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Work-in-Progress: Ethical, Legal, and Social Implications of Emergent Biotechnologies: Distributive justice and dual-use technology in the engineering design cycle curriculum

Cameron Kim (Assistant Professor of the Practice)

Cameron Kim is an Assistant Professor of the Practice in the Department of Biomedical Engineering at Duke University and serves as the Associate Director for Undergraduate Education. He is researching the role of ethics-guided design frameworks in the classroom for emergent biotechnologies, including gene and cell-based therapies. His education development in molecular engineering and biotechnology results from 10 years in developing protein and RNA-based control systems for mammalian synthetic biology applications. He also serves as the faculty advisor for the Duke International Genetically Engineered Machine undergraduate research group.

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Abstract

Emergent biotechnologies such as CRISPR-Cas9 and stem cell therapeutics have posed many questions in the bioethics debate as to the limits of engineering natural systems. To address our future intertwined with biotechnology and its ethical, legal, and social implications, we must develop curricula that addresses the role of academic, research, and industrial scientists in these debates and how to address societal concerns with emergent technologies. In BME 590L/490L: Biotechnology Design I/II, a two-semester senior/master's capstone design course at Duke University, students prepare for academic and commercial development of biological products with topics in synthetic biology, fermentation, intellectual property, and regulatory controls. Lectures, discussions, and laboratory exercises prepare students for independent design projects that are presented in the fall and implemented in the spring. Currently missing is a preparation for the role of ethics in the biodesign process, including questions of whether biotechnology can help and harm individuals or the environment.

With repetitive engagement of ethics in biodesign, I introduced active learning modules to discuss theories of ethics and purpose in biotechnology, assignments that explore a case study in biotechnology ethics, and stakeholder analyses that extend bioethics knowledge to independently designed emergent biotechnologies to assess transfer to novel situations. These exercises were analyzed for usage frequencies, patterns among stakeholder analyses and minimizing risk, and independent assessment of ethical dilemma that include bioethical theories. Initial findings support student's starting level of knowledge in defining bioethics theories (justice, autonomy, beneficence, non-maleficence), yet lacking expertise to apply theories to their novel designs in technology. Students interchangeably define ethics with morals as "good vs. bad" and aligning community values in decision making. Continued work will assess changes in identifying dilemma among students at the end of the second semester, the ethical responsibilities to mitigate risk and harm in independent biotechnology projects, and how to engage stakeholders during biodesign.

Introduction

In 1975, Paul Berg convened the Asilomar Conference on Recombinant DNA concerning emergent genetic engineering research that many predicted could permanently alter the natural landscape of humanity. After a voluntary moratorium imposed a year prior, this group of scientists, government officials, and legal experts recommended stricter guidelines on recombinant DNA research, but to allow its overall practice given potential benefits to society [1]. Fifty years later, bioengineers can chemically synthesize entire bacterial genomes on the order of millions of base pairs with speed, accuracy, and costs improving annually [2], [3]. DNA synthesis and sequencing has enabled much of the biobased economy with an estimated market size of >$1 trillion in the US [4]. <u>The biotechnology industry has no intention of slowing down.</u>

CRISPR-Cas9 has been lauded as the molecular scissors necessary to edit human diseases out of the genome with impunity. However, opponents against such biotechnologies criticize regulatory bodies for a lack of research oversight in promoting human genetic enhancements beyond natural capacities. From Josiah Zayner's Cas9 self-injection to knockout myostatin for larger muscles [5] to He Jiankui's editing of embryos to prevent HIV infection [6], public acceptance of biotechnology and synthetic biology is unfavorable and perceived as a highly risky discipline [7]. In addition, concerns of autonomy for genetically modified embryos with inter-generational consequences and uncertain risks of off-target edits raise important questions on the ethics of germ-line gene knockouts [8]. While CRISPR-Cas9 may be a transformative technology for treating diseases, there <u>exist dual-use opportunities to abuse gene editing</u> to evolve highly virulent pathogens in gain-of-function studies or engineer harmful mutations in crops or livestock that are improperly bio-contained. While we train biomedical engineers with an exceptional knowledge of harnessing these novel tools to improve quality of life and address global health disparities, we must equip them with an ethical toolbox to assess if and how such technologies should be deployed as part of the design-build-test-learn cycle. In addition, we must also prepare students to "recognize ethical and professional responsibilities in engineering situations and make informed judgments, which must consider the impact of engineering solutions in global, economic, environmental, and societal contexts" as indicated by the ABET Student Outcome 4.

Research Questions

This work-in-progress aims to answer three research questions:

- RQ1: How do students define fundamental theories in bioethics, including justice, autonomy, beneficence, and non-maleficence prior to formal education, and do these definitions change after engaging with ethics-guided design in biotechnology?
- RQ2: Which stakeholders do students assign more value and influence in biodesign, and can students analyze different perspectives and value-based viewpoints concerning issues in bioethics for emergent biotechnologies?
- RQ3: What risks and harms do students ascribe to biotechnology, and what strategies do teams implement in biodesign to mitigate certain dilemma that arises with dual-use technology?

Methodology and Results

Defining ethics and bioethical theories: An in-class exercise on Day 6 posed three questions to 16 students enrolled as senior undergraduate or master's students, first discussed in small groups and then collected using a shared Google Docs file. This exercise is adapted from the Markkula Center for Applied Ethics [9].

1. What does ethics mean to you?
2. What are ethical issues that arise when working in engineering? In bio/medical engineering?
3. Is ethics and ethical decision making a universal concept?

Responses were collected and word frequencies were identified for question 1, with moral/morality (8) and rules/principles (7) identified as the most frequent words. Students correctly identified ethics in guiding decisions on what is right and wrong and establishing principles to make those choices, yet still ascribed morality and personal/cultural norms to a universal definition of ethics versus individual decision making. In addition, one response considered ethics as "…using one's moral standards to decide whether their actions are subjectively right or wrong." While morality and ethics are often used interchangeably, Beauchamp and Childress' *Principles of Biomedical Ethics* emphasizes the "common morality" reliance on societal norms that are "widely shared that they form a stable social contract" [10]. Relativistic morality and ethics share common theories with bioethics principles in autonomy, justice, beneficence, and non-maleficence, but should be differentiated in this exercise. When polled on question 3, 75% of students responded that ethics and ethical decision making is not universal, with only 1 student responding yes and 2 students responding with "it depends," commenting on individual perspectives and cultural norms in this category (Figure 1).

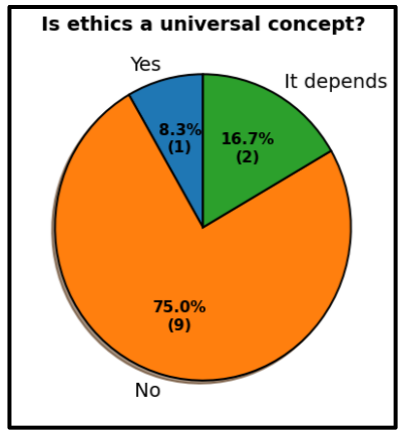

Figure 1: Responses to Question 3 indicate most students do not view ethics as universal.

While the debate on differences between ethics versus morals, its universal application to identify dilemma in biotechnology, and agreeing on ethical behavior is necessary to discuss [11], these in-class conversations provided students an opportunity to discuss these definitions in an active learning environment as part of a capstone design course. In addition to this conversation, students were tasked to define justice, autonomy, beneficence, and non-maleficence as fundamental theories in bioethics. Students were successful in defining these terms prior to a formal lesson, and instead were then tasked in future design projects to apply these principles to novel biotechnologies and assessing dilemma. Many students commented on their definition of justice to include distributive justice and equitable access, hallmark discussions with the deployment of the Covid-19 mRNA vaccines [12].

Identifying stakeholders and dilemma in independent biotechnology designs: As part of biotechnology design, students implement the design-build-test-learn cycle to develop novel therapeutics, cellular machines, and molecular diagnostics in an iterative fashion. Student teams present three design reports that address needs finding and market concerns for their proposal. While students discuss the helps of their proposed biotechnology, we have not required teams to identify the potential harms. Bioengineers must consider the impacts of their proposed designs and technologies and assess how intellectual property and operating costs will factor into global health disparities, especially if designed for majority white populations. Identifying ethical dilemma in such biotechnologies requires a thorough understanding of the techniques used to produce them.

To assess student self-efficacy in identifying dilemma and technical knowledge applied to risks and harms, I modified proposals to include written sections on stakeholder analysis and their relative influence, and ethical considerations in their proposals. This also provided multiple points of reinforcement for ethics in the engineering design cycle as iterative discourse and learning versus as a one-off exercise. An example statement from student design proposals on a novel diagnostic device asked teams to "state relevant stakeholders (at least 5) and their influence/power in the proposed design. State any ethical dilemma and concerns one may have with the project, especially with regards to the risks and harms of false positive and false negative results." Stakeholder activities were adapted from *BioBuilder* [13].

While projects differed in proposed solutions, teams identified many common stakeholders to the design and implementation of their novel biotechnologies (Figure 2). Notably, patients (7) and the Food & Drug Administration (6) were the most frequent stakeholders identified by students. When categorized, individuals (17), governmental and regulatory bodies (12), and funding supporters (6) were regularly identified as stakeholders in all projects. While power and influence were discussed, project teams did not assign quantitative measures to these analyses. Future work will incorporate numerical data in stakeholder identification and how to perform ethical decision-making to these perceptions.

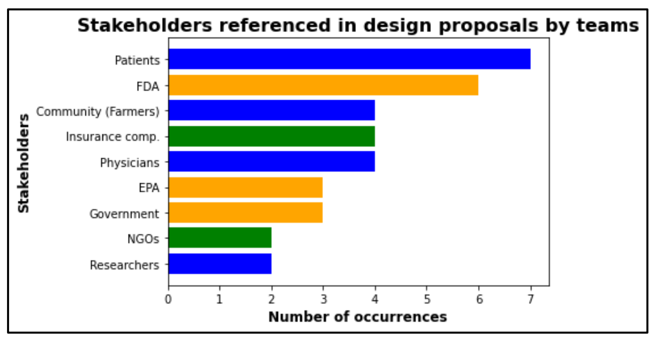

Figure 2: Number of mentioned stakeholders in nine design proposals. Groups are categorized as individuals (blue), governmental/regulatory (orange), and funders (green).

Students were specifically tasked in the diagnostics sector to comment on the risks and harms of inaccurate tests and prohibitive costs of novel diagnostics. One team identified that their diagnostic design for *Salmonella* antibiotic-resistant infection should be designed to favor sensitivity over specificity and thus reduce false negative results. In addition, all diagnostic teams made an implicit goal to minimize costs of diagnostics to increase accessibility for limited-resource nations that are most afflicted by these infections.

Future Directions

Robert McGinn identifies the *fundamental ethical responsibilities for engineers* to not cause harm, to try to prevent harm, to try to alert and inform about risks, and finally to serve legitimate interests of employers or clients [14]. Students must receive regular and active education on building an ethical toolbox that prepares them for bioengineering with a diverse set of stakeholders in mind. As students continue their capstone design projects, they will interview a stakeholder to share their preliminary designs and update their analyses from the fall semester. Future work will reexamine students' definitions of bioethical principles and ethical decision making as an integrated element of the design-build-test-learn cycle in developing their own emergent biotechnology. I will engage other design professors to collect similar data to assess vertical integration of bioethics and similar principles of universality between biomedical engineering disciplines, especially in pursuing student independence with emergent technologies developed in capstone projects.

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