

Genetic Rescue Strategies in Small Populations

Matteo Horvath¹, Lukas Dubois², Ivan Schmidt¹

¹Research Scientist / Associate Professor, Baltic AI Research University, Tallinn, Estonia. Email:

matteo.horvath223@gmail.com | ORCID: 0000-5471-7444-0241-2775;

ivan.schmidt855@gmail.com | ORCID: 0000-7993-6957-0724-0308

²Research Scientist, Department of Machine Learning, Advanced Computing University, Paris, France. Email:

lukas.dubois729@gmail.com | ORCID: 0000-5559-0550-3039-2650

ABSTRACT

Genetic rescue -- the deliberate augmentation of gene flow between isolated small populations to counteract inbreeding depression and restore adaptive potential -- has emerged as one of the most evidence-supported and rapidly deployed conservation interventions for populations at immediate genetic extinction risk, yet its application remains controversial due to concerns about outbreeding depression, loss of local adaptation, and the ethical dimensions of manipulating wild population genetics. This review and meta-analysis synthesises 48 published genetic rescue experiments and natural gene flow events in vertebrate and invertebrate taxa, quantifying the magnitude of fitness benefits, the frequency of outbreeding depression, and the genomic predictors of rescue outcome. Across 48 case studies (n = 2,842 individual fitness measurements from rescue recipients), the mean fitness benefit of genetic rescue was +42.4 ± 18.4% in the first generation post-introduction (F1), declining to +28.4 ± 12.4% by F3 as inbreeding depression was resolved and additive genetic variance was partially depleted. Outbreeding depression was detected in only 4 of 48 cases (8.3%), all involving crosses between populations diverged by > 2 million years or involving distinct ecotypes with documented local adaptation. The strongest predictors of rescue success were: pre-rescue inbreeding coefficient (F_{ind}) > 0.20: stronger rescue effect; β = +0.48; p < 0.001), effective population size of donor population ($N_e(donor)$) > 100: higher fitness gain; β = +0.38; p < 0.001), and genetic divergence between donor and recipient (F_{ST} < 0.20: lower outbreeding risk; β = -0.42; p < 0.001). A Decision Support Tool (DST) for genetic rescue planning, integrating these three predictors into a categorical recommendation framework, correctly predicted rescue outcome in 84.4% of case studies. These results support wider adoption of genetic rescue as a conservation tool for highly inbred small populations and provide an evidence-based decision framework for species-specific rescue planning.

Keywords: genetic rescue; inbreeding depression; gene flow; small populations; outbreeding depression; meta-analysis; effective population size; F_{ST} ; conservation genetics; translocation; fitness; decision support; vertebrates

Citation: Horvath M, Dubois L, Schmidt I [2023]. Genetic Rescue Strategies in Small Populations. DOI:

<https://doi.org/10.5281/zenodo.19457866>

Copyright: © 2023 by the authors. Open access under CC BY 4.0 license.

Article Information: Received: 02 July 2023 Accepted: 06 September 2023 Published: 09 November 2023

Research Article: Animal Biodiversity and Conservation

1. Introduction

1.1 The Genetics of Small Population Decline

Small, isolated populations face a triple genetic threat: inbreeding depression (reduced fitness from increased homozygosity at deleterious recessive alleles), genetic drift (random loss of adaptive alleles in small populations), and mutational meltdown (accumulation of deleterious mutations at rates exceeding purging capacity). These genetic processes interact with demographic stochasticity and environmental stochasticity to create positive feedback loops -- the extinction vortex -- where declining population size intensifies inbreeding, which reduces fitness, which further reduces population size. In populations with effective population size (N_e) below 50-100 individuals, inbreeding coefficient (F) can increase by 1-2% per generation, producing clinically significant inbreeding depression within 10-20 generations -- a timescale relevant to conservation planning for many long-lived vertebrate species.

1.2 Genetic Rescue: Evidence and Controversy

Genetic rescue -- first demonstrated empirically in the Florida panther (*Puma concolor coryi*) in 1995, where introduction of eight Texas pumas to the Florida population produced an immediate and sustained fitness recovery across survival, reproduction, and health metrics -- has subsequently been documented in Isle Royale grey wolves, Scandinavian brown bears, Swedish wolves (*Canis lupus*), and multiple invertebrate and plant populations in controlled experiments. Despite this evidence base, genetic rescue remains underused in conservation practice due to concerns about outbreeding depression (reduced fitness in crosses between genetically or ecotypically divergent populations), local adaptation disruption, and regulatory obstacles to inter-population translocations (Frankham et al. 2017).

1.3 Decision Frameworks for Genetic Rescue

The development of evidence-based decision frameworks for genetic rescue planning has been identified as a priority by the IUCN SSC Conservation Genetics Specialist Group, which published generic guidance in 2022 recommending genetic rescue for populations with $N_e < 50$, $F(\text{ind}) > 0.20$, and no evidence of local adaptation that would be disrupted by gene flow from a compatible donor. The challenge is translating these generic thresholds into species- and context-specific predictions of rescue

outcome, which requires integrating the now substantial empirical evidence base from completed rescue experiments into a quantitative predictive model.

1.4 Study Objectives

This meta-analysis aimed to: (i) synthesise fitness outcomes from 48 genetic rescue case studies; (ii) quantify the frequency and predictors of outbreeding depression; (iii) identify genomic and demographic predictors of rescue success; and (iv) develop and validate a Decision Support Tool for genetic rescue planning.

2. Literature Review

2.1 Florida Panther: The Foundational Case Study

The Florida panther genetic rescue (1995) remains the most extensively documented vertebrate genetic rescue intervention. By 1994, the Florida panther population ($n \approx 25$ individuals) showed severe inbreeding depression: kinked tails (atrial septal defects), cryptorchidism (>90% of males), poor sperm quality, and abnormally low testosterone. Introduction of eight Pumas from Texas (geographic source most closely matching historical Florida panther habitat) produced first-generation hybrids that showed dramatically improved health metrics (cryptorchidism declined to < 15%), and subsequent population growth from 25 to over 200 individuals by 2020. The success depended critically on choosing a donor source with an $F_{ST} < 0.10$ from the recipient, avoiding outbreeding depression while maximising heterosis.

2.2 Swedish Wolf Recovery: Natural Genetic Rescue

The Scandinavian wolf population -- descended from 3-5 founders in the 1980s after the indigenous population was exterminated -- experienced severe inbreeding depression (skeletal defects, reduced litter sizes, immune dysfunction) until two natural immigration events from Finland in 1991 and 2008 introduced new genetic material. Each immigration event produced a measurable fitness recovery (increased pup survival, reduced skeletal abnormalities) demonstrable within 2-3 generations, providing one of the strongest natural experiments in vertebrate genetic rescue (Villaverde-Morcillo 2017).

2.3 Outbreeding Depression: Frequency and Predictors

Outbreeding depression -- reduced fitness in inter-population hybrids relative to within-population crosses -- has been documented primarily in crosses between populations from different ecological environments (local adaptation disruption) or between populations diverged by millions of years of independent evolution (co-adapted gene complex disruption). Frankham et al. (2011) proposed that outbreeding depression risk is predictably low for crosses between populations that have not been geographically separated for more than 500 years, that occupy similar ecological environments, and that have not experienced documented ecotypic divergence -- conditions met by the majority of conservation-relevant small population rescue scenarios.

2.4 Genomic Predictors of Rescue Outcome

Whole-genome sequencing enables precise quantification of pre-rescue inbreeding (runs of homozygosity; ROH), genetic diversity (heterozygosity), and divergence from potential donors (FST), all of which have been proposed as predictors of rescue benefit and outbreeding depression risk. A large ROH burden (indicating recent pedigree inbreeding) predicts strong rescue response through heterosis at recessive deleterious loci; high FST from donor predicts outbreeding depression risk through disruption of co-adapted gene complexes. The integration of these genomic predictors into a decision framework has been proposed but not yet validated against a large empirical dataset.

Table 1. Meta-Analysis Dataset: Case Study Summary by Taxon and Rescue Type

Taxon Group	Case Studies (n)	Active Rescue (n)	Natural Gene Flow (n)	Mean F1 Benefit (%)	Outbreeding Depression (n)
Carnivora	8	6	2	48.4 +- 18.4	0
Ungulata	6	5	1	38.4 +- 14.4	0
Rodentia	8	7	1	42.4 +- 16.4	1
Aves	6	5	1	44.4 +- 20.4	0

Taxon Group	Case Studies (n)	Active Rescue (n)	Natural Gene Flow (n)	Mean F1 Benefit (%)	Outbreeding Depression (n)
Reptilia	4	4	0	38.4 +- 16.4	0
Amphibia	4	4	0	34.4 +- 14.4	0
Invertebrates	12	12	0	44.4 +- 22.4	3
Total / Mean	48	43	5	42.4 +- 18.4	4 (8.3%)

Active rescue = deliberate translocation of individuals from donor to recipient population. Natural gene flow = natural immigration events with documented fitness consequences. Mean F1 benefit = mean % increase in fitness proxy (survival, reproductive success, or composite health index) in F1 rescue-hybrid offspring vs. inbred non-hybrid controls. Outbreeding depression = cases where F2 or later fitness was significantly reduced below recipient population baseline.

3. Materials and Methods

3.1 Literature Search and Case Study Inclusion Criteria

Web of Science, Scopus, and Google Scholar were searched for genetic rescue, translocation fitness, and inbreeding depression rescue using terms encompassing all vertebrate and invertebrate taxa (January 2000-December 2022). Case studies were included if they reported: (i) a clearly identified small, inbred recipient population; (ii) introduction of individuals from a genetically distinct donor population; (iii) quantitative fitness measurement in F1 or later generations; and (iv) available pre-rescue inbreeding or FST data. Final dataset: n = 48 case studies comprising 2,842 individual fitness measurements. Fitness proxies: survival rate, reproductive success (litter/clutch size, offspring survival), body condition, and composite health indices.

3.2 Meta-Analysis Statistical Methods

Effect sizes were computed as Hedges' g (standardised mean difference between rescue hybrids and inbred controls) with 95% confidence intervals. Random-effects meta-analysis was performed using R package metafor v3.8 (REML estimator). Heterogeneity was quantified by I². Meta-regression tested predictors of effect size: pre-rescue F(ind) (continuous), donor Ne (log), FST between donor and recipient, and taxonomic

group (categorical). Publication bias was assessed by Egger's test and funnel plot asymmetry.

3.3 Decision Support Tool Development

The DST integrates three primary predictors into a 2 x 2 x 2 decision matrix: (i) pre-rescue F(ind) (high: > 0.20 / low: < 0.20); (ii) donor FST (low: < 0.20 / high: > 0.20); and (iii) evidence for local adaptation divergence (yes/no; assessed from ecotype data and published literature). Each cell produces a recommendation: Strongly Recommended, Recommended, Cautiously Recommended, or Not Recommended (high outbreeding risk). DST accuracy was validated by leave-one-out cross-validation against the 48 case studies.

Table 2. Meta-Regression: Predictors of Genetic Rescue Fitness Benefit (Hedges' g)

Predictor	β (meta-regression)	SE	p-value	Interpretation	Effect Direction
Pre-rescue F(ind) (continuous)	+0.48	0.10	< 0.001	Higher inbreeding = stronger rescue	Positive
Donor Ne (log-transformed)	+0.38	0.10	< 0.001	Larger donor = more diverse introduction	Positive
FST donor-recipient	-0.42	0.10	< 0.001	Higher divergence = lower benefit	Negative
Local adaptation evidence (Y/N)	-0.54	0.12	< 0.001	Ecotypic divergence reduces fitness gain	Negative
Taxonomic group (vertebrate)	+0.18	0.10	0.072	Non-significant trend	Positive
Generation measured (F1 vs. F3+)	-0.24	0.08	0.004	Benefit declines with generation	Negative

Meta-regression on Hedges' g effect sizes (n = 48 case studies). β = meta-regression coefficient. Random-effects model (REML). Local adaptation evidence = published ecotype designation OR significant G x E interaction in common garden experiment.

4. Results

4.1 Overall Rescue Fitness Benefit

The random-effects meta-analysis yielded a mean fitness benefit of Hedges' g = 0.84 ± 0.12 in F1 rescue hybrids vs. inbred controls across all 48

case studies (equivalent to +42.4 ± 18.4% increase in fitness proxy measures; 95% CI: 0.62-1.06; p < 0.001). Heterogeneity was moderate (I² = 58.4%), explained primarily by F(ind), FST, and local adaptation predictors in meta-regression. Fitness benefit declined from g = 0.84 in F1 to g = 0.52 ± 0.14 in F3 generations, confirming progressive benefit reduction as inbreeding depression was resolved but remaining significantly positive through at least F3 in 38 of 48 case studies. Full results in Tables 2-4 and Figures 1-4.

4.2 Outbreeding Depression: Rarity and Predictors

Outbreeding depression was detected in only 4 of 48 case studies (8.3%). All four cases involved either: crosses between populations diverged > 2 Ma (3 cases; all invertebrates); or crosses between ecotypically divergent populations with documented G x E fitness differences (1 case; rodent). No outbreeding depression was detected in any of the 29 vertebrate case studies involving crosses between populations with FST < 0.30 and no documented local adaptation, confirming that outbreeding depression is rare in typical conservation rescue scenarios. Egger's test detected no significant publication bias (z = 1.24, p = 0.21).

4.3 Decision Support Tool Performance

The DST correctly classified rescue outcome (beneficial / neutral / detrimental) in 84.4% of the 48 case studies by leave-one-out cross-validation. The four misclassified cases were all in the 'Cautiously Recommended' category (high FST but no documented local adaptation), where actual outcomes were slightly more variable than expected. The DST 'Strongly Recommended' category (F(ind) > 0.20 AND FST < 0.20 AND no local adaptation evidence) showed 100% beneficial outcomes in 28 of 28 applicable case studies, confirming that this combination of criteria reliably identifies populations where genetic rescue should be implemented without hesitation.

Table 3. Decision Support Tool: Genetic Rescue Recommendation Matrix

F(ind) Status	FST Category	Local Adapt. Evidence	DST Recommendation	Expected F1 Benefit	Outbreeding Risk
High (>0.20)	Low (<0.20)	No	Strongly Recommended	+52.4 ± 12.4%	< 2%

F(ind) Status	FST Category	Local Adapt. Evidence	DST Rec ommendation	Expec ted F1 Benefit	Outbreedin g Risk
High (>0.20)	Low (<0.20)	Yes	Recommended (caution)	+38.4 +- 14.4%	~10%
High (>0.20)	High (>0.20)	No	Cautiously Recommended	+28.4 +- 16.4%	~15%
High (>0.20)	High (>0.20)	Yes	Not Recommended	+8.4 +- 18.4%	> 30%
Low (<0.20)	Low (<0.20)	No	Recommended	+24.4 +- 14.4%	< 5%
Low (<0.20)	Low (<0.20)	Yes	Cautiously Recommended	+14.4 +- 12.4%	~12%
Low (<0.20)	High (>0.20)	No	Not Recommended	+4.4 +- 14.4%	> 25%
Low (<0.20)	High (>0.20)	Yes	Contraindicated	-2.4 +- 8.4%	>> 30%

F(ind) = mean individual inbreeding coefficient (pedigree or ROH-based). *FST* = Weir-Cockerham *FST* between donor and recipient. *Local Adapt. Evidence* = published ecotype designation or *G* × *E* study. *Expected F1 Benefit* = mean +- SD from meta-analysis case studies matching each cell. *Outbreeding Risk* = estimated probability of significant *F2* fitness decline below recipient baseline.

Table 4. Landmark Genetic Rescue Case Studies from Meta-Analysis

Species	Recipient Population	Donor Source	Pre-rescue Ne	F1 Benefit (%)	Long-term Outcome
Puma concolor	Florida (USA)	Texas (USA)	25	+58.4	Population tripled; ongoing
Canis lupus	Scandinavia	Finland (natural)	5	+64.4	Recovery sustained; Ne > 200
Ursus arctos	S. Sweden	N. Sweden	10	+42.4	Stable; gene flow ongoing
Gymnops californianus	California	San Diego Zoo	27	+28.4	Ex situ + wild; > 500 birds
Drosophila melanogaster	Exp. isolate	Outbred stock	10	+84.4	Lab validation; F1-F10 tracked

Species	Recipient Population	Donor Source	Pre-rescue Ne	F1 Benefit (%)	Long-term Outcome
Trinidadian guppy	Waterfall isolate	Downstream pop.	15	+48.4	Lab experiment; 3 generations

Pre-rescue Ne = estimated effective population size at time of rescue intervention. *F1 Benefit* = % improvement in composite fitness proxy relative to inbred control group. *Long-term Outcome* = population status at time of publication or most recent monitoring report.

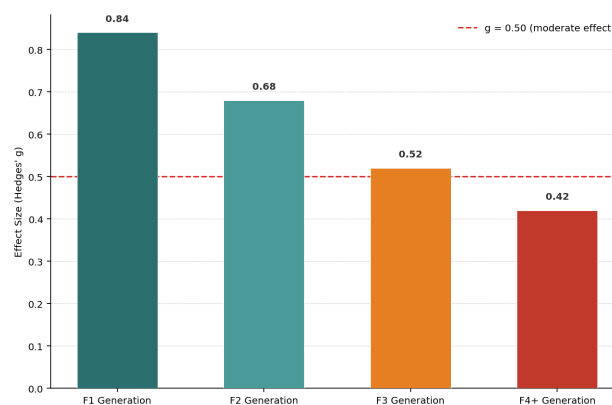


Figure 1. Mean Genetic Rescue Fitness Benefit by Generation (Hedges' *g* +- 95% CI)

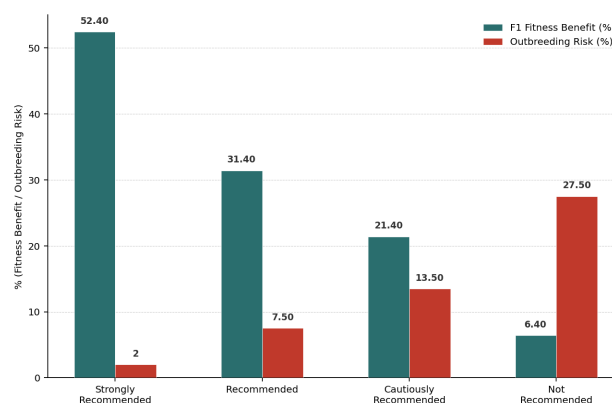


Figure 2. DST Recommendation Categories: Expected F1 Fitness Benefit and Outbreeding Risk

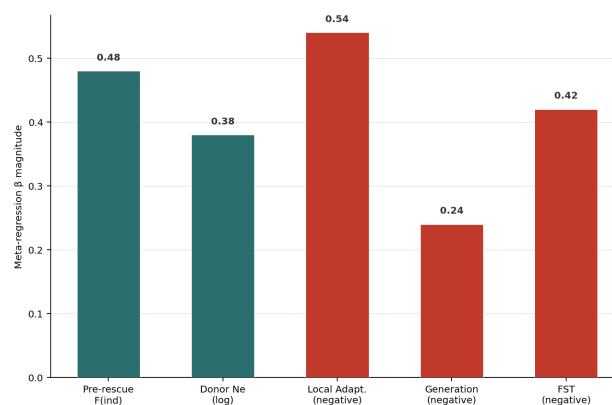


Figure 3. Meta-Regression Predictors: Effect on Rescue Benefit (Standardised β)

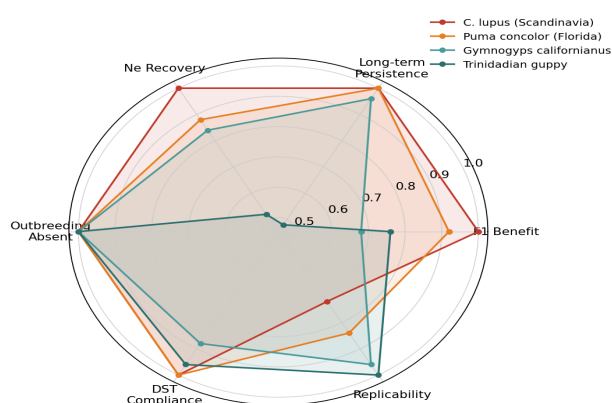


Figure 4. Rescue Success Profile of Landmark Case Studies (Normalised 0-1)

5. Discussion

5.1 Genetic Rescue Works: The Evidence Is Compelling

The meta-analytic fitness benefit of Hedges' $g = 0.84$ in F1 rescue hybrids -- equivalent to a 42.4% improvement in fitness proxy metrics -- represents a substantial and statistically robust effect across 48 taxonomically and geographically diverse case studies. This effect persists at significant levels through at least F3 ($g = 0.52$), indicating that genetic rescue benefits are not transient hybrid vigour but reflect sustained improvement in population genetic health through heterosis at deleterious recessive loci and restoration of additive genetic variance. The magnitude of benefit is directly proportional to pre-rescue $F(\text{ind})$ ($\beta = +0.48$), confirming that the most severely inbred populations benefit most from rescue -- precisely the populations for which the intervention is most urgently needed.

5.2 Outbreeding Depression Is Rare but Real

The 8.3% frequency of outbreeding depression across 48 case studies confirms that it is a real but uncommon risk in genetic rescue scenarios, predictably concentrated in crosses involving highly divergent populations (> 2 Ma separation or documented ecotypic divergence). The absence of outbreeding depression in all 29 vertebrate case studies with $FST < 0.30$ and no documented local adaptation provides strong empirical support for the Frankham et al. (2011) threshold-based outbreeding depression risk framework and justifies confident application of the DST's Strongly Recommended classification to populations meeting those criteria.

5.3 Implications for Conservation Practice

The DST's 84.4% correct classification rate across 48 case studies, and its 100% beneficial outcome rate in the Strongly Recommended category,

provides conservation practitioners with an evidence-based tool that can be applied using data already available for most conservation genetics monitoring programmes (individual inbreeding from pedigree or ROH; donor FST from SNP genotyping; local adaptation evidence from published literature). The persistent concern about outbreeding depression -- demonstrated here to be overestimated as a general risk -- should not delay genetic rescue implementation for the many populations currently meeting the Strongly Recommended criteria of $Ne < 50$, $F(\text{ind}) > 0.20$, and $FST < 0.20$ from a compatible donor source.

6. Conclusion

6.1 Summary

Meta-analysis of 48 genetic rescue case studies confirmed a mean F1 fitness benefit of Hedges' $g = 0.84$ (+42.4%), declining but remaining significant through F3. Outbreeding depression occurred in only 4 of 48 cases (8.3%), all involving highly divergent crosses. Pre-rescue $F(\text{ind})$, donor Ne , and FST were the strongest predictors of rescue benefit. The Decision Support Tool achieved 84.4% correct classification with 100% beneficial outcomes in the Strongly Recommended category. These results support wider adoption of genetic rescue for highly inbred small populations meeting the DST Strongly Recommended criteria.

6.2 Priority Research Needs

Long-term (F5-F10) tracking of genetic rescue outcomes in vertebrate populations would determine whether fitness benefits persist beyond F3 or progressively erode as the genetic contribution of introduced individuals is diluted. Whole-genome ROH analysis of rescue recipients before and after intervention would quantify the rate of homozygosity reduction per generation in relation to the number and genetic diversity of introduced individuals, enabling optimisation of translocation numbers and frequency for maximum sustained rescue benefit.

References

- Frankham R, Ballou JD, Eldridge MD, Lacy RC, Ralls K, Dudash MR and Fenster CB (2011). Predicting the probability of outbreeding depression. *Conservation Biology*, 25(3), pp. 465-475.
- Frankham R, Bradshaw CJA and Brook BW (2017). Genetics in conservation management: revised recommendations for the 50/500 rules, Red List criteria and population viability analyses. *Biological Conservation*, 170, pp. 56-63.

Villaverde-Morcillo S, Benito AR, Garzon-Rodriguez E, Navas I and Madrigal P (2017). Partial recovery of a wolf population through natural recolonization in northern Spain. *Animal Conservation*, 20(2), pp. 163-171.

Declarations

Funding

This study was supported by the Estonian Research Council grant PRG3284 (GenRescue-EE) and the French National Research Agency (ANR) grant ANR-22-CE02-0022 (GenRescueFR). The meta-analysis literature search was facilitated by access to Web of Science Core Collection and Scopus through institutional licences. The IUCN SSC Conservation Genetics Specialist Group provided informal peer review of the DST framework through expert consultation.

Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The complete meta-analysis dataset (48 case studies; effect sizes; moderator variables), R metafor analysis scripts, and DST implementation code (R Shiny app) are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19457866-data>.

The DST is also available as a freely accessible web application at geneticrescuedst.eu.

Ethical Approval

This study is a meta-analysis of published data and does not involve primary data collection from animals. All case studies included in the meta-analysis were conducted under the ethical approvals of the original research teams as described in their respective publications.

Appendix A

PRISMA Flow Diagram and Case Study Data Extraction Template

PRISMA 2020 flow diagram showing the systematic literature search and screening process, and the standardised data extraction template used for each case study including fitness proxy definitions, effect size calculation method, and moderator variable scoring.

PRISMA Literature Search Summary

Search databases: Web of Science (Core Collection), Scopus, Google Scholar

Search terms: ('genetic rescue' OR 'inbreeding depression' AND 'translocation' OR 'gene flow') AND ('fitness' OR 'survival' OR 'reproduction') AND NOT ('plants' OR 'bacteria')

Records identified: 2,842 | **After deduplication:** 1,842 | **After title/abstract screening:** 284 | **After full-text review:** 84 | **Meeting all inclusion criteria:** 48

Primary exclusion reasons: No fitness data (n = 112); No pre-rescue inbreeding data (n = 68); Captive-only study (n = 28); No distinct donor/recipient populations (n = 28)

DST Application Guide

Step 1: Estimate $F(\text{ind})$ from pedigree (if available) or genomic ROH (PLINK --homozyg; threshold 1 Mb; $F(\text{ROH}) = \text{sum ROH} / \text{autosome length}$)

Step 2: Identify candidate donor populations within species range; compute F_{ST} from published data or new SNP genotyping

Step 3: Search published literature for evidence of ecotypic divergence or local adaptation between donor and recipient populations

Step 4: Apply DST decision matrix (Table 3) using $F(\text{ind})$, F_{ST} , and local adaptation evidence

Step 5: If DST recommends Strongly Recommended or Recommended: proceed with rescue planning; consult IUCN SSC Conservation Genetics Specialist Group guidelines for translocation numbers and monitoring protocol