PharmGKB Training Exercise – Rheumatology

How to use this exercise

This exercise is intended to help new users familiarize themselves with the PharmGKB website and some of the different types of information available. **This exercise is not for use in a classroom setting for credit**, including professional development such as CME, as the answer sheet is freely available on the PharmGKB website.

We recommend that the trainer first provide an introduction to the PharmGKB website and its key features, including the genotype pickers available for the CPIC dosing guidelines. This exercise can then be used to reinforce areas covered in the introduction.

The 'What is PharmGKB?' page at www.pharmgkb.org/whatIsPharmgkb has helpful explanations of the different types of information that can be accessed on the PharmGKB website. This page will be useful for any trainers who are themselves unfamiliar with the PharmGKB website.

This exercise should take about 20-30 minutes to complete following an introduction to the website.

During the training session, each person will require access to an internet-connected computer where they can access the PharmGKB website.

This exercise is split into two parts; Part 1 and Part 2. Participants work through Part 1 to determine which genes they require genotype information for. Once they have completed Part 1, they should be given Part 2, which provides the genotype information. An answer sheet is provided at the end of this document.

PharmGKB is for research purposes only and does not provide medical advice or recommend when to order a pharmacogenetic test. All questions are written under the assumption that a patient's genetic information is already available.

If you have any questions or comments regarding this training exercise, please contact the PharmGKB team at feedback@pharmgkb.org

PharmGKB Training Exercise – Rheumatology

Part 1

A patient has been diagnosed with rheumatoid arthritis, which you would normally treat with either azathioprine or methotrexate.

The patient has previously received their genetic information from a direct-to-consumer testing company and has added it to their medical record. You check the information in case there is anything relevant to your prescribing decision.

1) Does azathioprine have any Clinical Guideline Annotations, FDA Drug Labels or Level 1A Clinical Annotations associated with it? If so, which genes are involved?

2) Does methotrexate have any Clinical Guideline Annotations, FDA Drug Labels or Level 1A Clinical Annotations associated with it? If so, which genes are involved?

3) Which gene(s) do you need to check for variants?

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Part 2

4) Briefly describe the relationship between TPMT and azathioprine.

5) Briefly describe the relationship between azathioprine and NUDT15

You check the patient's TPMT diplotype and find that it is *1/*3C. Their NUDT15 diplotype is *1/*1.

6) What is the patient's TPMT metabolizer status?

7) What is the patient's NUDT15 metabolizer status?

8) Does this affect your choice or dosage of drug? How?

9) Would your decision change if the patient was a TPMT poor metabolizer (e.g. *2/*4)? Why?

PharmGKB Training Exercise – Rheumatology Answers

A patient has been diagnosed with rheumatoid arthritis, which you would normally treat with either azathioprine or methotrexate.

The patient has previously received their genetic information from a direct-to-consumer testing company and has added it to their medical record. You check the information in case there is anything relevant to your prescribing decision.

1 Does azathioprine have any Clinical Guideline Annotations, FDA Drug Labels or Level 1A Clinical Annotations associated with it? If so, which genes are involved? Yes, a CPIC guideline for TPMT and NUDT15, DWPG guidelines for TPMT and NUDT15, a RNPGx guideline for azathioprine and TPMT, an FDA drug label for TPMT and NUDT15 and Level 1A clinical annotations for azathioprine and TPMT/azathioprine and NUDT15

2) Does methotrexate have any Clinical Guideline Annotations, FDA Drug Labels or Level 1A Clinical Annotations associated with it? If so, which genes are involved? A 'no recommendation' from RNPGx.

3) Which gene(s) do you need to check for variants? TPMT, NUDT15

4) Briefly describe the relationship between TPMT and azathioprine.
Azathioprine is metabolized by TPMT .

5) Briefly describe the relationship between NUDT15 and azathioprine.
NUDT15 metabolizes thiopurine metabolites, reducing the level of active thioguanine nucleotide metabolites which can cause DNA or RNA damage in the body.

You check the patient's TPMT diplotype and find that it is *1/*3C. Their NUDT15 diplotype is *1/*1.

6) What is the patient's TPMT metabolizer status? Intermediate metabolizer

7) What is the patient's NUDT15 metabolizer status? Normal metabolizer

8) Does this affect your choice or dosage of drug? How?
Can still prescribe either azathioprine or methotrexate. However, if azathioprine is prescribed, patient should be started on a reduced dose (CPIC recommends 30-80% of the normal dose, DPWG recommends 50% of the normal dose) then titrate based on tolerance.

9) Would your decision change if the patient was a TPMT poor metabolizer (e.g. *2/*4)? Why?
Do not prescribe azathioprine or start with 10% of the standard dose. Patient would be at risk of fatal toxicity due to extremely high concentrations of thioguanine nucleotide metabolites.