Mutation and Human Exceptionalism: Our Future Genetic Load

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ABSTRACT Although the human germline mutation rate is higher than that in any other well-studied species, the rate is not exceptional once the effective genome size and effective population size are taken into consideration. Human somatic mutation rates are substantially elevated above those in the germline, but this is also seen in other species. What is exceptional about humans is the recent detachment from the challenges of the natural environment and the ability to modify phenotypic traits in ways that mitigate the fitness effects of mutations, e.g., precision and personalized medicine. This results in a relaxation of selection against mildly deleterious mutations, including those magnifying the mutation rate itself. The long-term consequence of such effects is an expected genetic deterioration in the baseline human condition, potentially measurable on the timescale of a few generations in westernized societies, and because the brain is a particularly large mutational target, this is of particular concern. Ultimately, the price will have to be covered by further investment in various forms of medical intervention. Resolving the uncertainties of the magnitude and timescale of these effects will require the establishment of stable, standardized, multigenerational measurement procedures for various human traits.

MUTATION, the production of heritable changes in DNA, is one of the most fundamental concepts in genetics. Yet, a broad phylogenetic understanding of the rate and molecular spectrum of mutations and the mechanisms driving the evolution of these key parameters has only recently begun to emerge (Baer et al. 2007; Lynch 2010, 2011). Of special concern is the rate at which mutations are arising in our own lineage and their long-term consequences. In terms of cognitive abilities and proclivity for dominating the global ecosystem, humans are clearly exceptional. But how exceptional are we with respect to the genetic machinery that is the key to long-term genome stability and evolutionary flexibility? And in light of our unusual behavioral features, what are the long-term genetic consequences of being a modern human? Will the miracles of molecular biology and modern medicine reduce the incidence and/or effects of genetic afflictions to negligible levels, or might such applications have the opposite effect?

Two issues are of central relevance here. First, few other species willingly expose themselves to environmental mutagens to the extent that humans do. Presumably, there is some room for reducing the human mutation rate by minimizing negative environmental effects, e.g., through reductions in exposure to smoke from tobacco and other sources, harmful food additives, radon gas, UV irradiation, etc. What, however, is the lower bound to the achievable mutation rate at both the germline and somatic levels? And do factors that influence the somatic mutation rate also have germline effects and vice versa?

Second, owing to the remarkable advances in living conditions and medicine over the past century, and many more likely to come, humans uniquely modify the environment in ways that minimize the consequences of acquired genetic afflictions. Today’s ethical imperative for maximizing individual reproductive potential and longevity independent of genetic background raises significant questions about the future of the human gene pool. Specifically, what are the long-term consequences of the accumulation of mutations whose phenotypic consequences can be transiently minimized through medical intervention and/or a sheltering environment?

It is fitting to review both of these issues in the year 2016, as this would have been the 100th birthday of James Crow, who played a central role in the Genetics Society of America and had a long-standing interest in human mutation (Crow 1993, 1997, 2000, 2006). Many of the issues addressed below were raised by Crow prior to the genomics revolution and can now be evaluated in a more quantitative way.
The Human Germline Mutation Rate

Numerous lines of evidence, many based on whole-genome sequencing of parent–offspring trios, show that the average human mutation rate is in the range of $1.1 \times 10^{-8}$ per nucleotide site per generation for base-substitution mutations alone (Lynch 2009; Campbell et al. 2012; Kong et al. 2012; O’Roak et al. 2012; Séguére et al. 2014; Besenbacher et al. 2015). The mutation rate to small insertion/deletions is $8\%$ of the base-substitution rate (O’Roak et al. 2012; Besenbacher et al. 2015; Kloosterman et al. 2015), and large structural changes (involving mobile-element insertions and interchromosomal exchanges) arise at a rate of $0.08$ per haploid genome per generation (Kloosterman et al. 2015). Thus, keeping in mind that some mutations in repetitive DNA likely go undetected owing to mapping difficulties in genome-sequencing projects, with a diploid genome size of $6$ billion bases, an average newborn contains $100$ de novo mutations.

Some variation in mutation-rate estimates is undoubtedly a simple consequence of sampling error, but it is clear that the per-generation mutation rate is not a constant. Most notably, the mutation rate per generation increases by a factor of $2$ between males of age $20$ and $40$ years (Kong et al. 2012; Francioli et al. 2015), likely due to the temporal increase in cell divisions in the male germline. A convincing example of variation in the human mutation rate on a large geographic scale is a 1.6-fold increase in the incidence of one particular point-mutation type in Europeans relative to African and Asian populations (Harris 2015), although the contribution of environmental differences to this effect is unknown. However, it is remarkable how little we know about alterations in the human mutation rate that have arisen in even the most mutagenic of environments, with some increases observed in man-made disaster areas (Weinberg et al. 2001; Dubrova et al. 2002), but little known for populations inhabiting environments with extremely high natural levels of ionizing radiation (e.g., Guapari, Brazil and Ramser, Iran). Acquiring unbiased estimates of the standing level of genetic variation for the human mutation rate will minimally require formal quantitative-genetic analysis, which means the ascertainment of mutation rates in sets of independent relatives, e.g., both parents and their offspring.

Although the human germline mutation rate exceeds that for all other species so far analyzed, there appears to be nothing exceptional about it. After accounting for the genomic content of selected sites and the long-term genetic effective population size (which jointly influence the ability of natural selection to reduce the mutation rate), the per-generation human mutation rate is quite compatible with scaling observations derived from a wide variety of other species (Sung et al. 2012). The estimated mutation rate in chimpanzees, $2 \times 10^{-8}$ per nucleotide site per generation for base-substitution mutations, is not significantly different from that in humans (Venn et al. 2014). The per-generation mutation rate in the mouse is $50\%$ of the human rate (Uchimura et al. 2015), despite the dramatic differences in generation lengths, but this may be explained by the fact that selection operates on the mutation rate on the generational timescale, with natural selection being more effective in the mouse owing to its larger effective population size (Lynch 2011).

Given the consistency of the human mutation rate with that of other organisms (all of which have been estimated in benign, nonmutagenic settings), there is little reason to think that the situation can be improved much by a reduction in environmental mutagens, although this will certainly keep things from getting worse. As in all organisms, the baseline human mutation rate is a consequence of DNA damage associated with natural intracellular mutagens and base misloading associated with replication and repair. Such errors result from imperfections in the molecules responsible for replication fidelity, some of which are genetically encoded and others of which result from transcription/translation errors, owing to the fundamental biophysical limits to error detection. Despite $3$ billion years of natural selection, in no known organism has the base-substitution mutation rate evolved to $<10^{-11}$ per nucleotide site per cell division (Sung et al. 2012). Because this lower limit is not far from what occurs in the human germline per cell division ($\sim 5 \times 10^{-11}$ per nucleotide site per cell division (Drake et al. 1998; Lynch 2008)), no amount of human intervention at the molecular level is likely to improve the situation (although diminishing progeny production via sperm from old males would help).

Somatic Mutation

The preceding discussion focused on heritable germline mutations, the cumulative phenotypic effects of which are expressed only in the following generations. The situation is dramatically different for somatic mutations influencing our daily well-being, both because of the larger numbers of cells involved and the higher underlying mutation rates. Although somatic mutations are nonheritable, there is a potentially significant evolutionary link with the germline mutation rate because the DNA replication and repair machinery is shared between both types of cells. Substantial theory on the evolution of mutation rates focuses on the indirect consequences of mutant alleles remaining transiently associated with mutator alleles until disassociated by recombination and segregation (Kimura 1967; Dawson 1999; Lynch 2010), but this yields relatively weak selection on the mutation rate. For large multicellular species, the direct effects of somatic mutations may be the primary source of selection on the mutation rate (Crow 1986; Lynch 2008; Erickson 2010).

One of the many consequences of somatic mutations is cancer, although such effects almost certainly extend to other physical and psychological disorders. Observing that the majority of the variance in lifetime risk of cancer among different tissues is associated with variation in the number of cell divisions in self-renewing lineages, Tomasetti and Vogelstein (2015) argued that the majority of cancers are unavoidable consequences of the stochastic arrival of background
replication errors in normal, otherwise healthy cells (rather than responses to exogenous and avoidable carcinogenic factors). This idea that mutation is associated with DNA replication has precedence in work suggesting that variation in germline mutation rates among species, between males and females of the same species, and among males of different ages is in part due to variation in germline cell-division number (Drost and Lee 1995; Crow 2000; Wilson Sayres et al. 2011). Nevertheless, Tomasetti and Vogelstein’s conclusion that most cancers are unpredictable (and therefore unpreventable) elicited considerable controversy (e.g., Albini et al. 2015; Weinberg and Zaykin 2015).

Such engaged discussion makes clear the need for quantitative information on background rates of somatic mutation, which is difficult to achieve owing to the mosaic nature of somatic mutations within multicellular tissues. Early indirect estimates based on marker loci for phenotypes in four human tissue types suggested an $\frac{17}{10} \times$ increase in the base-substitution mutation rate per cell division relative to that in the germline (Lynch 2009, 2010). More recent results based on whole-exome sequencing imply $8 \times, 12 \times, 71 \times,$ and $112 \times$ inflations for brain, lymphocyte, colon epithelium, and skin cells (Tomasetti et al. 2013; Lodato et al. 2015; Martincorena et al. 2015). Although the mechanisms generating elevated somatic mutation rates remain unclear (possible explanations include elevated numbers of cell divisions, altered expression of components of the repair machinery, and elevated levels of mutagenic by-products of metabolism), it is clear that humans are not exceptional in this regard. In all other species for which data are available, somatic-mutation rates are substantially greater than those at the germline level (Lynch 2009, 2010).

Assuming a $50 \times$ inflation of the somatic mutation rate (the average of the above estimates), an average adult cell will contain $\sim 100 \times 50 = 5000$ de novo mutations. Although these will not all be independent, with $\sim 10^{13}$ cells in the human body, the total number of mutations carried by an adult will then be of order $10^{16}$, with every nucleotide site having been mutated in thousands of cells. A large fraction of such mutations may be completely innocuous, but even if the fraction of the human genome with fitness consequences is as small as 1% (Lindblad-Toh et al. 2011; Keightley 2012; Rands et al. 2014), the unavoidable conclusion is that there is no way to avoid the accumulation of somatic mutations with undesirable effects in an aging human. Thus, at least insofar as eliminating the source, the war on cancer appears to be unwinnable.

This is not to say that we should abandon goals toward reducing the incidence of environmental mutagens. Indeed, the possibility that the baseline human mutation rate will elevate over time (for reasons discussed below) motivates a strong argument to the contrary—the need to minimize all extraneous factors that might further exacerbate an already precarious situation. It should be of particular concern that procedures commonly employed in medical screening and intervention have the side effect of increasing our exposure to key mutagens. For example, the use of computed tomography (CAT scans), which involves X-ray irradiation, has increased dramatically in the past two decades, with $\sim 50\%$ of patients being of reproductive age or earlier (Kocher et al. 2011; Berdahl et al. 2013) and the administered radiation being well above levels known to affect somatic mutation rates (Leuraud et al. 2015). A second potential concern involves the extremely widespread application of antibiotics. It is now known that sublethal levels of antibiotics indirectly increase the mutation rate in target bacteria by inducing the stress response (Kohanski et al. 2010; Andersson and Hughes 2014), but for these and most other commonly applied medicines, we know little to nothing about the effects on DNA stability at the nucleotide level in eukaryotic host cells.

**Altered Fates of Deleterious Mutations**

Although humans are unexceptional with respect to mutational features, the human condition imposes unusual influences on the rates of deleterious germline mutations. On the one hand, for the case of genetic disorders involving one to a few loci with major effects, a combination of genetic screening and counseling can reduce the transmission of deleterious alleles across generations. But on the other hand, because the vast majority of heritable mutations have very minor effects (below), and because we are all born with large numbers of them, they are for the most part recalcitrant to identification for their individual effects. This means that the myriad of clinical procedures for mitigating the consequences of bad genes (e.g., surgical procedures, pharmaceuticals, nutritional supplements, and physical and psychiatric therapies) can only result in the relaxation of natural selection against a broad class of deleterious mutations.

The sensitivity of the incidence of deleterious mutations under both of these scenarios can be evaluated by considering the underlying model for allele-frequency dynamics. Alleles with discernible deleterious effects are generally maintained at low frequencies by a balance between the recurrent input by mutation and removal by selection. Letting $u_0$ be the historical mutation rate to deleterious alleles per generation and $s_0$ be the historical magnitude of selection against the allele (relative to a reference fitness value of 1.0), the expected equilibrium frequency is simply $p_0 \approx \frac{u_0}{u_0 + s_0}$, which is closely approximated by $u_0/s_0$ provided $s_0 \gg u_0$. Changes in the mutation rate and/or selection coefficient to $u_n$ and $s_n$ will yield a new equilibrium expectation of $\hat{p}_n \approx \frac{u_n}{u_n + s_n}$, which is approached asymptotically over time ($t_n$ in generations),

$$p_n \approx \frac{1}{\left(1 + \frac{u_n}{s_n}\right)^{t_n}}.$$

First, consider the situation for a genetic disorder involving mutations with major enough effects to be subject to direct screening in parents and/or early-stage embryos. Assuming an extreme situation in which a fraction $f$ of the population is
involved in DNA replication and repair. And because of our relaxation of selection against deleterious mutations will recessive lethals) is commonly on the order of sn.

Assuming the rate of mutation is much smaller than the strength of selection, this implies a resultant 21-fold reduction in the new equilibrium allele frequency. From the preceding expression, it can be shown that p1 reaches the halfway point to the new equilibrium after 0.7/sn generations and the 90% mark after 2.3/sn generations, which become ~3 and 11 generations (about three centuries) in this particular example. Thus, even a moderate level of genetic screening can be quite effective in lowering the incidence of a major disease gene, but unless such culling is continuous, recurrent mutation will drive allele frequencies back to their prior levels.

Now consider the effect of diminished selection on mutations with small enough effects to be impervious to detection by genetic screening but subject to amelioration by medical intervention (e.g., the removal of visual acuity issues by optometry). Ordinarily, a heritable mutation causing a 1% reduction in fitness will be eliminated from a population in ~100 generations, but the mitigation of fitness effects will extend the life span of preexisting deleterious mutations, and without a comparable reduction in the mutation rate, the equilibrium frequencies of deleterious alleles will increase. Assuming sn still exceeds the mutation rate, reducing the selective disadvantage to a fraction x of the natural state, i.e., sn = xsn, will increase the equilibrium allele frequency by a factor of 1/x (e.g., by a factor of 10 if the effect is reduced by 90%), although the time to reach the new equilibrium can be quite long (e.g., the halfway point being reached in ~700 generations if sn = 0.001).

For the most extreme case of completely relaxed selection (sn = 0), beneficial alleles will ultimately be lost entirely (p1 = 0.001), with the rate of increase of deleterious alleles (with hidden effects) being entirely governed by the mutation rate to defective states. Because the human mutation rate is on the order of 10^-8 per nucleotide site per generation, the timescale of such processes may appear to be low enough to be of negligible concern. However, with all such alleles behaving in the same way across a large number of loci, the net effect will be a decline in fitness equal to the product of the genome-wide mutation rate and the average (now hidden) effect of mutations.

This situation might increase in severity over time in a sort of positive feedback loop. Because hundreds of genetic loci influence the mutation rate either directly or indirectly, any relaxation of selection against deleterious mutations will naturally reduce the efficiency of selection operating on genes involved in DNA replication and repair. And because of our enormous current effective population size (10^6), all replication/repair loci in the human population must already harbor defective alleles at low frequencies, so this feedback process need not await the arrival of new mutator alleles. Furthermore, as noted above, any relaxation of selection on the consequences of somatic mutations is likely to simultaneously relax selection on the germline mutation rate. It is therefore plausible that the human mutation rate is destined to slowly increase toward exceptional levels.

To evaluate the long-term consequences of such processes at the population level, we require information on the fitness effects of spontaneously arising mutations. Numerous studies with model organisms indicate that such effects have a broad distribution (Lynch et al. 1999; Halligan and Keightley 2009)—most mutations have minor effects, very few have lethal consequences, and even fewer are beneficial. In all organisms, the majority of mutations with effects on fitness reduce viability/fecundity by something on the order of 1% per mutation (Lynch et al. 1999; Yampolsky et al. 2005; Eyre-Walker and Keightley 2007), and this class is thought to constitute 1–10% of all human mutations, the remainder being essentially neutral (Lindblad-Toh et al. 2011; Keightley 2012; Rand et al. 2014). Taking the lower end of the latter range suggests that the recurrent load of mutations imposed on the human population drags fitness down by ~100 × 0.01 × 1% = 1% per generation, more so if the fraction of deleterious mutations exceeds 0.01 or if the environment is mutagenic, and less so if the average fitness effect of a mutation were to be <1%. A less conservative calculation suggests that the recurrent load could be as high as 5% per generation (Lynch 2009). For all to be fine in the long run, selection must be capable of improving fitness at a rate at least as high as the mutational rate of deterioration.

Owing to the indirect way in which this estimate of the recurrent human mutation load has been obtained, skepticism is to be expected. However, a recent mutation-accumulation experiment with mice (Uchimura et al. 2015) provides independent insight into the matter, as mice and humans have very similar gene and genomic architectures. To elevate the rate of appearance of mutations with discernible effects, the authors maintained replicate inbred lines of a mutator strain for 20 generations, propagating each line by single full-sib mating to minimize the effectiveness of selection. Whole-genome sequencing revealed a base-substitution mutation rate of 9.4 × 10^-9 per nucleotide site per generation, which is ~6.7 × the average human mutation rate. Over the course of the experiment, the mean number of offspring per mating declined at an average rate of 3.35% per generation, although most of the change occurred within the first 6 generations, rendering line maintenance difficult and likely imposing some selection against further decline. Extrapolating by dividing by 6.7 suggests a human decline rate of ~0.5%. Body weight in these lines declined by 0.5% per generation, and obvious phenotypic abnormalities accumulated at rates of 0.68% per generation, each of which extrapolates to human expectations of ~0.1%. Although these traits may not have independent effects on fitness, and additional key fitness factors may have been ignored, the overall
results are qualitatively compatible with the ~1% recurrent mutation load noted above.

The Long-Term Prognosis

Summing up to this point, our current knowledge of the rate and likely effects of mutation in humans suggests a 1% or so decline in the baseline performance of physical and mental attributes in populations with the resources and inclination toward minimizing the fitness consequences of mutations with minor effects. A similar conclusion was arrived at previously in a less quantitative way at a time where today’s grand vision of personalized and precision medicine could hardly have been imagined (Muller 1950; Crow 1997). This ~1% decline applies to the extreme situation of complete relaxation of selection, which will likely be realized in only the most technologically advanced of populations. But for reasons to be discussed below, it is equally relevant that the 1% estimate may be too low. Although it has been argued that the magnitude of fitness effects is less consequential if selection is soft (in the sense that individual performance is simply measured against the moving mean) (Keightley 2012; Lesecque et al. 2012), physical defects involving cancer, metabolic disease, and psychiatric disorders have very real costs regardless of the average population state.

From the standpoint of individual survivorship, there is little question that natural selection has been substantially relaxed for the past century or so. The average human desires to remain in operation for as long as feasible, and the applied life sciences are increasingly devoted to making this possible. In the United States, mean life span has doubled over the past 160 years, although maximum longevity has not notably changed and based on the preceding arguments is not likely to. Over the past four decades, age-adjusted incidences of reported cancers have increased by ~20% but are now leveling off in the United States, whereas postdiagnosis survivorship has increased by ~20% and continues to do so (Siegel et al. 2014). Because only ~4% of cancers occur before the age of 40 years, presumably because of prior selection against such expression in reproductive years (Frank 2007), the direct effects of relaxed selection on late age-at-onset cancers may be of minimal concern. However, an increase in the incidence of cancer at earlier ages may be expected as such cases continue to be mitigated through medical treatment to the point of allowing transmission of causal genes via reproduction. Similarly, although the incidence of cardiac disease in the United States has not changed discernibly over the past 40 years, associated mortality rates have declined by ~60% and exhibit a continuing downhill trend (Ford et al. 2014). Given the very high heritabilities of most human traits (Lynch and Walsh 1998), it is likely that a substantial fraction of variation in the predisposition to heart disease has a genetic basis.

The preceding arguments need not imply that human behavior by natural selection has come to a standstill (Reed and Aquadro 2006), one key issue being that natural selection is a function of both survival and reproduction. Even if variance in survival were to be eliminated entirely, phenotypes that are associated with reproductive output will inevitably be promoted by the blind forces of selection. However, another aspect of modern human behavior—the tendency toward families of similar size (the two-child syndrome in middle-class neighborhoods in westernized societies)—may thwart this aspect of selection as well. Notably, this very strategy (equilibration of family sizes) has been used to accumulate deleterious mutations in experimental populations of Drosophila, yielding a 0.2–2% decline in fitness per generation (Shabalina et al. 1997).

Sexual selection presumably continues to play some role in human evolution, although cosmetic surgery, acquisition of wealth, and other factors may relax this as well. For example, although it has been argued that female choice for healthy males may aid in reducing the mutation load (Whitlock and Agrawal 2009), the strength of such reinforcement would also be diminished in human populations where suboptimal male phenotypes are hidden by various medical procedures. Moreover, sexual selection need not operate in the same direction as natural selection; e.g., given the very high heritabilities of human morphological traits (Lynch and Walsh 1998), female selection for large physical stature in males would be expected to lead to increased difficulties in the natural birthing process. Clearly, the issues here are highly complicated, and it is by no means even certain that traits that are beneficial in an absolute sense (e.g., exceptional physical or mental attributes) are the ones currently being promoted by natural or sexual selection.

Thus, without any compelling counterarguments at this time, it remains difficult to escape the conclusion that numerous physical and psychological attributes are likely to slowly deteriorate in technologically advanced societies, with notable changes in average preintervention phenotypes expected on a timescale of a few generations, i.e., 100 years, in societies where medical care is widely applied. In the United States, the incidences of a variety of afflictions including autism, male infertility, asthma, immune-system disorders, diabetes, etc., already exhibit increases exceeding the expected rate. Much of this change is almost certainly due to alterations in environmental factors. However, mitigating these effects by modifications in behavior and/or medical intervention will also simply exacerbate the issues noted above by relaxing selection on any underlying genetic factors. Determining the genetic contribution to any long-term trend in phenotypic attributes will require the development and implementation of standardized measurement methods that control for historical changes in ascertainment and environmental effects. Given the massive support devoted to biomedical research, surely this is a goal worth pursuing.

One final matter worthy of consideration is the fact that most prior work on the effects of mutations has focused on simple measures of survival and reproduction, usually in model invertebrate systems. Little consideration has been given to behavior, but work with Caenorhabditis elegans, a
nematode with a relatively simple nervous system, suggests a rate of decline in behavioral performance similar to that for immediate fitness traits (Ajie et al. 2005). This observational work may substantially underestimate the mutational vulnerability of the world’s most complex organ, the human brain. Because human brain function is governed by the expression of thousands of genes, the germline mutation rate to psychological disorders may be unusually high. At least 30% of individuals with autism spectrum disorders appear to acquire such behaviors by de novo mutation (Iossifov et al. 2015). Notably, human brain cells also incur up to dozens of mobile-element insertions per cell (Erwin et al. 2014; Richardson et al. 2014), implying a level of somatic mutation far beyond the expectation noted above based on point mutations.

Arguably, by providing a mechanism for partitioning of mentally demanding tasks, societal living may serve as still another way by which selection is relaxed on traits within individuals, although it may also be argued that complex societies impose selection for novel ways of processing information. It has been suggested that there has been a slow decline in intelligence in the United States and the United Kingdom over the past century (Crabtree 2013; Woodley 2015), although again the underlying issues with respect to environmental factors have not been fully resolved, and not surprisingly these arguments are controversial. The key point here is that the one truly exceptional human attribute, brain function, may be particularly responsive to mutation accumulation, possibly exhibiting a response to relaxed selection greater than the 1% benchmark suggested above.

A fitness decline of a few percent on the timescale of a century is on the order of the rate of global warming, and that is part of the problem. What will it take to promote serious discourse on the slowly emerging, long-term negative consequences of policies jointly promoted by political, social, and religious factors? Should such a discussion even be pursued or should the process of accelerated genetic change simply be allowed to run its course—a slow walk down the path to what Hamilton (2001) called “the great Planetary Hospital”? Unlike global environmental change, there is no obvious technological fix for the uniquely human goal of intentionally ameliorating the effects of mutation, nor is there a simple ethical imperative for doing otherwise, short of refocusing our ethical goals on future descendants. Unless some altered course is taken, as improved biomedical procedures continue to minimize the cumulative consequences of our genetic (and/or environmentally induced) afflictions, and the associated biomedical industries reap the financial rewards, this will come at a progressively increasing cost for individuals with the resources and/or desires to apply such solutions.

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