

Genetic rescue to the rescue

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Genetic rescue can increase the fitness of small, imperiled populations via immigration. A suite of studies from the past decade highlights the value of genetic rescue in increasing population fitness. Nonetheless, genetic rescue has not been widely applied to conserve many of the threatened populations that it could benefit. In this review, we highlight recent studies of genetic rescue and place it in the larger context of theoretical and empirical developments in evolutionary and conservation biology. We also propose directions to help shape future research on genetic rescue. Genetic rescue is a tool that can stem biodiversity loss more than has been appreciated, provides population resilience, and will become increasingly useful if integrated with molecular advances in population genomics.

Maintaining biodiversity and evolutionary potential

Rapid human population growth, environmental change, and habitat fragmentation all pose ever-greater threats to biodiversity and highlight the need for increasingly aggressive conservation efforts. Genetic rescue ([1] GR; see [Glossary](#)) has the potential to be one of the most powerful means to conserve small and declining populations, yet in practice, it remains controversial [2–4] and is rarely applied. The debate centers on whether the translocation of individuals or alleles into small, imperiled populations will have the desired effect of increasing population growth rates and maintaining a diverse array of local populations, or reduce population fitness through outbreeding depression and decrease biodiversity by homogenizing distinct gene pools. In this review, we clarify GR among a proliferation of related concepts, review work done since a comprehensive review [5] on the topic 10 years previously, and identify future directions for research and application.

What is genetic rescue?

GR is an increase in population fitness inferred from some demographic vital rate or phenotypic trait, by more than can be attributed to the demographic contribution of immigrants [5]. The top priority for preventing the extinction of small

and imperiled populations is to reduce extinction risk by increasing their absolute fitness, measured by an increase in population size or growth rate [6,7]. GR is especially useful for management and conservation because it induces a population-level demographic response to the introduction of new, beneficial alleles via prescribed gene flow ([Box 1](#)).

GR focuses on restoring genetic diversity and increasing fitness in small populations that are isolated and typically, but not necessarily, suffering from inbreeding effects (see [Figure 1A](#) in [Box 1](#)). GR can occur through heterosis or adaptive evolution. Heterosis occurs from GR when fitter hybrid offspring from matings between residents and immigrants increase demographic vital rates relative to the original population. Adaptive evolution can also increase population vital rates with a shift towards an optimal phenotype due to selection on newly introduced or recombinant genotypes. For example, small plant populations with only one self-incompatibility allele, so called *S*-alleles, cannot reproduce successfully [8]. An infusion of new *S*-alleles into this type of population would likely lead to an adaptive increase in the frequency of introduced *S*-alleles and an increased population growth rate. This restoration of population fitness would qualify as GR, even though alleviation of inbreeding depression was not the mechanism responsible.

Glossary

Absolute fitness: mean number of offspring per capita, measured as population growth rate (λ) or abundance (N).

Adaptive evolution: an increase in beneficial phenotypes in a population as a result of natural selection on genetic variation.

Adaptive management: a structured, iterative process of decision-making that includes system monitoring to reduce uncertainty.

Assisted gene flow: managed movement of individuals into populations to reduce local maladaptation to climate or other environmental change.

Epistatic load: combinations of alleles at different loci that reduce fitness.

Evolutionary rescue: an increase in population growth resulting from adaptation to otherwise extinction-causing environmental stress from standing genetic variation, *de novo* mutation or gene flow.

Genetic load: the relative difference in fitness between the theoretically fittest genotype and the average genotype in a population. Caused by deleterious alleles in the case of mutational load. Other types of load include segregation, drift, epistatic, and migration.

Genetic rescue: an increase in population fitness (growth) owing to immigration of new alleles.

Genetic restoration: an increase in genetic variation and relative, but not absolute, fitness owing to immigration of new alleles.

Heterosis: elevated fitness of offspring from matings between genetically divergent individuals.

Invasive hybridization: cross-breeding between invasive and native species.

Outbreeding depression: reduced fitness of offspring from matings between genetically divergent individuals.

Transgressive hybridization: the creation of hybrids with phenotypes more extreme than their parental lines.

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Box 1. Genetic rescue and related concepts

Small populations in need of genetic rescue have low genetic variation, low fitness, and low phenotypic variation (Figure 1A). Successful GR involves an increase in abundance, reflecting an increase in absolute fitness of the small population (Figure 1B). Admixture and increased individual (relative) fitness of admixed individuals (a shift towards a locally adaptive peak), but a lack of increased population growth result in genetic restoration (Figure 1C, distribution I), not GR. For Isle Royale wolves, the infusion of genetic variation increased individual fitness metrics and slowed population decline whereas other factors, such as deteriorating environmental conditions, prevented the population from expanding [11]. Another potential outcome is that too much gene flow leads to extensive hybridization (swamping), in which case the population moves away from the adaptive peak, and abundance remains low (Figure 1C, distribution II). GR with too much gene flow can resemble potential negative effects of invasive hybridization [57]

A closely related term to GR is assisted gene flow (AGF; [53]). Aitken and Whitlock [53] defined AGF as the managed movement of individuals or gametes between populations within species ranges to mitigate local maladaptation in the short and long term. AGF differs from GR in the emphasis placed on the introduction of alleles and genotypes that are pre-adapted to new (altered) local climates (Figure 1D [53]). To demonstrate this difference, we assume that environmental change (shift from gray to black fitness function in Figure 1D) causes a formerly locally adapted population to be maladapted and shrink in abundance (black distribution; Figure 1D). GR prescribes the addition of individuals from matched current environments, such that restored genetic diversity, alleviated inbreeding depression, and a subsequent adaptive response enable population growth (red distribution in Figure 1D). Source populations for AGF are chosen such that their historical environments are similar to the already changed environment in Figure 1D (black fitness function). A major challenge for implementation of AGF will be meeting the necessary high degree of understanding of local adaptation to past and future conditions, as well as overcoming the enhanced probability of outbreeding depression that comes from choosing geographically distant but potentially climate-matching sources of gene flow [53,56]. Evolutionary rescue (ER) involves the same distribution shift, but ER would rely on standing genetic

variation, *de novo* mutation, or immigration. For isolated populations with low genetic diversity and high inbreeding coefficients, ER is unlikely to be successful without external input of genetic diversity [9].

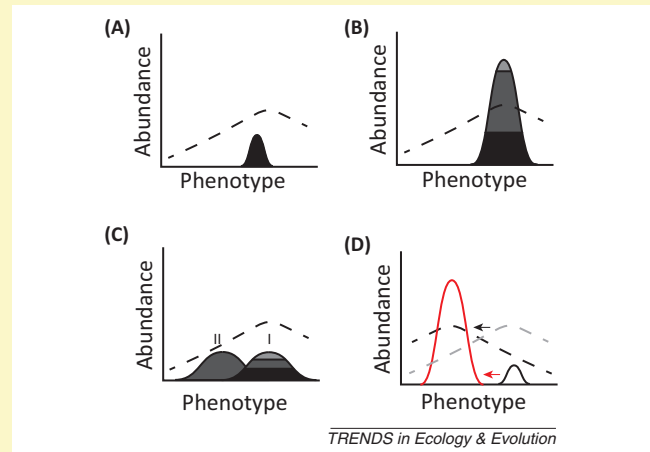


Figure 1. The fitness of individuals with a given phenotype is shown by the relation between the distribution of phenotypes (numbers of individuals or abundance) and the fitness function (broken lines) for a given environment. (A) represents a small, imperiled population with reduced phenotypic and genetic variation that could benefit from genetic rescue. (B) represents successful genetic rescue, with an increase in fitness following prescribed gene flow. (C) represents genetic restoration (distribution I) or genetic swamping (distribution II). Shown in (A), (B), and (C) are recipient (black), donor (light gray), and admixed (gray) genomes. Both (B,C) show the hypothetical outcome of human-mediated gene flow a short period (approximately five generations) following initiation. The size of shaded areas is meant as a heuristic guide and will vary case-by-case. An environmental shift in (D) is shown by a shift in the peak of the original fitness function (gray broken line) to the left (black broken line; shift shown with black arrow). The black distribution shows a population now maladapted and at low abundance following the environmental change (black distribution). The red arrow shows the desired extirpation-avoiding shift in population phenotype and abundance (red distribution) following assisted gene flow.

The important outcome for GR is that gene flow leads to an increase in population growth rate above and beyond the demographic effect of immigrants. Whether the growth occurs as a result of heterosis or adaptive evolution is often difficult to distinguish in wild populations because it requires careful experimental matings.

GR is related to, but distinct from, a recent surge of related terminology that surrounds growing empirical evidence that populations can respond rapidly to natural selection following the addition of genetic variation from mutation or gene flow [9,10] (Box 1). For example, it is possible for gene flow to restore levels of genetic variation, but not increase population growth (genetic restoration; Box 1) [11,12]. GR is particularly closely related to the concept of evolutionary rescue (ER), which has been defined as an adaptation-dependent reversal of demographic decline due to maladaptation to novel environmental conditions [9,10]. ER emphasizes the demographic benefits of genetic variation, regardless of whether the source of variation is immigration or arises within a population by *de novo* mutation or recombination of existing variation. ER also requires an environmental shift and rescue from extinction must occur via adaptive evolution to that changed environment [10].

Our definition of GR is the same as some previous definitions [5], but differs from definitions that restrict GR to solely focusing on alleviation of inbreeding depression

[10]. Although there is broad overlap between our definition of GR and ER when caused by immigration, ER (with immigration) is arguably more restrictive than GR because of ER's dependence on adaptive response to a shifting environment. In the *S*-allele example, the adaptive shift in *S*-allele frequencies would not qualify as ER because the adaptive change was not related to an environmental shift. ER spurred by extant genetic variation or mutation is unlikely to prevent extinction in small, genetically depauperate populations because they are unlikely to have sufficient genetic variation to adapt to new environmental conditions [9]. When small, extinction-prone populations are the focus, immigration (in many cases human mediated) is likely to be necessary to provide sufficient genetic variation on which selection can act and result in population growth [13]. Given the broad overlap between ER (with immigration) and GR (as defined here) when applied to small populations of conservation concern, we suggest that there are many opportunities for enhanced understanding and cross-collaborations among researchers working on these concepts.

Ten years of genetic rescue studies

Tests based on outcrossing experiments

An important point is that GR rests *not* upon outcrossing large numbers of individuals, but upon the introgression of

beneficial genetic variation from a small number of immigrants so that locally adaptive variation is not swamped [2,5]. In theory, low levels of immigration should be adequate to decrease the frequency of deleterious alleles and provide increased genetic variation for selection to act upon, leading to increased population fitness. By contrast, most experiments use large numbers of outcrosses, which increases the odds of finding an effect of outcrossing (Table S1 in the supplementary material online). Nonetheless, general patterns that emerge from outcrossing experiments remain relevant to GR. Many experiments have tested the relative fitness effects of outcrossing large numbers of individuals in the past 10 years (Table S1). Although outbreeding depression is a threat to locally adapted populations [3–5], outcrossing tends to boost molecular genetic variation and mean individual fitness-related traits for individuals, particularly those from inbred populations [14–20] (Table S1). While this relative fitness boost following outcrossing is not universal for all traits, individuals, and populations, it is often found when measured across multiple traits, individuals, and populations (Table S1).

Most studies have tracked the relative fitness of a large number of hybrids for one generation (F_1), leaving the longer-term effects of small amounts of outcrossing relatively untested (Table S1). In some recent cases, fitness benefits have been found beyond the first generation, suggesting that outbreeding depression should not be as much of a concern, and that selection on new recombinant genotypes can be more beneficial than was previously thought [21,22]. For example, outcrossing individuals of the rare buttercup *Ranunculus reptans* led to mean fitness boosts through the F_2 generation, especially for individuals from small populations [22]. *Drosophila* populations showed increased viability five and 10 generations after

a prescribed gene flow event, even though immigrants were from inbred sources [18]. Outcrossed copepod (*Tigriopus californicus*) and pea (*Chamaecrista fasciculata*) populations also showed elevated fitness relative to control populations several generations following outcrossing, because of selection on recombinant genotypes [21,23].

Tests based on small numbers of immigrants

Increased within-population genetic variation has been observed following translocations or natural immigration of small numbers of individuals into wild populations [20,24–29]. Adding individuals or alleles into isolated populations across a range of taxa and life histories has led to increases in fitness-related traits [18–20,24–26,28,30–33]. These boosts can be especially dramatic when the source population is large and the target population is small and inbred [19,30], exactly the conditions under which GR should be most effective. The next step of quantifying the absolute fitness effect of limited immigration across multiple generations is difficult for most wild populations, especially for species with generation lengths of many years [16]. Furthermore, it is difficult to replicate GR among populations with experimental controls that allow one to isolate relative and absolute fitness effects of small amounts of gene flow and infer causation with adequate statistical power.

Our literature search revealed that studies that have rigorously tested for absolute fitness effects of low levels of migration across generations remain rare (18 sets of crossing experiments or monitored immigration events involving 15 species; Table 1). The majority (14/18; 78%) of these sets of crossing experiments or monitored immigration events showed either positive ($n = 10$) or a mix of positive and no ('N') ($n = 4$) absolute fitness effects (Table 1). For the latter, studies tended to find positive relative fitness effects

Table 1. Summary of studies that report absolute fitness effects of gene flow^a

Species	Study type ^b	No. of migrants	Length ^c	Absolute fitness metric	Absolute fitness effect ^d	Refs	
Common name	Latin name						
Bacteria	<i>Pseudomonas pseudoalcaligenes</i>	exp	phage insertions	not measured	population size	+	[58]
Beach clustervine	<i>Jacquemontia reclinata</i>	exp	crosses	F1	population growth rate	+/N	[59]
Flour beetle	<i>Tribolium castaneum</i>	exp	20–45	F1–F24	population growth rate	+/N	[60]
Guppy	<i>Poecilia reticulata</i>	exp	2	F1	population size	+	[16]
Hoary sunray	<i>Leucochrysum albicans</i>	exp	crosses	F1	population size	+/N	[61]
Marine copepod	<i>Tigriopus californicus</i>	exp	crosses	F1–F20	population size	+	[23]
Marine copepod	<i>Tigriopus californicus</i>	exp	crosses	F1–F20	population size	–	[35]
Wood rat	<i>Neotoma magister</i>	exp	10	F1	population size	+	[39]
Yeast	<i>Saccharomyces cerevisiae</i>	exp	crosses	F1	population growth rate	+/-	[62]
Yeast	<i>Cryptococcus neoformans</i>	exp	crosses	unknown	colony size	N	[63]
Adder	<i>Vipera berus</i>	obs	20	F1	population size	+	[36,37]
Bighorn sheep	<i>Ovis canadensis</i>	obs	15	F2	population size	+	[24,27]
Florida panther	<i>Puma concolor coryi</i>	obs	8	F2	population size	+	[26]
Gray wolf	<i>Canis lupus</i>	obs	1	F2	population size	N	[11]
Mexican wolf	<i>Canis lupus baileyi</i>	obs	crosses	F1	population size	N	[34]
Prairie chicken	<i>Tympanuchus cupido</i>	obs	271	F6	population size	+	[25,38]
Scandinavian wolf	<i>Canis lupus</i>	obs	1	F2	population size	+	[64]

^aAll studies reported in [5] that measured absolute fitness and studies since 2004 that meet our search criteria (Table S1) and measured absolute fitness. Each row corresponds to a separate set of experimental crosses or an immigration event with the number of migrants shown.

^bAbbreviations: Exp, experimental; Obs, observational.

^cStudy length in generations following immigration or crossing.

^dMeasured fitness effect as beneficial (+), negative (–), or none (N).

Box 2. Insights from the Florida panther

Of all the studies of imperiled charismatic species, perhaps the best-known case of immigration and subsequent fitness rebound is that of the Florida panther [Figure 1](#). Several important fitness-related traits, molecular genetic variation, and abundance rebounded in the previously highly inbred population of approximately 22 Florida panthers, following the translocation of eight panthers from Texas [\[26\]](#). Individual panthers with greater admixture showed higher survival than purebred residents, the population tripled in size, and morphological correlates of inbreeding declined after the translocation effort. Detailed and rigorous demographic analyses suggest that an annual population growth rate of 4% replaced a 5% population decline following translocation, resulting from higher survival of admixed F_1 individuals [\[28\]](#). All told, this GR effort was a success.

As a consequence of the overwhelming success of GR for Florida panthers, habitat loss because of development in the north of the state and sea level rise in the south will remain the primary concern into the near future [\[26,28,65\]](#). Despite recent rapid population growth, a failure to escape small population size in the near future seems likely to return the population to high levels of inbreeding, and require another GR attempt [\[18,66\]](#). This potential for a cycle of inbreeding depression at limited population size, followed by fitness (demographic) decline, and subsequent GR, recalls the original extinction vortex [\[6\]](#), except that extinction is temporarily avoided

via GR. The only way out of this intensive management cycle is to add habitat and populations with gene flow among them.



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Figure 1. Florida panthers have recently shown positive demographic responses to gene flow, including greater survival and population growth.

following crossing or immigration that did not translate to a population-level response, consistent with what we define as genetic restoration. Genetic restoration was also observed in two of the three studies categorized solely as ‘N’ [\[11,34\]](#). Only one study reported a negative absolute fitness response (outbreeding depression) [\[35\]](#). This study is noteworthy because the authors chose populations that would be nearly incompatible and were highly genetically divergent [21% sequence divergence at the *cytochrome oxidase I* (*COI*) gene]. Populations this divergent would be unlikely to be considered for GR.

Intensive studies of single populations of charismatic megafauna provide some of the examples of favorable population-level fitness responses to low levels of immigration [\[24–26,29,36–39\]](#) ([Table 1](#)). High-profile recent examples include increased genetic variation and population growth responses to translocations of individuals into Florida panther *Felis concolor coryi* [\[26\]](#) ([Box 2](#)) and Rocky Mountain bighorn sheep *Ovis canadensis* [\[24,27\]](#) populations. Hybrid offspring from immigrant \times resident crosses had higher measures of genetic variation and superior fitness that led to increases in demographic rates and absolute population fitness. In the case of the Florida panther, genetic, ecological, and demographic studies have been exhaustive and encouraging ([Box 2](#)). The downside of all unreplicated and uncontrolled studies of single populations is that assigning definitive causal relations is impossible [\[40\]](#). For example, increases in population growth could be the result of favorable environmental factors. However, these studies provide high media exposure examples that, when analyzed collectively for the demographic and genetics insights that they provide, suggest that GR is a powerful means to support small, imperiled populations and could be employed more widely. They also imply that GR has repercussions beyond population dynamics to affect ecosystem dynamics, if GR can save ecologically important species such as top predators ([Box 3](#)).

The ability to follow the population-level fitness consequences of immigration for many generations across

replicate treatment and control populations highlights the value of experimental studies of GR in lab species with short generation times ([Box 4](#)). For example, inbred fruit fly (*Drosophila melanogaster*) populations showed increased viability several generations following a 10% immigration event, though this study did not estimate absolute fitness [\[18\]](#). Inbred guppy (*Poecilia reticulata*) populations exhibited more complicated sex-specific responses to immigration, but populations that received immigrants, whether male or female grew faster compared with control populations without immigration [\[16\]](#). Different population growth responses depending upon the sex of the immigrants suggests that not all immigrants are equal, and emphasizes that specific life histories and context-specific considerations must be made to maximize the benefits and minimize the risks of GR [\[3,5,41\]](#).

Threats from outbreeding depression

Among the primary concerns with GR attempts is outbreeding depression. This has a sound theoretical and empirical basis [\[3,18,35,42,43\]](#), but the pendulum appears to be swinging away from these concerns in light of evidence that re-establishing gene flow among relatively recently connected populations will often increase fitness [\[4,22,23\]](#). Although genomics is improving our ability to characterize the genetic basis of adaptation (see below), a general rule is that outbreeding depression risk generally increases with genetic, geographic, and environmental distance because these are hopeful surrogates for adaptive differences that can be difficult to determine [\[3,4,43\]](#). Most empirical examples of outbreeding depression occur when populations are geographically distant and genetically divergent (e.g., *Tigriopus californicus* populations [\[23,35\]](#)), or when life history or phenological differences are large). Crosses between domestic and wild individuals also often result in negative fitness consequences for hybrid offspring (e.g., [\[44\]](#)), especially when fitness is measured in the wild. Ideally, small numbers of immigrants

Box 3. Multilevel 'eco-evo' processes via genetic rescue

Successful genetic rescue inevitably increases genetic diversity, should generally increase effective population size (N_e) and, by our definition, also increases population size (N). Ideally, simultaneous changes in genetic and demographic trajectories following genetic rescue bolster the chances for imperiled populations to persist (Figure 1A). Yet another potential outcome of successful GR is the maintenance of community processes, also through genetic and demographic factors (Figure 1B). The increase in genetic variation attributed to GR can provide or restore individual variation in traits, such as resource use, behavior, or morphology, that contribute to the functional role of that species within its community. Furthermore, demographic patterns of coexisting species are known to co-vary, most famously through predator-prey dynamics. By increasing the abundance of potentially key players in such dynamics, genetic rescue could diminish the risk of trophic collapse [67].

Monitoring community-level responses to the implementation of genetic rescue could add to the argument for its use as an effective management tool or, alternatively, highlight cases where genetic rescue increases fitness for the target species but disrupts the community in other ways. Unfortunately, even when population and community dynamics are well studied, the use of GR as a management tool may be rejected. This appears to be the case in the recent management decision not to augment the isolated and inbred Isle Royale wolf population even though moose herds have increased in size as wolf abundance has declined, and wolf inbreeding coefficients and bone deformities have increased [11,12,68]. This may well turn out to be a missed opportunity to save this imperiled population from extinction.

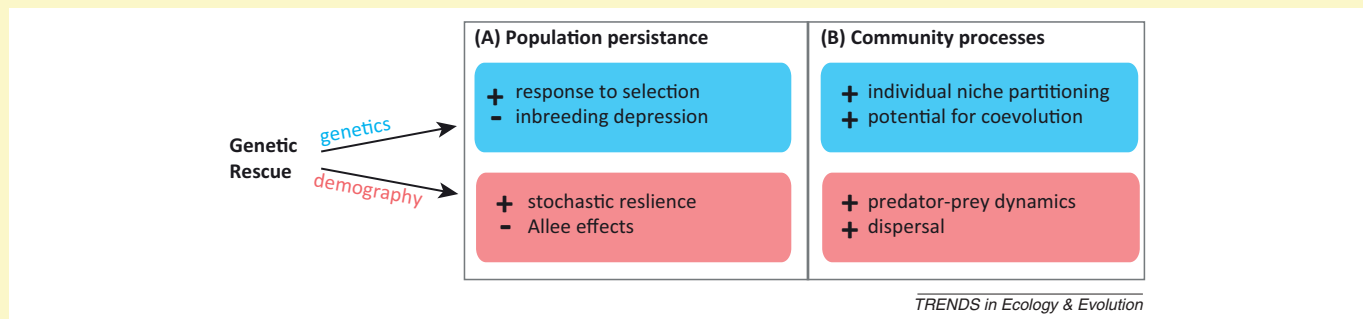


Figure 1. The benefits of genetic rescue include an increase in genetic diversity and an increase in abundance of individuals. Positive effects of genetic rescue on population persistence (A) can propagate to influence community processes (B).

chosen for GR will originate from other wild populations that experience environmental conditions that are best matched to the recipient environment.

The mechanisms underlying GR and outbreeding depression may have different implications for the ultimate long-term effects of gene flow on population fitness. Although teasing apart the mechanisms is difficult and often not possible in management scenarios, heterosis and adaptive evolution operate dynamically on different time frames. Heterosis is maximized in the F_1 generation,

whereas adaptive evolution typically requires from several to many generations. This reinforces the need to test for effects of GR over multiple generations. An initial increase in fitness of early-generation hybrids may not persist over multiple generations if co-adapted gene complexes are broken apart through recombination. Additionally, initially maladapted immigrants could reduce population fitness or introduce deleterious alleles that rise to high frequency [2]. In these situations, the optimal outcome is for selection and recombination to facilitate GR over time

Box 4. Elegant experiments

Experimental studies have tested GR for multiple generations under controlled conditions. The ability to follow the effects of immigration over multiple generations for many replicate populations is highlighted by a study of a rare perennial plant *Rutidosia leptorrhynchoidea* (Asteraceae) by Pickup and Field [30]. They performed 2455 experimental crosses between 12 population pairs (only 15 populations of this species remain) and reared F_1 , F_2 , F_3 , and backcrosses in a greenhouse. Populations were <1–600 km apart along a north–south gradient. Inbreeding, genetic diversity, and size of the source population best predicted heterosis across fitness components. Furthermore, heterosis was greater when the donor populations were large with high genetic diversity and low inbreeding and the recipient population was small and inbred. Interestingly, there was no evidence of outbreeding depression. Geographic distance among sites was not an important predictor of fitness. However, this study did not explicitly take into account genetic or adaptive divergence between crossed populations.

In another experimental study of immigration, Hwang *et al.* [23] examined controlled crosses (F_1 – F_3) and long term (15 months or approximately 20 generations) freely mating experimental hybrid populations of the copepod (*Tigriopus californicus*). Earlier work for this species demonstrated high F_1 hybrid fitness followed by

outbreeding depression in the F_2 , possibly because of drift-induced high genetic load (accumulation of deleterious recessive alleles) and epistatic load (accumulation of maladaptive allele combinations). A series of controlled crosses matched a pattern of outbreeding depression in the F_2 followed by recovery in the F_3 . Of experimental hybrid populations (50:50 or 80:20) surviving to 15 months ($N = 6$), half had at least a 12-fold greater abundance compared with surviving midparent treatments. The surviving freely mating and highly introgressed experimental populations showed fitness declines at 3 months followed by recovery and higher fitness than midparents by 15 months (20 generations), because of selection on recombinant genotypes. These results suggest that, given large enough population sizes, recombination and selection within hybrid populations can allow recovery from early outbreeding depression. A companion study [35] showed decreased fitness following experimental mixing of two more genetically divergent populations, demonstrating the need to take into account genetic divergence of the recipient and donor sources. Interestingly, this work suggests that morphological and fitness outcomes of crosses are difficult to predict in crosses where genetic drift has a large role (compared with more repeatable/predictable results from crosses in large effective populations [45]).

following immigration events. Furthermore, transgressive hybridization could produce individuals with new genetic combinations and outlier phenotypes that facilitate expansion into a new ecological niche, especially as environments shift with climate change [45,46]. It seems likely that concerns about outbreeding depression have limited efforts to use GR as a management tool, but practical guidelines for GR application have been created that should reduce uncertainty about when it is appropriate and facilitate its proper use [41].

Genetic rescue in the genomics era

How will genomics improve implementation of genetic rescue?

Over the past decade, genomics has revolutionized the life sciences. The combination of massive amounts of genomic data [e.g., single nucleotide polymorphism (SNP) genotypes from thousands to millions of loci] and the computational tools to analyze these data is rapidly improving our ability to address long-standing questions in evolution, ecology, and conservation. The subfield of GR is no exception. In this section, we focus on two ways in which genomics will improve the implementation and effectiveness of GR: (i) via improving the identification of the best source populations and even the best individuals to use for GR; and (ii) via improving our ability to monitor the outcome of GR attempts so that managers can adjust strategies as necessary.

Identification of the best source population for genetic rescue using genomics

One way in which genomics will increase the effectiveness of GR is by identifying which potential source populations are most likely to have the desired effect of increasing fitness and population growth rate in the declining target population. It is helpful to know the level of adaptive divergence between candidate source populations and the target population to predict the risk of outbreeding depression. However, characterizing adaptive divergence can be difficult or impossible for species of conservation concern using traditional approaches such as reciprocal transplant experiments.

Genomics now enables characterization of adaptive differentiation in species for which reciprocal transplant experiments are not practical [47,48]. In particular, by using genome scans with thousands of SNP loci, high F_{ST} outliers can be identified that are adaptive or linked to adaptive loci [49–52]. These loci can then be used to estimate how adaptively divergent various potential source populations are from the target population using various analyses, such as population dendrograms, multivariate approaches, or clustering algorithms [48]. To minimize outbreeding depression, the population with the lowest level of adaptive differentiation from the target population would be chosen. Alternatively, from the perspective of assisted gene flow, the goal would be to choose individuals from an adaptively divergent source population that has alleles predicted to be adaptive under future environmental conditions in the target population [53]. This may be a viable strategy for organisms with large populations and high fecundity (e.g., some forest

trees), because inbreeding rates should be low and selection can overwhelm genetic drift. However, for small and isolated populations, it may be more effective to alleviate inbreeding depression by introducing immigrants adapted to the current environment, so that the population will persist and grow, thereby increasing the potential for adaptation to future environmental change. More work is needed to learn how best to use outlier loci and other adaptive loci to characterize adaptive differentiation, but early results suggest that this approach has potential [48,54].

Identification of the best source individuals for genetic rescue using genomics

Once a source population is chosen for GR, genomics will also help identify which individuals are most likely to reduce inbreeding depression and thereby increase fitness and population growth rates in the target population. Importantly, all individuals in the source population are not necessarily equal in terms of their capacity to reduce inbreeding depression in the target population. Some individuals will have more alleles predicted to reduce inbreeding depression, for example by masking the deleterious recessive alleles fixed in individuals in the target population [47]. However, knowing which alleles and, therefore, which individuals, will reduce inbreeding depression first requires understanding the genetic basis of inbreeding depression in the target population.

With genomics, it is possible to select individuals with the highest genome-wide diversity or to link fitness to specific alleles and genotypes at thousands of loci across the genome, for example using association mapping [47]. Once the main loci underlying inbreeding depression are identified, it would then be possible to screen potential source individuals at these loci to identify those individuals with the combination of alleles at multiple loci predicted to reduce inbreeding depression the most. Hand picking source individuals for genetic rescue based on their genotypes will be particularly effective in cases in which inbreeding depression is primarily determined by relatively few loci of large effect. However, given that inbreeding depression can be caused by any number of loci that influence survival or reproduction, we might find that many loci of small effect are responsible for reduced fitness with inbreeding. In this case, it may prove difficult to perform this type of screening for organisms of conservation concern. Furthermore, other nongenetic factors will also need to be considered when choosing individuals for GR, such as their sex, age, and reproductive potential. However, if possible, picking individuals with genotypes predicted to reduce inbreeding depression the most could improve the effectiveness of genetic rescue.

Recently, it has been suggested that alleles predicted to reduce inbreeding depression could be transgenically added to individuals suffering from inbreeding depression [55]. Many technical hurdles must be overcome before this will be feasible and affordable. Thus for now, we recommend focusing on identifying and introducing individuals with the combination of alleles predicted to reduce inbreeding depression the most.

Monitoring the outcome of genetic rescue using genomics

Once genetic rescue has been implemented, genomics will also have a key role in monitoring the outcome. In particular, genomics can be used to characterize the spread of immigrant alleles in the target population, determine which immigrants contribute the most to population growth, and determine which immigrant alleles have the greatest effect on fitness. In this sense, genomic monitoring can be used to test predictions about which individuals and alleles have the greatest positive effect on fitness and population growth. For example, genomics has already been used effectively to assess the effects of genetic rescue on a population of bighorn sheep at the National Bison Range in Montana, USA [27]. The authors found that individuals with a greater proportion of immigrant alleles had higher fitness. In addition, they found that the extent of introgression of immigrant alleles was heterogeneous across the genome and that 30 loci had effects on fitness above and beyond that predicted by overall levels of introgression. This information could be used in future genetic rescue efforts to choose source individuals with alleles that had a disproportionate positive effect on fitness, as well as contribute to overall understanding of the efficacy of GR. The application of genomics to GR will become more feasible as genomics costs decline, but costs remain a barrier to widespread use of genomics in conservation.

Future directions for genetic rescue research and implementation

We might never have answers to all of the many complicated evolutionary and ecological questions that surround GR. Given the rates at which populations are going extinct, there is a need to test and use GR more aggressively in applied conservation efforts. Recent results suggest GR to be a more promising but underused tool than was previously appreciated. GR can be directed by several useful guidelines that are available to minimize the risks and maximize the benefits of using immigration to facilitate GR [3,4,41,56]. The use of genomic tools to identify GR sources and monitor the introgression of important genetic variants into target populations will also provide invaluable insights for management and basic research. The wisest approach would be to use GR in an adaptive management framework where it can be used to inform future species conservation decisions and land management planning. GR may not save imperiled populations over the long term (ultimately, sufficient habitat is required for that), but recent results show that GR can buy time by improving their fitness and increasing population sizes in the short term.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tree.2014.10.009>.

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