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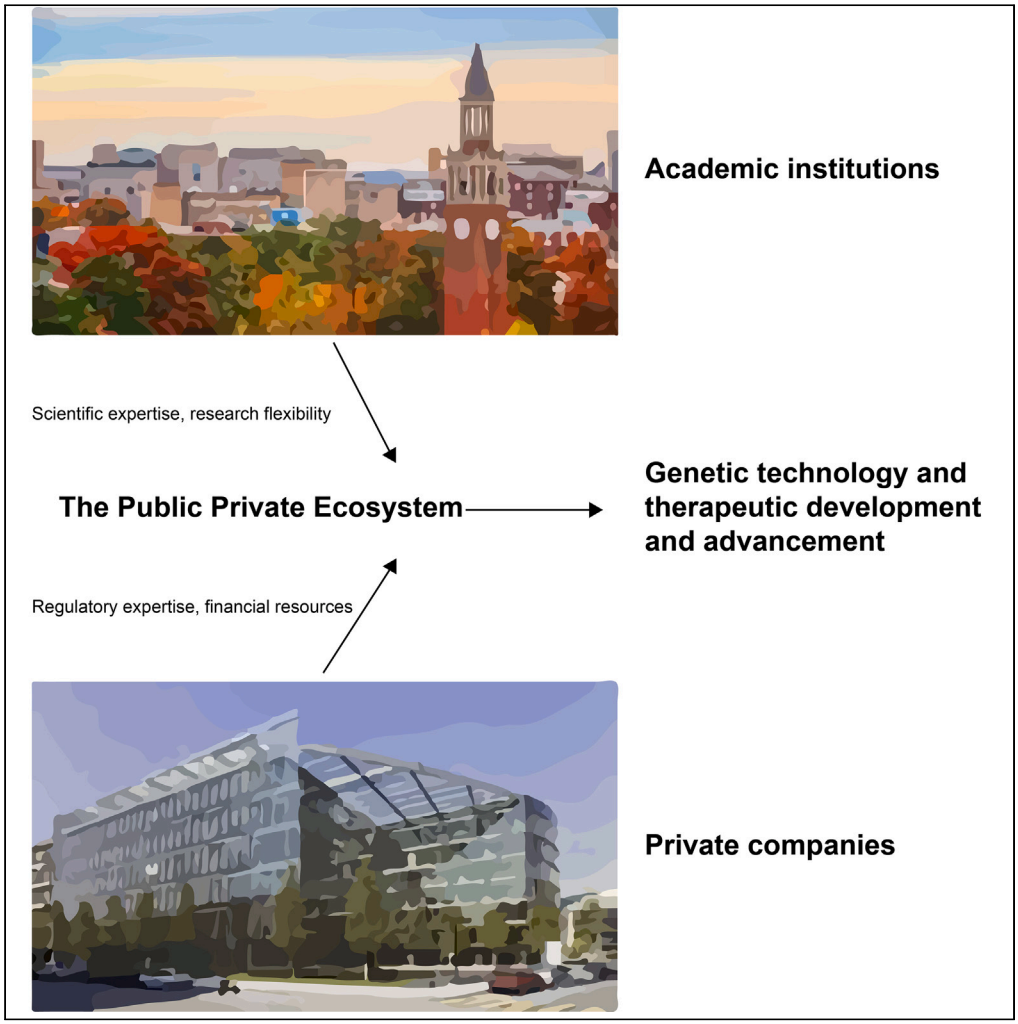

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Highlights

US-based participants believe that the PP ecosystem is overall effective

Participants outside of the US voice more skepticism of its value

Few participants are concerned about professional ethical issues

Some are concerned about access to treatments developed in the PP ecosystem

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The public-private research ecosystem in the genome editing era

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SUMMARY

Biomedical research in the US has long been conducted in a public-private (PP) "ecosystem." Today, especially with gene therapies and genome editing-based medicine, publicly funded researchers frequently hand off their research to the private sector for clinical development, often to small, venture capital-funded startups in which they have a financial interest. This trend raises ethical questions about conflicts of interest, effectiveness of regulatory oversight, and justice in therapy access, that we are addressing in a multi-year, multidisciplinary study of the evolving governance of genome editing. This paper draws on interviews with scientists working across the PP divide and their private sector business and financial partners. We find little concern about potential ethical dilemmas, with two exceptions expressed by public sector scientists: concerns about inequitable access to treatments due to disparities in wealth, ethnicity, and health insurance benefits; and about whether their private collaborators' profit motive may affect their research objectives.

INTRODUCTION

Biomedical research in the US has long been conducted in an environment of public-private partnership that we term the "public-private (PP) ecosystem." As this ecosystem has evolved, private financing has become increasingly important.[1,2] Today, publicly funded researchers often hand off their research to the private sector for clinical development, many times to small, venture capital-funded startups in which the same scientists have a financial interest. They are effectively handing off the research to themselves, albeit wearing a different hat. Dating back to the Bayh-Dole Act of 1980, these trends have been encouraged in the US by the National Institutes of Health as well as by research universities, most of which have policies and programs for PP technology transfer and licensing.[3] Gene therapies and genome editing-based medicine are active participants in this trend. In fact, those technologies may be significant drivers of the accelerating participation of the private sector. This paper reports the perspectives of a broad, international sample of participants in the genomics component of the PP ecosystem, drawing on an extensive qualitative interview study. We focus on our interviewees' insider perspectives on how the ecosystem works, how effective it is, and the scientific and ethical concerns it may raise.

In defining *ethics* as we use it here, we focus on *applied ethics* in the broadest sense of the term: the moral principles that a person relies on in shaping their behavior in particular contexts. Since the context of this project is biomedical research, most of the ethical discussion falls into the subcategory of *bioethics*, which comprises "practical ethical issues roughly at the intersection of morality, medicine, and the life sciences."[4] Within bioethics, we (and our interviewees) specifically focus on *research ethics*, which in the context of our study considers how scientific research is developed, conducted, and disseminated against the background of the foundational ethical principles of respect for persons, beneficence, and justice.[5]

The realities of the PP ecosystem are vividly illustrated by two recent events that have generated widespread media coverage. On December 8, 2023, the US Food and Drug Administration (FDA) approved Casgevy, a therapy for sickle cell disease that is the first FDA-approved treatment that relies on CRISPR-Cas 9 genome editing.[6] Casgevy is a product of PP partnerships, beginning with basic research at Boston Children's Hospital and the US NIH that was brought to clinical fruition by private companies Vertex Pharmaceuticals and CRISPR Therapeutics. In a manifestation of the equitable access issue identified by our interviewees, Casgevy is currently priced at $2.2 million per patient and requires a long and arduous treatment process in a highly specialized facility.[7]

Barely a month later, a group in Cambridge, Massachusetts, led by a co-founder of the Broad Institute, several billionaire venture capitalists, and a CRISPR research leader announced the founding of an independent biomedical institute called Arena BioWorks. With $500 million in initial funding, Arena intends to put basic research and for-profit private company development—in other words, the entire PP ecosystem—under one roof, with a goal of shortening the time from scientific breakthroughs to real-world therapies. At the time of the announcement, Arena had already recruited a team of 50 scientists (by offering premium salaries), including many life sciences stars.[8] The Arena founders

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seem to have recognized the benefits of the PP ecosystem and decided to use private money to make it more efficient, side-stepping the sometimes onerous university administrative hurdles in the hopes that therapies can be developed more quickly.

The growing importance of the PP ecosystem is also clearly evident in aggregate economic data. According to the National Venture Capital Association, venture capital investments in the scientific research sector rose from $5.3 billion in 2012 to $39 billion in 2021; that number dropped to $30.7 billion in 2022, but that was still the second highest on record. Public-sector funding over roughly the same period, while significant, has increased more modestly; NIH biotechnology funding, for example, grew from about $5.7 billion in 2013 to an estimated $9 billion in 2023.[9,10] A detailed 2023 analysis of private biotech investment published in *Nature Biotechnology* concludes that although "a more discriminate financing environment is emerging," "[t]here is still plenty of private money about."[11] Similar trends can be seen in data focused specifically on genome-editing technologies.[12,13]

The increasing importance of the PP ecosystem raises numerous ethical questions—especially conflicts of interest arising from the different organizational missions and cultures of the public and private sectors. Such conflicts have been the subject of a relatively small but valuable academic literature, none of which deals specifically with gene therapies. The general problem of potential conflicts of interest in PP research collaborations was well framed by Johnston in 2008.[14] She described an inherent tension between researchers' duty to adhere to ethical and scientific principles and their desire for financial gain and then identified such specific problems as shaping results so as to benefit sponsors and the suppression of negative data, leading to poor-quality research that could harm human subjects and erode public trust in biomedical science. A decade ago, Stevens et al.[15] surveyed the motivations of various stakeholders participating in biopharmaceutical research and development of PP partnerships. Research funding and the production of publishable results were the most common motives for academic participation, while profit and return on investment were most cited by the private sector. Stevens et al. postulated the existence of "conflicting missions, objectives, and cultures" among PP partners, but found little data on whether their relationships were complementary or conflicting. A study of dementia research found that the "number and heterogeneity of stakeholders" can produce "redundancy, opposing goals of partners, lack of inclusiveness, insufficient transparency and quality control issues,"[16] while a more recent infection prevention and control study that focused on such partnerships reported widespread financially motivated research misconduct.[17]

Normative writing on PP partnerships stresses many of the issues that we will discuss. Tierney et al., for example, analyze the intersection of the motives and priorities of the public and private sectors in medical research, calling for financially independent bodies to oversee PP research.[3] Most recently, Landers et al., focusing on health data research, attempt to balance "[p]ublic and private partners' often contradictory and competing incentives," which may threaten public and patient interests, against the PP ecosystem's "unique value contributions" to those same interests.[18] To promote that balance, they offer an ethical framework for each stage of a PP partnership and guidelines to enable stakeholders to "mitigate misaligned incentives and ensure that they can deliver societally beneficial innovation."[18] Among the key principles of this framework are protecting researchers' academic freedom, implementing a policy to manage conflicts of interest, facilitating data sharing and access, establishing effective project governance, protecting human subjects, publishing results, and structuring the research to maximize benefits for communities and society.

We are addressing these and other topics as a component of a multi-year, multidisciplinary study of the evolving governance of genome editing. The specific questions we pose include: First, how does the PP ecosystem work, from the perspectives of its multiple participants and stakeholders? Second, how do public scientists collaborate with industry partners to "hand off" their innovations for clinical development? Third, how effective is the PP ecosystem? Are there differences between the incentives and inhibitions facing researchers in the public and private sectors? Are these viewed differently by the two sides? Fourth, how does the PP ecosystem affect research? In particular, does the prospect of future commercialization affect the way that public-sector scientists conduct their research? Does that prospect influence their original choices of what to study, or how those original choices are subsequently refined? Fifth, what are the ethical implications of the PP ecosystem, particularly with respect to potential conflicts of interest, the effectiveness of regulatory oversight, and justice in access to therapies? Lastly, how well is the regulatory system responding to the PP ecosystem? That is, how efficient or inefficient are current oversight mechanisms?

Our primary data consist of the perspectives of 92 PP ecosystem participants as expressed in interviews. We choose the word "perspectives" deliberately. Because our interview strategy gave the interviewees freedom to develop topics as they wished (as we detail in the STAR Methods), the interview responses are an often-seamless blend of the subjects' personal experiences and observations (what might be called facts) and their broader, value-laden opinions and judgments about the PP ecosystem. Significantly, the subjects identified these issues with little guidance from us. These data thus enable us to build a framework of PP ecosystem issues from the ground up, as seen by those who experience them. As we have done on a variety of topics across our broader project (see STAR Methods), our findings will enable us and others to further explore these issues through a variety of other methods, including surveys and more structured interviews.

Our analysis suggests that there is little concern among scientists and their various partners about potential ethical dilemmas; whether such confidence is justified is a separate issue. Moreover, while some scientists recognize the potentially adverse effect of private collaborators' profit motives on research agendas and health equity more broadly, few if any acknowledge having experienced or seen it in specific cases.

RESULTS

Overview of the PP ecosystem

According to every kind of data we have, PP partnerships are pervasive in the genome-editing world, at least in the US—an important qualifier that we revisit in the following text. Scientists participate in the PP ecosystem in every conceivable way, with numerous references in our data

to private spinoff companies, consulting, private company directorships, and scientific advisory boards. From the perspective of publicly funded (principally university) scientists, PP partnerships are the norm, indeed, a way of life. The pervasiveness and gravitational pull of the PP ecosystem may have been captured most vividly by a physician-scientist at a major research university:

> It's hard not to be [involved with private companies] in the field of genome editing. I just came back from this American Society for Gene and Cell Therapy [meeting]… [E]veryone you talk to has started a company on their vector or the one Cas line that they have. It's overwhelming. It's hard not to be part of something like that. (Participant (P) 1)

According to a scientist from another research university, involvement can look frantic from the inside: "I'd say it's like four distinct lives… I'm wearing various hats just depending on where I'm going. I sit on the board of about 30 different companies and have four companies that are cofounded" (P2). This scientist may be an outlier in the scope of their participation, but the sentiment expressed—that researchers are routinely balancing multiple roles—is nearly universal.

In a related vein, we found it interesting to hear that some scientists may not feel any special pressure in the for-profit environment. As one scientist recounted, possible commercialization adds little to the pressures they already put on themselves to survive in the competitive gene editing field:

> Once you're addicted to being a scientist, your identity, your life, you don't want it to come to an end. So, there's massive pressure. So, I think the pressure of running a company, nah, it doesn't make any difference. You're at 100% already. (P3)

The components of the system look very similar from the perspective of private companies seeking partnerships, though private participants may characterize the public sector more as a repository of resources to be used and sometimes acquired. A private-sector executive described the value of the public sector in utilitarian terms:

> We work with academic collaborators… We can have them as a consultant, a so-called 'key opinion leader' is our lingo… We might send stuff to them to test. They might send stuff to us to test… And then the third typical bucket is a sponsored research agreement, which would be roughly equivalent to a grant… But we will typically pay salaries, overhead, etc., that are commensurate with the work that's being done. (P4)

As noted previously, these observations are focused on the US and, increasingly, the UK science. An Australian university scientist offered a different perspective:

> I'm from Australia. We look at America like, wow, that's the way to do it… [W]e don't have the critical mass of market to often get things up to speed and to start generating revenue before all the investment is gone. (P3)

Given apparently universal interest in forming partnerships, we looked for ways that our interviewees found training or strategies for collaboration, but found little—although podcasts and networking at conferences were both cited. One researcher stood out as someone who enjoys promoting engagement and finding promising recruits for the private sector among his students (P5). Despite the paucity of interview references to training resources, the art of developing PP partnerships is becoming a common conference topic. For example, the American Society for Gene and Cell Therapy's May 2023 annual meeting included, for an additional fee, a 4-h workshop entitled: "The Magic Year – Founders' Tips for What to Do in Your Last Months of Academia and First Six Months in Industry."[19] The workshop abstract reminds potential attendees that "[s]pinning a company straight out of academia can be a daunting task for first-time technical founders." It goes on to say that attendees will "hear first-hand experience from academic founders and VCs who put 'first money in' with actionable insights you can implement right away." Sessions within the workshop included information on intellectual property and contracts, money and venture capital, how to "vet if an idea is worthy of starting a startup," milestones for program development and fundraising, how to build the right team, and an approach to startups with the intriguing title "Don't Worry, Just Do it: Go Ahead and Create a Successful Biotech Startup."[20]

The smaller-scale July 2023 Genome Writer's Guild Annual Conference also included a session on "Building a Biotech Business."[21] One speaker, while talking about technology transfers and training programs, also mentioned the traits you have to display to investors: look coachable, as opposed to being a know-it-all, and seem both confident (about your science) and humble (about business). Concerning what motivates scientists, the speaker observed that people make this move to get their research "out," to make money, and to build their "brand," and named successful PP scientists on her campus. Another speaker had enrolled in Mayo's Employee Entrepreneur Program and offered slides of some of his earlier investment pitches. He pitched one group for $1M. They just smiled at the naivete of his pitch content but said they believed in him and his science so gave him the money anyway. His larger point was that he succeeded in spite of himself and last year left Mayo to go private full-time.

The public-to-private "handoff"

According to many accounts we heard, publicly funded researchers often reach a point where they hand off their research to the private sector for clinical development. These handoffs are frequently made to small, venture capital-funded startups in which the same researchers have a financial interest, sometimes as founders. The handoff of research from public to private sectors is driven by researchers looking for funding and expertise to get their promising projects into the clinic—the so-called bench to bedside pipeline. Few university researchers have that expertise, their publicly funded institutions rarely have that capability, and public grants almost never support such efforts. Helpfully, the private sector is always prospecting for potentially marketable treatments.

A university scientist gave this vivid account of the pipeline and explained the logic of the handoff:

> A lot of these things have to start in academic labs 'cause they're just super risky… [I]f labs don't do it with public funds, no one will do it. Once… it's been derisked… it comes time to translate it to a human therapeutic. That takes hundreds of millions of dollars to even do a clinical trial. That clearly requires a level of funding and support and even just attention on the details of regulatory and manufacturing and controls that is above and beyond an academic lab… NIH can make lots of small bets on lots of different things, see what emerges and bubbles up, and then the private sector can grab the things that work. (P6)

The quest for funding can be all-consuming for academic scientists. Scientists addressed this pressure, with one describing funding as "what we worry about all the time" in academia (P7). As another put it:

> In molecular biology, if I miss out on a single grant, I can't keep my mouse colonies going, I can't keep my cells going, I can't keep my students going. That could be the end of my career. (P3)

Funding burdens intensify the further scientists move down the translational pipeline. Labs that validate gene editing therapies in small animal models or human cell lines will eventually seek to test their therapeutics in large animal models, but this requires even more resources:

> We need to really get some industry involved in this kind of research to move to large animal models… as you know, they are quite expensive to create and maintain. (P8)

The private sector sees these pressures not as burdens but opportunities. A private-sector executive with long experience with PP partnerships offered this appraisal of the public sector's value:

> [W]hat they're amazing at is next to but not the same as what the company is trying to do… [M]ost technologies have an incubation period in academia that's much longer primarily because it takes longer for it to get to the point of working well. (P9)

Impact is another important theme when scientists talk about seeking out industry collaboration or moving to work in industry themselves. One scientist who transitioned to industry after running an academic lab for many years explained that they felt they would "have a bigger impact in helping to make drugs than I was going to have with my academic papers" (P4).

Several researchers, including (P5) quoted earlier, also noted the symbiotic training and employment relationship between the public and private sectors; for example:

> We've created a system where we generate more scientists than we have a need for in academia, right. If the only job you could get is a scientist in academia, the whole thing would fall apart because every PI needs 10 post-docs and 20 grad students to make their career, and where would those 10 or 20 go because we're not making any more universities, really. (P10)

Two things about these accounts are especially striking. First, academia and private companies are trying to do different things: the former to answer scientific questions and the latter to commercialize those answers. Second, academia allows technologies to incubate for extended periods to get to the point of "working well"—the point at which the private sector becomes interested. For us, this raises the question of whether the PP relationship is better characterized as symbiotic, with each side contributing unique and essential value, or exploitative, with publicly funded research doing the long-term work of sorting the candidates and educating post-docs and graduate students for jobs in industry, while private investors watch and wait, ready to cherry-pick the winners. We return to this question in our analysis section.

How effective is the PP ecosystem?

Publicly funded researchers in our sample, at least in the US, see their interactions with investors, businesspeople, and private sector scientists as generally positive, but those relations can be complicated by different objectives. Academic scientists also see the PP ecosystem as a

largely effective way to move their research from bench to bedside, a view that is colored by readily acknowledged self-interest. The private sector view is that there is no other way to get clinical benefits from genome editing and other novel biotechnologies. A nagging doubt, which is voiced by some scientists both within and outside of the US, is that the profit motive is distorting research priorities.

In a representative positive comment, an academic scientist who has co-founded three companies described the PP ecosystem as "fantastic" (P6). Another characterized the money involved as "insane" (P11). Continuing in this vein, a third academic physician-scientist evaluated the PP ecosystem as "both positive and negative," noting that "there's companies with very little proof of concept and, yeah, it's all just a little crazy" (P1).

A critical perspective rooted in a fundamentally different healthcare system was set out in detail by a European scientist:

> You don't need a profit to develop a therapy… You should develop a therapy because it's needed… Of course, that needs a lot of money, and there are two approaches to that. One is you have private companies or investors who have such money and provide it because they see a profit at the end of the tunnel. The other is you have a state who takes care of that, and the profit is somewhat shared within the state, within the population, if you wish. (P12)

The dominant private-sector evaluation of the PP ecosystem was summed up succinctly by a private biotech company executive: "I think that's the beauty of America. You know, you do the good research in universities and then companies take advantage of it" (P13).

Whether and how the PP ecosystem affects research

Throughout our interviews, it became apparent that the work of genome editing has led academic scientists to engage in more and deeper collaborations with the private sector, which is perceived as overflowing with money and a necessary collaborator for translation to the clinic. At conferences, speakers have emphasized to mostly academic audiences that the sooner industry partners are looped in, the sooner their therapies will get to the clinic. Industry partners can absorb high manufacturing costs, navigate regulatory hurdles, and facilitate patient outreach—tasks that are usually beyond the capabilities of an academic lab.

The experience of private industry in dealing with regulatory challenges is an important motivation for publicly funded researchers to seek out industry partners or spin their work off into a private company with knowledgeable backers:

> [Translation to the clinic] clearly requires a level of funding and support and even just attention on the details of regulatory and manufacturing and controls that is above and beyond an academic lab. That's when it makes sense to translate it to a company. (P6)

Consideration of these pressures and motivations to commercialize leads to the question of whether and how they affect the nature and quality of research. One category of potential effects involves the patient populations chosen for study—and those that are not. In the conventional model, academic scientists pursue basic research questions significantly upstream of any translational applications or explore therapeutic options for rare disorders that may not be commercially viable. Many of our interviewees see private biotech companies, by contrast, as focused predominantly on conditions with larger populations, like cancer or sickle cell disease. The latter example came up unprompted in over a third of our interviews, as here: "You need a lot of patients who all have the same mutation and can be treated with your one drug. And, sickle cell fits that category, whereas a lot of other rare inherited genetic diseases that might also be treated the same way are not all caused by the same mutation" (P14).

Although the ideal situation is one with a large patient population and a treatment that can move quickly down the pipeline, private companies may pivot to less common diseases as gene editing becomes better validated and therapeutics with fewer target patients consequently become more attractive. An example of this is Zolgensma, a one-time gene therapy made by Novartis, used to treat children younger than 2 with spinal muscular atrophy (SMA), a genetic condition which affects 1/10,000 infants. It costs over $2 million in the US.[22] A private biotech executive explained:

> Right now there's a clear place for academia to continue to focus on ultra-rare diseases because commercially biotech companies are going to be less focused on it for the next couple of years… However, if you are a company that has a program put in front of you that academia has developed and reached clinical proof of concept, then the probability of success has gone from three percent to, you know, 30 percent or something like that… [I]f you can pick up an asset that's reached pre-clinical proof of concept… years have been cut out of the development timeline… If academic groups continue to work on these, hopefully we'll be at the other end of this without saying there are less treatments for ultra-rare diseases— we're saying, "Well, those treatments were just progressed within academia, and now there's gonna be companies that will emerge to take them to the next steps." (P14)

Some reactions to this commercial logic are framed in ethical terms. For example, one researcher who studies a rare condition used rights language that transcends patient numbers:

> Well, all genetic conditions, including [the one they study], they have the right to be investigated. And they deserve to have someone to pay attention. Unfortunately, there are not many people investigating rare diseases across the world, and we have almost 7,000 of these rare conditions. (P15)

There are also patient populations that the private sector will avoid regardless of numbers. For instance, a population needing a tailored or "bespoke therapeutic" will likely go "unserviced" (P10). Disease progression may also make research challenging, as the same researcher illustrated by reference to Alzheimer's disease (AD):

> [T]he AD drug is a problem because, so far, we learned you need to start early when the patient has no symptoms. Because once the neuron dies, there is nothing else unless you kind of provide neurons. So, you have to start treatment when the neurons start going down, but not dying. In other words, you have to find candidates when they are middle age, for example. (P10)

According to our interviewees, a possible mitigating response to the rare condition/complex therapy problem is to establish connections with patients and other relevant stakeholders. Patients, disease advocacy groups, and clinicians can be potent allies in making the case for funding. As one scientist summarized this approach, "I co-founded a start-up working on this. It's been like three years in the space, and I have got… meaningful connections with clinicians, with patient advocacy groups, with different investors in biotech industry" (P16).

In another category of effects, PP partnerships can focus the research attention of publicly funded scientists, for better and worse. "Uncertainty is more on the academic side," an industry scientist explains (P17), while an academic scientist admits that "they [industry] tell us what is important" (P5). Although there could be a devaluation of curiosity and scientific freedom when industry partners become involved, academic scientists by and large do not report feeling stifled by their involvement. They emphasize the advantages that their private sector collaborators can bring to the table and view any potentially adverse influences as necessary to advance their work toward commercial applications. Biotech collaborations are viewed as aspirational by many academic scientists, a notch in the belt that denotes that one's research was worth investing in.

But there are dissenters, with some academic scientists we interviewed perceiving industry motivations more negatively:

> They have certain motivations. They want to recoup faster. They want to do all this with the least amount of money, accepting that all the stuff is really expensive. Recruit the patients that they need, there could be kind of aggressive tactics in doing that. (P1)

Yet none of the scientists we interviewed were concerned that the profit motive would influence the scientific integrity of the work being done, including the one just quoted:

> I find it very hard to see, at least in the world I'm in, to influence the data collection or the results. I don't think that happens. (P1)

Is this optimism misplaced? In the next section, we will discuss potential concerns about the profit motive on the integrity of PP partnerships.

Ethical implications of the PP ecosystem

Another major question that emerged from our interviews and observations is whether the PP ecosystem creates ethical issues that challenge the capacity of existing ethical oversight systems. Among the scientists interviewed, there was negligible concern that the profit motive of industry compromises the integrity of their research. According to one university researcher, potential conflicts of interest "are usually so obvious that the first question is always who has [a stake] in any venture. And the universities are looking out for that" (P11). While the financial motives of the private sector are generally acknowledged, the prevailing sentiment among academic researchers is that the private sector's own self-interest often serves as a policing mechanism to avoid ethical conflicts, with one noting that:

> [Industry is] concerned about liability, right, so in that sense they're [going to] do a good job… it's in their best interest to make sure [the work is done ethically]. (P1)

A private-sector executive described in detail how the private sector regulates itself:

> You have your precertification department, the legal department, your contracting department, you have representation from all aspects of the company review your policy from every single angle and work on it, right, from clinical, non-clinical, feasibility, accessibility, capability, all of those angles… Any concerns that they raise, you address them in the policy. (P18)

As a whole, our interviewees tended to view those in the private biotech industry as both fully cognizant of the potential for liability and eager to avoid entanglement in ethical dilemmas. The general consensus among interviewees is that while the private sector may prioritize profits, it understands the financial pitfalls associated with both conflicts of interest and rushed research and therefore actively seeks to avoid both—if only

because, according to some of our interviewees, they are threats to its bottom line. Those in the private sector largely came to the same conclusion—that tainted research motives and a deficient product are to be avoided at all costs. A long-time biotech executive explained:

> None of us want to be in the middle of an ethical debate… I think it would be hard to fund a company that knew it was walking into a big policy debate… [That would be] our nightmare… we're here to do good, and if we feel we're on the edge of doing good, that would be just awful. (P4)

While nearly all private sector scientists who were interviewed defended the ethical underpinnings of their work and maintained that PPs are critical for the timely development of novel treatments, one of them went even further, turning questions of ethics back at those critical of the private sector: "Nothing annoys me more than welfare activists stopping innovation in [industry] when they don't have a better solution to the problem that that innovation is trying to address" (P19).

Stances such as these appear to be informed by the belief that much of the criticism directed at the private sector originates from people incapable of properly assessing the science behind and the motives of private biotech. Nonetheless, several interviewees in our sample voiced significant concerns regarding how PP treatments are distributed and made available. A recurring concern was the likelihood that wealth disparities would produce inequitable access to treatments developed through PP partnerships. A publicly funded scientist summarized the dilemma succinctly: "One of the ethic[al] issues will be whether CRISPR will be, in the end, just used for wealthy people because poor people cannot afford to use CRISPR" (P20).

Several researchers outside of the US argued that such wealth disparities are exacerbated by the private healthcare system of the US, with one saying, "[w]ell, it's like anything in the US, if you've got money, you've got it. If you don't have money or you don't have good insurance, you're screwed" (P21).

Access in Europe, facilitated through national healthcare systems, was generally viewed more favorably. A scientist outside of the US commented that unequal access is likely "in the US where you have a private, health insurance-based economy," but less so in Europe, "but even there, situations where the wealthy will receive preferential treatment for therapies are foreseeable" (P22).

Relatedly, there was marked concern from one European scientist regarding the ultimate exclusion from treatment of the very research subjects who enabled its development:

> [I]t's completely immoral, completely immoral. The taking away of knowledge that was generated in France with funding that the patient community itself generated. Over time, that knowledge becomes corporate knowledge in the US leading to a genome editing innovation that is now unaffordable for the French patients that generated the knowledge in the first place… [That] is unethical [and] unsustainable. (P23)

The same scientist also suggested that this problem is enabled by and would continue to perpetuate racial marginalization, evoking past outrages to predict the future:

> Once proven successful through the experimentation on Black bodies, these innovations are going to be adapted to treat conditions for people who can afford the exorbitant amount of money that are going to be charged by the company that are going to own the IP. That is the reality. (P23)

Our analysis indicates minimal concern among scientists from both sides of the PP ecosystem about conflicts of interests, pressure to commercialize, and rushed or insufficiently vetted treatments. Many also expressed confidence in existing mechanisms to prevent ethical problems, including the incentives and disincentives facing both the public and private sectors. Rather, inequitable access to treatment as a result of disparities in wealth, ethnicity, and health insurance benefits was the primary ethical challenge identified by our interview participants.

The regulatory environment for the PP ecosystem

Despite confidence about avoiding potential ethical issues, our interviews revealed widespread concern that PP collaborations are currently handicapped by pervasive regulatory inefficiencies that manifest themselves in various forms. Scientists' general frustration with the current regulatory framework is illustrated by their comments regarding gene therapy generally. One called it "an overly onerous regulatory scheme that really only benefits the established industries" (P24) and another compared the FDA to Chicken Little: "Well, we don't know if the sky is going to fall in tomorrow, Chicken Little. So maybe we shouldn't go outside. That's the FDA." (P25)

More specifically, a genome-editing scientist described the confusion created when the two regulatory boards overseeing their experiment made conflicting recommendations:

> One animal care committee always said every year we have to kill the monkeys, and the other one said you have to keep them forever… It was a really not very helpful situation. (P26)

Some scientists further portrayed the regulatory landscape as one of exorbitant cost which permits only large, wealthy companies to succeed:

> The cost of making the animals is around 1/10th the costs of getting around the regulatory process. That puts this stuff way out of reach for any but the largest companies. And so, then you get to the Monsantos of the world, the most hated companies, they are the only ones who can afford to do it. (P27)

Thus, according to another researcher, an ironic consequence of stringent regulatory hurdles is the exclusion from the PP market of smaller-scale treatments and smaller companies whose involvement could result in greater equity in developing treatments for rare conditions:

> Unless we have a model that allows us to create drugs for a really small number of patients, and for it to be funded somehow, you know, by a company, many patients are going to go un-serviced. (P10)

Regulators are sometimes described as out of touch with the medical exigencies driving PP collaboration, and even those with a positive impression of the regulatory landscape of the US admit it is "slow" (P2). One researcher commented on a development landscape frozen by fear of regulators:

> [Certain scientific] communities are afraid of the regulators. They're afraid that if we invest in this then… the regulators will just say, no, or stall… Things won't progress. (P27)

We also heard that regulators fail to balance risk and benefit in a reasonable way. As one scientist noted:

> I think that the focus is a bit myopic, in that the regulators are really concerned with what's going to happen with these particular cells in this patient… [T]he regulators are really focused on is it safe in this person? I think that probably it's overkill. We could actually have a lighter regulatory scheme, particularly for a single patient or small numbers in small trials. I think the regulatory environment needs to balance itself against the cost of not doing something. (P24)

This scientist worries that the current regulatory system is not flexible enough to accommodate scenarios in which accepting more risk might be justifiable to increase the speed with which a therapy gets to a patient. But it is the job of regulators to be "really concerned with what's going to happen." The policy flexibility that this scientist seeks might thus be beyond the authority of "the regulatory environment," even if seemingly justifiable in individual cases.

The comments we heard about the regulatory environment revealed widespread concern about its largely negative effect on the entire PP ecosystem. Specifically, our interviewees complained about regulatory inefficiency and overreach, including a failure to balance patient benefits against potential costs in situations of medical urgency. They also noted that the regulatory system is biased in favor of big companies and against smaller entities which, they claim, are likely to be doing important work on serious conditions with small patient populations. An ironic consequence of this bias, some interviewees believe, might be to undermine the goal of health equity.

DISCUSSION

We organize this discussion according to the topics we pursued in our data analysis.

How does the PP ecosystem work?

A fundamental point that was made throughout our interviews, without dissent, is that PP partnerships are pervasive and indispensable, at least in the US. Indeed, everyone in the public research sector who hopes to translate their research into the clinic seems to be involved. The ecosystem looks much the same from the private side. Companies and investors interested in genome editing applications are constantly looking at public-sector researchers and their spinoff companies as acquisition targets, investment opportunities, and a source of scientists to be engaged and technology to be acquired or licensed.

But as some of our interviewees emphatically reminded us, this is an American perspective. Researchers from other parts of the world, including Continental Europe and Australia, noted—some with pride and some with envy—that the profit motive and its entailments, including a PP ecosystem, are not the norm in countries with fundamentally different social values and health care systems. One interviewee suggested that the United Kingdom currently occupies an intermediate position but is trending toward increased reliance on American-style PP partnerships.

If PP partnerships are increasingly necessary, or even coveted, academic researchers and private sector companies need strategies to implement these collaborations. Private sector actors generally claimed a solid understanding of academic research, perhaps because of its transparency. Public sector interviewees, by contrast, tended to see the private sector as more of an unknown, at least at the outset of their

PP endeavors. They mentioned podcasts, conferences, and trial and error as ways to learn the ropes. Conference sessions about PP partnerships directed at academics emphasize their "real world" quality, which implies that the private sector will be unfamiliar and perhaps daunting to academic researchers. The overriding message, though, is that combining the unique talents, resources, and needs of the two sectors make PP collaboration a win-win proposition.

The "handoff"

By many accounts, the critical point in the PP ecosystem is what we came to call the "handoff" of technology from the public to the private sector. Grant-funded researchers in universities have the capability and incentives (more grants, publications, tenure and promotion, and renown) to do wide-ranging basic research, which will rarely lead directly to clinical applications. Universities often do not have the resources to take promising translational research through the long and expensive FDA approval process.

Conversely, while the private sector can do that, it is not interested in long-term research that is, from a profitability perspective, "super-risky." At the point where clinical promise can be discerned, the private sector appears, offering the money and expertise to move the technology through the bench-to-bedside pipeline. The private sector cannot finance every promising project, of course, and its selection criteria may emphasize return on investment over broader notions of equity and social good.

The handoff recognizes and accommodates important features of both worlds. The private sector brings its efficiencies to bear to support scale-up because that is what brings in money and gets a product to market. The public sector is also given its due as the setting for painstaking research and the training ground for the scientists who will be headed for, or coaxed into, industry.

A final point about the handoff is that public-sector researchers are sometimes handing off to themselves, transferring their research to private companies in which they have a financial interest. This leads to researchers playing multiple roles simultaneously. This suggests the potential for conflicts of interest, but, as discussed in the following text, our interviewees rarely see or experience actual conflicts.

How effective is the PP ecosystem?

The functional evaluation of the PP ecosystem by our interviewees is strongly positive. On the public side, researchers described it as an efficient way to move therapies from bench to bedside. Some are effusive, with one describing it as "fantastic"; at a minimum, it seen is a necessary evil. There is acknowledgment that such positive evaluations have an element of self-interest, as well as some concern about the ease of getting access to "insane" amounts of money with "very little proof of concept." This concern is balanced by confidence that the participants are smart enough to do it right. Not surprisingly, private sector interviewees tend to see an unmitigated good, but some scientists outside of the US worry about the tyranny of the profit motive.

What are the effects of the PP ecosystem on research?

The PP ecosystem fosters a symbiotic relationship between public and private collaborators, with academic labs serving as incubators for technology that could ultimately be commercialized and private sector partners bringing vital funding and knowledge of the complicated translational pipeline. For academic labs hoping to advance their therapy to the clinic, the private sector is an attractive collaborator that can fund large animal model research and navigate the complex regulatory landscape of clinical trials and, in the US, FDA approval. If the cost of increased resources is less decision-making power in the research process, the academic scientists we interviewed seemed willing to make that sacrifice.

A third of our interviewees brought up sickle cell disease as an example of gene editing progress. This is unsurprising—sickle cell disease has a large and readily available patient population and, as recounted in the Introduction, the FDA has recently approved the first gene-editing therapy for the disease. Sickle cell disease progress illuminates a broader issue that surfaced in our interviews: the PP ecosystem tends to favor some disorders, and therefore some patient populations, and to avoid others. Cancer therapies appear to be given high priority while rare genetic disorders are not. The choice of disorders, and therefore of patient populations, seems a strategic one. This choice turns on calculations of issues such as speed in the pipeline, patient and family risk tolerance, perhaps especially in terminal conditions, and whether a "bespoke" therapeutic will be required.

Considerations of the PP ecosystem's impact on research necessarily turns attention to the ecosystem's presumed aim: to bring safe, effective, and profitable products to market for patients. Some of the researchers we interviewed, while not disputing these cold calculations, would add other, more subjectively human factors into the mix. These stem from their own close experience with the burdens posed by particular conditions and their relationships with the patients and families who understand those conditions best.

Ethical and regulatory implications of the PP ecosystem

Generally, interviewees maintained that PP collaboration is only rarely marred by conflicts of interest. While nearly all acknowledged the *potential* for conflicts, the vast majority felt confident that not only do universities and private companies actively seek to avoid conflicts, but they are almost always successful. This high level of confidence that such partnerships are largely free from ethical conflicts is a departure from prior literature, which tends to characterize conflicts as a pervasive issue for the biomedical industry. Of course, it should be noted that a significant portion of our sample consists of scientists who are themselves simultaneously involved in (and often profiting from) both public and private sector research and thus might have incentives to downplay potential conflicts. Regardless, our interviewees placed a high level of trust in the

ability of both public and private actors to police their collaborations and avoid conflicts—if only, as some acknowledged, because it is in the financial interest of both sides to do so.

While academic and industry scientists are largely confident that their research itself lacks improper motives and will not be used to develop unethical treatments, they nevertheless fear that global disparities in wealth and differences in the efficacy and financial structures of national healthcare systems will result in unequal access to the treatments being produced. Moreover, there is significant concern that future treatments may be developed according to demand from the wealthy rather than based on the needs of larger, vulnerable groups who can most benefit from the products of PP collaboration.

According to our interviewees, there are several regulatory issues that hamper PP efficacy. Individual projects may be overseen by multiple advisory boards which produce conflicting recommendations. Compared to other countries, the regulatory environment of the US is viewed as expensive and sometimes unpredictable and therefore conducive to dominance by resource-rich companies. Additionally, regulators themselves are perceived as disconnected from urgent medical realities that, at present, PP partnerships alone may be positioned to address. Despite concerns about the level of scrutiny and speed with which regulatory approval proceeds, our interviewees see this process as depending less on whether research is publicly or privately funded and more on risk to individual patients, which seems appropriate.

Conclusion

Our interviews and observations reveal that US-based participants in the PP ecosystem for genome editing believe that it is here to stay, essential for translating research from bench to clinic, and generally effective. Scientists outside of the US express more skepticism. Although they phrase their accounts somewhat differently, publicly and privately funded participants are in essential agreement on the major issues. While there is general agreement that professional ethical issues in the context of PP research are rare and that existing oversight mechanisms are adequate to handle those that arise, significant concern was expressed about social justice issues of access and equity beyond that context. These are, however, the views of the *participants in*—and the *beneficiaries of*—the PP ecosystem, since these are most of the people we interviewed and observed.

Limitations of the study

There were few people from low- or middle-income countries (LMICs) in our sample. However, it seems likely that greater LMIC representation would have reinforced concerns about health equity rather than contradicting them. We also acknowledge that the people we interviewed and observed who made us aware of the PP ecosystem were largely participants in it. A broader sample of stakeholders might well express more critical perspectives.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.109896.

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AUTHOR CONTRIBUTIONS

All authors participated in conducting the research reported and drafting and revising the manuscript.

DECLARATION OF INTERESTS

The authors declare no conflicts of interest.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
MAXQDA	VERBI Software	https://www.maxqda.com/
Zoom	Zoom Video Communications	https://zoom.us/
Other		
Interview transcript data	This paper	
Interview memos	This paper	
Interview guide	This paper	
Conference observation notes	This paper	

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources can be directed to and will be fulfilled by the lead contact, John Conley (jmconley@email.unc.edu).

Materials availability

There are restrictions to the availability of the interview transcripts and conference notes generated through this study to maintain the confidentiality of our participants. A general interview guide is available as a supplemental file.

Data and code availability

- The interview transcript data and conference notes generated through this study cannot be deposited in a public repository or shared by the lead contact to maintain the confidentiality of our participants. Interviews were semi-structured, and an example list of interview topics is included in File S1.
- This paper does not report original code.
- Any additional information to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

We interviewed 92 people, including scientists whose research involves genome editing; people active in groups seeking to influence the governance of human genome editing; and executives of private companies interested in genome editing. The governance group members came from science, medicine, law, and the humanities. Some interviewees fell into multiple categories. Potential participants were identified from literature searches on genome editing, genome editing conference schedules, recommendations from other participants, and membership lists of existing governance groups. Of the 92 interviewees, 35 are currently based in the United States. Of the other 57, 22 are based in Europe (not including the United Kingdom), 11 in the UK, 10 in Asia, 6 in Oceania (including Australia), 3 in Canada, 3 in Africa, and 2 in South America. Nineteen of the 92 indicated that they have industry ties, meaning that they either work in the private sector or work in the public or non-profit sector and have participated in collaborations with the private sector. The paper quotes directly from 26 of the 92 interviewees. At the end of each quote the speaker is identified by a number so that readers can see which interviewees are quoted more than once. Interviewees were informed that their participation was voluntary, that they could elect to have their transcript and recording destroyed at any time, and that they could elect to not answer any questions they chose. They were told that we would publish transcript excerpts in academic writings but that we would not identify interviewees beyond broad categorizations such as "a university scientist". All data was stored on password protected, secure drives. This study was determined exempt by the University of North Carolina at Chapel Hill Institutional Review Board (20-1330). We did not collect self-reported demographic data of participants which may limit the study's generalizability.

METHOD DETAILS

Data collection for qualitative analysis

This paper is a product of a multiyear study of the emerging governance of genome editing, both in the U.S. and internationally. We have surveyed genome scientists and other stakeholders,[23,24] interviewed an internationally representative group of scientists, policy makers, and advocates; observed 25 relevant scientific and policy conferences; and tracked, observed, analyzed, and in some cases participated

in the activities of groups engaged in governance advocacy. This paper draws primarily on our interviews and conference observations. Semi-structured interviews were conducted between April 2021 and March 2023. Before interviews were conducted, an interview guide was created that listed major topics to raise in every interview, including: the interviewee's own research using genome editing (where applicable); their views on human genome editing and its current and future uses; and their views on how genome editing should be governed. A representative list of topics raised across interviews is included in File S1. Interviews lasted about 60 minutes, were done via Zoom and recorded, and then transcribed. Interviewers wrote detailed notes on the key points discussed. Significantly, the PP ecosystem was not identified as a topic of specific interest at the outset of the interviews and was thus not included in the guide. Instead, the PP theme emerged in discussions of other topics, which drew the authors' attention and led to the analysis reported here. For conferences, all members of our group who observed any part of a particular conference took real-time notes and supplemented them with thematic observations; these notes and observations are archived and available to all members of the group. The group also discussed almost all conferences at bi-weekly meetings.

Transcript memoing and MAXQDA analysis

To begin data analysis and create a background resource for the project, the full research team developed memos that identified major themes, summarized how each occurred in the interviews, identified illustrative quotes, and commented on the interrelationship of the themes. Memos included basic information about the interviewee, including: their degree(s); the type(s) of research they conduct (if applicable; non-exclusive categories included animal, academic, basic, clinical, translational, and industry); basic descriptions of their research (if applicable); and whether or not they participated in any governance group. Memo themes that the full research team looked for in each interview transcript included: transnational professionalism; views on treatment, prevention, and enhancement; somatic vs germline; future of gene editing; proposed forms of governance; public engagement; scientific self-governance; research in animals; ethical issues; virtue signaling; and other, where research team members could note any interesting topics that did not fall under any of the previously identified categories.

For the analysis presented here, the authors also performed a character string search of the entire corpus of interview and conferences notes. All transcripts and notes were loaded into MAXQDA, a qualitative data analysis program that can search words, word roots, and terms. We asked it to search for: BOARD, CONSULT–, CORPORAT–, INVEST–, PRIVATE, PRIVATI–, STARTUP/START UP/START-UP, PROFIT–, SPINOFF. The search program produced one-to-two paragraphs of text on either side of each appearance of a target character string. Many of these texts proved to be spurious (e.g., "process of consultation" in an unrelated context) or repetitive. Having excluded all such texts, the authors read the remaining texts individually, revisiting the full transcript for more context when necessary, and commented on their possible significance to the paper's topic, and then discussed them as a group. We followed the same process for conference observation notes.