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Starting the conversation: CRISPR's role in India

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Abstract:

The applications of gene editing technologies such as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) have grown significantly in recent years. Several countries have adopted different stances on the regulation of such technology; however, India does not have any legally enforceable regulations in place. There is a need for such a development as India's regulatory, sociocultural, and economic landscape is unique. First, we discuss the uncertainty regarding India's regulatory capacity to enforce ethical standards for CRISPR use. Then, we discuss unique driving forces that could lead to the misuse of CRISPR in India, such as certain sociocultural norms like preferences for fair skin and public demand for sex determination. Given these previous concerns, we posit the question; where on the priority list does CRISPR stand in the context of public health in India?

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Perspective

Late in 2018, the world stood by in disbelief as a Chinese scientist reportedly created two genetically engineered human beings using CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) gene-editing technology (1). This development, which had been merely a challenging possibility not so long ago, has led to the resurgence of a host of ethical questions in the scientific community regarding the use of CRISPR, its off-target effects, access, and regulation (2). On a global front, the technology has been growing faster than our ability to reach any sort of moral consensus on its use and regulation. The successful genetic modification of human embryos, and now, human beings, has fueled apprehensions that this technology could one day be used to design and pick babies with certain designer character traits. Would it be ethical for parents to customise a baby that could run like Usain Bolt and sing like Beyoncé? While experts discredit these specific applications as being unlikely in the near future, the ability to control far less complex and highly heritable traits, such as skin color and gender, are not (3).

Currently, there are no internationally agreed-upon laws or regulations on gene editing, leaving scientific research and application of CRISPR technology to the discretion of individual countries (4). Although some countries, like the United States, the United Kingdom, Canada, and Germany, have strict rules prohibiting genetic modification of the human germ line either experimentally or clinically, other countries like France and Argentina are not as clearly regulated (4, 5). It was only last year that Japan set specific guidelines on CRISPR technology to move towards furthering research on gene-editing in early human embryo development (6). As it stands, Indian protocols prohibit human germ line editing and reproductive cloning, as detailed in the National Guidelines for Stem Cell Research by the Indian Council of Medical Research. However, the concern lies in the fact that these guidelines have not yet been converted into specific laws (7, 8). This concern was highlighted a few years ago by the Japanese bioethicist Tetsuya Ishii, who noted that some countries, such as China, Japan, and India, ban genomic editing for clinical use, yet these bans are not legally binding and are seen as unenforceable because of the large population and lack of specific criminal laws to act as a deterrent (5). This, coupled with factors such as the availability of do-it-yourself CRISPR kits and the huge number of commercial fertility clinics, has raised red flags because of the potential for misuse and manipulation (5,9).

Based on the management of scientific technology in the past, it is uncertain whether or not the current regulatory landscape in India would be capable of enforcing the regulation of such an immensely powerful technology in a safe and ethical manner. Past developments in genetic technology have been mishandled, demonstrating the capacity (or lack thereof) of India's regulatory organisations. For example, take the development of genetically modified crops. While the permissibility of these was still being debated in parliament, they were being illegally and prematurely sown in Gujarat in spades because of their perceived profitability (10). This was largely a result of corrupt practices in Indian regulatory agencies. In the medical field, India has even gone so far as to ban the clinical use of stem cell therapy because of "rampant malpractice" and the inability to regulate its commercial use (7). Corruption within such organisations is so rampant that India's medical administration is said to be one of the most corrupt in the world, with physicians, medical regulatory bodies, and even the government playing a part (11).

The Medical Council of India (MCI) and the Indian Medical Association (IMA) have faced numerous scandals regarding bribes for the establishment of ventures and even entire institutions. Efforts to hold them accountable through the legal systems have been null and void because of the backlog of cases, and only a small fraction of prosecutions have resulted in legal consequences (11). Therefore, there is little discouragement of the misuse and manipulation of medical technology for personal or commercial gain. The extensive growth of black markets for human organs and counterfeit medicine in India is the greatest testament to this statement. India's black market for organs is one of the largest in the world, with hospital administrators, doctors, and even law enforcement officials regularly caught for the procurement and sale of black market organs (12). This paints an alarming picture of the state of regulation with regard to medical services in India, and raises several concerns when considering the regulation of profitable gene-editing technology.

Translating these discussions into public discourse is urgent, as advances in gene-editing technology have already begun to gather momentum. Private companies have already sought to explore the commercial potential of such technology in India and they will surely march forward in due time (10). On a more positive note, Indian scientists have been making remarkable advances in research using gene-editing technology, which involves manipulating somatic cell samples from patients with blood disorders like sickle-cell anemia (9). The key question at hand is whether or not research will continue to be conducted in a safe and ethical manner, and this seems doubtful without legally enforceable guidelines and an effective regulatory and legal infrastructure.

The potential for misuse in an Indian context is driven by a number of sociocultural factors intrinsic to the subcontinent. For example, take the all too familiar preference for fair skin in Indian society. The pervasiveness of general concern over skin color is reflected in consumer markets, with the Indian population having spent over $500 million on "fairness" products in 2014 (13). This sociocultural obsession translates into discrimination against darker skin tones in the professional sphere. In 2012, close to 70% of the surveyed population preferred partners of a fairer complexion, and furthermore, many industries, including the film, hospitality, and aviation industries, are marred by cases of active discrimination against applicants with darker complexions (14,15). To what extent will these preferences take form in healthcare markets if consumers are able to manipulate such characteristics? The demand for these traits definitely exists, and it would not be unreasonable to be concerned over potential future misuse of technologies like CRISPR to meet such a demand.

Perhaps the sociocultural element that merits the greatest consideration is one that the Indian medical profession has been grappling with for centuries. The preference for a male child is behind some of the most severe ethical breaches among the medical profession. In fact, fairly recent technological advances have been shown to empower such preferences, contributing to the vastly skewed sex ratios observed in many Indian states (16). The normal sex ratio observed for children is 952 girls per 1000 boys, yet in states such as Haryana it remains as low as 830:1000, and states like Punjab, Delhi, Bihar, Gujarat, Andhra Pradesh, and Madhya Pradesh all fall significantly short of the normal (17). According to public health scholars, the increased availability of ultrasound machines in rural areas coupled with poor to no regulation of sex determination laws is one of the driving factors behind these skewed ratios (18). This is a worrisome trend that results in adverse effects to the Indian population as a whole, the effects of which have been extensively studied. From an economic perspective, according to a report by McKinsey & Co, India's GDP could be 60% higher in 2025 if women played the same role in the workforce as men (19). While there is no doubt that other factors (sexism in the work force, systemic patriarchy, etc.) also contribute to an unequal workforce, skewed sex ratios are not an insignificant driving factor. From a social standpoint, empirical studies have also linked skewed sex ratios to the increase in violent sexual crimes, specifically human trafficking and sexual abuse (19). Therefore, we see that we have a moral and economic imperative to safeguard these ratios and prevent unlawful sex selection. Current trends foreshadow the potential for future misuse and misapplication, and the way medical technology has been misused in the past can serve as important lessons. If past and existing medical technologies have been misused because of these driving sociocultural factors, it gives us reason to believe that this could be the case with gene-editing technology as well. Therefore, the efficacious and ethical regulation of CRISPR technology must take these factors into consideration.

Finally, given the unique sociocultural, economic, and regulatory landscape of India, we must also ask to what degree we are willing to allocate resources towards the development and application of technologies like CRISPR. Furthermore, to what extent might gene-editing technology worsen pre-existing injustice and inequality? It is unlikely that the substantial proportion of Indians who live in poverty 363 million to be exact would be the direct beneficiaries of CRISPR (20). In a country where the top 1% is responsible for 73% of the country's wealth and 60% of women do not have access to hospital care when giving birth, can we justify further reallocating valuable and limited resources that will likely benefit only the wealthy few? (21, 22). Should we also not be even more cautious if this technology could one day lead to cognitive or physical genetic enhancement for its beneficiaries? As the Western world gears up to allocate resources towards the development and application of CRISPR technology, we feel developing countries like India must be cautious. A technology should have an evidenced and favorable risk/benefit ratio in order to justify a higher prioritisation of resources. Approximately 423,000 Indians die from tuberculosis, 205,000 die from malaria and 105,000 die from diarrhoea each year, to name only a few diseases (23-25). Interventions that are effective and cost effective exist, and we feel these should take priority.

The promises of gene-editing technologies are discussed and disseminated to a great degree, and with good reason. They represent very real, tangible opportunities at positively impacting the lives of certain patients with certain diseases. However, it is important not to generalise this potential across societies and nations, but to recognise that each country is unique and has its own narrative. The sociocultural factors discussed above have been woven into medical practice in India for decades, despite the best attempts at regulation. Going forward, we must adopt an attitude of caution alongside our current optimism, with regulatory authorities pausing to consider these issues in depth.

If India is to pursue advancements in gene-editing technology, it is important that we do not follow the laws of other countries; rather, it is crucial that rules and regulations are created to take into account India's unique professional and sociocultural landscape and, in addition, its capacity for ensuring that such a technology is handled responsibly and ethically.

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What is the moral collapse in the Cochrane Collaboration about?

PETER C GØTZSCHE

Abstract

On September 13, 2018, one of the founders of the Cochrane Collaboration was expelled from the organisation, by a narrow vote of 6 to 5. Many see this as a moral collapse in what was once a magnificent grassroots organisation, guided by ethical principles and helping people make better decisions about healthcare interventions.

I am that excommunicated person. I review here the essential issues leading to my expulsion, which occurred primarily because, in my capacity as a board member, I had challenged the CEO's virtually total control over the board, his mismanagement of Cochrane, and the direction in which he was taking the organisation. My criticism of psychiatric drugs and the highly prestigious Cochrane review of HPV vaccines also played a role. Freedom of Information requests revealed that the CEO went well beyond his brief to demand my removal from the Nordic Cochrane Centre, resulting in my sacking.

Cochrane has become too close to industry and has introduced scientific censorship, which is detrimental for a scientific organisation. The board has announced a "zero tolerance" policy for repeated, serious bad behaviour. It would be beneficial if its CEO and board members applied this principle to themselves.

I also discuss a recent paper by Trisha Greenhalgh et al that purported to have analysed the current Cochrane crisis in a disinterested fashion, which it did not. Instead of discussing the undeniable facts and the horrific abuses of power, TG consistently used positive terms about Cochrane and negative ones about me and my supporters.

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On September 13, 2018, one of the founders of the Cochrane Collaboration was expelled from the organisation. This took place at the Cochrane Colloquium in Edinburgh, and it was the first time that anyone had been expelled. Many see this as a moral collapse in what was once a magnificent grassroots organisation, guided by ethical principles such as transparency, openness, democracy, collaboration, avoiding conflicts of interest, minimising bias and helping people make better decisions about healthcare interventions.

I am that excommunicated person and I have described the events in a book (1). In this commentary, I review the essential issues and discuss a recent paper that purports to analyse the Cochrane crisis in a disinterested fashion, which it does not.

Non-issues made big issues

The affair started with two petty complaints related to psychiatry levelled against me by Cochrane's CEO, Mark Wilson, about my use of the letterhead of the Nordic Cochrane Centre, of which I was the Director (1, 2). Both cases involved deaths likely caused by psychiatric drugs. Ryan Horath, a lawyer unbeknownst to me, described one of them this way: "JESUS CHRIST, WHAT IS WRONG WITH YOU PEOPLE. A researcher is making inquiries about the suppression of information regarding children who died in a clinical trial and everyone is worried about what letterhead it is written on?"(1).

As I disagreed with Wilson that I had violated his Spokesperson Policy, I appealed his decision to the Cochrane Governing Board, which it was my right to do according to the agreement my centre had with him. The whole affair should have ended with the board's arbitration, but a decision was never made. Instead, Wilson and his close ally, Martin Burton, co-chair of the board and Director of the UK Cochrane Centre, launched a full-scale assault on me (1).