# Genomics and the future of conservation genetics

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Abstract | We will soon have complete genome sequences from thousands of species, as well as from many individuals within species. This coming explosion of information will transform our understanding of the amount, distribution and functional significance of genetic variation in natural populations. Now is a crucial time to explore the potential implications of this information revolution for conservation genetics and to recognize limitations in applying genomic tools to conservation issues. We identify and discuss those problems for which genomics will be most valuable for curbing the accelerating worldwide loss of biodiversity. We also provide guidance on which genomics tools and approaches will be most appropriate to use for different aspects of conservation.

Neutral locus
A locus that has no effect on adaptation because all genotypes have the same fitness.

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The ability to examine thousands of genetic markers with relative ease will make it possible to answer many important questions in conservation that have been intractable until now. Simply increasing the number of neutral loci that we can screen will increase the power and accuracy of estimating a variety of important parameters in conservation (for example, kin relationships and inbreeding coefficients ($F$)). However, the most exciting contributions of genomics to conservation are those that will allow new questions to be addressed in a wide variety of species (BOX 1). For instance, it should be possible to estimate the effect size and distribution of loci affecting fitness across the genome or to ask whether the loci are coincident across populations[1,2] (FIG. 1).

Genomic approaches are currently being used primarily with a few species for which genomic information and tools are available[3]; for example, wolves, bison and bighorn sheep have been studied using genomic tools developed in related domestic species[4]. However, the range of species is expanding as new approaches are developed that are not dependent on genomic information from closely related species[5,6]. For example, van Bers *et al.*[7] obtained over 16 million short sequence reads and conducted *de novo* assembly of 550,000 contigs covering 2.5% of the genome to discover 20,000 novel SNPs in the great tit (*Parus major*). These markers will be used for quantitative trait locus mapping and whole genome association studies.

In addition, multiple taxa can be combined in a single sequencing analysis using genomic techniques that can assay large amounts of variable DNA sequence[8].

The application of metagenomics to conservation is still in its early stages, but shows promise. First, functional metagenomics of microbial communities provides a novel perspective on ecosystem processes, such as nutrient and energy flux. Although some studies have compared functions across a broad scale of biomes[9], similar comparative approaches may identify aspects of ecosystem function across sites within a habitat. The second potential application of metagenomics to conservation is in assessment of physiological condition of individual organisms. For instance, Vega Thurber *et al.*[10] have found numerous shifts in the endosymbiont community of corals in response to multiple stressors, such as reduced pH, increased nutrients and increased temperature. Third, a metagenomic analysis of human faecal samples catalogued 3.3 million microbial genomes and found substantial differences in the microbial metagenome between healthy individuals and those with inflammatory bowel disease[11]. It may be possible in the future to apply metagenomic techniques to faecal samples from wildlife species to assess physiological states, such as starvation stress.

Genomics already has provided some interesting surprises, such as the discovery of adaptive loci that show extremely high genetic divergence between populations of marine fish for which there is virtually no allele frequency divergence at neutral loci[12] (BOX 2). In addition, a multi-faceted genomic approach has provided important insights into the treatment of a facial tumour disease that threatens the persistence of the Tasmanian devil (*Sarcophilus laniarius*)[13].



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**Box 1 | What is 'conservation genomics'?**

Conservation genomics can be broadly defined as the use of new genomic techniques to solve problems in conservation biology. Frankham[72] recently reviewed the current status of conservation genetics and proposed 13 priorities for development in the field. Many of these priorities have been intractable through traditional genetic techniques. Although genomic techniques are not appropriate or necessary in all cases, we believe that genomics will have an important role in addressing several research challenges over the next few years.

Genomic techniques will be more immediately applicable to some questions than to others (TABLE 1). For example, in estimating neutral population parameters, such as effective population size, genomics simply provides a larger number of markers to an analytical and conceptual framework that is already widely used in conservation genetics. Genomic identification of functionally important genes is now common in other fields; conservation genomics can incorporate these approaches to study the genetic basis of local adaptation or inbreeding depression. By contrast, predicting a population's viability or capacity to adapt to climate change based on genomic information will require not only the identification of relevant loci, but also a quantitative estimate of their connection to fitness and demographic vital rates. These challenges must be tackled by conservation genomics over the longer term.

Understanding genomic approaches is crucial to the success of applying genomics to conservation (FIG. 1). A growing list of techniques is available for detecting DNA sequence differences across individuals in natural populations, and these vary widely in the density of markers across the genome, their ability to target candidate loci, the cost per sample, and so on. Genomic techniques can be roughly grouped into three classes: marker-based genotyping, including a diversity of array-based SNP genotyping platforms; reduced-representation sequencing, which uses next-generation sequencing technology to target a subset of orthologous regions across the genome of many individuals; and whole-genome sequencing. A crucial component of all genomic techniques is bioinformatics. The tools for handling genomic data are changing as fast as (and in response to) techniques for gathering the data, and we do not review the software and analytical issues here[111]. Nonetheless, researchers using genomic techniques should plan on a substantial investment of time and resources devoted to data storage and analysis.

Inbreeding coefficient
The probability that two alleles in an individual are both descended from a single allele in an ancestor (that is, that they are 'identical-by-descent').

Contig
An abbreviation for contiguous sequence; used to indicate a contiguous piece of DNA that is assembled from shorter overlapping sequence reads.

Metagenomics
The study of the collective genomic material contained in an environmental sample of microorganisms, facilitated by high-throughput sequencing technology that allows the direct sequencing of heterogeneous samples.

Endosymbiont
An organism that lives within the cells of a host organism.

Inbreeding depression
The loss of vigour and fitness that is observed when genome-wide homozygosity is increased by inbreeding.

There have been several excellent reviews on conservation genomics recently[3,14–17]. We have attempted to build on these reviews and to distinguish ours by making specific practical recommendations on how genomic approaches can be applied to key problems in conservation (TABLE 1). For example, Ouborg *et al.*[15] present a comprehensive view of how genomics will provide insights into the mechanisms behind the interaction between selectively important variation and environmental conditions. Nevertheless, if we are to apply this understanding of fitness to conservation, we need to address the population-level consequences of genetic variation, which include population subdivision, demography and population viability. We have incorporated population structure and demographic effects into FIG. 1, and have distinguished issues that only genomic approaches can thoroughly address from issues that can be adequately tackled with traditional techniques.

We have two primary objectives. The first is to identify those problems in conservation biology in which genomics will be most valuable in providing new insights and understanding. The second is to provide guidelines as to which new genomics approaches will be most appropriate for the different problems in conservation that can benefit from genetic analysis.

We begin by focusing on issues in conservation genomics that are immediately accessible (for example, increasing the number of neutral markers) and then proceed through issues that will become more feasible in the future. We consider how genomic approaches will allow us to understand the genetic basis of inbreeding depression and adaptation. We then apply these insights to important outstanding problems in conservation, including understanding the effects of hybridization and predicting outbreeding depression, as well as predicting evolutionary responses to climate change.

## 'Neutral' markers

The most straightforward contribution of genomics to conservation will be to enormously increase the precision and accuracy of estimation of parameters that require neutral loci (for example, effective population size ($N_e$) and migration rate ($m$)) by genotyping hundreds to thousands of neutral loci in numerous individuals. The accuracy of parameter estimation will be improved because examining several loci facilitates the identification and exclusion of loci under selection (outlier loci) that cause biased estimates of parameters. For example, a small proportion (1–5%) of non-neutral loci can change estimates of mean $F_{ST}$ by 30–50%[18–20], and change the topology and branch lengths of evolutionary trees[21,22]. Similarly, the assessment of demographic parameters, such as population bottlenecks or growth rates, requires many loci to identify outliers and reliably infer change in population size. Selection can shrink (by bottlenecks) or expand genealogies at a locus[23]. Therefore, inferences about population growth should be more robust if outlier loci are removed, for example by using a hierarchical Bayesian model to assess the parameters of each locus separately[24].

Increasing the number of markers will also facilitate estimation of directionality of migration (emigration and immigration rates), especially if haplotypes can be inferred from linked loci[25]. Certain questions require linked loci or can be vastly improved by using haplotype inference; for example, estimating relationships among individuals[26], population structure[27], admixture[28], dates of historical bottlenecks and directionality of migration[25].

Furthermore, it will become increasingly feasible to jointly estimate multiple parameters, which generally requires more loci than single parameter estimation. For example, likelihood, Bayesian and approximate Bayesian estimators combined with coalescent approaches will allow the simultaneous estimation of multiple parameters, such as $N_e$ and $m$[25,29], or $N_e$ and the selection coefficient ($s$)[30]. This is important because it will improve parameter estimation, allow parameter estimation in metapopulations (not just in isolated populations with no gene flow), and facilitate investigations of the relative importance and interactions among drift, selection and migration in populations of conservation concern.

By contrast, simulations suggest that as the number of loci increases, the accuracy of parameter estimation can decrease owing to non-independence or linkage among loci[31]. Failure to account for linkage could limit the utility of SNPs or multi-locus sequencing in studies using genealogical information[32]. Markers are usually assumed to be independent. Failure to account for non-independence can lead to overestimation of



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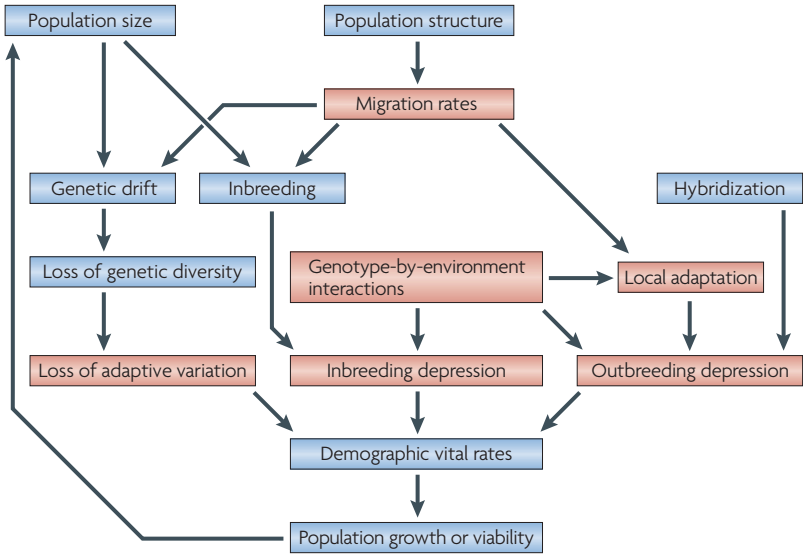


Figure 1 | **Schematic diagram of interacting factors in conservation of natural populations.** Traditional conservation genetics, using neutral markers, provides direct estimates of some interacting factors (blue). Conservation genomics can address a wider range of factors (red). It also promises more precise estimates of neutral processes (blue) and understanding of the specific genetic basis of all of these factors. For example, traditional conservation genetics can estimate overall migration rates or inbreeding coefficients, whereas genomic tools can assess gene flow rates that are specific to adaptive loci or founder-specific inbreeding coefficients.

Adaptation
Heritable changes in genotype or phenotype that result in increased fitness.

Hybridization
Interbreeding of individuals from genetically distinct populations, regardless of the taxonomic status of the populations.

Outbreeding depression
Reduced fitness of $F_1$ or $F_2$ individuals after a cross between two species or populations. It can result from genetic incompatibility or reduced adaptation to local environmental conditions.

Effective population size
The size of the ideal population that would experience the same amount of genetic drift as the observed population.

Outlier locus
A genome location (or marker or base pair) that shows behaviour or a pattern of variation that is extremely divergent from the rest of the genome (locus-specific effects), as revealed by simulations or statistical tests.

precision and overconfidence in subsequent inferences. Fortunately, the problem is likely to be minor unless loci are tightly linked[33]. Failure to consider linkage could also have other effects; for example, human loci in regions of lower recombination tend to have greater $F_{ST}$, apparently because of the greater probability of being associated with selected loci in chromosomal regions with less recombination[34].

***Description of kin relationships and pedigrees.*** Examining hundreds of loci will vastly increase the precision and accuracy of kinship estimates. For example, Santure *et al.*[35] showed that the average pair-wise relatedness estimated from 771 SNPs closely brackets known pedigree relationships for a pedigree population of zebra finch. This suggests that assessments of correlations between phenotypes and genetic relatedness and thus estimation of heritability will be feasible in natural populations. Nevertheless, the accuracy of estimating individual levels of inbreeding is somewhat limited, and the variances for relatedness between individuals remain substantial even with 771 SNPs[36].

Pedigree reconstruction will become feasible in some wild populations with hundreds of loci[33,37]. This will improve estimates of effects of inbreeding and outbreeding on fitness and the detection of paternities or pollen flow between populations and over long distances, if most individuals can be sampled over many years. Santure *et al.*[35] suggested that using marker information to reconstruct the pedigree, and then calculating relatedness from the pedigree, is likely to give more accurate relatedness estimates than using marker-based estimators directly. Skare *et al.*[26] conducted simulation power analyses and showed that relatively distant relationships (for example, cousins) can be inferred using 500,000 SNPs and likelihood-based relationship estimators.

Nonetheless, pedigrees often will not have sufficient depth or completeness because it is difficult to sample most individuals in a population over many years. In such cases, genotyping thousands of loci could potentially give more reliable estimates of relationships and individual heterozygosity (inbreeding) than pedigrees[26,38] or at least greatly improve pedigree reconstruction[37]. Future research is needed to quantify the trade-off point between using pedigree inference versus thousands of genetic markers to estimate individual inbreeding.

***Individual-based population genetics.*** Individual-based approaches can yield less biased delineation of populations than traditional population-based approaches that require somewhat subjective grouping of individuals[39] (for example, based on morphology or geographic origin). For population delineation, an empirical study of 377 microsatellites in humans has shown that using greater numbers of loci can increase statistical power to resolve between closely related ethnic groups ($F_{ST} < 0.05$) and infer the proportion of admixture[40,41].

Individual-based approaches can give less biased estimation of contemporary migration rates without assumptions such as mutation–migration–drift equilibrium[42]. However, the power to estimate contemporary migration rates is low unless $F_{ST}$ is relatively high (for example, $F_{ST} > 0.10$) when using only 10–20 microsatellite loci[43]. Little is known about power when genotyping hundreds of loci, although Rannala and Mountain[44] reported that an assignment test method using 50–100 loci gave reasonable power to identify individuals with grandparents from different countries, although the differentiation of allele frequencies among populations was low. Individual-based approaches are crucial for fine-scale spatial genetic analyses to localize genetic discontinuities (for example, barriers or secondary contact zones) on a landscape. Individual-based approaches in landscape genetics[45] also allow assessment of the influence of landscape features on dispersal and gene flow across spatial scales.

## Inbreeding depression

Genomic approaches can potentially address basic questions about the molecular basis and genetic architecture of inbreeding depression[46]. For instance, is inbreeding depression caused by a few loci with major effects or by many loci with small effects? How much of inbreeding depression results from dominance (or partial dominance) versus overdominace (heterozygous advantage)? What is the contribution of epistasis to inbreeding depression? Understanding the number of loci involved in inbreeding depression and the mechanism of their effects would allow prediction of the potential efficacy of purging.

Recent work indicates that the intensity of inbreeding depression can differ greatly depending on which specific individuals are founders[47,48]. This suggests that



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Box 2 | **Detection of cryptic subdivision and local adaptation in marine species**

There is little genetic drift in many marine fish and invertebrates because of their large population sizes[121,122]. As a consequence, population genetic studies of many marine species have failed to detect genetic substructure even between geographically disjunct subpopulations for which there is evidence of reproductive isolation[122]. The absence of genetic differentiation at neutral markers, however, should not be taken to mean the absence of adaptive differences. The amount of genetic divergence among subpopulations at selectively neutral markers is largely a function of the number of migrants per generation ($N_e m$) rather than the migration rate ($m$). With large population sizes, even very low migration or dispersal rates can result in enough migrant individuals to eliminate genetic evidence of population differentiation at neutral loci, but not at locally selected adaptive loci.

We expect this effect to be greatest in marine species because of the large local population sizes, which allow selection to be more efficient because drift is weaker. The amount of divergence at selected loci is determined by the relative values of migration and selection coefficient ($s$). Species with larger local populations ($N_e$) will have much lower rates of migration than species with small population size with the same number of migrants and amount of divergence at neutral loci. Therefore, even fairly weak selection may bring about genetic differentiation between subpopulations in species with large local population sizes because $s$ is much more likely to be greater than $m$.

This prediction is supported by a recent study[123] of Atlantic cod (*Gadus morhua*) in which almost no genetic differentiation ($F_{ST}$ = 0.003) was found at nine microsatellite loci, but substantial differentiation ($F_{ST}$ = 0.261) was found at the *Pan*I locus, which previous studies have shown to be under natural selection[105]. Similarly, Haemmer-Hansen *et al.*[124] reported an $F_{ST}$ of 0.45 at a heat shock protein locus in comparison to a mean $F_{ST}$ value of only 0.02 at nine microsatellite loci in the European flounder (*Platichthys flesus*). This approach of simultaneously comparing many neutral and candidate gene markers has been highly successful in a range of species[19].

In addition, the absence of genetic differentiation in marine species should not be interpreted to indicate that the populations are demographically connected as a single management unit[125]. Demographic connectivity is largely a function of the proportional amount of exchange. Therefore, low migration rates ($m < 0.001$) can result in a substantial number of migrant individuals when local population sizes are in the thousands, resulting in $F_{ST}$ values near zero. Much greater exchange is necessary for demographic connectivity between populations. For example, Waples and Gaggiotti[126] have suggested that $m$ must be greater than 10% for populations to be demographically interdependent.

$F_{ST}$
A measure of population subdivision that indicates the proportion of genetic diversity found between populations relative to the amount within populations.

Population bottleneck
A marked reduction in population size followed by the survival and expansion of a small random sample of the original population. It often results in the loss of genetic variation and more frequent matings among closely related individuals.

Hierarchical Bayesian model
A Bayesian model in which the prior depends on another parameter that is not in the likelihood function and that can vary and have another prior.

Haplotype
A set of genetic markers that are present on a single chromosome and that show complete or nearly complete gametic disequilibrium. They are inherited through generations without being changed by crossing-over or other recombination mechanisms.

Admixture
The production of new genetic combinations in hybrid populations through recombination.

Coalescent approach
A means of investigating the shared genealogical history of genes. A genealogy is constructed backwards in time starting with the present-day sample. Lineages coalesce when they have a common ancestor.

Selection coefficient
A term that describes the difference in average fitness between genotypes when fitness is measured relative to the average fitness of one of the genotypes (known as the reference genotype).

Metapopulation
A collection of populations of a species found in differing geographic locations and with restricted gene flow (exchange of genes) between the populations.

the genetic load is unevenly spread among founder genomes and supports the notion that inbreeding depression sometimes results from major effects at a few loci[49]. The founder-specific partial $F$ coefficient is the identical-by-descent (IBD) probability (for an individual) that is attributed to a particular founder. A study with Ripollesa domestic sheep found that most of the inbreeding depression resulted from individuals being IBD for genes from just two of the nine founders[49]. Managing founder-specific inbreeding depression using partial inbreeding coefficients could be extremely effective in cases in which inbreeding depression results primarily from a few loci with major effects; such partial inbreeding coefficients could be useful when selecting potential matings in a captive population.

***Identifying alleles responsible for inbreeding depression.*** Genome scans of large numbers of markers can detect the signature of inbreeding depression. Deleterious recessive alleles related to inbreeding depression have been identified in a few species[46,50,51]. In general, attempts to identify loci responsible for inbreeding depression may be less successful than those aimed at positive selection for a few reasons. First, detecting the multiple genetic mechanisms that may underlie inbreeding depression, including epistasis and genotype-by-environment interaction, may prove more difficult[52]. Second, populations of interest are likely to be small, necessitating small sample sizes, which reduce power and accuracy. Third, the longer regions of gametic disequilibrium expected in small inbred populations (observed in wolves by Hagenblad *et al.*[46]) mean that genotyped anonymous markers are more likely to lie within a genomic region affected by selection at a particular locus, but that fine-mapping of a selected locus will be more difficult. Ideally, researchers would study populations with both long and short chromosomal regions of gametic disequilibrium to allow for initial coarse-mapping and subsequent fine-mapping of loci under selection.

In the future, it could be possible to identify loci that contribute to inbreeding depression by sequencing the whole genomes of parents and offspring. For example, Roach *et al.*[53] analysed the complete genome sequence of two parents and their two children, who suffered from two clinical recessive disorders. They narrowed down the candidate genes for both of these Mendelian disorders to four using family-based genome analysis.

## Local adaptation

One of the most promising aspects of applying genomic tools to conservation is the simultaneous estimation of neutral (that is, genome-wide average) processes along with identification of specific genomic regions responding to selection, such as adaptation to local conditions that vary across a metapopulation. These specific genomic regions appear as outliers from the patterns observed at the neutral genomic background, which is determined primarily by genetic drift and gene flow. Researchers have developed multiple approaches to detect these outliers[54,55] (BOX 3). The utility of these approaches depends on the timescale over which selection has operated and the study's taxonomic scale (for example, the study might be investigating divergence among species, differentiation among populations within a species or evolutionary history within a single population), as well as on the techniques used[55].



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Table 1 | **Primary genetic problems in conservation and how genomics can contribute to their solution***

| Primary problem | Possible genomic solution |
|---|---|
| Estimation of $N_e$, $m$ and $s$ | Increasing the number of markers, reconstructing pedigrees and using haplotype information will provide greater power to estimate and monitor $N_e$ and $m$, as well as to identify migrants, estimate the direction of migration and estimate $s$ for individual loci within a population |
| Reducing the amount of admixture in hybrid populations | Genome scanning of many markers will help to identify individuals with greater amounts of admixture so that they can be removed from the breeding pool |
| Identification of units of conservation: species, evolutionarily significant units and management units | The incorporation of adaptive genes and gene expression will augment our understanding of conservation units based on neutral genes. The use of individual-based landscape genetics will help to identify boundaries between conservation units more precisely |
| Minimizing adaptation to captivity | Numerous markers throughout the genome could be monitored to detect whether populations are becoming adapted to captivity |
| Predicting harmful effects of inbreeding depression | Understanding the genetic basis of inbreeding depression will facilitate the prediction of the effectiveness of purging. Genotyping of individuals at loci associated with inbreeding depression will allow the selection of individuals as founders or mates in captive populations. Pedigree reconstruction will allow more powerful tests of inbreeding depression |
| Predicting the intensity of outbreeding depression | Understanding the divergence of populations at adaptive genes will help to predict effects on fitness when these genes are combined. Detecting chromosomal rearrangements will help to predict outbreeding depression |
| Predicting the viability of local populations | Incorporating genotypes that affect vital rates and the genetic architecture of inbreeding depression will improve population viability models |
| Predicting the ability of populations to adapt to climate change and other anthropogenic challenges | Understanding adaptive genetic variation will help to predict the response to a rapidly changing environment or to harvesting by humans and allow the selection of individuals for assisted migration |

*These problems are listed from top to bottom in sequence of those that can be immediately addressed to those that will become more feasible to address in the future. $m$, migration rate; $N_e$, effective population size; $s$, selection coefficient.

Proportion of admixture
The proportion of alleles in a hybrid swarm or individual that comes from each of the hybridizing taxa.

Epistasis
The dependency of the effects of alleles at one locus on the genotypes at other loci in the genome.

Purging
The selective reduction in frequency of deleterious recessive alleles in small populations because the increase in homozygosity increases the ability of selection to act on recessive alleles.

Identical-by-descent
An allele shared by two related individuals is said to be identical-by-descent if the allele is inherited from the same common ancestor.

Gametic disequilibrium
A measure of whether alleles at two loci in a population occur in a non-random fashion.

Type I and type II errors
Statistical errors in which a true null hypothesis is rejected (type I) or a false null hypothesis is not rejected (type II).

Expressed sequence tag
A short DNA fragment (several hundred base pairs) produced by reverse transcription of mRNA into DNA.

For most conservation purposes, only a subset of these tools will be most appropriate, and application of the wrong approach could result in type I and type II errors. Specifically, detecting genomic regions that are responsible for local adaptation in a species relies on comparisons among related populations that may or may not be linked by ongoing gene flow. In this case, the most appropriate analyses often will focus on differentiation in allele frequencies among populations (that is, $F_{ST}$[20]). Within a single population, the allele frequency spectrum can indicate regions under selection[55]. By contrast, techniques for detecting historical selection based on fixed sequence divergence between species or the relationship between divergence and polymorphism are likely to have only limited applications in conservation because of the longer timescale of selection that can be detected (but see Garrigan and Hedrick[56]). Here we focus on the first case — local adaptation among populations within a species.

***Methods for assessing local adaptation.*** There are two general ways to assess local adaptation in the genome (BOX 3): the first starts with a list of candidate loci or genomic regions and asks whether these lie in the tails of the genome-wide distribution of population differentiation[57–60]. Genomics can augment these studies indirectly by providing a list of candidates; for example, expressed sequence tag (EST) databases allow for the bioinformatic identification of microsatellites or other traditional markers closely linked with target genes, and primers or probes can be developed from these EST sequences[61–65]. Genomic databases may even come from related species, so that rare species of conservation concern are 'genome-enabled' by the resources of better-studied, related taxa[3]. A growing variety of genomic tools can also be used directly to genotype individuals at up to thousands of candidate loci (TABLE 2).

The second major approach to detecting local adaptation searches the genome for signatures of selection using anonymous markers[66,67]. A limitation here is that markers must be in gametic disequilibrium with selected loci to exhibit a signature of selection, and the signature can be quite small depending on the nature of the selection. In particular, local adaptation with ongoing gene flow between populations subject to differential selection is expected to produce a soft sweep; such a signature of selection can have a very narrow footprint along the genome and be difficult to detect, even given strong selection[68]. Nonetheless, the density of markers along the genome allowed by high-throughput genomic techniques can be sufficient to identify these regions, especially when replicate populations subject to similar selection pressures can be sampled[66]. The array of genomic techniques covers the range of trade-offs between density of markers and number of individuals or populations sampled. Any information on the overall amount of gametic disequilibrium can inform the experimental design of genome scans (see Supplementary information S1 (figure)).

There are trade-offs between the two general approaches outlined above. The first allows targeting of particular loci, which can be valuable if selection is



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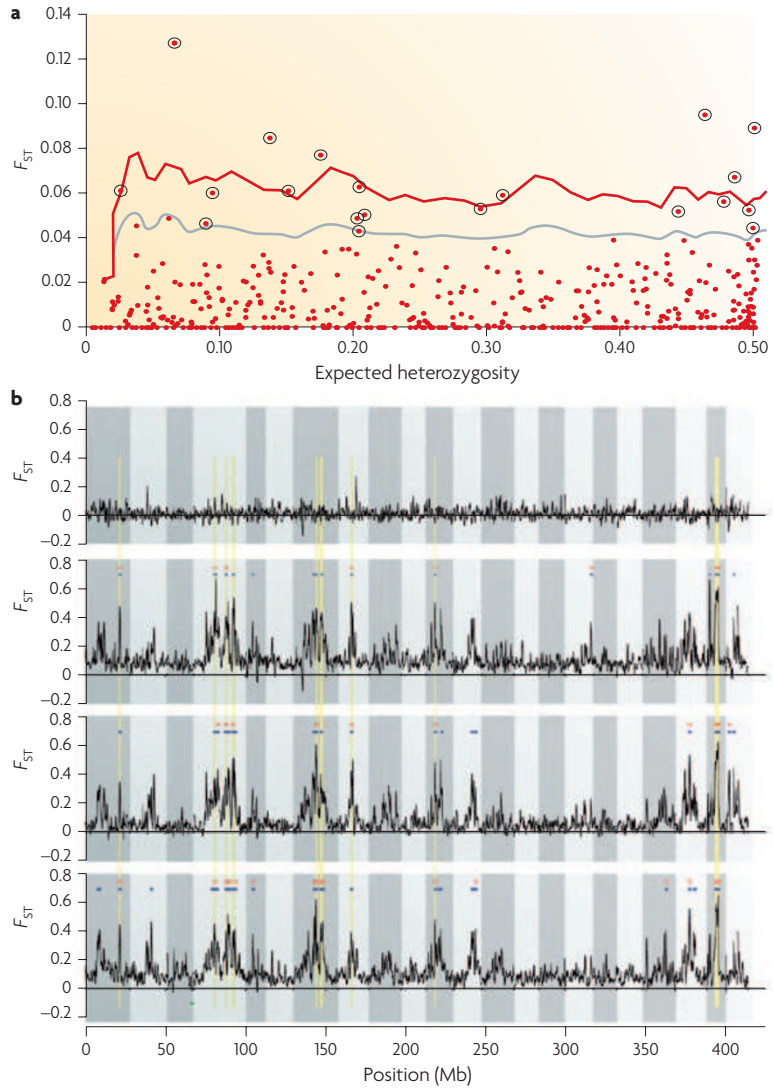
Box 3 | **Genome scans to detect local adaptation**




Genome scans for selection can focus on either candidate loci or anonymous loci. Namroud *et al.*[62] sampled white spruce (*Picea glauca*) from 6 populations in Quebec and genotyped 534 SNPs located on 345 candidate genes. Part **a** of the figure shows their $F_{ST}$ outlier analysis of these data, based on the relationship between $F_{ST}$ and expected heterozygosity[59]; the grey and red lines represent the 95% and 99% confidence levels, respectively. Against a background of little population differentiation ($F_{ST}$ = 0.006), this analysis identified 20 SNPs (circled dots) in 19 genes above the 95% confidence level. New genomic tools also allow anonymous markers to be assayed across the genome to identify local adaptation; for example, Hohenlohe *et al.*[66] sampled 100 threespine stickleback individuals across 5 populations in Alaska. They used sequencing of restriction-site-associated DNA (RAD) tags[127] to simultaneously identify and genotype over 45,000 SNPs across the genome. This density of markers allows population genetic statistics, such as $F_{ST}$, to be visualized as continuous distributions along chromosomes. In part **b** of the figure, the top panel shows $F_{ST}$ between the two marine populations. The next three panels show differentiation between each of the three freshwater populations and the two marine populations. Coloured bars above each graph show regions of significantly elevated $F_{ST}$, as indicated by bootstrap resampling (blue, $p \leq 10^{-5}$; red, $p \leq 10^{-7}$). Vertical grey shading indicates the chromosomes, and yellow shading indicates the nine most significant and consistent peaks of freshwater-versus-marine differentiation. Common patterns of population differentiation (yellow shading shared among the three populations) indicate genomic regions that have responded to divergent selection in parallel across populations.The image in part **a** is reproduced, with permission, from REF. 62 © John Wiley and Sons. The image in part **b** is reproduced from REF. 66.

suspected to act on particular phenotypic traits and functional genetic information is available from related species. This approach can also be applied to a larger number of individuals or populations for the same overall effort. By contrast, the second approach is most useful in the absence of *a priori* hypotheses about specific loci or selective pressures and can provide quantitative information, such as estimates of how many regions of the genome are subject to selection, as well as test whether selection is acting on similar genomic regions across populations. These approaches can also be combined; for example, genotyping arrays can be printed with a combination of probes for candidate and anonymous loci.

***Climate change and other anthropogenic challenges.*** An important component of conservation genetics is understanding how to maintain the ability to evolve in anticipation of environmental change; for example, climate change will affect a wide range of species and habitats. Genomic approaches may allow the identification of adaptive genetic variation related to key traits, such as phenology or drought tolerance, so that management may focus on maintaining adaptive genetic potential. In this context, a landscape genomics approach allows the mapping of associations between adaptive genome regions[69] and environmental gradients in space and time. This could allow forecasting of the effects of environmental change on gene flow of adaptive alleles by predicting spatial–temporal landscape change and modelling gene flow across landscapes expected in the future.

The harvest of phenotypically desirable animals from wild populations imposes selection that can reduce the frequencies of those desirable phenotypes[70]. In addition, genetic changes in response to the harvesting of animals by humans threaten the persistence of many species[71]. The use of genomics to monitor these genetic changes could be extremely important because early detection of potentially harmful changes will maximize our ability to implement management to limit or reverse the effects before substantial or irreversible changes occur[71].

## Units of conservation and hybridization

Describing units of conservation is one of the most important contributions of genetics to conservation[72]. The identification of appropriate taxonomic and population units for protection and management is essential for the conservation of biological diversity. For species identification and classification, genetic principles and methods are relatively well developed. Nevertheless, species identification remains controversial, and agreeing upon a uniform definition of species is Frankham's number two priority for conservation genetics[72].

A great deal of effort is currently involved in describing units within species that are distinct enough to require separate management: these units include evolutionarily significant units (ESUs), distinct population segments and management units. The identification of population units is necessary so that management and monitoring programmes can be efficiently targeted towards distinct or independent populations; such methods could be used to effectively plan harvesting



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Table 2 | **Major techniques for detecting DNA sequence variation and considerations for conservation applications**

| | Traditional markers | qPCR-based SNP chips | High-density SNP chips | Targeted DNA sequencing | Anonymous DNA sequencing | Whole-genome resequencing |
|---|---|---|---|---|---|---|
| Summary | Various techniques for small to moderate numbers of markers | Hybridizing array; genotyping by real-time qPCR | High-density oligonucleotide hybridizing array with fluorescent probes | Fragment capture with oligonucleotide array; genotyping by next-generation sequencing | High-throughput sequencing of reduced representation genomic DNA fragments | Sequencing of whole genome for multiple individuals in a sample |
| Examples | Microsatellites; exon-priming intron-crossing markers | Fluidigm dynamic arrays; Illumina Golden Gate; Applied Biosystems OpenArray[128] | Affymetrix GeneChip; Illumina BeadChip[129] | Exon capture[110] | RAD sequencing[127] | Next-generation and future sequencing technologies |
| *General considerations* | | | | | | |
| Cost per sample | Variable | US$10–50 | $200–500 | $200–1,000 | $50–150 | $500–5,000 |
| Number of markers | $10^1$–$10^2$ | $10^2$–$10^3$ | $10^4$–$10^5$ | $10^4$–$10^5$ | $10^4$–$10^6$ | Complete genome |
| Applicability to new taxa | Moderate | Low | Low | Low–moderate | High | Low |
| Ability to target candidate loci | Yes | Yes | Yes | Yes | No | Yes (bioinformatically) |
| DNA quality required | Low | Low | High | High | Low–moderate | High |
| Equipment needed | PCR machine; traditional sequencer | $100,000 platform | $150,000 platform | $5,000 for equipment; next-generation sequencer | PCR machine; next-generation sequencer | Next-generation sequencer, bioinformatics resources |
| *Utility* | | | | | | |
| Pedigree/kin in wild populations; individual-based population genetics | Limited | Limited–moderate | Yes | Yes | Yes | Data overkill in most cases |
| Neutral (genome-wide average) landscape genetics | Yes, but variance due to few markers | Yes, but variance due to moderate number of markers | Increased accuracy; can include candidate loci | Increased accuracy; can include candidate loci | Increased accuracy; no previous genomic resources | More data than needed |
| Detecting loci of interest (inbreeding depression, outbreeding depression, local adaptation) | Useful after markers at candidate loci have been identified | Useful after markers at candidate loci have been identified | Allows genome scanning along with candidate loci | Allows genome scanning along with candidate loci and targeting chromosome regions | Dense genome coverage for *de novo* mapping | Most appropriate in family-based studies |
| Marker-assisted restoration | Efficient screening of few known markers | Efficient screening of few known markers | Allows genomic selection approaches | Overkill after key markers are identified | Overkill after key markers are identified | Overkill after key markers are identified |

qPCR, quantitative PCR; RAD, restriction-site-associated DNA.

quotas (to avoid overharvesting, for example) or to devise ways to translocate and reintroduce individuals (to avoid, for example, the mixing of adaptively differentiated populations). It is sometimes necessary to prioritize population units for conservation owing to limited financial resources.

Hybridization is one of the major threats to conservation of many plant and animal species[73]. Rates of hybridization and introgression have increased dramatically worldwide because of widespread intentional and incidental translocations of organisms and habitat modifications by humans. Hybridization has contributed to the extinction of many species[73,74]. Genomics could have an important role in distinguishing between natural and anthropogenic hybridization[73]. Also, genomics provides the potential to predict the effects of hybridization on fitness (heterosis or outbreeding depression).

***Units of conservation.*** The description of conservation units generally requires two steps: estimating the amount of gene flow among populations and evaluating the amount of adaptive divergence. The ability to

Phenology
The timing of periodic biological phenomena that are usually correlated with climatic conditions.



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genotype many neutral loci will provide much better estimates of the patterns of reproductive isolation and demographic history of populations to address the first step. Genomic approaches for studying functional genes will provide the opportunity to evaluate the amount of adaptive divergence among populations required in the second step, and its distribution across the genome.

Conservation units have been described on the basis of divergence at loci that are assumed to be selectively neutral. It has been suggested that this could be improved by including genetic divergence at adaptive markers along with the divergence at neutral loci[75–77]. Adaptive markers could enhance and help set priorities for the identification and management of units of conservation. However, a complete understanding of adaptive divergence is unattainable. Moreover, a recent comparison of assumed neutral and putatively selected alleles in over 640,000 autosomal SNPs in humans concluded that average allele frequency divergence is highly predictive of adaptive divergence and that neutral processes (population history, migration and effective population size) exert powerful influences over the geographic distribution of selected alleles[78]. This result supports the use of neutral loci to provide useful descriptions of the patterns of divergence at adaptive loci.

There are pitfalls in focusing on individual adaptive loci rather than neutral patterns or genome-wide averages. Genes important for contemporary or past adaptations might not be those that will be crucial for adaptation in future environments. In addition, much effort has been devoted recently to genome-wide association studies for detecting the genetic basis of complex traits, particularly disease in humans, using large samples of individuals and genetic markers. Although many candidate genes have been identified, often a large proportion of the heritability remains unexplained[79]. A focus on detectable adaptive genomic regions could result in loss of important genetic variation at other regions. Moreover, even when the same genomic regions are implicated in, for example, local adaptation across populations, the particular alleles involved may be different and perhaps even result in outbreeding depression when combined.

Landscape genomics will help to identify management units by providing sufficient power to localize boundaries on the landscape that separate demographically independent groups. Examination of hundreds to thousands of loci in hundreds of individuals across landscapes will improve assessments of the interactions of gene flow, genetic drift and natural selection in influencing the evolution and persistence of populations. Landscape genomics will help to identify ESUs (and spatial locations of boundaries between them) by including both neutral and adaptive variation.

Recent papers have explored the potential of transcriptomic analysis of gene expression to assess functional genetic divergence among populations[80]; for example, Tymchuk *et al.*[81] hybridized a microarray with 16,000 salmonid cDNAs (16K cDNA microarray) to RNA extracted from whole fry raised in captivity in 12 Atlantic salmon (*Salmo salar*) populations to examine global patterns of gene expression and found they were concordant with patterns of divergence at seven microsatellite loci. These results support the notion that patterns of divergence at neutral loci reflect patterns of adaptive variation in gene expression.

***Detection of hybridization.*** Molecular detection of hybridization and estimation of the proportion of admixture between genetically divergent populations can be accomplished accurately with tens of loci[73,82]. However, accurate description of the dynamics of hybridization and introgression can require hundreds of loci[83]. In addition, estimation of the proportion of admixture within individuals will require many more markers.

For example, Halbert and Derr[84] found that 7 of 11 US federal bison (*Bos bison*) populations contained introgression from domestic cattle (*Bos taurus*) based on 14 nuclear loci. The conservation value of admixed populations has been controversial[73,85,86], and some believe that these herds should not be considered as bison for conservation purposes[87]. However, this position has not been generally accepted[87]. Regardless, the potential to estimate the proportion of cattle alleles in individual bison will allow the selection of individuals to reduce the magnitude of introgression from cattle in managed bison herds.

Genomics provides exciting opportunities to assess differential rates of introgression across different genomic regions following hybridization[88]. For example, Fitzpatrick *et al.*[89] found that 3 of 68 markers spread rapidly into native California tiger salamanders (*Ambystoma californiense*), whereas the other 65 markers show little evidence of spread beyond the region where introductions of non-native barred tiger salamanders (*Ambystoma tigrinum mavortium*) occurred. Differential introgression rates of genomic regions raises some difficult issues with regards to treating hybridized populations in conservation[89] and brings into question the efficacy of using a few (that is, ten or so) neutral markers to detect hybridization.

***Outbreeding depression.*** Concerns about the possibility of outbreeding depression have restricted, perhaps unnecessarily, the use of managed gene flow to avoid increased risks of extinction caused by loss of genetic variation because of habitat fragmentation and isolation. Frankham[72] has identified the development of methods for predicting outbreeding depression as the top priority in conservation genetics. Outbreeding depression can result from either chromosomal or genic incompatibilities between hybridizing taxa (intrinsic outbreeding depression) or reduced adaptation to local environmental conditions (extrinsic outbreeding depression)[90]. Genomic approaches can potentially provide valuable empirical information for predicting the probability of either of these sources of outbreeding depression; for example, next-generation sequencing using paired-end reads can be used to detect chromosomal rearrangements[91], such as large inversions or gene copy number variation[92].

Landscape genomics
The study of many markers, including markers in genes under selection, in spatially referenced samples collected across a landscape and often across selection gradients. It uses comparisons of adaptive and neutral variation to quantify the effects of landscape features and environmental variables on gene flow and spatial genetic variation.

Evolutionarily significant unit
A classification of populations that have substantial reproductive isolation which has led to adaptive differences so that the population represents a significant evolutionary component of the species.

Distinct population segment
A classification under the Endangered Species Act of the United States that allows for legal protection of populations that are distinct, relatively reproductively isolated and represent a significant evolutionary lineage to the species.

Management unit
A local population that is managed as a unit owing to its demographic independence.

Introgression
Gene flow between populations or species whose individuals hybridize.

Heterosis
When hybrid individuals have greater fitness than either of the parental types.



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Genomic approaches will also be increasingly used to detect outbreeding depression by estimating the number of progeny produced by individuals with different proportions of admixture. For example, Muhlfeld *et al.*[93] estimated the individual proportion of admixture between introduced rainbow trout (*Oncorhynchus mykiss*) and native westslope cutthroat trout (*Oncorhynchus clarkii lewisi*) (FIG. 2).

## Captive breeding and assisted migration

Genomic tools may assist the management of *ex situ* populations and reintroductions by providing increased precision and accuracy of estimates of neutral population genetic parameters and by identifying specific loci of importance, which is essential for selecting founder individuals. First, many neutral loci could be used to construct a more precise pedigree of the captive population and determine whether the founders from the wild are kin. Second, screening of the founders for known deleterious recessive alleles could substantially reduce any subsequent inbreeding depression in the captive population. In addition, screening of the founders for known adaptive alleles could increase the evolutionary potential of the captive population.

***Managing inbreeding depression.*** The overarching goal of maintaining genetic diversity in an *ex situ* population pre-dates genomic techniques. Nonetheless, genome scans may produce better estimates of genome-wide heterozygosity and genetic diversity than smaller numbers of traditional markers, such as microsatellites[94]. Methods are being developed to maximize the sampling of genetic variation for founders of captive breeding colonies based on genomic data[95]. A caveat here is that the relationship between genome-wide average heterozygosity and inbreeding depression is not always strong. As a result, a more powerful application of genomics may be to estimate pedigrees and degrees of relatedness among captive or founding individuals[35,96], allowing captive management plans to minimize inbreeding *per se*.

The ability to use genomics to identify specific loci related to local adaptation or inbreeding depression and the success of marker-assisted selection in livestock and crops[97] raise the possibility of managing specific loci in some conservation situations. For example, individuals with particular adaptive genetic variants could be chosen for reintroduction or genetic rescue. In captive breeding programmes, particular genetic variants could be selected against. In one example, the small population of the California condor (*Gymnogyps californianus*) has a relatively high frequency of a recessive lethal allele causing chondrodystrophy. A condor genomics project is seeking a marker to identify carriers of the chondrodystrophy allele, and members of this project have therefore developed several genomic resources, including a bacterial artificial chromosome library and a fibroblast cell line for transcriptomic analysis[17], with the goal of designing breeding programmes to select against heterozygotes for the chondrodystrophy allele while minimizing loss of genetic diversity elsewhere in the genome.

***Minimizing adaptation to captivity.*** The emphasis of captive breeding protocols has been to reduce genetic drift by maximizing effective population size[98], which is appropriate for captive breeding programmes of mammals and birds in zoos that have a relatively small number of individuals that are managed using pedigrees.

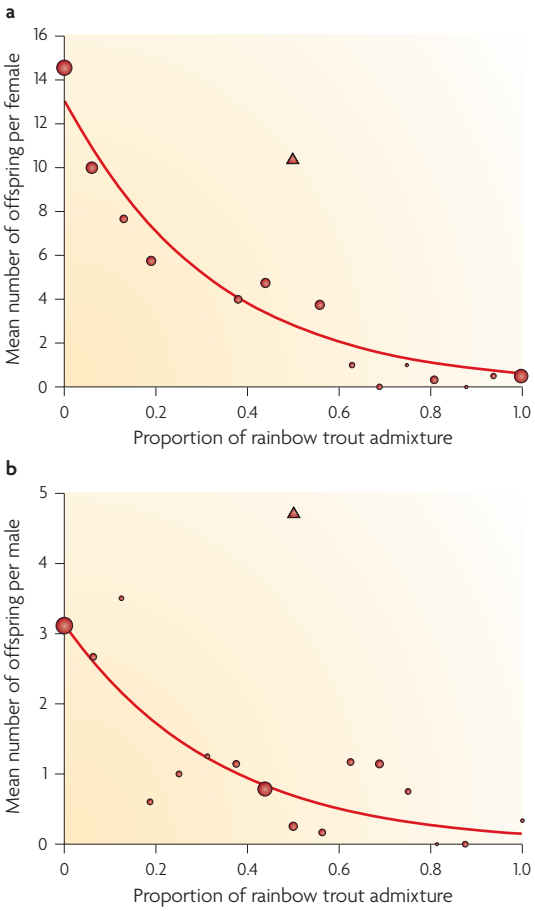


Figure 2 | **Effects of proportion of individual admixture with introduced rainbow trout on the fitness of native westslope cutthroat trout.** Sixteen microsatellite loci were used to estimate the individual proportion of admixture between introduced rainbow trout and native westslope cutthroat trout[93]. These same loci were used to identify the parents of progeny produced in a stream over a 5-year period. The bubble plots show the mean number of offspring per individual identified plotted against the proportion of rainbow trout admixture for females (**a**) and males (**b**). In a bubble plot, the size of the bubble is proportional to the number of observations with that value. The mean values for first-generation hybrids are shown as triangles; these points were not included in the regression. These results are striking in two ways. First, there was a strong reduction in the number of progeny produced as the amount of admixture with introduced rainbow trout increased in both females and males. Second, first-generation hybrids had much greater reproductive success than other individuals with 50% admixture. This suggests a strong heterotic effect in the first-generation hybrids caused by sheltering of deleterious recessive alleles. Figure is reproduced, with permission, from REF. 93 © (2009) The Royal Society.

Marker-assisted selection
The use of molecular genetic markers to increase the response to selection in a population by the favouring of reproduction by individuals with a certain allele or genotype. The marker is closely linked to a quantitative trait locus.

Genetic rescue
The recovery in the average fitness of individuals through increased gene flow into small populations, typically following a fitness reduction due to inbreeding depression.

Chondrodystrophy
A genetically based skeletal disorder that affects the development of cartilage.



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However, adaptation to captivity is a serious problem associated with captive breeding programmes for many species[99,100]. This will inevitably reduce the fitness of individuals reintroduced to wild or natural conditions. For example, tameness in response to humans is generally advantageous in captivity but can have serious consequences in the wild. In addition, increasing effective population size for some captive species (for example, fish and plants) may increase the rate of adaptation to captive conditions. Genetic monitoring[101] of many loci throughout the genome should become a standard tool for detecting adaptation to captivity (that is, rapid, locus-specific change in allele frequencies) in species for which adaptation to captivity is a concern[100].

***Restoration.*** The condor example highlights the complexity of identifying specific loci to allow targeted genetic management of populations, even when a single Mendelian locus is implicated. However, the success of marker-assisted selection in livestock is due in part to the fact that specific alleles and their functional roles need not be determined; rather a correlation between phenotype and genotype at multiple markers is established, and selection on genotype produces a correlated response in phenotype (for example, growth rate or disease resistance). Given the ability to identify genomic regions correlated with local adaptation (BOX 3), conservation genomics could similarly use this information in, for example, selecting source populations for translocation or reintroduction. A general risk in such efforts is outbreeding depression as a result of different and incompatible genetic bases of adaptation in the two populations. The choice of source population can now be informed by four factors: ecological similarity, phenotypic similarity, genome-wide similarity as indicated by neutral markers, and genetic similarity at adaptive loci.

Genetic rescue has been used as an effective restoration tool to avoid or reverse the consequences of inbreeding depression[102]. However, the identification of individual loci with major adaptive effects (for example, major histocompatibility complex in animals[103] and self-incompatibility loci in plants[104]) raises the possibility of allele-specific genetic rescue. Interestingly, other loci with exceptionally strong fitness effects are being found in a number of species, such as *Pan*I[105] in the cod family (Gadidae) and *Pgi* in butterflies and other insects[106]. It remains to be seen whether such loci are unusual or are present in most species.

Research in community genomics suggests that individual alleles can affect community diversity and composition[107–109]. For example, alleles at tannin loci in cottonwood trees increase the palatability and decay rate of leaves, which in turn influences the abundance of soil microbes, fungi and arboreal insects and birds[108]. Loss or restoration of such alleles to populations could thus influence community diversity and ecosystem function[108]. Nevertheless, the complexity of these interactions presents real challenges before it will be possible to use this information in a practical conservation situation.

Community genomics
The study of the effect of individual alleles or genotypes on the species composition, diversity or functioning of a community or ecosystem.

## Choosing genomic approaches

The diverse and growing list of genomic techniques provides a range of options for experimental design (TABLE 2). Currently, array-based techniques (SNP chips) can efficiently genotype markers across many individuals for a range of conservation applications. As the cost of sequencing continues to fall, reduced-representation sequencing may replace SNP chips as a preferred method in many cases[110]. Sequence data can provide additional information for functional assessment of candidate genes or detection of haplotype structure or inversion polymorphisms, and sequencing is easily applied to taxa without any existing genomic resources. However, at least in the near term, array techniques will retain their advantage of having a highly standardized protocol for genotyping a fixed set of markers. This makes them well-suited to, for example, long-term genetic monitoring of populations.

It is becoming feasible to sequence complete genomes in a reasonable research timeline and budget[111]. Whole-genome resequencing of all individuals in a study will become an option in conservation[112]. However, while there are potential uses for whole-genome resequencing, such as detection of Mendelian inherited traits in families[53], in most situations it is likely to create more challenges than it solves. First, because of linkage disequilibrium, dense marker genotyping already provides a nearly complete view of genomic variation[113]. Such genomic structure is likely to be even more pronounced in small populations of conservation concern than in traditional model organisms[46]; whole-genome resequencing is thus data overkill. Moreover, whole-genome resequencing introduces many challenges for computational bioinformatics; the resources simply to store, assemble and analyse such large data sets may outweigh their benefits, at least for the near future.

We envision an emerging standard for conservation genomics in which the starting point will be a reference genome sequence. A rapidly growing number of species, particularly vertebrates, have reference sequences available already[114], or an initial investment can be made to produce one. From this point, genotyping of multiple individuals from population samples would be done with array-based or reduced-representation sequencing techniques, with the reference sequence providing a valuable resource for sequence alignment and candidate gene identification and annotation.

## Perspective

This is an exciting and challenging time for conservation genetics. Genomic approaches have the potential to transform the management of populations for conservation in various ways, from estimates of pedigrees and inbreeding based on large numbers of markers to identification of loci responsible for local adaptation and outbreeding depression. Genomics also provides the potential to understand the genetic basis of interactions among species, which could greatly enhance our ability to manage communities rather than just individual species. Perhaps the greatest contribution of genomics to conservation will be the precise genomic monitoring



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Epigenetics
Changes in or gene expression caused by mechanisms other than changes in the underlying DNA sequence, such as DNA methylation and histone modifications.

Vital rates
Demographic values that affect population growth (for example, age-specific survival, fecundity and age at first reproduction).

of changes in allelic frequency to quantify the effects of genetic drift, natural selection and hybridization in wild and captive populations.

Although we have focused on genomic techniques that detect variation in DNA sequences, emerging techniques also allow the study of epigenetics, which may have an important role in conservation genetics in the future[115,116]. There is increasing evidence that epigenetic processes can be important following hybridization and in outbreeding depression[115,117]. In addition, epigenetic effects might be an important source of variation for invasive species. Richards *et al.*[118] have shown that the invasive Japanese knotweed (*Fallopia* spp.), which has little variation in DNA sequence, maintains substantial phenotypic variation even under controlled environmental conditions. Epigenetic effects associated with this phenotypic variation might enhance knotweed's ability to invade novel environments. This could partially explain the paradox of invasive species that have lost genetic variation during a bottleneck associated with their introduction but are nonetheless able to adapt to new environmental conditions[119].

Recognizing the limitations of new techniques is also essential. Improved basic scientific understanding through genomics will not necessarily lead to improved conservation. For example, genomics will make it possible to provide genome-wide estimates of functional genetic variation and fitness[1]. Nevertheless, this will not be sufficient to improve our estimates of population viability unless we are able to make the connections between individual fitness and population growth rates[120] (FIG. 1). To make these connections will require long-term studies of individual fitness and of the effects of fitness differences among individuals on demographic vital rates. This is perhaps the most important and difficult future challenge facing conservation genetics.


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**Competing interests statement**
The authors declare no competing financial interests.

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