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Amber Cipriani, PharmD, BCOP
Integrating Germline Pharmacogenomic Testing into Oncology Care
February 21
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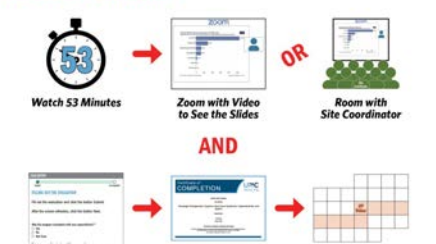
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Our Presenter

Amber B. Cipriani, PharmD, BCOP

Amber Cipriani, PharmD, BCOP, is a clinical pharmacist specialized in oncology care and pharmacogenomics. She currently serves as the Precision Medicine Pharmacy Coordinator at the University of North Carolina Medical Center where she works to implement initiatives that improve medication use and management through the utilization of technology, genetics, and clinical decision support tools.

She is a member of the Molecular Tumor Board and Precision Oncology Program. She serves as the leader of the Pharmacogenomics Initiative of the Program for Precision Medicine in Health Care (PPMH) at UNC.

Dr. Cipriani's position is a joint funded position with the UNC Eshelman School of Pharmacy, where she serves as a Clinical Assistant Professor coordinates elective courses in pharmacogenomics and hematology/ oncology pharmacotherapy for professional PharmD students.

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Our Presenter

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3. Enjoyed genetics before going into pharmacy-developed a companion diagnostic genetic test!

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4. She currently serves as the Precision Medicine Pharmacy Coordinator at the University of North Carolina Medical Center
3. Enjoyed genetics before going into pharmacy-developed a companion diagnostic genetic test!
2. Joint funded with the Eshelman School of Pharmacy where I coordinate courses and teach
1. Participates in multiple state and national groups working to implement pharmacogenomic testing

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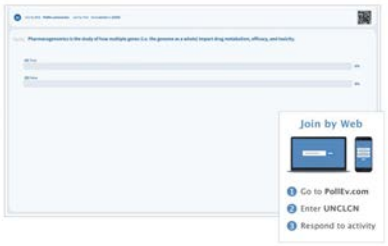
Sample Poll Everywhere Question



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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 and CPD staff have no relevant financial relationships with ineligible companies as defined by the ACCME.

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ANCC Disclosure

NCPD Activity #: 001-L23063
1.0 Contact Hours Provided

Relevant Financial Relationship:
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Criteria for Activity Completion:
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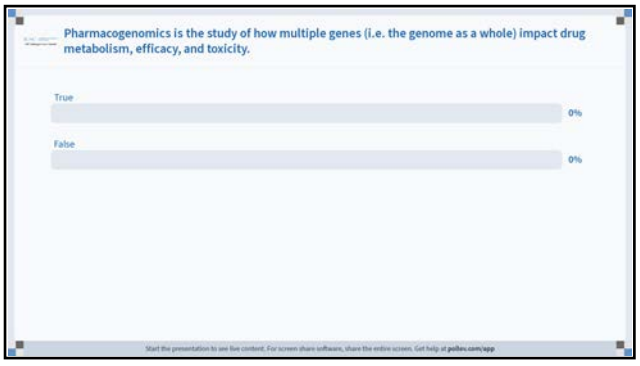

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Integrating pharmacogenomic testing into oncology care
Amber Cipriani, PharmD, BCOP
Precision Medicine Pharmacy Coordinator, UNC Health Medical Center
Clinical Assistant Professor, UNC Eshelman School of Pharmacy
UNC HEALTH

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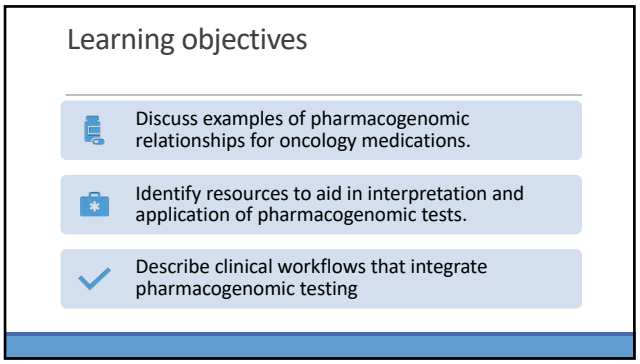
Learning objectives
Discuss examples of pharmacogenomic relationships for oncology medications.
Identify resources to aid in interpretation and application of pharmacogenomic tests.
Describe clinical workflows that integrate pharmacogenomic testing

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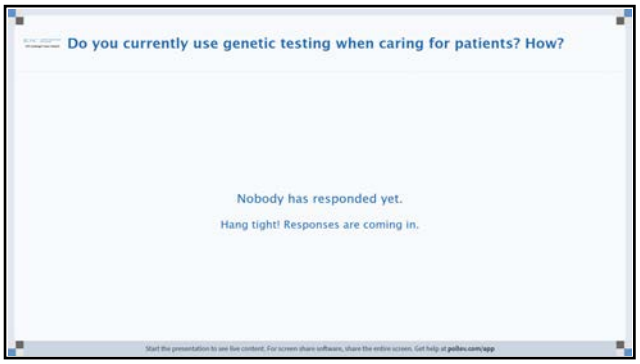
Do you currently use genetic testing when caring for patients? How?
Nobody has responded yet.
Hang tight! Responses are coming in.

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Background Information

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What is precision medicine?

Precision Medicine Initiative Definition	FDA Definition
"An emerging approach for disease treatment and prevention that takes into account individual variability in genes, microbiomes, environment, and lifestyle for each person"	"An innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles"
Goal of Precision Medicine: Target the right treatments to the right patients at the right time	

1. Garrido P, Aldaz A, Vera R, et al. Proposal for the creation of a national strategy for precision medicine in cancer: a position statement of SEOM, SEAP, and SEFH. *Clin Transl Oncol*. 2018;20(4):443-447.
2. US Food and Drug Administration. Precision Medicine. September 27, 2018. Accessed April 12, 2022.

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Pharmacogenetics vs. Pharmacogenomics

Pharmacogenetics

- Study of how a ***single gene*** impacts drug metabolism, efficacy, and toxicity

Pharmacogenomics

- Study of how ***multiple genes*** (i.e. the genome as a whole) impact drug metabolism, efficacy, and toxicity

Whirl-Carrillo M, Huddart R, Gong L, et al. An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. *Clin Pharmacol Ther*. 2021;110(3):563-572.

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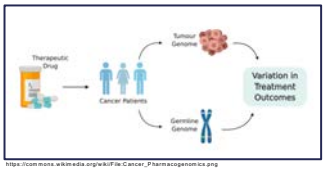
Germline versus somatic mutations



https://commons.wikimedia.org/wiki/File:Cancer_Pharmacogenomics.png

Germline	Somatic
Heritable	Not heritable
In all cells (usually)	Tumor specific
Detected with a cheek swab or blood test	Detected with a tumor sample or blood test

Cancer Genetics Overview (PDQ®)–Health Professional Version. Accessed 19 January 2023. https://www.cancer.gov/about-cancer/causes-prevention/genetics/overview-pdq#_2594 25

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Pharmacogenetics in Oncology: **Tumor biomarkers applied to drug selection**

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Case #1

LP is a 51-year-old male who initially presented with SOB for 6 months

LP's chest x-ray was concerning, so computed tomography (CT) was conducted and confirmed presence of a mass in the lung

A biopsy was obtained, and LP was diagnosed with metastatic non-small cell lung cancer (NSCLC)

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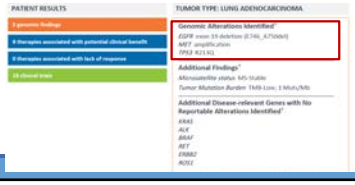
Case #1

- Tissue obtained from LP's biopsy was sent to anatomic pathology, who prepared a specimen block using a formalin-fixed paraffin embedded (FFPE) protocol
- DNA isolated from the tumor specimen was analyzed for genetic changes associated with cancer using DNA sequencing
- The following results were obtained:



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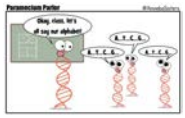
Somatic testing: Next-Generation Sequencing (NGS)

- "High-throughput": Utilizes DNA sequencing technologies that can process multiple DNA sequences in parallel (cancer.gov)
- For Patients: Think of it as a very fancy spell-checker for tumor DNA!



Examples of NGS tests used at UNC Health sites

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

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Example of Results

EGFR exon 19 deletion E746_A750del

TP53 R213Q

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Example of Results

EGFR exon 19 deletion E746_A750del

TP53 R213Q

Gene Name

** Remember our test is looking at the DNA level, but we are concerned with how the gene product (protein) is malfunctioning in cancer

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Example of Results

=Talking about amino acid

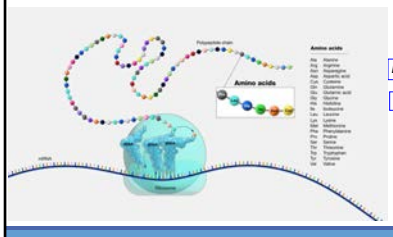
EGFR exon 19 deletion E746_A750del

TP53 R213Q

Gene Name

32

Example of Results



EGFR exon 19 deletion E746_A750del

TP53 R213Q

Image from: https://www.genome.gov/genetics-glossary/Amino-Acids

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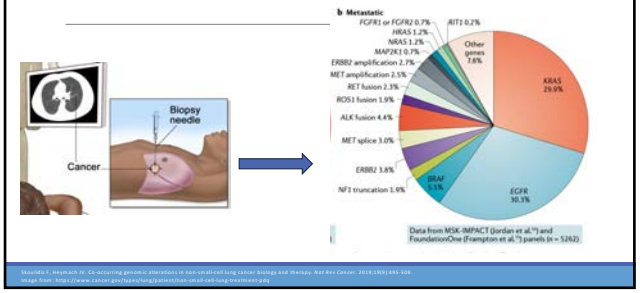
What do we do with somatic tumor testing results?



Skoulidis F, Heymach JV. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. Nat Rev Cancer. 2019;19(9):495-509.
Image from: https://www.cancer.gov/types/lung/patient/non-small-cell-lung-treatment-pdq

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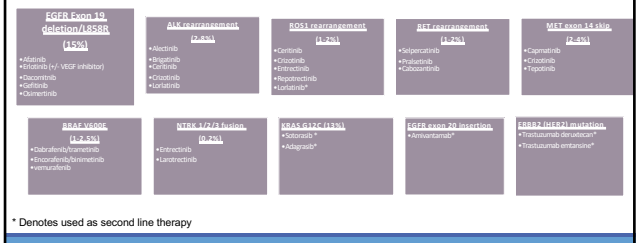
Biomarker-directed therapy for advanced NSCLC



* Denotes used as second line therapy

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.1.2024.

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Resources to identify biomarker directed therapies

- Disease Specific Guidelines (NCCN)
- Laboratory reports
- FDA Table of Pharmacogenomic Biomarkers in Drug Labeling
- OncoKB
- My Cancer Genome
- Precision Medicine Knowledge Base

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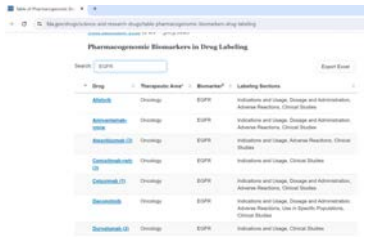

FDA Table of Pharmacogenomic Biomarkers in Drug Labeling

https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
(So, bookmark it or use your search engine…)

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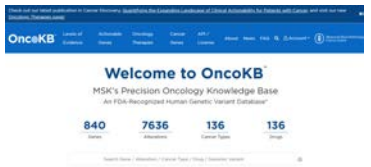

OncoKB

https://www.oncokb.org/

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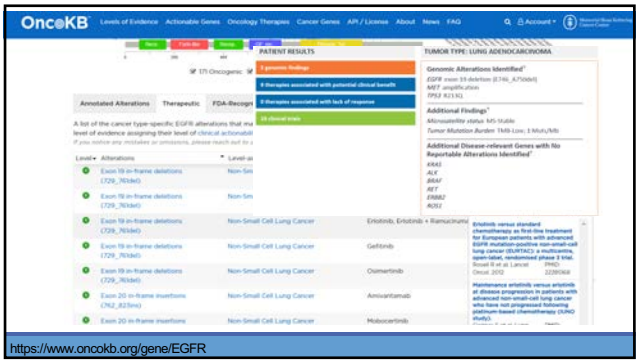
https://www.oncokb.org/gene/EGFR

39



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First Line Treatments EGFR Mutant NSCLC

EGFR Inhibitor	Dose	Tolerability	Notes
Erlotinib	150 mg PO daily	Acneiform rash, diarrhea	Reversible inhibitor
Gefitinib	250 mg PO daily	LFTs, diarrhea, rash	Reversible inhibitor Re-approved as first line therapy
Afatinib	40 mg PO daily	Higher rates of serious adverse events, diarrhea, stomatitis, treatment related deaths	Irreversible inhibitor Also inhibits HER2
Dacomitinib	45 mg PO daily	Higher rates of serious adverse events, diarrhea, stomatitis, treatment related deaths	Irreversible inhibitor Also inhibits HER2
Osimertinib	80 mg PO daily	Lower rates of diarrhea/rash Pneumonitis, ↓ LVEF	Irreversible inhibitor Active against T790M resistance mutation

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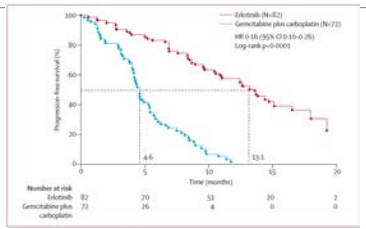
Ugggh…Why are we going through all of this trouble!



Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12(8):735-742.

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Case #2

RG is a 53-year-old female who is diagnosed with metastatic NSCLC

RG undergoes NGS

Results of NGS include MET exon 14 deletion and TP53 R175H

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RG is a 53-year-old female who is diagnosed with metastatic NSCLC

RG undergoes NGS

Results of NGS include *MET* exon 14 deletion and *TP53* R175H

What therapy would you recommend for RG?

Use OncoKB (https://www.oncokb.org) to assist in answering this question and determine if there are any FDA-approved therapies (OncoKB level 1 evidence) specific to her mutation profile

a. Osimertinib
b. Olaparib
c. Capmatinib
d. Crizotinib

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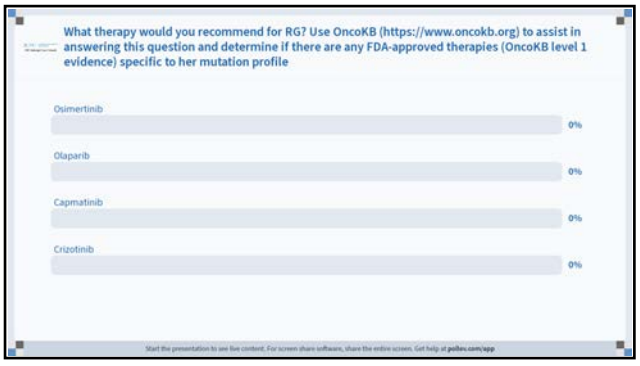

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Pharmacogenetics in Oncology:
Germline biomarkers applied to drug dosing

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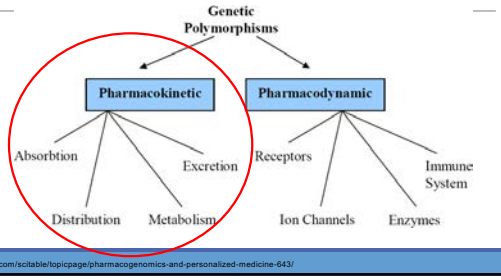
PHARMACOGENETIC BASICS



https://www.nature.com/scitable/topicpage/pharmacogenomics-and-personalized-medicine-643/

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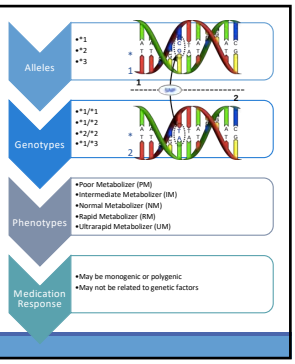
PHARMACOGENETIC BASICS

Allele = a specific genetic sequence at a location in the genome
- Think of as an alternative "spelling" of the gene instructions
- Star nomenclature
- SNP = single nucleotide polymorphism

Genotype = individual's collection of genes
- For each gene, you get one copy from your mom and one copy from your dad

Diplotype = the two "spellings" that a person has for a given gene

Phenotype = individual's observable trait
- The phenotype is predicted by the genetics, but other variables can change it



https://www.genome.gov/genetics-glossary

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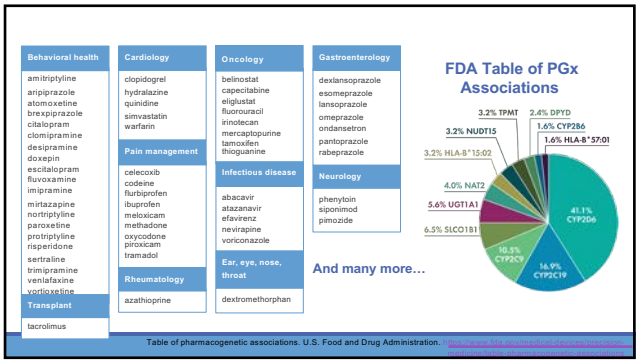

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Case #3

SK is a 55-year-old male with newly diagnosed stage IV colorectal cancer

His oncologist orders a DPYD genotype and finds that SK carries the DPYD *2A allele

You are seeing the patient to initiate cycle 1 of FOLFIRI (5-fluorouracil, leucovorin, irinotecan)

You see the genetic result in the patient's chart, but have no idea why the physician ordered it or what to do with it

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Case #3 FOLFIRI

Leucovorin
400 mg/m² IV on day 1 to match duration of irinotecan infusion

5-Fluorouracil
400 mg/m² IV bolus on day 1 followed by 2,400 mg/m² IV over 46 hours (as a continuous infusion) started after bolus

Irinotecan
180 mg/m² IV over 30-90 minutes on day 1

Leucovorin, 5-Fluorouracil, Irinotecan. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed April 12, 2022.

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About 5-fluorouracil (5FU)

Mechanism of Action
- Inhibits thymidylate synthetase, incorporation into DNA and RNA to block normal biosynthesis

Route of Administration
- Intravenous
- Oral formulation = capecitabine

Most Common Adverse Effects
- Bone marrow suppression (anemia, thrombocytopenia, neutropenia), diarrhea, mucositis, cardiac toxicity

FDA-Labeled Indication
- Colon cancer, gastric cancer, pancreatic cancer, breast cancer

Medscape. 2008 Aug; 13(8): 1551–1569.
Fluorouracil [Package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/012209s040lbl.pdf

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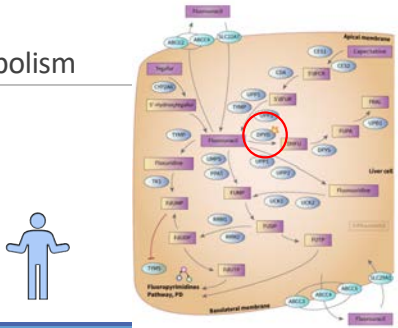
5FU metabolism



https://www.pharmgkb.org/pathway/PA150653776

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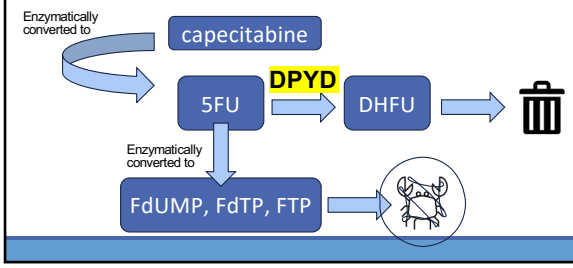
Fluorouracil (5FU) metabolism (Taylor's version)



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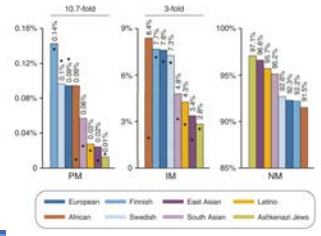
Individual differences in DPYD activity

- Turns out, there is considerable differences in activity of DPYD between individuals
- This activity is linked to the person's genotype for DPYD
- Knowing a genotype, we can predict a phenotype
- The prevalence of DPYD deficiency is rare, but it can cause serious toxicity to 5FU….



Br J Cancer. 2020;123(12):1782-1789.

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Impact of DPYD deficiency on 5FU toxicity

- Depending on the level of DPYD activity, patients treated with standard doses of 5FU had anywhere from a 2-10-fold increase in toxicities, such as myelosuppression and diarrhea
- FATALITIES HAVE BEEN REPORTED IN THOSE WHO LACK ANY DPYD ACTIVITY WHO ARE TREATED WITH NORMAL DOSES OF 5FU

Lancet Oncol. 2015 Dec;16(16):1639-50.;
Pharmacogenomics. 2019 Aug;20(13):931-938.
Cancer Chemother Pharmacol. 2006 Aug;58(2):272-5.

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What should we do?

Clinical Pharmacogenomics Implementation Consortium (CPIC)

- 26 guidelines on drug-gene interactions that require clinical attention
- Tells you "what to do"
- Does NOT tell you who, when, and how to do the genetic testing

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CPIC guidelines: DPYD and 5FU

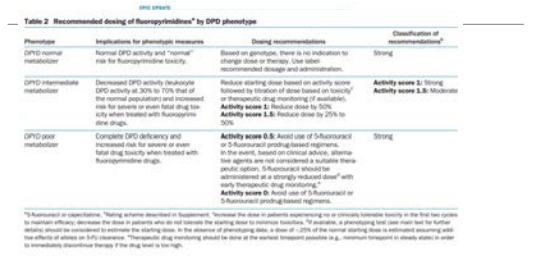

Table 2 Recommended dosing of fluoropyrimidines* by DPD phenotype

Phenotype	Implications for phenotypic measures	Dosing recommendations	Classification of recommendations†
DPYD normal metabolizer	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity.	Based on genotype, there is no indication to change dose or therapy. Use label recommended dosage and administration.	Strong
DPYD intermediate metabolizer	Decreased DPD activity (leukocyte DPD activity at 30% to 70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Reduce starting dose based on activity score followed by titration of dose based on toxicity‡ or therapeutic drug monitoring (if available). **Activity score 1:** Reduce dose by 50% **Activity score 1.5:** Reduce dose by 25% to 50%	**Activity score 1:** Strong **Activity score 1.5:** Moderate
DPYD poor metabolizer	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	**Activity score 0.5:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose‖ with early therapeutic drug monitoring.‖ **Activity score 0:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Strong

*5-fluorouracil or capecitabine. †Rating scheme described in Supplement. ‡Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities. §If available, a phenotyping test (see main text for further details) should be considered to estimate the starting dose. In the absence of phenotyping data, a dose of ~25% of the normal starting dose is estimated assuming additive effects of alleles on 5-FU clearance. ‖Therapeutic drug monitoring should be done at the earliest timepoint possible (e.g., minimum timepoint in steady state) in order to immediately discontinue therapy if the drug level is too high.

Clin Pharmacol Ther. 2018 Feb;103(2):210-216.
https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/

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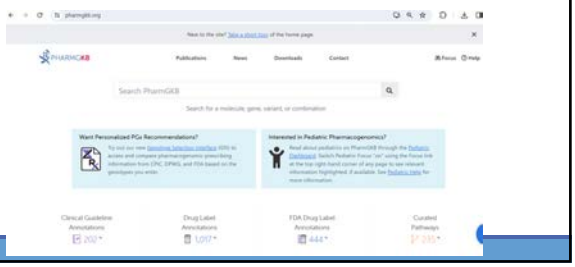
Another resource: PharmGKB



59

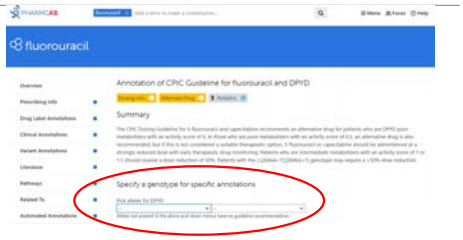
So what should we do?

1. Go to PharmGKB
2. Search for "fluorouracil"
3. Click "Prescribing Info"

https://www.pharmgkb.org/chemical/PA128406956/guidelineAnnotation/PA166122686

60

What should we do?



https://www.pharmgkb.org/chemical/PA128406956/guidelineAnnotation/PA166122686

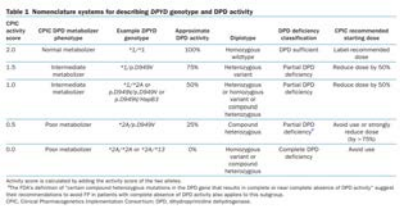
61

What should we do?

https://www.pharmgkb.org/chemical/PA128406956/guidelineAnnotation/PA166122686

62

Dosing of 5FU considering DPYD activity score

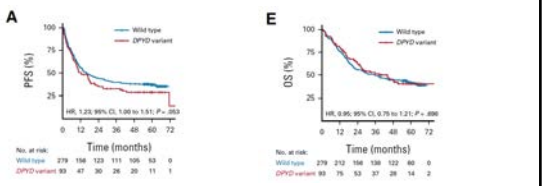


Clin Pharmacol Ther. 2023 Oct;114(4):768-779.

63

Do dose reductions compromise survival?

Comparison of patients who received dose-reduced 5FU based on the presence of DPYD variants (n=93) to matched controls who received full dose 5FU (n=279)



J Clin Oncol. 2023;41(35):5411-5421.

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But what do the "big guys" say?

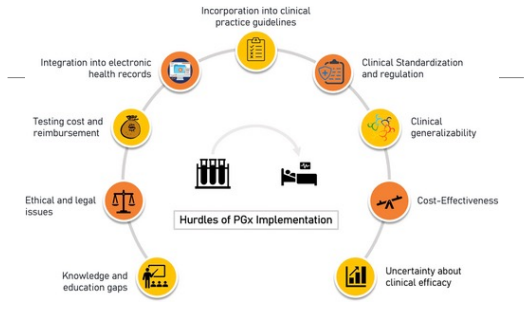
•DPYD testing is recommended in European guidelines, but not yet by American groups

---------- WARNINGS AND PRECAUTIONS ----------

- **Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent Dipyrimidine Dehydrogenase Activity:** Withhold or permanently discontinue fluorouracil in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of dipyrimidine dehydrogenase (DPD) activity. No fluorouracil dose has been proven safe in patients with absent DPD activity. (5.1)

Clin Pharmacol Ther. 2023 Oct;114(4):768-779

65

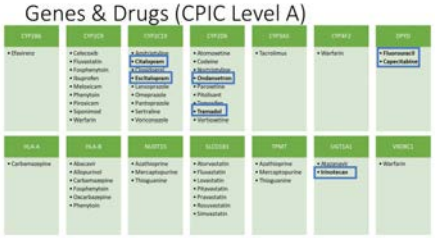


Psychiatry Clin. Neurosci. Rep. 2022;1:e26.

66

Is that all the genetic testing you need?

Genes & Drugs (CPIC Level A)



https://cpicpgx.org/genes-drugs/

67

Case #4

TR is a 10-year-old African American female diagnosed with acute lymphoblastic leukemia (ALL)

She presents for a follow-up visit for monitoring of mercaptopurine (6-MP), which she is prescribed at a dose of **7.5 mg/m² three times per week**

You notice that the usual dose for 6-MP is **75 mg/m² daily**

Her organ function is completely normal, and her CBC is within normal limits to continue the drug

Could this dosing be a mistake? Could there be a pharmacogenetic "force" at work here?

68

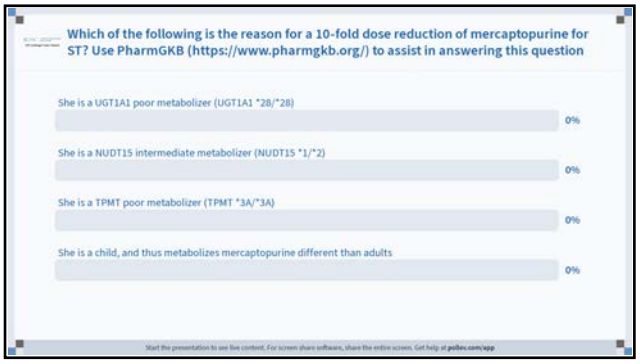
Case #4 Question

Which of the following is the reason for a **10-fold dose reduction** of mercaptopurine for ST?

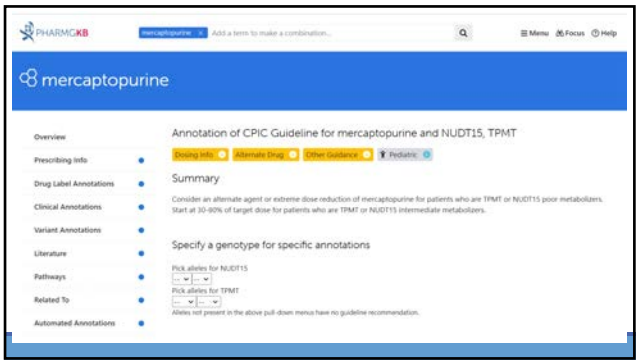
Use PharmGKB (https://www.pharmgkb.org/) to assist in answering this question

a. She is a UGT1A1 poor metabolizer (UGT1A1 *28/*28)
b. She is a NUDT15 intermediate metabolizer (NUDT15 *1/*2)
c. She is a TPMT poor metabolizer (TPMT *3A/*3A)
d. She is a child, and thus metabolizes mercaptopurine different than adults

69


Which of the following is the reason for a 10-fold dose reduction of mercaptopurine for ST? Use PharmGKB (https://www.pharmgkb.org/) to assist in answering this question
She is a UGT1A1 poor metabolizer (UGT1A1 *28/*28)
0%
She is a NUDT15 intermediate metabolizer (NUDT15 *1/*2)
0%
She is a TPMT poor metabolizer (TPMT *3A/*3A)
0%
She is a child, and thus metabolizes mercaptopurine different than adults
0%

70


PHARMGKB
mercaptopurine
Menu
Focus
Help
Overview
Prescribing Info
Drug Label Annotations
Clinical Annotations
Variant Annotations
Literature
Pathways
Related To
Automated Annotations
Annotation of CPIC Guideline for mercaptopurine and NUDT15, TPMT
Dosing Info
Alternate Drug
Other Guidance
Pediatric
Summary
Specify a genotype for specific annotations
Pick alleles for NUDT15
Pick alleles for TPMT

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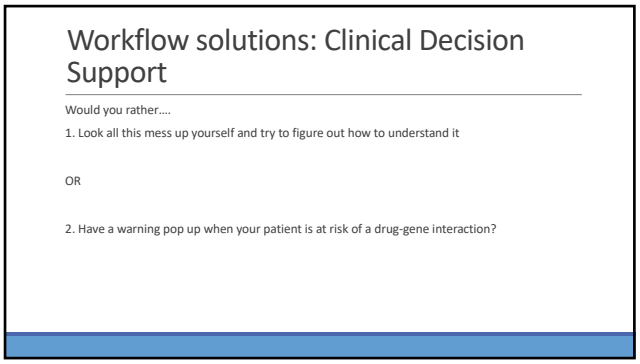
Workflow solutions: Clinical Decision Support
Would you rather....
1. Look all this mess up yourself and try to figure out how to understand it
OR
2. Have a warning pop up when your patient is at risk of a drug-gene interaction?

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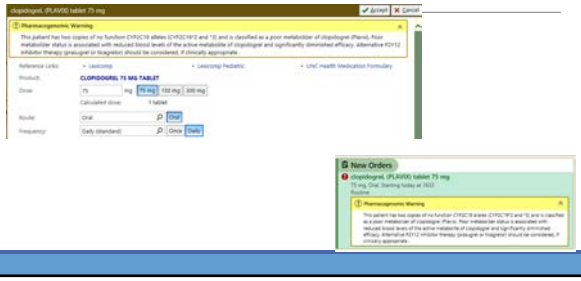
Clinical decision support



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Workflow solutions: Multigene testing

Would you rather…

1. Test for each individual pharmacogene when needed (and wait for the results to return before placing an order)

OR

2. Test for multiple important pharmacogenes at once, so that you have the results on hand when needing to prescribe drugs with pharmacogenetic interactions

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Who is doing multigene testing?

St. Jude

University of Florida

Vanderbilt

NorthShore

Duke

Levine

VA

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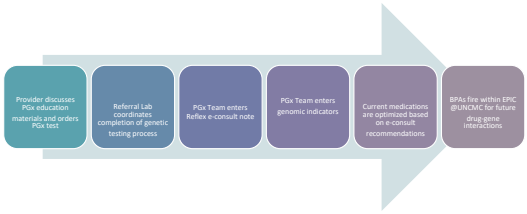
Multigene testing pilot in GI oncology at UNC Health



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Summary

- Targeted therapies used in oncology often require a biomarker test to determine treatment eligibility
- Large somatic tumor sequencing panels are becoming the gold standard in oncology, so your ability to understand the information is crucial to choosing the best treatment
  - RESOURCE: https://www.oncokb.org/
- Germline genetics can impact how a patient responds to treatment due to differences in drug metabolizing enzymes or pharmacodynamic markers
  - RESOURCE: https://www.pharmgkb.org/

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Questions/Comments?

Nobody has responded yet.

Hang tight! Responses are coming in.

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Extra slides (for questions)

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Oncology Specific Resources	Germline Pharmacogenetics Resources
OncoKB	CPIC
My Cancer Genome	PharmGKB
Precision Medicine Knowledge Base	FDA Table of Pharmacogenetic Associations

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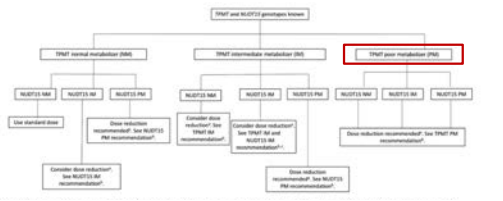
6-Mercaptopurine Dosing



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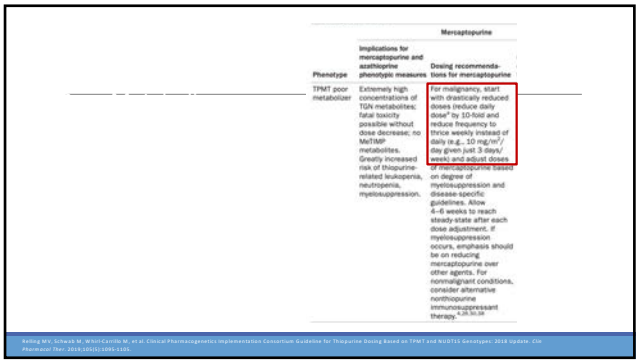

	Mercaptopurine	
Phenotype	Implications for mercaptopurine and azathioprine phenotypic measures	Dosing recommendations for mercaptopurine
TPMT poor metabolizer	Extremely high concentrations of TGN-metabolites; fatal toxicity possible without dose decrease; no MeTIMP metabolites. Greatly increased risk of thiopurine-related leukopenia, neutropenia, myelosuppression.	For malignancy, start with drastically reduced doses (reduce daily dose[a] by 10-fold and reduce frequency to thrice weekly instead of daily (e.g., 10 mg/m²/day given just 3 days/week) and adjust doses of mercaptopurine based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady-state after each dose adjustment. If myelosuppression occurs, emphasis should be on reducing mercaptopurine over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.

Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105.

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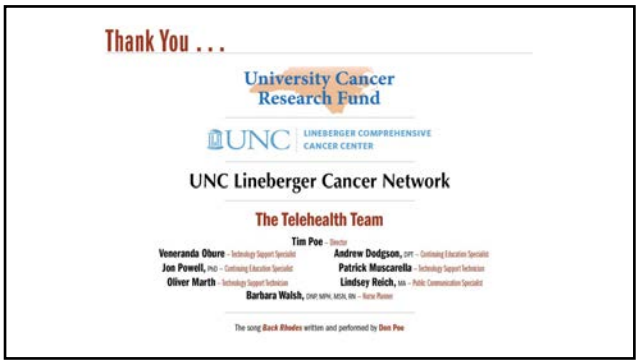

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Hung-Jui (Ray) Tan, MD, MSHPM
PATIENT CENTERED CARE
Next Generation Cancer Care Navigation
William A. Wood, MD, MPH

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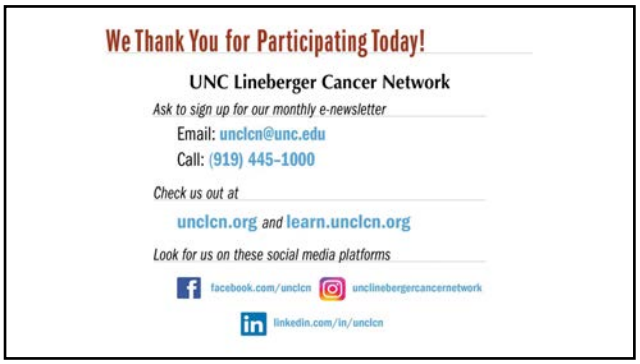
We Thank You for Participating Today!
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Look for us on these social media platforms
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unclinebergercancernetwork
linkedin.com/in/unclcn

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