

CASE AND COMMENTARY

Using the 4-S Framework to Guide Conversations With Patients About CRISPR

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Abstract

As patients with genetic diseases seek to have healthy biologically connected children, they will undoubtedly turn to trusted health care professionals for guidance. “Doctor, should I enter a clinical trial to edit my embryos?” is likely to become a query posed by patients with genetic illnesses. Physicians need both empathic communication skills and a framework for responding to this question. Applying the 4-S framework to gene editing can guide clinicians’ responses to patients’ CRISPR queries by facilitating discussion of (1) safety, (2) significance of harm to be averted, (3) impact on succeeding generations, and (4) social consequences.

Case

Dr H assists reproduction for couples who desire biological children. Ms A has struggled throughout her life to cope with a rare X-linked disease, so Dr H recommended genetic counseling. Ms A and her husband learned that their offspring would inherit at least one pathogenic allele without intervention. Ms A remains adamant about not passing on a pathogenic variant to a child.

When following up with Dr H, Ms A and her husband explain that they have seen reports of successful germline editing, and they inquire about what they’ve seen referred to as “genome microsurgery,” a technique for removing a pathogenic allele. Ms A states that she wants this done prior to Dr H’s intrauterine implantation of an embryo.

Dr H clarifies that there are currently no available “off-the-shelf” approaches to eliminating or correcting this specific allele. Ms A states, however, that she can access germline modification of this specific allele through a clinical trial. Dr H urges caution and further clarifies that, even if Ms A gains access to the germline modification, risks such as off-target effects (mutations at sites that were not the target site of modification) can generate unknown consequences that could potentially harm their child and future generations. Ms A asks Dr H to advocate on the couple’s behalf and help them enroll in the trial. Dr H struggles with how to help manage Ms A’s hopes and expectations and considers how to respond.

Commentary

Chinese scientist He Jiankui's announcement in November 2018 that he used CRISPR technology to create babies whose genomes were modified to have built-in resistance to HIV upended the scientific world and catapulted genome editing into the public square.^{1,2} While many scientists and ethicists condemned He's actions,³ the presumed success of his rogue experimentation also generated hope for individuals seeking to obliterate mutations for heritable diseases in their offspring. Patients like Ms A, who have suffered the consequences of [rare genetic diseases](#), will understandably go to great lengths to avoid transmitting a disease to their children. Although germline editing of human embryos is not yet being investigated in clinical trials in the United States, the first in vivo human study of a CRISPR-based intervention for a rare form of inherited blindness recently began enrolling patients.⁴ The reality of human genome editing will put health care professionals at the center of decision making with patients desperate to have healthy biologically connected children.

How should clinicians respond when a patient asks, "Doctor, should I enter a clinical trial to edit my embryos?" The 4S Framework (safety, significance of harm to be averted, succeeding generations, and social consequences) can guide a clinician's response to and subsequent conversations with patients desperate to find ways to avert illness and suffering in their children.⁵ Managing patients' hopes and expectations also requires empathic communication skills, including establishing trust, giving patients a clear recommendation while acknowledging uncertainty, and using ask-tell-ask as a method of confirming their understanding.

Empathic Counseling

Listening to patients' concerns and [eliciting their values](#) is a critical starting point for conversations with patients about editing their embryos. Ms A is looking to Dr H for guidance and seems to be expressing 3 primary values: she wants a healthy child, she does not want to transmit pathogenic alleles to her children, and she seems to have a preference for a biologically connected child. Clarifying whether and to what extent these are indeed her values, ensuring that her preferences are not based on faulty reasoning, and exploring alternatives to gene editing are important next steps in a conversation. While it would seem that these values are at odds with adopting a child or using a surrogate egg donor, exploring these alternatives is nevertheless reasonable.

Dr H might consider referring Ms A to a [genetic counselor](#), who can help ensure that she understands the inheritance of her disease, how likely it is for her children to be affected, the practical implications of transmitting a pathogenic allele to descendants, and the availability of treatment to mitigate harms of the disease in an affected child. If Ms A has an X-linked recessive disease and her husband is unaffected, barring skewed x-inactivation with each pregnancy, she has a 50% chance of having sons and daughters who carry one copy of the mutated gene but are not affected by the disease. If Ms A has

an X-linked dominant disease and her husband is unaffected, she will pass one normal or one affected chromosome to each child such that, with each pregnancy, she has a 50% chance of having either an affected daughter or son. If Ms A has an X-linked dominant disorder and her mutation is not de novo, there would be no male-to-male transmission of the mutation.

It is important for Ms A to understand whether her X-linked disease is recessive or dominant so that she can explore her options for preventing transmission of the disease to her children. If she has an X-linked recessive disease, she could use sex selection to ensure birth of a girl who would be unaffected but have a 50% chance of carrying a mutation for the disease.⁶ However, if she has an X-linked dominant disease, sex selection will not definitively prevent its transmission. In that case, her desire to have a healthy biological child could likely be achieved through [preimplantation genetic diagnosis](#), which would allow her to select for implantation only those embryos that do not carry the mutation. It would be important to explore with Ms A whether having a daughter who is a carrier but does not manifest the disease would alleviate her concerns. It would be unreasonable to accept the uncertain risks associated with CRISPR merely to prevent transmitting a mutation that would not actually cause disease in the carrier though it could be transmitted to the carrier's descendants.

It is, however, possible that none of Ms A's embryos obtained through preimplantation genetic diagnosis would be free of the disease she fears passing on. I am indeed aware of such cases, so this is not just a theoretical possibility. In such a circumstance, Ms A might eagerly turn to CRISPR as a technology that could allow, prior to implantation, editing of an embryo to remove the mutation associated with the X-linked disease.

In order for Dr H to help manage Ms A's hopes and expectations, Dr H will need to engage in a difficult conversation on this controversial topic. As with other difficult conversations, it will be important for Dr H to establish rapport with Ms A. Ms A's query of Dr H indicates her interest in Dr H's perspective and that she trusts Dr H's judgment. The conversation is likely to elicit an emotional response from Ms A, including, perhaps, expressions of fear and worry about the health of her descendants and her strong desire for biologically connected children. Dr H should acknowledge Ms A's predicament and respond to her emotional cues as a way to build rapport, align with Ms A's goals of having a healthy biologically connected child, and understand Ms A's concerns about the possibility of transmitting a genetic disease that could be prevented. Just as one does when delivering bad news, so one should be direct, use simple language, and give a clear recommendation when discussing gene editing with patients. The ask-tell-ask method can help to ensure mutual understanding of the risks and benefits of and alternatives to CRISPR.⁷

Applying the 4-S Framework

The 4-S framework can help guide Dr H's conversation with Ms A.

Safety. First, it is critical that the safety of CRISPR be discussed, since CRISPR carries uncertain risk of off-target mutations (ie, unintended edits in DNA).^{8,9,10,11} What we don't know is the rate at which off-target mutations occur and the harms associated with each off-target mutation, so it is important to consider the possibility that off-target mutations could introduce heritable errors associated with other diseases. As DNA constantly mutates, it is also possible that editing it could have little impact on patients or their descendants. Ms A should be encouraged to have a conversation with the principal investigator of the trial to better understand the results of animal studies that preceded the trial with human subjects. Additionally, if available, preliminary results from studies in humans could help inform her decision about whether to enroll in this study. Ms A would then be in a better position to weigh the uncertain risk of off-target mutations against the risks of alternatives to gene editing for creating a family.

Significance of harm to be averted. Second, Dr H should discuss eligibility criteria for the trial, including the significance of the harm to be averted through CRISPR relative to the uncertain risks associated with trial participation. The ethical justification for accepting an uncertain risk of off-target mutations that could lead to exchanging a known disease for an unknown disease depends on the harms to be averted and the availability of alternatives. That is, it is more ethically justifiable to accept uncertain risks of CRISPR to prevent a disease that is serious and for which there is no good treatment. If Ms A's primary goal is merely to prevent transmission to descendants of a carrier mutation that would not cause disease in her offspring, the benefits of participating in a CRISPR trial would not be outweighed by risks and she should be disqualified from participating. The harm associated with transmitting a carrier mutation would not rise to the threshold for which we should accept the uncertain risks of CRISPR.

Impact on succeeding generations. Third, Ms A should consider unknown consequences of germline gene editing on succeeding generations. This is an abstract and challenging conversation to have with a patient who is likely to be focused on tangible, short-term consequences of her decision. Dr H can inform Ms A that many countries agree with the view of the Oviedo Convention that "an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants."¹² Moreover, a group of scientists has recently called for a "global moratorium" on the use of heritable genome editing.¹³ This call for a pause in CRISPR use is intended to enable greater public engagement and discussion of its social and ethical implications as well as development of an international framework governing germline editing.

While concerns about CRISPR's impact on future generations should give us pause, it is unlikely to be a compelling reason to Ms A not to participate in a clinical trial. Given her own experience of suffering a rare genetic disease, she is likely to believe that it would be a very good thing to prevent descendants from having this mutation. The challenge

lies in helping Ms A understand that tampering with our genes is complex and that there could be unintended negative consequences for her descendants once a gene is altered. In order to avoid such consequences, human germline editing should first be explored in animal models, used only when there is no other way to prevent a devastating genetic disease in descendants, and delivered in the context of a clinical trial in which human subjects can be carefully monitored.

Social consequences. Lastly, Dr H should discuss social consequences of using CRISPR. The technology raises profound ethical questions, and there is currently no scientific or social consensus on whether and when it is ethically justifiable to use CRISPR. Concerns about “designer babies” whose genomes have been edited to enhance their intelligence, physical appearance, or athleticism have led some to fear that we are on the verge of sliding down a slippery slope. These concerns suggest the need for clear ethical and governance structures before proceeding with germline genome editing. In opposition to this view, it can be argued that genetic enhancement has the potential to level the playing field and bring health equity to those who did not win the biological lottery. The technology, if available to all, could be used to benefit the most vulnerable members of our society.

Navigating Uncertainty

Social anxiety associated with CRISPR is reflected in hyperrealist hybrid sculptures by the Australian artist Patricia Piccinini.^{14,15} Her sculptures compel us to be humble and cautious as we adopt this technology. Piccinini’s creations likely don’t reflect real risks associated with CRISPR, but they do remind us of the uncertainty associated with this technology. Proceeding with caution in the face of uncertain consequences has been urged by the National Academies of Sciences, Engineering, and Medicine¹⁶ and the Nuffield Council on Bioethics¹⁷ in the United Kingdom, both of which argue for broad and inclusive social debate. While there is need for discussion and deliberation, in our pluralistic society consensus is unlikely.

Yet CRISPR is a beacon of hope for patients who suffer genetic diseases. [Compassionate clinicians](#) focused on patients’ well-being and best interests can guide patients facing difficult choices accompanying its use. The 4-S framework, implemented with empathic communication skills, provides a structure for difficult conversations. As our patients begin to query us about whether to participate in CRISPR clinical trials, we should encourage consideration of CRISPR’s safety, the significance of harms it could help avert, its impact on succeeding generations, and social concerns about its use.

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Editor's Note

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