Pharmacogenomics In Oncology Practice

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Ochsner Health

Disclosures

- No relevant relationships to disclose

Learning Objectives

- Describe the role of pharmacogenomic testing in medication management
- Discuss barriers to and solutions for implementation of pharmacogenomic services in oncology care
- Rationalize pre-emptive testing of DPYD phenotypes prior to use of select chemotherapy agents
- Identify key components of a successful pharmacogenomic program

Common Abbreviations

ASCPT	American Society for Clinical Pharmacology & Therapeutics
ASHP	American Society for Health-System Pharmacists
CAP	College of American Pathologists
ClinGen	Clinical Genome Resource
CPIC	Clinical Pharmacogenetics Implementation Consortium
PGx	Pharmacogenomics
PGRN	Pharmacogenomics Research Network

What is Pharmacogenomics (PGx)???

- How DNA affects the way a patient responds to drugs
- Can identify whether a drug will help or have no effect
- Can identify risk of having a negative or adverse reaction to a drug

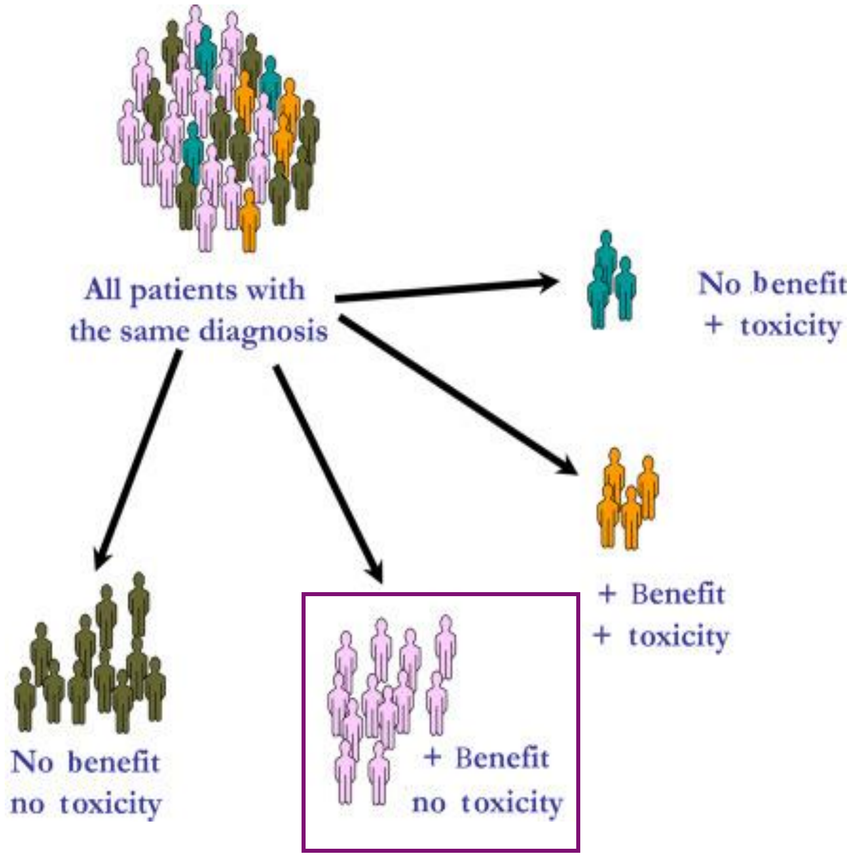
- Benefit to clinicians: use knowledge of genetic changes in metabolic enzymes, drug transporters, and drug receptors to guide medication selection and dosing

- PGx is not a crystal ball!

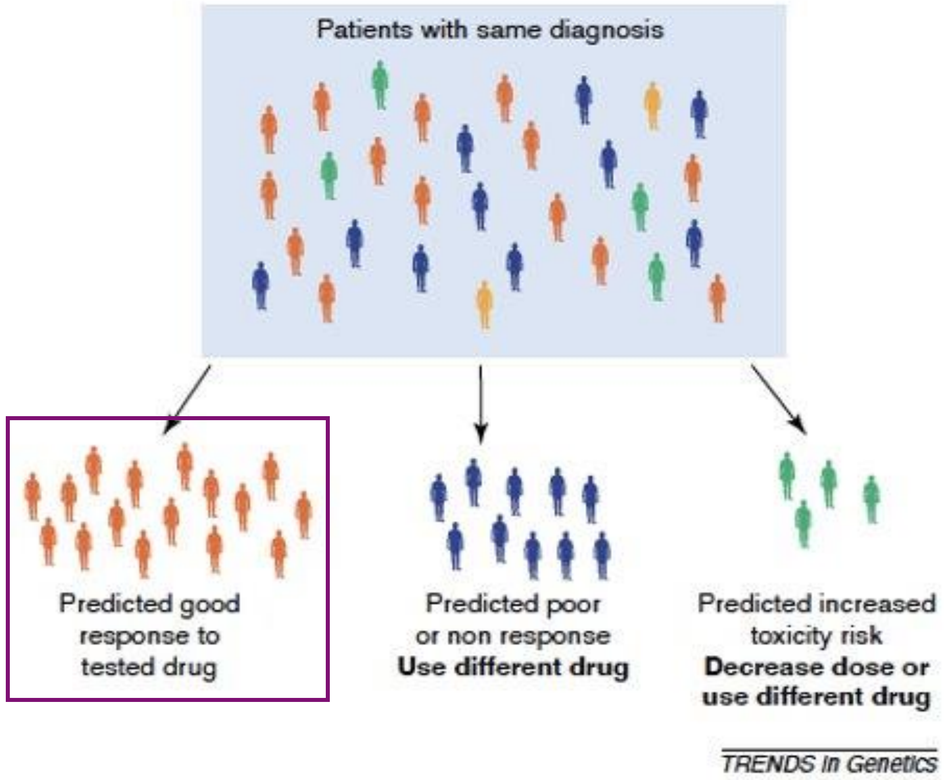
Pharmacogenomics (nih.gov)

What is Pharmacogenomics (PGx)???

OLD Current State



NEW Current State??



Johnson JA. Trends in genetics: Pharmacogenetics: potential for individualized drug therapy through genetics. TIG. 2003 Nov;19(11):660-6.

Pharmacogenetic Translation Process

Genotype

- A composite picture of genetic material at given DNA locations

Haplotype/Diplotype

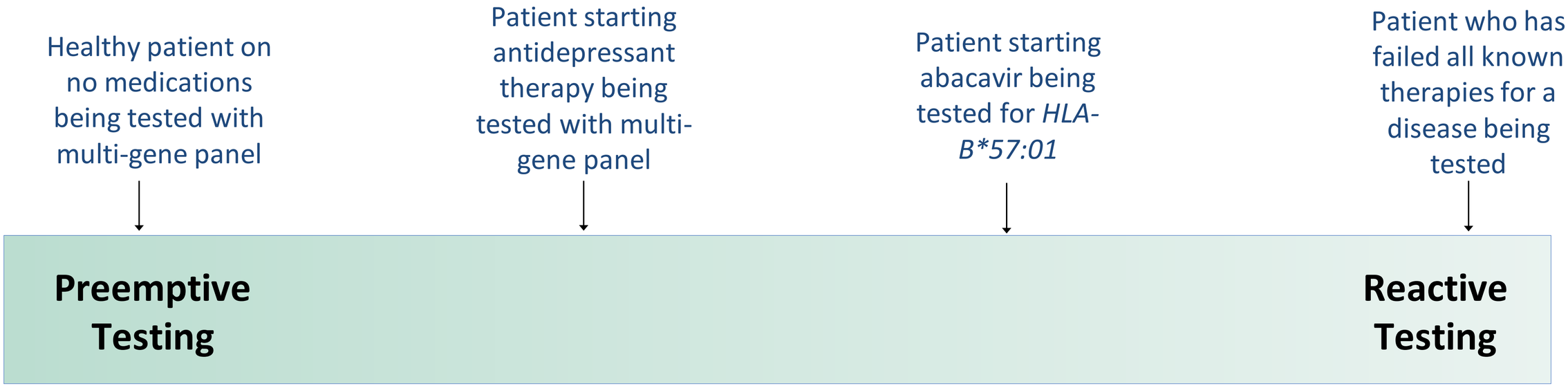
- The genetic contribution from each parent and combined to diplotype; commonly designated using the star (*) allele system (*1, *2, etc); each allele assigned a functional status. Haplotypes combined to make diplotype (ex. *1/*1)

Phenotype

- Diplotype interpretation of enzyme function

Therapeutic Recommendation

PGx Testing: Timing is EVERYTHING!!



Informative: results available when needed for future drug selection

Directive: results guide best option from start of treatment

Preventative: results prevent use in patients with high risk of adverse events

Explanative: results explain medication failures after trial-and-error approach to medication selection

What is CPIC?

- Clinical Pharmacogenetics Implementation Consortium
- International volunteers and staff
- Barrier to Implementation: difficulty in translating genetic info to actional recommendations for prescribing
- Goal: address barrier by creating, curating, and posting freely-available, peer-reviewed, evidence-based, detailed drug/gene clinical practice guidelines
- Indexed in PubMed as clinical guidelines
- Endorsed by ASHP and ASCPT
- Referenced in ClinGen and PharmGKB

CPIC (cpicpgx.org)

What is CPIC? Drug/Gene Guidelines

Anesthesiology

- Succinylcholine – *RYR1*, *CACNA1S*
- Volatile Anesthetics – *RYR1*, *CACNA1S*

Cardiology

- Clopidogrel – *CYP2C19*
- Statins – *SLCO1B1*, *ABCG2*, *CYP2C9*
- Warfarin – *CYP2C9*, *VKORC1*, *CYP4F2*

Infectious Disease

- Abacavir – *HLA-B*
- Aminoglycosides – *MT-RNR1*
- Atazanavir – *UGT1A1*
- Efavirenz – *CYP2B6*
- PegIFN – *IFNL3*
- Voriconazole – *CYP2C19*

Neurology

- Carbamazepine/Oxcarbazepine – *HLA-A*, *HLA-B*
- Phenytoin – *CYP2C9*, *HLA-B*

Oncology

- Fluoropyrimidines - *DPYD*
- Ondansetron/Tropisetron – *CYP2D6*
- Rasburicase – *G6PD*
- Tamoxifen – *CYP2D6*

Pain Management

- NSAIDS – *CYP2C9*
- Opioids – *CYP2D6*, *OPRM1*, *COMT*

Psychiatry

- Atomoxetine – *CYP2D6*
- SSRIs – *CYP2D6*, *CYP2C19*
- TCAs – *CYP2D6*, *CYP2C19*

Pulmonology

- Ivacaftor - *CFTR*

Rheumatology

- Allopurinol – *HLA-B*
- Thiopurines – *TPMT*, *NUDT15*

Solid Organ Transplant

- Tacrolimus – *CYP3A5*

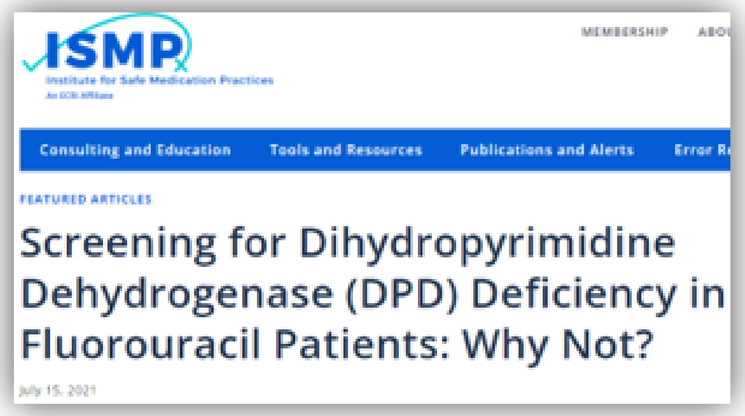
Other

- PPIs – *CYP2C19*
- Expanded list – *G6PD*

CPIC (cpicpgx.org)

Required DPYD Testing: Rationale

- Institute for Safe Medication Practices (ISMP)



- Cost of Screening
- Potential Delay in Care
- Potential Lack of Consensus Dosing
- Potential Decreased Efficacy Against Cancer
- NCCN Does Not Support Routine Screening

- European Medicines Agency (EMA)
- French regulatory agency (ANSM)
- Medicines and Healthcare Products Regulatory Agency (MHRA)

Screening for Dihydropyrimidine Dehydrogenase (DPD) Deficiency in Fluorouracil Patients: Why Not? | Institute For Safe Medication Practices (ismp.org)

Required DPYD Testing: Rationale

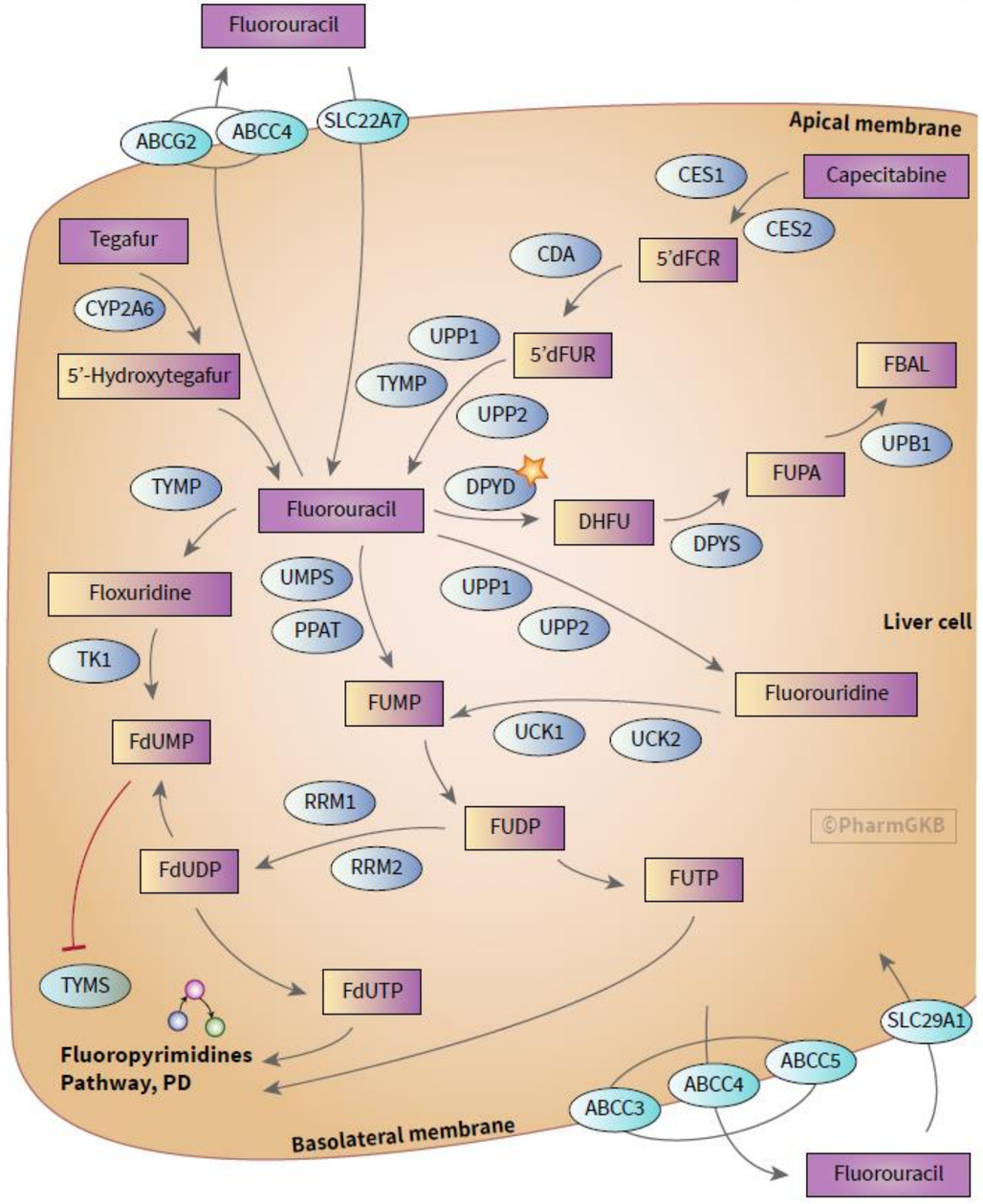
OHSU to pay $1 million, promises change to settle lawsuit from widow of cancer patient

Updated: May. 04, 2022, 11:05 a.m. | Published: May. 04, 2022, 7:00 a.m.

Oregon Health System Settles Chemotherapy Death Lawsuit: Oregon Health & Science University ("OHSU") reportedly has agreed to pay $1 million to the widow of a cancer patient who allegedly died as a result of a toxic reaction to a chemotherapy drug due to a genetic variant that affects about 8% of the population. OHSU reportedly also agreed as part of the settlement that its oncologists will advise patients about the genetic variant before initiating the chemotherapy drug capecitabine.

MEDICAL MALPRACTICE LAWYERS.COM SINCE 2003

DPYD: Dihydropyrimidine dehydrogenase



- 5-FU given IV for colorectal, breast, and other GI cancers
- 80% metabolized in the liver
- Capecitabine, tegafur activated to 5-FU

- 5-FU catabolism by DPYD to DFHU → FUPA → FBAL

PharmGKB summary: fluoropyrimidine pathways. *Pharmacogenetics and genomics.* 2011. Thorn Caroline F, Marsh Sharon, Carrillo Michelle Whirl, McLeod Howard L, Klein Teri E and Altman Russ B.

DPYD: Dihydropyrimidine dehydrogenase

- 83 known variants of DPYD
- 56 variants → Normal Function (Activity Score = 1)
- 6 variants → Decreased Function (Activity Score = 0.5)
- 21 variants → No Function (Activity Score = 0)

Table 1 Assignment of likely DPD phenotypes based on *DPYD* genotypes

Likely phenotype	Activity score[a]	Genotypes[b]	Examples of genotypes[c]
DPYD normal metabolizer	2	An individual carrying two normal function alleles.	c.[=];[=], c.[85T>C];[=], c.[1627A>G];[=]
DPYD intermediate metabolizer	1 or 1.5	An individual carrying one normal function allele plus one no function allele or one decreased function allele, or an individual carrying two decreased function alleles.	c.[1905+1G>A];[=], c.[1679T>G];[=], c.[2846A>T];[=]; c.[1129–5923C>G];[=][d]; c.[1129–5923C>G];[1129–5923C>G][d]; c.[2846A>T];[2846A>T]
DPYD poor metabolizer	0 or 0.5	An individual carrying two no function alleles or an individual carrying one no function plus one decreased function allele.	c.[1905+1G>A];[1905+1G>A], c.[1679T>G];[1679T>G], c.[1905+1G>A];[2846A>T] c.[1905+1G>A]; [1129-5923C>G]

[a]Calculated as the sum of the two lowest individual variant activity scores. See text for further information. [b]Allele definitions, assignment of allele function and references can be found on the CPIC website (*DPYD* Allele Functionality Table available at [ref 4]) [c]HGVS nomenclature using the reference sequence NM_000110.3 [d]Likely HapB3 causal variant. See *DPYD* Allele Functionality Table available at [ref 4] for other HapB3 proxy SNPs.

https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/

DPYD: Dihydropyrimidine dehydrogenase

Frequencies of DPYD phenotypes in biogeographical groups							
Phenotype	Activity Score	African American/ Afro-Caribbean	Central/ South Asian	East Asian	European	Latino	Sub-Saharan African
Normal Metabolizer	2.0	63.9%	34.0%	24.3%	42.6%	48.2%	68.2%
Intermediate Metabolizer	1.5	3.0%	3.1%	0.1%	3.6%	1.3%	4.6%
	1.0	1.0%	0.8%	0.2%	1.2%	0.1%	0.1%
Poor Metabolizer	0.5	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	0.0	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/

DPYD IM/PM Clinical Significance

- DPYD-Deficient patients have unacceptable toxicities

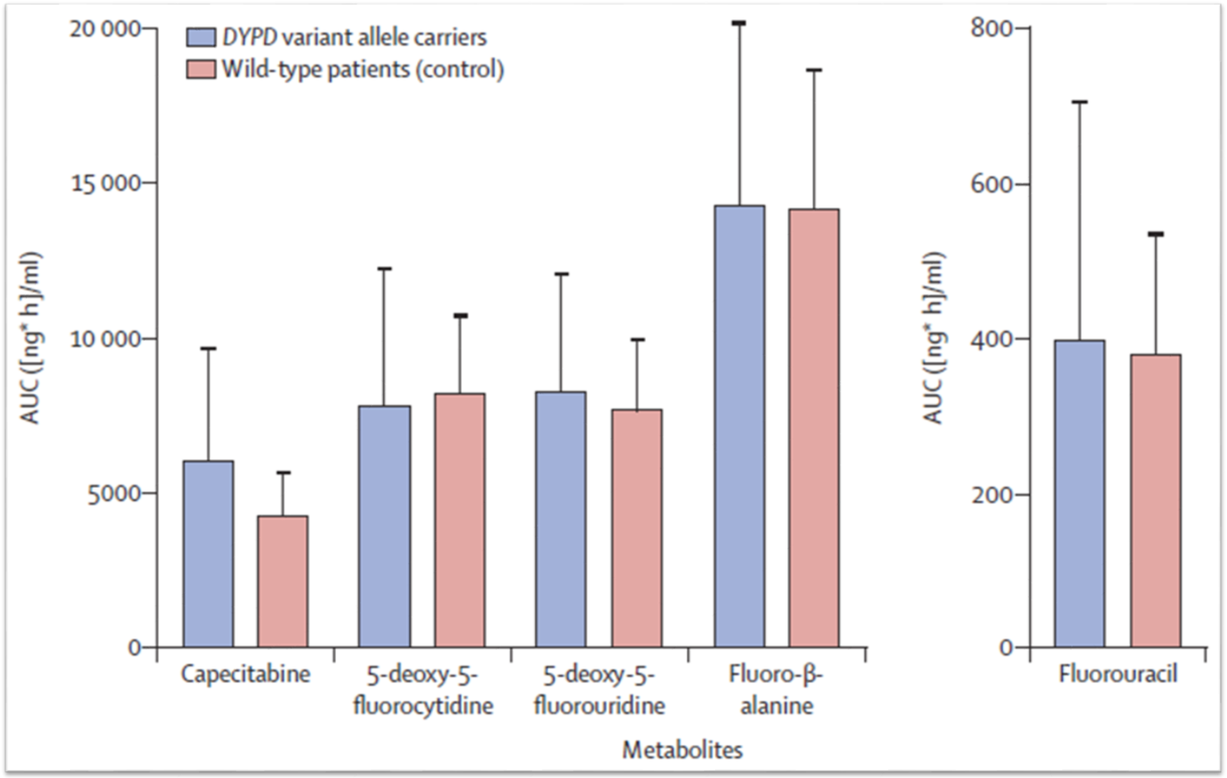
- 2014 Study: 2886 Stage III Colon Cancer with Grade 3+ Adverse Events to 5-FU
  - Wild type (**33%**) vs. variant *1/*2A (**88%**) vs. c.2846A>T (**82%)**
  - Significantly associated with N/V, diarrhea, leukopenia, neutropenia, thrombocytopenia

- 2021 Meta-analysis of 35 Studies (13,929 patients)
  - Carriers of variants has a **25.6x** increased risk of death
  - **Mortality rate of 3.7%** for carriers of c.1679T>G, c.1905+1G>A, or c.2846A>T

Lee AM. J Natl Cancer Inst. 2014;106(12): dju298
Sharma BB. Oncologist. 2021 Dec;26(12):1008-1016.

5-FU Dose Adjustment and Drug Exposure

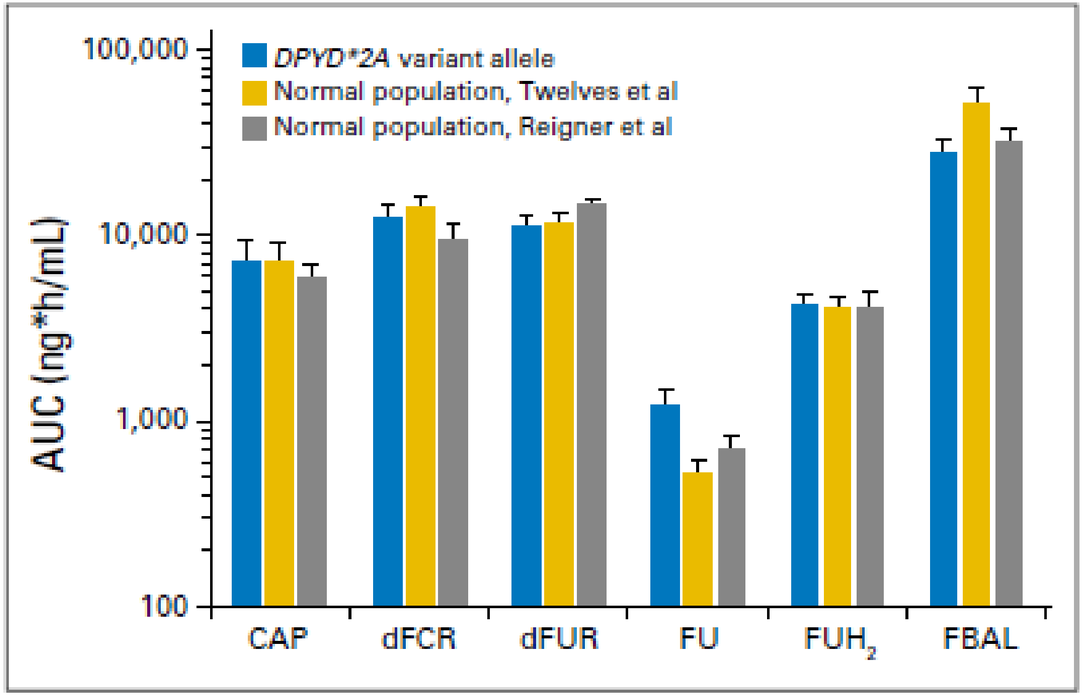
- 2018 Trial
- Demonstrate equivalent exposure for DPYD-deficient patients and dose reduction vs standard dose for wild type DPYD
- Reduced risk of Grade 3+ toxicity (31 vs 72% historical comparator)
- Similar frequency of hospital admissions and treatment discontinuation
- Concluded all variants tested should be dose reduced by 50%



Henricks LM. Lancet Oncol. 2018 Nov;19(11):1459-1467.

5-FU Dose Adjustment and Drug Exposure

- 2016 Trial
- Prospectively dose-reduced *2A carriers vs historical controls
- Grade 3+ toxicity reduced from 73 to 28%
- Drug-induced death reduces from 10 to 0%



Study	DPYD Genotype	Patients	Median Dose Intensity	Relative 5FU AUC
Deenen, et al.	*1/*2A	14	48%	85-115%
Henricks, et al.	*1/Variant	26	50-75% (Variant specific)	104%

Deenen MJ. J Clin Oncol. 2016 Jan 20;34(3):227-34
Henricks LM. Lancet Oncol. 2018 Nov;19(11):1459-1467.

Required DPYD Testing: Rationale

- Ochsner Health Experience January 2020 – May 2021
- 106 patients tested for DPYD genetic variation at provider discretion

- **11 patients had DPYD variants of clinical significance (IM) +2 patients could not rule out variants**
  - 5 patients admitted at the time of test (reactive)
    - 83 inpatient days
    - 5 emergency department visits
    - 1 urgent care visit
  - 2 other patients had avoidable adverse events at the time of test (reactive)
    - 1 ED visit, 1 urgent care visit
  - 1 received full dose, no complications (pre-emptive)
  - 1 dose reduced after test result, no adverse event
  - 4 did not receive chemotherapy

5 patients with reduced DPD had **83 total inpatient days (16.6 days/patient)** (range: 2-39 days)

Required DPYD Testing: Preliminary Findings

Required DPYD Testing Implementation (July 2022)

848 patients tested since March 2022

- 577 oncology patients tested (68%)

36 total patients had DPYD variants of clinical significance (IM/PM) – 4.2%

- 13 patients received fluoropyrimidine therapy
  - 8 were PRE-EMPTIVELY DOSE REDUCED due to PGx findings
    - 0 admissions (2 to 12 months' follow-up)
    - 0 ED visits (2 to 12 months' follow-up)
  - 5 were not dose reduced
    - 1 patient with ED visit & 3 days inpatient
    - 4 patients tolerated full dose

By pre-emptively testing and dose reducing, we avoided 97.9 inpatient days

February 2023 CPIC Meeting

ADVOCATES FOR UNIVERSAL DPD/DPYD TESTING

Advocates for Universal DPD/DPYD Testing

- Mission: To improve the standard of care for cancer patients undergoing F-FU or capecitabine through advocacy, education, and research
- Earned support for pre-screening in 2021 with ISMP and NCODA

Organizations leading in testing:

Institutes/MDs with at least partial implementation:

- **Dana Farber Cancer Institute, Boston MA**
- **Dartmouth Cancer Center, Lebanon NH**
- **Atrium Health, Charlotte NC**
- **University of Michigan**
- **Sanford Imagenetics, South Dakota**
- **University of Colorado**
- **Wentworth-Douglass Hospital, Seacoast Cancer Center, Dover NH**
- **Christ Hospital Health Network, Cincinnati OH**
- **Yale New Haven Health**
- **Dr. Rashid, Toledo Clinic Cancer Centers**
- **Dr. Kasi, Cornell**
- **Dr. Michael Castro, Los Angeles CA**

Implementing within prospective clinical trial:

- **University of Pennsylvania Perelman School of Medicine**
- **University of Chicago**
- **Moffitt Cancer Center, Tampa FL**

Considering test procedures*:

- **Oregon Health Sciences University**
- **Cleveland Clinic**
- **Georgetown University**
- **St. Elizabeth Hospital of Northern KY**
- **Intermountain Healthcare, UT**
- **Fred Hutchinson Cancer Care, Seattle WA**

*** Based on word of mouth; no public disclosure at this time**

LOS LOUISIANA ONCOLOGY SOCIETY

February 2023 CPIC Meeting: FDA Denial of Petition

Denied recommendation for dose adjustments in DPYD variant carriers

- Data about standard dose with DPYD IM patients is unclear
- Rigorous data is required for FDA to recommend specific doses or adjustments (prospective RCTs demonstrating non-inferiority or superiority clinical outcomes

Revised drug label

- Added Warnings/Precautions: “Consider Testing for DPYD”
- Patient Counseling: Discuss risks and if testing is appropriate
- Added Patient Information and PGx sections

CPIC advocating for members to contribute use of genotype-guided dosing based on pharmacokinetic data and equivalent drug exposure as sufficient.

DPYD Testing: Why not?

DPYD Testing: Time to Put Patient Safety First

Sharyn D. Baker, PharmD, PhD[1]; Susan E. Bates, MD[2]; Gabriel A. Brooks, MD[3]; William L. Dahut, MD[4]; Robert B. Diasio, MD[5];

"Pretreatment DPYD testing of all patients has the potential to identify the estimated 1%-2% of the population with truncating alleles that may herald an increased risk of severe toxicity."[23]

However, the NCCN statement is not broad enough: Other DPYD variants have sufficient levels of evidence to justify testing, raising the number of at-risk patients to **approximately 9%** of the US population.

Baker SD. J Clin Oncol. 2023 Feb 23;Online ahead of print.

Ochsner Health

- Demographic slide

Ochsner Health PGx Program

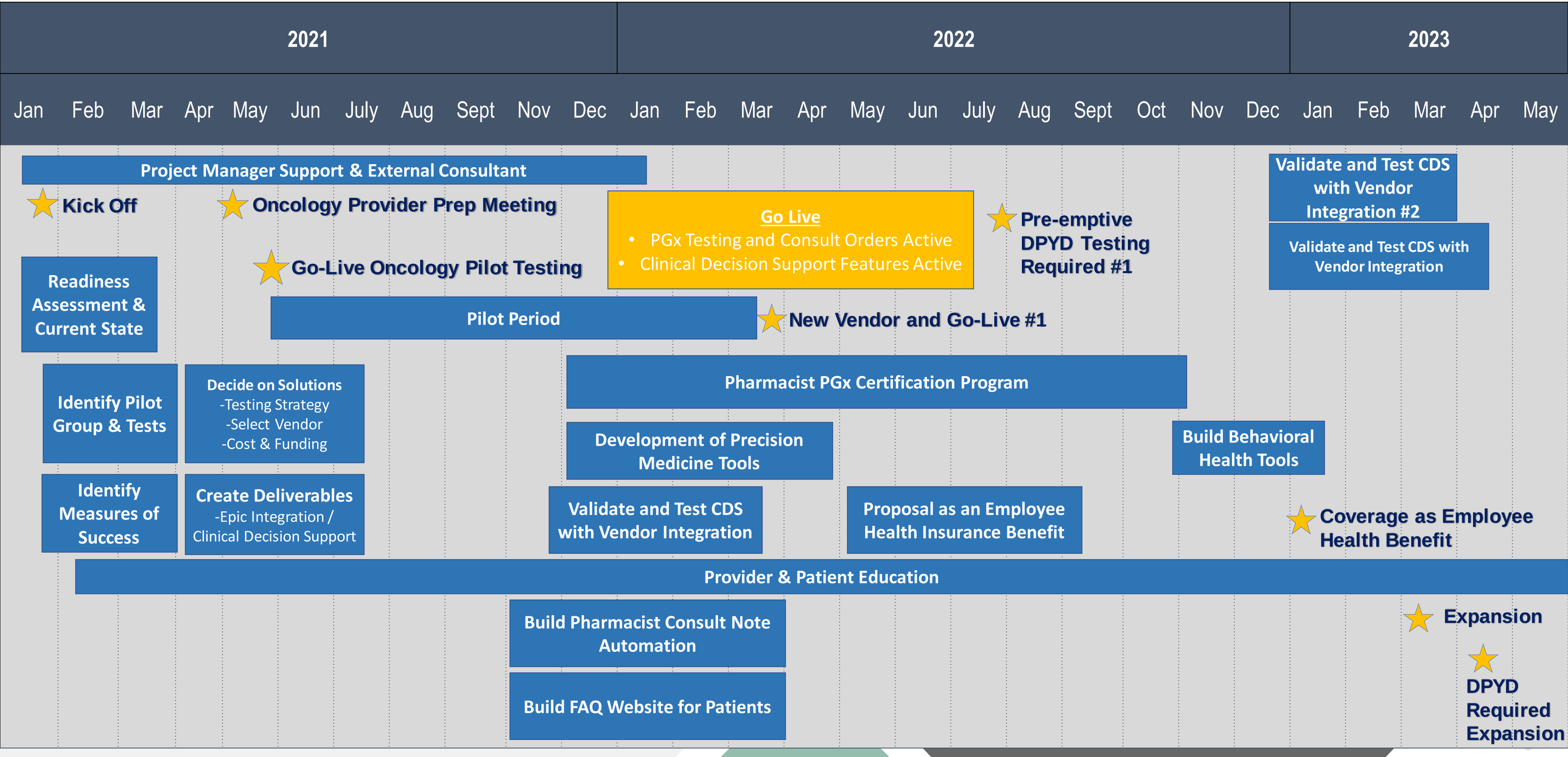
- PGx Subcommittee of System P&T Committee
- Physician Chair and Pharmacist Co-Chair
- Set and execute strategy for evidence-based design and expansion
- Key Stakeholders:
  - Target specialties: Pharmacy, Oncology, Primary Care, Cardiology, SOT, Genetics, Infectious Diseases, Rheumatology, Investigational Drug Service, others
  - Information Systems/EMR Analysts, Data Analytics
  - Operational leaders

Ochsner Health PGx Program Considerations

- Testing strategy (selection of method, genes and alleles)
- EHR integration (ordering, discrete results with standard nomenclature, interpretation, CDS tools)
- Billing and reimbursement (testing and interpretation)
- Healthcare professional education
- Therapeutic recommendations and patient education
- Expansion strategy
- Program maintenance

J Am Coll Clin Pharm. 2022;5:1161–1175.

Ochsner Health PGx Program Timeline



Role of the Pharmacist

- <u>All Pharmacists!!</u>
- Promote optimal use and timing of test, ordering
- Interpretation of test results; selection, dosing, monitoring
- Education: patients, health care professionals, and the public
- Implementation, integration into EMR, clinical decision support
- Research and publication

- <u>Pharmacists with specialized training and experience:</u>
- Develop guidelines and processes
- CDTM principles applied to PGx services
- Serve as subject matter experts, including tumor genomics/somatic variation
- Advocacy, advanced education, research and publication

Am J Health-Syst Pharm. 2022;79:704-707

Gratitude to Ochsner PGx Champions

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