Using Pharmacogenomics in Practice:

A Step-by-Step Guide

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Learning Objectives

1. Identify instances when the use of pharmacogenomic information should be considered to improve prescribing and patient outcomes

2. Using online evidence-based guidelines like CPIC and PharmGKB, discuss if actionable variants exist for medications, determine which tests should be ordered, and interpret the results.

3. Explain the rationale for pharmacogenetic testing to improve the likelihood and streamline the process of prior authorization.

MY Goal for Everyone

That you will be able to return to your practice next week and be able to order Pharmacogenetic (PGx) testing on a commonly prescribed drug.

With only 30 minutes available, the presentation will be focused more on practical instruction than concepts.

I will present our case, go over a few key principles and then walk through the case.

The Case

Your patient is a 52-year-old man who never comes in for routine care. He had a health screening at work and was told his cholesterol was very high. He reluctantly makes an appointment to discuss it. PMH negative except for appendectomy at age 12. He hasn't seen a doctor "in years." Medications: None. OTC/Supplements: None. FH: Father had an MI at age 45 and is living after CABG in his late 40s and 2 subsequent stents. Does not have a lot of contact with him. He thinks his paternal aunt may also have had some sort of "heart problem."

The Case

SH: Married. Works as a landscaper. 1 PPD smoker. 3-4 beers on Friday and Saturday night. Lives with wife and teenage son and daughter.

ROS: Gets a little winded raking and shoveling and walking up long inclines. Otherwise, negative.

PE: 69 inches. 192 lbs. BMI 28.4. BP 142/86. P 80. Resp. easy. O2 sat 96%. Positive for thick arcus cornealis. Normal cardiopulmonary exam. Carotids 2+ w/o bruits. DP and PT 1+ bilaterally with a hint of dependent rubor.

The Case

Fasting labs ordered. Fasting CBC w/ diff. Lipid profile. CMP.

Significant for:

Glucose	112
Lipids	
Total Cholesterol	303
TG	218
HDL	45
calc LDL	214
ALT	60 (ULN 35)

The Case

He returns to discuss his labs. He leads off by saying he does not want to be on one of those cholesterol medications. A couple guys at work were put on them by their doctor (One of them is your patient.), and they felt terrible. He has heard they make you achy, and he is already sore enough. And he doesn't want to give up his morning grapefruit juice. His 17-year-old daughter went on the internet after his health screen at work and told him he needed to get genetic testing. She helped him get 23AndMe testing, which he brings along. SLCO1B1 with decreased or poor function. What are your next steps?

Principles and Concepts

PGx at this point mostly involves drug metabolism (pharmacokinetics) and not disease-drug matching (pharmacodynamics-receptor affinity and other factors).

Drug-drug interactions also affect drug metabolism (sometimes referred to as phenoconversion) and this needs to be taken into account when applying PGx information.

Principles and Concepts

When applying genetic effects on drug metabolism it is important to distinguish metabolism of active drug to inactive metabolite from metabolism of inactive pro-drug to active metabolite.

Examples: statin➔inactive form. Poor metabolizers have elevated serum concentrations with more myopathy, and rapid metabolizers have decreased drug level and clinical effect.

Codeine/Tramadol➔active form. Poor metabolizers have reduced effectiveness, and rapid metabolizers have a risk of overdose and side effects.

Principles and Concepts

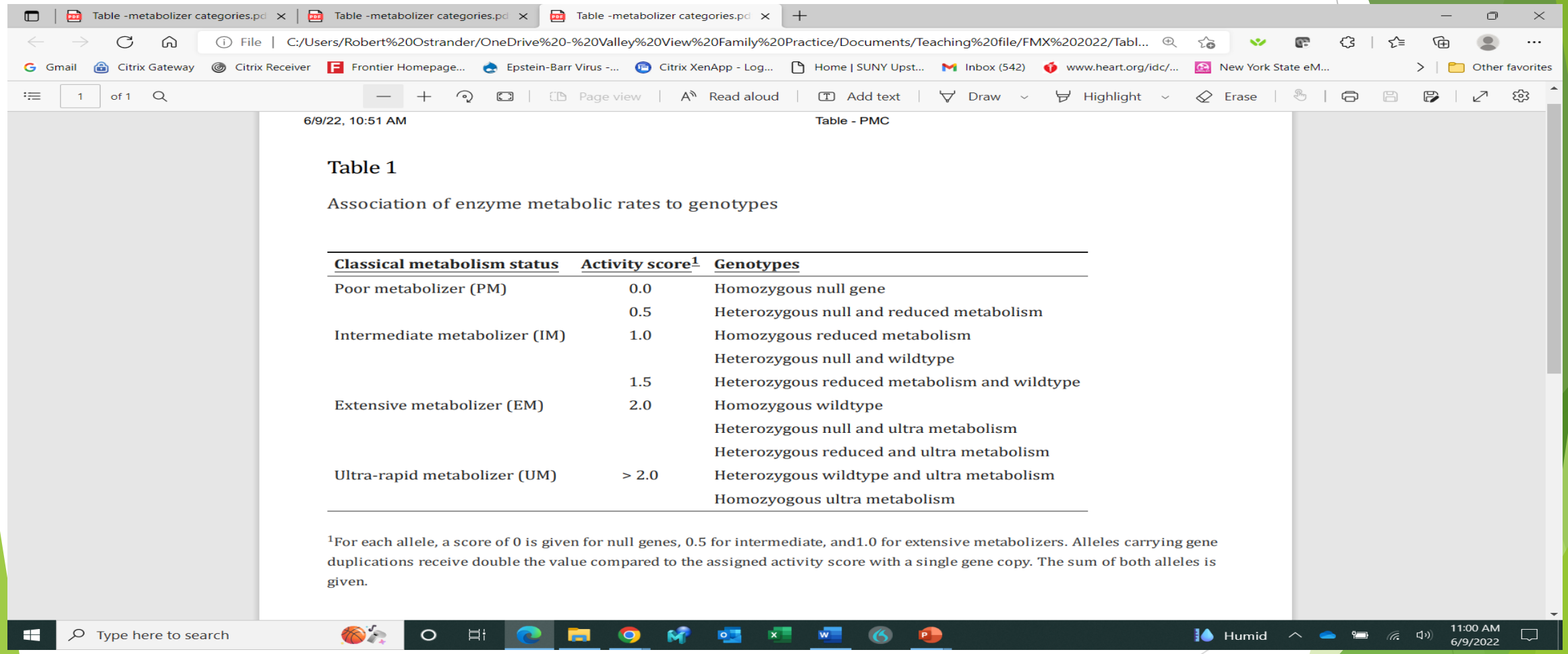


Table 1

Association of enzyme metabolic rates to genotypes

Classical metabolism status	Activity score[1]	Genotypes
Poor metabolizer (PM)	0.0	Homozygous null gene
	0.5	Heterozygous null and reduced metabolism
Intermediate metabolizer (IM)	1.0	Homozygous reduced metabolism
		Heterozygous null and wildtype
	1.5	Heterozygous reduced metabolism and wildtype
Extensive metabolizer (EM)	2.0	Homozygous wildtype
		Heterozygous null and ultra metabolism
		Heterozygous reduced and ultra metabolism
Ultra-rapid metabolizer (UM)	> 2.0	Heterozygous wildtype and ultra metabolism
		Homozyogous ultra metabolism

[1]For each allele, a score of 0 is given for null genes, 0.5 for intermediate, and1.0 for extensive metabolizers. Alleles carrying gene duplications receive double the value compared to the assigned activity score with a single gene copy. The sum of both alleles is given.

Principles and Concepts

Although there are guidelines about how to apply PGx information, there are few guidelines about when to order it.

- Limitations in the design of published pharmacogenetic studies (in particular, the lack of prospective randomized trials demonstrating improved clinical outcomes when drug therapy or specific dose is selected on the basis of genotype)
- Regulatory and ethical concerns
- Lack of cost effectiveness analyses
- Limitations in the number of available pharmacogenetic tests and lack of guidelines for test implementation
- A lack of education on the benefits of pharmacogenetic testing, both for patients and providers
- Potential for delay in therapy while awaiting results of genotyping

The problem is lack of data, not data that shows no benefit.

Principles and Concepts

- Common Classes of medications encountered in Family Practice with PGx Guidelines:

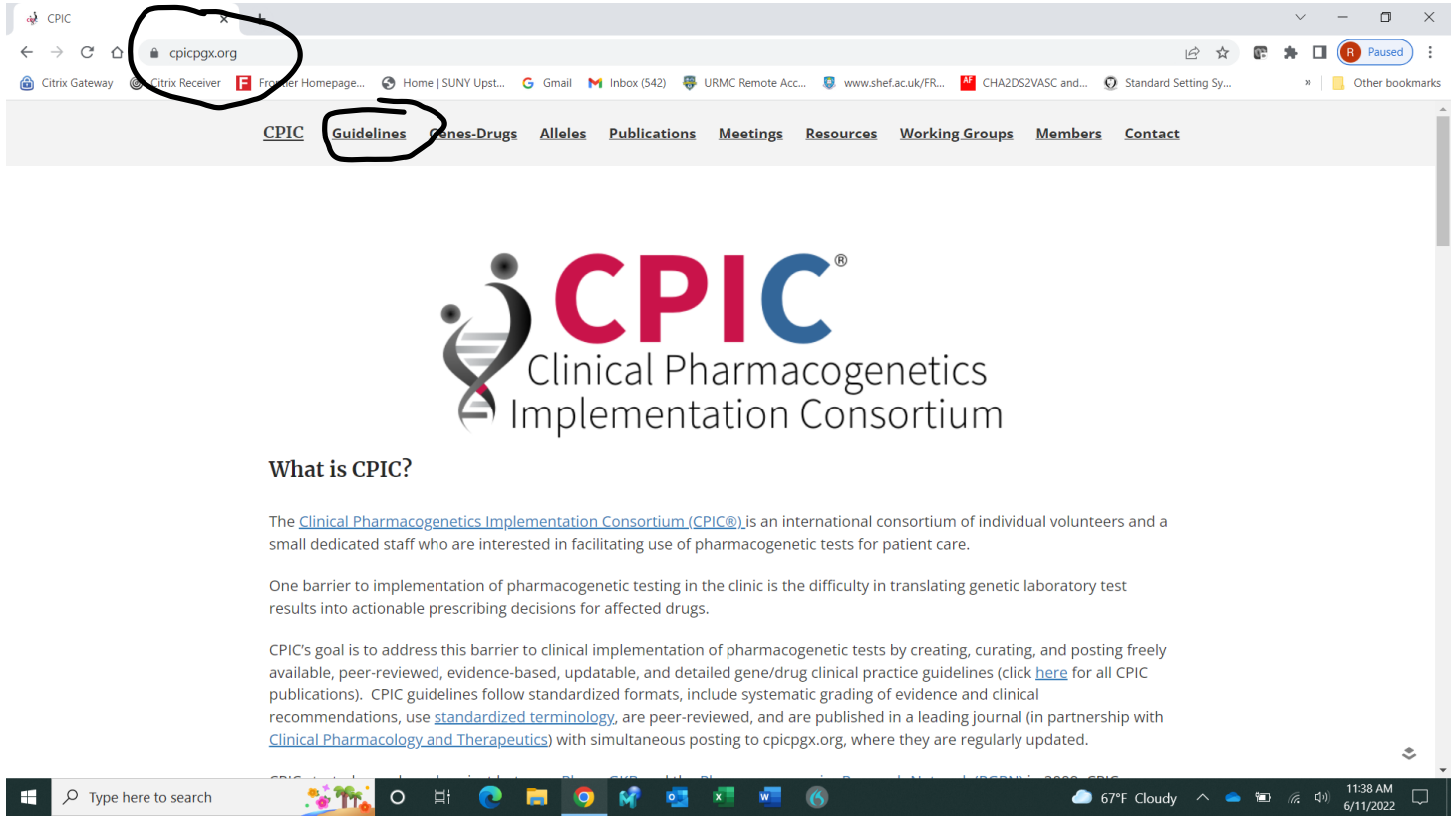
  SSRIs, Statins, NSAIDs, Codeine/Tramadol, Clopidogrel,

  Warfarin, TCAs, atomoxetine

Editorial Comment

Family Practice is the specialty of expert personalized care, especially of common conditions and undifferentiated problems. It is not the specialty of the simple and straightforward. Most of our patients expect the former. Much of the healthcare system and society, including many of our subspecialty colleagues, assume the latter. “Evidence Based” in its narrow sense is the starting point for personalized care. When guidelines and protocols have not yet been developed or do not apply to specific patients, failure to act, waiting for others to lead the way, is not appropriate. We are obligated to use our training-from basic science through learning throughout our careers, our reasoning, and our judgment to provide that expert personalized care.

Our Case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Meetings
Resources
Working Groups
Members
Contact
CPIC®
Clinical Pharmacogenetics Implementation Consortium
What is CPIC?
The Clinical Pharmacogenetics Implementation Consortium (CPIC®) is an international consortium of individual volunteers and a small dedicated staff who are interested in facilitating use of pharmacogenetic tests for patient care.
One barrier to implementation of pharmacogenetic testing in the clinic is the difficulty in translating genetic laboratory test results into actionable prescribing decisions for affected drugs.
CPIC's goal is to address this barrier to clinical implementation of pharmacogenetic tests by creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines (click here for all CPIC publications). CPIC guidelines follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology, are peer-reviewed, and are published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting to cpicpgx.org, where they are regularly updated.
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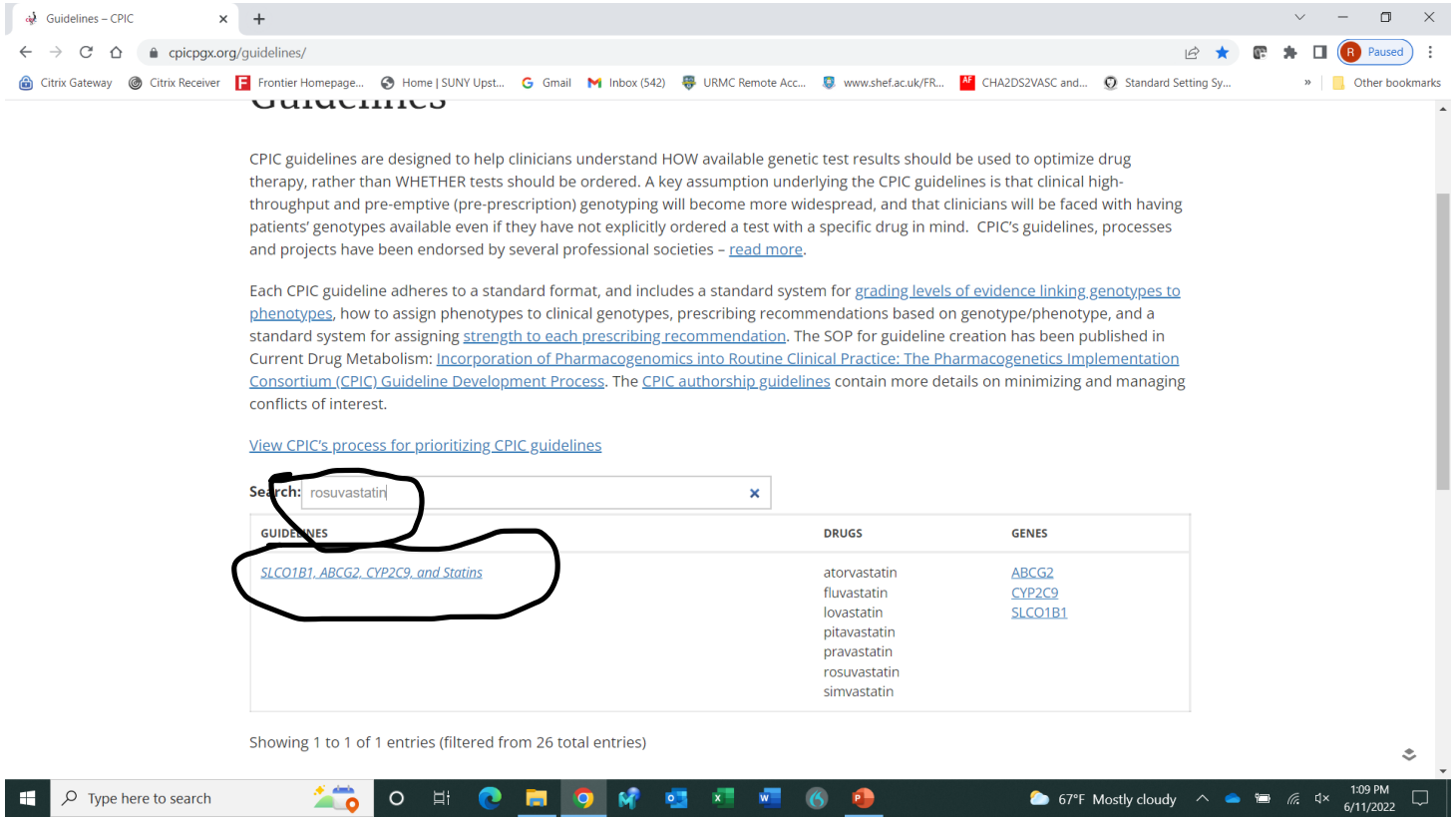
Our Case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Other bookmarks
CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A key assumption underlying the CPIC guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread, and that clinicians will be faced with having patients' genotypes available even if they have not explicitly ordered a test with a specific drug in mind. CPIC's guidelines, processes and projects have been endorsed by several professional societies – read more.
Each CPIC guideline adheres to a standard format, and includes a standard system for grading levels of evidence linking genotypes to phenotypes, how to assign phenotypes to clinical genotypes, prescribing recommendations based on genotype/phenotype, and a standard system for assigning strength to each prescribing recommendation. The SOP for guideline creation has been published in Current Drug Metabolism: Incorporation of Pharmacogenomics into Routine Clinical Practice: The Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process. The CPIC authorship guidelines contain more details on minimizing and managing conflicts of interest.
View CPIC's process for prioritizing CPIC guidelines
Search: rosuvastatin
GUIDELINES
DRUGS
GENES
SLCO1B1, ABCG2, CYP2C9, and Statins
atorvastatin
fluvastatin
lovastatin
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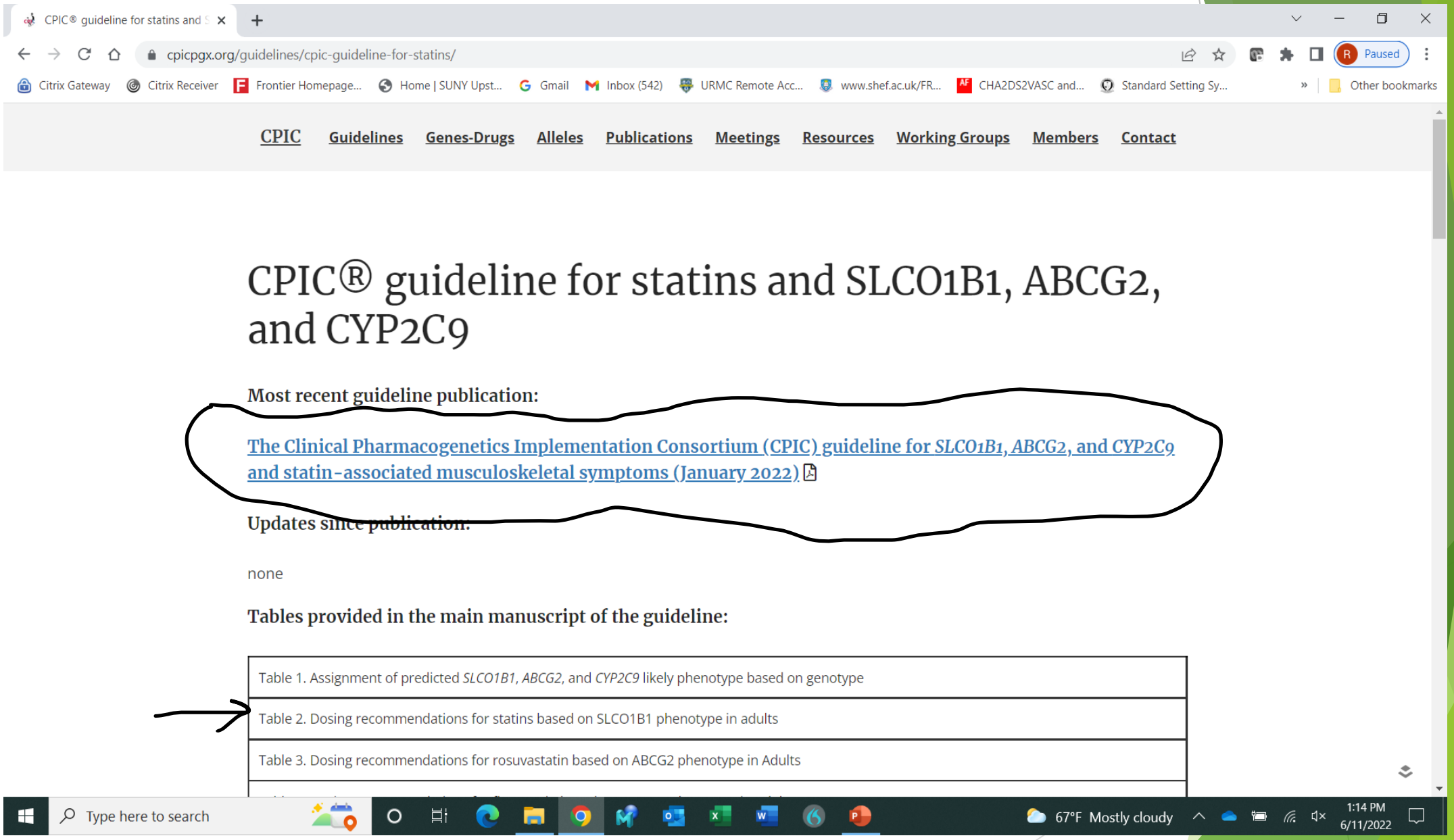
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CPIC® guideline for statins and SLCO1B1, ABCG2, and CYP2C9
Most recent guideline publication:
The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for SLCO1B1, ABCG2, and CYP2C9 and statin-associated musculoskeletal symptoms (January 2022)
Updates since publication:
none
Tables provided in the main manuscript of the guideline:
Table 1. Assignment of predicted SLCO1B1, ABCG2, and CYP2C9 likely phenotype based on genotype
Table 2. Dosing recommendations for statins based on SLCO1B1 phenotype in adults
Table 3. Dosing recommendations for rosuvastatin based on ABCG2 phenotype in Adults
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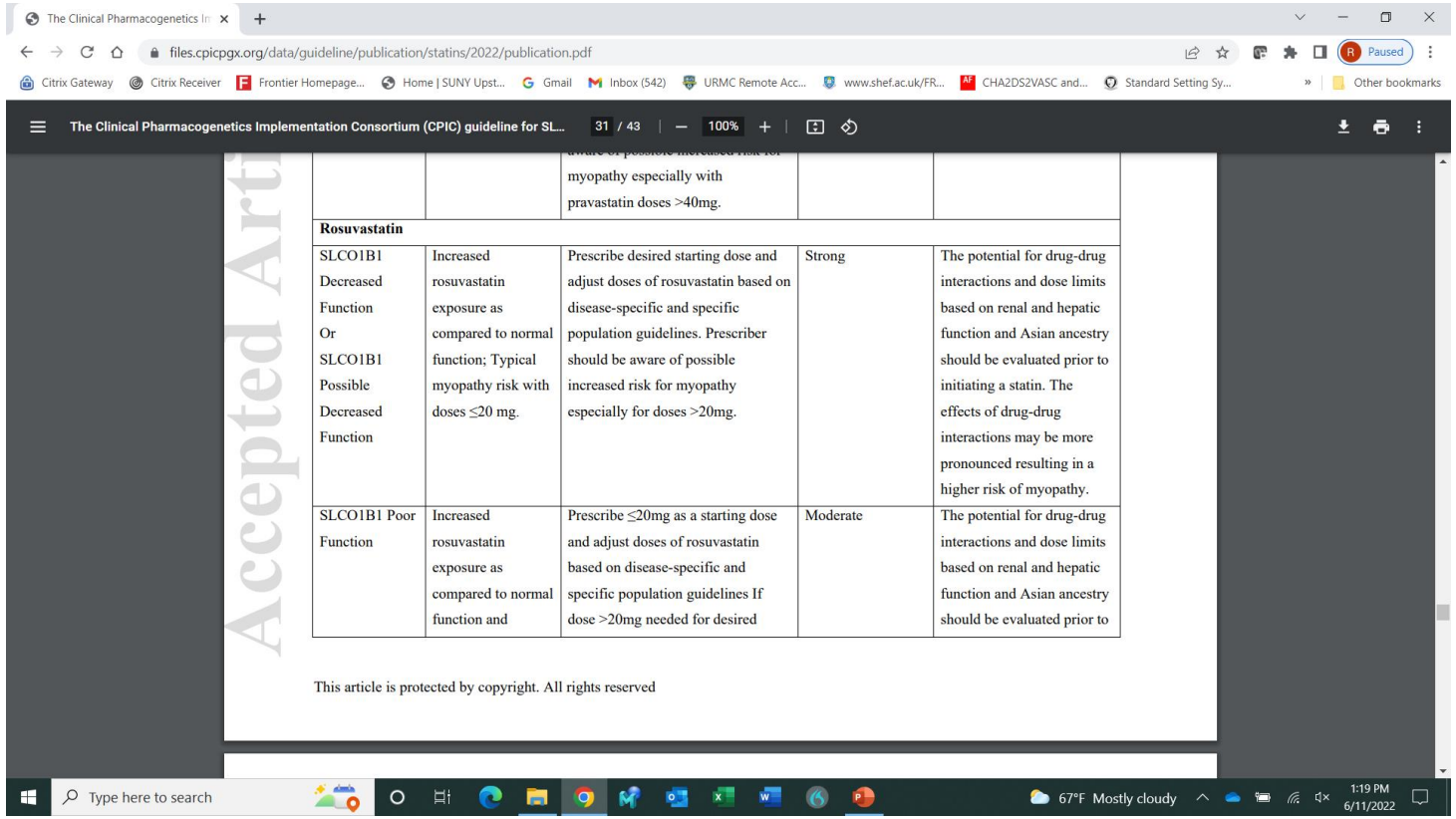
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myopathy especially with pravastatin doses >40mg.
Rosuvastatin
SLCO1B1 Decreased Function Or SLCO1B1 Possible Decreased Function
Increased rosuvastatin exposure as compared to normal function; Typical myopathy risk with doses ≤20 mg.
Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and specific population guidelines. Prescriber should be aware of possible increased risk for myopathy especially for doses >20mg.
Strong
The potential for drug-drug interactions and dose limits based on renal and hepatic function and Asian ancestry should be evaluated prior to initiating a statin. The effects of drug-drug interactions may be more pronounced resulting in a higher risk of myopathy.
SLCO1B1 Poor Function
Increased rosuvastatin exposure as compared to normal function and
Prescribe ≤20mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and specific population guidelines If dose >20mg needed for desired
Moderate
The potential for drug-drug interactions and dose limits based on renal and hepatic function and Asian ancestry should be evaluated prior to
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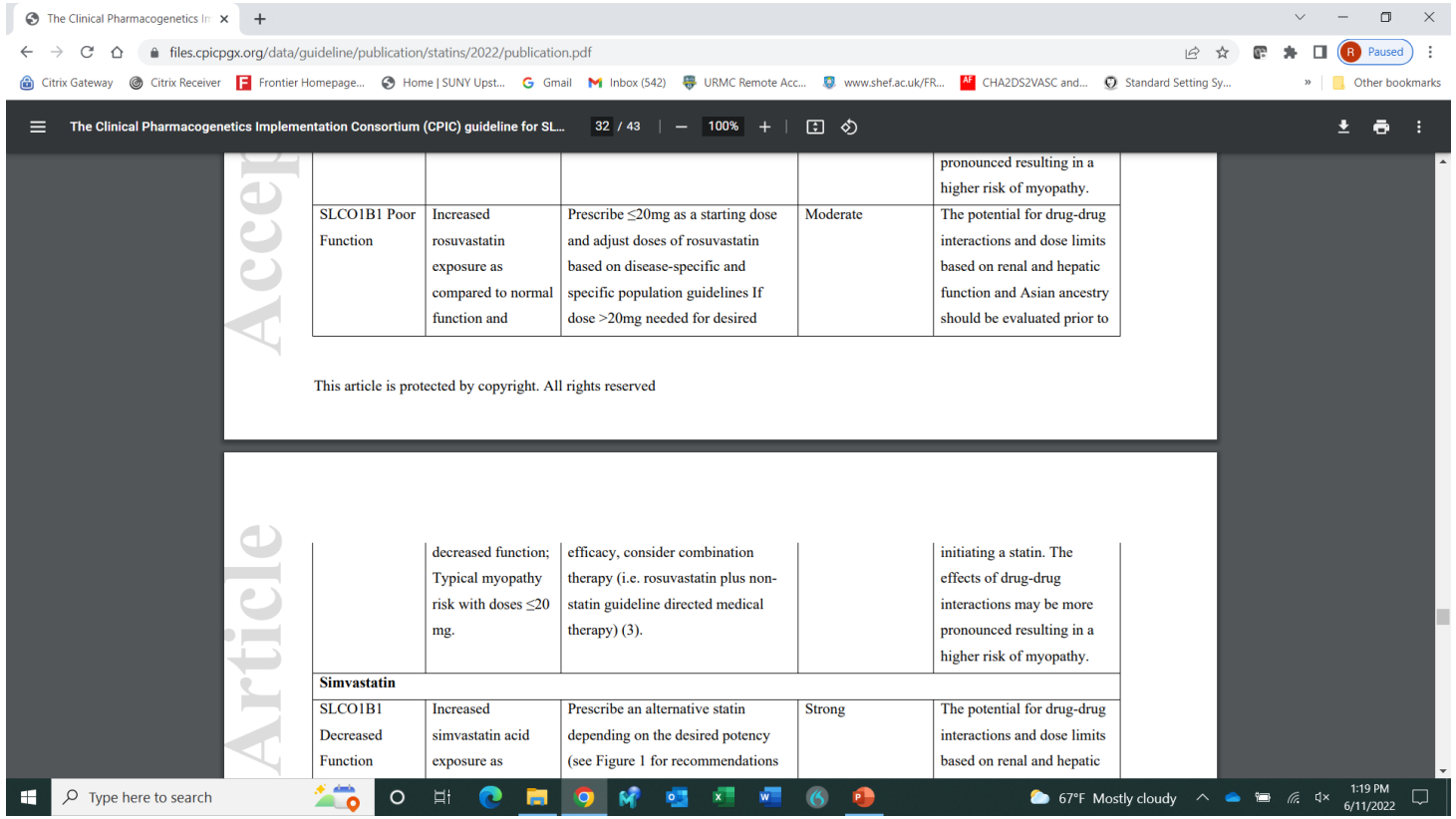
Our Case



The Clinical Pharmacogenetics In

files.cpicpgx.org/data/guideline/publication/statins/2022/publication.pdf

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for SL... 32 / 43 100%

				pronounced resulting in a higher risk of myopathy.
SLCO1B1 Poor Function	Increased rosuvastatin exposure as compared to normal function and	Prescribe ≤20mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and specific population guidelines If dose >20mg needed for desired	Moderate	The potential for drug-drug interactions and dose limits based on renal and hepatic function and Asian ancestry should be evaluated prior to

	decreased function; Typical myopathy risk with doses ≤20 mg.	efficacy, consider combination therapy (i.e. rosuvastatin plus non-statin guideline directed medical therapy) (3).		initiating a statin. The effects of drug-drug interactions may be more pronounced resulting in a higher risk of myopathy.
Simvastatin				
SLCO1B1 Decreased Function	Increased simvastatin acid exposure as	Prescribe an alternative statin depending on the desired potency (see Figure 1 for recommendations	Strong	The potential for drug-drug interactions and dose limits based on renal and hepatic

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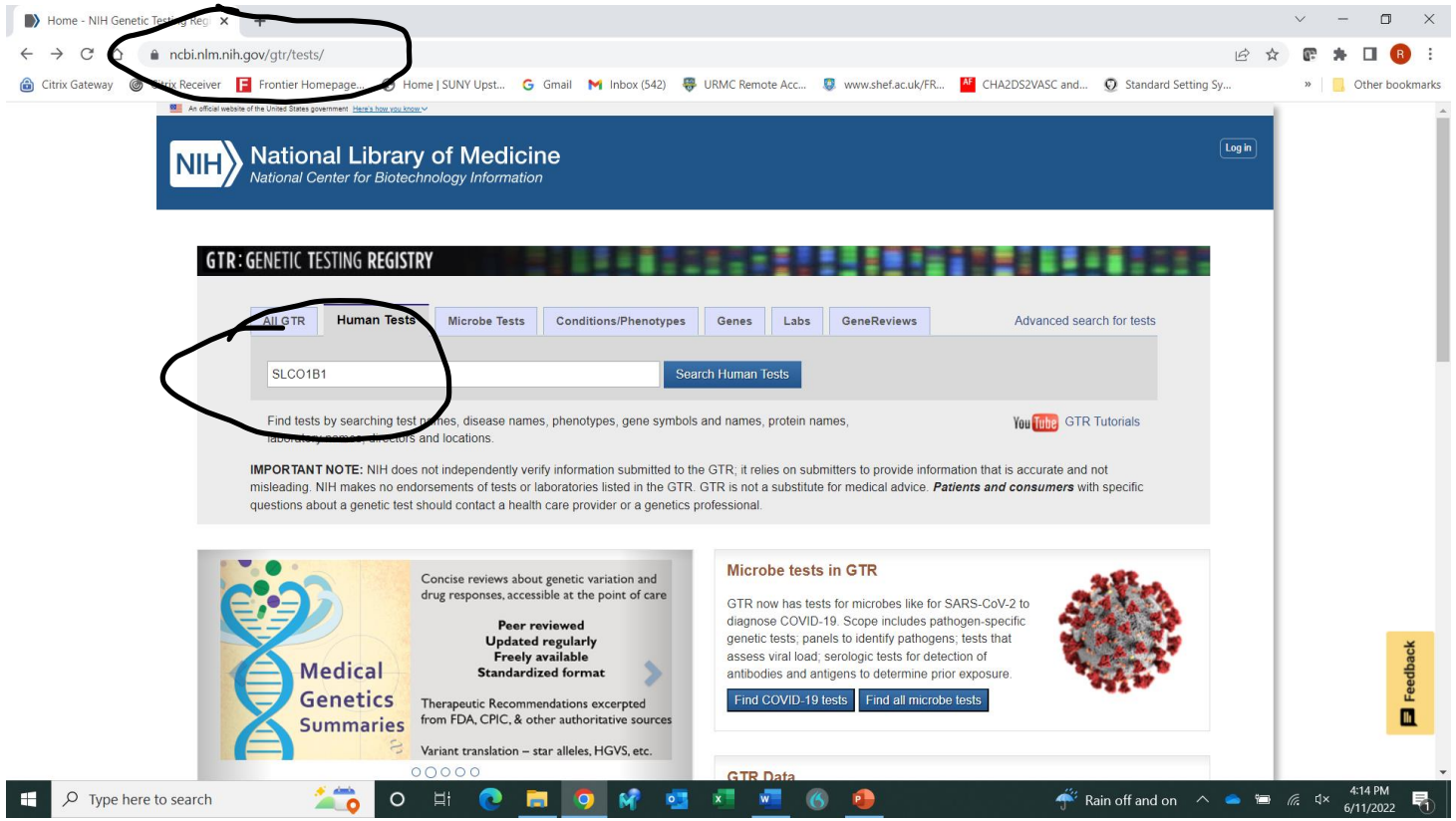
Our Case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Genes
Labs
GeneReviews
Advanced search for tests
SLCO1B1
Search Human Tests
Find tests by searching test names, disease names, phenotypes, gene symbols and names, protein names,
GTR Tutorials
IMPORTANT NOTE: NIH does not independently verify information submitted to the GTR; it relies on submitters to provide information that is accurate and not misleading. NIH makes no endorsements of tests or laboratories listed in the GTR. GTR is not a substitute for medical advice. Patients and consumers with specific questions about a genetic test should contact a health care provider or a genetics professional.
Medical Genetics Summaries
Concise reviews about genetic variation and drug responses, accessible at the point of care
Peer reviewed
Updated regularly
Freely available
Standardized format
Therapeutic Recommendations excerpted from FDA, CPIC, & other authoritative sources
Variant translation – star alleles, HGVS, etc.
Microbe tests in GTR
GTR now has tests for microbes like for SARS-CoV-2 to diagnose COVID-19. Scope includes pathogen-specific genetic tests; panels to identify pathogens; tests that assess viral load; serologic tests for detection of antibodies and antigens to determine prior exposure.
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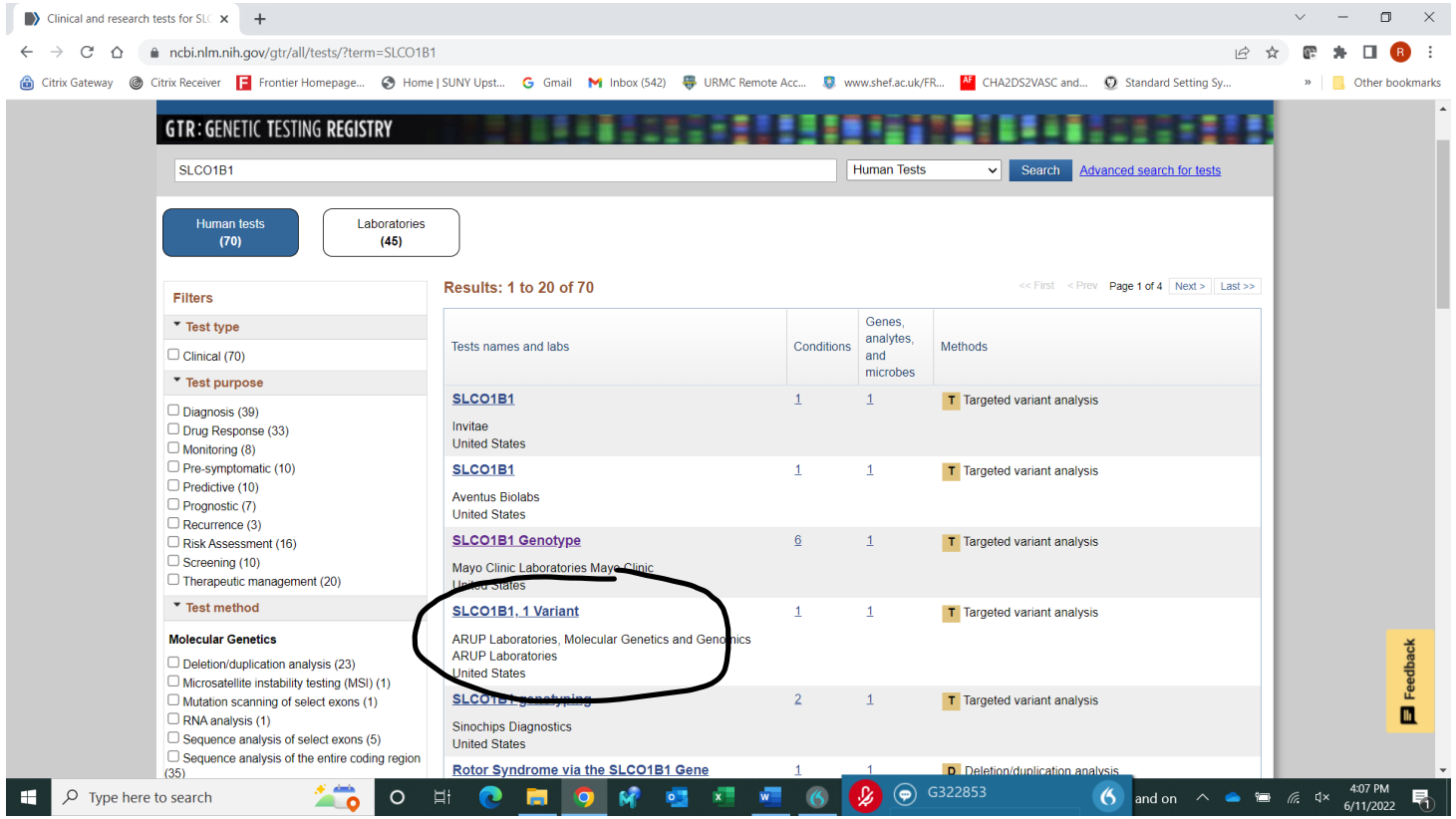
Clinical and research tests for SLC
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Human tests (70)
Laboratories (45)
Filters
Test type
Clinical (70)
Test purpose
Diagnosis (39)
Drug Response (33)
Monitoring (8)
Pre-symptomatic (10)
Predictive (10)
Prognostic (7)
Recurrence (3)
Risk Assessment (16)
Screening (10)
Therapeutic management (20)
Test method
Molecular Genetics
Deletion/duplication analysis (23)
Microsatellite instability testing (MSI) (1)
Mutation scanning of select exons (1)
RNA analysis (1)
Sequence analysis of select exons (5)
Sequence analysis of the entire coding region (35)
Results: 1 to 20 of 70
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Tests names and labs
Conditions
Genes, analytes, and microbes
Methods
SLCO1B1
Invitae
United States
Targeted variant analysis
SLCO1B1
Aventus Biolabs
United States
SLCO1B1 Genotype
Mayo Clinic Laboratories Mayo Clinic
SLCO1B1, 1 Variant
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Our Case

- A/P: Familial hypercholesterolemia. Genetic testing confirmation not necessary based on meeting criteria. Counseled on significance, lifestyle and advised to share information with family members. Guidelines recommend high dose statin to target, >60% reduction in LDL, atorvastatin 80mg per day or rosuvastatin 40 mg/day.

- DTC test with potentially poor metabolizer variant in SLCO1B1, increasing risk of statin myopathy. FDA requires commercial lab confirmation to verify before using it to make treatment decisions. CPIC guidelines provide dosing recommendations for statin therapy based on the results of PGx testing. Confirmatory testing ordered.

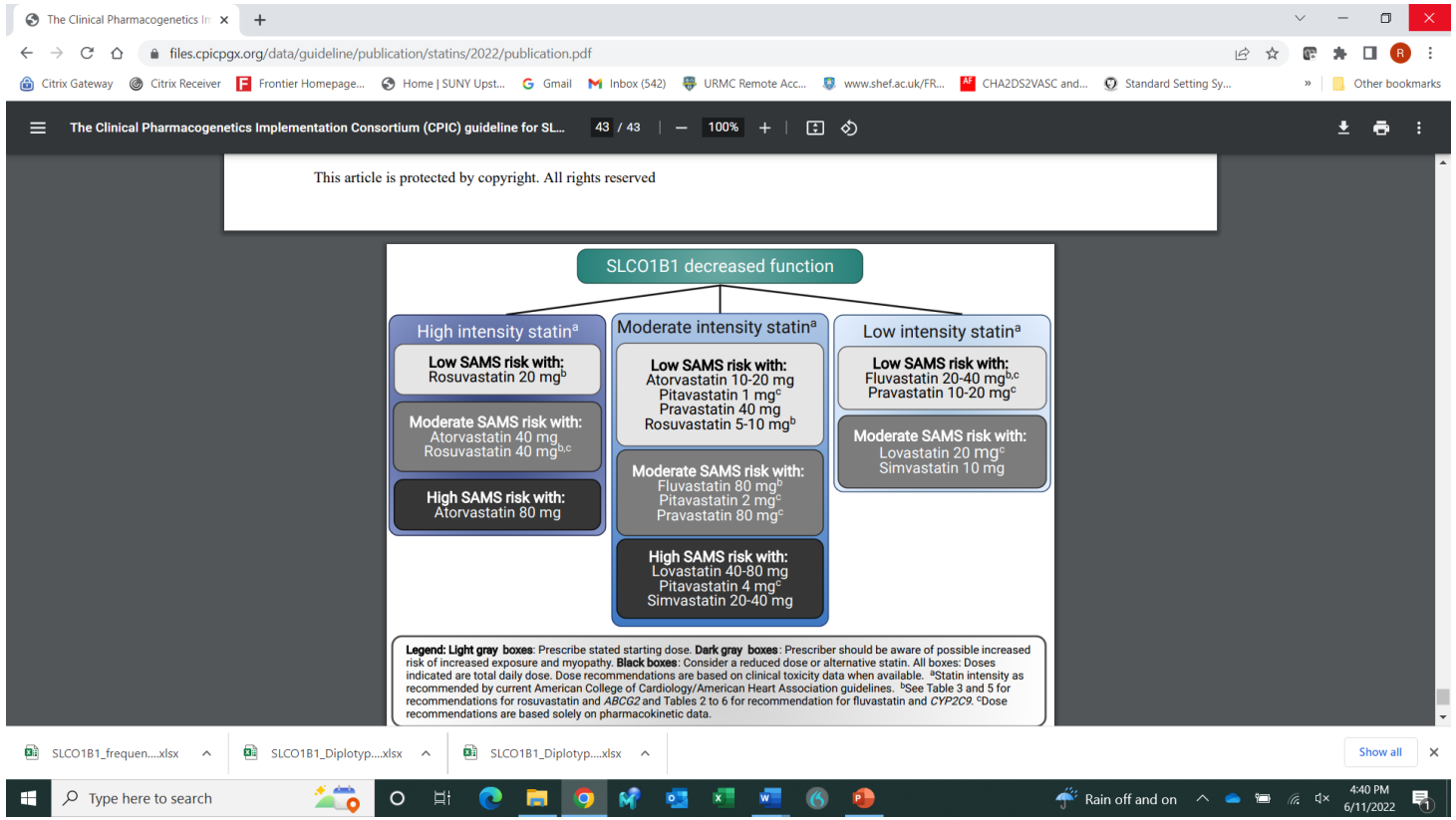
Our Case

- After a polite discussion with the insurer's prior authorization physician, you obtain authorization for the genetic testing.

- Results show SLCO1B1 *1/*5 which the report notes correlates with decreased function.

You consult the CPIC guideline:

Our case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The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for SL...
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SLCO1B1 decreased function
High intensity statin[a]
Low SAMS risk with:
Rosuvastatin 20 mg[b]
Moderate SAMS risk with:
Atorvastatin 40 mg
Rosuvastatin 40 mg[b,c]
High SAMS risk with:
Atorvastatin 80 mg
Moderate intensity statin[a]
Low SAMS risk with:
Atorvastatin 10-20 mg
Pitavastatin 1 mg[c]
Pravastatin 40 mg
Rosuvastatin 5-10 mg[b]
Moderate SAMS risk with:
Fluvastatin 80 mg[b]
Pitavastatin 2 mg[c]
Pravastatin 80 mg[c]
High SAMS risk with:
Lovastatin 40-80 mg
Pitavastatin 4 mg[c]
Simvastatin 20-40 mg
Low intensity statin[a]
Low SAMS risk with:
Fluvastatin 20-40 mg[b,c]
Pravastatin 10-20 mg[c]
Moderate SAMS risk with:
Lovastatin 20 mg[c]
Simvastatin 10 mg
Legend: Light gray boxes: Prescribe stated starting dose. Dark gray boxes: Prescriber should be aware of possible increased risk of increased exposure and myopathy. Black boxes: Consider a reduced dose or alternative statin. All boxes: Doses indicated are total daily dose. Dose recommendations are based on clinical toxicity data when available. [a]Statin intensity as recommended by current American College of Cardiology/American Heart Association guidelines. [b]See Table 3 and 5 for recommendations for rosuvastatin and ABCG2 and Tables 2 to 6 for recommendation for fluvastatin and CYP2C9. [c]Dose recommendations are based solely on pharmacokinetic data.
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Our Case

- In addition to counseling on diet and exercise, along with smoking cessation, you prescribe rosuvastatin 20mg daily. You begin antihypertensive treatment, assuring that there are no drug-drug interactions that might affect rosuvastatin metabolism. Follow up lipids are ordered for 3 months, with an individualized goal LDL reduction of <100, preferably <70.

- If goal is not reached, you plan to consider adding ezetimibe.

Summary

- 1 There are significant pharmacogenetic variants in medications commonly used in Family Practice
- 2 Being prepared to use pharmacogenetics in clinical practice will require an initial investment in time.
- 3 Once the groundwork is laid, clinical application of pharmacogenetics in day-to-day practice is feasible.

Resources

The NIH Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC-PEG), on which I serve as the AAFP Liaison has a pharmacogenetics project group. Over the past 2 years we have produced several interactive modules in pharmacogenetics. At the time I am writing this, they are in the final stages of approval and CME sponsorship through the University of Pittsburgh. The links will be posted on:

https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Resources#pharmacogenomics

Pharmcogenomics Resources
Pharmcogenomics Nomenclature
Genotype-Guided Clopidogrel Treatment
Psychiatric PGx
Genetic Testing
Direct to Consumer Genetic Testing
Practical aspects of Pharmacogenomics Implementation
Navigating PGx Test Coverage in Medicare Populations
Economics of Pharmacogenomic Testing

Resources

- Genetic testing registry: https://www.ncbi.nlm.nih.gov/gtr/
- https://www.genome.gov/health/For-Health-Professionals
- https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Resources
- https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Resources/Healthcare-Provider-Direct-to-Consumer-Genetic-Testing-FAQ

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- https://www.23andme.com/test-info/pharmacogenetics/
- https://www.uptodate.com/contents/familial-hypercholesterolemia-in-adults-overview?search=familial%20hypercholesterolemia&source=search_result&selectedTitle=1~111&usage_type=default&display_rank=1
- https://www.uptodate.com/contents/familial-hypercholesterolemia-in-adults-treatment?search=familial%20hypercholesterolemia&source=search_result&selectedTitle=2~111&usage_type=default&display_rank=2

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- ACMG Board of Directors. Direct-to-consumer genetic testing: a revised position statement of the American College of Medical Genetics and Genomics. *Genet Med* **18,** 207–208 (2016). https://doi.org/10.1038/gim.2015.190

Practice Recommendations

1. Read the CPIC guidelines in detail for three classes of medications that have known actionable gene-drug interactions.
2. For these classes, develop a cognitive framework of when you will consider pharmacogenetic testing (realizing that there are few standards or guidelines at this time for when to order testing.)
3. Investigate whether your usual clinical lab has contracted to make these tests available and review the process. If not, become familiar with one of the labs on www.ncbi.nih.gov/gtr/tests
4. Create a template for your progress notes that will satisfy prior authorization requirements, including documenting the need for the medication, the known potential gene-drug interaction and naming a specific guideline, e.g. CPIC.