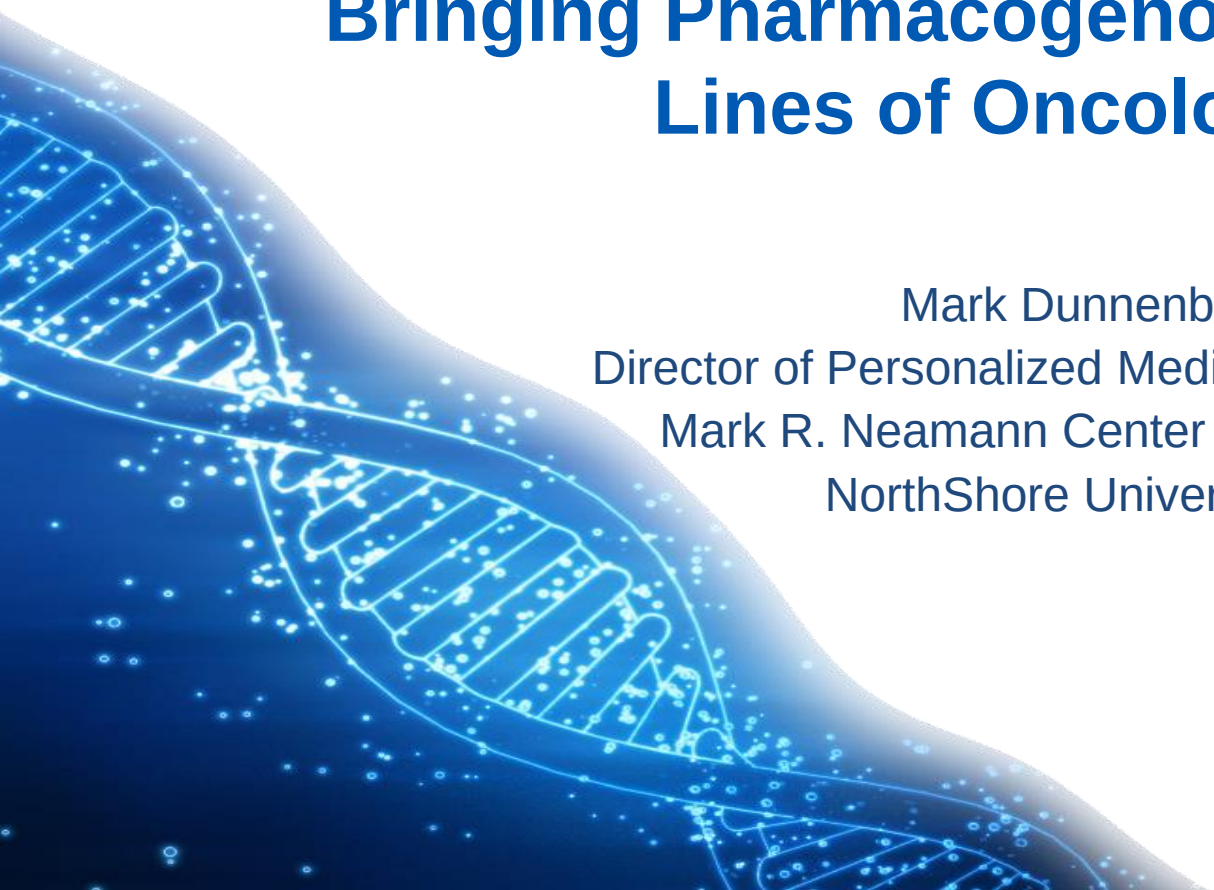
Bringing Pharmacogenomics to the Front Lines of Oncology Care



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Conflicts of interest

Nothing to disclose

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Topics covered

1. Definitions
2. Patient case
3. Value
4. System building
5. Ochsner's Pharmacogenomic Program

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Patient DPYD Case

- 34 y/o Asian female
- Stage 3A breast cancer with metastasis

Date	Event
4/1/2021	Treatment with capecitabine ordered: 5 tabs bid for 2 weeks every 3 weeks
5/7/2021	Admitted with tachycardia, acute kidney injury, chemotherapy-induced diarrhea, mucositis, prolonged neutropenia, more; numerous interventions including vancomycin and dialysis
5/9/2021	DPYD test ordered
5/14/2021	Test resulted, DPYD positive for mutation, heterozygous for rs1057516388, c.1863G>A (p.Trp621*Ter [nonsense mutation, premature stop]): Intermediate metabolizer
5/27/2021	Discharged

atgttctcag caatgctgca gtcaaacagg atgggctcct gggacacga tgcccaggtg gctcggagcc
actgaacatt cagtcgcttt atttctttgccatcaagcag ctgaaaacaa gagttcacag atcaacttca
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gcccaggtgt gctcggagcc actgaacatt cagtcgcttt atttctt 3 billion bases acaa
gagttcacag atcaacttca ggaccagcac actttgaatg tagcaca 10 million variations acac
tgaaactgcc gggacacgat gcccaggtgt gctcggagcc actgaacatt cagtcgcttt atttctttgc
catcaagcag ctgaaaacaa gagttcacag atcaacttca ggaccagcac actttgaatg tagcacaatt
aacatcatta tttcttacac gggacacgatgcccaggtgt gctcggagcc actgaacatt cagtcgcttt
atttctttgccatcaagcag ctgaaaacaa gagttcacag atcaacttca ggaccagcac actttgaatg
tagcacaatt aacatcatta tttcttacac

Medicine “B” might be better than medicine “A” for you

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catcaagcag ctgaaaacaa gagttcacag atcaacttca ggaccagcac actttga
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atttctttgc catcaagcag ctgaaaacaa gagttcacag atcaacttca ggaccagcac actttgaatg
tagcacaatt aacatcatta tttcttacac

We have to find the important needles in a big haystack

Single Nucleotide Polymorphisms (SNP)

Definition of Pharmacogenetics/Pharmacogenomics

How changes in your DNA affect the way your body responds to medication

- Pharmacokinetic (CYP enzymes and drug transporters)
- Pharmacodynamic (HLA and immune response)

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Germline vs. Somatic Variants

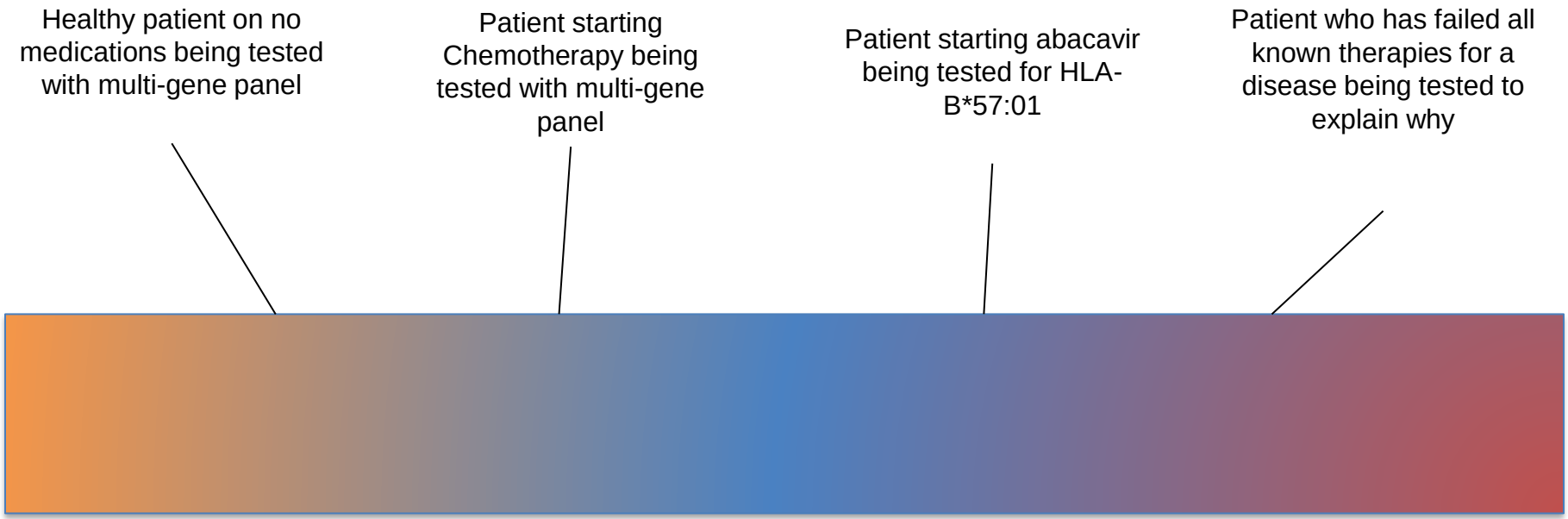
Germline variants are inherited from your parents and transmitted to your offspring. These variants are helpful for predicting pharmacodynamic and pharmacokinetic effects

Somatic variants are not inherited and are present in the tumor. These variants are helpful for predicting pharmacodynamic effects

Colorectal Cancer

Drug	Gene	Variant type	Phenotype
Irinotecan	*UGT1A1*	Germline	Neutropenia
5-fluorouracil	*DPYD*	Germline	Neutropenia, stomatitis, diarrhea
Cetuximab	*KRAS/EGFR*	Somatic	Disease response

Reactive vs. Preemptive Genotyping



Audience Question

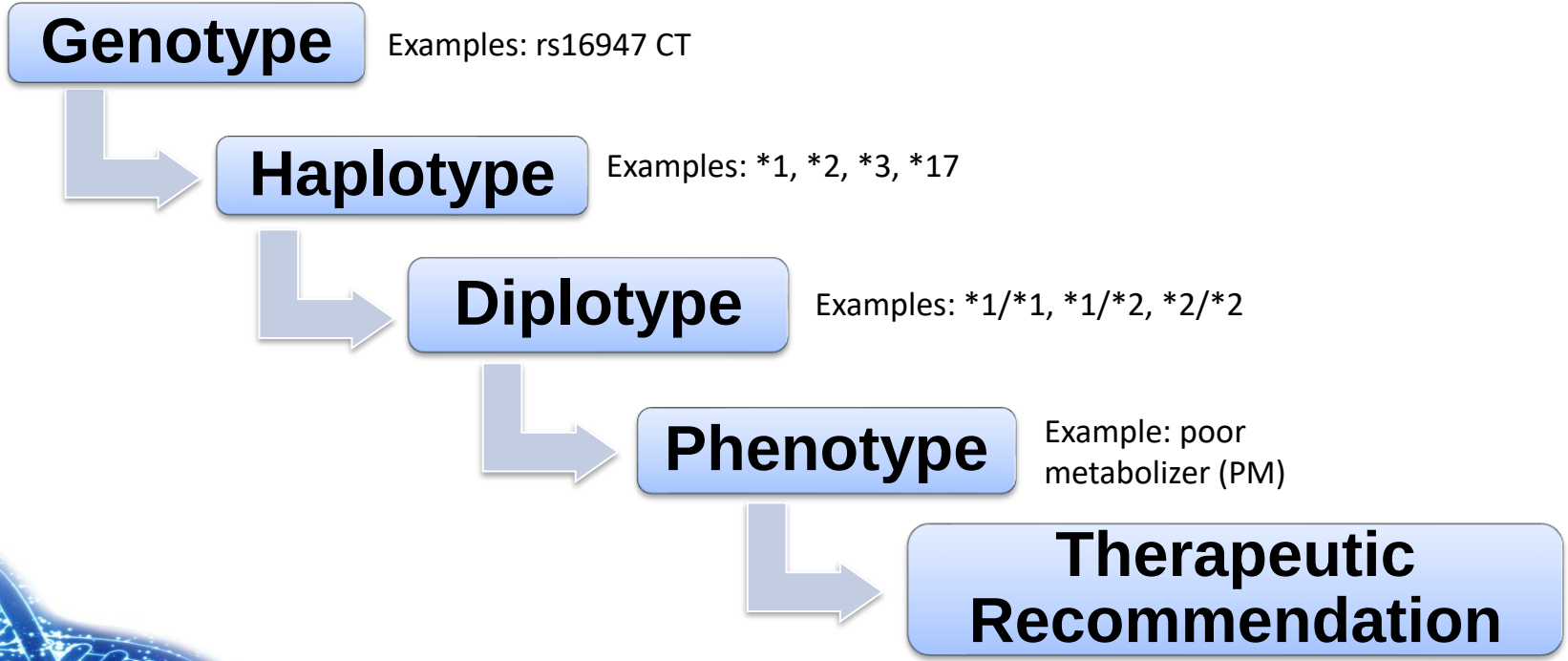
Have you ordered a pharmacogenomics test for a patient before?

Why did you order it?

```
#PatientName=XXXXX
#DMETfile=DMET_8170.dmet_GT.txt
#TubeNumber=8170
#PatientID=(0000)02XXXX
#SampleType=PGEN DNA
#TranslationFile=DMET_Plus.v1.20101104DRAFT.full.translation
#AnnotationFile=DMET_Plus.v1.20090910.dc_annot.csv
#ReporterBuild=0.8.5
#VerifiedList=VerifiedbyAffy_Nov08 marker list.txt
PharmGKB link   http://www.pharmgkb.org/do/serve?objId=PA128&objCls=Gene
Independent Copy Number 2
Called Interpretation Code      UNIQ+UNK
Called Diplotypes Possible      *1/*41
Called Novel Diplotypes Possible        *2/UNK
Copy Number Corrected Alleles   NA
Number Non-reference Probe Sets 5
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Descri
AM_12261        Y       Ch22:40853887   rs16947 C/T     Ref/Var *2,*8,*11,*12,*14A,*14B,*17,*19,*20,*21,*29,*40,*41,*4
AM_12257        Y       Ch22:40853749   rs28371725      G/A     Ref/Var *41     CYP2D6*41_2988G>A(SpliceDefect)
AM_15502        N       [illegible]     [illegible]     [illegible]     [illegible]     [illegible]
AM_12277        Y       Ch22:40855076   rs1058164       G/C     Ref/Var -       CYP2D6_1661G>C(V136V)
AM_12247        [illegible]     [illegible]     [illegible]     [illegible]     [illegible]
Number Reference only Probe Sets        25
Probe Set ID    Affy Verified   Genome Position dbSNP RS ID     Genotype        Call    Contributes To Alleles  Descri
AM_12285        Y       Ch22:40856638   rs1065852       C/C     Ref/Ref *4,*10,*14A,*56B,*64    CYP2D6_100C>T(P34S)
AM_12284        Y       Ch22:40856614   rs5030862       G/G     Ref/Ref *12     CYP2D6*12_124G>A(G42R)
AM_12283        N       Ch22:40856600   rs72549357      T/T     Ref/Ref *15     CYP2D6*15_137insT
AM_12281        Y       Ch22:40855856   rs5030863       G/G     Ref/Ref *11     CYP2D6*11_883G>C(SpliceDefect)
AM_12280        Y       Ch22:40855716   rs28371706      C/C     Ref/Ref *17,*40,*64     CYP2D6_1023C>T(T107I)
AM_12278        N       Ch22:40855078   rs61736512      G/G     Ref/Ref *29     CYP2D6*29_1659G>A(V136I)
AM_12276        Y       Ch22:40855030   rs5030655       T/T     Ref/Ref *6      CYP2D6*6_1707delT
AM_12275        N       Ch22:40854979,Ch22:40854979     rs5030865       G/G     Ref/Ref *14A,*14B,*8    CYP2D6*14or*8_
AM_12274        Y       Ch22:40854891   rs3892097       G/G     Ref/Ref *4      CYP2D6*4_1846G>A(SpliceDefect)
AM_12272        Y       Ch22:40854873   rs72549356      -/-     Ref/Ref *40     CYP2D6*40_1863ins(TTTCGCCCC)2
AM_12270        Y       Ch22:40854763   rs72549354      -/-     Ref/Ref *20     CYP2D6*20 _1973insG
AM_12268        Y       Ch22:40854195   rs72549353      AACT/AACT       Ref/Ref *19     CYP2D6*19_2539delAACT
AM_12267        Y       Ch22:40854188   rs35742686      A/A     Ref/Ref *3      CYP2D6*3_2549delA
AM_12266        Y       Ch22:40854157   rs72549352      -/-     Ref/Ref *21     CYP2D6*21_2573insC
AM_12265        Y       Ch22:40854147   rs72549351      GACT/GACT       Ref/Ref *38     CYP2D6*38_2587delGACT
AM_12264        Y       Ch22:40854120   rs5030656       AGA/AGA Ref/Ref *9      CYP2D6*9_2615delAAG
AM_12259        Y       Ch22:40853802   rs5030867       A/A     Ref/Ref *7      CYP2D6*7_2935A>C(H324P)
AM_12258        Y       Ch22:40853787   rs72549349      G/G     Ref/Ref *44     CYP2D6*44_2950G>C(SpliceDefect)
AM_12255        Y       Ch22:40853554   rs59421388      G/G     Ref/Ref *29     CYP2D6*29_3183G>A(V338M)
AM_12254        Y       Ch22:40853536   rs72549347      C/C     Ref/Ref *56A,*56B       CYP2D6*56_3201C>T(R344X)
AM_12252        Y       Ch22:40853477   rs72549346      -/-     Ref/Ref *42     CYP2D6*42_3259insGT
AM_12248        Y       Ch22:40852603   rs1135836       T/T     Ref/Ref *18     CYP2D6*18_4125dupGTGCCCACT
AM_15506        N       Ch22:40858920   rs28360521      G/G     Ref/Ref -       CYP2D6_-2178G>A
AM_15503        N       Ch22:40858703,Ch22:40858703     -       C/C     Ref/Ref -       CYP2D6_-1961C>G>A
AM_12291        Y       Ch22:40858326   rs1080985       C/C     Ref/Ref -       CYP2D6_-1584C>G
```

Her CYP2D6 genotype is consistent with an increased risk of therapeutic failure with paroxetine. Please consider alternative therapies when initiating drug therapy to treat depression.

Pharmacogenetic translation process



Hicks JK, *et. al.*

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Patient Case

13 y/o female who is diagnosed with depression and anxiety. Her mother reports she has had numerous problems tolerating the medications tried over the past 18 months.

Medication history

Drug	Depression	Side Effects
Escitalopram	✘	✓
Sertraline	✘	✘
Fluoxetine	✘	✘
Aripiprazole	✘	✘
Venlafaxine	✘	✘

Genetic results

Gene	Genotype	Gene	Genotype	Gene	Genotype
CYP2D6	*4/*4	CYP3A4	*1/*1	SLCO1B1	*1/*5
CYP2C19	*1/*2	CYP3A5	*3/*3	OPRM1	GG
CYP2C9	*1/*1	CYP1A2	*1F/*1F	COMT	158 Val/Met
VKORC1	AA	SLC6A4	S/S		
TPMT	*1/*3A	MTHFR	677 CC		

Genetic interpretation

- CYP2D6 Poor Metabolizer
- CYP2C19 Intermediate Metabolizer
- SLC6A4 Poor Responder

Interpretation and Recommendations

Drug	Genetic Risk	Description
Escitalopram	✘	Likely ineffective and cause side effects
Sertraline	✘	Likely ineffective and cause side effects
Fluoxetine	✘	Likely ineffective and cause side effects
Aripiprazole	✘	Likely cause side effects
Venlafaxine	✘	Likely cause side effects

Recommendations

Consider an SNRI like desvenlafaxine, duloxetine, or bupropion for depressive symptoms for this patient

Patient Case Outcome

Tried bupropion and risperidone but failed

Now stable on duloxetine and lurasidone for >24 months

Audience Question

What would it take for you to order PGx testing for all of your patients?

WHY ONCOLOGY?

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CPIC™
Clinical Pharmacogenetics Implementation Consortium

CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy.

- Not WHETHER tests should be ordered.

Key Assumption:

- Clinical high-throughput and pre-emptive genotyping will become more widespread.
- Clinicians will be faced with having patients' genotypes available even if they did not order test with drug in mind.

CPIC™
Clinical Pharmacogenetics Implementation Consortium

As of June 2021:

- >400 Members
  - » Clinicians and scientists
  - » > 260 institutions
  - » 35 countries
- 14 Observers (NIH, FDA, professional societies)
- CPIC Informatics
  - » >35 members from 25 organizations

26 guidelines; 22 genes and > 65 drugs

CPIC™ Clinical Pharmacogenetics Implementation Consortium

- *TPMT, NUDT15*
  - MP, TG, azathioprine
- *CYP2D6*
  - Codeine, tramadol, hydrocodone, TCAs, tamoxifen, SSRIs, ondansetron, tropisetron, atomoxetine, beta-blockers (in progress)
- *CYP2C19*
  - TCAs, clopidogrel, voriconazole, SSRIs, PPIs
- *VKORC1*
  - Warfarin
- *CYP2C9*
  - Warfarin, phenytoin, NSAIDs
- *CYP4F2*
  - Warfarin
- *HLA-B*
  - Allopurinol, CBZ, Oxcarbazepine, abacavir, phenytoin
- *HLA-A*
  - CBZ
- *CFTR*
  - Ivacaftor
- *DPYD*
  - 5FU, capecitabine, tegafur
- *G6PD*
  - Rasburicase
- *UGT1A1*
  - Atazanavir
- *SLCO1B1*
  - Simvastatin
- *IFNL3 (IL28B)*
  - Interferon
- *CYP3A5*
  - Tacrolimus
- *CYP2B6*
  - Efavirenz, methadone (in progress)
- *RYR1, CACNA1S*
  - Inhaled anesthetics
- *MT-RNR1*
  - Aminoglycosides
- *OPRM1*
  - Opioids (CPIC level C-no recommendation)
- *COMT*
  - Opioids (CPIC level C-no recommendation)

https://cpicpgx.org/guidelines/

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Current drug-gene pairs with CPIC Guidelines by disease state

Cardiology
- Clopidogrel – *CYP2C19*
- Simvastatin – *SLCO1B1*
- Warfarin – *CYP2C9* and *VKORC1*

Infectious disease
- Abacavir – HLA-B*57:01
- Atazanavir – *UGT1A1*
- PEG-interferon – *IL28B*

Neurology
- Carbamazepine – *HLA-B*15:02*
- Phenytion – *CYP2C9, HLA-B*15:02*

Oncology
- Thiopurine – *TPMT*
- Capecitabine/5-FU – *DPYD*
- Rasburicase - *G6PD*

Pain management
- Codeine – *CYP2D6*
- Tramadol – *CYP2D6*
- Tricyclic antidepressants – *CYP2C19, CYP2D6*

Psychiatry
- Tricyclic antidepressants – *CYP2C19, CYP2D6*
- Selective serotonin reuptake inhibitors– *CYP2C19, CYP2D6*

Rheumatology
- Thiopurine – *TPMT*
- Allopurinol – *HLA-B*58:01*

Solid organ transplant
- Tacrolimus – *CYP3A5*

Respiratory
- Ivacaftor - *CFTR*

ISMP
Institute for Safe Medication Practices
An ECRI Affiliate

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FEATURED ARTICLES

Screening for Dihydropyrimidine Dehydrogenase (DPD) Deficiency in Fluorouracil Patients: Why Not?

July 15, 2021

European Medicines Agency, the French regulatory agency, the Medicines and Healthcare products Regulatory Agency in the United Kingdom, have all provided guidelines for preemptive DPD testing for patients scheduled for treatment with fluoropyrimidine chemotherapy.

BUT not from NCCN or FDA.

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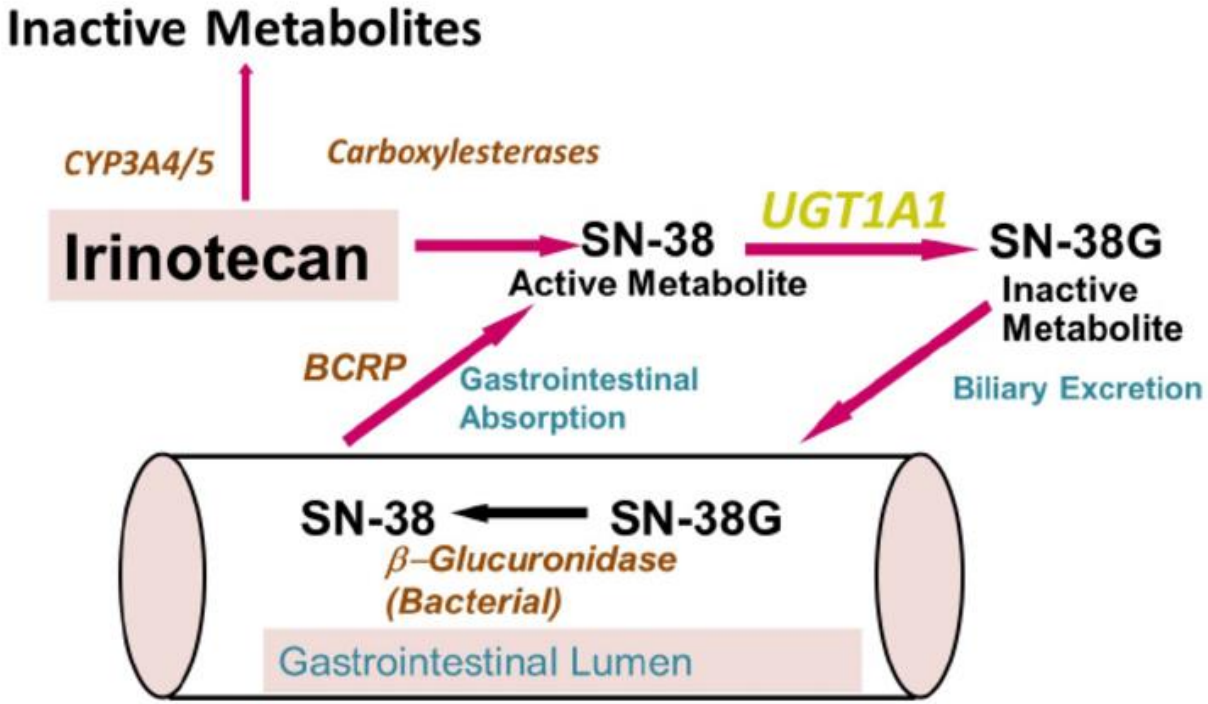
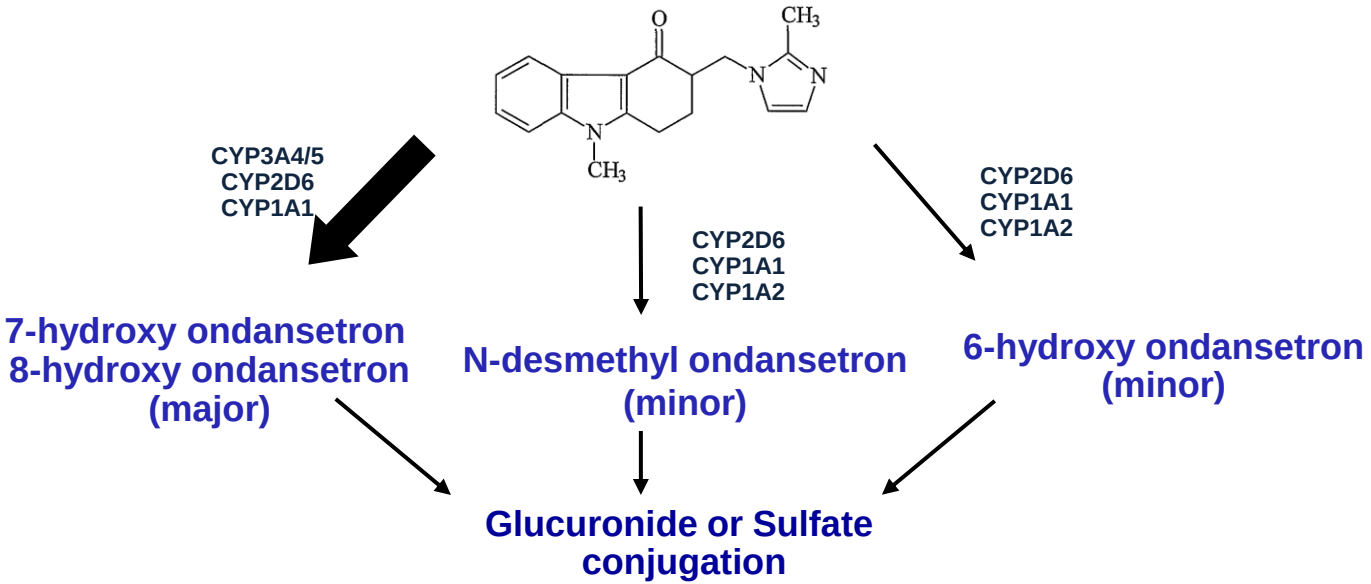
Irinotecan and *UGT1A1*



Ondansetron



CYP2D6 (along with other CYP450 enzymes) metabolizes ondansetron to major inactive metabolites 7- and 8-hydroxy ondansetron and minor inactive metabolites 6- hydroxy and N-desmethyl ondansetron.

Dixon CM, et al. *Drug Metab Dispos* 23:1225-1230, 1995
Fischer V , et al. Drug Metab Dispos 22:269-274, 1994.

CYP2C19 and Voriconazole

Cost saving model

Assumptions

- Proactively screen all AML patients
- CYP2C19 UMs would receive higher dosing of voriconazole

Considerations

- Cost of testing, therapeutic drug monitoring, cost of treating an invasive fungal infection

Outcomes

- Cost of testing - $291.80
- Avoids 2-3 invasive fungal infections per 100 patients
- Saves $415 per patient

Mason NT, Bell GC, Quilitz RE. J Antimicrob Chemother. 2015 Nov;70(11):3124-6.

VALUE

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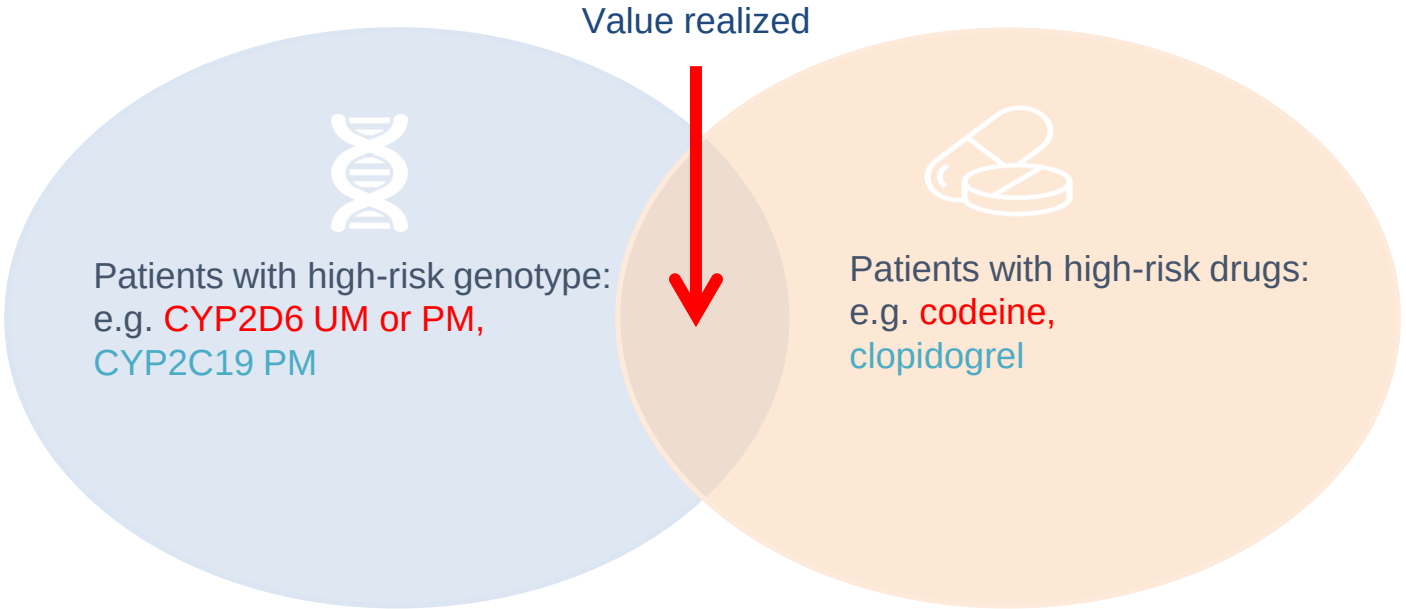
Value – Changing medications



Audience Question

What percent of the US population has a high-risk pharmacogenomic variant?

A. 5%

B. 20%

C. 77%

D. 99%

Annu Rev Pharmacol Toxicol. 2015;55:89-106.

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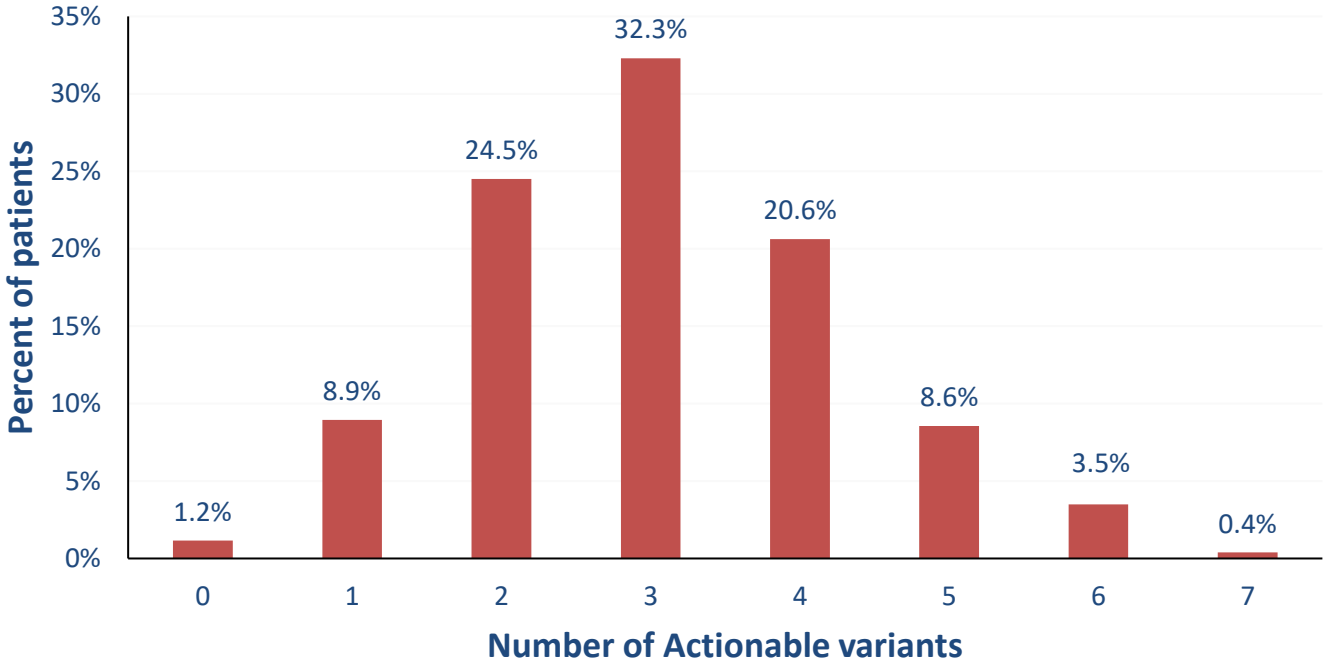
98% of patients have at least one clinically actionable variant



Am J Health Syst Pharm. 2016 Dec 1;73(23):1956-1966.

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Audience Question

What percent of prescriptions filled in the US in 2013 were for pharmacogenetically high-risk drugs?

A. 5% or 188 million prescriptions
B. 20% or 750 million prescriptions
C. 77% or 2.89 billion prescriptions
D. 99% or 3.71 billion prescriptions

Recent analysis of 40 Advanced Cancer patients

All 40 patients were exposed to at least 6 pharmacogenomics linked medication while receiving care at NorthShore

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Value – Patient reactions to testing

Survey Statement	5	4	3	2	1
I feel more confident that medication(s) prescribed to me will not cause side effects and/or will help my condition, compared to past prescriptions I've received without testing. (n=56)	24 (42.9%)	17 (30.4%)	7 (12.5%)	6 (10.7%)	2 (3.6%)
I am more likely to take medications prescribed by my healthcare provider. (n=56)	16 (28.6%)	16 (28.6%)	18 (32.1%)	5 (8.9%)	1 (1.8%)

5= Strongly agree 4= Somewhat agree 3= Neither agree or disagree
2= Somewhat disagree 1= Strongly disagree

Pharmacogenomics. 2018 Mar;19(4):321-331. doi: 10.2217/pgs-2017-0191.

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Provider Study

Value and Utility

- Aide to individualize treatment
- Aide to guide mutual medical decision-making
- Increased patient satisfaction and other psychological benefits

Challenges

- Communicating results
- Cost
- Time constraints

Per Med. 2017 Sep;14(5):389-400.

SYSTEM BUILDING

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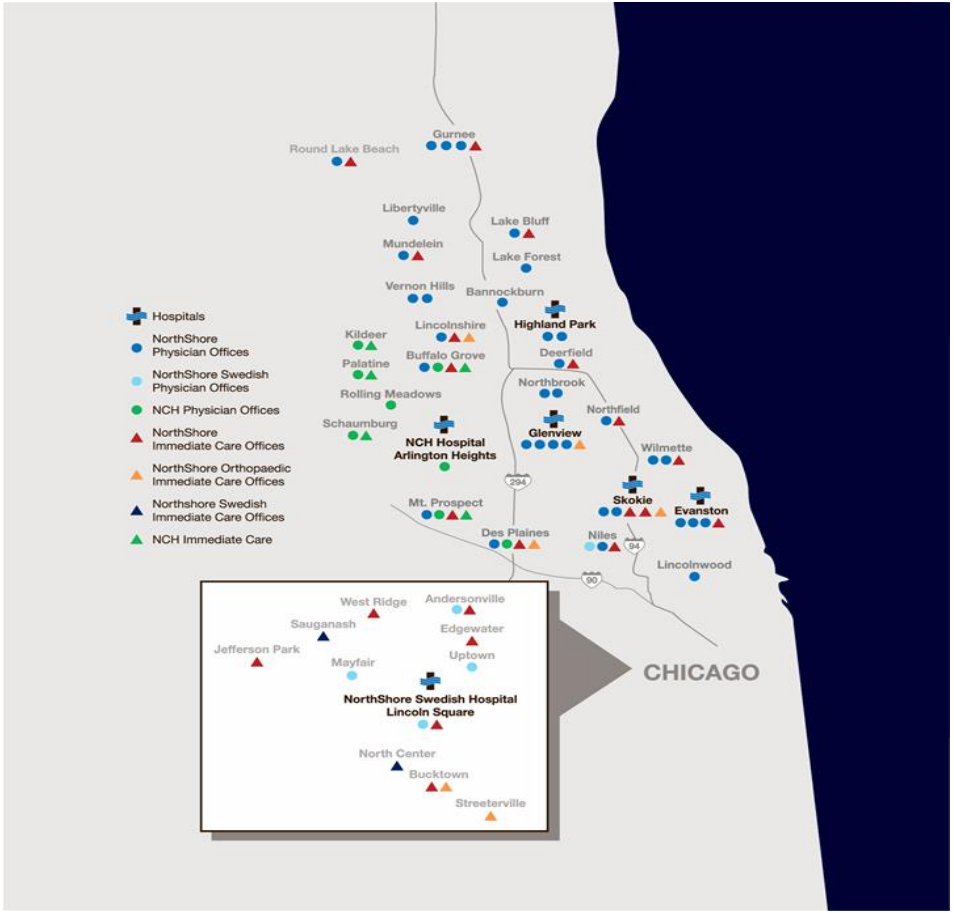
NorthShore University HealthSystem

- Medical Group
  - 1000 + medical group physicians
  - 100+ offices
  - 5 hospitals (adding 6th)
- 42,000 admissions/year
- 120,000 ER visits/year
- Integrated EHR since the early 00s



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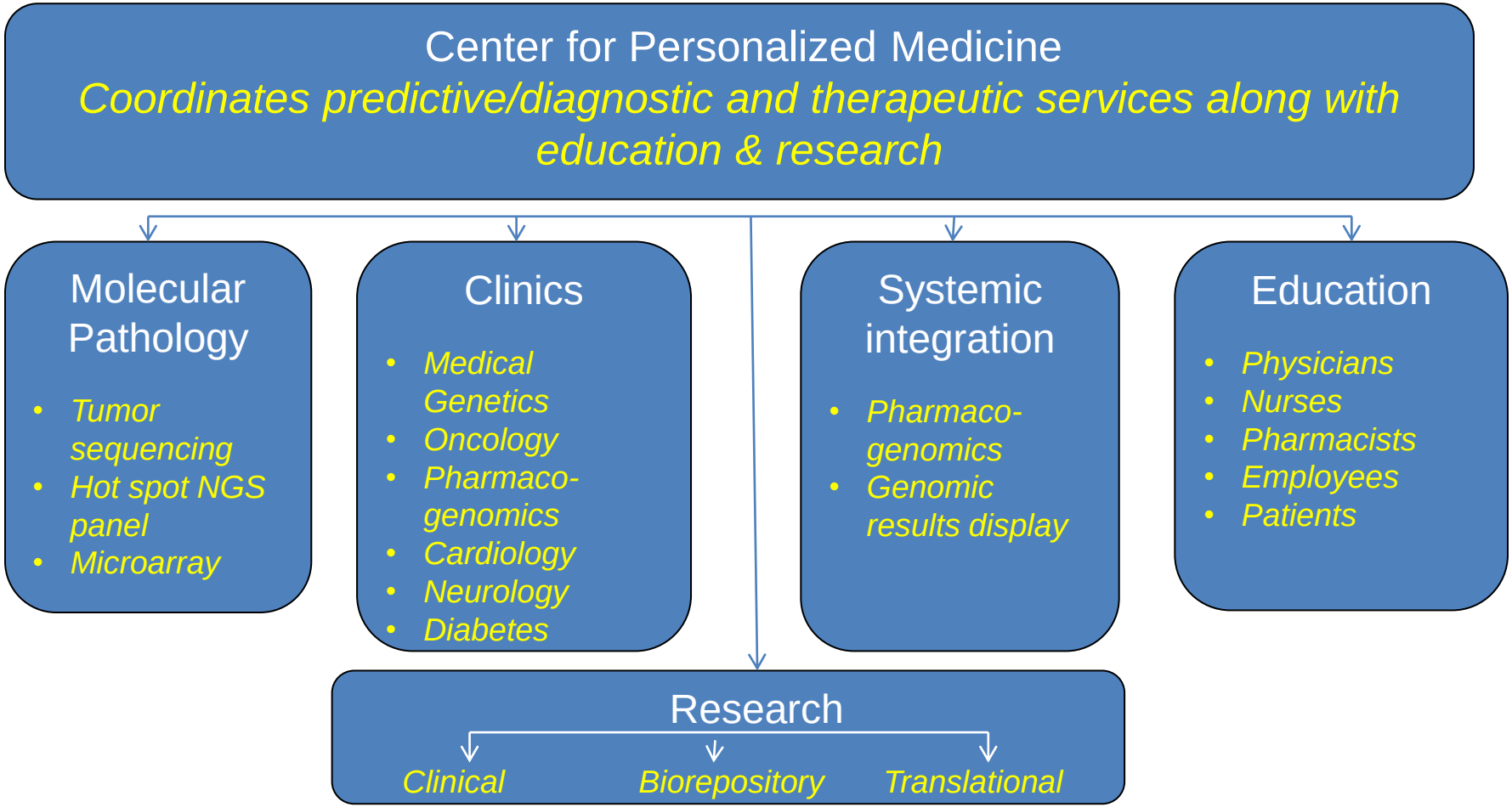
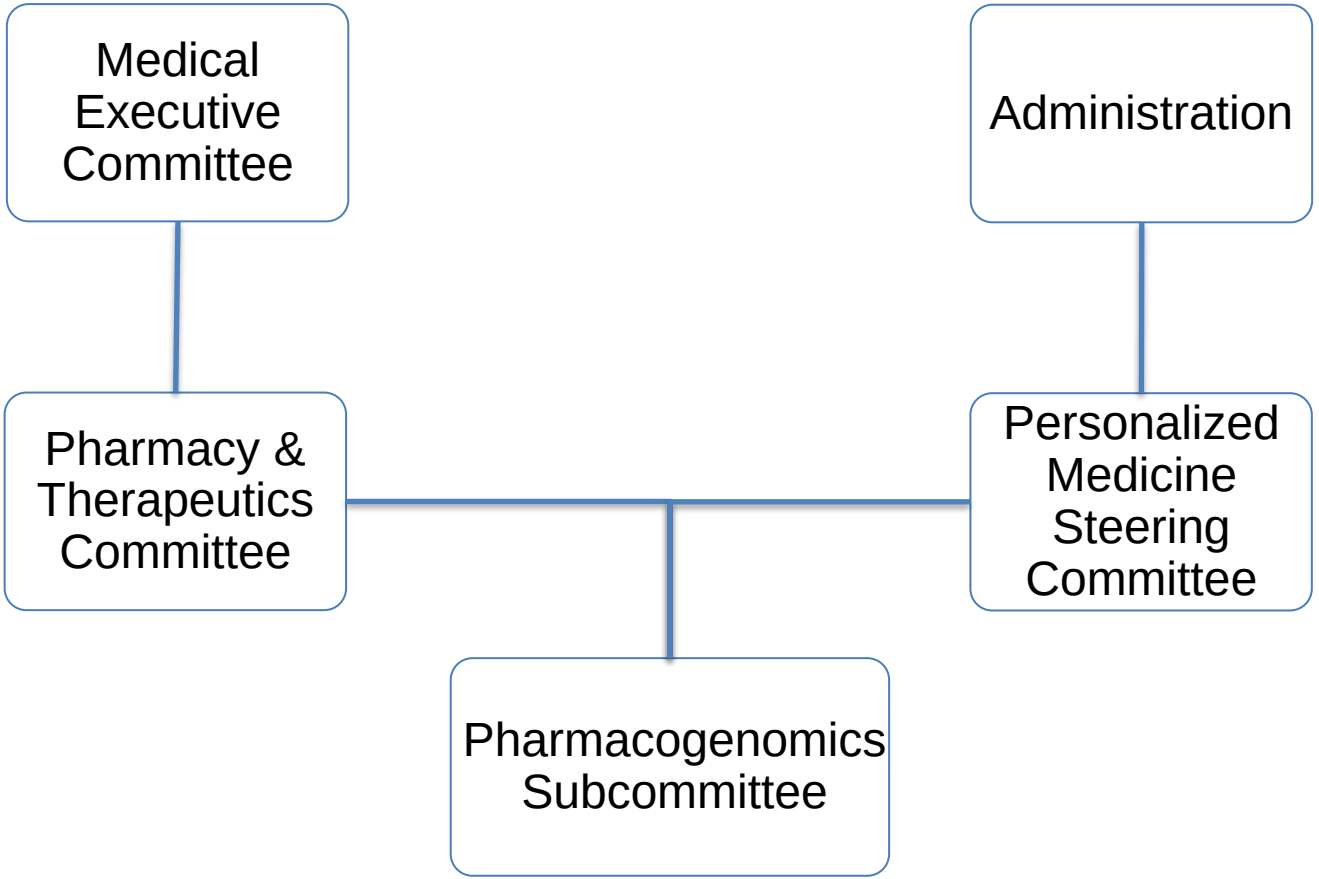
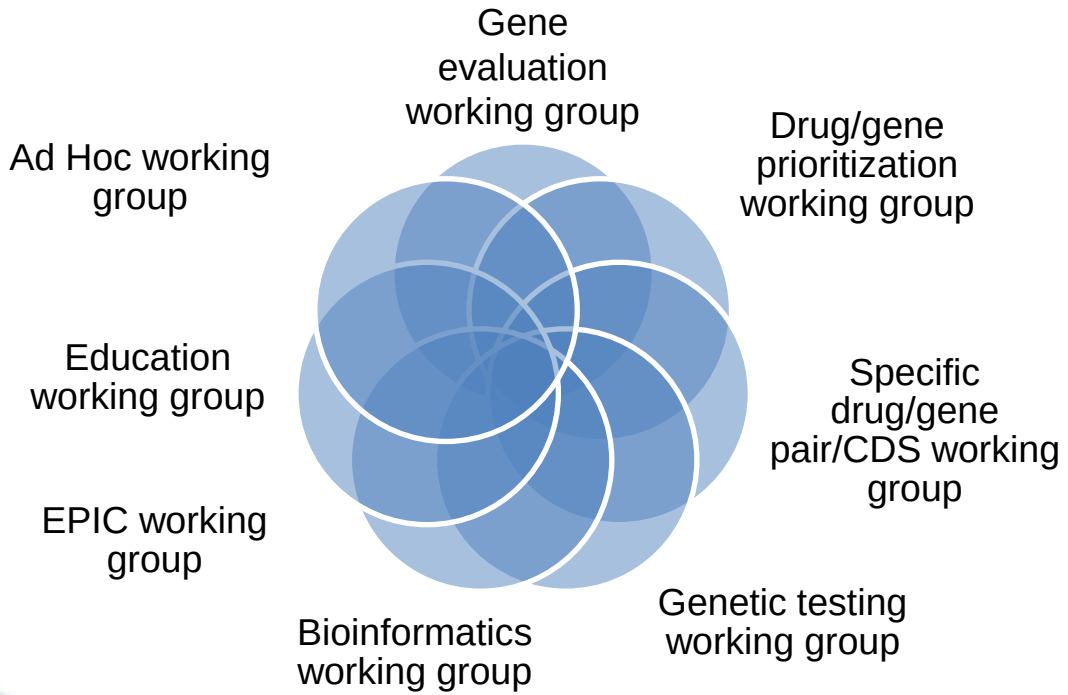

Center for Personalized Medicine
Coordinates predictive/diagnostic and therapeutic services along with education & research
Molecular Pathology
Tumor sequencing
Hot spot NGS panel
Microarray
Clinics
Medical Genetics
Oncology
Pharmaco-genomics
Cardiology
Neurology
Diabetes
Systemic integration
Pharmaco-genomics
Genomic results display
Education
Physicians
Nurses
Pharmacists
Employees
Patients
Research
Clinical
Biorepository
Translational

Governance Structure



NorthShore's Pharmacogenomics Subcommittee



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Key Players

Stakeholders

- Administrators
- Clinical leadership
- Providers
- Patients

Personnel

- Program Leader
- Physician Champions
- Laboratory Specialists
- Informaticians
- Educators
- Patients

Clin Transl Sci. 2016 May 23. doi: 10.1111/cts.12404

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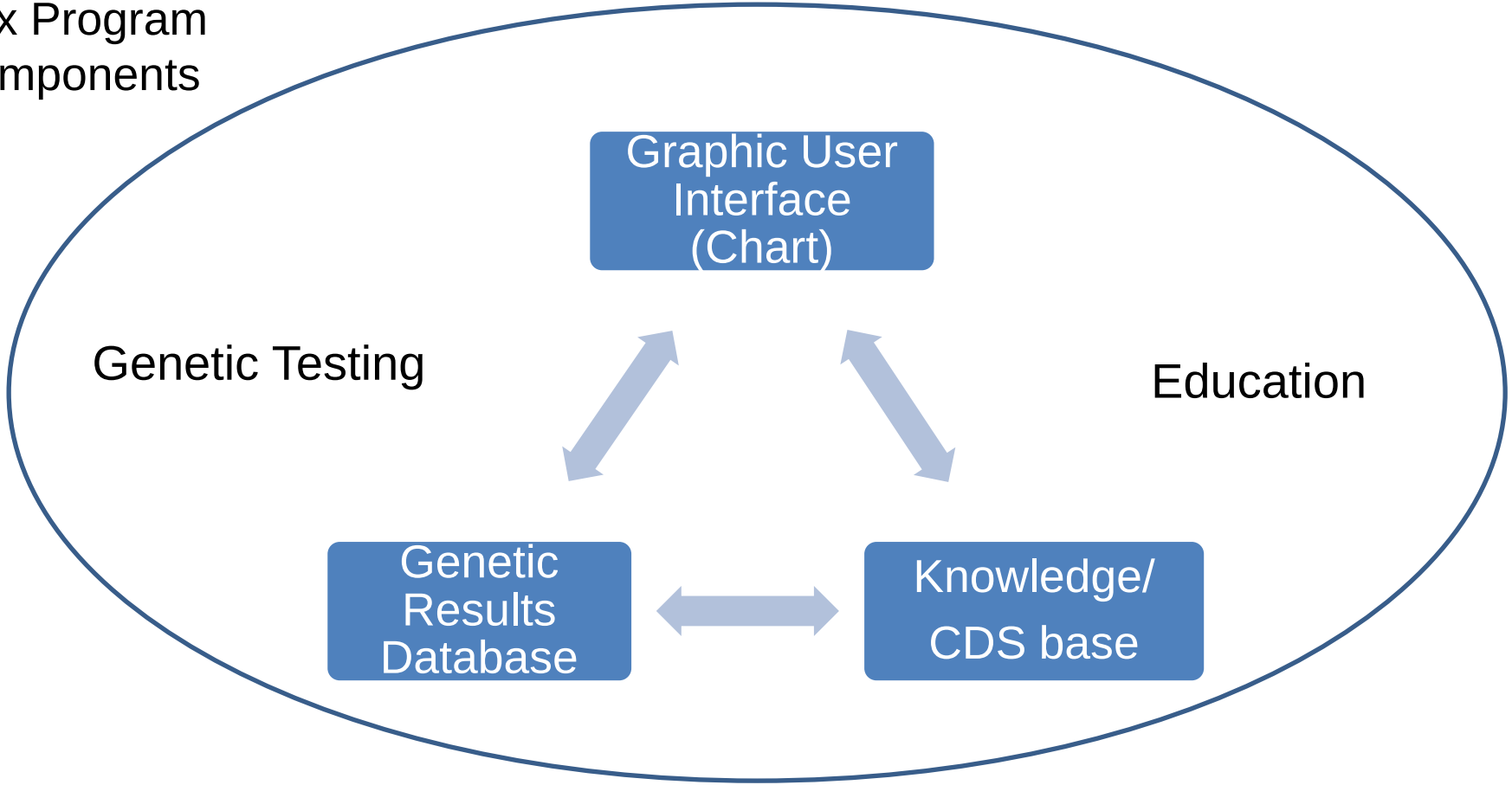
Pharmacogenomics Team at NorthShore

Physician	Pharmacist	Pathologist	Administrator	Physician
Pharmacist	Bioinformatician	Physician	Physician	Physician
Administrator	Bioinformatician	Pharmacist	Pathologist	Pharmacist
Pharmacist	Physician	Physician	HIT	Pharmacist
Laboratory HIT	Pharmacist	Genetic Counselor	Nurse	Pharmacist
HIT	Pathologist	Genetic Counselor	Pharmacist	

Pgx Program Components



Need discrete, standardized data as a foundation for CDS!

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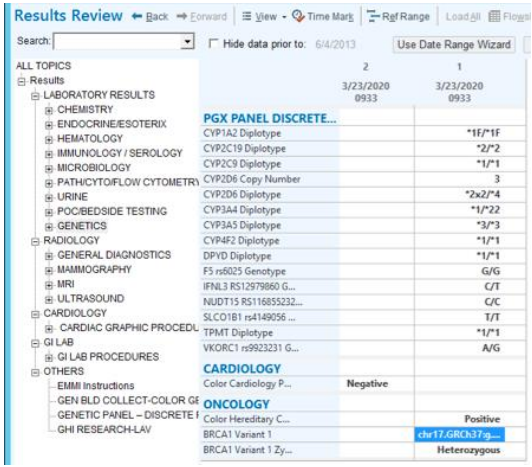
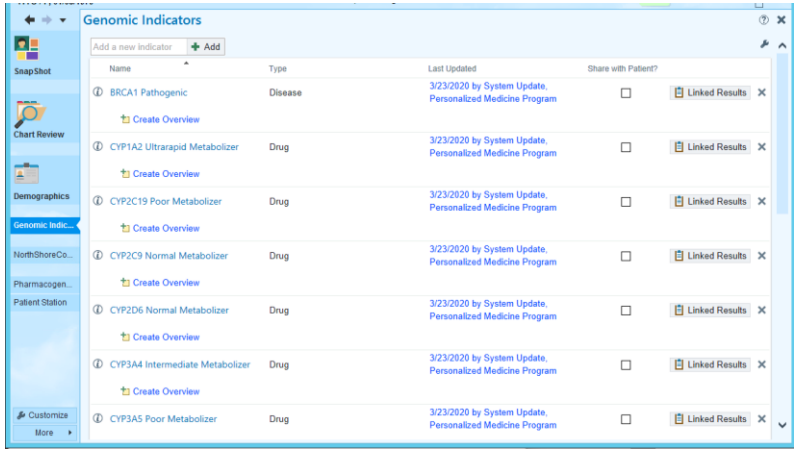
Current state of genetic data in the EHR

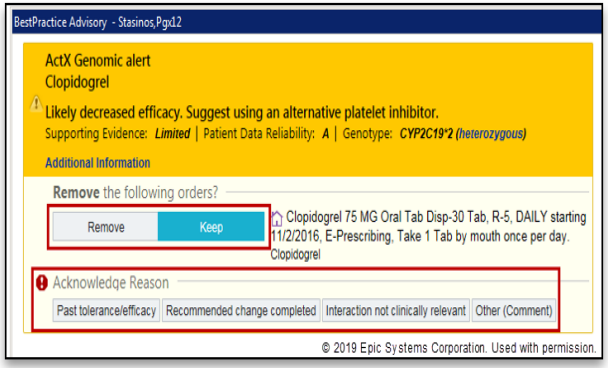


Order and results interface for multiple genetic testing labs includes discrete results, PDF, and clinical notes



+150,000 phenotypes on +11,000 patients

CDS based on discrete results and GIs including PGx BPA supporting 20 genes and 70 drugs



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Educational Content

Clinical knowledge

- Why is Pgx important
- Drug/gene pairs
- Testing interpretation
- Ethical, legal, and social issues

Operational knowledge

- How to use the CDS tools

OCHSNER PHARMACOGENOMICS PROGRAM

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Ochsner Pharmacogenomics (PGx) Program

Goal:

- To provide patients with another access point to personalized medicine using genetic testing to optimize their medications in terms of drug selection, dose, and regimen.

Infrastructure:

- PGx testing platform: ActX-affiliated lab transitioning to another lab early 2022

- Epic genomic indicator activity for recording phenotype and genotype results
- Best practice advisories (BPAs) built for high-value PGx interactions
- Act-X software platform integrated into EPIC to provide clinical decision support (CDS)

- Consultant PGx subject matter expert, Jan 2021 through October 2021
- In-house clinical PGx pharmacist and consult service, Jan 2021
- IS/IT staff: clinical decision support builds and Epic expertise

Ochsner Pharmacogenomics (PGx) Program

Oncology Pilot (5/10/2021)

- Test 250 consented outpatients interested in/suitable for PGx testing
- Exclude patients with
  - allogeneic bone marrow or liver transplant
  - recent whole blood transfusion
  - absolute neutrophil count = 0
  - life expectancy of <6 months
- Original population: patients w/ advanced (Stage 3+) colorectal cancer or head & neck cancers
- Expanded population: patients w/ any cancer treated by participating oncologists
- Participating providers: 9 original MDs/2 CNPs, expanded to 16 providers [10/8/2021]
- DNA from blood, send-out lab, 4 to 6 week turn-around
- Focus on CPIC drug-gene pairs / FDA PGx-actionable drugs

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Genetic Results

Gene	Medications Affected	Poor Metabolizer	Intermediate Metabolizer	Genotype Not Reported
DPYD	5-FU and Capecitabine	0	3*	97
UGT1A1	Irinotecan	16*	45	39
TPMT	Thiopurines	1*	12*	87
NUDT15	Thiopurines	0	1*	99

*Potential opportunity to dose modify to reduce risk of severe AEs.

DPYD CASE REVIEW: Jan 2020 – May 2021

- Identified 11 cancer patients positive for DPYD genetic variants
- Treated with or scheduled to receive capecitabine or fluorouracil
- All at risk for severe adverse reactions
  - 2 urgent-care visits
  - 7 ED visits
  - 5 admissions = 83 hospital days
    - Renal failure
    - Severe neutropenia
    - Fungemia
  - Delays in treatment, changes in treatment
- Pre-emptive pharmacogenomics testing could have avoided many (all) of these complications.

Conclusion

Now is the right time to bring PGx to the frontlines of care

Start with manageable projects based on your resources

Collaboration is key

Pharmacists are well suited to drive the clinical value of pharmacogenomics

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