Planning for Tomorrow Today:

Evolving Patient Care Through Pharmacogenomics

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Disclosures

- Lead oncology clinical pharmacist for Northside Hospital Cancer Institute's Cancer Genomics Team
- Molecular Tumor Board independent consultant and expert reviewer for Clariifi (Clarified Precision Medicine)

Learning Objectives

- *After completion of this activity, pharmacists will be able to:*
  1. Define pharmacogenomics and its associated clinical implications
  2. Identify value of pharmacists as key team members in precision medicine
  3. Discuss interpretation of genomic findings to evolve patient care
- *After completion of this activity, pharmacy technicians will be able to:*
  1. Describe the importance of precision medicine through individualized patient care
  2. Recognize biomarkers and corresponding treatment agents for therapeutic benefit
  3. Outline strategies to support pharmacists in caring for patients who express clinically actionable mutations

Precision Medicine

OHSU to pay $1 million, promises change to settle lawsuit from widow of cancer patient

Updated: May. 04, 2022, 10:05 a.m. | Published: May. 04, 2022, 7:00 a.m.

David McIntyre had a fatal reaction to OHSU's chemotherapy for his cancer. His wife Jeri claims in a lawsuit filed against the university.

447 shares

By Fedor Zarkhin | The Oregonian/OregonLive

Oregon Health & Science University has promised to change an aspect of its cancer treatment and pay out $1 million to settle a lawsuit claiming the university's negligence killed a cancer patient.

The patient's widow, who sued the university in 2019 after her husband died of a toxic reaction to a chemotherapy drug, was overjoyed.

"We're going to be saving more lives," Joanne McIntyre said of the settlement. "I'm happy. OHSU is happy."

Current Oncology MDPI

Case Report

Near Miss or Standard of Care? *DPYD* Screening for Cancer Patients Receiving Fluorouracil

Lauren E. Winquist [1], Michael Sanatani [1,2], Richard B. Kim [1,3] and Eric Winquist [1,2,4,*]

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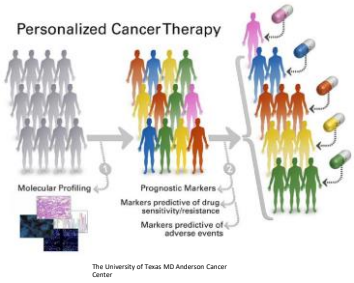
Abstract: 5-fluorouracil (5-FU) and its pro-drug capecitabine are widely used anticancer agents. Most 5-FU catabolism is dependent on dihydropyrimidine dehydrogenase (DPD) encoded by the *DPYD* gene, and *DPYD* variants that reduce DPD function increase 5-FU toxicity. Most DPD deficient patients are heterozygous and can be treated with reduced 5-FU dosing. We describe a patient with a genotype associated with near complete absence of DPD function, and severe and likely fatal toxicity with 5-FU treatment. The patient was treated effectively with alternative systemic therapy. Routine pretreatment *DPYD* genotyping is recommended by the European Medicines Agency, and guidelines for use of 5-FU in DPD deficient patients are available. However, outside the province of Quebec, routine pretreatment screening for DPD deficiency remains unavailable in Canada. It is likely our patient would have died from 5-FU toxicity under the current standard of care, but instead provides an example of the potential benefit of *DPYD* screening on patient outcomes.

Winquist LE, Sanatani M, Kim RB, Winquist E. Near Miss or Standard of Care? DPYD Screening for Cancer Patients Receiving Fluorouracil. Curr Oncol. 2020 Dec 18;28(1):94-97. doi: 10.3390/curroncol28010012. PMID: 33704279; PMCID: PMC7838174.

Pharmacogenomics (PGx)

- Defined as the study of the role of the genome in drug response
- Treatment strategy centered on the ability to predict which patients are more likely to respond to specific treatments
- Founded upon the idea that an individual's genetic makeup and tumor biomarkers are associated with their prognosis and tumor response to therapy
- Patient genetic factors can be associated with drug metabolism, drug response, and drug toxicity
- Sequencing of tumor DNA can reveal genomic alterations with implications for cancer treatment



Precision Medicine Initiative

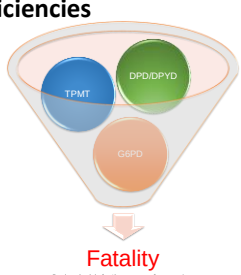
- Established by President Obama and led by Vice President Joe Biden in 2016
  - Renamed "All of Us" Research Program
- 21st Century Cures Act
  - Authorized $1.8 billion in funding towards the initiation and advancement of Cancer Moonshot over 7 years
- Abundant funding allocated to the National Cancer Institute (NCI) to scale up efforts to identify genomic drivers in cancer and develop more effective approaches to cancer treatment
- NCI's Genomic Data Commons (GDC) - repository of cancer genomic studies in support of precision medicine

Audience Response Question #1

A BMT patient with ALL is under consideration for a maintenance chemotherapy regimen including mercaptopurine. Which gene should be tested for, and what are the clinical implications of this gene?

A. DPYD - mucositis, neutropenia, thrombocytopenia
B. TPMT - life-threatening myelosuppression
C. G6PD - hemolytic anemia
D. EGFR - drug resistance

Deadly Deficiencies

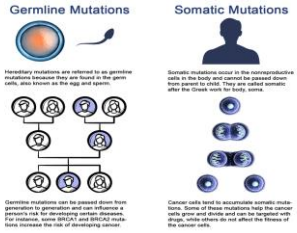


Common Drug/Gene Pairs

Drug	Gene
Allopurinol, Carbamazepine, Abacavir, Phenytoin	HLA-B
Azathioprine, Mercaptopurine, Thioguanine	TPMT, NUDT15
Fluorouracil, Capecitabine	DPYD/DPD
Codeine, Tramadol, Hydrocodone, Oxycodone, TCAs, Ondansetron	CYP2D6
Irinotecan	UGT1A1
Rasburicase	G6PD
Tacrolimus	CYP3A5
Tamoxifen	CYP2D6
Voriconazole, Clopidogrel, TCAs	CYP2C19
Warfarin	CYP2C9, CYP4F2, VKORC1

PharmGKB

Germline vs. Somatic Mutations



Testing Rationale and Source

	Germline	Somatic
Rationale	Disease predisposition for family members Drug selection (BRCA-associated)	Drug selection
Timing	Part of diagnostic work-up, but can be performed at any time	Recent biopsy is important
Tissue Source	Blood (WBCs) or buccal	Tissue (formalin-fixed or fresh frozen) or liquid biopsy (blood for cfDNA)
Frequency	Once	Diagnosis, progression

Cancers with Routine Testing for Hereditary Genes

Disease	Gene	Guidelines
Breast (criteria)	Panel, BRCA-associated, TP53	NCCN
Ovarian (all)	Panel, BRCA-associated, TP53	NCCN
Pancreas (all)	Panel, BRCA-associated, TP53	NCCN
Prostate (metastatic)	Panel, BRCA-associated, TP53	NCCN
Colon (criteria)	Panel, Lynch or HNPCC	NCCN

Audience Response Question #2

Which of the following types of genetic variation would <u>not</u> be found in all of the cells of an individual's body?

A. a germline mutation
B. an inherited variant
C. a somatic mutation
D. a de novo mutation

Driver vs. Passenger Mutations

Which gene mutations could be driving the cancer?
Which gene mutations do we likely not want to target?

Prognostic vs. Predictive

- **Prognostic Biomarkers**
  - Does the gene mutation provide information about cancer outcomes independent of treatment?
  - These mutations represent the underlying biology of the tumor
  - TP53 mutations in CLL are a poor prognostic indicator
- **Predictive Biomarkers**
  - Does the gene mutation provide information about response or resistance to a particular therapy?
  - Activating EGFR mutations in non-small cell lung cancer are associated with increased response to an EGFR-inhibitor

Proto-oncogene vs. Tumor Suppressor Gene

Proto-oncogene

- **Oncogenes are mutant forms of proto-oncogenes**
- **Usually druggable**
- **i.e., point mutations (EGFR, KRAS, BRAF), Chromosomal translocation (BCR-ABL), Gene amplification (HER2, c-MYC)**

Tumor suppressor gene

- **Prevent cancer**
- **But when mutated, cancer can occur**
- **Many are involved in DNA repair**
- **Hard to target**
- **i.e., BRCA, TP53**

Audience Response Question #3

Which of the following describe proto-oncogenes?

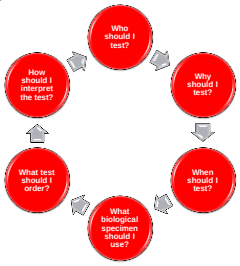
A. a kinase that halts the cell cycle in response to DNA damage
B. a protein that prevents apoptosis in healthy cells
C. a receptor that promotes cell growth
D. a DNA damage repair protein
E. A and D
F. B and C

Audience Response Question #4

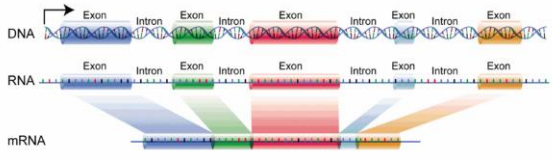
_____ mutations must occur in _____ copies of a tumor suppressor gene to drive the development of cancer, assuming the gene is not haploinsufficient.

A. Gain-of-function; two
B. Loss-of-function; two
C. Gain-of-function; one
D. Loss-of-function; one

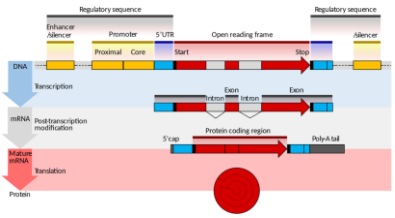
Key Clinical Questions



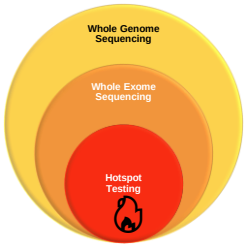
DNA → RNA → Protein



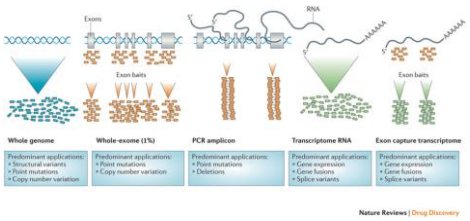
DNA → RNA → Protein



Types of Sequencing



Testing Modalities

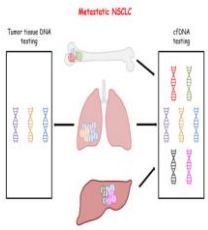


Audience Response Question #5

What are the primary advantages of sequencing cfDNA (liquid biopsy) over tumor sequencing?

A. standard methods and high tumor DNA concentration
B. comprehensive panels and short turn around
C. high tumor DNA concentration and short turnaround time
D. minimally invasive and repeatable

Tissue Source



Characteristic	cfDNA	Tumor
Minimally invasive	✓	
Easy to repeat	✓	
Standard methods	✓	✓
Short turnaround	✓	✓
High tumor DNA concentration		✓
Low contamination with non-tumor DNA		✓
Comprehensive profile	✓	✓
Tumor heterogeneity	Intratumor and intralesion	Intratumor
Real-time monitoring	✓	
Early detection of resistance	✓	

Common Commercial NGS Assays

FOUNDATIONONE CDx™
CARIS LIFE SCIENCES
GUARDANT360 CDx
INVITAE
NEO GENOMICS
TEMPUS

Commercial Diagnostic Testing Companies

Platform	Genes	Sequencing Strategy	FDA Approval	Use
FoundationOne CDx	324	Capture	Yes	Substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs)
Foundation Liquid	70	Capture	Yes (NSCLC, Prostate, Ovarian, Breast)	Substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs)
Caris Molecular Intelligence CDx	~20,000 592 reported	Exome (DNA and RNA)	No	Whole exome and transcriptome, pretty much everything
Guardant360	73	Capture	Yes (NSCLC)	Substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) + fusions

Companion Diagnostics (CDx) - NSCLC

BIOMARKERS	FDA-APPROVED THERAPY[]
EGFR exon 19 deletions & ***EGFR*** exon 21 L858R alterations	EGFR Tyrosine Kinase Inhibitors (TKI) approved by FDA[1]
EGFR exon 20 T790M alterations	**Tagrisso®** (osimertinib)
ALK rearrangements	**Alecensa®** (alectinib), **Alunbrig®** (brigatinib), **Xalkori®** (crizotinib), or **Zykadia®** (ceritinib)
BRAF V600E	**Tafinlar®** (dabrafenib) in combination with **Mekinist®** (trametinib)
MET single nucleotide variants (SNVs) and indels that lead to ***MET*** exon 14 skipping	**Tabrecta™** (capmatinib)

Companion Diagnostics (CDx) - Melanoma

BIOMARKERS	FDA-APPROVED THERAPY[]
BRAF V600E	BRAF inhibitors approved by FDA[1]
BRAF V600E or V600K	**Mekinist®** (trametinib) or BRAF/MEK inhibitor Combinations approved by FDA[1]

Companion Diagnostics (CDx) - Breast Cancer

BIOMARKERS	FDA-APPROVED THERAPY[]
ERBB2 (HER2) amplification	**Herceptin®** (trastuzumab), **Kadcyla®** (ado-trastuzumab-emtansine), or **Perjeta®** (pertuzumab)
PIK3CA C420R, E542K, E545A, E545D (1635G>T only), E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	**Piqray®** (alpelisib)

Companion Diagnostics (CDx) - Colorectal Cancer

BIOMARKERS	FDA-APPROVED THERAPY[]
KRAS wild-type (absence of mutations in codons 12 and 13)	**Erbitux®** (cetuximab)
KRAS wild-type (absence of mutations in exons 2, 3, and 4) and ***NRAS*** wild type (absence of mutations in exons 2, 3, and 4)	**Vectibix®** (panitumumab)

Companion Diagnostics (CDx) - Ovarian Cancer

BIOMARKERS	FDA-APPROVED THERAPY[]
BRCA1/2 alterations	**Lynparza®** (olaparib) or **Rubraca®** (rucaparib)

Companion Diagnostics (CDx) - Cholangiocarcinoma

BIOMARKERS	FDA-APPROVED THERAPY†
FGFR2 fusions and select rearrangements	**Pemazyre®** (pemigatinib) or **Truseltiq™** (infigratinib)

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Companion Diagnostics (CDx) - Prostate Cancer

BIOMARKERS	FDA-APPROVED THERAPY†
Homologous Recombination Repair (HRR) gene (***BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D*** and ***RAD54L***) alterations	**Lynparza®** (olaparib)

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Companion Diagnostics (CDx) - Solid Tumors

BIOMARKERS	FDA-APPROVED THERAPY†
TMB ≥ 10 mutations per megabase	**Keytruda®** (pembrolizumab)
NTRK1/2/3 fusions	**Vitrakvi®** (larotrectinib)
MSI-H	**Keytruda®** (pembrolizumab)

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Tissue Agnostic Approvals

In 2017, FDA granted its first tissue-agnostic approval (**pembrolizumab** for patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors) and first tissue-agnostic orphan-drug designations (**larotrectinib** and **entrectinib**, each for the treatment of solid tumors with NTRK-fusion proteins).

The FDA granted accelerated approval to Jemperli (**dostarlimab-gxly**) for adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumor that have progressed on or following prior treatment.

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Genomic Signatures

Biomarker	Method	Analyte	Result
Microsatellite Instability (MSI)	Seq	DNA-Tumor	Stable
Tumor Mutational Burden (TMB)	Seq	DNA-Tumor	Result: High 34 (Low 10 High)
Genomic Loss of Heterozygosity (LOH)	Seq	DNA-Tumor	Low - 12% of tested genomic segments exhibited LOH (assay threshold is ≥ 16%)

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Common Components of NGS Reports

- **"Front Page" findings**
- **Detailed individual gene descriptions**
- **Clinical trials**
- **Variants of uncertain significance**
- **References**
- **Appendix information**
  - Test methodology
  - Genes and alterations assessed
  - Lower limits of detection

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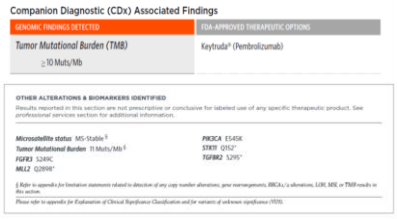
FoundationOne CDx®


Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
Tumor Mutational Burden (TMB) ≥10 Muts/Mb	Keytruda® (Pembrolizumab)

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‡	PIK3CA E545K
Tumor Mutational Burden 11 Muts/Mb‡	STK11 Q152*
FGFR3 S249C	TGFBR2 S295*
MLL2 Q2898*	

‡ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCA1/2 alterations, LOH, MSI, or TMB results in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

CARIS MI Profile®


High Impact Results

BIOMARKER	METHOD	RESULT	THERAPY ASSOCIATION	BIOMARKER LEVEL*
BRCA1	NGS	Mutated, Pathogenic Exon 21 p.Y1853*	BENEFIT olaparib, talazoparib	Level 1
			BENEFIT carboplatin + cisplatin	Level 1A
ER	IHC	Positive (n= 90%	BENEFIT endocrine therapy	Level 1
			BENEFIT abemaciclib, palbociclib, ribociclib	Level 2
			BENEFIT everolimus	Level 3
PR	IHC	Positive (n= 3%	BENEFIT endocrine therapy	Level 1
			BENEFIT abemaciclib, palbociclib, ribociclib	Level 2
ERBB2 (HER2/Neu)	CISH	Not Amplified	BENEFIT ado-trastuzumab emtansine (T-DM1), lapatinib, neratinib, pertuzumab, trastuzumab	Level 1

CANCER TYPE RELEVANT BIOMARKERS

Biomarker	Method	Result
MSI	NGS	Stable
Mismatch Repair Status	NGS	Proficient
Tumor Mutational Burden	NGS	Intermediate (11 Mutations/Mb
MGMT	NGS	Mutation Not Detected
HR	IHC	Positive (n= 90%
BRCA1	NGS	Mutation Not Detected
ERBB2 (HER2/Neu)	NGS	Mutation Not Detected
ESR1	NGS	Mutation Not Detected
PGR	IHC	Positive (n= 3%
PD-L1	IHC	Negative (0

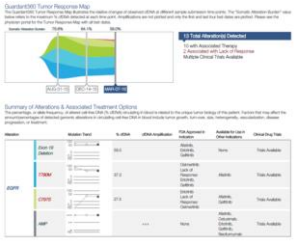
CANCER TYPE RELEVANT BIOMARKERS (cont.)

Biomarker	Method	Result
PIK3CA	NGS	Mutated, Pathogenic Exon 21 p.H1047R
PTEN	IHC	Positive (n= 100%
	NGS	Mutation Not Detected

OTHER FINDINGS (see page 3 for additional results)

Summary	Method	Result
BRCA1	NGS	Mutated, Pathogenic Exon 21 p.P1157L

Guardant360® CDx

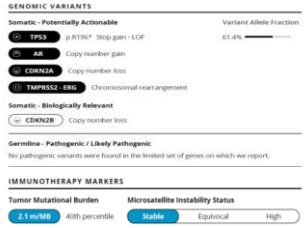

Guardant360 Tumor Response Map

10 Total Alteration(s) Detected

10 with Associated Therapy
2 Associated with Lack of Response
Multiple Clinical Trials Available

Summary of Alterations & Associated Treatment Options

TEMPUS xT®


GENOMIC VARIANTS

Somatic - Potentially Actionable — Variant Allele Fraction

TP53 p.R196* Stop gain - LOF 61.4%

AR Copy number gain

CDKN2A Copy number loss

TMPRSS2 - ERG Chromosomal rearrangement

Somatic - Biologically Relevant

CDKN2B Copy number loss

Germline - Pathogenic / Likely Pathogenic

No pathogenic variants were found in the limited set of genes on which we report.

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden: 2.1 mv/MB, 40th percentile

Microsatellite Instability Status: Stable | Equivocal | High

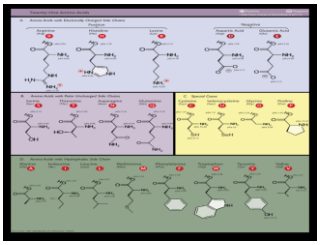
Genomic Sequencing Nomenclature

DNA		
	coding DNA	c.
	genomic DNA	g.
	mitochondrial DNA	m.
RNA		r.
Protein		p.

Code:

substitution (for bases)	>
range	_
more change in one allele	;
more transcripts / mosaicism	/
uncertain	()
allele	[]
deletion	del
duplication	dup
insertion	ins
inversion	inv
conversion	con
extension	ext
stop codon	X
frame shift	fsX
opposite strand	o
translocation	t

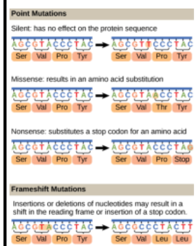
Amino Acid Nomenclature



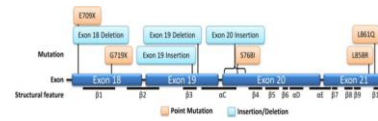
Genomic Sequencing Interpretation Examples

Substitution	
c.123A>G	on cDNA, A in 123 is replaced by G
p.P252R	on protein, proline (P) replaced by arginine (R)
Deletion	
c.546delT	deletion of T in 546
c.586_591del	for six bases deleted
p.F508del	deletion of phenylalanine (F) in 508
Duplication	
c.546dupT	duplication of T in 546
c.586_591dup	duplication of the segment 586 to 591
p.G4_Q6dup	duplication of the segment from glycine (G) in 4 to glutamine (Q) in 6
Insertion	
c.546_547insT	insertion of T between 546 and 547
c.1086_1087insGCGTGA	insertion of GCGTGA
p.K2_L3insQS	insertion of glutamine serine between lysine (K) in 2 and leucine (L) in 3
Inversion	
c.546_2031inv	segment 546 to 2031 inverted
Frameshift	
p.R83SfsX15	arginine (R) is the first amino acid changed, it is in position 83, it makes serine (S) instead, the length of the shift frame is 15, including the stop codon (X)

Types of Mutations

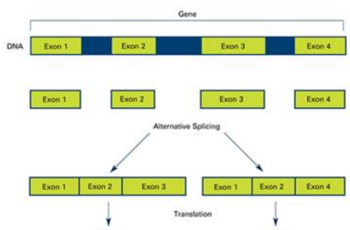


Source: CNX OpenStax



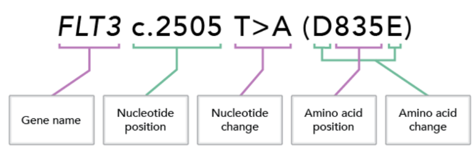
Harrison, et al. 2020. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. 61(167-179)

Gene Splicing



The New Genetics, NIH Publication No. 07-662

Gene Mutation Interpretation



Source: HMX Pro Course

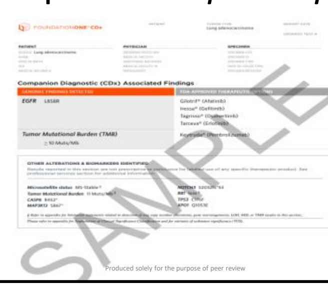
Audience Response Question #6

You examine the sequencing report from a patient with a gastrointestinal stromal tumor (GIST). It indicates that the patient's tumor has the following mutation: ***PDGFRA* c.2525A>T (D842V)**.

This is a ______ mutation at position ______ of the coding region of the *PDGFRA* gene.

A. nonsense; 2525
B. missense; 2525
C. nonsense; 842
D. missense; 842

Audience Response: *NGS Report Interpretation*



Genomics Public Databases

CPIC Clinical Pharmacogenetics Implementation Consortium

cBioPortal FOR CANCER GENOMICS

gnomAD genome aggregation database

OncoKB

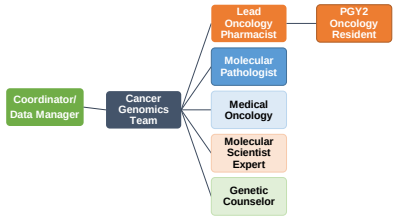
PharmGKB

COSMIC CANCER MUTATION CENSUS

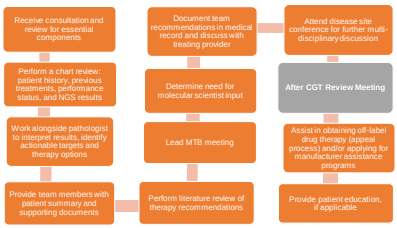
CIViC CLINICAL INTERPRETATIONS OF VARIANTS IN CANCER

ClinVar

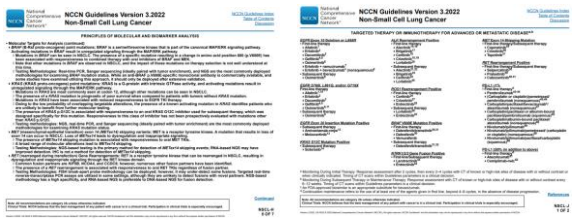
Molecular Tumor Board (MTB)



Role of Pharmacogenomics Pharmacist



NCCN PGx Treatment Guidelines


NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

TARGETED THERAPY OR IMMUNOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

Audience Response Question #7

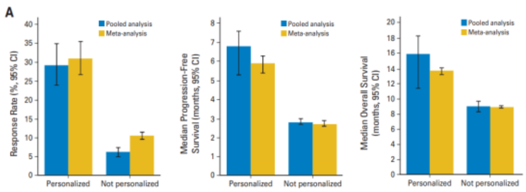
Which of the following is <u>not</u> a role of a pharmacogenomics pharmacist?

A. perform a chart review
B. interpret the NGS report
C. perform literature reviews
D. finalize the individual patient's treatment decision
E. provide patient education, if applicable

Clinical Implications

- Both cancer *(somatic)* and inherited *(germline)* genomes are clinically important
- Genetic alteration provides diagnostic, prognostic, and predictive information (including PK/PD)
- Impact on drug safety or response (benefit, resistance, toxicity)
- FDA-approved therapy for the patient's type of cancer\Use of FDA-approved therapy for "off-label" types of cancer
- Clinical trial for the particular alteration or reasonable based on molecular biology
- More than 200 commercially available drugs contain genetic information in their FDA-approved labeling
  - *Majority are either anti-cancer agents or oncology supportive care drugs*

PGx Outcomes Data



Schaederle et al. JCO.2015

A Retrospective Analysis of Precision Medicine Outcomes in Patients With Advanced Cancer Reveals Improved Progression-Free Survival Without Increased Health Care Costs

Derrick S. Haslem, S. Burke Van Norman, Gail Fulde, Andrew J. Knighton, Tom Belnap, Allison M. Butler, Sharanya Rhagunath, David Newman, Heather Gilbert, Brian P. Tudor, Karen Lin, Gary R. Stone, David L. Loughmiller, Pravin J. Mishra, Rajendu Srivastava, James M. Ford, and Lincoln D. Nadauld

QUESTION ASKED: What are the clinical outcomes and health care–associated costs in patients with advanced cancer who receive precision cancer medicine?

www.impactjournals.com/oncotarget/ Oncotarget, 2018, Vol. 9, (No. 15), pp: 12316-12322

Research Paper

Precision oncology in advanced cancer patients improves overall survival with lower weekly healthcare costs

Derrick S. Haslem[1], Ingo Chakravarty[2], Gail Fulde[1], Heather Gilbert[1], Brian P. Tudor[1], Karen Lin[1], James M. Ford[3] and Lincoln D. Nadauld[1,3]

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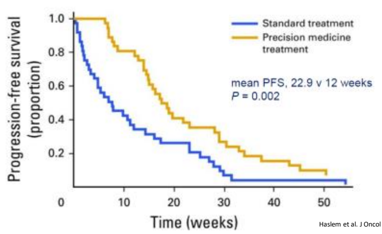
Keywords: *precision medicine, oncology, outcomes, costs, overall survival*

Received: *May 17, 2017* **Accepted:** *September 15, 2017* **Published:** *February 02, 2018*

PGx Impact on PFS



Haslem et al. J Oncol Pract. 2017

United Healthcare

UnitedHealthcare® Commercial *Medical Policy*

Pharmacogenetic Testing

Policy Number: 2022T0587J
Effective Date: January 1, 2022

Instructions for Use

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Related Commercial Policies
- Cardiovascular Disease Risk Tests

Community Plan Policy
- Pharmacogenetic Testing

Medicare Advantage Coverage Summaries
- Genetic Testing
- Laboratory Tests and Services

Coverage Rationale

The use of pharmacogenetic Multi-Gene Panels to guide therapy decisions is proven and medically necessary for antidepressant and antipsychotic medications when all the following criteria are met:
- The individual has a diagnosis of major depressive disorder or generalized anxiety disorder; and
- The individual has failed at least one prior medication to treat their condition; and
- The Multi-Gene Panel has no more than 15 relevant genes

The use of pharmacogenetic Multi-Gene Panels for genetic polymorphisms for any other indication, including but not limited to pain management, cardiovascular drugs, anthracyclines, or polypharmacy, is unproven and not medically necessary for evaluating drug-metabolizer status due to insufficient evidence of efficacy.
Examples of these Panels include, but are not limited to the following:
- GeneSight® Analgesic
- GeneSight® ADHD
- SureGene Test
- Pain Medication DNA Insights®
- PharmacoDx

The use of the PrismRA® molecular signature test is unproven and not medically necessary for evaluating likelihood of inadequate response to anti-TNF therapies for rheumatoid arthritis due to insufficient evidence of efficacy.

Medical Coverage Policy

Cigna

Effective Date ... 1/15/2022
Next Review Date ... 1/15/2023
Coverage Policy Number ... 0500

Pharmacogenetic Testing for Non-Cancer Indications

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Related Coverage Resources

Cystic Fibrosis Transmembrance Conductance Regulator (CFTR) Modulators
Enzyme Related Therapies
Genetic Testing Collateral: Genetic Tests and Biomarkers File
Genetic Testing Collateral: Not Covered Single CPT® & HCPCS Code Tests
Genetics
Lomatipide Mesylate
PCSK9 Inhibitors
Serological Testing for Inflammatory Bowel Disease

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Medical Coverage Policy

Cigna

Effective Date ... 7/15/2021
Next Review Date ... 7/15/2022
Coverage Policy Number ... 0518

Genetic Testing for Hereditary Cancer Susceptibility Syndromes

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Related Coverage Resources

Genetics
Genetic Testing Collateral File
Transvaginal Ultrasound, Non-Obstetrical

Pharmacogenomics and Companion Diagnostics

Humana.

Medical Coverage Policy

Effective Date: 06/23/2022
Revision Date: 06/23/2022
Review Date: 06/23/2022
Policy Number: HUM-0533-044

Page: 1 of 39

Change Summary: Updated Description, Coverage Determination, Coverage Limitations, Provider Claims Codes, References

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Pharmacogenomics – Noncancer Indications

Humana.

Medical Coverage Policy

Effective Date: 04/28/2022
Revision Date: 04/28/2022
Review Date: 04/28/2022
Policy Number: HUM-0466-067

Page: 1 of 10

Change Summary: Updated Description, Coverage Determination, Coverage Limitations, References

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Pharmacogenomics — Cytochrome P450 Polymorphisms and VKORC1

Humana.

Medical Coverage Policy

Effective Date: 10/28/2021
Revision Date: 10/28/2021
Review Date: 10/28/2021
Policy Number: HUM-0531-017

Page: 1 of 17

Change Summary: Updated Description, Coverage Determination, Coverage Limitations, References

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Calling All Pharmacists!!

- Pharmacists are well-positioned to have integral roles in MTBs and clinical implementation based on our developed skill sets:
  - Experience with literature searching
  - Ability to integrate cancer biology with pharmacotherapy options
  - Clinical trial assessment and matching based on patient characteristics
  - Patient counseling skills
  - Off-label therapy acquisition

Diverse opportunities for MTB engagement from participation to leadership

Clinical Pearls

- Pharmacogenomics attempts to eliminate the trial-and-error method of prescribing
- Recognize the importance of clinical judgment and patient individualization in treatment planning, dosage modifications, and toxicity prevention
- Consent to genetic testing requires in-depth counseling for well-informed decision-making by patients
- The implementation of precision medicine requires buy-in from involved stakeholders to evolve best practices and standard of care
- **Concierge vs. transactional pharmacy practice model**

Key Terminology

Cell-free DNA (cfDNA): fragments of DNA released by cells during apoptosis and necrosis, which circulate in the bloodstream

Copy number variation (CNV): a type of variant that increases or decreases the number of times a sequence is present in the genome, including deletions, duplications, unbalanced translocations, and unstable repeats

Driver mutation: a type of mutation that confers a selective growth advantage to the cells carrying it

Gain-of-function mutation: a type of mutation that confers a novel or enhanced activity on a protein, and which is usually dominant

Germline: mutations found in the germ cells (egg and sperm) passed to offspring

Indel: a small insertion or deletion affecting between 1 and 50 base pairs of DNA

Loss-of-function mutation: a type of mutation that results in reduced or abolished protein activity

Microsatellite instability (MSI): a form of genetic instability characterized by changes in the length of repetitive DNA features called microsatellites; Loss of DNA mismatch repair (dMMR) activity may cause microsatellite instability.

Mismatch repair (MMR) status: a status of cancer cells that indicates whether the DNA mismatch repair (MMR) machinery is proficient (MMR-P) or deficient (MMR-D)

Missense mutation: a sequence change affecting a single nucleotide in the protein coding sequence of a gene that alters a codon in a manner that changes the encoded amino acid

Nonsense mutation: a sequence change affecting a single nucleotide in the protein coding sequence of a gene that alters a codon in a manner that introduces a premature stop codon

Key Terminology

Passenger mutation: type of mutation that does not confer a selective growth advantage to the cells carrying it

Proto-oncogene: a gene that, when mutated, can become an oncogene, which promotes the development of cancer; typically activated by gain-of-function mutations by which they promote cell growth, proliferation, migration, or inhibiting apoptosis

Rearrangement: variation resulting in structural reorganization of a chromosome without gain or loss of genetic material

Single nucleotide variant (SNV): a variant affecting a single nucleotide in the genome

Somatic: mutations found in the cells of the body/tumor and are not passed to the next generation

Tumor mutational burden (TMB): a measure of the number of coding changes present in the genome of a cancer cell

Tumor suppressor gene: a gene that, when mutated, can promote the development of cancer by controlling cell cycle progression or growth, or promoting apoptosis under appropriate conditions; typically inactivated by loss-of-function mutations, and often both copies of the gene must be lost to promote cancer

Two-hit hypothesis: a hypothesis that states for a cell to become cancerous, both copies of a tumor suppressor gene must be mutated

Unknown/uncertain significance (VUS): an allele identified by genetic testing which cannot be definitively categorized as either pathogenic or benign due to lack of evidence

Variant allele frequency (VAF): the fraction of reads covering a particular genomic region that contains a variant

Whole exome sequencing (WES): a method by which the sequence of the protein-coding (exonic) regions of the genome are determined

Whole genome sequencing (WGS): a method by which the sequence of the entire genome of an organism is determined

Useful Resources

NCCN Guidelines
- Principles of Molecular and Biomarker Analysis

CPIC
- Professional organization
- Useful guidelines (https://cpicpgx.org/guidelines/)

Literature
- PCCP Study Guide – Pharmacogenomics Chapter
- Vogelstein B, et.al. Cancer genome landscapes (Science Journal)
- ASCO Provisional Clinical Opinion Somatic Genomic Testing in Patients with Metastatic or Advanced Cancer (57-page document)

Certification Courses
- ASCP
- HMX Pro
- PGx101

Webinars
- Precision Oncology News/GenomeWeb

Podcasts
- PCCI for Pharmacists (Dr. Howard McLeod episode: "Pharmacogenomics Leader Series: Howard McLeod")
- Caris Molecular Minute
- Inside the GENOME
- OncoPharm (Dr. Howard McLeod episode: "Precision Medicine Demystified")

Apps
- Pharmazam

Questions

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