Submission # 1:

Date	2/2/2020
Name	Matthew G. Endrizzi
Organization:	
Email:	*Personal Information*@gmail.com
Comment:	Attached is a brief report that summarizes my concerns around novel nucleic acids and offers suggestions for future directions. Could you please forward it to the NExTRAC as public comments? I worked in molecular biology research at Florida State University, Harvard Medical School, and the Whitehead Institute Center for Genome Research (now the Broad Institute). I am currently a public high school teacher. I am submitting these comments as a private citizen with no affiliation to any organization. Please do not hesitate to contact me if any questions arise.
Attachment:	Submitter indicates the attachment to be a private communication; not intended for publication

Submission # 2:

Date	6/25/2020
Name	Matthew G. Endrizzi
Organization:	
Email:	*Personal Information*@gmail.com
Comment:	I wrote to you on February 2 this year to share with NExTRAC a summary of my concerns regarding the work I used to do making recombinant DNA, as well as suggestions to consider. Since sending my last communication, I came across data that was published by Katherine Smith in 2014 that summarizes trends in global human infectious disease outbreaks between 1980 and 2010 which prompted me to write the attached manuscript. My concerns are no longer just for what might happen in the future but what is happening now. The question I pose is whether this data indicates biotechnology practices might be contributing to the number of zoonotic viruses we are observing making their way to humans. Please read the manuscript for more thorough context. Because I do not write with any institutional affiliation and I am addressing a highly controversial issue, I would not expect Dr. Smith (or Dr. Eugene Koonin whom I also contacted for an opinion) to comment back to me. I submitted this manuscript to Science magazine for review, which was rejected for publication in the Perspectives section. I did not receive any meaningful comments back from an editor, either. Personally, I am relieved not to get published because I am less and less convinced this conversation should be public, especially as I see how so many people are responding to information about SARS-CoV-2. I also have taught high school science for 16 years now and have a better sense of how little people know about what scientists have worked really hard to figure out. For nearly twenty years, I have chosen to send my communications with scientists and other leaders through email as a way to maintain a record that could be shared publicly. I have also not always maintained the most professional tone. For the latter, I am sorry, and extremely regretful. I admit to being frustrated that I see significant danger in work I used to do, but the people I used to do it with don't seem to see any danger in it at all, and would rather not discuss it. This worries me a great deal. I am a rather insignificant nobody, but the ideas I pose have important implications for everyone, I think. I have been mocked for conjuring up scenarios that only exist in my head. The extreme challenge here is that I don't want to describe something that might give a bad person a good idea, so I don't go into details online (hence, why details of Asilomar are so scarce?). The folks at the Future of Humanity Institute educated me on the importance of information hazards. I welcome explaining the details of what I imagine to NExTRAC members in person.

I wish more than anything for the scenarios I imagine to remain phantasms, but 78 out of 95 scientists at the Gordon Research Conference on Nucleic Acids in 1973 seemed to have similar visions. I understand the conversations between scientists at the Asilomar Conference were purposefully kept private. It is frustrating to try and research an issue where the key ideas are not in print! This feels very insular and disingenuous to how science is supposed to work, but I can also now see ethical reasoning to it. On the other hand, how am I supposed to know if I have ideas that are actually the first of their kind? Normally, I would think "someone else must have already thought of that" but the more I dig the more I wonder if I have a unique perspective that has not been considered yet. I am also in the position to not have a conflict of interest, whereas I imagine almost every employed molecular biologist on the planet otherwise does in this regard, if not directly then through institutional affiliation.

Please know my comments are sincere and I do not wish to be sardonic. Many people have told me to write a book. One editor from Nature magazine suggested science fiction can be quite prescient, to which I replied that I preferred to keep the conversation in the non-fiction realm. For starters, I don't think I am a very good writer, but I can also point to the fact that since I started communicating my concerns in 2002, I have never tried to profit off of what people might perceive as fear mongering. (I have drafted two separate short books, but decided not to pursue either of them.) I gave 7 years of my life to molecular biology research, without making a whole lot of money. I turned down a promotion to senior staff under Eric Lander shortly before the Broad Institute was formed. I was burned out managing the finishing team at his genome sequencing facility. I thought I was making one costly mistake after another and was starting to lose confidence in myself, and I could not see a way to support the kind of family life my wife and I hoped for - in the Boston area - on 50K a year. So I resigned. I will never forget being in my direct supervisor's office after sharing my resignation letter when his wife called. He told her he couldn't talk at the moment because I was currently "committing suicide" in front of him. That phrase has never left my memory. Several months later I had my own insight into the risks of recombinant DNA, after I had some quiet time to ponder big ideas about the work I had just been part of. I was applying for work in the environmental consulting business, looking for ways to use my DNA sequencing skills to identify microorganisms in the environment. The question that entered my head at that time was "What is the worst thing your business process can do to the environment, and how can you do it differently to minimize impact?" Ka-boom! I did not immediately discover the 1973 Gordon Research Conference on Nucleic Acids or the subsequent Asilomar Conference, because I was searching "risks of transgenics" and not "risks of recombinant DNA." I hope that gets a little chuckle, because this issue needs a dash of humor for it to be digestible.

	Humans have done remarkable things, but we are still human. I have yet to hear a convincing argument why I should stop worrying about this. When I mentioned lunar facilities in person to Francis Collins and Paul Berg, their first responses were not to argue the safety of recombinant DNA but to question the cost and feasibility of such a facility. I also accept that it would be unethical NOT to try and alleviate suffering with genetic manipulation. I get that lunar facilities are not even close to feasible and could never gain traction anytime soon in a political system built on 4-year cycles, but there are other things we can be doing that seem fairly reasonable to me. However, as long as the scientific community holds to the notion that human-derived sequences are no more risky than naturally-derived sequences, then how could those conversations ever get started? I am also concerned public discourse about this very fundamental issue with biotechnology would lead to mass confusion and divisiveness. Look what the COVID-19 mask issue has turned into! So, all of this hush-hush-ness makes sense, but I am still left in a knotted, stressful mess. The alarm has been going off in my head for 18 years! Do I talk? Don't I talk? What do I say and to whom? Did I miss my opportunity to be part of the conversation because I am no longer employed in scientific research? Should I only make phone calls? Should I only speak to people in person? Or is there something seriously wrong with my thinking and I am not yet aware of unarguable evidence of safety that exists? (Are you and your colleagues looking at each other waiting for someone to say, "Who wants to tell him?" If so, PLEASE TELL ME!) I pray to God that for the sake of humanity I have been improving my efforts and that what I am doing is more beneficial than harmful, but if there is any guidance anyone can give me, I would GREATLY appreciate it. I must believe the scientific community I was once a part of is an ethical, generally-uncorrupted, nonconspiratorial bunch. If NExTRACT members feel any of my comments are helpful, then I trust they will pass them along accordingly.
Attachment:	Proprietary Unpublished Manuscript

Submission #:3

Date	10/20/2020
Names:	Matt Endrizzi
Organization:	
Email:	*Personal Information*@gmail.com
Comment:	I would like to submit the following for consideration by the NExTRAC. The subject matter relates to the upcoming NExTRAC agenda item "(2) discussion of a draft report conceptualizing a framework for NExTRAC deliberation of issues surrounding emerging biotechnologies." The main objective of these comments is to address what Wallace Rowe articulated at the NIH Director's Advisory Council meeting held December 15-16, 1977: "Historically it is just the vision of viral genomes being delivered in new host-range systems that had many people concerned. ... We very deliberately said let's placate the fears that were very clear at this time. ... This was an over-political decision. You can't divorce the scientific from the political. We said this was an unpalatable type of scenario, and we had better ... have some more data." (quoted from D.S. Fredrickson's The Recombinant DNA Controversy) Below is a proposal for how we might produce more data regarding biosafety, not just focused on viral genomes, but rather all novel nucleic acids larger than 100 base pairs long. I write with no institutional affiliation, but instead as a private US citizen. I hope some members of the NExTRAC might be moved to discuss this further with Dr. Collins and other leaders. Matt Endrizzi [*Personal contact information redacted*] Biosphere experiments to test impacts of a variety of different nucleic acid constructs **Phase 1: Planning** Following in the footsteps of Robert Sinsheimer who first brought a group together to consider sequencing the human genome, a small group of interested scientists could brainstorm a list of a dozen or so scientists to bring together and begin the foundational talks about logistics and experimental design. Recommending specific experiments as an individual prior to such a meeting is purely for brainstorming purposes. Here, I will offer some questions and responses. **How big would biosphere models need to be?** I imagine several levels of size. A bunch of small biospheres approximately 1/4 acre in size. Several mid-size biospheres 1 acre in size, and a few large biospheres, like

Biosphere 2, a few acres in size. People would need to be able to enter the biospheres to collect samples and perform maintenance, but they would not be environments intended for human dwelling. They should all be able to support some amount of animal life. The larger the biosphere, presumably the more the diversity.

What would be independent and dependent variables?

We could test different biosafety level containment practices having a control with no rDNA, controls with no safety precautions for all biosafety levels, and then models of BSL 1-4 labs following safety guidelines. This would involve a minimum of 9 biospheres.

We could test GMO crops and try to track phenotypic and genotypic outcomes. Are there unwanted effects on crops or adjacent plants directly? Can we see traces of engineered DNA sequences in other parts of the biosphere? Are nitrogen, carbon, or other nutrient cycles affected?

We could also test specific gene-drive technologies, like those being developed in mosquitos. How does the mosquito population recover? Do pathogens in mosquitos move to other hosts when the mosquito population is stressed in a variety of ways, both genetically and chemically?

Do CRISPR constructs pose any risks to the environment? We could test both prokaryotic and eukaryotic constructs, together and separately, to see if adapting CRISPR constructs to function in eukaryotic cells poses a special risk.

I can see all of these areas being addressed by each biosphere size level, so the more biospheres, the better. A consortium of scientists, I think, would be needed to prioritize experiments.

This will be a challenging coordination of tracking phenotypes and genotypes. We can randomly sequence DNA samples throughout each biosphere and compare those sequences looking for divergent patterns. That might in and of itself answer many questions and reveal many more. However, there should be a concerted effort to also track phenotypic changes in organisms that we know are connected to viral infections or other types of sudden genetic changes. How might we detect infectious disease outbreaks in animals? Counting deaths is one measure, but can we also track whether birds and mice, for example, might be sick based on taking their temperatures, respiratory testing, and/or antibody detection in blood?

Where would these biosphere be constructed?

Perhaps the University of Arizona's property in Oracle, Arizona would be a good centralized location, but scientific ventures occurring at multiple sites, with coordinated goals and analysis efforts, like the Human Genome Project, could foster more potential for crosscutting discovery. Being isolated in desert biomes might be the most prudent for safety reasons, but many of the experiments would be testing

laboratory conditions that already exist in densely populated cities, so perhaps the smaller and mid-sized biosphere experiments involving less-hazardous experiments could be spread around to several institutions with high expertise but limited land.

Phase 2: Fund Raising

NIH, NASA, and the NSF would hopefully support these biosphere experiments. Perhaps dollars already selected for military spending could be directed toward Space Force goals. Additionally, Congress might find support for such spending through other initiatives with relevant goals. Elon Musk, Jeff Bezos, and Richard Branson may express interest in funding such experiments given their investments in SpaceX, Blue Origin, and Virgin Galactic. Go Fund Me might be a fruitful campaign as well. These are suggested sources of money in America. There very well might be international interest in funding and participating in these experiments. Given what the United States and the rest of the world has spent responding to COVID-19, $10 billion dollars might not be that big of an ask. Perhaps $50-100 billion is a better goal, not to spend all at once, but to create an economic foundation for experiments that might need to run for 40 years, and to support small groups that could appear anywhere in the world who propose meaningful ways to analyze the enormity of data that will be generated. Unforeseen beneficial technologies will undoubtedly come out of such a scientific project. Thousands of people could be employed to work on something important, technically challenging, and really awesome, too!

Phase 3: Construction

I imagine small and medium biospheres would be constructed first to hopefully start generating some results that will inform future directions. Focus on larger biospheres might be to build environments that could support people while also addressing whatever most pressing questions arise from the first wave of experiments.

Using $200 million to construct the 3.5-acre Biosphere 2 as a guide, (assuming $50 million/acre) a facility 1/4-acre in size, the smallest size level suggested here, would cost $13 million to construct. We could build 75 of these 1/4 acre biospheres for $1 billion. Mid-sized, 1-acre biospheres would be about $50 million each. We could build about a 20 of those for $1 billion. Allot another $1 billion for 3-4 acre biospheres, and we could build 4 of those facilities. $3 billion, at $50,000,000/acre could build 60 acres of biosphere space to use for scientific experiments.

Assuming $500,000/acre/year in utilities and maintenance costs, these facilities will require $30 million/year to run.

Assuming $100,000 per employee and 1,000 employees (on average over 40 years) and expect $100,000,000/year in payroll.

$10 billion covers 60 acres of construction ($3 billion), 40 years of operation ($1.2 billion), and 40 years of pay ($4 billion), and almost $2 billion for lab reagents and computer infrastructure over a 40 year period.

Phase 4: Running the Experiments

Some thought should be given to the order of experiments. Experiments will run in waves, starting in smaller biospheres first. Experiments should be designed so that the first wave of experiments answers questions that will inform what to do in subsequent waves of experiments.

Will GenBank be the depot for sequence data? If so, perhaps a section dedicated to Biospheromics, or some such name, could be created so people know they are looking at data from a biosphere and not from nature. Other features could be added to data files denoting specific biosphere location, conditions of the facility, and any phenotypic data of organisms or the biosphere itself.

I imagine data will be collected daily and appropriately time stamped. To try and collect tightly controlled clusters of data in perfect time intervals might be untenable. For example, instead of collecting the 50 exact mice you want, all on day 30, collect samples from a few mice everyday, seeking a variety of individuals as you go, assuming you will not find all of them. If data files contain appropriate fields that trace back to the origins of that data, then the data can be sorted as needed on the analysis end.

Phase 5: Analyzing the Data

Anyone, anywhere, could access and analyze the data.

What should we analyze? Whole genome sequences of various Acytota could be analyzed regularly, and perhaps less-frequently, whole genome sequences of prokaryotes and eukaryotes could be compared to discover genomic changes that might be occurring under different biosphere conditions. Additionally, there might be specific genomic loci of key prokaryotes and eukaryotes that we might want to track in certain experiments.

As patterns emerge in phenotype data, they can be correlated with genotypic patterns.