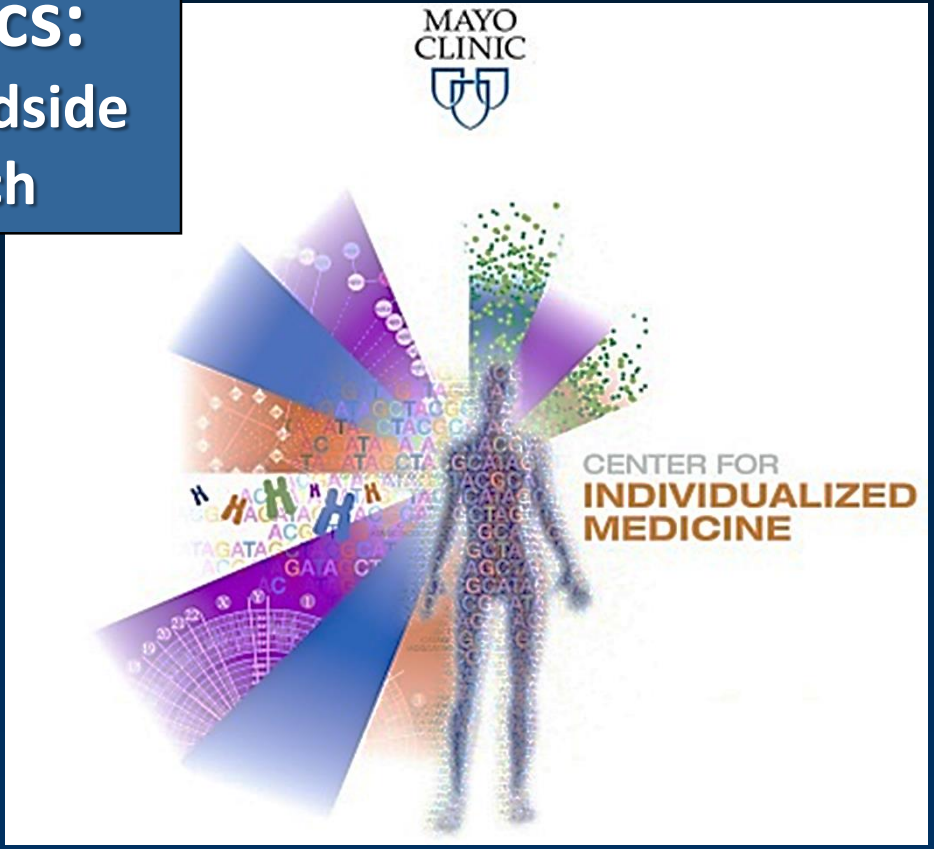
Pharmacogenomics:
Implementation at the Bedside
A Team Based Approach



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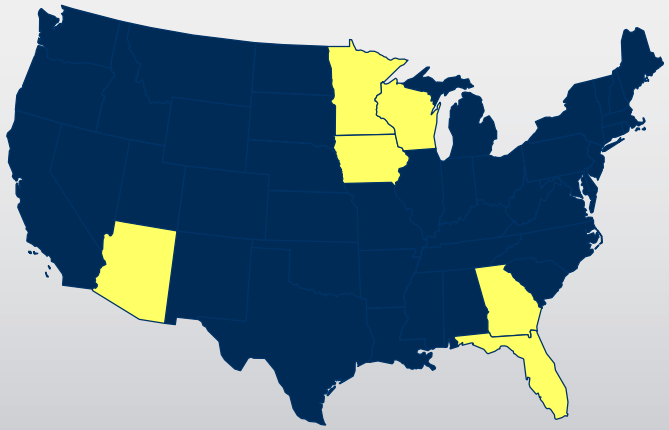
Objectives

- Describe implementation of bedside pharmacogenomics at the Mayo Clinic.
- Define modalities to provide prescribers pharmacogenomics information at the bedside.
- Briefly discuss current and future PGx state at Mayo Clinic.

After 150 years...



5 SCHOOLS

6 STATES

2,580 RESIDENTS & FELLOWS

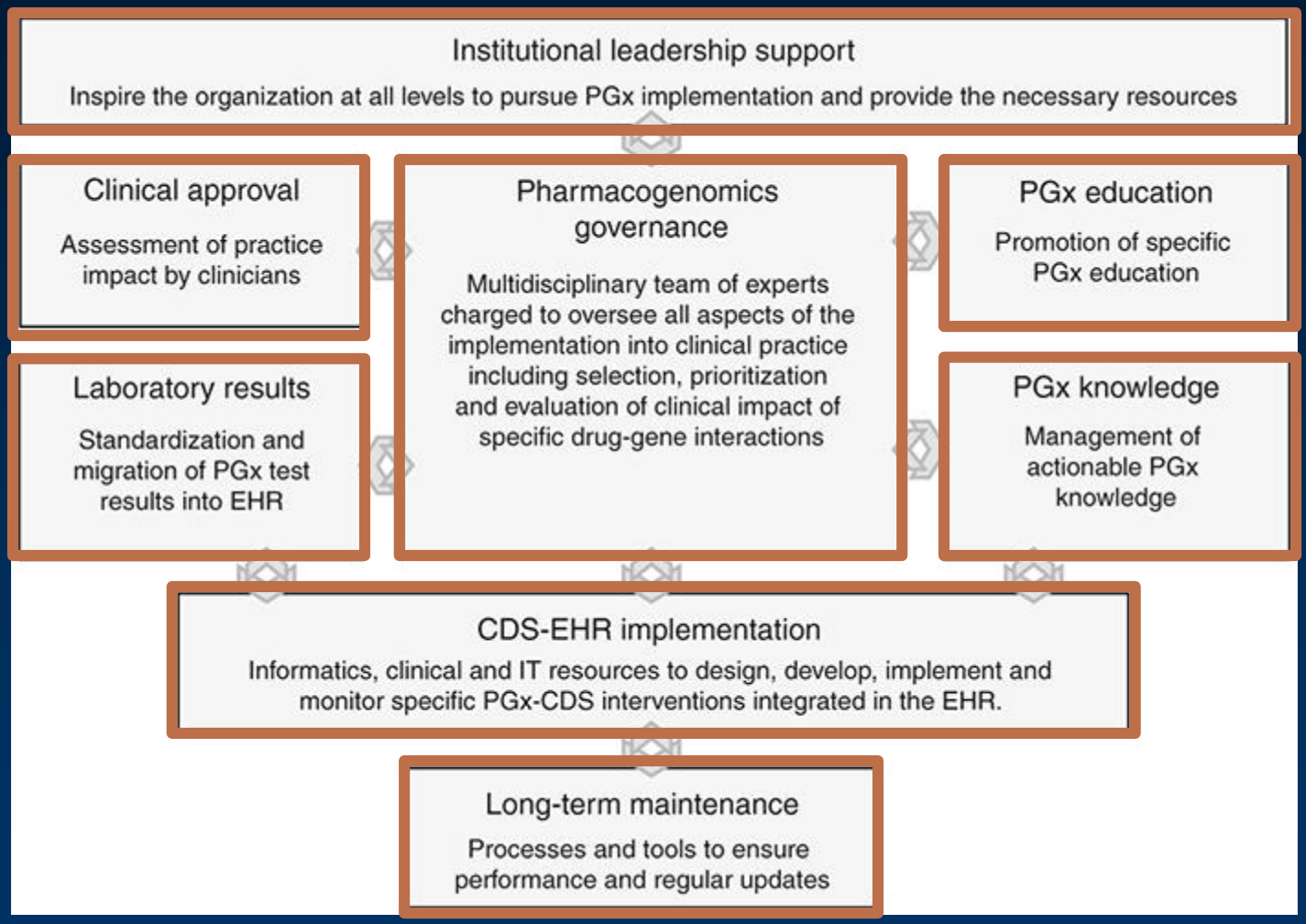
4,100 STAFF PHYSICIANS & SCIENTISTS

60,000 EMPLOYEES

1.3 million PATIENTS

from every state and 144 countries

Mayo's model for PGx Operations



How are results reported and interpreted?

For example CYP2D6 :

Ultra-rapid metabolizer. Greatly increased activity accelerating clearance or activation
Extensive (Normal) metabolizer. The norm.
Intermediate metabolizer. Heterozygotes for normal and reduced activity genes.
Poor metabolizer, absent or greatly reduced ability to clear or activate drugs.

Associated Phenotypes

Mayo Clinic for CYP 2D6

- Ultra-rapid
  - Extensive to Ultra-rapid
- Extensive – (normal)
  - Intermediate-Ultra-rapid
  - Intermediate to Extensive
- Intermediate
  - Poor to Intermediate
- Poor

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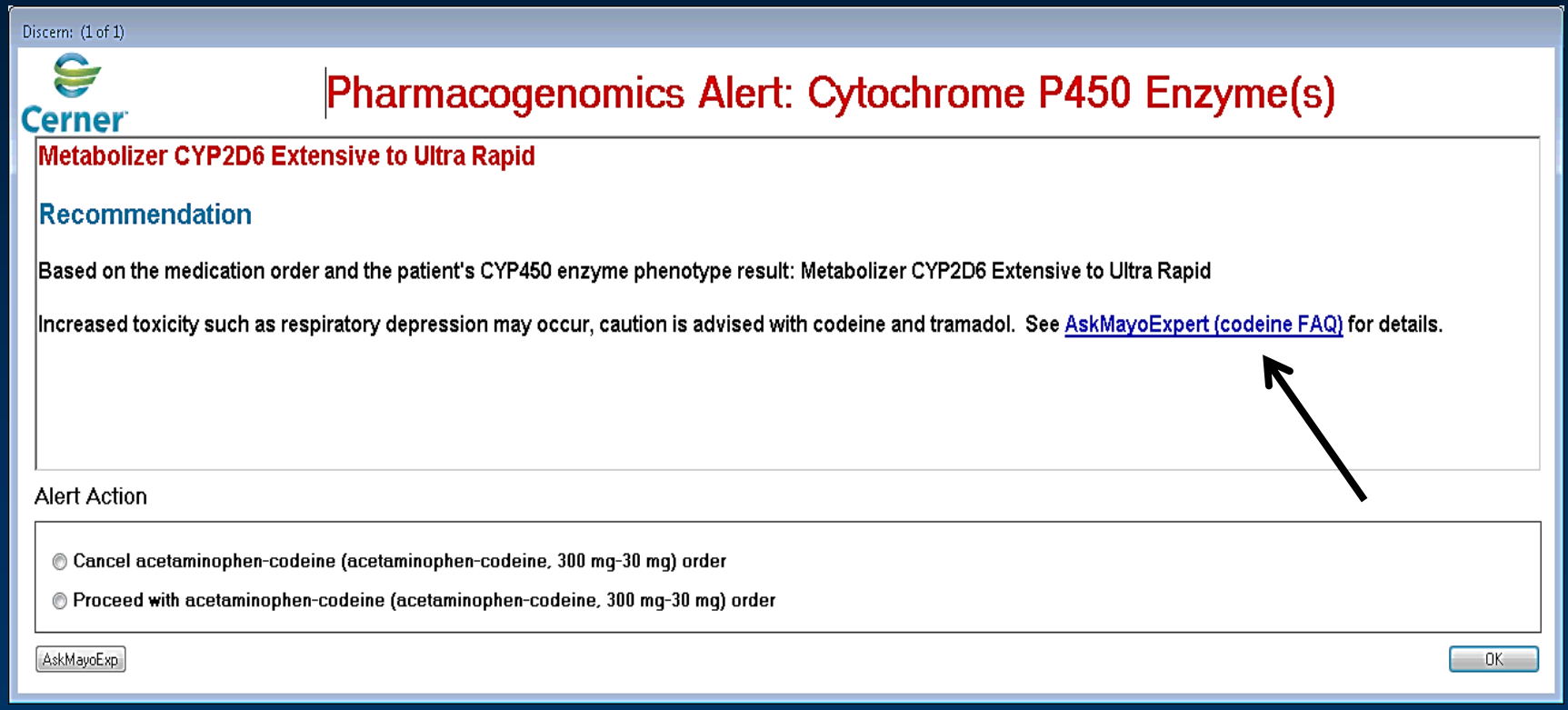
Table 2 Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

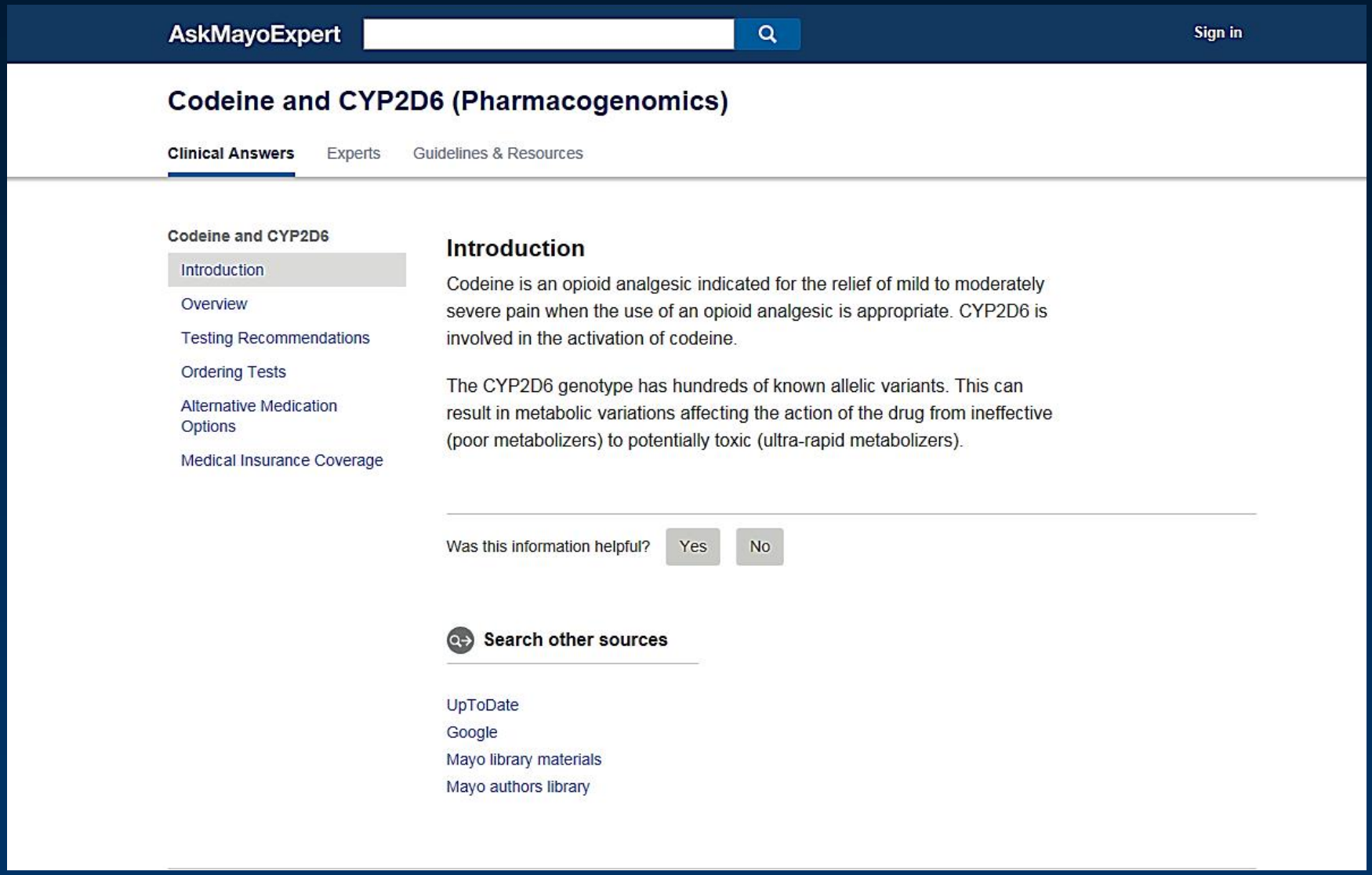
Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]	Considerations for alternative opioids
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[b,c]
Extensive metabolizer	Normal morphine formation	Use label-recommended age- or weight-specific dosing.	Strong	—
Intermediate metabolizer	Reduced morphine formation	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Moderate	Monitor tramadol use for response.
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.[b,c]

Crews KR. etal 2014 CPIC update CYP2D6 Codeine

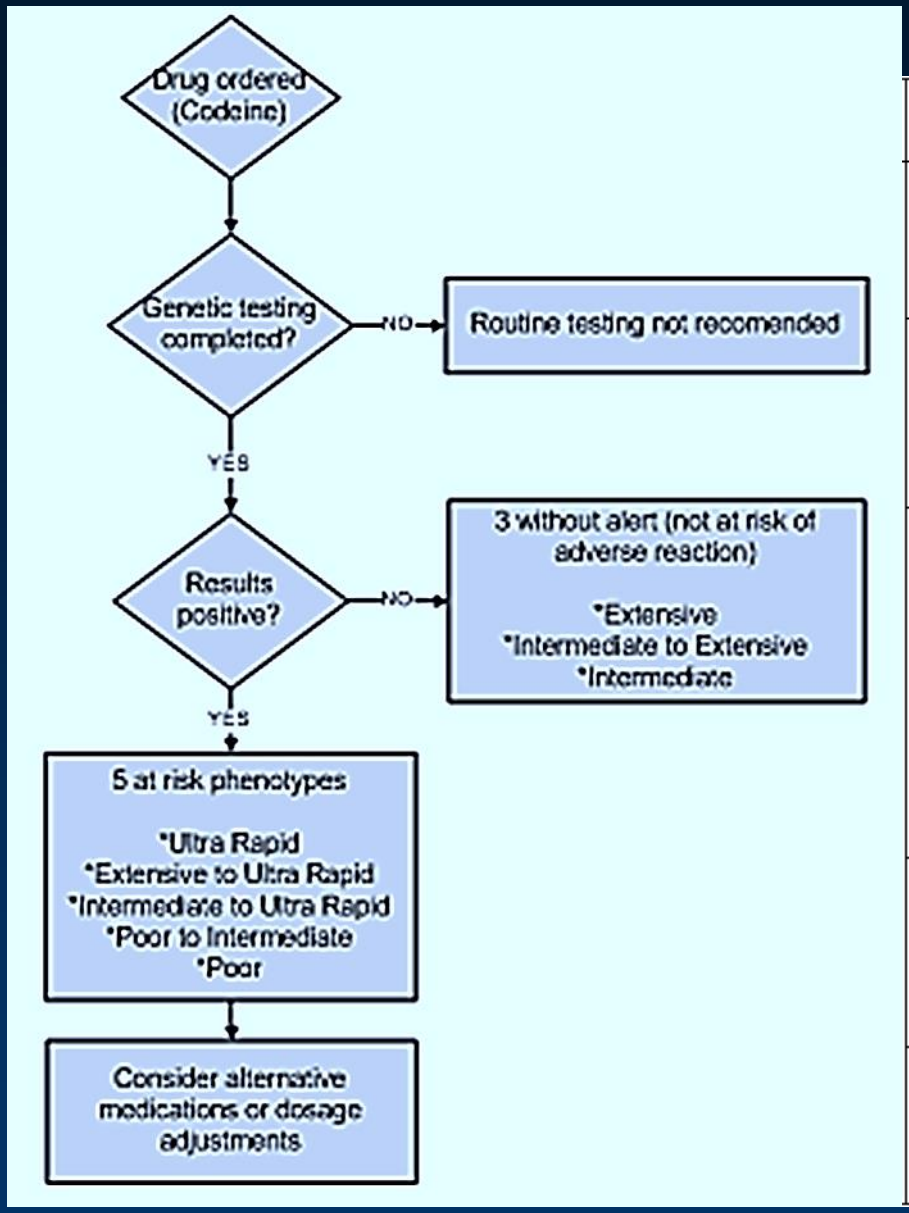
Electronic Order Support



AskMayoExpert (AME)



AME Recommendations

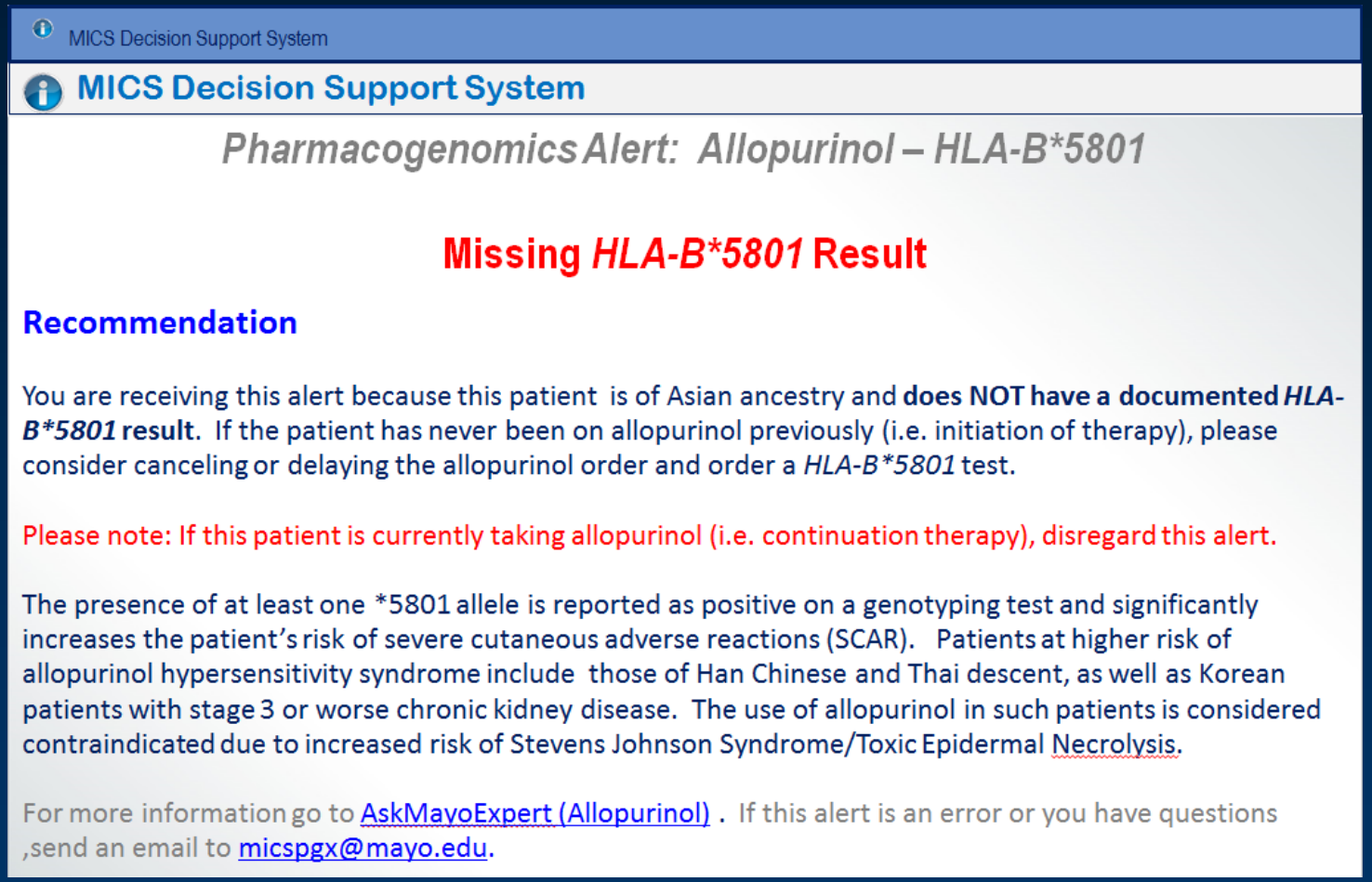


CYP2D6 Test Result	Recommendations
Metabolizer CYP2D6 Ultra Rapid	Avoid codeine due to potential for toxicity. May consider avoiding tramadol
Metabolizer CYP2D6 Extensive to Ultra Rapid	Increased toxicity such as respiratory depression may occur; caution is advised with codeine and tramadol.
Metabolizer CYP2D6 Intermediate to Ultra Rapid	Reduced efficacy may occur if an intermediate metabolizer, or risk of toxicity may occur if an ultra rapid metabolizer. Caution is advised and an alternative medication other than codeine or tramadol might be considered.
Metabolizer CYP2D6 Poor to Intermediate	Efficacy may be reduced for codeine and tramadol. Other treatments should be considered
Metabolizer CYP2D6 Poor	Avoid codeine due to lack of efficacy. May consider avoiding tramadol

Allopurinol

- Drug: Allopurinol is indicated for the therapy of gout and conditions of elevated urinary uric acid levels.
- Problem: Risk of developing Stevens-Johnson syndrome or toxic epidermal necrolysis risk largest in Asian population.

Electronic Order Support



MICS Decision Support System

MICS Decision Support System

*Pharmacogenomics Alert: Allopurinol – HLA-B*5801*

Missing *HLA-B*5801* Result

Recommendation

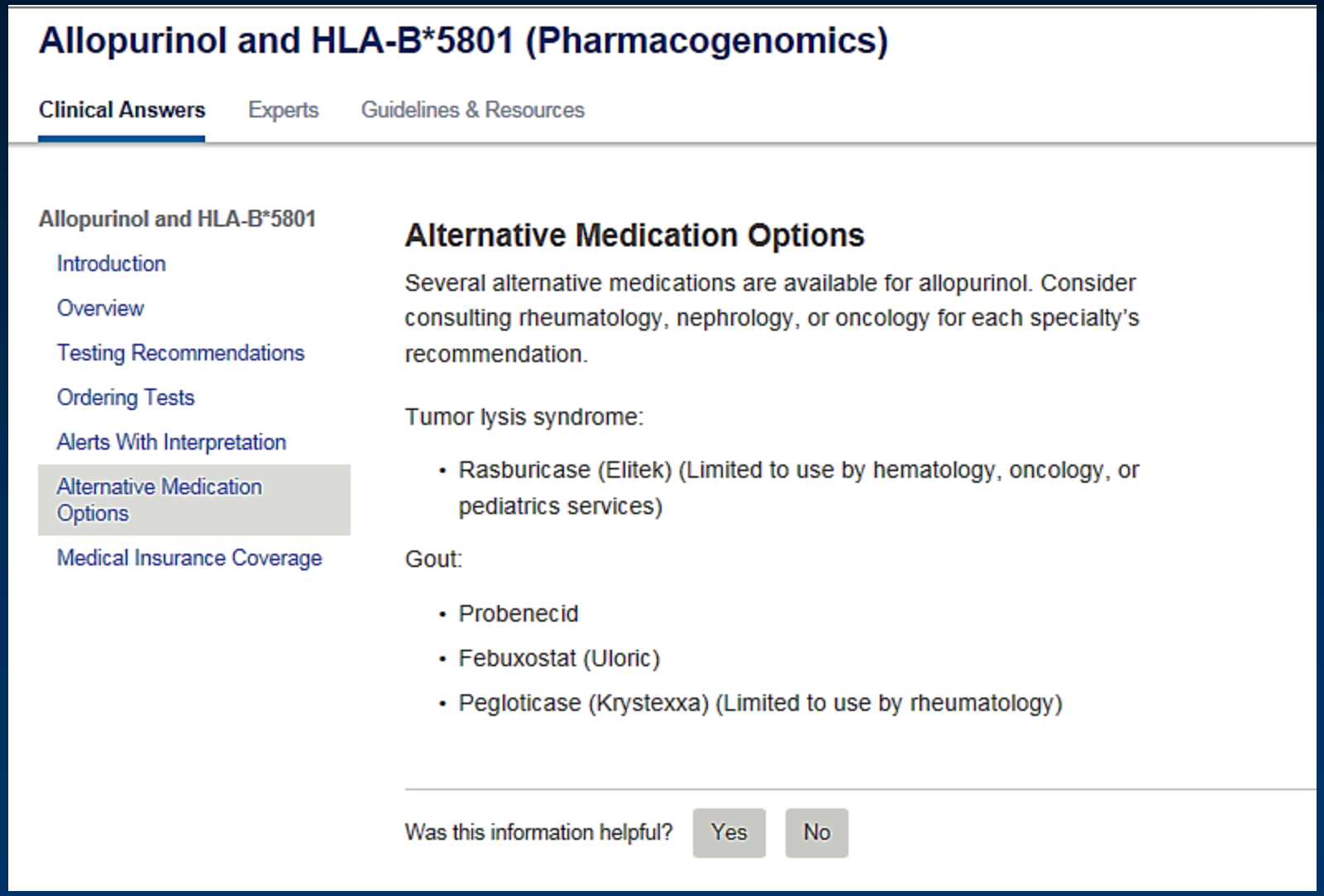
You are receiving this alert because this patient is of Asian ancestry and **does NOT have a documented *HLA-B*5801* result**. If the patient has never been on allopurinol previously (i.e. initiation of therapy), please consider canceling or delaying the allopurinol order and order a *HLA-B*5801* test.

Please note: If this patient is currently taking allopurinol (i.e. continuation therapy), disregard this alert.

The presence of at least one *5801 allele is reported as positive on a genotyping test and significantly increases the patient's risk of severe cutaneous adverse reactions (SCAR). Patients at higher risk of allopurinol hypersensitivity syndrome include those of Han Chinese and Thai descent, as well as Korean patients with stage 3 or worse chronic kidney disease. The use of allopurinol in such patients is considered contraindicated due to increased risk of Stevens Johnson Syndrome/Toxic Epidermal Necrolysis.

For more information go to AskMayoExpert (Allopurinol) . If this alert is an error or you have questions ,send an email to micspgx@mayo.edu.

Alternatives



Current Drug Gene Pairs at Mayo

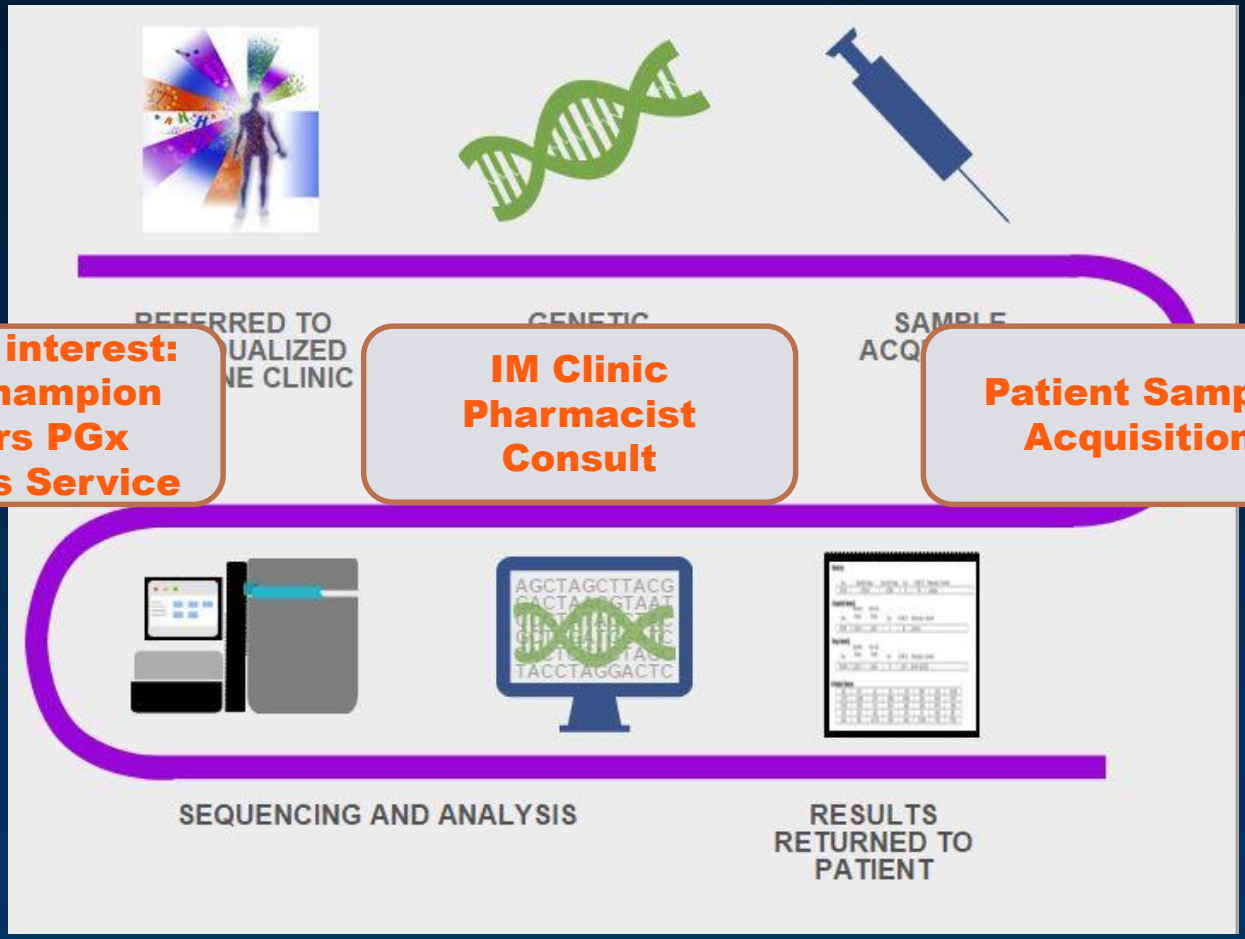
- Carbamazepine - HLA-B*5702
- Abacavir - HLA-B*1502
- Allopurinol - HLA-B*5801
- Codeine - CYP2D6
- Tramadol - CYP2D6
- Tamoxifen - CYP2D6
- Fluoxetine, Paroxetine, Fluvoxamine - CYP2D6
- Venlafaxine - CYP2D6
- Clopidogrel - CYP2C19
- Citalopram, Escitalopram - CYP2C19
- Warfarin - CYP 2C9/VKORC1
- Thiopurine -TPMT
- Simvastatin - SLCO1B1

It takes a village

Building Blocks

- Institutional support
  - Center of Individualized Medicine
- Agreement with Practice
  - PGx Committee
  - Pharmacy and Therapeutics
- IT Infrastructure
  - Programming ability
- Education

Basic Flow- PGx Profile Service



Patient interest: CIM Champion orders PGx Express Service

IM Clinic Pharmacist Consult

Patient Sample Acquisition

Mayo Lab Sequencing, Analysis and Results: EMR Result and OneOme Report in patient record

Results Returned to Patient by Pharmacist

Patient Case

Initial Presentation:

- 18 year old female
- History of depression, suicide attempts and cutting
- Consumes 7 vodka shots 4x/week, smokes marijuana to sleep
- Hx of medication intolerance

Medications:

- Current: multivitamin and Vitamin D3
- PMH: Escitalopram, sertraline, fluoxetine, bupropion, duloxetin

Side Effects:

- Worsened depression, dilation of eyes and tremors

Action:

- After medication reconciliation performed, 9-gene pharmacogenomics panel ordered

Patient case: Genetic Test Results

Gene (Metabolizing Enzyme)	Genotype	Phenotype
CYP2D6	***4/*9**	**Poor to Intermediate**
SLCO1B1	***1/*5**	**Increased Risk**
HLA-B*5801	Negative	Normal Risk
CYP1A2	Multiple Variations	Extensive
CYP2C9	*1/*1	Extensive
CYP2C19	*1/*2	Intermediate
VKORC1	-1639 GG	Normal Sensitivity
CYP3A4	*1/*1	Extensive
CYP3A5	*3/*3	Poor (Normal)

Patient Case: Drug-Gene Interactions

medication Hx	Metabolizing Enzyme	Phenotype
escitalopram	CYP2D6, CYP2C19	Poor to Intermediate, Intermediate
fluoxetine	CYP2D6	Poor to Intermediate
duloxetine	CYP2D6, CYP1A2	Poor to Intermediate, Extensive
sertraline	CYP2C19, many others	Intermediate
cefuroxime	none	n/a
cyclafem	CYP3A4, CYP1A2	Extensive, Extensive
bupropion	CYP2B6, CYP2D6	Not tested, poor to intermediate

Patient case: Recommendations

- **Desvenlafaxine 50 mg daily**
  - Is active metabolite of venlafaxine (CYP2D6 substrate)

- **6 month follow-up:**
  - Improvement in symptoms and no side effects
  - Buspirone (CYP3A4 substrate) recommended for mood management

The Year of PGx: 2017

- Expand PGx Panel Options
- Expand PGx Pharmacist team
- PGx Certification Program

22 GENE PANEL COVERING MORE THAN 240 DRUGS

GENE	ALLELES	GENE	ALLELES
CYP1A2	1D, 1F, 1J, 1K, 1L, 1W	F5	1691G>A
CYP2B6	*3, *4, *5, *6, *18	OPRM1	118A>G
CYP2C19	*2, *3, *4, *4B, *10, *17, *18	COMT	322G>A (Val158Met)
CYP2C9	*2, *3, *4, *5, *6, *8, *11, *18	DRD2	939A>G, -241A>G,
CYP2D6	*2A, *2, *3, *4, *4N, *4M, *5, *6, *7, *9, *10, *11, *12, *13, *14, *15, *17, *18, *20, *21, *29, *31, *35, *36, *41, *42, *58, *63, *64, *68, *69, *70, *91, *109	HTR2C	-759C>T
CYP3A4	*1B, *22	HTR2A	IN2T>C, 1354C>T, 102T>C, -1438G>A
CYP3A5	*3, *6, *7	DPYD	*2A, *13, 97547947T>A
SLCO1B1	*5, *17	TPMT	*2, *3A, *3B, *3C, *4
UGT1A1	TA6, TA7	GRIK4	120663363T>C
VKORC1	-1639G>A		
F2	2021G>A	SLC6A4	La/Lg/S
IL28B	39248147C>T		

Future

- In collaboration with Baylor use the PGRN-Seq Ver 3 panel and the Illumina HiSeq platform to sequence 76 pharmacogenes from 10,000 of Biobank patients who receive all of their healthcare at Mayo Rochester.
- Genotype results from a subset of the pharmacogenes will be prospectively placed into the EHR
- An interpretive report will be placed into the patient's medical record.
- With the specific genotypes loaded into the EHR for 10,000 patients, we can systematically evaluate the clinical and fiscal impact of pre-emptively firing the drug-gene pair CDS alerts already in the Mayo Clinic EHR.

Thank you!


Mayo Clinic in Minnesota
MAYO CLINIC
Mayo Clinic in Arizona
Mayo Clinic in Florida

Questions?