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Review

Principles for introducing new genes and species for conservation

Michael K. Schwartz [1,*], Summer L. Dunn[2], William A.C. Gendron[3], Jennifer E. Helm[1], W. Sebastian Kamau[4], Melanie Mark-Shadbolt[5], Axel Moehrenschlager[6], Kent H. Redford[7], Gregory Russell[8], Ronald L. Sandler[9], Courtney A. Schultz[8], Blake Wiedenheft[10], Amanda S. Emmel[11], and Jedediah F. Brodie[11,12,13]

Introducing new genes and new species into ecosystems where they have not previously existed presents opportunities and complex, multivalue decisions for conservation biologists and the public. Both synthetic biology and conservation introductions offer potential benefits, such as avoiding extinctions and restoring ecological function, but also carry risks of unintended ecological consequences and raise social and moral concerns. Although the conservation community has attempted to establish guidelines for each new tool, there is a need for comprehensive principles that will enable conservation managers to navigate emerging technologies. Here, we combine biological, legal, social, cultural, and ethical considerations into an inclusive set of principles designed to facilitate the efforts of managers facing high-consequence conservation decisions by clarifying the stakes of inaction and action, along with the use of decision frameworks to integrate multiple considerations.

Highlights

Synthetic biology and conservation introductions serve as conservation tools to introduce new genes and species into ecosystems and can offer potential solutions to combat biodiversity loss.

Despite their potential conservation benefits, these approaches pose ecosystem-level risks to both nature and humans, highlighting the dangers of both action and inaction.

By adopting a multidisciplinary approach, we derive principles that consider biological, legal, social, cultural, and ethical concerns to evaluate actions that introduce new genes and species into extant ecosystems.

When used in a participatory decision-making framework, our multidisciplinary principles can be readily adapted to existing and emerging technologies.

Emerging technologies pose new challenges for conservation

Species extinction rates greatly exceed background levels from the fossil record, which may herald the beginning of Earth's sixth mass extinction [1]. Rapid environmental change in a world of fragmented habitats is leading to substantial loss of biodiversity [2]. Active, targeted, human interventions may be the last option to avert the extinction of many species [3]. Emerging technologies and novel approaches have substantially increased the breadth of tools and associated conservation strategies potentially available to conserve species, as well as the extent and depth of public concern and interest. With the rapid pace of human innovation, we expect to see more tools, more attention, and more controversy. Yet, a big question remains: under what circumstances should any of these tools be put to use for biodiversity conservation? Here, we provide a set of principles that can be adapted to existing and new tools and technologies, focusing on those that introduce new genes or new species into ecosystems.

Moving genes and species

Synthetic biology (see Glossary) is an interdisciplinary field that involves the design of artificial biological pathways, organisms, and ecosystems, including the redesign of existing natural biological systems [4,5]. Although the development of these tools has been driven by the medical and agricultural sectors [6] and many of these technologies are still in development, there are also potential conservation applications, such as improving biodiversity persistence or restoring ecosystems. These applications range from modifying invasive species to reduce their impacts to facilitating organismal adaptation to novel conditions to recreating proxies of extinct species that have not been in ecosystems for thousands of years. Synthetic biology activities, such as

[1]USDA Forest Service, Rocky Mountain Research Station, Missoula, MT, USA
[2]USDA Forest Service, Policy Office, Strategy and Analysis Branch, Washington, DC, USA
[3]Department of Cell and Developmental Biology, School of Biological Sciences, University of California, San Diego, La Jolla, CA, USA
[4]Media Laboratory, Massachusetts Institute of Technology, Cambridge, MA, USA
[5]Te Tira Whakamātaki and Biological Heritage National Science Challenge, New Zealand
[6]Panthera, New York, NY, USA
[7]Archipelago Consulting, Portland, ME, USA
[8]Department of Forest and Rangeland Stewardship, Colorado State University, Fort Collins, CO, USA

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genetic engineering of species, have received considerable attention, because they can add or subtract genomic elements of species to aid conservation objectives (Box 1).

Innovation in synthetic biology is happening at a pace that is outstripping legal, cultural, and policy frameworks [7,8]. Genetic engineering has switched from invention to application in a matter of years, so fast in fact that society has progressed from inventing **clustered regularly interspaced short palindromic repeats (CRISPR)**-Cas technology [9] to creating educational modules for high-school classes [10,11] in under a decade (Figure 1 and Box 1). CRISPR-modified organisms are becoming so commonplace that, like it or not, conservationists and resource managers must grapple with synthetic biology as they make decisions about how to conserve and manage species and habitats [4].

In addition, genes can be added to a target population without synthetic biological mechanisms via techniques such as **genetic rescue** and **targeted gene flow**, which involve moving individuals with desired genes or traits into extant populations, but they can also be modified in frequency using synthetic biology via **targeted genetic intervention** [12–15]. If there is no population in the area, one can be created using **assisted colonization** or ecological replacement, both of which are forms of **conservation introduction** [16]. The use of conservation introductions is proliferating across taxa including plants, animals, and fungi [17,18]. For the most endangered groups of organisms, assisted colonization may be essential for avoiding global extinction when the causes of original extirpation within indigenous ranges cannot be ameliorated [19,20].

Synthetic biology and conservation introductions aim to create novel ecosystems or novel mixtures of species and genes in places where they have not naturally occurred. They may offer major benefits for conservation and human cultural values, but concerns remain about associated risks, yielding a challenging environment for decision-makers. Here, we focus on synthetic biology and conservation introductions as two key sets of interventions that introduce novel biological materials into native ecosystems, just at different scales of biodiversity.

To guide the implementation of activities that release new genes or new species for conservation purposes, we need holistic principles that can bridge social and biophysical concerns, are flexible

[9]The Ethics Institute and Department of Philosophy and Religion, Northeastern University, Boston, MA, USA
[10]Department of Microbiology and Cell Biology, Montana State University, Bozeman, MT, USA
[11]Wildlife Biology Program, University of Montana, Missoula, MT, USA
[12]Division of Biological Sciences and Wildlife Biology Program, University of Montana, Missoula, MT, USA
[13]Institute for Biodiversity and Environmental Conservation, Universiti Malaysia Sarawak, Kota Samarahan, Sarawak, Malaysia

*Correspondence:
michael.k.schwartz@usda.gov
(M.K. Schwartz).

Box 1. Synthetic biology for mosquito control

Scientists are developing and implementing a variety of genome-engineering methods (Figure 1 in the main text) for combating vector-borne diseases. Here, we provide examples of control technologies that have been applied to mosquitoes and note that these technologies can be applied to other species for conservation purposes.

(i) Targeted gene disruption can be implemented in two main forms: (i) Precision guided Sterile Insect Technique (pgSIT); and (ii) gene disruption for disease suppression. PgSIT involves disrupting genes responsible for female survival and male fertility [97]. With this approach, genetically engineered mosquitos are released as eggs. In addition to using this as a species suppression mechanism, targeted edits could be introduced to reduce the ability of mosquitoes to spread infectious diseases [98]

(ii) Transgenesis for the use of disease prevention in vectors such as mosquitoes takes two forms: (i) population suppression via Release of Insects carrying a Dominant Lethal (RIDL [99]); or (ii) the introduction of transgenes with antidisease capabilities. RIDL relies on using a drug to suppress a lethal gene and then releasing mosquitoes that contain a lethal gene. This requires repeated releases and spreads transgenes throughout the target population, but, as lethal transgenes, they should not persist without the drug. Antidisease transgenes are spread by mass releases with the intent of interrupting disease spread [100].

(iii) **Gene drive** is the method of using a genetic element that copies itself, typically to the same site on the sister chromosome, to ensure that it is inherited by the next generation [101]. This can be done with the goal of suppression or to spread a transgene [102]. Gene drives can be purposefully made to be split gene drives, in which two elements (e.g., gRNA and Cas9) needed for the gene drive are encoded separately. This prevents unlimited spread theorized from full drives because only one of the elements is inherited in a super-Mendelian fashion when both elements are in the same organism [103].

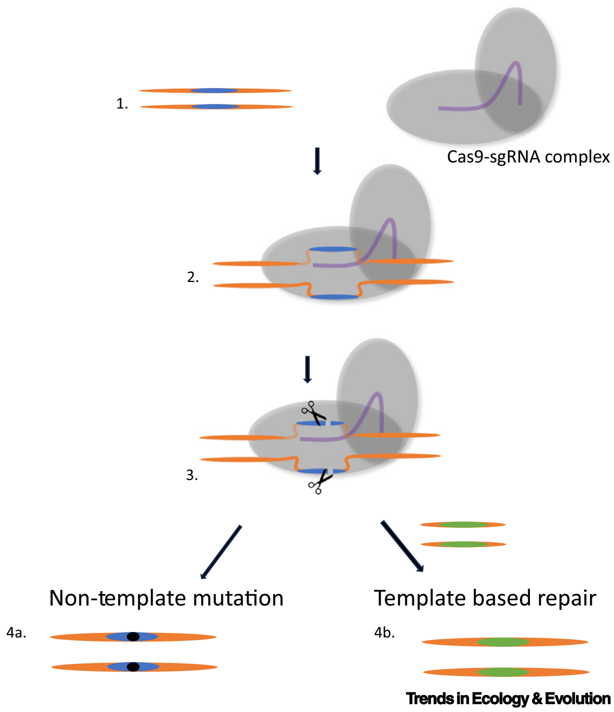

Figure 1. General steps in genomic engineering using the clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 system. (1) A DNA strand (orange) contains an area targeted for cutting ('target sequence', in blue) and the Cas9 protein complexes with the single guide RNA (sgRNA, in purple). (2) The Cas9-sgRNA complex scans the DNA within a cell for complements to its sgRNA. (3) Once found, the Cas9-sgRNA complex acts like a pair of 'molecular scissors' and cleaves both strands of DNA. (4a) The cut DNA can be repaired without using a template, typically introducing small insertions and deletions disrupting the sgRNA site (black; non-template mutation). Alternatively, DNA templates that contain homology to the target region can take part in the DNA repair process. (4b) This can result in the insertion of other DNA (green) at the cut site, disrupting the gRNA site, preventing further cleavage (template base repair).

to account for as-yet unknown technologies, and can be responsive to local contexts and values, while still recognizing that each case is unique and should be judged on its own merits. These principles must go beyond specific guidance for each strategy or technology (e.g., [20–23]); given the rapid pace of invention [24], we need overarching guidance that can be applied broadly to ensure that natural resource managers are prepared to make decisions about whether to use a particular tool for a conservation purpose as soon as the question arises.

We assembled a working group of experts in conservation introductions, synthetic biology, genomics, ethics, conservation biology, Indigenous perspectives, communication, policy, and law. Together, we derived a list of the dangers of inaction and action. We subsequently derived principles to consider before undertaking any actions that introduce new genes or new species for conserving biodiversity. These principles are rooted in questions about how to weigh the danger of taking an action to address a conservation concern, even if that action comes with risks, against the danger of not taking an action, which comes with risks of its own. Here, we lay out the dangers of inaction and action associated with moving genes and species that underpin the guiding principles.

Dangers of inaction

Extinction concerns from not moving genes or species

Numerous species will go extinct if we continue to operate with 'conservation as usual' [25]. The bramble cay melomys (*Melomys rubicola*), a rodent in Australia that was found only on a limited number of offshore islands, is the first documented case of extinction from contemporary climate change, which could have been avoided with assisted colonization [26]. Due to climate change projections, the existing global network of protected areas is too limited to serve as effective steppingstones for species to migrate and shift their ranges [27,28]. Even if we massively expand protected areas and habitat corridors (and even more so if we do not), widespread conservation

Glossary

Assisted colonization: type of conservation translocation whereby populations are moved outside their indigenous range to avoid extinction.
Assisted evolution: use of human intervention to accelerate the rate of naturally occurring evolutionary processes.
Clustered regularly interspaced short palindromic repeats (CRISPR): technology that selectively modifies the DNA of living organisms. It was adapted for use in the laboratory from naturally occurring genome-editing systems found in bacteria. CRISPR allows researchers to easily alter DNA sequences and modify gene function, with potential applications including correcting genetic defects, treating and preventing the spread of diseases, and improving the growth and resilience of crops.
Conservation introduction: intentional movement of a species from its current location to an area outside its indigenous range to improve its overall conservation status or restore ecological function.
Dual use: items, goods, or technologies that are designed and approved for one use (e.g., commercial), but are also suitable for different (e.g., military) purposes.
Gene drive: natural process and a technology of genetic engineering that propagates a particular suite of genes throughout a population. It works by altering the probability that a specific genetic variant will be transmitted to offspring. Instead of the typical Mendelian inheritance probability of 50%, gene drives can dramatically increase this likelihood. This allows the genes to rapidly spread through a population, potentially overriding natural selection.
Genetic engineering: deliberate modification of the characteristics of an organism by manipulation of its genetic material.
Genetic rescue: increase in population growth due to immigration of new alleles to a recipient population.
Monitoring: in the context of biodiversity, refers to the systematic observation and measurement of changes in measurements of biodiversity in its various forms, such as genes, taxa, structures, functions, connectivity, and ecosystems over time.
Moral hazard: situation in which an entity is more likely to engage in risky

translocations, likely including assisted colonizations, will be needed to avoid extinction for many species. Such biodiversity loss includes not only species decline, but loss of genetic diversity [29], removing the underlying material for adaptation.

Alterations or loss of ecological function from not moving genes or species

All species interact with others around them and with their environment; thus, the loss of species may have dramatic effects on other taxa and alter ecological function [30]. For example, the overhunting of large frugivores across the world threatens many plant species that depend on these animals for seed dispersal [31,32]. Given that trees whose seeds are dispersed by large animals often contribute disproportionately to aboveground biomass, such overhunting can even affect ecosystem carbon storage, a critically important ecological function globally [33,34].

Replacing extinct species with ecological proxies may be an important tool for avoiding secondary extinctions or loss of ecological function. To mitigate risks to plants the seeds of which were dispersed by the extinct saddlebacked giant tortoise (*Chelonoidis abingdonii*) in the Galapagos Islands, for example, conservationists introduced ecological replacements by moving non-native tortoises from a neighboring island to fill the lost seed dispersal function [35]. Introducing genetically recreated species [e.g., passenger pigeons (*Ectopistes migratorius*)] or using **assisted evolution** to save ecologically important species [e.g., whitebark pine (*Pinus albicaulis*) or coral reefs] may serve similar purposes [36,37]. In short, synthetic biology offers tools to reduce the risks of secondary extinctions and the loss of ecological functions, including ecosystem services (e.g., forest carbon storage) important to humans and the rest of life on Earth.

Alterations or loss of cultural values from not moving genes or species

The loss of species not only has ecological ramifications, but can also profoundly erode cultural values of Indigenous people whose stories, identities, and traditions may rely on the species (Box 2). For example, the emerald ash borer (*Agrilus planipennis*), an invasive species in North America, is destroying black ash (*Fraxinus nigra*) stands and wetlands throughout its

behavior because they do not have to bear the full cost or consequences of that risk.

Synthetic biology: involves the creation of new biological components, devices, and systems, or the re-engineering of existing biological systems, ranging from genomes to ecosystems [4].

Targeted gene flow: conservation translocation approach whereby individuals with favorable traits are brought into a recipient population.

Targeted genetic intervention: category of approaches that increase fitness in a population by changing the occurrence or frequency of targeted alleles in a population.

Box 2. Māori perspectives on synthetic biology for conservation

Māori, the Indigenous Peoples of Aotearoa (New Zealand), have a deep cultural and spiritual connection to their lands, waters, and the inhabitants of those spaces. In Aotearoa, assisted colonization is a tool that is being used to protect vulnerable and sacred species, and the use of genetic engineering is being explored as part of this approach. Much work has already been done to understand Māori perspectives on genetic technologies [104–106], and it largely suggests that Māori are more likely to positioned at the 'antigenetic engineering' end of the spectrum.

Much of the opposition to genetic technologies stems from key Māori concepts of *whakapapa*, *mauri*, *mana*, and *kaitiakitanga*. *Whakapapa* is a genealogical framework that shapes how Māori understand their identity and their relationship with all species throughout space and time. *Mauri* relates to the distinctive and special nature of an organism, including its right to life, and is often defined as 'life essence'. *Mauri* and *whakapapa* are, for Māori, a window into the world, past, present, and future, and are vital for maintaining the balance and harmony of the web of inter-relationships across the environment. Combined, they are what genetic technologies arguably touch and disrupt. Another core concept, *mana,* relates to authority and denotes a responsibility to act in the interests of the broader community, while *kaitiakitanga* represents the responsibility that Māori have to steward their natural resources in ways that maintain *mauri*, *mana*, and *whakapapa*. Collectively, these concepts and ways of seeing the world guide Māori decision-making and allow for philosophical, moral, and ethical concerns about the use of genetic technologies on Māori and public lands. These concepts encourage Māori to examine Māori traditions for examples that might help them understand and respond to an issue. In the genetics space, such examples include traditional stories of shape-shifting, where demigods, such as *Maui*, change from one form to another or change forms completely, potentially facilitating adoption of genetic engineering approaches. These stories are part of Māori *whakapapa* (genealogy) and can be used to explain the creation of various life forms, new and old, but must be balanced with core principles and always with balance and harmony, and the collective community's interest in mind.

Accordingly, consent and/or social license from Māori for the use of genetic technologies will only be achieved through facilitated discussions on the potential risks and benefits to *mauri* and *whakapapa* combined with methods for honoring Indigenous perspectives on conservation and land stewardship (*kaitiakitanga*).

range. The loss of black ash has already altered nutrient cycling, hydrological activity, and wildlife habitat in the Lake State region of the USA [38–40]. Loss of this cultural keystone species also threatens cultural practices, such as basketmaking and creation of traditional medicines [41]. Similarly, many other North American plants, such as Port-Orford cedar (*Chamaecyparis lawoniana*), butternut (*Juglans cinerea*), and redbay (*Persea borbonia*), have seen population reductions in parts of their range due to invasive fungi to the point where they are functionally eliminated [42]. Each of these species has cultural values as important food and wood sources, sources of medicine, and materials used for ceremonies and lifeways to local Indigenous peoples [42]. Tools, such as genetic engineering, could be used to ameliorate the threat by eliminating the invasive species (Box 1) or by providing resistance for the host species.

Hazards of nonsynthetic biology methods

Critics of using conservation introductions or synthetic biology to restore ecosystems sometimes champion the restoration effort itself, only using other methods, yet the hazards associated with these approaches are often overlooked. There are numerous techniques for controlling invasive species, many of which also adversely affect indigenous species. The toxin rotenone is used to eradicate invasive fish in many areas, but indiscriminately suffocates all gill-breathing organisms, therefore harming many indigenous vertebrates in systems where it is deployed [43]. Toxins are also used to remove introduced rats (*Rattus* spp.) on islands where they endanger indigenous seabirds; these toxins can spread to indigenous predators and scavengers, including threatened species [44]. Large fenced exclosures are used in Australia to protect indigenous fauna and vegetation from introduced rabbits and predators, but these fences are expensive and disrupt the dispersal and other behaviors of the indigenous species [45]. Finally, biocontrol agents introduced to limit populations of invasive species have themselves become invasive, threatening indigenous taxa [46]. Mongooses (*Herpestes auropunctatus*) were introduced to some oceanic islands to control non-native rats, but they have devastated many island endemics [47]. While mongoose introductions may not be undertaken with current ecological understandings of the dangers of releasing such a predator, many insect predators are released annually without knowledge of their potential ecological effects [48].

Dangers of action

Unintended consequences of moving genes and species

One of the largest concerns about moving genes and species is triggering unintended or unforeseen ecological consequences. The literature is replete with examples of negative impacts stemming from species introductions including (albeit very rarely) conservation translocations [29,49–51]. For example, the introduction of the American red squirrel (*Tamiasciurus hudsonicus*) to Newfoundland to enhance the food availability for declining American martens (*Martes americana*) resulted in the near extinction of the Newfoundland red crossbill (*Loxia curvirostra percna*), with which the squirrels competed for food [52].

Similarly, bioengineered genes conferring a selective advantage or disadvantage may escape the target population and influence a nontarget population. Individuals with these genes may also experience unintended consequences, such as increased disease susceptibility or off-target mutations [13]. Such unintended consequences have been seen in transgenic crops [53] and genetically engineered fish that hybridize with their wild relatives, leading to the transfer of synthetic genes [54,55]. This has raised concerns about potential ecological effects and the spread of engineered traits in natural ecosystems. Given that few releases of genetically engineered species for conservation have occurred into the wild to date, no unintended consequences have yet been documented. However, despite the many proposed safeguards [23,56], negative fitness consequences to wild relatives remain a concern.

Moral hazards of moving genes and species

A **moral hazard** is a situation where an entity is more likely to engage in risky behavior because it does not bear the full cost or consequences of that risk [57,58]. If scientists believe they can mitigate any unforeseen ecological problems that arise from using synthetic biology to enhance species survival, they might be more inclined to release genetically engineered organisms without conducting thorough, precautionary assessments [22]. A moral hazard is born if developers do not bear the full environmental consequences of any negative outcomes. Similarly, when conservation introductions are used to prevent biodiversity loss, practitioners may lose focus on the underlying mechanisms, such as habitat loss or climate change. These tools may be treated as another 'techno-fix' that absolves humans of the obligation to address the underlying problems [59]. Moving species beyond their indigenous ranges could be seen as opening a Pandora's box, by which releases outside of their native range could be normalized or seen as compensatory offsets instead of protecting species within indigenous ranges [60].

Social concerns of moving genes and species

At present, only a few entities have ownership and control over the tools to engineer organisms as well as the engineered organisms themselves. This generates issues related to equity, ownership, restitution, and public input over what is created, by what means, and the distribution of profits versus costs and risks. The situation becomes more complex when considering regulations about who will own the genetic code and the organisms that are created [23,61]. Conservation is filled with well-intentioned actions that have been heralded as success by one group and as colonial conservation by others [62].

With synthetic biology and conservation introductions, it is critical to meaningfully engage Indigenous and local communities that are directly affected by these types of decisions [63]. It is also crucial that initiatives involving conservation introductions and synthetic biology meet treaty obligations, include Indigenous Peoples in decision-making, and recognize Indigenous knowledge [64] (Box 2). An informative case is that of the American chestnut (*Castanea dentata*), where genetic engineering was used to produce a version of the ecologically important but functionally extinct species that is resistant to the introduced blight that almost eliminated it from the wild. There was minimal engagement and no communal authorization from sovereign Tribal Nations about the early stages of release of these trees before either the genetic engineering or the outplanting at field sites, some within just a few kilometers of tribal territories [65]. According to Barnhill-Dilling, one Onondaga Nation elder lamented their exclusion from the initial process noting '…they're already planted over here aren't they?' The possibility of transgenic material traveling across established sovereign borders of US federally recognized tribes raises significant concerns for Indigenous communities [65].

Similarly, moving species to novel locations to avoid their global extinction in the face of local extirpation via assisted colonization means that some Indigenous Peoples may be confronted with species with which they have no historical, cultural, or spiritual connection (Box 2). Translocations to new sites may be beneficial for species viability or the restoration of lost ecological function, but can also generate human–wildlife conflict, such as with the release of elephants (*Loxodonta africana*), black rhinoceros (*Diceros bicornis*), or lions (*Panthera leo*) [66,67]. Approaches to engagement must transcend 'consultation' from a Western-driven science perspective to arrive at genuine and respectful co-management of conservation translocations with Indigenous Peoples. Local group participation leads to more successful outcomes; for instance, in Kenya, the movement of lions into Maasai lands without this participation has led to more negative attitudes toward the species and retaliatory killing of lions [68,69]. There has been a longstanding legacy of distrust between Indigenous communities and western scientific researchers; co-creating solutions is an important step forward [65,70,71].

Loss of natural conditions and baselines from moving genes and species

Another social/philosophical danger concerns whether these human-assisted conservation actions reduce the 'naturalness' of place [4,72–74]. For example, the American Wilderness Act [75] focuses on areas "protected and managed so as to preserve its natural conditions and which generally appears to have been affected primarily by the forces of nature, with the imprint of man's *[sic]* work substantially unnoticeable". Introduced species (assisted colonization or ecological replacement) or genes (genetic engineering) could be considered as compromising naturalness of American Wilderness and other protected areas in the USA, as defined by law.

There is also concern that, by imposing an overly interventionist and engineering-oriented approach to conservation, we will lose baselines for nature, including the baseline for evaluating human-independent ecological and evolutionary processes that create the tapestry of life. Some consider the natural processes of evolution a creative and spontaneous process the products of which should be preserved, and value having landscapes where the imprint of humans is minimized [76–78]. In this view, synthetic biology and conservation interventions may fundamentally change the conservation paradigm from one of attempting to reduce or mitigate the human footprint on the natural world to one where the natural world becomes open to human intervention, which might range from a healthy and responsible human–environment relationship to one where the natural world is rendered nothing more than a garden to meet the desires and needs of humans [4,13,24,58]. Concomitantly, we must also recognize that many of these biodiverse landscapes, from which we hope to derive natural baselines, were areas frequently used and managed by Indigenous Peoples. Attempts to keep these areas 'pristine' by limiting contemporary management action may, in fact, be degrading the ecological condition as well as marginalizing Indigenous practices and worldviews [79,80].

Security and dual-use concerns of moving genes and species

Synthetic biology poses dangers beyond biological conservation, including security and ownership issues. For example, there is a concern that permitting the development of genetically engineered species for biodiversity conservation may also advance the technology for other purposes, such as biological weaponry [81,82]. This **dual use** concern, also called a Trojan horse, may be an issue with the public perception of genetically engineered organisms in the wild. The public is often worried about the insertion of genes whereby the technology appears legitimate and innocuous but contains hidden genetic code or functionality [83]. Releasing genetically engineered organisms may also lead commercial or other entities involved to make ownership or intellectual property claims over shared public goods or be used as part of the justification for allowing ecologically damaging activities on the promise that their technology will later repair it. While some of these concerns may seem implausible to conservation practitioners, they are frequently mentioned by a concerned public [4].

Animal welfare concerns of moving genes and species

There are ethical concerns regarding welfare of animals that humans modify or move, such as the risk of inducing suffering in sentient beings [84]. The animal welfare community has raised individual-level concerns (as opposed to population-level or species persistence-level concerns) about the stress and trauma associated with relocation of individuals for assisted colonization [84,85]. There are also concerns that there will be unintended behavioral selection or changes in animals used in assisted colonization or synthetic biology efforts [86]. In addition, removing animals from historical habitats to be placed in novel environments where the recipient population needed assistance and where their success may be uncertain is considered unjust by some [87]. However, the contrasting argument is that leaving species in degraded environments often devoid of the elements needed for survival can lead to prolonged suffering, and possibly death [87,88]. Similar concerns are arising regarding the welfare of individuals of species that have genes inserted with unknown downstream effects that could lead to animal suffering and health risks [89].

Guiding principles

We developed guiding principles that address each of the dangers of inaction and action to help conservation practitioners consider all components of a potential action (Box 3). These principles are intended to ensure that any potential project is well justified, includes input from people who may be affected by it, and can be executed responsibly. Taken together, the principles ensure that any action that introduces genes or species considers available scientific evidence and can feasibly produce a beneficial outcome addressing an underlying threat against biodiversity conservation, while minimizing risks of undue harm and unintended consequences (Box 3). The principles also ensure that decisions about introducing genes and species are based on equity and inclusion, that impacted people have autonomy in the decision-making process, and that effects on human condition and animal welfare are considered. Lastly, the principles ensure transparency in decision-making, that potential actions are weighed against other approaches, and that exit strategies or off-ramps are defined in case of unforeseen problems (Box 3). When used in a participatory decision-making framework, these principles can readily adapt to existing and emerging technologies and aid practitioners in deciding whether to move new genes and new species.

Existing regulatory structures

To use our principles, it is helpful to consider how assisted colonization, ecological replacement, and synthetic biology fit into existing guidelines and regulations. Conservation introductions have been the subject of guidance issued by the International Union for Conservation of Nature (IUCN), which published decision-making principles, a risk assessment, and suggestions about long-term **monitoring** [16,20]. These guidelines have been incorporated into some national policies, such as in the English Code for Reintroductions and Other Conservation Translocations [66]. Principles outlined in the guidance include justification, planning, feasibility and design, risk

Box 3. Principles to consider before undertaking assisted colonization, ecological replacement, or synthetic biology for conservation purposes

1. Principle of Intent: conservation of biodiversity should be the primary intent of the action.
2. Principle of Feasibility: the goal of the proposed activity should be likely to be accomplished according to some clearly defined criteria.
3. Principle of Underlying Threat: the action should address the underlying cause of the original reason for endangerment.
4. Principle of Open Science: the science used to justify the action should be peer-reviewed and open to the public.
5. Principle of Beneficence: the action should be taken for producing good.
6. Principle of Justice: there should be equity and inclusion in the decision-making process.
7. Principle of Non-maleficence: the principle of *primum non nocere* or do no harm should be considered.
8. Principle of Unintended Consequences: the action should be evaluated for potential unintended consequences.
9. Principle of Autonomy: those who will be impacted by the action should be included in the decision-making process to uphold their rights to make their own decisions based on their beliefs and values.
10. Principle of Human Condition: the impact on the human condition should be considered.
11. Principle of Welfare: for animals, welfare issues should be considered.
12. Principle of Open Decision-Making: the process used for decision-making should be transparent.
13. Principle of Cost-Benefit Analysis: potential actions should be weighed against other approaches, the strength of evidence for each, and their risks and benefits.
14. Principle of Reversibility: actions may not go as planned; knowing whether an action is reversible and having an exit strategy when confronted with unforeseen circumstances should be considered.

assessment, implementation, monitoring and management, and dissemination of information [22,66].

Meanwhile, the release of bioengineered organisms is subject to federal legislation in the USA, Europe, and with international treaties (Box 4). The United National Convention on Biological Diversity (CBD) produced the Cartagena Protocol [23,56], which provides a regulatory protocol for the safe handling, transport, and use of living modified organisms, suggests a risk assessment (Annex III of the protocol), and includes points to consider. However, the protocol falls short of providing principles to consider other than generally suggesting that risks 'should be considered in the context of the risks posed by the non-modified recipients…in the likely potential receiving environment' [56]. Thus, in the case of new synthetic biology techniques, it is unclear how new technologies will be evaluated, since the review of these protocols differs across agencies [90] and, globally, there has not been agreement reached by either the IUCN or CBD [56,63]. This variation in governance and the remaining uncertainty about how new technologies will be evaluated further demonstrate the need for principles and a decision-making framework with which to evaluate any action.

Concluding remarks and implementing the guiding principles

How does a conservation manager or governing body decide whether to move forward with a proposed action given existing regulatory structures and our principles? We recommend that the guiding principles (Box 3) serve as a structure upon which a decision-making framework evaluating these principles can be built. The natural resource literature demonstrates that incorporating a broad suite of values leads to more sustainable outcomes [91,92]. However, there is no single formula for how to balance all the principles described (see Outstanding questions). The salience of each will vary depending on context, including the spatiotemporal scale of the action and the communities involved or affected. Some principles will be incommensurable with others and some principles will be immutable, thus limiting a trade-off analysis, and must be treated 'in parallel' [91].

Box 4. Existing guidelines and legal frameworks for gene editing

The release of bioengineered organisms is subject to federal legislation in countries, such as the USA, and in Europe. In the USA, the release of bioengineered organisms (including synthetically derived organisms) into natural environments must be consistent with the Coordinated Framework for Regulation of Biotechnology, hereinafter 'Coordinated Framework' [107]. Proposed in 1984 and finalized in 1986, the Coordinated Framework allocates jurisdictional authority among three federal agencies: US Department of Agriculture, US Food and Drug Administration, and the Environmental Protection Agency. When reviewing biotechnology products, these agencies consult with each other on matters concerning regulatory jurisdiction [108].

The underlying principles of the Coordinated Framework include the following: '(1) US policy would focus on the product of genetically modified techniques, not the process itself, (2) only regulation grounded in verifiable scientific risks would be tolerated, and (3) genetically modified products are on a continuum with existing products and, therefore, existing statutes are sufficient to review the products' ([109], p. 738). The Coordinated Framework was designed to be responsive to technological innovation, but has seen only relatively minor regulatory changes since its adoption in 1986 [110]. In the case of synthetic biology, it is unclear how new technologies will be evaluated, since review protocols will differ across agencies [90]. Given that agencies evaluate biotechnology according to its unique features and not its production method [108], it is possible that synthetic biotechnologies derived from the same process could be evaluated differently by separate agencies. When an agency reviews a new biotechnology, its evaluation is often based on justifications that are just as novel as the technology itself.

The European Union (EU) has a different approach based on an underlying precautionary principle. Referenced specifically in Directive 2001/18/EC (Directive), the precautionary principle has served as the primary legislative framework for regulating genetically modified organisms in the EU since 2001. In the case of gene drives, the European Parliament recently passed two resolutions that called for a moratorium on the release of gene drive organisms into wild environments, including field tests. Unlike the USA, where the product is subject to law, the EU is focused on the process by which it was created. A 2018 ruling by the European Court of Justice (ECJ) upheld the Directive's authority to regulate organisms engineered using new genomic techniques, such as CRISPR.

Outstanding questions

When contemplating the introduction of new genes and new species into ecosystems, how should practitioners weigh the trade-offs inherent in the guiding principles? Should each principle be weighted evenly, or should some be given greater weight in certain contexts? We suggest that these principles may fit into decision-making frameworks, such as structured participatory decision-making, which is an organized method for making transparent choices in complex environments. This decision-making framework is widely used to address challenging conservation questions and could be integrated here.

Given that species move and gene flow occurs, how do we ensure collective action according to shared rules? For instance, how do we avoid a situation where many parties agree to not undertake an assisted colonization or genetic engineering action, but one or a few parties pursues the action in a different regulatory or ethical environment? For example, two adjacent countries with different regulations may arrive at different conclusions about whether to release genetically engineered organisms, even though the consequences of the action span regulatory boundaries.

As synthetic biology approaches proliferate and continue to become publicly available, how do we avoid illegal or accidental releases of 'unofficial' modified organisms? This is already an issue with conservation introductions because there are cases of private entities releasing organisms into the wild.

How do we ensure that decision-making processes are inclusive and equitable? Historically, the decision process has been limited to a few, but with these tools, the impacts of actions could affect many.

What is the best way to monitor for both targeted and unwanted effects of synthetic biology activities and conservation introductions? How can tools be developed, considered, or applied while allowing maximum reversibility or exit strategies if consequences are undesirable or damaging?

A potential way to weight different principles is through structured participatory decision-making frameworks, which are increasingly used to enhance collaborative governance and provide just outcomes [67,93], including procedural justice, recognition, and distributive justice [67,94]. These frameworks focus on decentralized power-sharing and collaborative governance, and aim to engage stakeholders in consensus-oriented decisions [93,95,96]. Alternatively, if decisions are made in a regulatory framework, decision-makers will first be faced with deciding which of the more than 50 existing frameworks will be adopted to provide lasting and just outcomes [91]. Overall, by using our derived principles and an agreed-upon decision-making framework, conservation practitioners can navigate complex decisions responsibly amid rapid technological, climatic, and conceptual change.

In summary, his body of work presents guiding principles rooted in the biological, social, cultural, and ethical considerations that guide decision-making processes about whether and when to introduce new genes and new species to address conservation challenges and combat biodiversity loss. The advent of new tools for biodiversity conservation holds the potential of both risk and promise; yet, until now, answers to the questions of how to structure bigger-picture thinking about whether and when to implement these tools have remained elusive. By synthesizing information about the suite of available tools, the dangers of both inaction and action, the regulatory frameworks governing action, and the wisdom of Indigenous perspectives on using synthetic biology for conservation, we hope to have provided a useful guide for evaluating the introduction of new genes and new species for biodiversity conservation.

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Declaration of interests

None declared by authors.

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