Smart Cities Project, which deploys information technology for urban development and service delivery.[4,5] Nevertheless, it may take years for the right mix of political will, financial resources, and health system capacity to deliver on the full promise of universal health care.

With increased regional autonomy for social-sector spending, Indian states with visionary leadership and good governance may launch transformational initiatives, but others will lag behind, and health disparities will probably increase. Multiple models may emerge for health financing, public–private mix in service delivery, and emphasis on primary care and health equity. India's diversity will continue to manifest in regional health systems for some years to come.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Public Health Foundation of India, New Delhi.

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Brave New Genome

Eric S. Lander, Ph.D.

Fifty years ago, microbiologists sparked the recombinant-DNA revolution with the discovery that bacteria have innate immune systems based on restriction enzymes. These enzymes bind and cut invading viral genomes at specific short sequences, and scientists rapidly repurposed them to cut and paste DNA in vitro — transforming biologic science and giving rise to the biotechnology industry.

Ten years ago, microbiologists discovered that bacteria also harbor adaptive immune systems, and subsequent progress has been breathtakingly rapid.[1] Between 2005 and 2009, microbial genetic studies conducted by the laboratories of Mojica, Jansen, Koonin, Horvath, van der Oost, Sontheimer, Marraffini, and others revealed that bacteria have a programmable mechanism that directs nucleases, such as Cas9, to bind and cut invading DNA that matches "guide RNAs" encoded in specific bacterial genome regions containing clustered regularly interspaced short palindromic repeats (CRISPR). In 2010 and 2011, Moineau and Charpentier defined the critical components of the CRISPR-Cas9 system, and Siksnys showed that it could be reconstituted in new bacterial species. Biochemical studies in 2012, by Charpentier and Doudna and by Siksnys, confirmed these results in vitro. In 2013, Zhang and Church each described how to repurpose the CRISPR-Cas9 system to work in mammalian cells, creating a general-purpose tool for editing the genome in living human cells. Over the past 2 years, thousands of laboratories around the world have begun to use CRISPR-Cas9 in research.

Genome editing also holds great therapeutic promise. To treat human immunodeficiency virus (HIV) infection, physicians might edit a patient's immune cells to delete the *CCR5* gene, conferring the resistance to HIV carried by the 1% of the U.S. population lacking functional copies of this gene. To treat progressive blindness caused by dominant forms of retinitis pigmentosa, they might inactivate the mutant allele in retinal cells. To prevent myocardial infarctions that kill patients with homozygous familial hypercholesterolemia, they might edit liver cells to restore a functional copy of the gene encoding low-density lipoprotein receptors. Editing of blood stem cells might cure sickle cell anemia and hemophilia.

These goals will require overcoming serious technical challenges (such as avoiding "off-target" edits elsewhere in the genome, which might give rise to cancer), but they pose no unique ethical issues because they affect only a patient's own somatic cells.

However, the technology also raises a more troubling possibility: creating children carrying permanent, heritable changes to the human germline DNA. The press has dubbed such brave new progeny "designer babies" or "genetically modified humans."

When scientists realized in the

mid-1970s that recombinant DNA posed potential hazards, they called for a voluntary moratorium on experiments and organized a now-famous gathering in Asilomar, California, to develop biosafety principles for handling recombinant organisms, setting the field on its successful course. Now, several groups have urged a moratorium on human germline editing,[2,3] and the National Academy of Sciences has announced a fall 2015 meeting, which it plans to coordinate with academies from other countries, to begin an international conversation on the topic.

The task now is to develop a clear framework for evaluating human germline editing. Here, I offer a starting point, focusing on four key issues. (When considering these issues, readers should note that the Broad Institute, which I head, has filed patents on some of this technology, as detailed in my disclosure statement.)

The first is technical: whether genome editing can be performed with sufficient precision to permit scientists to responsibly contemplate creating genetically modified babies. Currently, the technology is far from ready: Liang and colleagues recently applied genome editing to human tripronuclear zygotes (abnormal products of in vitro fertilization [IVF] that are incapable of developing in vivo) and documented problems including incomplete editing, inaccurate editing, and off-target mutations.[4] Even with improved accuracy, the process is unlikely to be risk-free.

The second issue is whether there are compelling medical needs that outweigh the risks — both from inaccurate editing and from unanticipated effects of the intended edits. Various potential applications must be considered.

The most common argument for germline editing concerns preventing devastating monogenic diseases, such as Huntington's disease. Though avoiding the roughly 3600 rare monogenic disorders caused by known disease genes is a compelling goal, the rationale for embryo editing largely evaporates under careful scrutiny. Genome editing would require making IVF embryos, using preimplantation genetic diagnosis (PGD) to identify those that would have the disease, repairing the gene, and implanting the embryo. Yet it would be easier and safer simply to use PGD to identify and implant the embryos that aren't at risk: the proportion is high in the typical cases of a parent heterozygous for a dominant disease (50%) or two parents who are carriers for a recessive disease (75%). To reduce the incidence of monogenic disease, what's needed most is not embryo editing, but routine genetic testing so that the many couples who don't know they are at risk can avail themselves of PGD.

Genome editing would add substantial value only when all embryos would be affected — for example, when one parent is homozygous for a dominant disorder or both parents are homozygous for a recessive disorder. But such situations are vanishingly rare for most monogenic diseases. For dominant Huntington's disease, for example, the total number of homozygous patients in the medical literature is measured in dozens. For most recessive disorders, cases are so infrequent (1 per 10,000 to 1 per million) that marriages between two affected persons will hardly ever occur unless the two are brought together by the disorder itself. The most common situation would probably be two parents with recessive deafness due to the same gene (among the many that can cause inherited deafness) who wish to have a hearing child.

Another potential application is reducing the risk of common diseases, such as heart disease, cancer, diabetes, and multiple sclerosis. The heritable influence on disease risk is polygenic, shaped by variants in dozens to hundreds of genes. Common variants tend to make only modest contributions (for example, reducing risk from 10% to 9.5%); rare variants sometimes have larger effects, including a few for which heterozygosity provides significant protection against disease.

Some observers might propose reshaping the human gene pool by endowing all children with many naturally occurring "protective" variants. However, genetic variants that decrease risk for some diseases can increase risk for others. (For example, the *CCR5* mutations that protect against HIV also elevate the risk for West Nile virus, and multiple genes have variants with opposing effects on risk for type 1 diabetes and Crohn's disease.) The full medical effect of most variants is poorly characterized, let alone the combined effects of many variants. Safety studies would be needed to assess effects across various genetic backgrounds and environmental exposures. The situation is particularly dicey for rare protective heterozygous variants: most have never been seen in the homozygous state in humans and might have deleterious effects. Yet heterozygous parents would routinely produce homozygous children (one quarter of the total) — unless humans forswore natural reproduction in favor of IVF.

Currently, the best arguments might be for eliminating the ε4 variant at the *APOE* gene (which

increases risk for Alzheimer's disease and cardiovascular disease) and bestowing null alleles at the *PCSK9* gene (which reduces the risk of myocardial infarction). Still, our knowledge is incomplete. For example, APOE ε4 has also been reported to be associated with better episodic and working memory in young adults.

Some scientists might ask: Why limit ourselves to naturally occurring genetic variants? Why not use synthetic biology to write new cellular circuits that, for example, cause cells to commit suicide if they start down the road toward cancer? But such efforts would be reckless, at least for now. We remain terrible at predicting the consequences of even simple genetic modifications in mice. One cautionary tale among many is a genetic modification of the *tp53* gene that protected mice against cancer while unexpectedly causing premature aging.[5] We would also need to anticipate the potential interactions among the diverse genetic circuits that creative scientists will cast into the gene pool. Mistakes would be inevitable, and there would be no way to recall novel genes from the human population.

A more distant frontier would be to reshape nonmedical traits. Height may prove challenging (the hundreds of natural variants have tiny effects), but hair and eye color may be pliable. Disruption of the *MC1R* gene is associated with bright red hair, although it also heightens the risk of melanoma. Sports-minded parents might want to introduce the overactive erythropoietin gene that conferred high oxygen-carrying ability on a seven-time Olympic medalist in cross-country skiing. Nonnatural genetic modifications hold even bolder prospects — and risks.

The third key issue is who has the right to decide. Some people will argue that parents should have unfettered autonomy — that modifying one's progeny is akin to using PGD to avoid genetic diseases or choosing sperm donors on the basis of intellectual or athletic prowess. Yet parental autonomy must be weighed against the interests of future generations who cannot consent to the genetic modifications their flesh will be heir to.

The final issue concerns morality — what's right and wrong and how we ought to live as a society. Although scientists may be reluctant to debate ethics, we have a responsibility to do so and insights to offer. How would routine genome editing change our world? Would we come to regard our children as manufactured products? Would marketers shape genetic fashions? Would the "best" genomes go to the most privileged? If we cross this threshold, it's hard to see how we could ever return.

The recombinant-DNA moratorium of the 1970s was a temporary pause to establish safety rules for laboratory research. Today's debate concerns not research (which should proceed) but clinical applications to human beings that result in permanent changes to the human gene pool.

Genetic modification of human embryos is not a new idea. At least among Western governments, there has been a longstanding consensus that manipulating the human germline is a line that should not be crossed. Some European countries have outlawed genetic modification of embryos. The United States lacks a legislative ban, but the Food and Drug Administration — whose approval is needed for introducing substances, including DNA, into embryos — has said it will not permit genetic modification, and the National Institutes of Health (NIH) Recombinant DNA Advisory Committee will not currently approve such work at institutions receiving NIH funding (www.nih.gov/about/director/04292015_statement_gene_editing_technologies.htm). In many other countries, the situation remains unresolved.

The discussions that will begin in the fall may solidify a broad international consensus that germline editing should be banned — with the possible exception of correcting severe monogenic disease genes, in the few cases in which there is no alternative. For my own part, I see much wisdom in such a position, at least for the foreseeable future. A ban could always be reversed if we become technically proficient, scientifically knowledgeable, and morally wise enough and if we can make a compelling case. But authorizing scientists to make permanent changes to the DNA of our species is a decision that should require broad societal understanding and consent.

It has been only about a decade since we first read the human genome. We should exercise great caution before we begin to rewrite it.

The Broad Institute, which Dr. Lander directs, holds patents and patent applications on uses of genome editing with CRISPR-Cas9.

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Placebo Effects in Medicine

Ted J. Kaptchuk and Franklin G. Miller, Ph.D.

Placebo effects are often considered the effects of an "inert substance," but that characterization is misleading. In a broad sense, placebo effects are improvements in patients' symptoms that are attributable to their participation in the therapeutic encounter, with its rituals, symbols, and interactions. These effects are distinct from those of discrete therapies and are precipitated by the contextual or environmental cues that surround medical interventions, both those that are fake and lacking in inherent therapeutic power and those with demonstrated efficacy. This diverse collection of signs and behaviors includes identifiable health care paraphernalia and settings, emotional and cognitive engagement with clinicians, empathic and intimate witnessing, and the laying on of hands.

Placebo effects rely on complex neurobiologic mechanisms involving neurotransmitters (e.g., endorphins, cannabinoids, and dopamine) and activation of specific, quantifiable, and relevant areas of the brain (e.g., prefrontal cortex, anterior insula, rostral anterior cingulate cortex, and amygdala in placebo analgesia).[1] Many common medications also act through these pathways. In addition, genetic signatures of patients who are likely to respond to placebos are beginning to be identified.[2] Such basic mechanistic discoveries have greatly enhanced the credibility of placebo effects. Moreover, recent clinical research into placebo effects has provided compelling evidence that these effects are genuine biopsychosocial phenomena that represent more than simply spontaneous remission, normal symptom fluctuations, and regression to the mean.[1] So what have we learned about placebo effects to date, and what does our current understanding say about medicine?

First, though placebos may provide relief, they rarely cure. Although research has revealed objective neurobiologic pathways and correlates of placebo responses, the evidence to date suggests that the therapeutic benefits associated with placebo effects do not alter the pathophysiology of diseases beyond their symptomatic manifestations; they primarily address subjective and self-appraised symptoms. For example, there is no evidence that placebos can shrink tumors; however, experiments demonstrate that common symptoms of cancer and side effects of cancer treatment (e.g., fatigue, nausea, hot flashes, and pain) are responsive to placebo treatments. Similarly, an experiment in patients with asthma showed that placebos do not affect patients' forced expiratory volume in 1 second (FEV_1) but can nonetheless dramatically relieve perceived symptoms.[3] This conclusion tracks evidence related to many conditions, such as musculoskeletal, gastrointestinal, and urogenital disorders.

Second, placebo effects are not just about dummy pills: the effects of symbols and clinician interactions can dramatically enhance the effectiveness of pharmaceuticals. For example, a recent study of episodic migraine demonstrated that when patients took rizatriptan (10 mg) that was labeled "placebo" (a treatment that theoretically had "pure pharmacologic effects"), the outcomes did not differ from those in patients given placebos deceptively labeled "rizatriptan" (pure expectation effect). However, when ritzatriptan was correctly labeled "rizatriptan," its analgesic effect increased by 50%.[4] Similar results have been observed when other drugs, including morphine, fentanyl, and diazepam, have been administered openly and covertly and with procedures such as deep-brain stimulation for mobility symptoms in Parkinson's disease.

Third, the psychosocial factors that promote therapeutic placebo effects also have the potential to cause adverse consequences, known as nocebo effects. Not infrequently, patients perceive side effects of medications that are actually caused by anticipation of negative effects or heightened attentiveness to normal background discomforts of daily life in the context of a new therapeutic regimen. For example, nocebo effects were demonstrated in a study of