This course proposal and syllabus was written by Katerina Tori '18, Brooke Spencer '19 and Robert K Campbell for Brown University's College Curriculum Council. It was submitted March 6, 2018 and approved March 23 with curriculum designations for i) Community-Based Learning & Research. ii) Diversity & Inclusion Action Plan-Race, Gender & Inequality; and iii) Sophomore Seminar. Further refinements were made in each semester of the course.

BIOL-0940E Precision Medicine or Privileged Medicine? Addressing disparities in the inclusiveness of biomedical research.

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Office hours: TBD

Semester: Fall 2018 *Classroom location*: TBD *Meeting time*: TBD (2 hours, 30 minutes)

Enrollment: Limited to 15 sophomores

Prerequisites: None. All students must contact instructor to express interest and request override

Course materials and resources: All required readings will be available through the Brown Library, Canvas, or open access online. There is no textbook for this course. Supporting resources to help students approach and assess scientific papers will be posted in the course Canvas site prior to the first day of class.

***Course description*:** This sophomore seminar will examine the biomedical research behind precision medicine, disparities in the inclusiveness of this research, and their implications for the relevance of precision medicine innovations for people and places in Rhode Island. Our examination will consider multiple diseases and therapeutic needs. We will also explore the complex network of stakeholders who collectively influence how research is translated into patient care. Our approach will include four questions: What new knowledge is making precision medicine possible? Who has been the focus of the biomedical research generating this knowledge, and why? How might inclusiveness of this research impact healthcare disparities in Rhode Island? What is needed to improve the design and outcomes of precision medicine research so that it provides benefits and mitigates harms for all? The goal of this course is for students to gain an understanding of the societal context in which biomedical research takes place and how active community engagement will lead to improved inclusivity and a reduction in health disparities.

***Learning goals*:**

i. Identify key questions, evidence, and decisions for translating biomedical research into precision medicine.
ii. Understand how non-inclusiveness of biomedical research may bias the distribution of benefits, harms and risks for people, stakeholders and communities.
iii. Analyze one's own assumptions and beliefs when working to facilitate civic engagement that makes a difference for others.
iv. Recognize power imbalances and issues of trust that can marginalize people and places from research.
v. Assess and present different ethical perspectives when considering decisions and actions for biomedical research.
vi. Proactively advance team success through active listening, empathy and facilitation of team member contributions.

***Intellectual engagement beyond the classroom - the problem of interest*:** Precision medicine initiatives such as the Cancer Moonshot aspire to transform disease treatment by considering how

individual variability in genes, environment and lifestyle of each person may influence the benefits and harms they experience from medical care. Most US biomedical research is currently limited to subsets of patients and treatment settings that do not represent the diversity of the country or Rhode Island. If biomedical research does not develop more inclusiveness, it risks creating new forms of privileged medicine limited to select subsets of people and communities. The urgency of now is that the design of today's biomedical research will determine who can benefit from medicines developed over the next two decades.

***Community engaged scholarship*:** A key aspect of this course will be the consideration of communities of people, communities of place, and communities of action. Our first emphasis is to learn from the experience and needs of patients, their families, and their caregivers. We will add to this a consideration of the diversity of settings where people live and receive health care. As we define issues and opportunities for change, we will add consideration of the stakeholders who collectively set priorities and take actions in biomedical research and innovation.

***Position of this course in Brown University's Program in Biology*:** The proposed course will help advance several goals of the 15 September 2016 Diversity and Inclusion Action Plan (DIAP) for the Program in Biology. It will provide sophomores with learning opportunities about issues of diversity and inclusion in the design of biomedical research. It will facilitate their reflection and development of ideas on ways to better align biomedical research with needs of historically marginalized communities at local and national levels. The design of this course as a sophomore seminar reflects the goal of providing these learning experiences when students are making decisions about their scholarship focus and next steps at Brown. The learning goals of the course will also introduce sophomores to topics from the Program's Diversity and Inclusion Module on questions, experimental plans, collaborations and dissemination practices that consider diversity and inclusion. Topics and guest speakers in the course may facilitate new opportunities for participants in the Department's programing for seminars and panel discussions. And the issues, topics, and stakeholders covered in the course can help students envision and explore new career paths in addition to the graduate student-postdoc-professorial track.

***Teaching strategies and assignments*:** Learning will be facilitated through student-led discussion of weekly readings, case examples and group projects on the inclusiveness of NIH initiatives and FDA drug approvals vis-a-vis Rhode Island's diversity, case examples and group projects to consider different ethical perspectives on biomedical research, conversations/visits with representatives from RI communities and organizations, and community-focused investigation into barriers to participation in research. These experiences are intended to help each student develop a creative project that highlights some of the issues and potential actions for disparities in how biomedical research considers needs of communities or populations in Rhode Island.

The learning goals, assignments and assessments are based on best practices from real world work and related rubrics from the Association of American Colleges and Universities. The rubrics are also useful as guides for what student and professional work should look like at progressively higher levels of performance.

Through these readings and our analysis of them, students will be able to understand how to analyze primary literature and what questions to ask, a skill that will prove most useful when carrying on to upper level classes.

a. Pre-class readings and reflections

To facilitate our in-class discussions you are expected to read the assigned papers and come to class prepared to engage with the group. To help you prepare, you will be asked to write a 150 word reflection on one of the assigned readings each week. We will introduce and explore several types of reflection over the semester - reflection on scientific evidence and interpretation, reflection on who is considered/should be considered in the research, reflection on assumptions and actionability of results from research, and reflection on ethics in research. The reflections are formative assignments due the day before class.

b. In-class discussions

Small group conversations will be used to share and integrate perspectives from readings and class activities, following which each group will report out to the full class. As the semester progresses, topics for these discussions will increasingly guided by student interests and goals for their group and individual projects. Successful teams often use a charter to guide these types of discussions, and we will develop one for our class in the first two weeks of the term. We will also explore and practice active listening and empathy as part of our in-class activities.

c. Class facilitation

Each student will participate in co-facilitating one of the class discussions of the readings. Facilitators will develop a 20 minute group presentation on their choice of topics and learnings/impressions from the week's readings, and lead the initial class discussion after the small group conversations at the start of class. You can start the discussion with questions you define as well as questions submitted by your fellow students, after which you will facilitate the sharing of comments and perspectives from each group. Student facilitators will meet together with the instructor at least a day before class to discuss their approach to the presentation and conversation. The instructor and TAs will introduce methods for facilitation in the first class and continue to model these throughout the term.

d. Analysis of scientific practice and inclusiveness of research: Group presentation Week 6

Students will participate in small groups to investigate and assess the goals and inclusiveness of research shaping precision medicine for a specific disease, therapeutic area, or population, and determine how these disparities may adversely impact benefits and harms of new innovations for people of Rhode Island. The instructor will provide an initial list of potential topic areas prior to the first class. Students can sign up to participate in a group on one of these topics, or propose their own group topic (before week 3). Issues and approaches for the projects will be introduced over the first weeks of the course, culminating in a session focused on breast cancer in Week 4. Each group will present their analysis in the Week 6 class session (20 minutes for each group). Group members will be evaluated individually, using rubrics for critical analysis to assess the explanation

of issues, consideration of context and assumptions, and the inclusion of potential consequences and implications in their conclusions.

e. Analysis of scientific practice in the context of ethical and social issues: Group presentation Week 10

Students will participate in one of four groups to investigate and assess ethical considerations for specific decisions on the path translating biomedical research into precision medicine. Students can propose topics for investigation that could supercede the case examples from this initial list:

- Europe's adaptive pathways initiative for new drug approvals
- NIH Precision Medicine Initiative Cohort
- First use of a new drug in people - TeGenero, a catastrophic first-in-human study
- Stakeholder responsibilities when issues arise with drugs in development or on the market - Vioxx, a drug with serious safety issues plus poor communication/transparency.

Group presentations (15 minutes) will be made as part of the guest Ethics Panel discussion being planned for Week 10. Group members will be evaluated individually, using rubrics for critical analysis to assess the explanation of issues, consideration of context and assumptions, and the inclusion of potential consequences and implications in their conclusions (using a higher performance standard that will build on the Week 6 experience and feedback).

f. Final project: Individual project/presentation Weeks 12/13

Students will apply their learning in a final project that addresses issues and potential actions relevant to the question, "Precision Medicine or Privileged Medicine?" For example, a student could choose to highlight issues and potential actions for one of the following:

- Addressing disparities in how biomedical research considers diversity, perspectives and needs of communities or populations in Rhode Island.
- Facilitating awareness and advocacy for more inclusive biomedical research at the campus, community, state or national level.

This is meant to be creative project such as a scientific perspective or review paper, a fictional short story or other form of creative writing, a dramatic performance, or another personal creation. It should reflect how the student could see themselves as a potential agent for change, and convey the issue and proposed actions in a way that would be understandable to a lay audience. It should be a substantive piece of work. Each project is to be supported by a written summary of what is being presented/conveyed, and why it is relevant. The written summaries are due before the start of the first presentation in Week 12. The instructor will meet provide opportunities to meet with students to discuss their interests and this assignment during the first half of the term.

g. Individual Learning Goals and Reflections

At the start of the course you will submit a description of your learning goals for the course. As the course progresses you are expected to periodically write reflections about your experience, learning, and intellectual growth with the topics, material and course activities. We will also utilize an in-class group reflection on the course learning goals in the Week 11 review. Your last assignment will be a final reflection on your intellectual journey in the class, and how your initial goals may have evolved over the semester. This final reflection is not a course evaluation. It should

focus on how you as an individual engaged with the material in the class and how you assess your intellectual growth from the class. The learning goals and reflection are requirements, but will not be graded.

***Attendance and Participation*:** Active participation on the part of students includes being in class and participating in the class conversations. Most of the topics we will cover do not have one "correct" answers - and the instructor and others in the field have failed to identify best solutions for most of the challenges we will cover. Your ideas and perspectives will be meaningful to share! Absences will affect your grade.

***Grading*:** A/B/C/NC Grading with Optional S/NC option

Weighting of assignments:

Reflections on readings	20%
Class participation	10%
Class facilitation	10%
Disease analysis	20%
Ethics analysis	20%
Final project	20%
Course reflection	Ungraded but required when submitting final project

Overall course grade calculation:

A: 87-100% B: 73-86% C: 60-72% NC: <60%

***Hours spent on class*:** The total in-class hours and out-of-class work for full credit courses at Brown is approximately **180** hours. In this class, students expecting success can expect to spend **32** hours in class (2.5 hours per week), **45** hours on reading for class (approximately 5 hours for each week with readings), **28** hours completing the weekly reading reflections and preparing for discussions, **10** hours preparing to facilitate one class discussion, **10** hours researching and preparing the group disease analysis, **10** hours researching and preparing the group ethics analysis, **40** hours preparing the Final Project assignments and **5** hours for site visits and external talks.

***Diversity and Inclusion Statement*:** A key tenet of this course is that a diverse and inclusive approach to biomedical research is important for achieving a relevant understanding of diseases and meaningful innovations for health. I would like to create a learning environment for students that supports a diversity of thoughts, perspectives and experiences. Throughout my career I have found it fulfilling to learn from people who can see issues and possibilities that I do not, and who have ideas that I have not considered. The fields of biomedical research and innovation have many limitations and problems, and new perspectives and ideas are very much needed!

***Student accessibility and accommodations*:** Brown University is committed to full inclusion of all students. Please inform me early in the term if you might require accommodations or modification of any of these course procedures (for example, a disability or other condition that may impact accessibility). You may speak with me after class or during office hours. You may

wish to contact Student and Employee Accessibility Services at 401-863-9588 or SEAS@brown.edu for additional guidance and information that could be helpful.

***Course policies and additional expectations of students*:** Students are expected to attend all lecture periods and to have completed all assignments and preparatory work on time. Students are also expected to be in the class sessions on time and ready to actively engage in class activities and effective discussion. Out of respect for the investment all are making to our class meetings together, multitasking on electronic devices while class is in session is not acceptable.

Assignments turned in after the due time will automatically lose 1 point, with a further deduction at a rate of 20% per day. Requests for extensions on assignments and exams will be considered only if accompanied by a written memo from a dean or from Health Services. Attendance at all lectures and class periods is mandatory. Additionally, a portion of your grade is based on class participation. Attendance does not automatically equate with participation.

Issues of cheating or plagiarism will be handled in accordance with Brown Academic & Student Conduct Codes: https://www.brown.edu/academics/college/degree/policies/academic-code

***Course schedule, topics and candidate readings (to be finalized prior to start of class)*:**

BIOL-0940E Precision medicine or privileged medicine? - Sequence of topics for Fall 2018	
Week 1	Precision medicine and the diversity of Rhode Island 1. Patient-physician challenges and decisions - the hope of precision medicine 2. Current disparities in the inclusiveness of biomedical research and innovation
Week 2	The expanding authority of the patient in biomedical research 1. Ethics and practices for conducting biomedical research on people 2. Patient advocacy and leadership of research
Week 3	Place matters 1. The primacy of place for translating research into effective healthcare 2. Case example: propagation of harms from prescription opiate drugs
Week 4	Breast cancer - successes and gaps in the inclusiveness of precision medicine 1. Who needs to be included for biomedical research to result in treatments for all?
Week 5	Communities, trust, and engagement in biomedical research 1. Patient and caregiver in the context of community 2. Dimensions of trust and power - historic abuses, ongoing concerns
Week 6	Student-led session on the current situation and concerns for inclusiveness of biomedical research in specific disease or therapeutic areas. *(We will choose up to four therapeutic/disease areas from initial suggestions of the instructor and student suggestions made in the first 3 weeks of the course)*
Week 7	Physician perspectives and concerns

	1. Clinical practice and research that does not violate the Hippocratic Oath 2. Emerging challenges for clinicians in the era of genomic medicine
Week 8	Drug discovery and development perspectives and concerns (NIH, Biopharma, FDA) 1. Legislation and guidance to improve the inclusiveness of biomedical research 2. Evidence and decisions for approving entry of new medicines in healthcare
Week 9	Healthcare system and payer perspectives and concerns 1. Gatekeeper decisions and reimbursement science for innovations to reach patients 2. The emerging power of health systems to lead research that influences priorities for drug discovery and development
Week 10	Ethics Session - Group Presentations and Guest Panel on Ethics
Week 11	Review and reflection on topics and learnings from the course
Week 12	Student project presentations
Week 13	Student project presentations

Readings and resources under consideration for Fall 2018, *and questions for readings in Week 1 that should be considered in advance of the first class session*:

Week 1: Precision medicine and the diversity of Rhode Island

US National Library of Medicine: Genetics home reference: Your guide to understanding genetic conditions. https://ghr.nlm.nih.gov/primer/precisionmedicine/definition

The right prevention and treatment for the right patient at the right time: Strategic Research Agenda for Innovative Medicines Initiative 2 (Executive summary and Chapter 3). https://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf

Q1. What are some of the challenges currently facing the European healthcare system?
Q2. Why is the current healthcare system not sustainable?
Q3. What do you think the IMI2 does well and what can they improve? How are they trying to achieve their goals?

Wells J. White Wash: Biomedical research doesn't reflect diversity of American public. University of California San Francisco New Center. 2016 Dec 5; https://www.ucsf.edu/news/2016/12/405091/white-wash

Q1. How does precision medicine vs. priviledge unravel in Steven Mendoza's case?
Q2. What is the difference between equity and equality? How are they different in the context of health?

Oh SS et al. Diversity in clinical and biomedical research: a promise yet to be fulfilled. PLoS Med. 2015 Dec 15; 2(12):e1001918. doi: 10.1371/journal.pmed.1001918. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4679830/

Q1. What are some of the take-home messages from this publication? What do we do wrong?
Q2. What are some diseases that experience clear race-drive differences in terms of treatment methods and response?

Gardner, K. The science of cancer health disparities: A young discipline with an old heritage. Am J Pathol. 2018 Feb;188(2):268-269. https://www.ncbi.nlm.nih.gov/pubmed/29137949

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Q1. What are some of the way health disparities research has been characterized as? Is any of these approaches accurate in your understanding? How would you (re)define health disparities research?

Ramirez AG & Thompson IM. How will the 'cancer moonshot' impact health disparities? Cancer Causes Control 2017 Sep;28(9):907-912. https://www.ncbi.nlm.nih.gov/pubmed/28770362

Q1. What are some of the discusses causes leading to health disparities? What else could be leading to health disparities?

Q2. How is precision medicine defined here? What is your understanding of it?

Q3. Why is it imperative for the Cancer Moonshot, precision medicine and cancer centers to develop a multifaceted approach to address health disparities?

Week 2: The expanding authority of the patient in biomedical research

Sullivan M. The new subjective medicine: taking the patient's point of view on health care and health. *Social Science & Medicine* 2003 Aug;56(5):1595-1604. https://www.ncbi.nlm.nih.gov/pubmed/12614708

Patrick-Lake B. Patient engagement in clinical trials: The Clinical Trials Transformation Initiative's leadership from theory to practical implementation. *Clin Trials* 2018 Feb;15(1_suppl):19-22. https://www.ncbi.nlm.nih.gov/pubmed/29452519

Baker DB *et al.* Governance through privacy, fairness, and respect for individuals. EGEMS 2016 Mar 31;4(2):1207 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4827784/

Anderson M and Manganiello M. Back to basics: HIV/ AIDS advocacy as a model for catalyzing change. New York: Faster Cures and HCM Strategists, 2011. http://hcmstrategists.com/wp-content/themes/hcmstrategists/docs/Back2Basics_HIV_AIDSAdvocacy.pdf

Rodriguez LL and Galloway E. Bridging genomics to medicine: ethical, policy and social considerations. Chapter 19 in Genomic and Precision Medicine: Foundations, Translation, and Implementation. 3rd ed. Ginsburg GS and Willard HF. Elsevier 2017. *Available as eBook through Brown University Library*

PREVAIL II Writing Group. A randomized controlled trial of ZMapp for Ebola virus infection. New England Journal of Medicine 2016 Oct 13;375(15):1448-1456. http://www.nejm.org/doi/full/10.1056/NEJMoa1604330

LeBlanc TW and Abernathy AP. Patient-reported outcomes in cancer care - hearing the patient voice at greater volume. *Nature Reviews Clinical Oncology* 2017 Dec;14(12):763-772). https://www.ncbi.nlm.nih.gov/pubmed/28975931

U.S. Congress Right to Try Act of 2017 https://www.congress.gov/bill/115th-congress/senate-bill/204

Week 3: Place Matters:

Place Matters for Health in Boston: ensuring opportunities for good health for all. Joint Center for Political and Economic Studies.

Berube A. City and metropolitan income inequality data reveal ups and downs through 2016. Brookings Institute 5 Feb 2018. https://www.brookings.edu/research/city-and-metropolitan-income-inequality-data-reveal-ups-and-downs-through-2016/

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Graham GN. Why Your ZIP Code Matters More Than Your Genetic Code: Promoting Healthy Outcomes from Mother to Child. *Breastfeed Med*. 2016 Oct;11:396-7. doi: 10.1089/bfm.2016.0113. PubMedID 27513279 https://www.ncbi.nlm.nih.gov/pubmed/27513279

Rothschild D *et al*. Environment dominates over host genetics in shaping human gut microbiota. *Nature* 2018 Feb 28 doi: 10.1038/nature25973. https://www.ncbi.nlm.nih.gov/pubmed/29489753

Hampton T. Gut microbes may shape response to cancer immunotherapy. *JAMA* 2018 Feb 6;319(5):430-431. https://www.ncbi.nlm.nih.gov/pubmed/29411013

Depp C and Lebowitz BD. Clinical trials: bridging the gap between efficacy and effectiveness. *International Review of Psychiatry* 2007 Oct;19(5):531-539. https://www.ncbi.nlm.nih.gov/pubmed/17896233

Califf RM *et al*. Transforming evidence generation to support health and health care decisions. *New England Journal of Medicine* 2016 Dec 15;375(24):2395-2400. http://www.nejm.org/doi/pdf/10.1056/NEJMsb1610128

Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse; Phillips JK, Ford MA, Bonnie RJ, editors. Washington (DC): National Academies Press (US); 2017 Jul. https://www.ncbi.nlm.nih.gov/pubmed/29023083

Week 4: Breast cancer - successes and gaps in the inclusiveness of precision medicine

United States Census Bureau. QuickFacts - Rhode Island.
https://www.census.gov/quickfacts/fact/table/RI/PST045217

Center for Disease Control and Prevention (CDC) - Breast Cancer statistics from CDC's National Program of Cancer Registries and National Cancer Institute's Surveillance, Epidemiology, and End Results program:
- incidence/death rates by state: https://www.cdc.gov/cancer/breast/statistics/state.htm
- incidence/death by race/ethnicity: https://www.cdc.gov/cancer/breast/statistics/race.htm
- incidence/death rate trends: https://www.cdc.gov/cancer/breast/statistics/trends.htm

Crowson CS *et al*. Primer: demystifying risk - understanding and communicating medical risks. *Nat Clin Pract Rheum.* 2007 Mar;3(3):181-187. https://www.ncbi.nlm.nih.gov/pubmed/17334341

Jiagge E, Chitale D and Newman LA. Triple-negative breast cancer, stem cells and African ancestry. *Am J Pathol* 2018 Feb;188:271-279. https://www.ncbi.nlm.nih.gov/pubmed/29137951

DeSantis CE *et al.* Breast cancer statistics, 2017, racial disparity in mortality by state. *CA Cancer J Clin* 2017 Nov/Dec;67(6):439-448. https://www.ncbi.nlm.nih.gov/pubmed/28972651

Daly B & Olopade OI. A perfect storm: How tumor biology, genomics, and health care delivery patterns collide to create a racial survival disparity in breast cancer and proposed interventions for change. *CA Cancer J Clin*. 2015 May/Jun;65(3):221-238. https://www.ncbi.nlm.nih.gov/pubmed/25960198

Gaston-Johansson F *et al.* The effects of symptoms on quality of life during chemotherapy in African-American women with breast cancer. *J Black Nurses Assoc.* 2015 Dec;26(2):7-16.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5544776/

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FDA approves olaparib for germline BRCA-mutated metastatic breast cancer. U.S. Food and Drug Association. 12 Jan 2018. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm592357.htm

Nerlynx (neratinib) Drug Trials Snapshot for 2017 approval for use in breast cancer. U.S. Food and Drug Association. https://www.fda.gov/Drugs/InformationOnDrugs/ucm568138.htm

Week 5 - Communities, trust, and engagement in biomedical research

Goering S *et al* . Transforming genetic research practices with marginalized communities: A case for responsive justice. *Hastings Center Rep*. 2008 Mar-Apr;38(2):43-53. https://www.ncbi.nlm.nih.gov/pubmed/18457228

Quinn SC *et al*., Building trust for engagement of minorities in human subject research: Is the glass half full, half empty, or the wrong size? *Am J Public Health* 2013 Dec;103(12):2119-2121. https://www.ncbi.nlm.nih.gov/pubmed/24134371

Calain P. The Ebola clinical trials: a precedent for research ethics in disasters. J Medical Ethics 2018 Jan;44(1):3-8. http://jme.bmj.com/content/44/1/3.long

Wilson E *et al*. Ethical Challenges in Community-Based Participatory Research: A Scoping Review. Qual Health Res 2018 Jan;28(2):189-199. https://www.ncbi.nlm.nih.gov/pubmed/29235941

Video of Dr. Consuelo Wilkins presentation on patient engagement for Alzheimer's disease research. Milwaukee, WI 21 March 2016 http://videos.med.wisc.edu/videos/67264

Joosten YA *et al*. Community engagement studios: a structured approach to obtaining meaningful input from stakeholders to inform research. Acad Med. 2015 Dec;90(12):1646-1650. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4654264/

Erves JC *et al*. Needs, priorities, and recommendations for engaging underrepresented populations in clinical research: A community perspective. *J Community Health*. 2017 Jun;42(3):472-480. doi: 10.1007/s10900-016-0279-2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5408035/

Week 6 - Student-led session on the current situation and concerns for inclusiveness of biomedical research in specific disease or therapeutic areas. *(We will choose up to four therapeutic/disease areas from initial suggestions of the instructor and student suggestions made in the first 3 weeks of the course)*

Alzheimer's Disease

Tang MX et al . The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics. JAMA 1998 Mar 11;279(10):751-755. https://www.ncbi.nlm.nih.gov/pubmed/9508150

Shin J & Doraisswamy PM. Underrepresentation of African-Americans in Alzheimer's trials: a call for affirmative action. Front Aging Neurosci. 2016 Jun 3;8:123. doi: 10.3389/fnagi.2016.00123 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4891330/

Corriveau RA et al . Alzheimer's disease-related dementias summit 2016: National research priorities. Neurol 2017 Dec;89(23)2381-2391. https://www.ncbi.nlm.nih.gov/pubmed/29117955

Multiple sclerosis

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Rivas-Rodriguez E & Amezcua L. Ethnic considerations and multiple sclerosis disease variability in the United States. Neurol Clin . 2018 Feb;36(1):151-162. https://www.ncbi.nlm.nih.gov/pubmed/29157396

I*nequity in inclusion of women in clinical research*

Nowogrodzki A. Clinical research: inequality in medicine. *Nature* 2017 Oct 5;S18-S19. https://www.nature.com/articles/550S18a

Wenger N. A heartfelt plea. *Nature* 2017 Oct 3:550:S9 https://www.nature.com/articles/550S9a

Challenges/issues for biomedical research to support use of medicines in pregnant women, children, neonates:

Thielking M. Pregnant women who need medications face a risky guessing game. Boston Globe, STAT: Stories from the frontiers of health and medicine. 2017 Winter. https://www.statnews.com/2017/12/05/pregnant-women-medication-use/

Prevention of potentially fatal sides effects from treatment (example of Stevens-Johnson Syndrome):

Manolio TA *et al*. Research directions in genetic predispositions to Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis. *Clin Pharmacol Ther*. 2018 Mar;103(3):390-394. https://www.ncbi.nlm.nih.gov/pubmed/29105735

White KD et al. SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation. *J Allergy Clin Immunol Pract* 2018 Jan - Feb;6(1):38-69. https://www.ncbi.nlm.nih.gov/pubmed/29310768

Week 7 - Physician perspectives and concerns

Umscheid CA *et al.* Key concepts of clinical trials: A narrative review. *Postgrad Med* . 2011 Sep; 123(5): 194–204. https://www.ncbi.nlm.nih.gov/pubmed/21904102

Freedman B. Equipoise and the ethics of clinical research. *New Engl J Med*. 1987 Jul 16;317(3):141-145. https://www.ncbi.nlm.nih.gov/pubmed/3600702

De Meulemeester J *et al*. Many randomized clinical trials may not be justified: a cross-sectional analysis of the ethics and science of randomized clinical trials. J Clinical Epidemiology 2018 Jan 3. pii: S0895-4356(17)30769-2. doi: 10.1016/j.jclinepi.2017.12.027 https://www.ncbi.nlm.nih.gov/pubmed/29306063

Hey SP *et al*. Research ethics for emerging trial designs: does equipoise need to adapt? BMJ 2018 Jan 25;360:k226. https://www.ncbi.nlm.nih.gov/pubmed/29371211

Van Karnebeek CDM et al. The role of the clinician in the multi-omics era: are you ready? J Inherited Metabolic Disease 2018 Jan 23. doi: 10.1007/s10545-017-0128-1 https://www.ncbi.nlm.nih.gov/pubmed/29362952

Week 8 - Drug discovery and development perspectives and concerns (NIH, Biopharma, FDA)

Testimony on implementation of the 21st Century Cures Act: Progress and the path forward for medical innovation. Francis S Collins, Director, National Institutes of Health. Witness appearing before the Senate Committee on Health, Education, Labor, and Pensions. 7 Dec 2017. https://www.nih.gov/about-nih/who-we-are/nih-director/testimony-implementation-21st-century-cures-act-progress-path-forward-medical-innovation

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Vaduganathan M and Prasad V. Modern Drug Development: which patients should come first? JAMA 2014 Dec 24-31;312(24):2619-2620. https://www.ncbi.nlm.nih.gov/pubmed/25420013

Plenge, RM. Disciplined approach to drug discovery and early development. Science Translational Medicine 2016 July 27;8(349):349ps15

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Video introduction to the Innovative Medicines Initiative European Prevention of Alzheimer's Dementia (EPAD) project - http://ep-ad.org

Week 9 - Healthcare system and payer perspectives and concerns, and the emerging power of health systems to lead research that influences priorities for drug discovery and development

Reed SD *et al*. Developing the Value Proposition for Personalized Medicine. Chapter 22 in Genomic and Precision Medicine: Foundations, Translation, and Implementation. 3rd ed. Ginsburg GS and Willard HF. Elsevier 2017. *Available as eBook through Brown University Library*

Fojo T, Mailankody S and Lo A. Unintended consequences of expensive cancer therapeutics – The pursuit of marginal indications and a me-too mentality that stifles innovation and creativity. *JAMA Otolaryngology-Head & Neck Surgery*. 2014 Dec;140(12):1225-1236. https://www.ncbi.nlm.nih.gov/pubmed/25068501

Pezalla EJ. Payer view of personalized medicine. *Am J Health-Syst Pharm.* 2016 Dec;73(23):2007-2012. https://www.ncbi.nlm.nih.gov/pubmed/27864208

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> Presentation slides:
> https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/PCAST/Yancopoulos.pdf
> Transcript:
> https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/PCAST/150515_PCAST_Transcript.pdf (search in document for Yancopolous to find the section of the transcript with his presentation)

Rader DJ and Damrauer SM. "Pheno"menal value for human health. Rare genetic variants are linked to electronic health record phenotypes at a population scale. *Science* 2016 Dec 23;354(6319):1534-1536. https://www.ncbi.nlm.nih.gov/pubmed/28008030

Week 10: Ethics panel - Potential Topics for students to choose for student-led discussion:

Expedited approval - Europe's Medicines Adaptive Pathways to Patients [MAPPs]

a. Eichler HG *et al*. From adaptive licensing to adaptive pathways: delivering a flexible life-span approach to bring new drugs to patients. *Clin Pharmacol Ther*. 2015 Mar;97)3)_234-246. https://www.ncbi.nlm.nih.gov/pubmed/25669457

b. EU Innovative Medicines Initiative ADAPT-SMART project - stakeholder presentations on their preferences, must-haves, deal breakers and concerns for early/accelerated approval of new medicines (files in BIOL-0940E Zotero library - Learning Objectives / Ethical Practice / IMI Stakeholder views on

accelerated approvals) - and online at http://adaptsmart.eu/outputs-from-the-29th-february-multi-stakeholder-workshop/

c. Breckenridge A *et al*. Precision medicine and the changing role of regulatory agencies. *Nature Rev Drug Discov.* 2016 Dec;15(12):805-806. https://www.ncbi.nlm.nih.gov/pubmed/27739512

d. Eichler HG and Sweeney F. The evolution of clinical trials. Can we address the challenges of the future? *Clin Trials* 2018 Feb;15(1_suppl):27-32. https://www.ncbi.nlm.nih.gov/pubmed/29452522

NIH Precision Medicine Initiative Cohort

a. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease. Washington (DC): National Academies Press (US); 2011. https://www.ncbi.nlm.nih.gov/pubmed/22536618

b. The Precision Medicine Initiative Cohort Program - Building a Research Foundation for 23st Century Medicine. Precision Medicine Initiative (PMI) Working Group Report to the Advisory Committee to the Director, NIH. 2015 Sep 15. https://www.nih.gov/sites/default/files/research-training/initiatives/pmi/pmi-working-group-report-20150917-2.pdf

c. National Institutes of Health All of Us Research Program https://allofus.nih.gov

d. Khoury MJ and Galea S. Will precision medicine improve population health? *JAMA* 2016 Oct 4;316(13):1357-1358. https://www.ncbi.nlm.nih.gov/pubmed/27541310

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f. Ioannidis JPA and Khoury MJ. Evidence based medicine and big genomic data. Hum Mol Genet. 2018 Feb 20 doi: 10.1093/hmg/ddy065 https://www.ncbi.nlm.nih.gov/pubmed/29474574

TeGenero

a. Horvath CJ and Milton MN. The TeGenero incident and the Duff Report conclusions: a series of unfortunate events or an avoidable event? *Toxicol Pathol*. 2009 Apr;37(3):372-383. https://www.ncbi.nlm.nih.gov/pubmed/19244218

b. Nada A and Somberg J. 2007. First-in-Man (FIM) clinical trials post-TeGenero: a review of the impact of the TeGenero trial on the design, conduct and ethics of FIM trials. *American Journal of Therapeutics* 2007 Nov-Dec;14(6):594-604. https://www.ncbi.nlm.nih.gov/pubmed/18090886

c. Grady C *et al*. Motivations, enrollment decisions, and socio-demographic characteristics of healthy volunteers in phase I research. *Clin Trials* 2017 Oct;14(5):526-536. https://www.ncbi.nlm.nih.gov/pubmed/28783972

d. Elliott C. Commentary on Grady et al: Using poor, uninsured minorities to test the safety of experimental drugs. 2017 Oct;14(5):547-550. https://www.ncbi.nlm.nih.gov/pubmed/28747074

e. Jotkowitz AB *et al*. Ethics consultation: whose ethics? *Am J Bioethics* 2007 Feb;7(2):41-42. https://www.ncbi.nlm.nih.gov/pubmed/17366192

Vioxx

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b. Krumholz HM *et al*. What have we learnt from Vioxx? *BMJ* 2007 Jan 20;334(7585):120-123. https://www.ncbi.nlm.nih.gov/pubmed/17235089

c. Fitzgerald GA. Coxibs and cardiovascular disease. *N Engl J Med*. 2004 Oct 21;351(17):1709-1711. https://www.ncbi.nlm.nih.gov/pubmed/15470192

d. Topol EJ. Failing the public health - rofecoxib, Merck, and the FDA. *N Engl J Med*. 2004 Oct 21;351(17)1707-1709. https://www.ncbi.nlm.nih.gov/pubmed/15470193