Biology Without Borders: Need for Collective Governance?

Todd Kuiken

"College students try to hack a gene – and set a science fair abuzz" (Swetlitz 2016); "Amateurs Are New Fear in Creating Mutant Virus"(Zimmer 2015); "DIY Gene Editing: Someone Is Going to Get Hurt" (Baumgaertner 2018); and "In Attics and Closets, Biohackers Discover Their Inner Frankenstein (Whalen 2009)"—these are the headlines the public reads in major publications like the *New York Times*, *Wall Street Journal*, and others about the increasing accessibility to biotechnologies. Read aloud; they sound like the opening trailers for horror movies. Have there been missteps? Stunts? Individuals that spark controversy? Of course. But pandemics? Environmental disasters? Of course not. What has occurred though, and the story that is rarely told, are the tens of thousands of students and everyday citizens that have been introduced to biology, biotechnology, and science more broadly, who might not otherwise have had the opportunity to explore it. As with any broad reaching loosely affiliated community, there will always be those pushing the boundaries and trying to steal the spotlight with hyperbole and stunts. And with the help of some in the press, have misbranded and misrepresented the entire community of citizens interested in biology. Unfortunately these stories overshadow the educational opportunities this community provides and dismisses the safety, security, ethical, and responsible innovation practices and programs they have established.

For nearly a decade, I have been involved with the International Genetically Engineered Machines (iGEM) competition, Do-It-Yourself Biology, and, more recently, the growing citizen health innovation movements. What I have discovered is that these sometimes separate and sometimes merged communities have been both proactive and adaptive in addressing safety, security, and ethical concerns.

By examining the safety, security, and human practices programs of iGEM (Part 1), the policies and practices the DIYbio community has established (Part 2), and a

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B. D. Trump et al. (eds.), *Synthetic Biology 2020: Frontiers in Risk Analysis and Governance*, Risk, Systems and Decisions, https://doi.org/10.1007/978-3-030-27264-7_12

strategy to enable citizen health innovators to conduct responsible research (Part 3), this chapter will present an argument for collective governance. If funded properly, collective governance could address the biosafety, biosecurity, and ethical concerns brought about by the rapid advances in biological and information technologies that have democratized biology and broken down the traditional mechanisms of governance.

The International Genetically Engineered Machines (iGEM) Competition

The iGEM competition is an annual synthetic biology event where undergraduates, graduate, high school students, and community biotech labs (DIYbio) compete to build genetically engineered systems using standard biological parts called BioBricks. According to the Registry of Standard Biological Parts, which is maintained by the iGEM Foundation, a BioBrick or a biological part "is a sequence of DNA that encodes for a biological function, for example a promoters or protein coding sequences. At its simplest, a basic part is a single functional unit that cannot be divided further into smaller functional units. Basic parts can be assembled together to make longer, more complex composite parts, which in turn can be assembled together to make devices that will operate in living cells" (iGEM 2017). Teams are provided with an initial kit that contains about 1700 parts, and throughout the competition, they create new parts and improve other parts contained in the Registry. All these parts are available for anyone to access, use, and share. There are over 20,000 documented genetic parts in the Registry, and "teams and other researchers are encouraged to submit their own biological parts to the Registry to help this resource stay current and grow year to year" (iGEM 2017).

iGEM began in January 2003 as an independent study course at the Massachusetts Institute of Technology (MIT) where students developed biological devices to make cells blink. This course became a summer competition with 5 teams in 2004 and continued to grow to 13 teams in 2005; it expanded to 340 teams in 2018, reaching 42 countries and over 5000 participants. Since 2004, over 40,000 students have participated in iGEM from across the globe (Fig. 1, iGEM map; Fig. 2, iGEM participation). Team projects have ranged from simple biological circuits to developing solutions to local and global environmental conservation issues.

iGEM places as high a priority on students learning the technical skills of synthetic biology as it does on them understanding and contextualizing how "human practices" (iGEM Competition 2018) will influence the impacts of their technology and how to best plan for potential consequences. Through the human practices component of iGEM, teams are required to study "how your work affects the world, and how the world affects your work" by imagining their projects in a social/environmental context and engaging with communities outside their lab to better understand issues that might influence the design and use of their technologies. Teams creatively engage with issues in ethics, sustainability, inclusion, security, and many other areas.

Fig. 1 Map of 2018 iGEM teams (iGEM 2018)

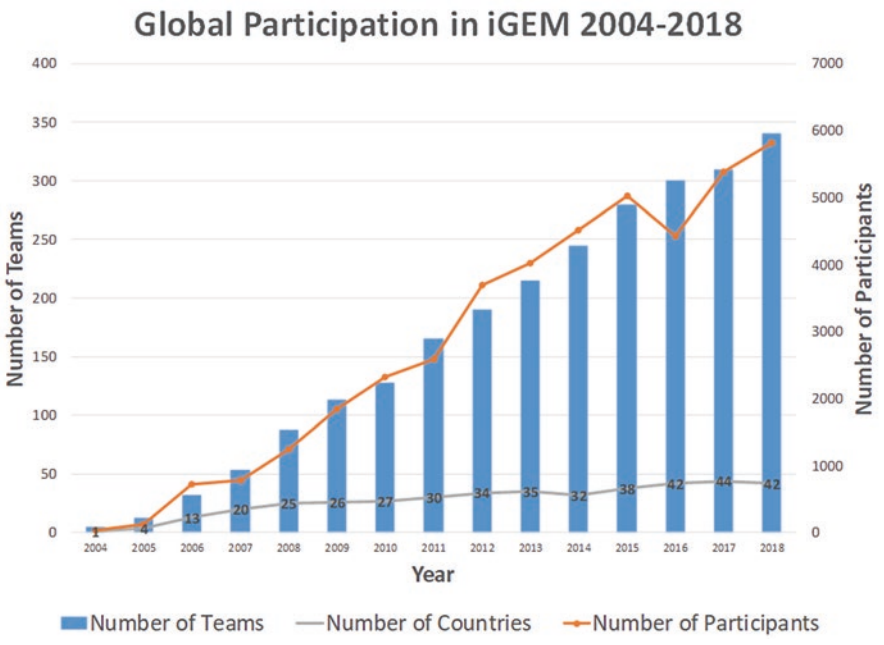


Fig. 2 Global participation in iGEM from 2004 to 2018 (iGEM 2018)

To address safety and security issues associated with projects, iGEM has established a safety and security committee that has evolved over the years into a comprehensive, adaptive collective governance system that manages the potential risk of the competition. iGEM's Safety and Security Program addresses a wider than usual range of issues including laboratory biosafety, laboratory biosecurity, environmental biosafety, dual-use research, animal use, and, increasingly, elements of bioethics.

iGEM comes across important issues, sometimes before there are formal rules or international regulations leading iGEM to sometimes create its own policies. These complement national or institutional rules and can help bridge differences between national approaches. The following sections will briefly describe how the human practices and safety and security programs address and train students around issues of safety and security and the societal impacts of their work.

Human Practices Program (iGEM 2019)

The Human Practices Program inside iGEM asks teams to consider the process of developing solutions to real-world problems in ways that are socially responsible, sustainable, safe, and inclusive. It recognizes that these issues are complex and do not have a single or simple answer. So human practices work requires teams to look beyond the lab. Inviting stakeholder input, building interdisciplinary collaborations, and understanding relevant regulations and codes of conduct in order to examine whether they are developing a responsible and impactful research project. Stakeholders can have different and sometimes conflicting values that can be equally valid. Human practices therefore require teams to think critically, be able to appreciate different views, and co-develop solutions that best serve the concerned communities. By reaching out to and learning from diverse communities, iGEM teams are creating opportunities for broader publics to help shape the practice of synthetic biology (iGEM 2019).

Teams are encouraged to explore whether their projects are both "good" and "responsible":

Responsible:

- How might your team's solution to one problem lead to other problems (e.g., social/political/ecological)? Could your project be misused?
- How can your team anticipate and minimize the impact of these concerns?
- What's your plan to inform and work with relevant authorities or stakeholders of potential risks related to your project?
- How might current policies and regulations apply to your project? Are they sufficient, and if not, how might they be changed?
- How does the iGEM community expect your team to be safe and responsible, both inside and outside of the lab?

Good:

- In what ways might your project benefit society?
- Which communities may be most interested or most affected by your project?
- Which communities may be left out or negatively impacted if your project succeeds?
- How might you get feedback on the viability and desirability of your approach? How will you adapt your project based on this feedback?
- How might your approach compare to alternative solutions to the same or similar problems (including approaches outside of biotechnology)?

*To examine the above questions, teams have (*iGEM 2019*):*

- Interviewed stakeholders who might make use of their work, like farmers, fashion designers, and factory workers
- Conducted environmental impact analyses
- Created museum exhibits and creative public engagement activities
- Written intellectual property guides
- Facilitated "white hat" biosecurity investigations
- Held forums with local legislators
- Spoken at the United Nations
- Developed tools to help other teams examine questions of ethics and responsibility

Through these activities, teams have engaged with topics and issues including ethics, safety, risk assessment, environmental impact, social justice, product design, scale-up and deployment, public policy, law and regulation, and much more. In each case, these activities have helped shaped the goals, execution, and communication of their projects (iGEM 2019).

Human practices work is a requirement of the competition in order for teams to qualify for awards and medals. To qualify for a bronze medal, teams must document how they came up with their idea and what inspired them. To qualify for a silver medal, teams must demonstrate how they have identified and investigated one or more human practices issues in the context of their project. To qualify for gold using their human practices work, teams must expand on their silver medal activities by demonstrating how their investigation of human practices issues has been integrated into the purpose, design, and/or execution of their project. Teams must demonstrate how they have responded to the conversations they have had with people outside the lab; how it influenced the goal, design, and execution of their project; and how they think about their work. Teams must demonstrate that their project (e.g., intended applications and their limits, potential users and stakeholders, experimental design, methods to deliver products and communicate results, etc.) has evolved based on their human practices work (iGEM 2019).

In addition to the medal requirements, teams can compete for two special prizes related to human practices. The Best Integrated Human Practices prize recognizes exceptional work based on the gold medal requirements for human practices.

To qualify for this award, teams must demonstrate how they have considered how their project affects society and how society influences the direction of their project. For example, how might ethical considerations and stakeholder input guide your project purpose and design and the experiments you conduct in the lab? How does this feedback enter into the process of your work all through the iGEM competition? Teams must document a thoughtful and creative approach to explore these questions and show how their project has evolved in the process to compete for this award (iGEM 2019).

Biosafety and Security

[The following section is taken in part from: (Millett et al. 2019)*]*

The Safety and Security Program expects teams to engage on these issues outside of their own community and even with non-specialists and the public. It does this through an approach that combines both incentives (such as through a Safety and Security Award for excellence) and penalties for non-compliance, up to and including disqualification (iGEM Foundation 2018a, 2018f).

The way iGEM addresses safety and security is an adaptive approach that builds on lessons learned each year in the competition. iGEM is a unique platform—offering both opportunities to innovate new tools and approaches but also to act as an international test bed for those developed elsewhere. iGEM believes biosafety and biosecurity are everyone's responsibility and need to be integrated throughout the competition's life cycle. The whole-of-life cycle approach iGEM currently employs requires teams to consider risk issues from the initial project design and continue to think about risks throughout their project, revisiting these issues as their plans change. Teams are also encouraged to think about any risks that might arise if their projects became final products. A separate, yet coordinated, biosafety system relates specifically to iGEM's Registry of Standard Biological Parts. iGEM believes safety and security is everyone's responsibility, from the team members to the instructors to the Safety and Security Program. The program is managed by the iGEM Director of Safety and Security, Piers Millett, and advised by the iGEM Safety Committee. The iGEM Safety Committee is a group of experts (all volunteers) in biosafety, biosecurity, and risk management. Its members come from diverse elements of industry, academia, and government. It includes members from North America, South America, Europe, and Asia. The committee is the ultimate arbiter of decisions on safety and security in iGEM.

iGEM requires teams to think about biosafety and biosecurity issues throughout the competition life cycle. These issues are included in project design and help shape what teams do in the lab and how they transfer the fruits of their work—both the tangible and intangible results.

As part of being responsible scientists and engineers, all iGEM teams are required to identify and manage risks associated with their project. This starts during the project design phase. All teams must share what risks they have identified and the

procedures, practices, and other measures they have taken to mitigate them. When thinking about possible risks, teams need to consider potential harm to themselves, their colleagues, communities, and the environment. They are encouraged to think about both "What is being done" and "What is being used."

The competition makes use of a White List which details organisms and parts deemed safe to work with in a standard laboratory (iGEM Foundation 2018g). Teams are encouraged to reduce risks by using safer substitutes for more dangerous organisms/parts. iGEM recognizes that all biological lab work, even simple experiments, carries some risk. To manage these risks, iGEM teams must follow a set of safety and security rules:

- Teams must provide information on any safety and security risks from their project and steps taken to manage them.
- Teams must request permission before using parts and organisms not on the White List.
- The instructor or primary contact must sign off safety and security information provided by the team.
- All deadlines for providing safety and security information must be met.
- Teams must fully comply with the safety and security policies.
- Teams must work in the biosafety level appropriate for their project (and should not be using greater containment than necessary).
- Teams must follow shipment requirements when submitting samples.
- Teams must follow all biosafety and biosecurity rules of their institution and all biosafety and biosecurity laws of their country.
- Teams cannot conduct work with Risk Group 3 or 4 organisms.
- Teams cannot conduct research in a Safety Level 3 or 4 laboratory.
- Teams cannot conduct work with parts from a Risk Group 4 organism.
- Teams cannot release or deploy their project outside of the laboratory (including putting them in people) at any time during the competition.
- All experiments with human subjects (including noninvasive experiments, such as surveys) must comply with all relevant national and institutional rules.

The iGEM Safety and Security Committee has the authority to immediately disqualify any team found to be in non-compliance with these rules. If teams satisfy the Committee that they have modified their project to be in compliance, they may be re-qualified. As disqualification from the competition is the largest penalty iGEM can impose, we have found that this sends a clear message to the teams on the importance of thinking seriously about safety and security in their projects.

Working with Biological Parts

Because they are working with biological parts, teams need to consider the function of each part to determine whether, and how, it can be handled safely. When assessing the hazard posed by parts they want to use, teams need to think about the part's

origin, its function, and how it may interact with other parts in their project. Teams are encouraged to avoid the use of dangerous parts and to seek safer alternatives. Even if the individual parts in a project are safe, they may have a dangerous function when combined with other parts or placed in specific systems. Teams are required to think about how their parts will work together. For example, could they imitate the function of a virulence factor? Could they be harmful to humans or the environment in some other way? In order to help teams understand any risks associated with parts developed in the past, iGEM puts "Red Flags" on any part in the Registry that might pose a risk when combined in certain systems with certain other part. iGEM does not accept dangerous parts (such as those that encode toxins). If a team wants to work with any part with a "Red Flag," they require special permission from the Safety and Security Committee.

On a regular basis, a commercial partner screens all parts in iGEM's registry for hazardous potential. The screening process looks at the likely origin of the part (by conducting blast searches against sequence databases) and approximate function using internal databases maintained by the partner firm. Any part that might pose a risk is identified and can result in the part receiving a "Red Flag."

Reviewing Biosafety and Biosecurity Information

All iGEM teams provide details of their risk assessment and how they are managing these risks, via a Safety and Security form. An initial draft of the form is required when most teams begin to move from the planning to laboratory phases of their projects. The form details what they plan to do in their project. They are expected to update their draft whenever their plans change. A final version becomes due as teams wrap up their lab work and begin to focus on how to communicate about their project (iGEM Foundation 2018d).

Whenever a team wants to use an organism or part not on the competition's White List, they have to seek approval from the Safety and Security Committee via a Check-In form. This provides additional details as to what they want to use, how they will obtain it, what they will do with it, what risks this might involve, and how they are managing these risks (iGEM Foundation 2018c).

If a team wants to use vertebrates (e.g., rats, mice, guinea pigs, hamsters), or higher-order invertebrates (e.g., cuttlefish, octopus, squid, lobster), they must seek approval from the Safety and Security Committee via an Animal Use form. This provides a thorough justification of why they want to use the animals based on the three Rs:

- *Replace*—whenever possible alternatives to animal models should be used. Teams must explain why no alternative approaches are possible.
- *Reduce*—if animals are to be used, the fewest possible needed to accomplish the goal of the research should be used. Teams must show they are using the appropriate number of animals to power their study.

- *Refine*—animal research must use methods that minimize or alleviate pain, suffering, or distress and enhance animal welfare. This includes appropriate housing, environment, stimulation, and feeding of animals (iGEM Foundation 2018b).

A second commercial partner screens all the forms provided by teams. They use a network of internationally certified biosafety and biosecurity professionals to review the details provided and highlight potential issues to the Safety and Security Committee.

Issues in Environmental Biosafety

iGEM has a strict no release policy. Projects have to stay inside the lab. Some projects, however, would envisage environmental release should they ever be sufficiently developed. Past examples have included the creation of engineered systems to clean up environmental contaminants or the use of biosensors to detect the presence of compounds of interest. Through their human practices work, teams working on these projects often explore what it might take to get regulatory approvals for such a product. Teams are also required to consider both immediate risks to the environment and potential risks should their project be fully realized.

In 2016, an iGEM team attempted to make a gene drive. They did not make a functional drive but did manage to get some of the components to work. As gene drives do not include any pathogens or parts connected with virulence or transmissibility, they do not appear on common control lists. None of their components was specifically captured by iGEM's safety and security rules and policies at that time. The Safety and Security Committee began working with team, noting that they were eloquent and engaged in considering broader implications of their project but had not anticipated the amount of scrutiny their project would receive (Minnesota 2016). iGEM has taken a number of gene drive-specific steps that have been shared with regulators around the world. They have been fed into a number of national policy development processes. In the months following the 2016 competition, where a team had attempted to develop a gene drive (Minnesota 2016), iGEM constructed the world's first policy on gene drives (iGEM Foundation 2018e). This project was reported in the wider press, noting that (a) international gene drive experts reported project was "not dangerous" and (b) the team had designed in specific safety precautions (Swetlitz 2016). iGEM's policy ensures robust review by requiring that any iGEM team's research on gene drives is dependent on special permission from the Safety and Security Committee. This requires a team to convince the Safety and Security Committee of the following:

– There will be no environmental release.
– The project is safe, based on host organism, parts, and containment measures.
– Best practices in containment developed by leading gene drive researchers are being implemented.

– The planned project has been discussed on a conference call with recognized international experts on gene drives and biosafety and biosecurity.
– Any commercially acquired parts are produced by companies that screen against regulated sequences (i.e., Australia Group List of Human and Animal Pathogens and Toxins for Export Control [The Australia Group 2019]).

Teams have to self-declare their intent to use gene drives—helping to address the challenge of identifying relevant work. A functional description of gene drives (rather than a list of specific parts) was developed to help teams describe the specific functions of the gene drive components they intend to use. Gene drive-specific language and examples were inserted into the White List to embed them into iGEM's routine safety and security activities. A ban on gene drives as parts in the competition Registry also helps to mitigate risks of accidental release.

iGEM has expanded the concept of safety and security by:

- Going beyond traditional agent-based risk assessment.
- Evaluating risk on "a case-by-case basis" as opposed to "in a broad and generic manner."
- Embracing a more whole-of-life cycle approach with the "aim to review the research before it begins and then periodically assess and evaluate the project concerning changes in the research that may present additional elements of importance for risk management."
- Utilizing multiple risk management approaches, including both biological tools, and human solutions.
- Embedding consideration of certain bioethics elements into biological risk assessments and management processes. For example, "What trade-off between the chance of benefit and the risk of harm is justifiable and acceptable and for whom?"
- Involving a wider set of stakeholders, including "scientists, biosafety officers, institutional leadership, and ethics consultants, with the aim of maximizing safety as well as scientific progress" (Lunshof and Birnbaum 2017).
- Human practices have been a core component of the competition, and successful teams universally consider "how their project affects the world and how the world affects their project" (iGEM 2019). More specifically, iGEM's belief that safety and security are the responsibility of all promotes the involvement of the widest possible group of stakeholders. This approach has proven successful in addressing a number of practical, real-world challenges for lab biosafety, environmental biosafety, biosecurity, and bioethics.

Do-It-Yourself Biology

Do-It-Yourself Biology, or DIYbio, is a global movement spreading the use of biotechnology and synthetic biology tools beyond traditional academic and industrial institutions and into other publics (Grushkin et al. 2013). Practitioners include a

broad mix of citizen scientists, amateurs, enthusiasts, students, and trained scientists. Some of the practitioners focus their efforts on using the technology and gained knowledge to create art, explore biology, create new companies, or simply tinker. Others believe DIYbio can inspire a generation of bioengineers to discover new medicines, customize crops to feed the world's exploding population, harness microbes to sequester carbon, solve the energy crisis, or even grow our next building materials. The DIYbio movement now represents community labs, individual labs, and group-like incubator spaces spread across the globe (see Fig. 3).

The concept of amateur biotechnologists—what eventually became DIYbio—began to take shape around 2000 after a working draft of the human genome was completed by the Human Genome Project (Grushkin et al. 2013). People began setting up home labs (Carlson 2005), which evolved into dedicated labs in commercial spaces. The organizers pooled resources to buy, or take donations of, equipment and began what have become known as "community labs." The first opened in Brooklyn, NY, USA, in 2010. Community labs sustain themselves on volunteers, membership donations, and paid classes. DIYbio continues to grow rapidly. There are now community laboratories and other types of community incubator spaces spread across six continents (see Fig. 3). They participate in iGEM, provide educational and start-up opportunities and at a more basic level, and have exposed thousands of citizens to biology, biotechnology, and science more broadly who might not otherwise have had the opportunity.

The DIYbio community believes that wider access to the tools of biotechnology, particularly those related to the reading and writing of DNA, has the potential to spur global innovation and promote biology education and literacy that could have

Fig. 3 Map of community biotech labs and community incubator spaces as of 2018, based in part from http://sphere.diybio.org/ and personal communications

far-reaching impacts. These potential innovations raise valid questions about risk, ethics, and environmental release for all scientists, policymakers, and the public (Kuiken 2016). For instance, the Odin, a company that believes "the future is going to be dominated by genetic engineering and consumer genetic design," creates "kits and tools that allow anyone to make unique and usable organisms at home or in a lab or anywhere" (Odin 2018). Some of these kits raise serious environmental and ethical issues regarding animal welfare (Bloomberg 2018), along with societal questions about who should be able to access these technologies.

Efforts by the DIYbio Community to Address Safety, Security, and Ethics

"People overestimate our technological abilities and underestimate our ethics," Jason Bobe, one of the founders of DIYbio.org, told the *New York Times* in 2012 (Zimmer 2015). Safety, security, and ethics have been topics of discussions within the DIYbio community since its formation. In 2011, the Woodrow Wilson Center and DIYbio.org brought together the DIYbio leadership in Europe and United States to establish their own codes of ethics. Debated over the course of a few days, these codes came directly from the community at the time. Both codes are remarkably similar (Fig. 4). While the codes were never meant to be static or adopted by every member of the community, they help strengthen the culture of responsibility burgeoning in DIYbio. At the 2018 Global Community Biosummit (Biosummit 2018), a shared purpose statement was developed to complement these codes (Figs. 5 and 6).

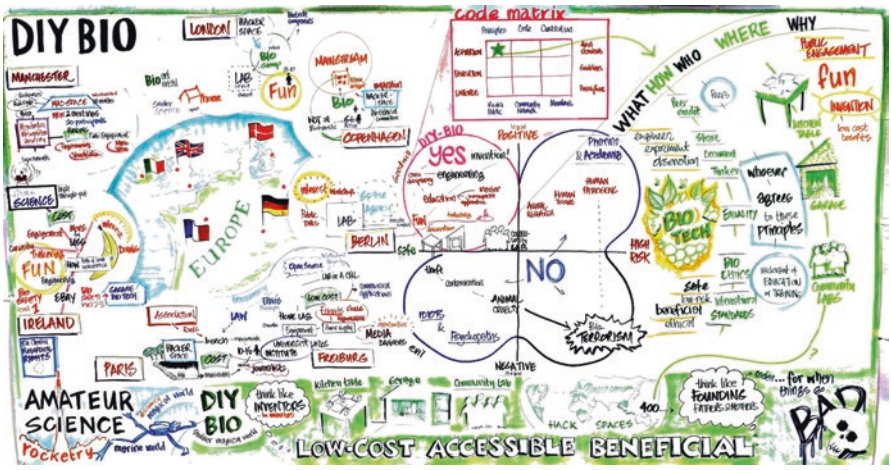
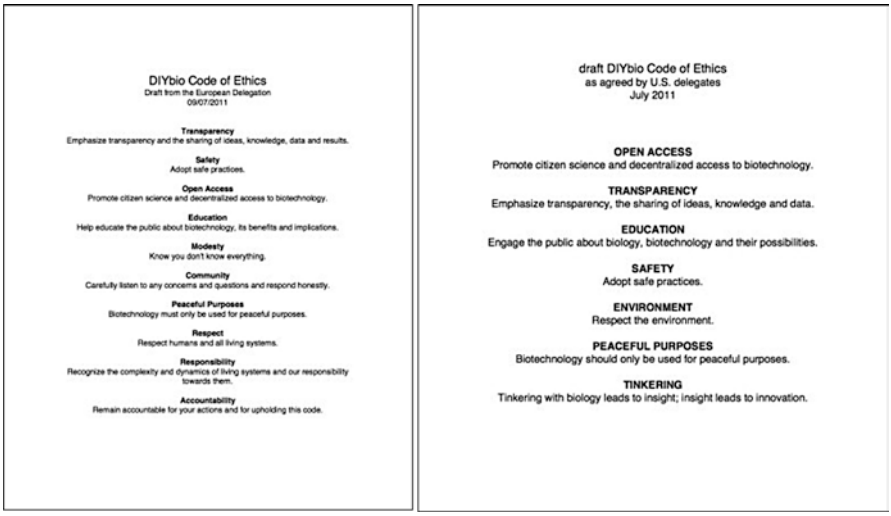


Fig. 4 Graphic representation of the DIYbio codes of conduct workshop, London 2011



DIYbio Code of Ethics
Draft from the European Delegation
09/07/2011

Transparency
Emphasize transparency and the sharing of ideas, knowledge, data and results.

Safety
Adopt safe practices.

Open Access
Promote citizen science and decentralized access to biotechnology.

Education
Help educate the public about biotechnology, its benefits and implications.

Modesty
Know you don't know everything.

Community
Carefully listen to any concerns and questions and respond honestly.

Peaceful Purposes
Biotechnology must only be used for peaceful purposes.

Respect
Respect humans and all living systems.

Responsibility
Recognize the complexity and dynamics of living systems and our responsibility towards them.

Accountability
Remain accountable for your actions and for upholding this code.

draft DIYbio Code of Ethics
as agreed by U.S. delegates
July 2011

OPEN ACCESS
Promote citizen science and decentralized access to biotechnology.

TRANSPARENCY
Emphasize transparency, the sharing of ideas, knowledge and data.

EDUCATION
Engage the public about biology, biotechnology and their possibilities.

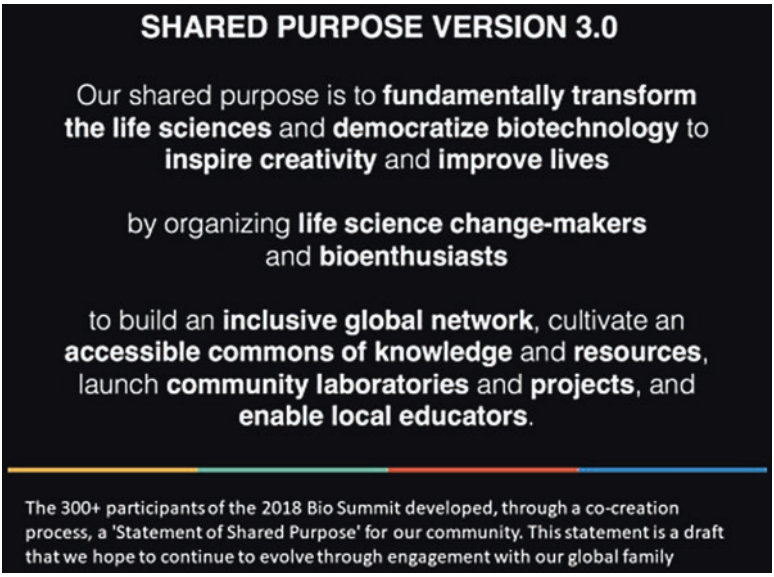
SAFETY
Adopt safe practices.

ENVIRONMENT
Respect the environment.

PEACEFUL PURPOSES
Biotechnology should only be used for peaceful purposes.

TINKERING
Tinkering with biology leads to insight; insight leads to innovation.

Fig. 5 DIYbio codes of conduct



SHARED PURPOSE VERSION 3.0

Our shared purpose is to **fundamentally transform the life sciences** and **democratize biotechnology** to **inspire creativity** and **improve lives**

by organizing **life science change-makers** and **bioenthusiasts**

to build an **inclusive global network**, cultivate an **accessible commons of knowledge** and **resources**, launch **community laboratories** and **projects**, and **enable local educators**.

The 300+ participants of the 2018 Bio Summit developed, through a co-creation process, a 'Statement of Shared Purpose' for our community. This statement is a draft that we hope to continue to evolve through engagement with our global family

Fig. 6 Global Community Biosummit shared purpose

While codes of conduct can serve to provide a framework for responsible conduct, they are not a substitute for biosafety/security procedures. Over the years, the DIYbio community has developed collective governance mechanisms to address both safety and security. As part of the FBI's Biological Sciences Outreach Program, an agency effort designed to strengthen the relationship between the science and

law enforcement communities, FBI representatives and some DIYbio leaders have begun a dialogue about safety and security. These dialogues inform the DIYbio community about the FBI's interests/concerns and inform the FBI agents about the types of work done at community labs, in particular what a DIYbio lab looks like (as opposed to a methamphetamine lab). Over the years, the program has built individual relationships between FBI agents and the DIYbio community. Because of these relationships, lab members have contacts within the FBI in the event of suspicious activity, and agents better understand the community and can respond appropriately to either false alarms or legitimate issues (Grushkin et al. 2013).

While each individual community lab has its own processes and procedures, many DIY community labs have strict rules about lab access and biosafety training programs and procedures in place. At Brooklyn's Genspace, for example, community lab directors evaluate each new member and their project for safety. In cases where the directors do not have the expertise to evaluate a project, they consult with the lab's safety advisory committee made up of university professors and biosafety officers. In the absence of such a committee, DIYbio.org provides the Ask a Biosafety Expert service (DIYbio 2013), where experts and members of the American Biological Safety Association answer safety questions (see Fig. 7). If the

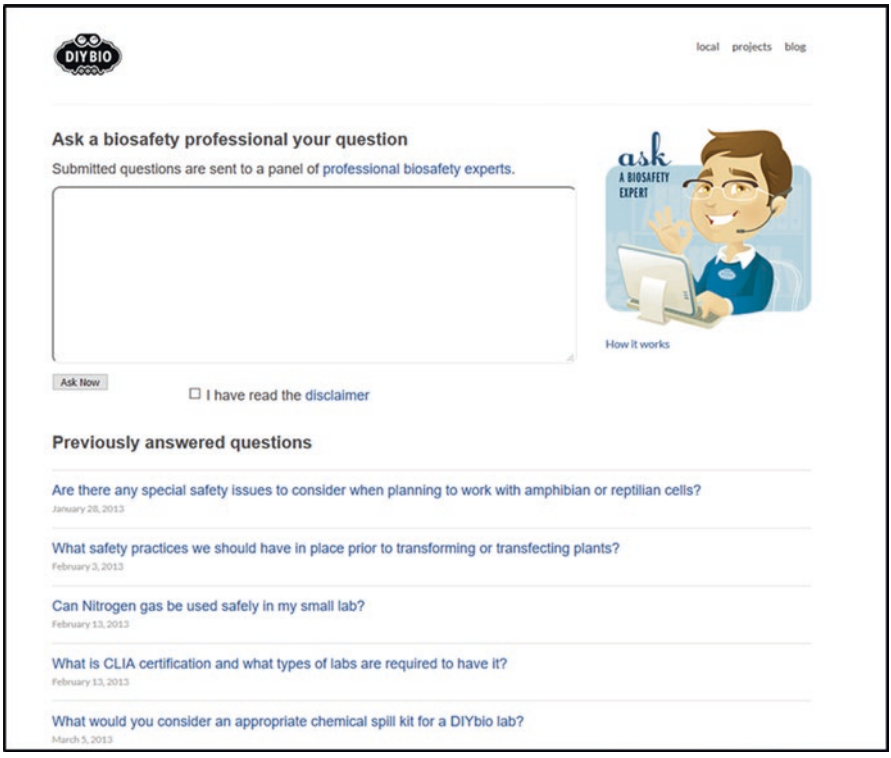


Fig. 7 DIYbio Ask a Biosafety Expert (DIYbio 2013)

potential member or project seems suspicious or unsafe, the project/person may not pass this screen. In addition, directors in most labs approve the reagents and biological materials that are purchased, brought in, and removed from the lab (Grushkin et al. 2013). With a grant from the Open Philanthropy Project (Open Philanthropy Project 2019), new hands-on training programs are being developed for 2019 but will need to be funded in the future to sustain them over the long term.

Taken collectively, these programs demonstrate that the DIYbio community has a responsible, proactive attitude that is well-suited for collective governance (Kuiken 2016).

The Bio-citizen

Taken in part from (Kuiken, Pauwels and Denton 2018; Pauwels and Denton 2018).

Stories of bio-citizens, people operating outside the traditional biomedical research community in order to address health-related issues, have astonished some and empowered others. Similar to the DIYbio movement, access to tools, technology, and information offers the lay public new opportunities to guide the direction of biomedical innovation and enables individuals to generate and mobilize new knowledge. The *Rise of the New Bio-Citizen* workshop (Kuiken et al. 2018) gathered key actors in citizen-driven biomedical innovation and advocacy, democratized biology (community bio-labs), and policy experts. Participants held an open discussion centered on the ethical, safety, and governance issues related to citizen-driven biomedical research. Collectively they discussed codes of conducts, guidelines, and policies that address governance issues identified in the Citizen Health Innovation Report (Pauwels and Denton 2018) and identified barriers and ways to enable increased participation among bio-citizens.

Under the designation "patient-led research" (PLR) or "citizen-driven biomedical research," citizens, patients, and families have increasingly become the leading force in the initiation or conduct of health research projects. Their activities may involve analyses of genomic data for diagnosing rare diseases, identification of potential therapeutic drugs, organization and crowdfunding of clinical trials' cohorts, and even self-surveillance or self-experimentation. Many of the participants in citizen-driven biomedical research are patients and families confronted with a condition that is the subject of their research, therefore facing new epistemic and governance challenges and often testing the ethical and regulatory limits within which health research has traditionally operated.

This new form of research where citizens and patients are the primary producers and mobilizers of knowledge promises to break new ground in underserved health domains. However, it suffers from a lack of legitimacy when it comes to assessing the quality of patients' experiential data. This endeavor also gradually transfers the responsibility of safety and ethics to lay experts, raising new ethical concerns—from blurring boundaries between treatments and self-experimentation, peer pressure to

participate in trials, exploitation of vulnerable individuals or third parties (children), to a lack of regulation concerning quality control and risk of harm.

Patients often have in-depth experiential knowledge of their conditions along with a stake in making sure that a treatment or device will be effective, safe, and beneficial. Yet, facing regulatory uncertainty and potential stringency, they might not overcome the "chill factor"—a phenomenon described by citizen scientists and DIY inventors as the fear to confront regulators by sharing the recipe for a new invention.

Perspective from Regulators

Using patient experience data is not unprecedented in drug regulation, as the US Food and Drug Administration (FDA) approved Exondys 51 in September 2016 in part utilizing this type of information. Legislators describe "real-world evidence" (RWE) in Section 3022 of the twenty-first Century Cures Act as any drug performance data which does not come from randomized control trials. This information can originate from "ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities" (FDA 2018). Notable examples of RWE include electronic health records, personal health devices and/or apps, billing records, and social media. As defined by twenty-first Century Cures, RWE exclusively applies to drug regulation (potentially including regenerative therapies). This type of data would aim to enhance the generalizability of clinical trial findings (Sherman et al. 2016, p. 2293).

Twenty-First Century Cures directs FDA to create a trial framework for implementing the use of RWE by the end of 2018. This draft framework would use input from the public (e.g., industry, academia, patient groups) and apply only to drugs. FDA will then publish guidance on when RWE will be applicable and how best to collect this data. However, in July 2017, the FDA published draft guidance on utilizing RWE in medical device oversight (FDA 2017), suggesting RWE could become applicable across FDA regulation. RWE may help address issues with current clinical trial designs, which require large patient cohorts and high costs but still lack generalizability (Sherman et al. 2016). However, existing sources of RWE were not designed to aid regulatory decision-making and could present analytical challenges (Sherman et al. 2016). Patient experience data may be able to serve a similar role, but limited literature exists on the potential risks and benefits of using patient experience data in regulatory approval.

Interestingly, "patient experiences and perspectives," which the FDA has been tasked with measuring and analyzing, do not seem to align with citizen-driven biomedical research and patient-led health innovation. Since RWE applies to drug regulation, many of the case studies in this report would not fall under this classification of research because not all citizen-driven biomedical research aims

to produce drugs that will require regulatory approval. At best, the definitions of these two terms—RWE and citizen-driven biomedical research—do not align; at worst, the FDA has been tasked with measuring and analyzing only a small subset of patient-led health innovations within the broader scope of citizen-driven health research. Even more recently, in November 2017, the FDA released information about the self-administration of gene therapy (FDA 2017; Smalley 2018). According to that statement:

> [the] FDA is aware that gene therapy products intended for self-administration and "do it yourself" kits to produce gene therapies for self-administration are being made available to the public. The sale of these products is against the law. FDA is concerned about safety risks involved. Consumers are cautioned to make sure that any gene therapy they are considering has either been approved by FDA or is being studied under appropriate regulatory oversight. (Ibid.)

These themes were present throughout the *Rise of the New Bio-Citizen* workshop discussions (Kuiken et al. 2018).

Breaking Barriers to Innovation

A recurring theme throughout the discussions at the workshop, "The Rise of the New Bio-Citizen: Ethics, Legitimacy, and Responsible Governance in Citizen-Driven Biomedical Research and Innovation" (Kuiken et al. 2018) was, broadly speaking, about regulations. What are the regulations that govern the bio-citizen? Should there be regulations that govern the bio-citizen? Are current regulations, or the threat of regulations, preventing or discouraging more bio-citizens from participating in biomedical research? How can the bio-citizen better understand the goals of regulation, and how can the regulator better understand the goals of the bio-citizen?

These questions around governance and regulatory systems require further discussion, but the overall sense from the participants is that regulations would not necessarily be a barrier to innovation. Providing resources for the bio-citizen to gain access to regulators in order to help reinterpret the regulations to fit their unique circumstances could help mitigate the potential for regulations to build barriers.

The diagram (Fig. 8. Context and constraints in bio-citizen spaces) below, which describes the innovation ecosystem, is one example of an accessible resource that may benefit bio-citizens, community bio-labs, and regulators. Community bio-labs have the potential to prototype and experiment in an environment with ongoing risk and safety oversight. In this way, community bio-labs could be a bridge between individual bio-citizens and regulators by serving as a safe space to experiment and test governance systems.

Fig. 8 Context and constraints in bio-citizen spaces. (Adapted from Jeremy de Beer and Jain (2018))

Informed Consent and Centralized Decentralization

Expanding the health innovation platform to include the bio-citizen raises the issue of informed consent in a novel way. Participants in the workshop, *Rise of the New Bio-Citizen* (Kuiken et al. 2018), wrestled with the concept asking questions like:

- Is bringing consent into the governance process too burdensome?
- What are the "right" levels of consent? Are there different levels of consent in different situations? If so, where does self-experimentation fall on this spectrum of consent?
- How much does one need to know to understand in order to give consent? How do we deal with known unknowns?
- How should we deal with incomplete information/knowledge transfer?
- Are the operating and rigid institutional framework of scientific and professional values problematic?
- Is the systematic institutionalization of ethical values problematic?
- Could you develop a citizen service provider for informed consent, a centralized institutional review board (IRB) that operates via decentralized community labs/ IRBs to increase access?
- If you are filming and broadcasting everything that you are working on and/or doing, are you providing a resource and therefore a need for consent from those receiving that information?
- Where does the burden of consent and liability lie?

The discussion around adequate informed consent evolved into a discussion about institutional review boards (IRB) and how such a system might operate in the age of the bio-citizen.

- What is the practicality of such a system?
- Are there different levels of approval that should be applied to the bio-citizen?
- Would such a system provide a level of legitimacy for the bio-citizen?
- Do rigid institutional governance frameworks prevent permissionless sandboxes?
- Do permissionless sandboxes hinder the establishment of a social license to operate for bio-citizens?

One idea was whether you could design a "peer-to-peer" IRB system or, more basically, provide access to the expertise and information that preserves the spirit of what a traditional IRB does. A similar type of project was developed around biosafety for the DIYbio community with its Ask a Biosafety Expert web portal (DIYbio 2013). Whether this type of system could work for issues that an IRB handles requires further thought and deliberation. For instance, could community IRBs lead to unconventional or non-traditional studies? Is approving unconventional and non-traditional experiments necessarily a sign of permissionless innovation?

One critical aspect is the liability associated with programs like this. Experience from the Ask a Biosafety Expert program suggests liability insurance is both needed and difficult to acquire without dedicated funding, which bio-citizens do not always have. How might bio-citizens who crowdfund the resources necessary to innovate acquire liability insurance? This type of program would also need some semblance of infrastructure and management in order for it to be useful for the community.

Other ideas that emerged from the discussion around intuitional review boards revolved around developing ethical and safety workshops/curriculums aimed at bio-citizens, incubators, and community labs. These were also seen as potential capacity building opportunities for community biology labs and health incubators. The organization, Public Responsibility in Medicine and Research, was presented as a model that could be used. Their stated goals and activities focus on "creating a strong and vibrant community of ethics-minded research administration and oversight personnel, and providing educational and professional development opportunities that give that community the ongoing knowledge, support, and interaction it needs to raise the bar of research administration and oversight above regulatory compliance" (PRIMR 2019).

Ethical Innovation

There was a sense among the participants in the workshop, *Rise of the New Bio-Citizen* (Kuiken et al. 2018), that we need a better understanding of the underlying ethical issues associated with the bio-citizen and creating opportunities for inclusive innovation (de Beer and Jain 2018). Issues such as treatment vs enhancement or self-experimentation vs survival were discussed, and consensus was reached on the need for conceptual clarification. It was felt that we have little understanding on

how to extrapolate health innovation "on the individual" to issues affecting society at large, particularly when discussed under the concept of social license to operate. A social license to operate "is an informal agreement that infers ongoing acceptance of…a project by a local community and the stakeholders affected by it" (Gallois et al. 2017). However, while many of the ethical issues focused on the individual, it was suggested that the issue be expanded beyond the individual to include public health, environmental health, and the impact on public science at large. This discussion led us to contemplate issues of power and control. Who gets to control another person's acts; who is the real villain or victim? The person who may engage in self-experimentation, the person who tries one of these innovations, or the person trying to stop any potential harm that might incur? The lines are fuzzy particularly when people, or the individual, think they are helping those who are seeking cures that do not currently exist or that they cannot afford.

One suggestion was for the community to address, or at least better understand, the underlying ethical issues associated with the bio-citizen. This would help to unpack how the regulatory structure affects the bio-citizen and evaluate how these ethical issues can guide what is happening, not stand in the way. It was felt that not meeting these ethical standards could cause others in society to reject what the bio-citizen might be doing and place societal roadblocks to the innovation platform or inclusive innovation.

It was suggested that innovators need to have some friction or speed bumps in the innovation process in order for them to see, or acknowledge, issues that are beyond the technical. Technologists and scientists typically focus on generating a specific kind of knowledge and are not well-suited, in the context of time, education, and influence, to assess and address potential ethical issues. By enabling ethicists, and other biosafety professionals, to work alongside scientists and technologists could provide this friction in order for the innovator to "take a step back" and think about the ethical and biosafety issues their projects raise. This type of reflection is evident in how the human practices and biosafety programs of iGEM operate. Interdependent issues encompassing ethics, social license to operate, and legitimacy were major underlying themes discussed throughout the workshop.

Though a social license to operate has typically been associated with industrial and energy industries (Ibid.), the concept elicits opinions about who/when/if you ask permission and whether acquiring a type of social license to operate establishes legitimacy. The "expression refers to mainly tacit [or, experiential] consent on the part of society toward the activities of business (or in our case the bio-citizen)…it constitutes grounds for the legitimacy of these activities" (Demuijnck and Fasterling 2016). A social license to operate does not necessitate or prevent permissionless innovation; rather, a social license to operate allows community bio-labs and bio-citizens to innovate in safe innovation spaces with ongoing risk and safety oversight. While establishing a social license to operate may help to break barriers to bio-citizen innovation, some questions remain in the social context. For instance, what is the entry point? Is it a social license, a market license, or an ethical or legal license? When do you ask for permission? Whom do you ask?

Finding the narrative story that shows the social good was suggested as a way to address this in part. You have to demonstrate the value of innovation for and by the bio-citizen. However, how do we establish communication between communities in order for them to understand what they are getting in return (particularly when sharing data)? How do we find the incremental value in bio-citizen innovation? How is that value or equity going back to the individual or community at large? Issues of equity and privilege are also important to recognize. For instance, some bio-citizens performing innovations with diseases, and innovations around those diseases, might not have the means to turn that into a business. Or gain access to the results of having participated if, for instance, those results were utilized by a company, resulting in therapies that the individual may not be able to afford.

The bio-citizen and their societies will need to define what a "social license to operate" means to them, particularly in a health context. There was a sense among the participants that we need to collectively shift the urgency toward these issues if we want to build an inclusive and trusted innovation platform for the bio-citizen, in part because our collective trust in institutions is declining. While clinicians are trusted, institutions are not, and there is even lower trust in government. At the same time, some participants in the workshop felt that people/publics may be scared of the bio-citizen and that increasing engagement channels (i.e., DIYbio days at local hospitals) could be an avenue to increase trust among these groups. Having bio-citizens coming in to answer the questions for themselves could help move toward a better understanding of the social good. Permissionless innovation can support experimenting in safe innovation spaces. However, how do we protect human rights in an ecosystem of permissionless innovation?

A Living Bio-citizen Tool Kit

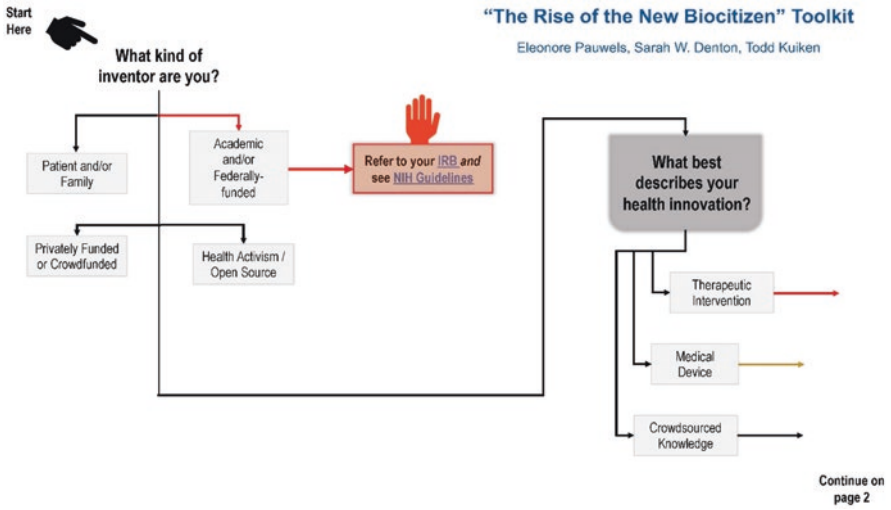
Governance and ethical issues play a role in participatory health research and innovation—even if traditional regulatory approval does not. Traditionally, knowledge legitimacy has been tied to scientific knowledge; but citizen health innovators are beginning to change that paradigm and inject their experiential knowledge into biomedical research. Before bio-citizens can be seen as legitimate health innovators, they will need to gain the trust of other scientists and regulators.

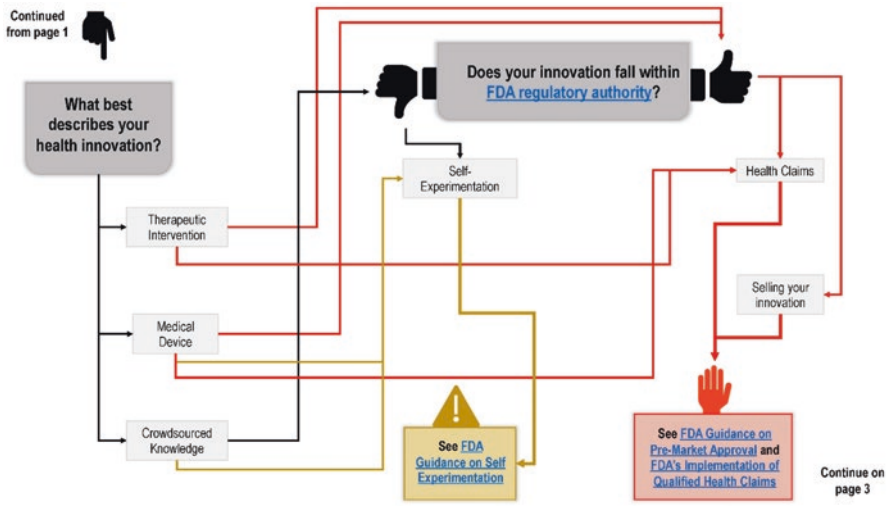
Building off the ideas and discussions throughout the workshop, a living tool kit for future bio-citizens was developed that can evolve as the community of bio-citizens evolves. It provides engagement channels between patients-innovators, crowdfunders, ethicists, and regulators to design adaptive oversight mechanisms that will foster a culture of empowerment and responsibility.

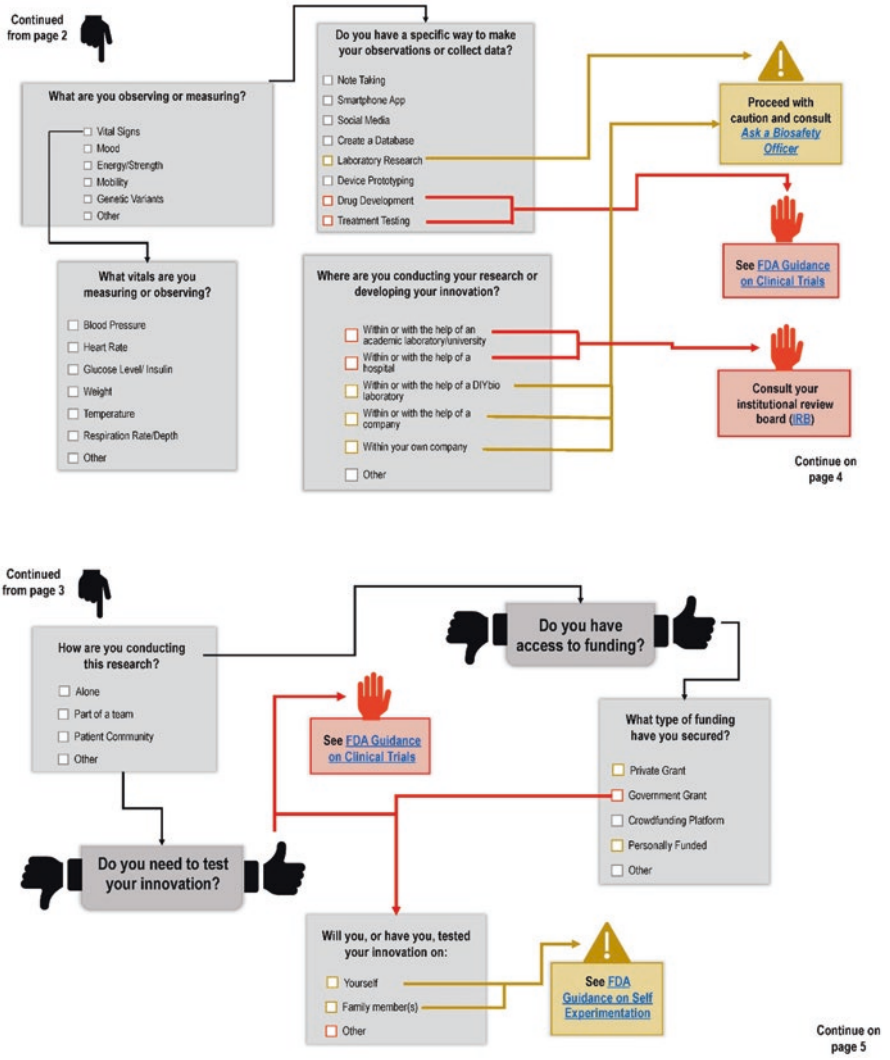
Broadly, this tool kit seeks to address the following questions:

- How can we create a safe space for health innovators and community bio-labs to share and experiment with their data, value trade-offs, and ethical concerns in ongoing conversations with regulators?

- How can regulators and crowdfunding platforms help bio-citizens modernize practices that will give legitimacy to their research, devices, and treatments?
- Instead of trying to fit citizen-driven innovation into the existing regulatory framework, a more adaptive approach might help these citizens become literate in how to conduct research and help them identify the regulatory checkpoints. See the "Rise of the New Bio-citizen Tool Kit."






Continued from page 2
What are you observing or measuring?
Vital Signs
Mood
Energy/Strength
Mobility
Genetic Variants
Other
What vitals are you measuring or observing?
Blood Pressure
Heart Rate
Glucose Level/ Insulin
Weight
Temperature
Respiration Rate/Depth
Other
Do you have a specific way to make your observations or collect data?
Note Taking
Smartphone App
Social Media
Create a Database
Laboratory Research
Device Prototyping
Drug Development
Treatment Testing
Where are you conducting your research or developing your innovation?
Within or with the help of an academic laboratory/university
Within or with the help of a hospital
Within or with the help of a DIY/bio laboratory
Within or with the help of a company
Within your own company
Other
Proceed with caution and consult Ask a Biosafety Officer
See FDA Guidance on Clinical Trials
Consult your institutional review board (IRB)
Continue on page 4
Continued from page 3
How are you conducting this research?
Alone
Part of a team
Patient Community
Other
Do you need to test your innovation?
Do you have access to funding?
See FDA Guidance on Clinical Trials
What type of funding have you secured?
Private Grant
Government Grant
Crowdfunding Platform
Personally Funded
Other
Will you, or have you, tested your innovation on:
Yourself
Family member(s)
Other
See FDA Guidance on Self Experimentation
Continue on page 5

Thinking Forward: Is Collective Governance the Answer?

The examples discussed above represent a type of collective governance that involves multiple parties/stakeholders. These collective governance systems have functioned based on the following two principles:

1. *Direct buy-in from the community*

The iGEM participants, iGEM Foundation, and the larger iGEM community have all collectively bought into the need for the human practices and safety/security programs. These programs have captured most, if not all, country jurisdictional rules and universalized them to create a level playing field for all participants. Since the Safety and Security Committee has the authority to disqualify teams for not complying, they have a unique and important role in this type of collective governance, similar to legal consequences present in individual country regulations. While the goal is never to have to disqualify a team, this mechanism provides incentive for teams to comply with the program. In addition, providing awards for both human practices and safety provides additional incentives for teams to comply.

The DIYbio and citizen health communities have separate but similar reasons for buy-in. They have collectively recognized their responsibility to their own local communities and the larger global community, including the larger DIYbio and citizen health communities. Beyond the codes of conduct, which highlights the ethical and safety guidelines they follow, members of the DIYbio community understand that the actions, or missteps of one, will affect the entire community. In addition, the interactions and relationships built with both regulators and law enforcement from the beginning of the communities' development have provided the atmosphere and

opportunities for this type of collective governance, without the typical top-down regulatory systems. The absence of a top-down regulatory system could be based on regulatory authorities' recognition of the responsible conduct the DIYbio and citizen health communities have developed and/or the inability for typical governance structures to realistically govern such a diverse and multinational community. In a sense, regulatory authorities and the DIYbio community need each other's buy-in to acquire a larger "social license" to operate.

2. *Flexibility in adapting to fast-changing technologies and applications*

The iGEM Safety and Security Program displays why flexibility in adapting to fast-changing technologies and applications is crucial for governing these types of communities. iGEM has the ability to adjust its rules and regulations annually and, if needed, during the working period leading up to the giant jamboree where the teams present their work. The Safety and Security Committee is similar to a governments' regulatory authority that reviews applications for permits. However, iGEM's Safety and Security Committee has more flexibility in terms of its authority and ability to adapt its rules based on the application/technology it encounters. Replicating this type of flexibility in a more traditional regulatory authority would be difficult, unless governments provided that flexibility in its overarching legal frameworks. The tool kit for citizen health innovators was developed in part with help from various US regulatory authorities. Similar to the buy-in discussed above, this partnership represents a "flexibility" in part by some US regulatory agencies and a recognition that the traditional regulatory structures are not capturing all that are participating. While they may not be adapting the regulations in real time, they are enabling these "outside" actors to maneuver through the system.

A Way Forward?

Synthetic biology and other evolving biotechnologies have given rise to a set of communities operating across countries and tied together by the technologies and purposes they ascribe. The iGEM community now represents over 40,000 students spread across 6 continents and over 40 countries. The DIYbio and citizen health innovator communities follow a similar trend in relation to geography with nearly 100 locations (see Fig. 3). Replicating the collective governance systems put in place at iGEM and within the DIYbio communities may require new legal and societal authorities to govern these and other emerging technologies. Yet, while the circumstances are unique, they provide guidance toward how a collective governance system could work.

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