PHG 513
Basic Concepts in Pharmacogenetics and Toxicogenomics

Winter Quarter, 2025
Tuesday and Thursday 9:00 – 10:20 AM, Room HSEB 235

Course Coordinator

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Office hours: on-line, by appointment

Prerequisites: Biochem 440/441/442 or Genome 372 or equivalent, or instructor permission.

Canvas Website: canvas@uw.edu

Course Description: This course will draw from multiple disciplines to provide a general understanding of molecular approaches to DNA sequence, epigenome, transcriptome, proteome and metabolome analyses, as well as an understanding of pharmacogenetic relationships and gene-environment interactions as determinants of drug response and disease susceptibility. It will examine the molecular basis for interindividual differences in drug/xenobiotic disposition and application of that information for individualized drug treatment regimens. It will also cover the application of genomics technologies for the discovery of new drug targets in the treatment of common disease and in the diagnosis and treatment of rare diseases and cancer (i.e., Precision Medicine). Finally, it will explore ethics and policy issues relevant to testing for pharmacogenetic and toxicogenomic traits in healthcare settings and the workplace.

Learning Objectives: At the end of this course students should be able to:

1. identify and understand the conceptual basis behind basic methodologies used to identify variability in human genome, transcriptome, proteome, epigenome and metabolome;
2. understand the role of genetic polymorphisms as determinants of adverse drug reactions and pharmacological efficacy;
3. explain the significance of genetic polymorphisms in the development, progression, and treatment of selected examples of rare human disease;
4. explain the difference in penetrance of genetic variation for rare Mendalian diseases and chronic diseases;
5. understand the connection between environmental exposures, genetic polymorphisms, and risk for chronic diseases of public health importance;
6. read critically original scientific literature related to pharmacogenetics, precision medicine and 'gene-environment interactions';
7. have the technical background necessary to appreciate the ethical, legal, social and policy implications that arise out of pharmaco- and toxicogenomic research and its translation into clinical or public health practice.
8. write professionally about one area of pharmacogenetics or 'gene-environment-disease' interaction with clinical or public health importance

9. integrate basic concepts of ethics and health policy into arguments for and against prospective genotyping of individuals in clinical and public health practice.

Grading

The course will include 3 exams (multiple choice /short answer) over materials covered in class that will count for 75% of your grade (25% for each exam). The remaining 25% of your grade will be based on your class term paper. An average numeric score of 80 will be equal to a grade point score of 3.0 and average scores of 95 and above will be 4.0.

Readings

Textbook: There is no textbook required for this class; class notes, the lectures and posted readings should be sufficient for comprehension of the material. However, if you would like additional background material, we recommend the textbook, *Pharmacogenetics, edited by Kim Brosen, Elsevier, 2019* (expensive, but relatively up to date) for basic principles and examples and *Clinical Decision Support for Pharmacogenomic Precision Medicine: Foundations and implementation, edited by Devine, Boyce and Wilsanen, Elsevier, 2022* for clinical practice applications. For students who feel that their background in basic molecular biology and genetics requires updating, we recommend any basic textbook in molecular genetics or medical genetics. A good text is: Strachan and Read's *"Human Molecular Genetics," 5th Edition,* 2019 (in paperback).

Selected readings from the current literature will be posted on the course website. Again, these are intended primarily as an enrichment of the experience, although some parts of the readings may be discussed in class.

Hard copies of lecture notes will not be provided. Powerpoint and pdf files of the lecture notes can be accessed on-line, through the Canvas course website.

Term Paper

You will be asked to choose a particular disease that has both a genetic and an environmental component to it, and write a brief paper (~15 pages, double spaced) describing what is known about the etiology of the disease or condition. In the paper, you should cover:

1. the fundamental biology of the disease/condition, including which genes are involved
2. identify candidate genes that might act as susceptibility genes, and discuss their function
3. review the basic epidemiology of the disease that has led to discoveries that genetic factors are involved
4. identify and discuss any environmental factors that have been implicated in the etiology of the disease; environmental factors are defined in their broadest terms, and include diet, viruses and other microbiological factors, occupational exposures, lifestyle factors, etc.
5. identify and discuss at least one "ELSI" problem – real or potential, that has surfaced in your study of the disease.
6. include all appropriate references

Possible diseases for discussion include, but are not limited to:
Parkinson's Disease, Amyotrophic Lateral Sclerosis (ALS: Lou Gehrig's Disease), Diabetes, Heart Disease, Smoking Dependence, Alcohol Dependence, Cancer of any type (especially leukemias, colon cancer, lung cancer, breast cancer), Lung diseases (asthma, COPD), Immune diseases (Crohn's, IBS, IDP).

LECTURE SCHEDULE, WINTER QUARTER, 2025

Date	Topic	Lecturer
Jan 7 Tuesday	Introduction: genes, environment and health outcomes	Thummel
Jan 9 Thursday	Technological approaches to understanding genotype-phenotype relationships I – DNA analysis	Kelly
Jan 14 Tuesday	Technological approaches to understanding genotype-phenotype relationships II – Epigenetics	Kelly
Jan 16 Thursday	Technological approaches to understanding genotype-phenotype relationships III – RNA analysis	Kelly
Jan 21 Tuesday	Technological approaches to understanding genotype-phenotype relationships IV – Proteomics and metabolomics analyses	Thummel
Jan 23 Thursday	Toxicogenomics: Overview and Case examples	Kelly
Jan 28 Tuesday	**EXAM 1 (material from Jan 7 – Jan 23)**	Thummel/Kelly
Jan 30 Thursday	Precision Medicine Overview	Thummel
Feb 4 Tuesday	Mechanisms of DNA damage, polymorphisms in DNA repair and CRISPR gene editing	Kelly
Feb 6 Thursday	Precision Medicine – I (Cystic Fibrosis, Duchenne Muscular Dystrophy)	Kelly
Feb 11 Tuesday	Precision Medicine – II (Cancer Genetics and Phenotypes)	Thummel
Feb 13 Thursday	Genomics and Drug Discovery – I (Intro, CCR5, SOST)	Thummel
Feb 18 Tuesday	Genomics and Drug Discovery – II (PCSK9, APOC3, Nav1.8)	Thummel
Feb 20 Thursday	**EXAM 2 (material from Jan 24 – Feb 18)**	Thummel/Kelly
Feb 25 Tuesday	Polymorphisms, Enzyme Kinetics and Pharmacokinetics	Thummel
Feb 27 Thursday	Pharmacogenetics – I (CYP2D6, CYP2C19, ALDH2)	Thummel
Mar 4 Tuesday	Pharmacogenetics – II (CYP2C9, VKORC1. OATP1B1)	Thummel
Mar 6 Thursday	Pharmacogenetics – III (TPMT, NUDT15, HLA)	Thummel
Mar 11 Tuesday	Genetics and Health Disparities	Thummel
Mar 13 Thursday	ELSI Relevant to Pharmaco- and Toxicogenomics	Thummel
Final Week	**EXAM 3: Wednesday, March 19, 2025, 10:30 am-12:30 p.m.; material from Feb 18 – Mar 13);** **Term paper – due 5 PM, Thursday March 20**	Thummel

Last updated: 1/20/25

NOTE: Lecture slide/notes will be made available on Canvas at least 24-hr before class day. <u>You are strongly encouraged to attend all lectures in-person</u> for an optimum learning experience. Any additional readings will be listed on the Canvas website.

Other Course Lecturers

Ed Kelly, Associate Professor, Dept of Pharmaceutics, UW; edkelly@uw.edu

Alie Fohner, Assistant Professor, Dept Epidemiology, UW; afohner@uw.edu

Course Policies

Attendance and Participation

Students are expected to participate actively in their learning and as a member of the courses in which they are enrolled. Students should arrive on time for the beginning of class; entering the room late is a distraction to others, and you may miss key information. Students who miss classes are responsible for the information presented in their absence.

Exams

All students must take exams at the time and date specified. Students are expected to manage their schedules to take the exams at the times listed on the syllabus. If this is not possible due to a pre-existing conflict, the student must contact the instructor before the start of the quarter. The decision on granting a delay (or make-up) will be at the sole discretion of the instructor. During the quarter, should an unforeseen hardship (such as an infectious illness or a death in the family or hospitalization) arise, the student should make every attempt to contact the instructor prior to the exam to discuss arrangements to reschedule the exam. The format of a make-up exam may be different from the missed exam and is at the sole discretion of the instructor. Any absence that remains unexcused after four days of the exam will result in a score of zero for the missed exam.

Disability Accommodations

Your experience in this class is important to us. If you have already established accommodations with Disability Resources for Students (DRS), please communicate your approved accommodations to the course master at your earliest convenience so we can discuss your needs in this course.
If you have not yet established services through DRS, but have a temporary health condition or permanent disability that requires accommodations (conditions include but not limited to; mental health, attention-related, learning, vision, hearing, physical or health impacts), you are welcome to contact DRS at 206-543-8924 or uwdrs@uw.edu or disability.uw.edu. DRS offers resources and coordinates reasonable accommodations for students with disabilities and/or temporary health conditions. Reasonable accommodations are established through an interactive process between you, your instructor(s) and DRS. It is the policy and practice of the University of Washington to create inclusive and accessible learning environments consistent with federal and state law.

Religious Accommodations

"Washington state law requires that UW develop a policy for accommodation of student absences or significant hardship due to reasons of faith or conscience, or for organized religious activities. The UW's policy, including more information about how to request an accommodation, is available at: https://registrar.washington.edu/staffandfaculty/religious-accommodations-policy/ Accommodations

must be requested within the first two weeks of this course using the Religious Accommodations Request form (https://registrar.washington.edu/students/religious-accommodations-request/)."

Other Important Policies & Resources

Academic Integrity

Students at the University of Washington (UW) are expected to maintain the highest standards of academic conduct, professional honesty, and personal integrity.
The UW School of Public Health (SPH) is committed to upholding standards of academic integrity consistent with the academic and professional communities of which it is a part. Plagiarism, cheating, unauthorized use of artificial intelligence (AI) tools, and other misconduct are serious violations of the University of Washington Student Conduct Code (WAC 478-121). We expect you to know and follow the university's policies on cheating and plagiarism, and the SPH Academic Integrity Policy. Any suspected cases of academic misconduct will be handled according to University of Washington regulations. For more information, see the University of Washington Community Standards and Student Conduct.

Inclusion & Diversity

Diverse backgrounds, embodiments and experiences are essential to the critical thinking endeavor at the heart of University education. In SPH, we are expected:

1. To respect individual differences, which may include, but are not limited to, age, cultural background, disability, ethnicity, family status, gender, immigration status, national origin, race, religion, sex, sexual orientation, socioeconomic status and veteran status.

2. To engage respectfully in the discussion of diverse worldviews and ideologies embedded in course readings, presentations and artifacts, including those course materials that are at odds with personal beliefs and values.

3. To encourage students with concerns about classroom climate to talk to their instructor, adviser, a member of the departmental or SPH EDI Committee, the Assistant Dean for EDI, or the program's director.

Classroom Climate

We are co-creators of our learning environment. It is our collective responsibility to develop a supportive learning environment for everyone. Listening with respect and an open mind, striving to understand others' views, and articulating your own point of view will help foster the creation of this environment. We engage our differences with the intent to build community, not to put down the other and distance our self from the other. Being mindful to not monopolize discussion and/or interrupt others will also help foster a dialogic environment.

The following guidelines can add to the richness of our discussion:

- We assume that persons are always doing the best that they can, including the persons in this learning environment.
- We acknowledge that systematic oppression exists based on privileged positions and specific to race, gender, class, religion, sexual orientation, and other social variables and identities.

- We posit that assigning blame to persons in socially marginal positions is counter-productive to our practice. We can learn much about the dominant culture by looking at how it constructs the lives of those on its social margins.
- While we may question or take issue with another class member's ideology, we will not demean, devalue, or attempt to humiliate another person based on her/his experiences, value system, or construction of meaning.
- We have a professional obligation to actively challenge myths and stereotypes about our own groups and other groups so we can break down the walls that prohibit group cooperation and growth.
  [Adapted from Lynn Weber Cannon (1990). Fostering positive race, class and gender dynamics in the classroom. *Women Studies Quarterly, 1 & 2, 126-134*.]

We are a learning community. As such, we are expected to engage with difference. Part of functioning as a learning community is to engage in dialogue in respectful ways that supports learning for all of us and that holds us accountable to each other. Our learning community asks us to trust and take risks in being vulnerable.

Here are some guidelines that we try to use in our learning process:

- LISTEN WELL and be present to each member of our group and class.
- Assume that I might miss things others see and see things others miss.
- Raise my views in such a way that I encourage others to raise theirs.
- Inquire into others' views while inviting them to inquire into mine.
- Extend the same listening to others I would wish them to extend to me.
- Surface my feelings in such a way that I make it easier for others to surface theirs.
- Regard my views as a perspective onto the world, not the world itself.
- Beware of either-or thinking.
- Beware of my assumptions of others and their motivations.
- Test my assumptions about how and why people say or do things.
- Be authentic in my engagement with all members of our class.

Pronouns

We share our pronouns because we strive to cultivate an inclusive environment where people of all genders feel safe and respected. We cannot assume we know someone's gender just by looking at them. So we invite everyone to share their pronouns.

Bias Concerns

The Office of the Dean has a student concern policy, a faculty concern policy and standard HR procedures for staff concerns. Our 2018 climate survey states that most people in SPH do not report bias incidents because they do not know where to go. Students are encouraged to report any incidents of bias to someone they feel comfortable with, including instructors, advisers or department staff. They can email dcinfo@uw.edu for immediate follow up. Bias concerns can be anonymously and confidentially reported via the online form found here: https://sph.washington.edu/about/diversity/bias-concerns. Data is collected by the Assistant Dean for EDI and the Director of Program Operations for Student and Academic Services and tracked for resolution and areas are identified for further training.

Sexual Harassment

Sexual harassment is a form of harassment based on the recipient's sex that is characterized by:

1. Unwelcome sexual advances, requests for sexual favors, or other verbal or physical conduct of a sexual nature by a person who has authority over the recipient when:
    - Submission to such conduct is an implicit or explicit condition of the individual's employment, academic status, or ability to use University facilities and services, or
    - Submission to or rejection of the conduct affects tangible aspects of the individual's employment, academic status, or use of University facilities.
2. Unwelcome and unsolicited language or conduct that creates an intimidating, hostile, or offensive working or learning environment, or has the purpose or effect of unreasonably interfering with an individual's academic or work performance.

If you believe that you are being harassed, or have observed harassment, you can report it to SPH using the bias concerns link. The University also has designated offices to help you: SafeCampus; Office of the Ombud; Title IX Investigation Office; and University Complaint Investigation and Resolution Office.

Campus Safety

Please visit the UW Campus Safety site (www.uw.edu/safety) for information regarding the University's emergency and safety policies and procedures. Additional helpful resources include SafeCampus (www.uw.edu/safecampus) and UW Alert (www.uw.edu/alert).

COVID-19

Please refer to the EHS guidance: https://www.ehs.washington.edu/covid-19-prevention-and-response/covid-19-health-and-safety

Those who have positive COVID tests, follow the instructions here: https://www.ehs.washington.edu/covid-19-prevention-and-response/covid-19-case-response.

Please follow the Quarantine and Isolation Guidance here: https://www.ehs.washington.edu/covid-19-prevention-and-response/quarantine-and-isolation-guidance.