HUGEN 2029: Introduction to Gene Mapping
3 credits / Fall Term 2021 / Mondays and Wednesdays, 9:30-10:55 am / 2121C Public Health

- Brenda Diergaarde, PhD; Associate Professor of Human Genetics, Pitt Public Health, and UPMC Hillman Cancer Center

Contact information:
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UPCI Cancer Pavilion, Suite 4C
412-623-5891 (office)
bbd3@pitt.edu
Office Hours: By appointment

Faculty Availability: I welcome your questions and suggestions. Please feel free to set up an appointment. Also, if you are having any problems with the course, please contact me as soon as possible. E-mail is a good way to reach me. However, since I get many e-mails, please use an informative subject line starting with “HUGEN 2029”.

Course Description: This course presents a literature-based approach to understanding and interpreting results from gene mapping papers in the field of human genetics. Traditional and state-of-the-art genetic mapping methodologies will be explored.

COVID: If you are required to isolate or quarantine, become sick, or are unable to come to class, contact me as soon as possible to discuss arrangements.

Course Overview and Learning Objectives:
This course covers the (currently) most commonly-used technologies and methodologies for discovering and exploring genotype-phenotype associations. Each methodology will be covered in one or two didactic class sessions, and then participants will read, critique, and present papers that apply the methodology.

At the end of this course, participants should be able to:
• Describe the mathematical and scientific underpinnings of each methodology
• Discuss how the choice of study design influences the choice of methodology (and vice versa)
• Discuss the strengths and limitations of each methodology
• Evaluate gene mapping results in the current literature
• Critique the study design and methodology choices in published gene-mapping studies

Texts/assigned materials:
Participants will need to read and be prepared to discuss assigned materials that will be posted for personal use on Canvas. There is no required textbook for this course.

Exams and Assignments:
- Exams: There will be two (take-home) exams, a mid-term exam and a final exam, to assess students’ ability to understand and critique gene mapping methods. The format will be open-ended questions.

- Student presentations: Each student will review, present and discuss a (recently) published paper in class. Presentations should be short, approximately 20 minutes, and primarily be an introduction to the topic and briefly highlight the paper. The student will subsequently lead a discussion of the paper. The goal of these presentations is to learn to critically review papers, evaluate the strengths and weaknesses of the papers, and to gain experience in public speaking. Everyone is expected to have read the selected papers in advance and come prepared to discuss.
- **Discussions**: In addition to the student presentations, the class as a whole will review and discuss several papers. Everyone is expected to have read the selected papers in advance and come prepared to discuss.

**Student Performance Evaluation:**
All course requirements must be completed to receive credit for the course. Evaluation will be based on the following components:

- **Attendance and Quality of Contribution to Discussion** (25% of final grade)
  Attendance, active participation in class discussions, and evidence of being prepared for class (including having read the assigned readings and completion of assignments) are expected. While cell phones and laptops/tablets may be used to access slides or assigned readings, take notes, etc., please do not use them during class time for non-class purposes. If you will miss a class, please let me know in advance (bbd3@pitt.edu).

- **Student Presentations** (25% of final grade)

- **Mid-term Exam** (25% of final grade)
  Take-home mid-term exam will be posted on Canvas on October 20. The mid-term exam is due on October 25 (by midnight; please submit to: bbd3@pitt.edu).

- **Final Exam** (25% of final grade)
  Take-home final exam will be posted on CANVAS on December 8. The final exam is due on December 15 (by midnight; please submit to: bbd3@pitt.edu).

<table>
<thead>
<tr>
<th>Grade option</th>
<th>Grading scale</th>
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</thead>
<tbody>
<tr>
<td>Letter grade</td>
<td>97 - 100% A+</td>
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<tr>
<td>93 – 96.9% A</td>
<td>77 – 79.9% C+</td>
</tr>
<tr>
<td>90 – 92.9% A-</td>
<td>70 – 72.9% C-</td>
</tr>
<tr>
<td>87 – 89.9% B+</td>
<td>67 – 69.9% D+</td>
</tr>
<tr>
<td>83 – 86.9% B</td>
<td>63 – 66.9% D</td>
</tr>
<tr>
<td>80 – 82.9% B-</td>
<td>60 – 62.9% D-</td>
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**Canvas:**
The University’s Canvas will be used to post announcements, assignments, and readings for personal use.

**Course Policies:**
The Internet generally should not be accessed during class, except to access course slides or assigned readings, help resolve a disputed point in discussion or otherwise enhance discussion. Students should check their email regularly to ensure that they receive relevant communication regarding the course.

Students should familiarize themselves also with the following policies:

- **Academic Integrity Policy:**
  All individuals (students, faculty, post-doctoral researchers, and staff) at Pitt Public Health abide by the University's policy on academic integrity. In accordance with this policy, the school maintains an outline of the procedural sequence of events to occur when violations of academic integrity are brought to the attention of administrative leaders. The full policy is available in the Academic Handbook.
  All students are expected to adhere to the school’s standards of academic honesty. Cheating/plagiarism will not be tolerated. The Graduate School of Public Health’s policy on academic integrity, which is based on the University policy, is available online in the Pitt Public Health Academic Handbook www.publichealth.pitt.edu/home/academics/academic-requirements. The policy includes obligations for faculty and students, procedures for adjudicating violations, and other critical information. Please take the time to read this policy.
Students should be especially mindful of guidelines on academic integrity and take care to avoid plagiarizing the work - including the ideas or words - of their colleagues (fellow course participants) or other authors. Students are encouraged to discuss their ideas and work together; however, a citation to a fellow student should be provided when appropriate.

- Diversity and Academic Civility Statement:
In this course, students, faculty and guests represent a diversity of individual perspectives, backgrounds, and experiences, which enriches our classes. We urge all to be respectful of others.
The University of Pittsburgh Graduate School of Public Health considers the diversity of its students, faculty, and staff to be a strength and critical to its educational mission. Pitt Public Health is committed to creating and fostering inclusive learning environments that value human dignity and equity and promote social justice. Every member of our community is expected to be respectful of the individual perspectives, experiences, behaviors, worldviews, and backgrounds of others. While intellectual disagreement may be constructive, no derogatory statements, or demeaning or discriminatory behavior will be permitted.
If you feel uncomfortable or would like to discuss a situation, please contact any of the following:
• the course instructor (bbd3@pitt.edu or see phone number above);
• the Pitt Public Health Associate Dean responsible for diversity and inclusion (Dr. Tiffany Gary-Webb: tgary@pitt.edu // 412-624-3131);
• the University’s Office of Diversity and Inclusion at 412-648-7860 or https://www.diversity.pitt.edu/make-report/report-form (anonymous reporting form)

- Accommodation for Students with Disabilities:
If you have any disability for which you may require accommodation, you are encouraged to notify both your instructor (bbd3@pitt.edu) and the Office of Disability Resources and Services (DRS), 140 William Pitt Union (Voice or TTD 412-648-7890), http://www.studentaffairs.pitt.edu/drs/, drsrecep@pitt.edu, as early as possible in the term.

- Copyright Notice:
Course materials may be protected by copyright. United States copyright law, 17 USC section 101, et seq., in addition to University policy and procedures, prohibit unauthorized duplication or retransmission of course materials. See Library of Congress Copyright Office and the University Copyright Policy.

- Classroom Recording:
To ensure the free and open discussion of ideas, students may not record classroom lectures, discussion and/or activities without the advance permission of the instructor, and any such recording properly approved in advance can be used solely for the student's own private use or for all students enrolled in this class only but may not be further copied, distributed, published, or otherwise used for any other purpose without the express written consent of the course instructors. Any student who records a class session must provide a copy of the recording to the instructors if requested to do so.

- Sexual Misconduct, Required Reporting, and Title IX:
The University is committed to combatting sexual misconduct. As a result, you should know that University faculty and staff members are required to report any instances of sexual misconduct, including harassment and sexual violence, to the University’s Title IX office so that the victim may be provided appropriate resources and support options. What this means is that as your professor, I am required to report any incidents of sexual misconduct that are directly reported to me, or of which I am somehow made aware.
There are two important exceptions to this requirement about which you should be aware:
(1) A list of the designated University employees who, as counselors and medical professionals, do not have this reporting responsibility and can maintain confidentiality, can be found here: https://www.diversity.pitt.edu/civil-rights-title-ix/make-report/report-form
(2) An important exception to the reporting requirement exists for academic work. Disclosures about sexual misconduct that are shared as part of an academic project, classroom discussion, or course assignment, are not required to be disclosed to the University’s Title IX office

If you are the victim of sexual misconduct, Pitt encourages you to reach out to these resources:
• Title IX Office: 412-648-7860 (https://www.titleix.pitt.edu/)
• SHARE @ the University Counseling Center: 412-648-7930 (8:30 A.M. TO 5 P.M. M-F) and 412-648-7856 (AFTER BUSINESS HOURS)
If you have a safety concern, please contact the University of Pittsburgh Police, 412-624-2121.
<table>
<thead>
<tr>
<th>Date</th>
<th>Topics</th>
</tr>
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<tbody>
<tr>
<td>Monday August 30</td>
<td>Course introduction</td>
</tr>
<tr>
<td>Wednesday September 1</td>
<td>cancelled</td>
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<tr>
<td><strong>Monday September 6</strong></td>
<td><strong>LABOR DAY HOLIDAY – No class (university closed)</strong></td>
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<tr>
<td>Wednesday September 8</td>
<td>Study design, study populations, diversity</td>
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<td><strong>September 10-12</strong></td>
<td><strong>Human Genetics retreat</strong></td>
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<tr>
<td>Monday September 13</td>
<td>cancelled</td>
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<tr>
<td>Wednesday September 15</td>
<td>Candidate gene association studies / discussion</td>
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<tr>
<td>Monday September 20</td>
<td>Genome-wide association studies (GWAS)</td>
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<tr>
<td>Wednesday September 22</td>
<td>GWAS – imputation and combining datasets</td>
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<tr>
<td>Monday September 27</td>
<td>Polygenic risk scores (and what about the environment?)</td>
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<tr>
<td>Wednesday September 29</td>
<td>GWAS discussion</td>
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<tr>
<td>Monday October 4</td>
<td>GWAS follow-up; eQTL analysis, gene set analysis</td>
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<tr>
<td>Wednesday October 6</td>
<td>GWAS follow-up discussion</td>
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<tr>
<td>Monday October 11</td>
<td>Sequencing - biochemistry, rare variants, and cancer</td>
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<tr>
<td>Wednesday October 13</td>
<td>Sequencing - association studies</td>
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<tr>
<td>Monday October 18</td>
<td>Sequencing discussion</td>
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<tr>
<td><strong>October 18-22</strong></td>
<td><strong>ASHG virtual meeting:</strong> <a href="https://www.ashg.org/meetings/2021meeting/">https://www.ashg.org/meetings/2021meeting/</a></td>
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<tr>
<td>Wednesday October 20</td>
<td>No class – mid-term exam posted on Canvas</td>
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<tr>
<td><strong>Monday October 25</strong></td>
<td><strong>No class – mid-term exam due (by midnight)</strong></td>
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<tr>
<td>Wednesday October 27</td>
<td>Family-based designs, linkage analysis</td>
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<tr>
<td>Monday November 1</td>
<td>Family-based studies discussion</td>
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<tr>
<td>Wednesday November 3</td>
<td>Epigenetics, methylation</td>
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<tr>
<td>Monday November 8</td>
<td>Methylation studies discussion</td>
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<tr>
<td>Wednesday November 10</td>
<td>Expression data, transcriptome-wide association studies, RNA-seq, single cell RNA-seq</td>
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<tr>
<td>Monday November 15</td>
<td>Expression discussion</td>
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<tr>
<td>Wednesday November 17</td>
<td>Copy number variants (CNVs) / role of CNVs in disease</td>
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<tr>
<td><strong>Monday November 22</strong></td>
<td><strong>THANKSGIVING HOLIDAY – No class</strong></td>
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<tr>
<td><strong>Wednesday November 24</strong></td>
<td><strong>THANKSGIVING HOLIDAY – No class</strong></td>
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<tr>
<td><strong>Monday November 29</strong></td>
<td><strong>Post-transcriptional regulation</strong></td>
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<tr>
<td>Wednesday December 1</td>
<td>Other genomes: the microbiome and mitochondria</td>
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<td>Monday December 6</td>
<td>Multi-omics approaches</td>
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<tr>
<td>Wednesday December 8</td>
<td>Mendelian randomization</td>
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<tr>
<td>Monday December 13</td>
<td>Topic tbd – <strong>final exam posted on Canvas</strong></td>
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<tr>
<td><strong>Wednesday December 15</strong></td>
<td><strong>No class – final exam due (by midnight)</strong></td>
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General Outline for Student Presentations – HUGEN 2029

- Paper title, journal, authors (1 slide)

- Introduction: brief description of the central question addressed in the paper and its significance (1-2 slides).
  What is the goal of the described study? What is the hypothesis?

- Previous studies: summarize previous studies relevant to the paper (1-2 slides).

- Study design: give overview of study design used.
  Anything in previous studies or background that made going with this design obvious or that argues against this type of design? What are the strengths and limitations of this design? Would you have used this design? Discuss why or why not?

- Methods: describe what methods are used in the paper.
  What are the strengths and limitations of the methods used? Do the methods employed make sense given the study design? Would you have used these/similar methods? Discuss why or why not?

- Results: show and discuss the results.
  Do the results make sense? Do you agree with the authors’ interpretation of the results? Discuss why or why not.

- Summary/Conclusions: briefly reiterate key findings and the strengths and limitations of the study in particular in relation to study design and methods employed.
  Did the authors use appropriate design and methods? Do you agree with the interpretation of the results? Discuss why or why not.

Rubric for Student Presentations – HUGEN 2029

<table>
<thead>
<tr>
<th>Category</th>
<th>Elements</th>
<th>Weight</th>
</tr>
</thead>
</table>
| Knowledge and explanation of topic, discussion: | • Conveys understanding  
  • Presents the essential information  
  • Accurate description of methodology, study design, goals and hypotheses, etc.  
  • Good discussion of strengths and limitations | 75     |
| Overall organization of section/talk      | • Content introduced in logical, easy-to-follow sequence  
  • Main points emphasized, repeated  
  • Use of transition statements | 10     |
| Overall effectiveness of slides (text and visuals) and delivery | • Good balance of text & figures/tables  
  • Text/figures/tables large enough to be seen  
  • Not too many or too few slides  
  • Confident, enthusiastic delivery  
  • Eye contact  
  • Get to main points quickly | 15     |
Background/suggested readings (all posted on CANVAS)

**Study design, study populations, diversity:**

- Ballouz et al. Is it time to change the reference genome? (uploaded)
- Too many scientists still say Caucasian. Racist ideas of categories for human identity continue to warp research and medicine. Alice B. Popejoy [Too many scientists still say Caucasian](https://www.nature.com) (nature.com)

**Candidate gene association studies:**


**Genome-wide association studies:**

- Howie et al. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. *Nature Genetics* 2012 (attached)
**Polygenic risk scores:**

- What are polygenic risk scores and why are they important? *JAMA* May 14, 2019 Volume 321, Number 18
- Lambert et al. The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. Nature Genetics 2021

**Sequencing:**

Websites:

BEST PRACTICES FOR VARIANT CALLING WITH THE GATK - Link to presentations filmed during the March 2015 GATK Workshop, part of the BroadE Workshop series. This workshop focused on the core steps involved in calling variants with Broad's Genome Analysis Toolkit, using the "Best Practices" developed by the GATK team. View the workshop materials below to gain an understanding of the rationale, theory, and real-life applications of GATK Best Practices. Learn why each step is essential to the calling process, what key operations are performed on the data at each step, and how to use the GATK tools to get the most accurate and reliable results out of your dataset. [Best Practices for Variant Calling with the GATK | Broad Institute](https://www.broadinstitute.org/scientists/technical-workshops)

GATK: [GATK (broadinstitute.org)](https://www.broadinstitute.org/scientists/technical-workshops) (Links to an external site.)

The Broad technical workshops: [https://www.broadinstitute.org/scientists/technical-workshops](https://www.broadinstitute.org/scientists/technical-workshops) (Links to an external site.)

On CADD (Combined Annotation Dependent Depletion; variant annotation): [https://cadd.gs.washington.edu/](https://cadd.gs.washington.edu/) (Links to an external site.)

Papers:


Daniel C. Koboldt Best practices for variant calling in clinical sequencing. *Genome Medicine* volume 12, Article number: 91 (2020) [Koboldts13073-020-00791-w.pdf](https://cadd.gs.washington.edu/)
Family-based approaches:


Methylation, chromatin profiling - background papers

Methylation:


Chromatin:


**Gene expression, TWAS, RNA-seq:**


CNV and other structural variation:


Tech note from Illumina: Interpreting Infinium® Assay Data for Whole-Genome Structural Variation technote_cytoanalysis.pdf


