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Review

Direct and indirect impacts of synthetic biology on biodiversity conservation

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SUMMARY

The world's biodiversity is in crisis. Synthetic biology has the potential to transform biodiversity conservation, both directly and indirectly, in ways that are negative and positive. However, applying these biotechnology tools to environmental questions is fraught with uncertainty and could harm cultures, rights, livelihoods, and nature. Decisions about whether or not to use synthetic biology for conservation should be understood alongside the reality of ongoing biodiversity loss. In 2022, the 196 Parties to the United Nations Convention on Biological Diversity are negotiating the post-2020 Global Biodiversity Framework that will guide action by governments and other stakeholders for the next decade to conserve the worlds' biodiversity. To date, synthetic biologists, conservationists, and policy makers have operated in isolation. At this critical time, this review brings these diverse perspectives together and emerges out of the need for a balanced and inclusive examination of the potential application of these technologies to biodiversity conservation.

INTRODUCTION

The loss of Earth's biodiversity is accelerating, with species extinction proceeding a thousand times faster than baseline (Díaz et al., 2020; Pimm et al., 2014). Meanwhile, in recent years, biotechnology, in which we include synthetic biology, has emerged as a suite of techniques that enable humans to read, interpret, modify, design, and manufacture DNA segments in order to rapidly influence the forms and functions of cells and organisms. Synthetic biology applications are already changing business, industry, and medicine. In 2019, the global synthetic biology market was valued at $5.3 billion and is expected to grow to $4 trillion per year in the next 10 to 20 years (Chui et al., 2020). This fast-emerging field has great potential to reshape biodiversity conservation in myriad ways, seen and unseen, positive and negative.

Decades of conservation work have produced some major successes (Bolam et al., 2021), yet threats are accelerating, and current tools may not be able to address some emerging threats to biodiversity. The growing field of synthetic biology might be able to help conservation address some of these intractable problems. At the same time, applying synthetic biology tools to environmental questions is fraught with uncertainty and there is deep concern about potential threats to cultures, rights, livelihoods, and nature itself (Redford et al., 2014, 2019).

This complexity has permeated intergovernmental relations. In mid-2022, the 196 Parties to the United Nations Convention on Biological Diversity (CBD) are negotiating the post-2020 Global Biodiversity Framework that will guide action for the next decade by governments and other stakeholders to conserve the worlds' biodiversity. Synthetic biology has been discussed within the CBD for over 10 years (Lai et al., 2019), but as of June 2021, the sole reference to synthetic biology in the draft framework deals only with mitigating harm (https://www.cbd.int/conferences/post2020). Nevertheless, this issue is under active discussion, and there is a broad community of researchers, conservation practitioners, and policy makers who think there may be benefits of applying synthetic biology to conservation (Phelan et al., 2021). This review emerges out of the need for a balanced and inclusive examination of the application of these technologies to biodiversity conservation.

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Continued

For the purposes of this paper, synthetic biology is considered as a subset of biotechnology. While investment in synthetic biology is expanding rapidly, especially in the fields of medicine and agriculture, little of that investment is directed at applications intended for specific conservation benefits. The bulk of synthetic biology effort so far has been on products and processes that may improve industrial applications, agriculture, or human health—but these may nevertheless have significant indirect impacts on biodiversity.

Synthetic biology applications can affect conservation through a variety of existing and potential new pathways (Graphical Abstract), with both intended and unintended impacts on biodiversity (Figure 1). The tools and techniques of synthetic biology, from gene and genome editing using CRISPR-Cas9, to site-directed mutagenesis, gene synthesis, transgenesis, and gene drives, may be useful in addressing conservation challenges such as invasive alien species (Godwin et al., 2019), wildlife trade (Maloney et al., 2018; McPhee et al., 2014), and disease (Novak et al., 2018), although with the potential for serious adverse effects as well. At the same time, efforts are underway to change the production methods and raw materials used for consumer products, like Omega-3 oils (Sprague et al., 2017), vanillin (Bomgardner, 2016), and others, which may change patterns of land use and nature-based supply chains in ways that may be harmful or beneficial to biodiversity (Redford et al., 2019).

We first review synthetic biology applications designed with a direct conservation benefit in mind, and then cover those for which potential impacts on conservation are indirect. We next discuss particular environmental governance challenges posed by synthetic biology and conclude by emphasizing the importance of case-by-case decision-making for synthetic biology applications of relevance to biodiversity conservation.

DIRECT IMPACTS

Certain synthetic biology applications, if appropriately designed and implemented, have potential to advance biodiversity conservation by directly reducing threats. Although none of these applications for conservation purposes have yet been deployed in nature, significant progress is being made toward some. Development of direct approaches to date has largely focused on suppressing invasive alien species, the second biggest driver of species extinction (Bellard et al., 2016; Clavero and García-Berthou, 2005). For example, male-biased reproductive sex-ratio-engineered gene-drive approaches have been proposed to help eradicate invasive rodents from islands where current methods have significant drawbacks (Godwin et al., 2019). In a similar vein, the *Wolbachia* incompatible insect technique has been proposed as a method of controlling invasive species of mosquitoes to protect threatened Hawaiian birds from avian malaria and other diseases (Atyame et al., 2015; Mains et al., 2016; Zabalou et al., 2004).

Other applications have potential to improve species resilience to threats. For example, in another disease-related case, synthetic biology approaches have been proposed for improving resistance to sylvatic plague in the black-footed ferret (*Mustela nigripes).* Plague immunity is antibody-mediated (Hill et al., 2003), and transgenic approaches are being explored to create inheritable immunity (Novak et al., 2018). Synthetic biology solutions could potentially help increase resilience in the face of environmental threats. Coral reefs are extremely vulnerable to thermal stress caused by the climate crisis (Hughes et al., 2017), and synthetic biology approaches have been proposed to enhance thermal tolerance (Van Oppen et al., 2017), or prevent algal symbionts from becoming parasitic during heat stress (Baker et al., 2018; Blasiak et al., 2020). Additionally, it has been suggested that community or even ecosystem function and resilience could be improved through creating proxies of extinct species (''de-extinction''), although it may be practically difficult to implement (IUCN-SSC, 2016; Shapiro, 2015; Wagner et al., 2017).

Significant concerns exist that synthetic biology may cause harm to individual organisms, populations, or communities (Lander, 2015). For example, transgenes or genetic manipulations may have the potential to transfer horizontally among species causing negative impacts or unforeseen consequences (Champer et al., 2018; Science for Environment Policy, 2016; Unckless et al., 2017). Biodiversity-related reservations of this sort may be particularly relevant when target species can breed with other related species (Moro et al., 2018). Perhaps the environmental impact of greatest concern is the potential that synthetic biology approaches intended to be self-disseminating, such as engineered gene drive, might impact non-target populations (Backus and Delborne, 2019; Connolly et al., 2021). Multiple strands of research are thus exploring self-disseminating approaches that are self-limiting or controllable in other ways (Esvelt et al., 2014; Noble et al., 2019; Sudweeks et al., 2019; Willis and Burt, 2021).

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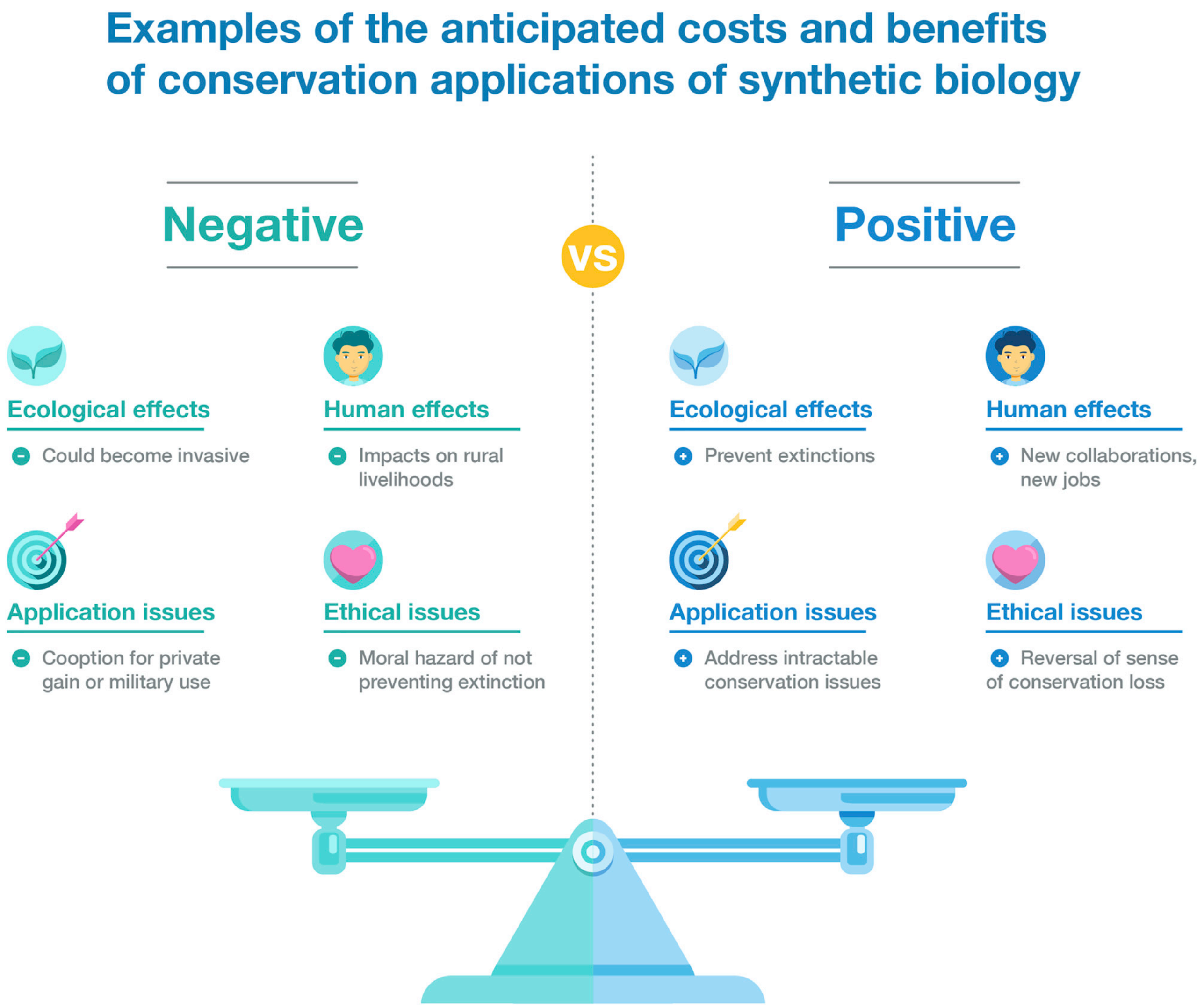

Figure 1. Examples of the anticipated costs and benefits of conservation applications of synthetic biology (adapted with permission from K.H. Redford et al., 2019)

INDIRECT IMPACTS

Most synthetic biology applications are not designed for conservation purposes, but some have the potential to have an indirect impact, either positive or negative, on biodiversity (Graphical Abstract). Agriculture is a significant factor accounting for biodiversity loss (Chaudhary et al., 2016), and one of the major sectors for investment, research, and development in synthetic biology. Agricultural challenges that are being addressed with synthetic biology include climate change (Abberton et al., 2016), soil fertility (Bender et al., 2016), plant microbiomes (Borel, 2017), photosynthesis (Bourzac, 2017), and crop nutrient content (De Steur et al., 2017). Intervening in agricultural systems, both in general and in the case of synthetic biology, can have positive or negative consequences for biodiversity (Secretariat of the Convention on Biological Diversity, 2015). Various applications have also been proposed for using synthetic biology to combat different types of agricultural pests; for example, addressing honeybee colony collapse by controlling the pathogens involved in co-infection with fungi of the genus *Nosema* and invertebrate iridescent virus (Foster and Pummill, 2011). Using synthetic biology to modify a brassica pest, the diamondback moth to control its population, has now been trialled in open field release (Shelton et al., 2020).

Many such agricultural applications are in relatively early stages of development, and clear evidence is not yet available to fully evaluate their impacts on biodiversity. Potential negative impacts on biodiversity might include transfer of genetic material to wild populations through horizontal or vertical gene transfer, toxic effects on other organisms, creation of new invasive species, increased application of agrochemicals, reduction of soil fertility and structure, and creation of crops that can tolerate previously unusable land leading to increased habitat conversion (Science for Environment Policy, 2016). Meanwhile, potential benefits to biodiversity include enhancement of decomposition rates and nutrient fixation (Good, 2018), reduction in the application of fertilizer (Cohen, 2017), more efficient production of farm animals with concomitant reductions in feed and land use (Van Eenennaam, 2017), forest restoration (Dumroese et al., 2015), and production of livestock feed based on more efficient industrial production of microbial proteins (Pikaar et al., 2018).

In addition to its applications to agriculture, synthetic biology is being applied in public health settings, where significant investment in vector control of diseases may impact biodiversity through decreased pesticide use and land use change (World Health Organization, 2020). Synthetic biology is also being applied in industrial settings, where it is used to change either production methods or raw material inputs (e.g. from petroleum to bio-based). For example, the development of a synthetic biology-based approach for detecting endotoxins could provide an alternative to the current method, which relies on the blood of threatened horseshoe crabs (Maloney et al., 2018), whose eggs in turn are a vital food source for migrating birds. In some cases, these shifts in inputs could have substantial impacts on biodiversity, which again could be positive or negative depending on whether, in the eyes of the consumer or regulatory agencies, the derived product is an actual substitute for the natural one. Thus, while synthetic biology has the potential to replace existing products derived from threatened species, shifts to a synthetic biology alternative could inadvertently increase the demand for the natural product if that is perceived as superior, a particular concern for the critically endangered rhinoceros' horn where the derived product is unlikely to be seen as a perfect substitute (Rademeyer, 2012; Redford et al., 2019).

Using synthetic biology to derive these products could reduce carbon emissions and land use, or improve nutrient cycles, and hence ameliorate biodiversity loss. For example, livestock raised for meat currently uses 30% of global ice-free terrestrial land while producing 18% of greenhouse gases, which could potentially be reduced through the production of cultured meat (Tuomisto and Joost Teixeira de Mattos, 2011). Nevertheless, global commerce could translate the production of a synthetic biology application in one part of the world into land conversion in another (Liu et al., 2013, 2015; Melillo et al., 2009), such as if an engineered yeast produces vanillin glucoside as a substitute for natural vanilla but requires feedstocks for glucose.

There are also socio-economic and regulatory uncertainties surrounding affected communities' interests in the deployment of synthetic biology tools (Delborne et al., 2020; Kofler et al., 2018; Thizy et al., 2021). For example, rising demand for synthetic biology feedstocks may also have socio-economic impacts on local communities via market shifts; for instance, if it causes fluctuations in food prices (Liu et al., 2015; Westhoff, 2010). In turn, these effects could drive changes in land use and livelihoods, potentially impacting indigenous peoples' cultural heritage as well as conservation efforts (Barnhill-Dilling and Delborne, 2019; Barnhill-Dilling et al., 2020; George et al., 2019).

Social science research and stakeholder engagement will thus play a critical role in understanding societal values around any environmental application of synthetic biology, and whether such proposed tools are acceptable for use (Barnhill-Dilling and Delborne, 2021; Delborne et al., 2020; George et al., 2019; Stirling et al., 2018; Van Mil et al., 2017). What form risk and benefit assessment guidelines take and who is involved in conducting these assessments will inform the production and synthesis of relevant evidence for decision-making. Moreover, the evidence will often depend not just on scientific rigor but also on the way that multiple perspectives and values create the context for knowledge production. Case-by-case assessments of risks and benefits of any proposed field sites and trial designs are essential (Redford et al., 2019).

IMPLICATIONS FOR SOCIETIES

The application of synthetic biology in ecosystems raises numerous governance challenges and implications, regarding risk assessment and management, liability for harm, intellectual property and ownership, and sharing of benefits. No existing international, regional, or national legal frameworks comprehensively cover synthetic biology applications, and such applications interact with a patchwork of statutory, religious, customary, and indigenous governance systems, as well as scientific norms and practices. Many existing

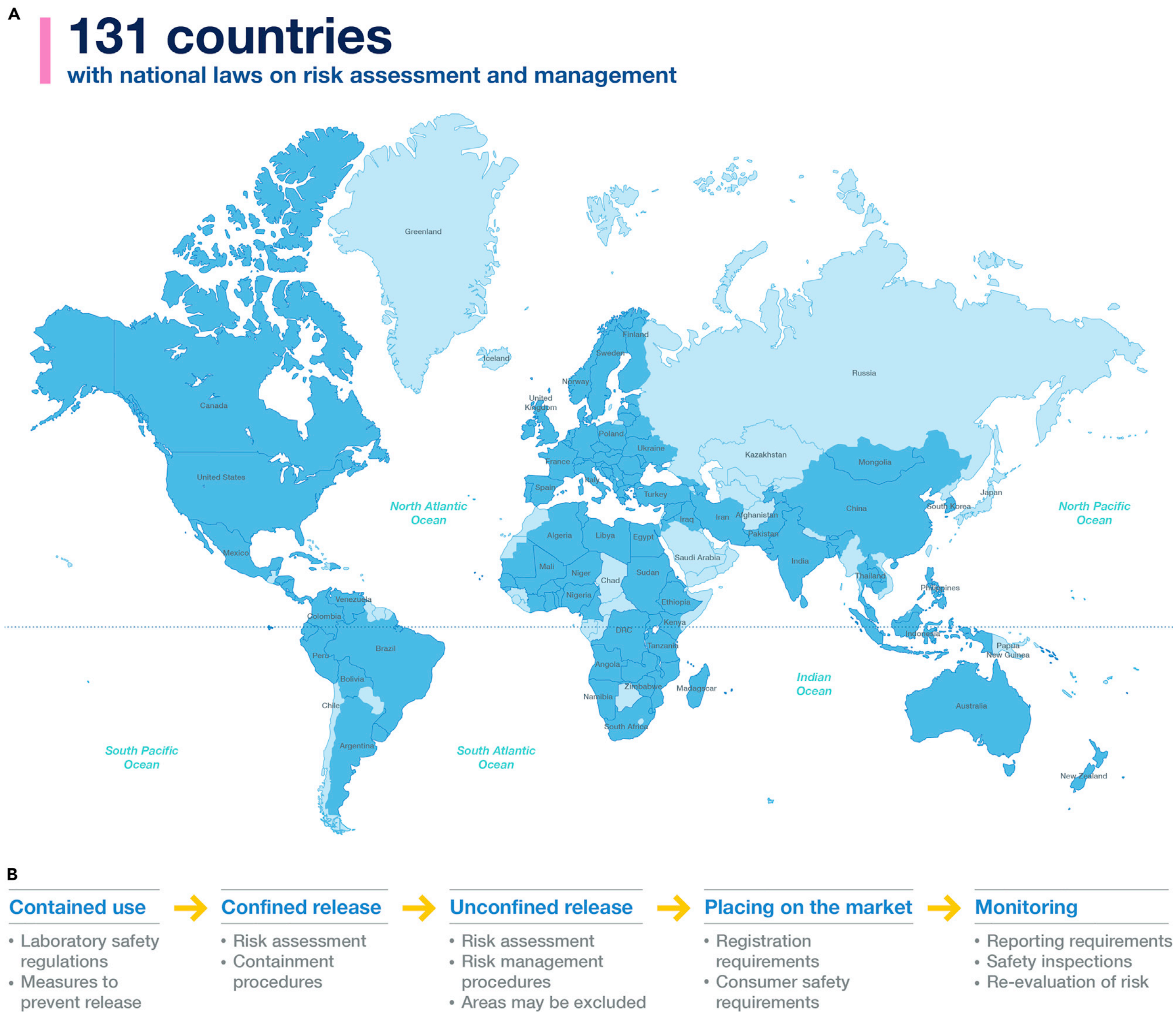

Figure 2. Global regulatory context for synthetic biology

(A) Countries with national laws on risk assessment and management related to genetically modified organisms (dark blue). The map shows those countries whose laws appear in the CBD Biosafety Clearing House or ECOLEX legal database (so lack of inclusion on this map does not necessarily mean that the country has no biosafety regulation).

(B) Typical stages in risk regulation applicable to synthetic biology (adapted with permission from K.H. Redford et al., 2019).

governance frameworks were developed in the context of the "traditional" genetic engineering of the 1990s prior to genome sequencing and may have to be revised in order to cope with challenges raised by advances in present-day synthetic biology, which spans the broad spectrum of activities across the colors of biotechnology (see e.g. DaSilva, 2004), deploying new processes, automation, and abstraction, and emphasizing genetic information rather than specimen-based genetic material (Wynberg and Laird, 2018).

Most countries have national regulatory frameworks for risk assessment and management in relation to genetically modified organisms (Figure 2A drawn from data presented in Redford et al., 2019), which are potentially applicable to synthetic biology. Such national risk-management legislation includes not only specific biosafety regulations but also legislation covering plant-breeding, food and drug safety, pesticides, toxic substances, sanitary and phytosanitary measures, and environmental protection. However, in many countries, there are extensive gaps in legal frameworks and limited capacity for regulatory oversight.

Few countries have enacted biosafety laws that could act as reference points for synthetic biology development and application, especially with respect to phases following confined release (Figure 2B). These capacity issues may limit the ability to implement global frameworks governing synthetic biology.

The risk of some applications of synthetic biology is uncertain and the consequences potentially irreversible, which would require the precautionary approach (Peterson, 2006; Wiener and Rogers, 2002). A CBD decision on synthetic biology explicitly calls for the application of the precautionary approach (https://www.cbd.int/decisions/cop/11/11/4). However, there is no consensus on what the approach dictates in terms of regulatory measures. Some organizations have argued that the precautionary approach mandates a moratorium on synthetic biology use until relevant government bodies have conducted assessments and developed international oversight mechanisms (Friends of the Earth et al., 2012). Others respond that a moratorium on synthetic biology could block beneficial advances (The Royal Society, 2018). Another perspective calls for an interpretation that allows for some, well-regulated, risk in order to manage the tension between a desire for caution regarding the risk of intervention on the one hand, and concern about the risks of non-intervention (Wareham and Nardini, 2015) and the potential economic benefits of synthetic biology applications (Kingiri and Hall, 2012) on the other. Moreover, the ethical considerations raised by synthetic biology will in turn influence the determination of acceptable risk, and the weighing of benefits and risks in decision-making (Winter, 2016a; Zetterberg and Edvardsson Björnberg, 2017).

At the global level, a number of multilateral governance mechanisms are applicable to synthetic biology. For example, Article 8 of the CBD creates obligations for its Parties to manage risks associated with living modified organisms that could have a negative impact on biological diversity (https://www.cbd.int/convention/articles/?a=cbd-08). Likewise, the United Nations Cartagena Protocol on Biosafety (https://bch.cbd.int/protocol/) and the Nagoya-Kuala Lumpur Supplementary Protocol to the CBD (https://www.cbd.int/abs) concern the safe transfer, handling, and use of living modified organisms resulting from modern biotechnology and provide rules and procedures for liability and redress. The Nagoya Protocol establishes the international framework for access to genetic resources and fair and equitable sharing of benefits resulting from their utilization.

Given the transboundary nature of synthetic biology, the United Nations Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) has established an Intersessional Working Group of the Standing Committee on "Specimens produced through biotechnology", to assess how CITES should respond if such specimens might potentially affect international trade in CITES-listed species in a way that would threaten their survival (cites.org). The international legal principle of state sovereignty and responsibility implies that States have both the right to prevent modified organisms from entering their territory and the responsibility to ensure they do not release organisms that might cause harm to the environment of another country or areas beyond national jurisdiction (UN Stockholm Declaration, https://www.un.org/en/conferences/environment/stockholm1972). Key international procedural norms such as the Aarhus Convention (https://unece.org/environment-policy/public-participation/aarhus-convention) and Escazú Agreement (https://www.cepal.org/en/escazuagreement) specify that any person has access to information about, participation in, and justice in decision-making around activities impacting biodiversity and natural resources. Furthermore, as outlined by a CBD decision (https://www.cbd.int/decisions/cop/14/31), regulation and governance of synthetic biology interacts with a variety of global and regional policies protecting indigenous peoples' rights to self-determination, free, prior, and informed consent, and inclusivity and non-discrimination (Ad Hoc Technical Expert Group on Synthetic Biology, 2017).

Statutory frameworks are not the only sources of law relevant for synthetic biology. Legally binding norms and authorities governing research and use of synthetic biology can draw from religious, indigenous, or customary systems (Subsidiary Body on Scientific, Technical and Technological Advice, 2018). A recent report explored how Māori (indigenous people of Aotearoa/New Zealand) values may be impacted by moving genes between species, the introduction of genes from non-native species, and the extraction of genetic material from organisms, concluding that the perceived benefits of the technology vary according to the intended use of the techniques (Environmental Protection Authority, 2020; Hudson et al., 2019). Several groups of indigenous peoples have developed formal statements and declarations on the topic of genetic technologies asserting, for example, the right to free, prior, and informed consent for research relating to their biological resources, and the right to restrict patenting of such resources (George et al., 2019; Mead and Ratuva, 2007).

Synthetic biology raises significant questions for existing governance systems. Genetic modification techniques that modify the genome without introducing new genetic material may fall outside the scope of existing regulations (Duensing et al., 2018). Synthetic biology applications may fall between the jurisdiction of different agencies. For example, in the United States, a modified dengue-transmitting mosquito intended to be used to reduce mosquito populations for health purposes raised questions about whether it should be regulated as an animal drug under the FDA or a pesticide under the EPA (U.S. Department of Health and Human Services Food and Drug Administration Center for Veterinary Medicine, 2017; Bergeson et al., 2015; Lin, 2017). Entirely novel organisms may not fit into risk assessment systems that are based on comparing a modified organism with a corresponding non-modified organism (National Academies of Sciences, Engineering, and Medicine, 2016; Winter, 2016b). Technologies associated with synthetic biology, such as digital sequence information, can call into question the benefit sharing arrangements developed on the basis of physical transfer of genetic material (Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources, 2018a; Bagley, 2016; Wynberg and Laird, 2018). Conversely, sharing of digital sequence information can itself be seen as a benefit, which could increase developing country researchers' ability to engage with the global biotechnology community (Ad Hoc Technical Expert Group on Digital Sequence Information on Genetic Resources, 2018b).

OUTLOOK

As the world's governments negotiate the future of biodiversity, the conservation implications of synthetic biology applications should be considered on a case-by-case basis depending on the evidence for the positive and/or negative impacts they are likely to have on any given conservation objective. The fact that one application may be beneficial or detrimental in a certain social, political, economic, and ecological context does not mean that the same technology would have the same impacts in another context. Lumping synthetic biology applications might therefore mask the complexity of the issues.

When specific applications of synthetic biology for conservation are being considered, there must be a comparison with the state of biodiversity if nothing were done and business as usual is allowed to continue. Thus, decisions about whether or not to use conservation applications of synthetic biology should be understood alongside the reality of ongoing biodiversity loss. However, the evidence necessary to provide unequivocal guidance does not yet exist, and any potential applications of synthetic biology for biodiversity conservation must be evaluated with considerable humility, due care, and appropriate plans for transparent monitoring and surveillance. To date, the communities of conservation scientists, synthetic biologists, and policy makers have operated largely in isolation from one another (Piaggio et al., 2017; Redford et al., 2014). Deeper collaboration will be necessary to both develop evidence and create the frameworks for understanding and using that evidence (Phelan et al., 2021). Such collaboration must also include civil society and use best norms and practices.

Any new and powerful technology, particularly one with the potential to touch nearly any species and ecological system anywhere in the world, challenges humanity's views on and valuations of "nature." Since parts of synthetic biology are still in their infancy, many applications for conservation benefit have an uncertain future, and societies have not decided if they will support their application. Responses to the idea of applying synthetic biology to biodiversity conservation have been forceful—both from those convinced of the likelihood of negative ecological and ethical impacts, and from those encouraged by the potential of new tools to solve intractable challenges. This strength of feeling suggests that the impact of synthetic biology on society's views of biodiversity and conservation will potentially be substantial (Redford and Adams, 2021).

Perhaps the most important cultural factor in the future relationship of synthetic biology to biodiversity conservation will be the attitudes and experiences of young people growing up now with synthetic biology as a fact of life, as well as future generations who will interact with it in ways we cannot predict. Raised in a world in which many technologies are already deployed, younger generations may not share the views of older people to whom such technologies appear novel. For example, the International Genetically Engineered Machine Competition (iGEM) began in 2004 with five teams and 31 participants. By 2019 there were 353 teams from 45 countries, and over 6,000 participants each year. All told, as of

2022, over 60,000 young people in high school and college—most under the age of 23—have participated in iGEM synthetic biology experiments. Many more have been exposed to the field through do-it-yourself biology community labs now operating around the world or through classroom experiences. The application of synthetic biology tools and technologies to conservation will no doubt remain contested, but the attitudes of people now learning about synthetic biology in college, high school biology classes and beyond, will have an increasingly powerful say in the outcome of the debate. Integrating consideration of biodiversity impacts in their technical designs may influence the future application of synthetic biology.

More generally, the way people will answer the question of how synthetic biology should intersect with biodiversity conservation will depend variously on their views on technology, science, society and risk, and their perceptions of their own future and the future of the natural world. Those complex intellectual and emotional issues are tied together by powerful stories that help people organize and make sense of the world and their place in it. As the decision-making processes regarding synthetic biology and biodiversity conservation move forward, the evidence reviewed here will become part of new narratives that will help all concerned understand the possibilities and the perils of this new suite of techniques and technologies.

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AUTHOR CONTRIBUTIONS

N.B.W.M. led the drafting of the manuscript, production of figures, and incorporation of co-author comments. J.A., E.L.B., T.M.B., J.A.D., H.E., D.E., K.M.E., B.K., T.K., M.J.O., S.P.M., L.S., R.B.S., D.T., D.M.T., and W.W. contributed text and commented on revisions. K.H.R. led conceptualization of the manuscript and contributed text and comments on revisions.

DECLARATION OF INTERESTS

L.S. is on the advisory board (unpaid) of the Modern Agriculture Foundation, an Israeli non-profit organization that supports and promotes development of alternative protein including cultured meat. J.A.D. is a leader of U.S. stakeholder engagement for the Genetic Biocontrol of Invasive Rodents (GBIRd) partnership. D.E. holds stock in Ginkgo Bioworks Inc. and Antheia Inc., and is also an unpaid Director of the BioBricks Foundation, iGEM Foundation, and BioBuilder Foundation - all charities working to advance synthetic biology for public benefit.

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