Introducing first year medical students to personalized medicine concepts in a small group activity

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Abstract

An individuals' genetic profile is becomingly an increasingly important parameter in healthcare decisions. This small group activity was developed to introduce first year medical students in the Molecules to Cells and Tissues course to the concept and significance of Pharmacogenomics and personalized medicine. Additionally, this activity provided students with an opportunity to work with a large dataset and use the information to impact clinical decision making.

This activity has two cases, takes student groups approximately 2 hours to complete, and requires internet access. Case materials are available through the learning management system Canvas, and include open-ended questions to guide students through the cases. In these cases students explore the functional significance of different alleles of a panel of cytochrome P450 genes. The group activity has the students examine a large data set of cytochrome P450 genes and cognate alleles to determine their prevalence in the local population and calculate the individuals' gene scores. The students are then asked to explain the impact of the genotype (or gene score) on the resulting patient phenotype (i.e. the functional significance of the genotype). The first case involves a breast cancer survivor support group in which patients taking Taxol discuss lack of adequate pain relief from opioids and the potential impact of concomitant use of natural compounds/supplements on drug metabolism. The second case involves a patient presenting with recurrent stroke-like symptoms despite being on the anticoagulant medication clopidogrel. The patient is initially suspected to be non-compliant, but is later determined to be a poor metabolizer of the anticoagulant clopidogrel to its active form thus decreasing its efficacy.

The expertise of the IUSM Medical Genetics research faculty was leveraged to provide a large data set of cytochrome P450 genes and cognate alleles. The selection of cytochrome P450 was based upon delivering content focused on the biochemistry of the enzyme system and provided an opportunity to highlight the drug interaction database available through IUSM Clinical Pharmacology (The Flockhart Table™ ; https://drug-interactions.medicine.iu.edu/). The addition of natural compounds was to draw students' attention to the Natural Medicines database, which is the recommended source for evidence-based data on complementary and alternative medicine. Natural Medicines is available through the Ruth Lilly Medical Library and can be searched by substance or condition. It provides both a summary of the literature available on substances as well as the level of evidence or quality of studies done on the substance.

Materials & Methods

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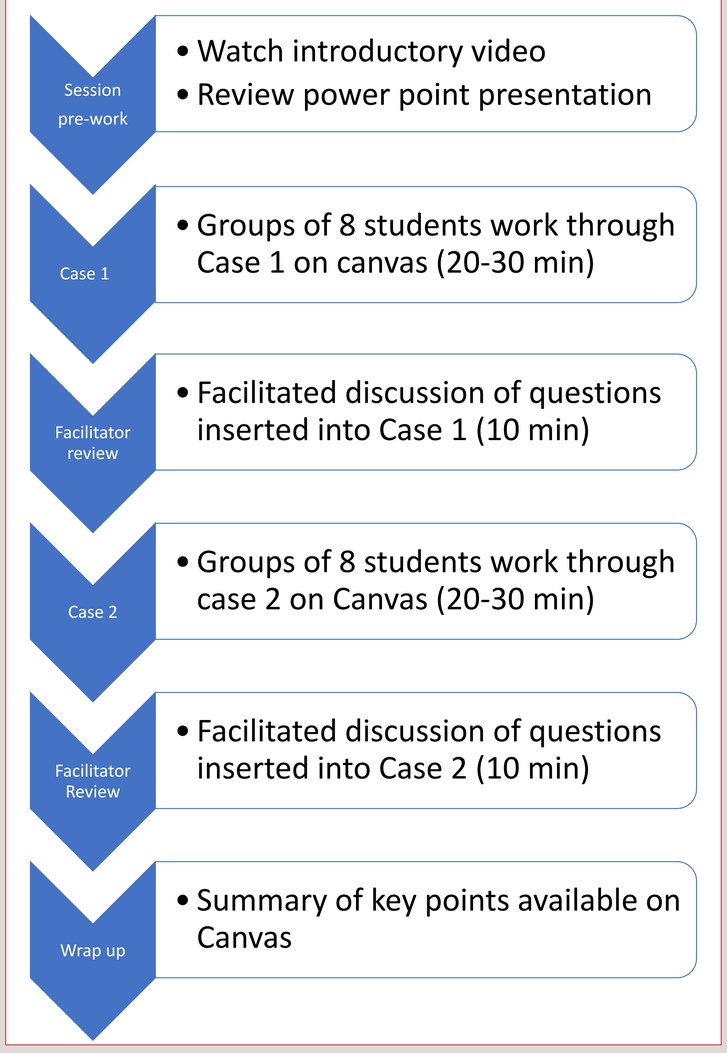
Small Group Session Objectives

- Describe the reaction catalyzed by members of the CYP450 superfamily, focusing on how the substrate is modified.
- Explain how variation at the gene/allele level influences health.
- Explain how phenotypic variability in drug responsiveness can result from allelic variation in distinct CYP450 genes.
- In a group learning situation, demonstrate effective communication and professionalism.

Session outline

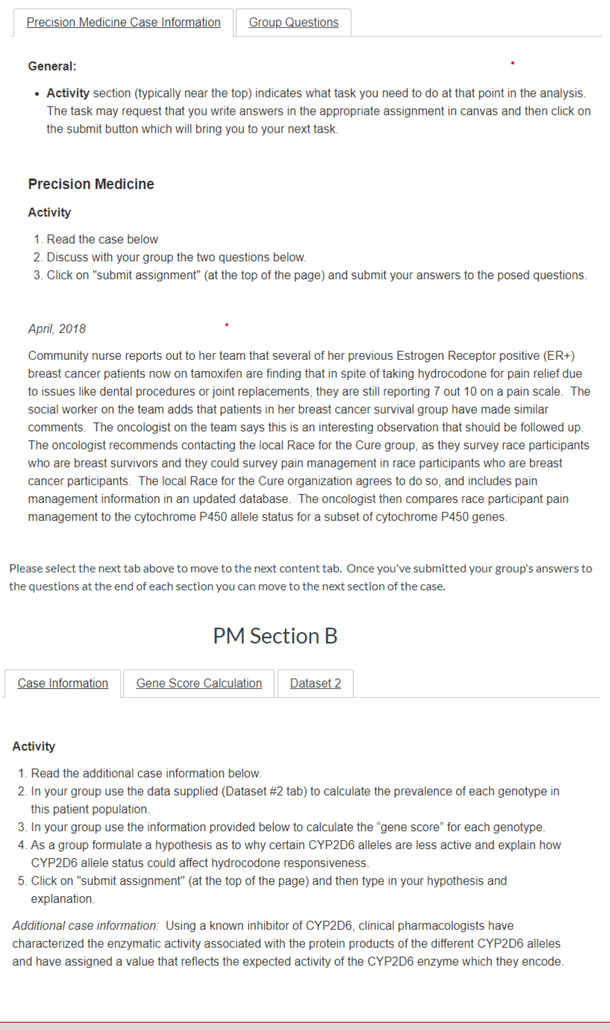


Session Objectives

- Review Session Pre-work materials
  - Relationship between scientific method and clinical reasoning
  - 3 slide overview of cytochrome P450 family and enzymatic mechanism
- Following the instructions work through the materials with your group

Session Content

PM Section A



Precision Medicine Case Information | Group Questions

General:

- **Activity** section (typically near the top) indicates what task you need to do at that point in the analysis. The task may request that you write answers in the appropriate assignment in canvas and then click on the submit button which will bring you to your next task.

Precision Medicine

Activity

1. Read the case below
2. Discuss with your group the two questions below.
3. Click on "submit assignment" (at the top of the page) and submit your answers to the posed questions.

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Community nurse reports out to her team that several of her previous Estrogen Receptor positive (ER+) breast cancer patients now on tamoxifen are finding that in spite of taking hydrocodone for pain relief due to issues like dental procedures or joint replacements, they are still reporting 7 out 10 on a pain scale. The social worker on the team adds that patients in her breast cancer survival group have made similar comments. The oncologist on the team says this is an interesting observation that should be followed up. The oncologist recommends contacting the local Race for the Cure group, as they survey race participants who are breast survivors and they could survey pain management in race participants who are breast cancer participants. The local Race for the Cure organization agrees to do so, and includes pain management information in an updated database. The oncologist then compares race participant pain management to the cytochrome P450 allele status for a subset of cytochrome P450 genes.

Please select the next tab above to move to the next content tab. Once you've submitted your group's answers to the questions at the end of each section you can move to the next section of the case.

PM Section B

Case Information | Gene Score Calculation | Dataset 2

Activity

1. Read the additional case information below.
2. In your group use the data supplied (Dataset #2 tab) to calculate the prevalence of each genotype in this patient population.
3. In your group use the information provided below to calculate the "gene score" for each genotype.
4. As a group formulate a hypothesis as to why certain CYP2D6 alleles are less active and explain how CYP2D6 allele status could affect hydrocodone responsiveness.
5. Click on "submit assignment" (at the top of the page) and then type in your hypothesis and explanation.

Additional case information: Using a known inhibitor of CYP2D6, clinical pharmacologists have characterized the enzymatic activity associated with the protein products of the different CYP2D6 alleles and have assigned a value that reflects the expected activity of the CYP2D6 enzyme which they encode.

Facilitated Group Discussion

1. Why does the oncologist identify the cytochrome P450 gene family as a focus?

Cytochrome P450s are a family of genes, a subset of which are involved in many aspects of drug metabolism. In some cases (eg hydrocodone; tamoxifen) they are needed to generate the active drug; in others they are needed to conjugate the drug with sugars/sulfate for elimination.

2. Which of the cytochrome P450 genes catalogued in the database (Dataset #1 tab) is/are likely to be important for hydrocodone usage in these patients?

Cytochrome P450 2D6: Cytochrome P450 2D6 (CYP2D6) is involved in the metabolism of approximately 20% of all drugs in clinical use, including β-blockers, anti-arrhythmics, antidepressants and antipsychotics. It is also responsible for the metabolic activation of opioids like codeine, hydrocodone and oxycodone. The students will also learn that it is required to convert tamoxifen to its active metabolite Endoxifen. CYP3A4 will convert hydrocodone to norhydrocodone which is active but significantly less potent as an analgesic (~70-fold). The analgesic potency of hydrocodone metabolites follows the general order: hydromorphone (HM) >hydrocodone (HC) >dihydrocodeine (DHC).

Student Feedback

- Pre-work was difficult to understand – requesting a lecture before the small group
- Many admitted they did not do the pre-work and were therefore confused during the small group session
- Requesting the pre-work to include information on calculating gene scores and how gene scores related to phenotype
- Generally liked the cases & application of the information (felt had to "google" some questions blindly) but overall felt the cases were interesting
- Liked the information on natural supplements and the impact they can have on metabolism of prescription medications
- Several comments saying this is an interesting topic they would like to learn more about

Summary

This small group session has been delivered twice. Adjustments made after the first iteration involved logistics: shortening the pre-work; providing the excel sheet containing the raw data; and providing an example of how to calculate gene scores.
Facilitators felt the session was too short for the time allotted so a second case was created. Since small group sessions in the pre-clerkship courses provide an opportunity to introduce concepts with direct applications to patient care the second case was built around a concern over patient compliance.
Based upon student and facilitator feedback from the second iteration of the case, modifications to the session are to remove the emphasis on the biochemistry of Cytochrome p450, which will be integrated into an earlier session on enzymes. Secondly, in collaboration with the IUSM Personalized Medicine pillar we will increase the emphasis on the pharmacogenomics and personalized/precision medicine.

Conclusions

This small group activity was developed to introduce first year medical students in the Molecules to Cells and Tissues course to the concept and significance of Pharmacogenomics and personalized medicine. Additionally, this activity provided students with an opportunity to work with a large dataset and use the information to impact clinical decision making.

Goals

An individuals' genetic profile is becomingly an increasingly important parameter in healthcare decisions. The cost of generating an individuals genetic profile is steadily declining, and thus is becoming more accessible. Challenges facing the integration of –omics type data into clinical practice span ethical considerations, cost effectiveness and at a fundamental level how well the biological processes are understood. This small group activity is meant to provide an introduction into the value of genomic information. Future iterations of the session need to address equally important aspects of ethics and health care costs.

Alyass, A., Turcotte, M and Meyre, D. (2015) From big data analysis to personalized medicine for all: challenges and opportunities. BMC Medical Genomics 8:333