

CASE AND COMMENTARY

How Should Physicians Respond When They Learn Patients Are Using Unapproved Gene Editing Interventions?

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Abstract

Hundreds of gene therapies are currently in various stages of research and development. A subset of these involve gene editing technologies such as CRISPR. In this hypothetical case, a patient with chronic pain has initiated a CRISPR-based intervention obtained from a clinic in the Cayman Islands. His physician doubts it is approved by the US Food and Drug Administration and worries about its safety. The case presents ethical questions about potential violations of US regulations regarding the sale of products intended to affect human health, patients' lack of understanding about risks of unproven drugs, and suboptimal support for and management of patients with chronic pain. We discuss how physicians should address these questions.

Case

Dr T is surprised to see a patient, Mr J, at the gym. For years, chronic pain has kept Mr J away from most physical activity. Not having seen Mr J for a couple of years, Dr T asks how he's doing and learns that Mr J had been using a recently developed clustered regularly interspaced short palindromic repeats (CRISPR) tool designed to permanently modulate inflammation. Mr J explains that he ordered this intervention from an American clinic in the Cayman Islands, reports improved sleep and capacity to exercise, and notes heartburn as the only side effect. Dr T suspects this CRISPR application is not approved by the US Food and Drug Administration (FDA) and asks Mr J to schedule an appointment for follow-up. Dr T's view is that direct-to-consumer CRISPR tools should remain prescription only, since peer-reviewed clinical evidence in support of this CRISPR application is minimal. She's concerned that Mr J's use of it is too risky and wonders whether she should both gather more information from Mr J to help him and report the case to the FDA.

Commentary

A patient has obtained—likely via an internet-mediated mail order—a CRISPR gene editing product from “an American clinic in the Cayman Islands.” Presumably, the intervention was not prescribed by another physician but was advertised and marketed by the entity providing the so-called therapy “designed to permanently modulate

inflammation.” Although this case is hypothetical, it does bear similarity to events that have actually happened.

Similar Cases

In October 2017, a biohacker livestreamed himself self-administering a CRISPR-based experimental intervention for muscle enhancement.¹ That year, another man recorded himself self-injecting an experimental gene therapy supplied by a Singaporean company; he hoped the investigational agent would stimulate his immune response to HIV.^{2,3} This company’s late chief executive officer also recorded himself using an investigational gene therapy—this one intended to treat herpes simplex virus.⁴ He catalogued the company’s experimental gene therapies in a Facebook post, noting that they would be made available to the public.⁴ In another case, a scientist affiliated with both an academic institution and a company administered an investigational herpes vaccine to people in both the United States and St. Kitts, without approval from the FDA, St. Kitts regulatory authorities, or local institutional review boards.^{5,6}

One might dismiss these and similar cases as of small public health concern, but these [unproven products](#) could harm those who use or consume them. There is additional concern, albeit small, that these products could pose risks to people who do not actually take them. For example, Germany banned all imports from a California-based company that sells DNA reagents and gene editing kits because some of its products were contaminated with pathogenic bacteria.²

The hypothetical case, as well as the real ones, prompts questions about proper roles of government in regulating drugs and biological interventions, the health and media literacy of the public, and how patients might respond when a health care system does not or cannot meet their needs. The case also highlights ethical obligations of clinicians to (1) communicate with patients and provide appropriate care, (2) report potential violations of US regulations regarding sale of products intended to affect human health, (3) educate patients about risks of unproven drugs in the context of the FDA’s mission to protect public health, and (4) optimally support patients with chronic pain.

Caring for the Patient

Dr T is right to ask Mr J to schedule an appointment, especially since he is experiencing heartburn, which he seems to attribute to the CRISPR product. Other more serious conditions, such as angina, can mimic heartburn pain. Since she suspects the product Mr J used is not FDA approved, its safety profile is uncertain. Although side effects will likely be product specific, clinical concerns about gene editing products include possible infection, immunologic reactions, and unanticipated molecular and cellular effects.⁷ Dr T will want to get an updated health history from Mr J. She will also want to check his vital signs and order tests to check for possible intervention-associated toxicity. Because Mr J

might not realize why she wants him to come in, Dr T should communicate her concerns to Mr J before she leaves the gym.

Duty to Report

The FDA is tasked with protecting public health by ensuring the safety and efficacy of human drugs, biological products, and devices. According to the agency, sale of gene-editing products or kits intended for self-administration is illegal.⁸ Companies, institutions, or individuals who want to do clinical research on experimental gene editing products in the United States must first submit an investigational new drug application to the FDA before administering any product to humans.⁸ To market a gene editing product, companies must first receive authorization from the FDA, a process that includes submission of evidence of the product's safety and efficacy via a biologics license application.⁸ A product marketed on the basis of its efficacy for a particular disease would be within the agency's jurisdiction.² Furthermore, it is generally illegal to import unapproved products or devices for personal use into the United States.⁹ However, FDA regulatory guidance suggests it might be appropriate for agency personnel to refrain from taking enforcement action against illegal personal importation under specific circumstances.¹⁰ Enforcement discretion may be exercised when there is "no known commercialization or promotion to persons residing in the U.S. by those involved in the distribution of the product at issue" and when other criteria are met.¹⁰

Notwithstanding these policies, there is much confusion about rules regarding self-experimentation and [importation of drugs or devices](#) for personal use. Companies might intentionally leverage regulatory loopholes to justify freedom to operate. For example, one company executive claimed in 2017 that the company's products were labeled as not for human consumption and that individuals had a right to use them to self-experiment.² Although the FDA has authority to enforce marketing claims about a drug or device, DNA editing reagents are widely available for research use and it is difficult for the agency to regulate self-administration.² The agency itself has maintained that "the use of FDA resources to provide comprehensive coverage of unapproved new drugs imported for personal use is generally not justified."¹⁰

Does Dr T have an obligation to report this incident and, if so, to whom? In general, physicians must maintain patient confidentiality unless there are significant reasons not to, such as risk of serious harm to third parties. If Dr T is worried about others' safety after learning more about Mr J's situation, she should discuss her concerns with Mr J. Ideally, Mr J would agree that information about the product he self-administers should be shared with the FDA. Dr T could likely alert the FDA while still maintaining Mr J's confidentiality. The American Medical Association *Code of Medical Ethics* asserts that physicians should "consider the health of the community when treating their own patients and identify and notify public health authorities if and when they notice patterns in patient health that may indicate a health risk for others."¹¹ Although this

recommendation likely refers to infectious diseases, it is also applicable to Mr J's case. The FDA has a website, "Reporting Unlawful Sales of Medical Products on the Internet,"¹² which lists phone numbers and provides links to online forms that can be used to report.¹³ There are different forms to use, depending on whether life-threatening or serious reactions are involved.^{12,13}

Educating Patients and the Public

Mr J's hypothetical case and the real-life ones indicate the need to educate the public about risks associated with investigational drugs and biologics. *Therapeutic misconception* is a concept that describes the common [misperception held by research participants](#) that enrolling in a clinical trial will have therapeutic benefit for them personally¹⁴; similarly, they might overestimate the benefits and underestimate the risks of using unapproved drugs. Given that less than 12% of new molecular and biologic entities make it from phase I clinical trial investigation to FDA approval and that even those that reach phase III clinical trial investigation only have about a 56% chance of getting FDA approval,¹⁵ it's fair to say that many experimental agents do not meet minimal safety and efficacy standards. It makes sense that patients like Mr J—who have illnesses that reduce their quality of life and needs left unmet by the allopathic health community—would be willing to try experimental agents. However, they might not fully appreciate that most investigational agents likely lack effectiveness and can cause serious harm. Dr T should discuss these points with Mr J.

According to the FDA's website, the agency has responsibility for "helping the public get the accurate, science-based information they need to use medical products ... to maintain and improve their health."¹⁶ Physicians share in this obligation.¹⁷ Challenges to FDA authority (in the form of illegal sales or loophole exploitation) should be addressed proactively. The FDA and health professional associations can and should do more through social and mainstream media to educate patients about risks of unapproved drugs and benefits of public health protections provided by the regulatory process for marketing authorization in the United States. For example, the FDA's Real Cost campaign, launched in 2014, educates youth about the dangers of tobacco use.¹⁸ The Federal Trade Commission also has a website that advises consumers to check whether they are dealing with a legitimate US pharmacy before buying health products online,¹⁹ but perhaps the messaging could be amplified to reach a wider audience.

Treating Pain

Since Mr J resorted to alternative interventions for his pain, he might have felt unheard and possibly abandoned by his physician or by the health care system at large. It also might be the case that therapeutic options were available for Mr J in the United States but that he was unable to access them. If Dr T had been able to help Mr J with his pain, Mr J might not be mail-ordering gene editing tools from a company in the Cayman Islands. Recall the real-life case in point of one man's decision to inject himself with gene

editing reagents after problems with his insurance prevented his access to HIV medication.³ In an environment in which significant numbers of patients are seeking alternative and complementary interventions,²⁰ Lo argues that “the medical research community should listen to and respond to the concerns that lead patients to seek untested therapies, including deep frustration over the lack of effective treatments, perceived disrespect, and marginalization of their needs.”⁶

What could Dr T have done better? The case suggests that Dr T was aware that Mr J’s quality of life had been significantly undermined by his pain. Yet Dr T had not seen Mr J in an office visit for a couple of years. One hopes that Dr T reached out to Mr J by phone when he did not show for or canceled his last appointment. Physicians who treat pain must make every effort to support their patients in accordance with up-to-date clinical practice recommendations and guidelines. Reducing the burden of pain has been identified as a significant public health challenge that must be addressed to stem the ongoing opioid crisis.²¹ Notably, the US Health and Human Services Pain Management Best Practices Inter-Agency Task Force recently issued its final report.²² The task force recommends that physicians employ a multidisciplinary approach to deliver individualized care to patients experiencing pain.²² Treatment options include medications and restorative therapies as well as interventional, behavioral, complementary, and integrative health approaches.²² If Dr T does not feel she can provide [optimal pain treatment](#), a referral to a specialist would be in order. In the future, her clinical practice could also implement policies to better support patients in achieving continuity of care.

Conclusion

This case highlights several physician obligations, some of which are patient centered while others are focused on public health. If physicians suspect that a patient is using an unapproved product, their first duty is to ensure the health and well-being of the patient. They also have an ethical and legal obligations to report to the FDA if they are concerned about harm to others. In addition, they should educate patients about the risks of using unapproved products or devices. More generally, health professionals have a responsibility to foster health literacy and public understanding of the benefits of a regulatory system for overseeing and authorizing product and device marketing in the United States. Lastly, physicians must stay abreast of up-to-date pain treatment recommendations to help patients access the best possible care.

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Editor's Note

The case to which this commentary is a response was developed by the editorial staff.

Citation

AMA J Ethics. 2019;21(12):E1021-1028.

DOI

10.1001/amajethics.2019.1021.

Conflict of Interest Disclosure

The author(s) had no conflicts of interest to disclose.

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