Syllabus Fall 2024

MCB 474: Genetic Disorders and Counseling

3 credit hours

Location: 432 Armory

Course Description

This course is designed for graduate students and upper-level undergraduates because it builds on basic concepts like Mendelian genetics and principles of inheritance that were covered in earlier molecular biology and genetics classes. Here, the students will explore and apply basic principles of medical ethics, emphasizing the personal nature of genetics and patient autonomy. Students will also learn the underpinnings of chromosome disorders and importantly, prenatal diagnosis and the newborn screen. Essentially, GDC is at the interface of science and technology and clinical practice. The course uses feature articles in Science and peer-reviewed articles in other top-ranking journals on the genetics of neurodevelopment, autism, intelligence, and Alzheimer’s disease. At the same time, respect for patient autonomy and an appreciation of what it means for someone to be a carrier of a genetic disorder or have a tumor with genetic abnormalities will be explored through videos.

Course Goals and Objectives

The goals of this course are to:

- Prepare students to be proficient in medical genetics by understanding the principles identified in the MCAT topics in genetics and to prepare students for a career in genetic counseling.
- Prepare students to be able to evaluate emerging genetic technologies in the care of patients.

Course Structure

This is a 3-credit hour course that meets Tuesday and Thursday for the entire Fall semester from 11:00-12:20 PM. The expected number of hours of student work outside of class is 6 hours, including review of the week’s material, preparation of weekly Reflections and authored exam questions. There will be opportunities for constructivism, in-class participation using case-based vignettes, problem-solving and writing.

Instructor

Professor Stephanie Ceman is the instructor and has been teaching medical genetics to medical students and undergraduates since 2004. She received her PhD in Genetics from the University of Wisconsin-Madison. Her office is room 423 in the Medical Sciences building and she is happy to arrange appointments by email (sceman@illinois.edu). She will also reserve 3:15-4:15 PM on Monday afternoon of the Fall semester as an office hour, beginning September 9th.
Textbooks

The recommended text for this course is: *Thompson & Thompson Genetics in Medicine*. Cohn, Scherer and Hamosh. 9th edition. 2024. W.B. Saunders Company, which can be accessed in either link below

https://www.clinicalkey.com/#/browse/book/3-s2.0-C2009059798X

Medical Genetics by Jorde *et al* is also an excellent resource (linked below)

https://www-clinicalkey-com.proxy2.library.illinois.edu/#/browse/book/3-s2.0-C20170009679.

Readings from the textbook are optional but recommended for any topics with which you may have questions. You will not need to read entire chapters: please use the index or search function.

You can also order this textbook from the Illini Union Bookstore (IUB) (217-333-2050). Be certain you select the correct term from the "Search by Course" dropdown list. Used books are often available and can be provided at a cost savings to you. Note that the cost and postage for all books must be prepaid. You can charge your order using VISA, Discover, or MasterCard. If you are ordering books elsewhere (e.g., Amazon.com), please be sure to order the correct edition and year of publication.

Prerequisites

MCB 317, or equivalent, or consent of instructor

Student Learning Outcomes

At the end of this course, students should be able to do the following:

1. Apply the four basic principles of Bioethics
2. Use online tools like OMIM or other NIH sponsored websites to facilitate diagnosis and prognosis
3. Describe the three liveborn trisomies and the karyotypes of the parents
4. Calculate the recurrence risk for multifactorial disorders using empirical data
5. Understand the genetic basis of common diseases like autism and Alzheimer’s disease
6. Understand the role of a genetic counselor and how to pursue training in that field

Course Outline

**Tentative Dates and Lecture topics**

<table>
<thead>
<tr>
<th>Date</th>
<th>Title/topic</th>
<th>Associated readings in Thompson and Thompson or other sources</th>
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<tbody>
<tr>
<td>T, Aug. 27</td>
<td>1. Introduction to the course and principles of bioethics</td>
<td>Chapter 1 and 20</td>
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<tr>
<td>Date</td>
<td>Topic</td>
<td>Chapter/Reference</td>
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<tr>
<td>R, Aug. 29</td>
<td>2. Human variation and prevalence of human disease</td>
<td>Chapter 4</td>
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<tr>
<td>T, Sept. 3</td>
<td>3. Review of Mendelian inheritance</td>
<td>Chapter 7, refresher ppt on Mendelian genetics</td>
</tr>
<tr>
<td>R, Sept. 5</td>
<td>4. Prenatal diagnosis and the newborn screen.</td>
<td>Chapter 18; Video interview with genetic counselor Judy Miller on how to give a diagnosis</td>
</tr>
<tr>
<td>T, Sept 10</td>
<td>5. Chromosome nomenclature</td>
<td>Chapter 2 and 5</td>
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<tr>
<td>R, Sept 19</td>
<td>Review</td>
<td></td>
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<tr>
<td>T, Sept 24</td>
<td>Exam 1</td>
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<tr>
<td>R, Sep 26, T October 1</td>
<td>7. Calculating disease incidence and population genetics. These calculations are relevant for risk calculations in families of specific ancestries</td>
<td>Chapters 10 and 17; Watch “Sunkissed” documentary</td>
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<td>T, Oct 8</td>
<td>9. Principles of cloning and stem cell production</td>
<td>Chapter 3</td>
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<tr>
<td>R, Oct 10</td>
<td>10. Introduction to cystic fibrosis and gene linkage</td>
<td>Chapter 13</td>
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<tr>
<td>R, Oct 17</td>
<td>Review</td>
<td></td>
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<td>T, Oct. 22</td>
<td>Exam 2</td>
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<tr>
<td>T, Oct 29, R, Oct 31</td>
<td>13. Complex inheritance and gene by environment interactions. These calculations are relevant for recurrence risk calculations</td>
<td>Chapter 9</td>
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**Course Activities**

You are expected to complete your work independently, in accordance with University policy. Failure to do so will result in strict disciplinary action, including loss of all credit for the assignment, notification of a dean, and possible dismissal from the University. You may work with others on homework, but the final product must be your own.

**Assignments, Weights, and Deliverables**

You can access your scores on the Course website.

Points for weekly Reflections, authored exam questions, in-class participation points (please note that the latter cannot be made-up) are described below.

**Reflections**

At the end of each week, you will take time to reflect on what you have learned in the week, which is worth 15% of the total grade. The focus of this reflection is a review of your initial thoughts and how your knowledge about the week’s content has changed. The grading rubric is on the course website.

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<thead>
<tr>
<th>Date</th>
<th>Activity</th>
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<tbody>
<tr>
<td></td>
<td>Supplemental article: Ceman and DeThorne</td>
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<tr>
<td>R, Nov 7</td>
<td>Review</td>
</tr>
<tr>
<td>T, Nov 12</td>
<td>Exam 3</td>
</tr>
<tr>
<td>R, Nov 14</td>
<td>15. Genetics of neurodevelopmental disorders with a focus on trinucleotide repeat disorders</td>
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<td></td>
<td>Chapter 13</td>
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<tr>
<td>T, Nov 19</td>
<td>16. Genetics of intelligence</td>
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<td></td>
<td>Supplemental article: Sniekers, 2017 Nat.Genetics</td>
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<td></td>
<td>Chapter 9</td>
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<td></td>
<td>Thanksgiving break</td>
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<tr>
<td>T, Dec 3</td>
<td>18. Hereditary cancers</td>
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<tr>
<td></td>
<td>Chapter 16</td>
</tr>
<tr>
<td>R, Dec 5</td>
<td>19. Genetics of spontaneous cancers</td>
</tr>
<tr>
<td></td>
<td>Chapter 16</td>
</tr>
<tr>
<td>T, Dec 10</td>
<td>Exploring a career in genetic counseling; review of relevant websites</td>
</tr>
</tbody>
</table>
Authored exam questions.

Writing a question that tests knowledge of concepts and does not merely reflect memorization is an important learning tool. 10% of your grade will be earned by authoring an exam question/test so they are worth 2.5% apiece. Please note, you may see your question on the exam!

In-Class participation points.

During each class period, there will be at least one opportunity–likely more– to answer a complicated multiple-choice question, after discussion with your peers, using your i-clicker. You do not need to answer it correctly, but to receive the participation points, you need to click in.

Final Paper

Please prepare a research paper that explores and importantly, builds upon any topic you learned about this semester. The broad goal is to pitch an idea or a next direction that is a natural and novel development of what you learned in the course. You may have pages of research but I will only be grading the first page of this part of the Final Paper.

The Final Paper has three parts: 1) the research paper itself, described above (I will give an example below); 2) the generative AI response to your final hypothesis or “pitch” (I suggest you use Perplexity AI because it gives citations); 3) your critique of the AI response.

Specific example of a final essay topic that was not covered in this course, thus, is not a possible topic: the genetics of longevity. The question is “why do some human beings live to be 100 years or older?” One hypothesis is that centenarians have specific alleles at the apolipoprotein C3 locus that contribute to their longevity. Now provide the evidence that supports or refutes this hypothesis. If the hypothesis is refuted by your research, describe how it was refuted and state a new hypothesis. For this example, in the last sentence or 2 of the assignment, pitch or propose a way to increase human longevity through a possible treatment approach supported by your research: examples might be a specific diet, or small molecule activators or inhibitors, or microbiome changes, etc..

Continuing with the example of longevity, the query to Perplexity AI might be “Why do some human beings live to be 100 years or older?” Then you could enter your hypothesis. Please copy-paste the entire exchange with Perplexity AI into your Final Paper on a new page and label this is as #2 AI response. If you do not use Perplexity AI, please include the name of the generative AI program that you used.

For part 3 of the Final paper, evaluate the AI-generated response to your Final Paper. Specifically, note what was accurate; what was inaccurate or missing from the AI-generated response, and finally, your own summary assessment of the AI response. This assessment need only be a couple of sentences.

Grading Rubric.

- Identify a topic or disease that you find interesting and identify the question and hypothesis that you will test (10 pts)
- Indicate lecture number or date (5 pts)
- Explain why you found it interesting (5 pts)
- Research part (40 pts):
  - What aspects would you explore next and why (you will need references here)
  - Speculate on the next break-through or treatment approach (you will likely need references here supporting your idea). Please insert the citations after the sentence they are supporting.
• As references, you must have at least two primary papers and one review (10 pts) but they are outside of the word limit. Insert the references immediately after you use that information (more on that below)
• This is the first part of the Final Project and should be about a page (350 words). Please note, you may have pages of research but I will only grade this first page pitch or “abstract.”
• The second part is the AI response (15 pts)
• The third part is your critique of the AI response (15 pts).

This activity is worth 100 pts or 10% of your grade and is due on …TBA

References. You should include references/citations after every fact you state—either as first-author/year or number—inserted immediately after the relevant sentence where the information is cited. On a separate page at the end of this first document, please include the list of the complete references (authors, date, title, journal, page numbers and DOI). The reference list is not included in the word limit.

If you would like feedback about your idea, please contact me and we will set up a time to meet.

Exams
Four exams will be given in-class. Each will be comprised of ~35 multiple choice questions.

Final grade: There are 15 weeks of instruction. The contribution of each activity to your total grade is as follows
  Reflections: 15% (1.0%/week)
  Authored exam questions: 10%
  Participation points identified by iClicker polling 5.0% (0.25% x 20 lectures)
  Final Project/essay: 10%
  Exams: 60% (15% for each exam).

Scale:

<table>
<thead>
<tr>
<th>Letter Grade</th>
<th>Point Ranges</th>
<th>Grade Point Value</th>
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<tbody>
<tr>
<td>A+</td>
<td>1000–920</td>
<td>4.000</td>
</tr>
<tr>
<td>A</td>
<td>919–880</td>
<td>4.000</td>
</tr>
<tr>
<td>A-</td>
<td>879–840</td>
<td>3.667</td>
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<tr>
<td>B+</td>
<td>839–800</td>
<td>3.333</td>
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<tr>
<td>B</td>
<td>799–760</td>
<td>3.000</td>
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<tr>
<td>B-</td>
<td>759–720</td>
<td>2.667</td>
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<td>C+</td>
<td>719–680</td>
<td>2.333</td>
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<td>C</td>
<td>679–640</td>
<td>2.000</td>
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<tr>
<td>C-</td>
<td>639–600</td>
<td>1.667</td>
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<tr>
<td>D+</td>
<td>599–560</td>
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<td>559–520</td>
<td>1.000</td>
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<td>D-</td>
<td>519–480</td>
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</table>
A note about sources of information: It is highly recommended that you only consult the following sources of information in studying for this class. Use of another source (such as Internet sites found via Google) may provide information that is unreliable.

- Suggested books and readings
- Supplemental information posted on course website
- Internet links provided in class or on course website
- Any website that is sponsored by the National Institutes of Health (NIH)

Course Policies and Resources (ex. MCB Core Curriculum Policies)

For non-academic campus assistance and support:
- See Office of Diversity, Equity and Access (ODEA) information at the end of this document.

Student Advocacy Resources:
- For student-centered advocacy programs and services visit: mcb.illinois.edu/undergrad/advising/resources.

Contacting MCB Course Personnel:
- MCB course personnel are more than happy to assist students.
- Emails to instructors, TAs, or course coordinators will only be answered if they come from an @illinois.edu account. We will only use this account in order to protect your educational information and profile. As a student, please remember that when you email a staff member, it is important to include all pertinent information so that we can assist you in the most efficient and effective manner possible. This information includes:
  o The course rubric in the subject line
  o Your full first and last name
  o Your NetID (the first part of your illinois.edu email account)
  o Your UIN (9 digit number that can be found on your ICard)
  o The course that you are concerned about (the course personnel often work with multiple courses)
  o Your section letter/number
  o The previous email “thread” or previous communicated information pertinent to the situation
- Your cooperation will help us respond much more quickly to your concerns.

Religious Observances and Practices:
- Students are required to submit the Request for Accommodation for Religious Observances Form (which can be found at www.odos.illinois.edu/.../Religious_Observance_Accommodation_Request_Form.docx) to their instructors and the Office of the Dean of Students requesting accommodation by the end of the second week of the course. Requests that are not submitted within this time frame may not be granted. Information about accommodations can be found in the Student Code: http://studentcode.illinois.edu/.
Students with Disabilities

To obtain disability-related academic adjustments and/or auxiliary aids, students with disabilities must contact the course instructor as soon as possible. To ensure that disability-related concerns are properly addressed from the beginning, students with disabilities who require assistance to participate in this class should contact Disability Resources and Educational Services (DRES) and see the instructor as soon as possible. If you need accommodations for any sort of disability, please speak to me after class, or make an appointment to see me or see me during my office hours. DRES provides students with academic accommodations, access, and support services. To contact DRES you may visit 1207 S. Oak St., Champaign, call 333-4603 (V/TDD), or e-mail disability@illinois.edu. http://www.disability.illinois.edu/.

Class Absences:

- Regular class attendance is expected of all students at the University. (http://odos.illinois.edu/studentAssistance/absence/revised_code.asp)
- The Office of the Dean of Students will only provide informative letters to instructors for protracted illness of 3 or more days, certain emergencies and to be present during the serious illness of immediate family members (parents, legal guardian, spouse/partner, siblings, children, or grandparents). These letters do not excuse you from class but merely provide information for the instructor to consider with regard to excusing the absence and permitting make-up work. Students must request absence letters from the Office of the Dean of Students after the student has returned to class but not more than 10 business days after the last date of absence.
- Absences that may be excused without a letter include circumstances beyond the student’s control such as medical treatment, surgery related to prolonged illness or injury, pregnancy, legal matters, citizenship or naturalization processes, or acts of nature which cause destruction to a primary residence or disrupt air travel. All will require documentation.
- Absences that may also be excused without a letter include job, graduate or professional school interviews, though a best effort should be made to schedule these events to minimize class attendance disruption.
- Absences planned for the items listed in previous bullet point must be communicated to your instructor or course coordinator at least two weeks in advance of the absence. Failure to do so may result in the loss of opportunity to reschedule the missed class period and the portion of the grade associated with this class period.
- Absences that will not be excused include family events such as reunions or weddings, or presence during serious illness of extended family members (aunt, uncle, niece, nephew, or cousin).
- Unplanned absences may result in the loss of opportunity to reschedule the missed class period and, therefore, the portion of the grade associated with this class period.
- Absences will be handled according to individual course policy.

Exam Conflicts:

- If you have a regularly scheduled University course that conflicts with the exam, you should contact the instructor about taking the exam through Proctor U. This request must be made by 5:00 pm not less than 3 business days prior to the exam. Requests made after 5:00 pm and less than 3 business days prior to the exam will not be granted. See course policies for a specific deadline for your course.
- Work schedules should be adjusted, if at all possible, in order to eliminate a conflict with scheduled exams. Please plan accordingly at the beginning of the semester. If eliminating a conflict is not possible, the student should complete the online Conflict Exam Request Form on
the course website. This request must be made by 5:00 pm not less than 3 business days prior to the exam. Requests made after 5:00 pm and less than 3 business days prior to the exam will not be granted.

- Students that are formally participating in officially recognized groups, such as athletic teams and performing groups, with a conflict should request a conflict exam by 5:00 pm not less than 3 days prior to the exam via the online Conflict Request Form. Formal participation does not include general meetings of RSOs or any other recognized groups. Documentation of the event will be required prior to scheduling the conflict exam. Requests made after 5:00 pm and less than 3 business days prior to the exam will not be granted.
- Students with DRES accommodations should also submit the online Conflict Request Form by 5:00 pm no later than 3 business days prior to the exam. Requests made after 5:00 pm and less than 3 business days prior to the exam will not be granted.

**Final Exam Absence or Conflict:**
- If you must miss a final exam due to unforeseen circumstances, you are required to contact your instructor or course coordinator within 24 hours of the absence. You must also contact the Dean of your college. You will receive an ABS (absent) in the course if you miss the final exam. This ABS will result in an F in the course unless action is taken. The Dean can approve the change of the ABS to an Incomplete, which then allows a limited window of time for you to complete the final exam and earn a grade in the course.
- If the absence is a result of a protracted illness, you should follow the procedure for obtaining a letter from the Office of the Dean of Students. The request may be made once the student recovers but not more than 10 business days after the date of absence.
- Information about final exams can be found in the Student Code: http://studentcode.illinois.edu/.

**Academic Integrity:**
- Science cannot exist without honesty. The faculty and staff in MCB require students, as scientists-in-the-making, to hold the highest standards of scientific and academic conduct. Any form of cheating on any graded work in courses is unacceptable, and will be dealt with as outlined below, and in accordance with the University-wide standards in the Code of Policies and Regulations Applying to All Students.
- We require that all graded work be entirely your own, and that anything you write using the words of other writers be correctly attributed. Some specific points follow.
- On exams, the answers that your turn in for grading must be your own, formulated during the exam from your own understanding of the material and without any supporting information, be it written, verbal or electronic. Copying the work of another student, or allowing another to copy your work, or copying work from any other source, is unacceptable. Since we cannot always monitor you as you complete your work, we must rely upon appearance of your work from which to judge. If the work you submit resembles that of another student or another source too closely, we may conclude that it was not your original work. Always make a conscious effort to complete your work on your own and to protect it from the view of others, in order to ensure that it will be seen as your own. Failure to adhere to these standards for any portion of an exam may result in a grade of zero for the entire exam or quiz for all persons involved.
- Texting, or the use of a cell phone or any other device for any purpose, during a quiz or exam is prohibited. Doing so may earn you a zero or a more extreme penalty on the quiz or exam at the discretion of the instructor.
Use of any social or electronic media to share information, request information or make confidential information public is prohibited. Any use of this type may earn you a zero on the exam or a more extreme penalty at the discretion of the instructor.

On written or electronic assignments, the answers that you turn in for grading must be written in your own words, formulated from your own understanding of the material. While you may be working with other students in the course, you must formulate and submit your own answers. Copying or paraphrasing the work of another student, or allowing another to copy or paraphrase your work, is unacceptable. Since we cannot monitor you as you complete your work, we have only the appearance of your work from which to judge. If the work you submit resembles that of another student too closely, we may conclude that it was not your original work. Always make a conscious effort to complete your work on your own and to protect it from the view of others, in order to ensure that it will be seen as your own. You must also make a conscious effort to protect your passwords and accounts. Failure to adhere to these standards may result in a grade of zero for the entire assignment for all persons involved.

On written or electronic assignments, if you use a statement taken directly from any book or other publication, including the course textbook, you must provide a citation. That is, you must put the text in quotes and put the author of the publication in parentheses after the quotation. Failure to do so will result in zero credit for that answer. Further, using only the words of another author as your entire answer or as the majority of your answer to any question is never sufficient to earn credit. If the majority of your work has been taken directly from a publication, you are likely to receive no credit for the work, since you would not be demonstrating knowledge beyond the ability to copy. Even if you quote another, your answer must be substantially your own words, drawn from your own understanding of the material.

Social Media Use:

- Use of any social or electronic media to share course information, request course information or make confidential course information public is prohibited. Any use of this type may earn you a zero or a more extreme penalty at the discretion of the instructor on an assignment or exam.
- Any social media sites created in relation to MCB courses must grant access to course personnel upon request. Failure to provide access will result in a failing grade in the course for the group/site’s administrator(s).

Course Material:

- Students are welcome and encouraged to make audio recordings of course lectures.
- The material recorded is intellectual and copyrighted property of the University of Illinois Board of Trustees and may be made for personal use only.
- Video recordings of any kind are strictly prohibited.
- Posting of audio recordings or transcriptions on social or electronic media platforms is strictly prohibited.
- Posting or redistributing of course material in any format is strictly prohibited.

University Information on Student Safety

Active Threats:

- General Emergency Response Recommendations (Emergency Response Guide):
- Security Threat. The Department of Homeland Security and the University of Illinois at Urbana-Champaign Office of Campus Emergency Planning recommend the following three responses to any emergency on campus: **RUN > HIDE > FIGHT**
• **Only follow these actions if safe to do so.** When in doubt, follow your instincts - you are your best advocate!

• **RUN** — Action taken to leave an area for personal safety.
  - Take the time to learn the different ways to leave your building **before** there is an emergency.
  - Evacuations are mandatory for fire alarms and when directed by authorities! No exceptions!
  - Evacuate immediately. Pull manual fire alarm to prompt a response for others to evacuate.
  - Take critical personal items only (keys, purse, and outerwear) and close doors behind you.
  - Assist those who need help, but carefully consider whether you may put yourself at risk.
  - Look for **Exit** signs indicating potential egress/escape routes.
  - If you are not able to evacuate, go to an Area of Rescue Assistance, as indicated on the front page of this plan.
  - Evacuate to Evacuation Assembly Area, as indicated on front page of this plan.
  - Remain at Evacuation Assembly Area until additional instructions are given.
  - Alert authorities to those who may need assistance.
  - Do not re-enter building until informed by emergency response personnel that it is safe to return.
  - Active Threat: **IF** it is safe to do so, run out of the building. Get as far away as possible. Do NOT go to the Evacuation Assembly Area.

• **HIDE** — Action taken to seek immediate shelter indoors when emergency conditions do not warrant or allow evacuation.
  - **Severe Weather:**
    - If you are outside, proceed to the nearest protective building.
    - If sheltering-in-place due to severe weather, proceed to the identified Storm Refuge Area or to the lowest, most interior area of the building away from windows or hazardous equipment or materials.
  - **Active Threat:**
    - Lock or barricade your area.
    - Get to a place where the threat cannot see you.
    - Place cell phones on silent.
    - Do not make any noise.
    - Do not come out until you receive an Illini-Alert advising you it is safe.

• **FIGHT** — Action taken as a last resort to increase your odds of survival.
  - Active Threat: If you cannot run away safely or hide, be prepared to fight with anything available to increase your odds for survival.

**We Care at Illinois:**
- For sexual misconduct support, response and prevention visit: wecare.illinois.edu

Title IX makes it clear that violence and harassment based on sex and gender are Civil Rights offenses subject to the same kinds of accountability and the same kinds of support applied to offenses against other protected categories such as race, national origin, etc. If you or someone you know has been harassed or assaulted, you can find the appropriate resources here:
The Office of Diversity, Equity and Access (ODEA):
- For non-academic support visit: diversity.illinois.edu
  - Discrimination & Harassment Prevention
  - Title IX
  - Accessibility & Accommodations
  - Inclusive Illinois

Mental Health Statement
- Significant stress, mood changes, excessive worry, substance/alcohol misuse or interferences in eating or sleep can have an impact on academic performance, social development, and emotional wellbeing. The University of Illinois offers a variety of confidential services including individual and group counseling, crisis intervention, psychiatric services, and specialized screenings which are covered through the Student Health Fee. If you or someone you know experiences any of the above mental health concerns, it is strongly encouraged to contact or visit any of the University’s resources provided below. Getting help is a smart and courageous thing to do for yourself and for those who care about you.
- Counseling Center (217) 333-3704
- McKinley Health Center (217) 333-2700
- National Suicide Prevention Lifeline (800) 273-8255
- Rosecrance Crisis Line (217) 359-4141 (available 24/7, 365 days a year)

This statement is approved by the University of Illinois Counseling Center.