In my recent Perspectives article, I reviewed what we know about human mutation rates and their effects, and I highlighted the potential long-term consequences of established goals in human medicine (Lynch 2016). Given the complexity of the personal and societal issues, with conflicting short- and long-term consequences, I made no policy recommendations, as should have been apparent in the final paragraph of the article. I recognize, however, that the subject warrants a well-reasoned, broader discussion.

In their letter to GENETICS, Roth and Wakeley (2016) (hereafter, R&W) present several criticisms of my treatment. Unfortunately, a number of their own statements are inaccurate, and here I address those errors.

R&W claim that everything outlined in my review was known when Hermann Muller discussed the topic in 1950 (Muller 1950). That is not true. In 1950, we had not yet come to understand the significance of DNA and its nucleotide content, let alone the per-nucleotide mutation rate or even the nature of the genetic basis of mutation. What is remarkable, however, is that much of what Muller surmised in the absence of data is now seen to be in qualitative, if not quantitative, accord with the data. Most of this information has accumulated only in the past 5 years, postdating Jim Crow’s (1993, 1997, 2000) writings on the subject.

R&W state that the suggested 0.1–1.0% decline in human fitness with a complete relaxation of selection is erroneous because such conditions would lead to a new equilibrium in which all four nucleotides are present at each genomic site (driven by mutation pressure alone). There are multiple problems with this statement. First, the argument that I presented makes no assumptions about equilibrium: with variation in fitness effects distributed over the entire genome in the current population, relaxation of selection will lead to a steady reduction in fitness for many thousands of generations owing to drift to higher frequencies of preexisting mutations alone. The introduction of new mutations only further contributes to the decline (Lynch and Hill 1986).

Second, the idea that a four-nucleotide equilibrium would be reached is inconsistent with basic population-genetic theory and biological reality. We know from coalescent theory (Wakeley 2008) that the expected depth of a nucleotide-site genealogy is 4N_e generations under neutrality, where N_e is the effective population size. Unless N_e of the human population is well over an order of magnitude greater than the reciprocal of the mutation rate, which appears not to be the case, maintenance of a four-allele polymorphism is impossible. Even in an infinite human population, a neutral equilibrium would require millions of generations to be achieved. Moreover, the idea that a human phenotype could remain encoded in a completely random string of nucleotides is questionable.

R&W question whether hundreds of genetic loci influence the human mutation rate. Yet, there are at least a dozen genes
in the human genome encoding DNA polymerases, all of which operate with various cofactors and most of which are highly prone to error (Kunkel 2009). Furthermore, dozens of pathways are involved in mismatch repair; base-excision repair; nucleotide-excision repair; and nucleotide-pool cleansing (Friedberg et al. 2005); and many of these are known to harbor deleterious allelic variants in the human population (Lynch 2008). A wide variety of metabolic stresses influence cellular mutation rates, and hundreds to thousands of gene products are known to engage in metabolic activities. Thus, although it is difficult to state the exact number of genes influencing the production of genomic errors, the idea that the mutation rate is a small mutational target is implausible.

R&W correctly state that it is the current environment in which fitness should be considered, but it is difficult to fathom how, for example, psychological disorders, hereditary cancers, etc., will not continue to have absolute effects in essentially all environments. Their statement that we can solve visual acuity problems by investing a few hundred dollars every few years for afflicted individuals simply highlights the primary issue: a reduction in costs for cosmetic amelioration will result in a further relaxation of selection, leading eventually to still further need for medical intervention. Their interesting statement that much of human mortality in the United States is a result of metabolic errors and/or psychological disorders further supports this point, especially given the substantial investment now being made to develop pharmaceuticals for modifying human behavior.

Contrary to R&W’s assertion, I did not argue that natural selection has been or ever will be completely eliminated from the human population. However, the extent to which selection is favoring unconditionally beneficial alleles is unclear. For example, it has recently been argued that despite a very substantial increase in the level of educational achievement through social change in the United States, selection is causing the genetic component of this trait to decline by ~1% per generation (Beauchamp 2016); this suggestion, of course, merits further scrutiny. R&W’s view that the application of modern medicine to enhance survivorship and reproduction is not fundamentally different from the ways in which other species operate is novel. I am unaware of any other animal species in which individual or population-level resources are devoted on any comparable scale to help individuals with genetically based defects to survive.

R&W argue that the establishment of standardized, multigenerational methods for monitoring human traits could be dangerous, as it would be open to abuse. One can, however, easily make the opposite argument. For example, some of the most pressing uncertainties in human health, such as the elevated incidence of autism spectrum disorders, are a result of the absence of information on the long-term effects of the environment vs. genetic change as causal factors. R&W’s unclear reference to family-size variation is a case in point. The key issue here is whether the variance in family size is declining, as this reduces the power of selection at the among-family level (although not necessarily influencing within-family selection). Data on historical trends in these statistics, in fact, exist: Imaizumi et al. (1970) showed that the variance in family size declined more than fourfold from the 1880s to the 1920s in Japan as birth control practices became widely adopted; a similar trend is seen in Mormon families in Utah between 1840 and 1940 (Wise and Condie 1975).

For historical reasons, the word eugenics has largely been relegated to the dustbin of our vocabulary. It is irrevocably associated with state-sponsored programs that are now rightly seen as abhorrent. However, regardless of the word we use, the fact remains that biomedical scientists are embarked on a program with clear eugenic implications—the generation of information that minimally enables individuals to make decisions regarding the survival and/or reproductive capacity of themselves and other individuals. Those of us engaged in such an agenda should bear some responsibility for addressing the long-term, population-genetic consequences of this program.

R&W accuse me of suggesting that “we must change our ethical values and take the accumulation of deleterious mutations seriously enough to do something about it.” Again, I made no such recommendations, but simply pointed out a significant dilemma that is unique to the human species. Whether anything can or should be done about it is open to debate. As scientists, however, we have a responsibility to present what we believe to be the facts, and the release of information should not be biased by preconceived notions of what is good vs. bad. Little good has ever come from hiding scientific information; in contrast, plenty of bad things have happened when powerful people/institutions have been allowed to redefine or withhold the facts. Such behavior fueled the battles between human-health advocates and the tobacco and coal industries, and between environmental biologists and the detergent industries, and today supports the agenda of climate-change deniers.

It might be argued that freedom of reproductive choice, provided the resultant behavior does no harm to others, is a fundamental human right. This, however, raises a major dilemma: the question of what we mean by reproductive choice. R&W accuse me of suggesting that freedom of reproductive choice, or the right to determine whether to reproduce, is a fundamental human right. Their interesting statement that much of human mortality in the United States is a result of mental and emotional illness also suggests the possibility that we might choose to breed only those who are mentally and emotionally healthy. This, however, raises a major dilemma: the question of what we mean by reproductive choice. R&W’s view that the application of modern medicine to enhance survivorship and reproduction is not fundamentally different from the ways in which other species operate is novel. I am unaware of any other animal species in which individual or population-level resources are devoted on any comparable scale to help individuals with genetically based defects to survive.

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Not long ago, the economics professor Julian Simon (1981) suggested that the human population will never run out of resources because we scientists are too smart. This remains to be seen, and the question with respect to human health is whether biomedical innovations will emerge at a sufficiently high rate to solve both our short- and long-term challenges.

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Literature Cited