease treatment and prevention that takes into account individual variability in genes, microbiomes, environment, and lifestyle for each person"
THE PRECISION MEDICINE INITIATIVE
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33

How is genetic testing used to guide treatment decisions?

- **Diagnostic**
  - Genetic tests can be used to help diagnose cancer on the molecular level
    - Example: Presence of gene fusions with EWSR1 gene can help confirm a diagnosis of Ewing sarcoma
- **Prognostic**
  - Genetic tests can help clinicians determine the aggressiveness of a person's cancer and better stratify groups of patients for clinical trials
    - Example: In glioma, IDH1/2 mutations are associated with a more favorable prognosis
- **Therapeutic biomarker**
  - Genetic tests can predict response or resistance to a give drug/regimen
    - Often times these are somatic mutations in the tumor, but some examples of germline mutations (i.e. BRCA1/2)
- **Drug dosing**
  - Testing for germline (inherited) mutations in drug metabolizing enzymes can help determine if patient requires a different dose of a drug
    - Example: Patients with UGT1A1*28/*28 genotype may require a dose reduction of irinotecan to minimize their risk of severe neutropenia

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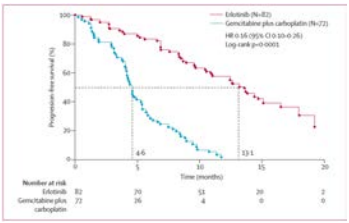
34

Why do we look for therapeutic biomarkers of efficacy?

- In patients who have stage 4 non-small cell lung cancer (NSCLC) and an EGFR mutation, treatment with erlotinib more than doubled progression-free survival
- Erlotinib could be given orally and has a different side effect profile compared to cytotoxic chemotherapy



Landmark Study: Lancet Oncol. 2011 Aug;12(8):735-42

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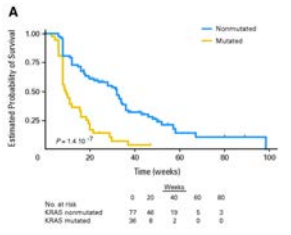
35

Why do we look for therapeutic markers of resistance?

- Treatment with cetuximab (an EGFR targeted monoclonal antibody) demonstrated efficacy in chemotherapy resistant colorectal cancer (CRC)
- However, later subgroup analysis demonstrated that patients with KRAS mutations did not benefit from the treatment to the same degree as those with wild-type KRAS



Landmark Study: J Clin Oncol. 2008 Jan 20;26(3):374-9.

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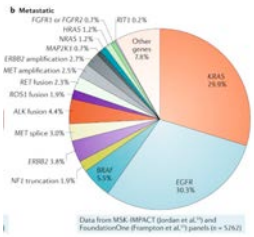
36

How do we identify therapeutic biomarkers?



Nat Rev Cancer **19,** 495–509 (2019).

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37

First line options for mEGFR

EGFR Inhibitor	EGFR mutations with FDA approval	Dose	Tolerability	Notes
Erlotinib	Exon 19 deletion L858R	150mg PO daily	Acneiform Rash, diarrhea	Reversible inhibitor
Gefitinib	Exon 19 deletion L858R	250mg PO daily	LFTs, diarrhea, rash	Reversible inhibitor Re-approved as first line therapy
Afatinib	"non-resistantEGFR mutations"	40mg PO daily	Higher rates of serious adverse events, diarrhea, stomatitis, treatment related deaths	Irreversible inhibitor Also inhibits HER2
Dacomitinib	Exon 19 deletion L858R	45mg PO daily	Higher rates of serious adverse events, diarrhea, stomatitis, treatment related deaths	Irreversible inhibitor Also inhibits HER2
Osimertinib	Exon 19 deletion L858R T790M	80 mg PO daily	Lower rates of diarrhea/rash Pneumonitis, ↓ LVEF	Irreversible inhibitor

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38

Precision Oncology and the FDA

- 164 oncology-related biomarkers and drug pairs included in FDA-approved products' labeling
- 35 (out of 37) oncology-related FDA approved companion diagnostics
- 56 oncology-related FDA approved nucleic acid based tests

https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm (11/16/2020) [accessed 6/8/2020]
https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm624726.htm (12/20/2019) [accessed 6/8/2020]
https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm330711.htm (11/04/2020) [accessed 6/8/2020]
https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm (09/19/2020) [accessed 6/8/2020]

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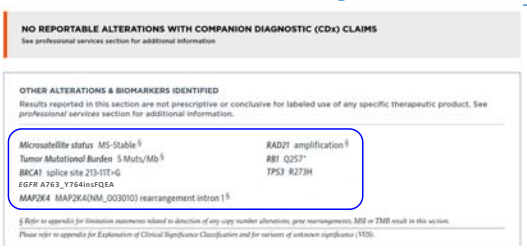
39

Results: Foundation Medicine CDx Lung Cancer



NO REPORTABLE ALTERATIONS WITH COMPANION DIAGNOSTIC (CDx) CLAIMS

See professional services section for additional information

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

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Microsatellite status MS-Stable§
Tumor Mutational Burden 5 Muts/Mb§
BRCA1 splice site 213-11T>G
EGFR A763_Y764insFQEA
MAP2K4 MAP2K4(NM_003010) rearrangement intron 1§
RAD21 amplification§
RB1 Q257*
TP53 R273H

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result in this section.
Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

40

How can I do this on my own?

- **Laboratory reports (i.e. Foundation medicine results)**
- **NCCN guidelines**
- **Drug package inserts**
- **OncoKb**
  - https://www.oncokb.org/
- **My Cancer Genome**
  - https://www.mycancergenome.org/
- **Precision Medicine Knowledge Base**
  - https://pmkb.weill.cornell.edu/

41

Poll Question # X

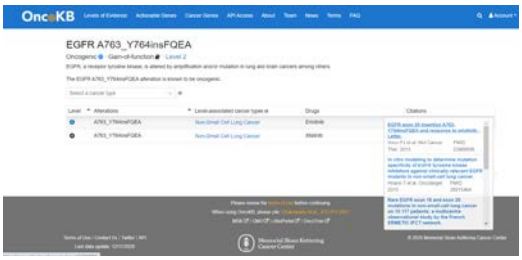
Which EGFR inhibitor would you recommend to treat a patient with NSCLC found to have an EGFR A763_Y764insFQEA mutation?

Hint: Use OncoKB

a. **Erlotinib**
b. **Gefitinib**
c. **Osimertinib**
d. **Afatinib**

42

Using OncoKB



43

Molecular Tumor Board

- MISSION:
  - *Our mission is to empower clinicians to integrate evidence-based personalized therapies into their practice and thus improve patient outcomes.*
  - *The MTB will focus both on assisting clinicians in their pursuit to efficiently use new technologies, as well as providing expertise on emerging targeted therapies and biologics, which require careful deliberation to ensure appropriate use and fiscal responsibility.*
- GOALS:
  - *To assist in the interpretation of somatic and/or germline variants associated with a spectrum of cancers to guide patient care*
    - *this includes decision support for physicians that request genomic expertise for challenging cases*
  - *To enable oncology providers throughout the health system to adopt routine utilization of data-driven precision oncology practices.*

44

Discussing targeted therapy with patients

- **Tailor your discussion to the individual**
  - **Health literacy, baseline knowledge, experience with cancer**
- **The discussion may occur over multiple visits**
  - **Focus on the "need to know", but revisit the "want to know"**
- **Compare and contrast treatments based on patient personal experience**
  - **Chemotherapy versus targeted therapy**

45

Questions?

Actually, that's the coffee machine...this is the next-gen sequencer.

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46