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COMMENTARY

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# Detoxifying the Fear of Epigenetic Changes Due to COVID Vaccination

Vaccinations have long been established to a be a relatively safe and cost-effective way to induce immunity to infectious diseases.[1,2] In the United States, a study showed that a single birth cohort who received all of their routine childhood immunizations could prevent 42,000 early deaths and 20 million cases of disease, saving $13.5 billion in health care costs and $68.8 billion total costs to society.[2] The most recent coronavirus disease 2019 (COVID-19) vaccines that induce immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) strain have already prevented 250,000 COVID-19 cases and 10,000 hospitalizations, as well as the deaths of 39,000 seniors in the United States.[1] Among those with COVID-19, those who have been vaccinated show significantly slower viral growth rates and lower total viral loads.[3] Yet despite vaccines' long-standing history of safety and studies supporting efficacy of the latest vaccines, there continue to be fear, increased mistrust, and a greater desire for quick fixes for the anxiety and grief brought about by COVID-19. These feelings and attitudes only intensify with each new variant of COVID-19 and each new wave of infections.

Much of the current discussion of vaccine avoidance has been cast in terms of potential effects on the vaccinated individual. The novelty of the mRNA vaccines such as BNT162b2 and mRNA-1273, developed by Pfizer-BioNTech and Moderna, respectively, as well as the adenovirus vector vaccine Ad26.COV2.S developed by Johnson & Johnson/Janssen, has led many to be fearful of permanent side effects, including epigenetic changes and purported effects on future generations[3,4] Among the reasons given by patients for vaccine avoidance is the fear that vaccines will modify their genetic endowment in a toxic way. This fear is so pronounced that the Centers for Disease Control and Prevention (CDC) has stated on its website that vaccines are not genetically toxic because the genetic "mRNA never enters the nucleus of the cell where our DNA (genetic material) is located, so it cannot change or influence our genes."[4] However, this statement itself has been challenged in internet chatter and now by some patients who hyperfocus on epigenetic changes that may occur with vaccination. In what follows, we aim to provide the clinician with a model for listening to and communicating with patients who harbor such epigenetic concerns and to address those concerns via an informed-consent process.

Epigenetic modifications do in fact occur with novel infections and inoculations with vaccines, but they are a natural mechanism by which the body maintains homeostasis and provides an effective immune defense. Infection by influenza A, herpes simplex virus, adenovirus, HIV-1, hepatitis B/C, Kaposi sarcoma-associated herpes virus, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV) has been shown to alter our immune response via epigenetic mechanisms. The production of cytokines such as interleukin (IL)-1$\beta$, IL-6, IL-12, and tumor necrosis factor alpha (TNF-$\alpha$) as well as chemokines CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10 seems to be altered by methylation and acetylation following infection and epigenetic changes associated with coronavirus antigens. The cytokine storm that is the proposed primary mechanism for the development of acute respiratory distress syndrome (ARDS) is often thought to be the major contributory factor to severe COVID-19 cases,[5] but it is more likely part of an acute immune response, rather than the manifestation of long-term epigenetic modifications. Further, epigenetic changes in immune cells are not transferred to progeny; this would require modification of the epigenome in gametes, which is not an expected effect of vaccinations.

It is vital to think of informed consent not as an event but as a process.[6] Informed consent must be a dynamic process that takes into account present and future concerns shaped by a patient's past experience. The newly emerging concerns about future generations, relative to COVID-19 and vaccination, include not only genetic but also epigenetic effects that need to be acknowledged and put in perspective. It is also vital to be mindful of the limits of our knowledge not only of the effects of COVID but also of potentially iatrogenic effects on the lives of this generation

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and future generations—both epigenetically and psychosocially. For instance, such necessary but painful steps as social isolation and wearing masks may well have harmful epigenetic impact by virtue of disruption of interpersonal communication. However, so can the helplessness attendant on not taking such measures. Moreover, taking such measures, to the extent that they empower people, may also have beneficial epigenetic consequences. How such preventive measures are understood matters not only to the morale of this pandemic generation but epigenetically perhaps also to that of future generations.

Our knowledge of epigenetics is dynamic and continues to expand, as is true of much of what is currently called "precision medicine." For ourselves and our patients, we must respond to this unavoidable uncertainty not by denying or claiming to be able to do away with it, but by putting it in the context of the uncertainty that runs through life's vicissitudes and medical advances alike. In doing so, we can help patients cope with uncertainty by reducing it to the more manageable form of probabilities.[7]

Informed consent is most effectively understood and practiced as a dynamic process of alliance-building through sharing the patient's uncertainty and the fear that may accompany it.[8] The clinician listens to the patient's concerns with the awareness that those are often unspoken. A good opening question may be "What have you read or heard about vaccines?" followed up by "What are your experiences with vaccines? What do you know about others' experiences?" Bringing such past exposures to the surface helps prepare the ground for exploring the patient's concerns about the present and future: "Do you have any concerns about what effects this vaccination may have on you?" Especially with patients of childbearing age, one may ask, "Do you have any concerns about the effects your getting this vaccination may have on your children and grandchildren?" Questions such as these foster a healthy physician-patient relationship, clear understanding, and a healthier community.[9]

With the benefit of such empathic exploration, patients can become more receptive to learning that there is a far higher likelihood of toxic effects across generations resulting from COVID-19 itself than from vaccination. There is every reason to believe that being unvaccinated and, therefore, at greater peril for COVID infection places those we love at far greater future epigenetically mediated emergent autoimmune risk than do the currently administered COVID vaccines.[10] Thus, although we empathize with patients by acknowledging their and our wish for perfect knowledge, we can inform them that, based on what we currently know, "the risk for you and those you love, both in this and in future generations, is far greater if you are not vaccinated than if you are vaccinated." We can make clear that although we have a lot more to learn about epigenetic effects generally, we have already learned that the epigenetic risks associated with vaccines are far lower than those associated with COVID infections.

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