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Effects of germplasm exchange strategies on genetic gain, homozygosity, and genetic diversity in dairy stud populations: A simulation study

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ABSTRACT

Although genomic selection has led to considerable improvements in genetic gain, it has also seemingly led to increased rates of inbreeding and homozygosity, which can negatively affect genetic diversity and the long-term sustainability of dairy populations. Using genotypes from US Holstein animals from 3 distinct stud populations, we performed a simulation study consisting of 10 rounds of selection, with each breeding population composed of 200 males and 2,000 females. The investigated selection strategies consisted of selection using true breeding values, EBV, EBV penalized for the average future genomic inbreeding of progeny (PEN-EBV), or random selection (RAND). We also simulated several germplasm exchange strategies where germplasm of males from other populations was used for breeding. These strategies included exchanging males based on EBV, PEN-EBV, or low genomic future inbreeding value (GFI) of progeny, or randomly (RAND). Variations of several parameters, such as the correlation between the selection objectives of populations and the size of the exchange, were simulated. Penalizing genetic merit to minimize genomic inbreeding of progeny provided similar genetic gain and reduced the average homozygosity of populations compared with the EBV strategy. Germplasm exchange was found to generally provide long-term benefits to all stud populations. In both the short and the long term, germplasm exchange using the EBV or PEN-EBV strategies provided more cumulative genetic progress than the no-exchange strategy; the amount of long-term genetic progress achieved with germplasm exchange using these strategies was higher for scenarios with a higher genetic correlation between the traits selected by the studs and for a larger size of the exchange. Both the PEN-EBV and GFI exchange strategies allowed decreases in homozygosity and provided significant benefits to genetic diversity compared with other strategies, including larger average minor allele frequencies and smaller proportions of markers near fixation. Overall, this study showed the value of breeding strategies to balance genetic progress and genetic diversity and the benefits of cooperation between studs to ensure the sustainability of their respective breeding programs.
Key words: inbreeding, genetic progress, Holstein

INTRODUCTION

Genetic diversity is a necessary resource that allows populations to maintain selection potential. In livestock populations, the exploitation of genetic diversity via artificial selection allows for genetic improvement for traits of economic or cultural importance. However, selection alters genetic variability by a myriad of processes that cause changes in the allelic frequency of QTL and linked neutral variants, such as hitchhiking (Charlesworth and Jensen, 2021). Reduced genetic variation has been theoretically and experimentally shown to decrease both the generational response to selection and overall selection limits (Lerner and Dempster, 1951; Falconer and Mackay, 1996; Pujol and Pannell, 2008). A population's effective size indicates its level of genetic diversity and ability to respond to selection (Wright, 1931; Falconer and Mackay, 1996). Multiple experiments have shown that total selection response increases with larger population sizes at given levels of selection intensity (Jones et al., 1968; Weber and Diggins, 1990).

Increased inbreeding is another consequence of intense artificial selection. In US dairy cattle, the introduction and rapid adoption of genomic selection has led to a monumental increase in the rate of genetic progress for many traits, particularly for those of low heritability (García-Ruiz et al., 2016; Guinan et al., 2023). However,

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recent studies in several Holstein and Jersey dairy cattle populations that have implemented genomic selection have reported an associated increase in yearly and generational inbreeding (Doekes et al., 2018; Makanjuola et al., 2020b; Scott et al., 2021; van Kaam et al., 2023). In addition, the use of high-intensity reproductive technologies such as ovum pickup and in vitro fertilization can lead to a faster accumulation of inbreeding than lower-intensity reproductive methods (Doublet et al., 2020). In the United States, the rates of pedigree and genomic inbreeding have been found to have increased in recent years, coinciding with the implementation of genomic selection and increased use of reproductive technologies, particularly for Holstein bulls (Lozada-Soto et al., 2022; Guinan et al., 2023). Recent increases in the rate of genomic inbreeding have also been found for Brown Swiss, Ayrshire, and Guernsey bulls in the United States (Lozada-Soto et al., 2022). High rates of inbreeding concern not only the associated loss in genetic variability but also the inbreeding depression that has been observed to affect dairy cattle production. Pedigree and genomic inbreeding have been found to negatively affect virtually all traits of economic importance for dairy production, including milk production, reproductive performance, conformation, and health (Sørensen et al., 2006; Bjelland et al., 2013; Makanjuola et al., 2020a; Lozada-Soto et al., 2023).

Several selection and mating strategies have been proposed to manage inbreeding rates, accumulation of homozygosity, and genetic diversity while maximizing genomic progress; some of these include linear programming (Jansen and Wilton, 1984), using a mate allocation strategy to minimize progeny inbreeding (Pryce et al., 2012), and selection incorporating the variance of gametic diversity (Santos et al., 2019). However, optimum contribution selection is the most popular method to achieve this (Meuwissen, 1997). Optimum contribution selection is a method that finds the optimum level of genetic contributions from selection candidates to maximize genetic gain and maintain a predefined rate of inbreeding. This method is highly flexible, as it can incorporate pedigree or genomic relationships and can be used for breeding programs with different breeding objectives, including minimizing global and region-specific kinship, maximizing different genetic diversity parameters, or recovering the lost historic or native genomic background of populations through introgression (Toro et al., 2014; Wang et al., 2017). However, the adoption of optimum contribution selection methodology is impeded for dairy populations where breeding decisions are decentralized and controlled by individual farmers, such as the US dairy population.

The preferred strategy to control inbreeding in the United States is by adjusting EBVs, parental transmitting abilities, and daughter yield deviations by the expected future inbreeding of progeny (VanRaden, 2005). However, even with these adjustments, rates of inbreeding have increased. This is partly due to current practices in the management and dissemination of the germplasm of elite animals. Presently, elite animals are identified and used within stud populations, which has caused the proliferation of elite males descended from just a few bull families (Yue et al., 2015; Cole et al., 2021). The introduction of genetic material from other lines has been proposed as an alternative to alleviate decreases in genetic diversity. Still, several logistical obstacles must be traversed first, and the method and scale of potential implementation are yet to be determined.

Therefore, we have designed a simulation to determine the effects of selection and germplasm exchange strategies on genetic progress, homozygosity, and genetic diversity in dairy stud populations.

MATERIALS AND METHODS

Populations and Traits Simulated

Founder Population. We used actual genotypes from US Holstein animals born between 2010 and 2020 to create 3 distinct founder populations using the 'importHaplo' AlphaSimR (v.1.3.4; Gaynor et al., 2021) function. Specifically, we sampled 200 males and 1,000 females from 3 large stud populations to serve as the founder animals for each population. We simulated random mating between these founder animals to create a sizable initial selection population of 3,720 animals (220 males and 3,500 females). The initial 220 males in the selection population were randomly assigned to be third-year and older (n = 180), second-year (n = 20), or immature first-year males (n = 20). Similarly, for the initial 3,500 females in each selection population, these were randomly assigned to be third-year females (n = 500), second-year females (n = 1,500), or immature first-year females (n = 1,500).

Genotypes. We first performed quality control on 76,389 imputed autosomal SNP to obtain markers for the founder population. Methodologies on variant selection and imputation are described by VanRaden et al. (2017). Quality control included the removal of markers with a minor allele frequency smaller than 5% or a call rate smaller than 99%. For computational ease, only markers in the first 5 autosomal *Bos taurus* chromosomes (BTA1 to BTA5) were retained, a total of 18,683 SNP. Animals with a call rate smaller than 99% were removed. Genotypes were phased using SHAPEIT v2 (Delaneau et al., 2012, 2013) with default parameters. Finally, we randomly sampled 2,000 markers from each chromosome to have a reduced set of 10,000 markers for the simulation.

Traits. We simulated 3 yield traits controlled by the same 500 QTL (100 per chromosome). For simplicity,

only additive effects for the QTL influencing each trait were simulated. The additive effects for each trait were sampled from a normal distribution with a mean of \$0 and SD equal to \$200; these parameters were chosen to approximate those of lifetime net merit (VanRaden and Cole, 2014; Cole, 2015). The additive genetic correlation between traits was parametrized according to an epsilon parameter (ε) so that the matrix of correlations was

$$\begin{vmatrix} 1 & \varepsilon & \varepsilon \\ \varepsilon & 1 & \varepsilon^2 \\ \varepsilon & \varepsilon^2 & 1 \end{vmatrix},$$

where the correlation between the first trait and the other 2 traits was ε and the correlation between the second and third trait was ε^2. Three different values of ε were simulated: 0.90 (representing a high genetic correlation between all traits), 0.50 (representing moderate and low correlations between traits), and 0.10 (representing low and very low correlation between traits). Each trait served as the selection objective for one of the populations, with traits 1, 2, and 3 being selected for in populations 1 through 3, respectively. This was done to measure the effects and possible benefits of germplasm exchange when breeding programs between studs are not entirely aligned.

Software. The AlphaSimR R package (v.1.3.4; Gaynor et al., 2021) was used to import founder animals, initiate and track simulated populations and genotypes, simulate the genetic architecture of yield traits, and perform selection and mating steps.

Genetic Merit

The true breeding value (**TBV**) was calculated as the expected genotypic value of the performance of an animal's offspring when the animal is randomly mated either within or across populations (Stock et al., 2021). The TBV of animals was obtained either within population (**TBVw**; i.e., merit of animals in population 1 for trait 1) or across population (**TBVa**; i.e., merit of animals in population 1 for trait 2) in each selection round. The TBVw was calculated using $\text{TBVw}_{ij} = \sum_{k=1}^{nQTL}\left[\left(x_{ijk}\right)\left(p_{kj}a_k\right)\right] + \left[\left(1-x_{ijk}\right)\left(-q_{kj}a_k\right)\right]$, where x_{ik} is the genotype of ith animal of the jth population for the kth QTL (AA=1, Aa=0.5, and aa=0); p_{kj} and q_{kj} are the frequencies of the A and a alleles, respectively, for QTL k in population j; and a_k is the true additive effect for QTL k. Similarly, to calculate TBVa we used $\text{TBVa}_{ij} = \sum_{k=1}^{nQTL}\left[\left(x_{ijk}\right)\left(p_{kj'}a_k\right)\right] + \left[\left(1-x_{ijk}\right)\left(-q_{kj'}a_k\right)\right]$, where the only difference is that the allelic frequencies used (p_{kj} and q_{kj}) are of the target population (j') for mating (i.e., population 2 if the merit of population 1 for trait 2 is being calculated).

We also obtained animals' EBV by producing a random vector of normally distributed values with a specified Pearson correlation with the vector of TBV of 0.75. This was done using the 'rnom_pre' function of the faux R package (v.1.1.0; https://debruine.github.io/faux; DeBruine, 2021). For males, a penalized EBV (**PEN-EBV**) was calculated using PEN-EBV = $\text{EBV}_i - 2\lambda\text{GFI}$, where EBV_i is the EBV of the animal; **GFI** is the genomic future inbreeding value, calculated as half the average relationship (based on a genomic relationship matrix) of an animal to the breeding population of females from the target population at each selection round; and λ is a weighting factor on the average progeny inbreeding. In this study, we used a fixed value of \$25 for λ (Cole, 2015). To track genetic gain, each animal's true genomic value (**TGV**) was calculated as $\text{TGV}_{ij} = \sum_{k=1}^{nQTL} x_{ijk}a_k$, where x_{ijk} and a_k were as previously described.

Selection and Germplasm Exchange Strategies

Ten selection rounds were simulated using a general selection scheme implemented within each population (see Figure 1).

Within each population, 200 males were mated with 2,000 females to generate 10,000 selection candidates with an equal sex ratio in each selection round (5 offspring per female). Mating was done randomly, and each male mated with exactly 10 females. The age classifica-

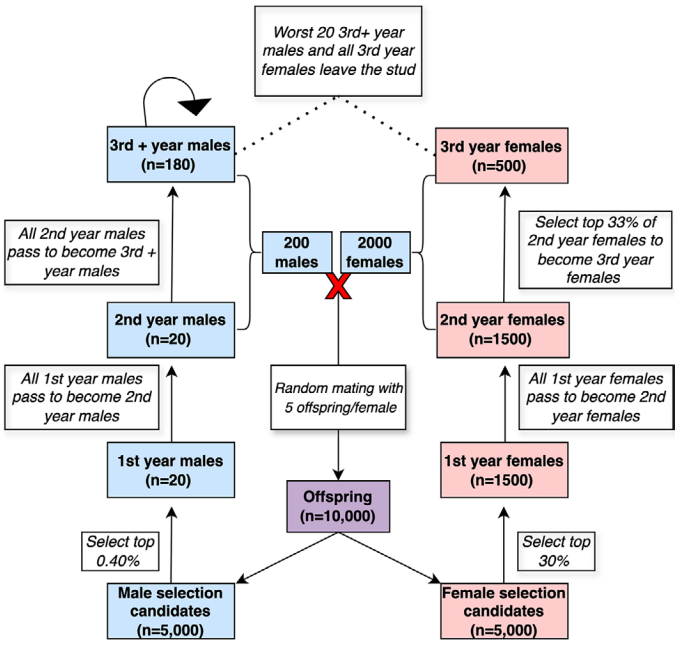

Figure 1. Diagram of selection within population.

tions of the males and females were consistent with the method described in the "Founder Population" subsection. All offspring were considered as selection candidates. We selected 20 males and 1,500 females to become immature first-year males and females and eventually join the breeding population. To maintain constant size of each population, a portion of the breeding population of equal size to the number of selected individuals was removed at each selection round. Further details on this procedure are provided in Figure 1.

The study explored several strategies of selection and germplasm exchange. The first set of strategies (selection) included selection exclusively within a given stud population where males were selected randomly (**RAND**), on TBV, on EBV, or on EBV penalized for the average genomic kinship with the female breeding population (PEN-EBV). In each respective strategy, the selection objective for females was the same as for males, except for the PEN-EBV selection strategy, in which case the females were selected based on EBV. The second set of strategies (germplasm exchange) explored the effect of allowing germplasm from either 10 or 100 breeding males from the other 2 populations to be used for mating with the females of a given population. We simulated several different germplasm exchange strategies, including random exchange of male germplasm (RAND), exchange based on EBV, PEN-EBV, or GFI. When PEN-EBV or GFI were used, genomic kinships with the female population intended for mating were calculated.

For germplasm exchange strategies, all breeding males from each population were available for use in the other 2 populations. Germplasm from the other populations effectively replaced a portion of breeding males (10 or 100 males, depending on the size of exchange simulated) for mating purposes, specifically those that had the lowest merit (or randomly in some scenarios). This was done to keep the number of males and females used in mating and the number of females mated to each male constant. Males replaced in mating at a given selection round were not immediately removed from the population and had the opportunity to be chosen for mating in future rounds.

Population Parameters Tracked

In this simulation study, we tracked various population parameters of interest. We calculated the cumulative genetic progress (Δ_G) toward the selection objective within each population by comparing the average initial TGV to the average TGV at each selection round. We also calculated the relative change in the average genomic homozygosity (RC_{HOM}) for each population at each selection round.

To assess the effects of the selection and germplasm exchange strategies on genetic diversity across populations, we tracked several measures, including genetic distance, changes in the average minor allele frequency (**MAF**), and changes in the proportion of genome-wide markers nearing fixation. The genetic distance between populations was calculated at each selection round using the fixation index (F_{ST}) as defined by Wright (Wright, 1951; Nei, 1977). We also calculated the relative change in the average MAF (RC_{MAF}) across markers and populations at each selection round. Finally, we calculated the relative change in the proportion of allele marker fixation (RC_{MONO}). We considered alleles nearing fixation as those with an across-population MAF below 1%.

Simulated Scenarios and Statistical Analysis

Several scenarios were simulated to answer relevant questions (Table 1). In the first scenario (scenario 1), we explored the effects of selection strategy on genetic progress and homozygosity. In scenario 1, we tested all 4 selection strategies, TBV, EBV, PEN-EBV, or RAND, in the case that germplasm was not exchanged. In scenario 2, we simulated no germplasm exchange or germplasm exchange of 10 males by using each germplasm exchange strategy (EBV, PEN-EBV, GFI, and RAND) and when selection was performed using either the EBV or the PEN-EBV strategy with ε correlation parameter being held constant at 0.50. Finally, scenarios 3A and 3B included scenarios aimed at evaluating the effect of different factors on germplasm exchange strategies. For both scenarios 3A and 3B, selection was performed

Table 1. Simulation scenarios investigated and parameters varied within each scenario[1]

Scenario	Selection strategy	ε correlation parameter	Germplasm exchange strategy	Size of exchange[2]
1	TBV/EBV/PEN-EBV/RAND	0.50	None	NA
2	EBV/PEN-EBV	0.50	None/EBV/PEN-EBV/GFI/RAND	10
3A	PEN-EBV	0.10/0.50/0.90	EBV/PEN-EBV/GFI	10
3B	PEN-EBV	0.50	EBV/PEN-EBV/GFI	10/100

[1]TBV = true breeding value strategy; EBV = estimated breeding value strategy; PEN-EBV = penalized EBV strategy; RAND = random strategy; GFI = genomic future inbreeding strategy.

[2]Except in the case that the germplasm exchange strategy was none; in this case no males were exchanged (NA = not applicable).

using the PEN-EBV strategy and germplasm exchange was done using each of the 4 strategies, but either the ε correlation parameter (0.10, 0.50, or 0.90) or the size of the exchange (10 or 100) was varied, corresponding to scenarios 3A and 3B, respectively.

The effects of the variable factors in each simulation scenario were evaluated using the "lmer" function of the lme4 R package (Kuznetsova et al., 2017) to fit mixed linear models in R (v.4.1.2). All models included a random effect of replicate, and models in which the response was a within-population parameter (Δ_G and RC_{HOM}) included a fixed effect of population. A table including the effects of the model used to evaluate each scenario can be found in Supplemental File S1 (see Notes). Least squares means (LSM) for all fixed effects were obtained using the emmeans R package (v.1.8.5; Lenth, 2022). Confidence intervals for the mean estimates were constructed based on a 95% confidence level. Estimates with nonoverlapping CI were said to be significantly different from each other.

RESULTS

Comparison of Selection Strategies

Results for the effect of the selection strategy (scenario 1) on within-population measures of genetic gain and homozygosity can be found in Figure 2 and Supplemental File S2 (see Notes). Figure 2a depicts the average Δ_G and RC_{HOM} with respect to generation 1 across 25 replicates for each selection round and for all 3 populations when each of the selection strategies was used. All other parameters were fixed to values specified for scenario 1. Figure 2b and 2c contain the LSM estimates (averaged across population) for the effect of selection strategy on Δ_G or RC_{HOM} at selection rounds 3 and 10, respectively.

Genetic Progress. As expected, selection based on TBV resulted in the most considerable genetic progress of any of the selection strategies after 10 selection rounds (LSM = 4.52 genetic SD; SE = 0.02). Also expected was the lack of genetic improvement of random selection after 10 selection rounds (LSM = −0.02 genetic SD; SE = 0.02). When comparing the 2 most realistic selection scenarios (EBV and PEN-EBV), we found that, although using a PEN-EBV selection strategy resulted in significantly lower genetic progress, the cumulative genetic gain achieved by both strategies was of similar magnitude in the short and long term. For example, after 10 selection rounds, the LSM estimates of cumulative genetic gain of the PEN-EBV and EBV strategies were 3.26 genetic SD (SE = 0.02) and 3.37 genetic SD (SE = 0.02), respectively.

Homozygosity. In the absence of germplasm exchange, selection using PEN-EBV was the only strategy to not increase the average homozygosity of the populations in both the short (LSM = −0.01% change; SE = 0.02%) and the long term (LSM = −0.41% change; SE = 0.06%). However, when examining the trend in the change in homozygosity for each population (see Figure 2, panel A), selection using PEN-EBV decreased homozygosity in each successive selection round, until selection rounds 8 and 9 when a minimum was reached. All other selection strategies increased homozygosity, with LSM estimates after 10 selection rounds ranging from 0.17% (SE = 0.06%) to a 1.44% increase for RAND and TBV selection strategies, respectively.

Effects of Germplasm Exchange Strategies

We explored the effects of exchanging 10 bulls based on EBV, PEN-EBV, low GFI, or randomly (RAND) in the cases where the within-population selection strategy was using EBV or PEN-EBV. Results for the effects of germplasm exchange (scenario 2) on within-population measures of genetic gain and homozygosity can be found in Figure 3 and Supplemental Files S3 and S4 (see Notes). Panel A of Figure 3 depicts the average Δ_G and RC_{HOM} across 25 replicates for each selection round. The correlation between traits was kept at the moderate value (ε = 0.50), and the size of the exchange was of 10 bulls. Panels B and C of Figure 3 depict the LSM estimates (averaged across population) for the interaction between germplasm exchange strategy and selection strategy (EBV or PEN-EBV) on each measure at selection rounds 3 and 10, respectively.

Figure 4 shows results of the effect of germplasm exchange method on the across-population measures of genetic diversity. Panel A of Figure 4 depicts the average F_{ST}, RC_{MAF}, and RC_{MONO} across 25 replicates and in each selection round using different germplasm exchange strategies and either the EBV or PEN-EBV selection strategies. Panels B and C of Figure 4 depict the LSM estimates for the interaction between germplasm exchange strategy (none, PEN-EBV, GFI, or RAND) and selection strategy (EBV or PEN-EBV) on each measure at selection rounds 3 and 10, respectively. Estimates can be found in Supplemental Files S5 and S6 (see Notes).

Genetic Progress. Germplasm exchange in the short term (3 rounds of selection and germplasm exchange) resulted in more genetic progress than not performing germplasm exchange, regardless of which strategy was used, although only to a small extent, with the most considerable difference in genetic progress being 0.08 genetic SD between using PEN-EBV selection with no germplasm exchange (LSM = 0.90 genetic SD; SE = 0.004) and using EBV for both selection and germplasm exchange (LSM = 0.98 genetic SD; SE = 0.004). In both the short and long term and within a given selection strat-

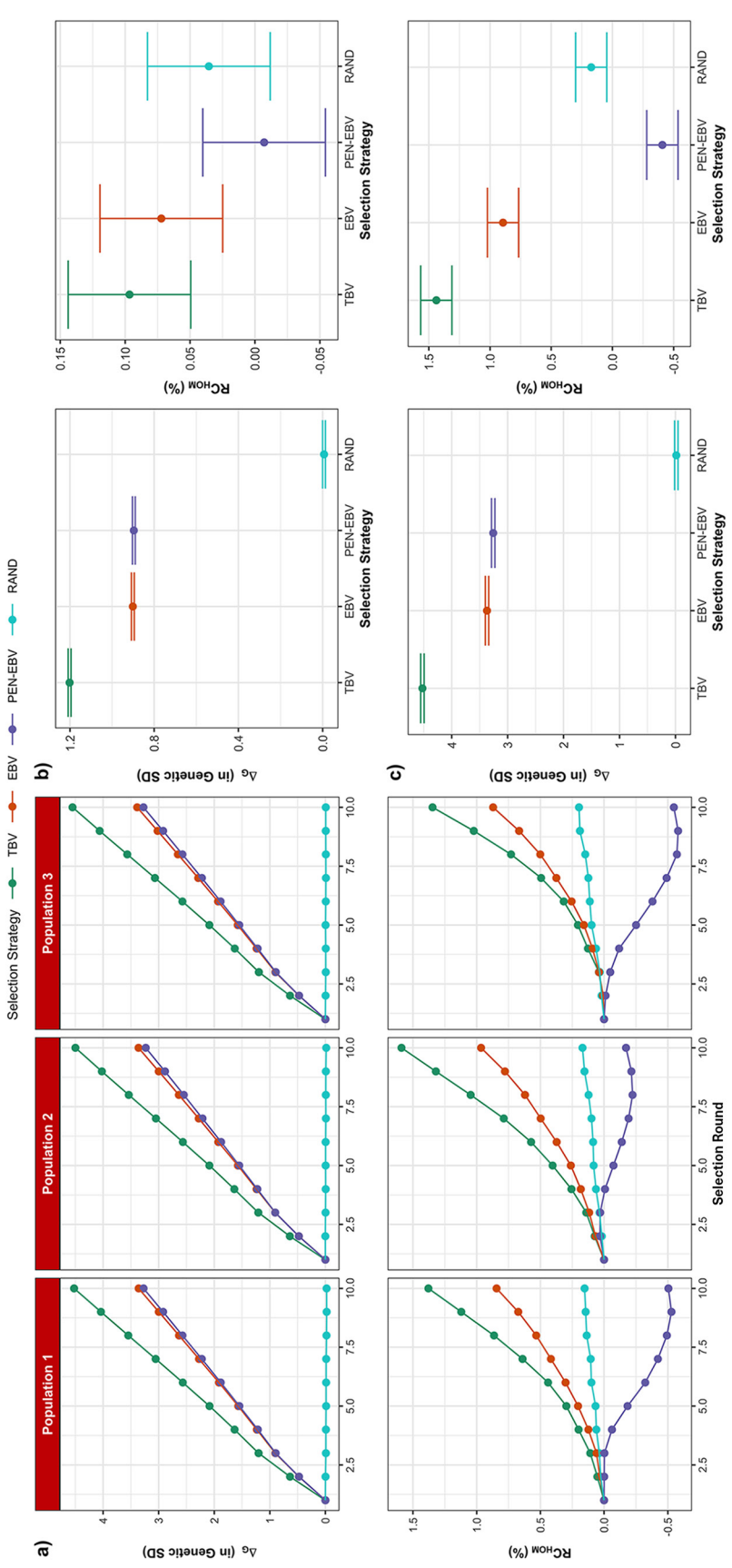

Figure 2. Effects of selection strategy on genetic gain and homozygosity. (a) Average across 25 replicates for each measure at each selection round using different selection strategies (TBV, EBV, PEN-EBV, and RAND). (b) Least squares means for the effect of selection strategy on each measure averaged across populations at selection round 3. (c) Least squares means for the effect of selection strategy on each measure averaged across populations at selection round 10.

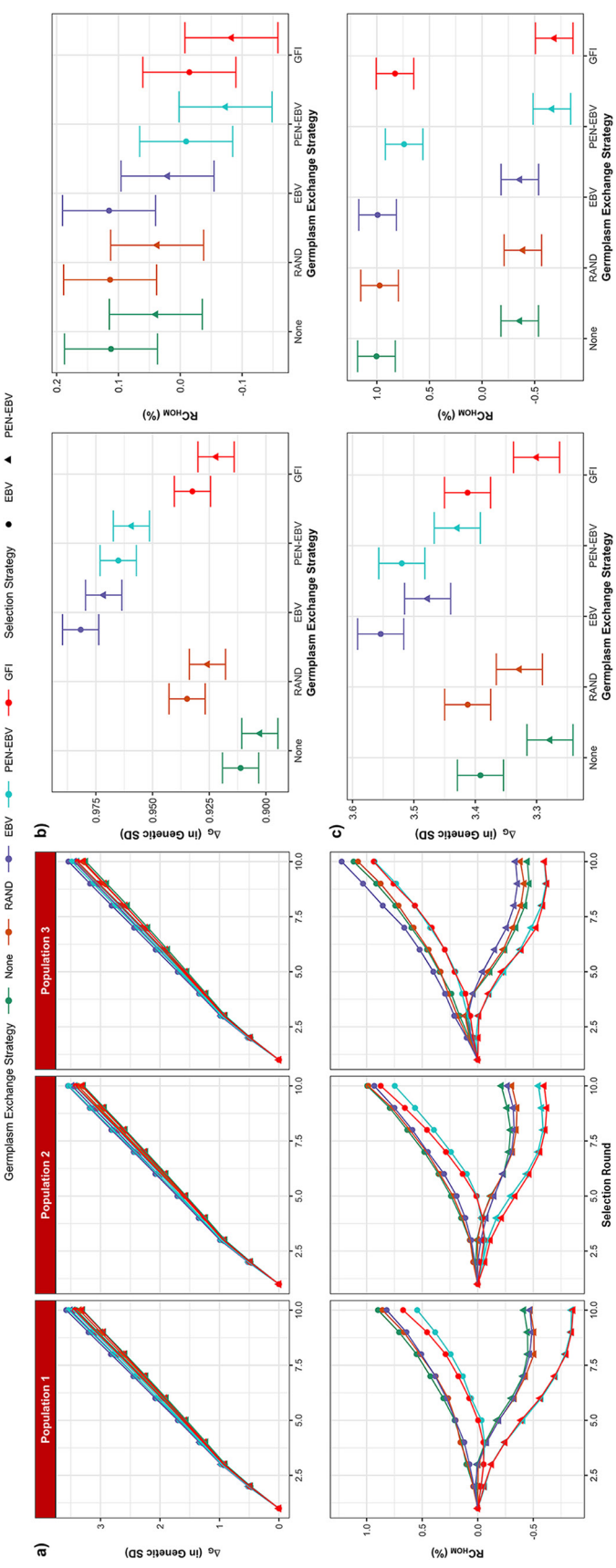

Figure 3. Effects of germplasm exchange strategy on genetic gain and homozygosity. (a) Average across 25 replicates for each measure at each selection round using different germplasm exchange strategies (no exchange [None], PEN-EBV, GFI, and RAND) when selection strategy was EBV or PEN-EBV. (b) Least squares means for the interaction between selection strategy and germplasm exchange strategy on each measure averaged across populations at selection round 3. (c) Least squares means for the interaction between selection strategy and germplasm exchange strategy on each measure averaged across populations at selection round 10.

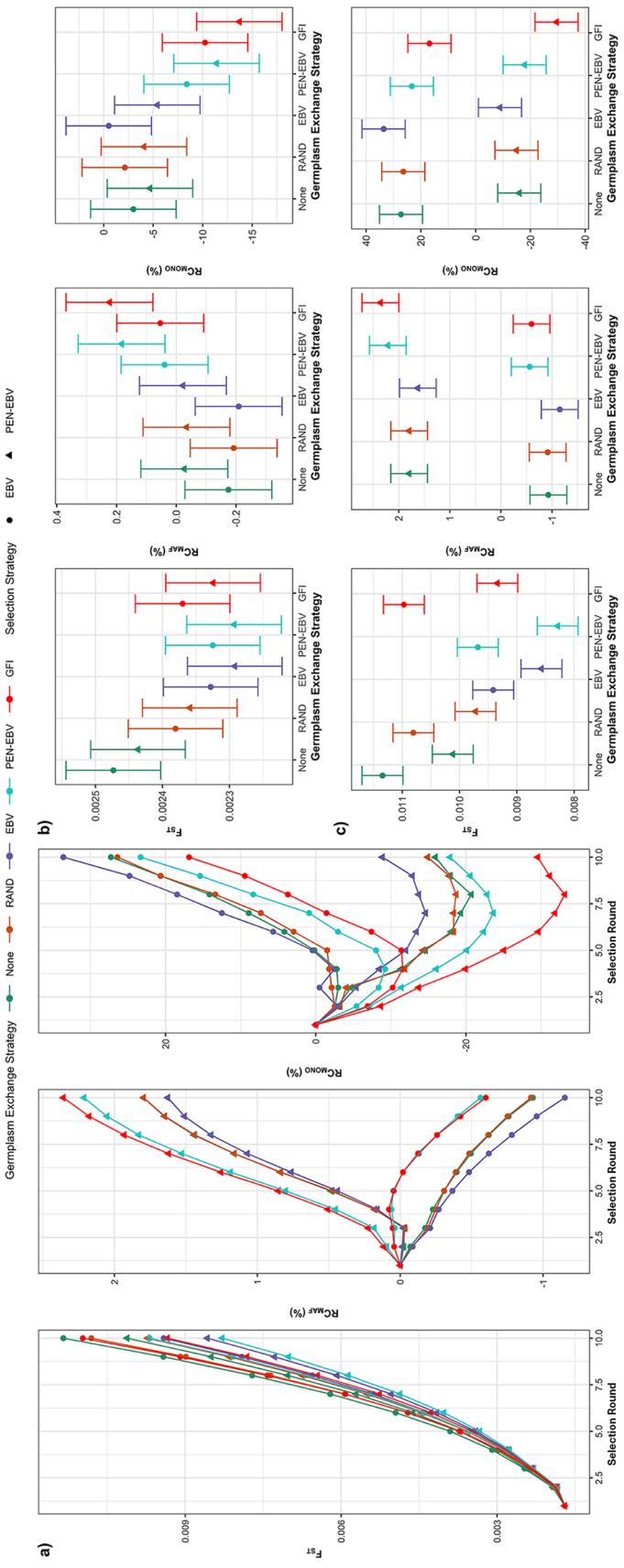

Figure 4. Effects of germplasm exchange strategy on measures of across-population genetic diversity. (a) Average across 25 replicates for each measure at each selection round using different germplasm exchange strategies (no exchange [None], PEN-EBV, GFI, and RAND) when selection strategy was EBV or PEN-EBV. (b) Least squares means for the interaction between selection strategy and germplasm exchange strategy on each measure averaged across populations at selection round 3. (c) Least squares means for the interaction between selection strategy and germplasm exchange strategy on each measure averaged across populations at selection round 10.

egy, germplasm exchange using GFI or RAND resulted in comparable genetic progress. Although using either of these 2 exchange strategies (GFI or RAND) led to more genetic progress than no exchange (albeit a minimal advantage) in the short term, they did not perform better in the long term.

We found a significant advantage of exchanging germplasm using EBV or PEN-EBV over no exchange when done for long enough. For example, after 10 rounds of selection using EBV, we found LSM estimates of cumulative genetic gain of 3.39, 3.52, and 3.55 genetic SD for no germplasm exchange, germplasm exchange using PEN-EBV, and germplasm exchange using EBV strategies, respectively. Within a given selection strategy, germplasm exchange using EBV performed slightly better than PEN-EBV in the short term. For example, when selection was performed using EBV, the LSM estimates of cumulative genetic progress after 3 rounds were 0.97 (SE = 0.004) and 0.98 (SE = 0.001) for the EBV and PEN-EBV germplasm exchange strategies. However, after 10 rounds of selection and exchange, we did not find a difference between these strategies.

Homozygosity. Germplasm exchange using the PEN-EBV or GFI exchange strategies generally resulted in a lower accumulation of homozygosity than no exchange or using other exchange strategies. This was most noticeable in the long term under both the PEN-EBV and EBV selection strategies. For example, after 10 selection rounds and under EBV selection, performing no germplasm exchange resulted in the largest increase (positive relative change) in homozygosity (LSM = 1.00% SE = 0.09%), whereas exchanging germplasm using PEN-EBV or GFI resulted in the lowest increase, with LSM estimates for RC_{HOM} of 0.74% (SE = 0.09%) and 0.83% (SE = 0.09%), respectively. Within a selection strategy, we did not find any significant differences in the estimates of RC_{HOM} between the PEN-EBV and GFI exchange strategies. In terms of the RAND and EBV germplasm exchange strategies, we did not find any scenario in which implementing either led to a different pattern of homozygosity accumulation than not doing germplasm exchange at all.

Genetic Diversity. After 10 selection rounds, F_{ST} estimates were generally low for all germplasm exchange strategies evaluated. Within a given selection strategy, doing no germplasm exchange led to the highest levels of population differentiation in the long term, with LSM estimates of 0.011 (SE = 1.79×10^{-4}) and 0.010 (SE = 1.79×10^{-4}) when selection was performed using EBV and PEN-EBV, respectively. The 2 germplasm exchange methods where a measure of genetic merit was used (EBV and PEN-EBV) resulted in the lowest long-term estimates of F_{ST} between populations. Germplasm exchange using the EBV and PEN-EBV strategies resulted in similar F_{ST} estimates within selection strategy, with values around 0.009 and 0.008 for the EBV and PEN-EBV selection strategies, respectively.

For both RC_{MAF} and RC_{MONO}, the largest long-term differences were observed between selection strategies regardless of how or whether germplasm was exchanged. When PEN-EBV selection was used, RC_{MAF} was positive, and therefore the average MAF increased across selection rounds. At selection round 10, germplasm exchange with the PEN-EBV and GFI strategies achieved the largest RCMAF, with LSM estimates of 2.21% (SE = 0.18%) and 2.36% (SE = 0.18%), respectively. When using EBV selection, only the PEN-EBV or GFI exchange strategies resulted in a positive value of RC_{MAF} at selection round 3. At generation 10, all germplasm exchange strategies resulted in negative estimates of RC_{MAF}, with the PEN-EBV and GFI exchange strategies decreasing the average MAF by the lowest amount, with LSM estimates of RC_{MAF} of −0.56% (SE = 0.18%) and −0.60% (SE = 0.18%), respectively.

For both selection methods (EBV and PEN-EBV) we found a trend of a decreasing proportion of markers nearing fixation in the initial selection rounds, followed by a trend of increasing values of RC_{MONO} that started after about 5 selection rounds for EBV selection and about 8 selection rounds for PEN-EBV selection. After 10 selection rounds using the EBV selection strategy, we found an increased RC_{MONO} with estimates ranging from 16.87% (SE = 3.92%) to 33.61% (SE = 3.92%) when using the GFI and EBV germplasm exchange strategies, respectively. After 10 selection rounds using the PEN-EBV selection strategy, germplasm exchange using GFI resulted in the largest decrease in the proportion of nearly fixed markers, with an RC_{MONO} estimate of −29.56% (SE = 3.92%).

Do Populations Benefit Disproportionately? By examining the interaction between germplasm exchange strategy and population, we were able to investigate whether the benefits of germplasm exchange are disproportionate between populations. Results of the interaction between germplasm exchange strategy and population can be found in Supplemental File S7 (see Notes). In the short term, we did not find much evidence of differences between populations in terms of genetic progress or changes in homozygosity. Estimates of long-term genetic progress were not significantly different between populations for any germplasm exchange method; however, we found a consistent advantage for population 1, where the estimates of genetic progress were larger than the other populations, particularly when compared with population 3. The difference in genetic progress between populations 1 and 3 ranged from 0.03 to 0.06 genetic SD higher when random exchange was done and when germplasm exchange was done using the PEN-EBV strategy.

Estimates of long-term changes in genome-wide homozygosity similarly did not show significant differences between populations but generally showed a consistent point estimate advantage for population 1 over population 3. The largest difference between these 2 populations was found for germplasm exchange using the PEN-EBV strategy, where the estimate of RC_{HOM} for population 1 was 0.32 percentage points lower than for population 3. For comparison, when no germplasm exchange was done, population 1 had an RC_{HOM} estimate 0.09 percentage points lower than that of population 3.

Factors Affecting the Success of Germplasm Exchange

In scenarios 3A and 3B, we explored the effects of the genetic correlation between traits and the size of germplasm exchange on the performance of the EBV, PEN-EBV, and GFI germplasm exchange strategies when the selection strategy was PEN-EBV. Results for the LSM estimates for the interaction between germplasm exchange strategy and ε correlation parameter on genetic gain, homozygosity, and genetic diversity at selection rounds 3 and 10 can be found in Table 2. Similarly, results for the interaction between germplasm exchange strategy and the size of germplasm exchange can be found in Table 3.

Genetic Progress. At 3 selection rounds, we did not find any significant difference between the cumulative genetic progress achieved by the different ε correlation parameter levels (0.10, 0.50, and 0.90) for any exchange strategy. In the long term (selection round 10), genetic progress was found to increase by increasing the genetic correlation between traits when the germplasm exchange strategy was EBV or PEN-EBV. Estimates of cumulative genetic progress increased from 3.44 (SE = 0.02) to 3.58 (SE = 0.02) genetic SD and from 3.42 (SE = 0.02) to 3.56 (SE = 0.02) genetic SD when going from $\varepsilon = 0.10$ to $\varepsilon = 0.90$ for the EBV and PEN-EBV exchange strategies, respectively.

In both the short and the long term, increasing the size of germplasm exchange increased the amount of genetic progress achieved by the EBV and PEN-EBV exchange strategies. Interestingly, when using the GFI exchange strategy, increasing the size of germplasm exchange from 10 to 100 bulls increased the estimate of short-term genetic progress by around 0.07 genetic SD; however, it did not result in any long-term differences

Homozygosity. We did not find any short- or long-term difference in the relative change in homozygosity when the ε correlation parameter was varied. Increasing the size of germplasm exchange also significantly increased the amount of homozygosity lost across most germplasm exchange strategies and in both the short and the long term. For example, when GFI was used as the exchange strategy, we found a long-term estimate of relative change in homozygosity of −0.75% (SE = 0.07) and −1.64% (SE = 0.07) when 10 or 100 bulls were exchanged, respectively.

Genetic Diversity. Increasing the genetic correlation between traits decreased the short- and long-term estimates of F_{ST} for all germplasm exchange strategies. We found that varying the ε correlation parameter had little effect on short-term average MAF; however, after 10 selection rounds, increasing the ε correlation parameter from 0.10 or 0.50 to 0.90 significantly decreased the estimate of RC_{MAF} for all germplasm exchange strategies. No differences were observed for the change in the proportion of monomorphic alleles in the short term when varying the ε correlation parameter. After 10 rounds of selection, we found a smaller decrease in the proportion of monomorphic alleles when going from $\varepsilon = 0.10$ or $\varepsilon = 0.50$ to $\varepsilon = 0.90$ for the PEN-EBV and EBV exchange strategies. For the GFI exchange strategy, we did not observe long-term differences when the correlation parameter was varied.

The germplasm exchange size was an important factor in short- and long-term changes in genetic diversity. For F_{ST}, increasing the size of germplasm exchange from 10 to 100 bulls decreased population differentiation, regardless of exchange strategy, at both time points. For changes in the average MAF, increasing the size of exchange increased the average MAF in the short term for the PEN-EBV and GFI strategies; however, in the long term, only for the GFI strategy did we see a significant difference between the 2 levels of exchange size. Similarly, for the change in the proportion of monomorphic alleles, the increase from 10 to 100 bulls exchanged led to a larger decrease of monomorphic alleles in the short term for the PEN-EBV and GFI exchange strategies, but not in the long term. However, unlike its effect on average MAF, increasing the exchange size did not provide any long-term differences for any exchange strategy. Interestingly, although nonsignificant, for both the EBV and PEN-EBV exchange strategies, a larger exchange size resulted in a smaller long-term decrease in the proportion of monomorphic alleles.

DISCUSSION

The apparent decrease in genetic diversity found in multiple dairy cattle populations coinciding with the propagation of genomic selection methodology has led the dairy industry to rally behind the search for solutions to mitigate further losses. In this study, we performed a simulation to examine the effect of several breeding-based solutions to constrain further losses in genetic diversity for the US dairy cattle population. The general scheme of the simulation targeted the potential use of selection and germplasm exchange strategies at the dairy

Table 2. Least squares means for the interaction between germplasm exchange strategy and the epsilon parameter (ε) trait correlation parameter on measures of within-population genetic gain and homozygosity, and across-population genetic diversity at selection rounds 3 and 10[1,2]

		EBV			PEN-EBV			GFI		
Parameter[3]	Time point	$\varepsilon = 0.10$	$\varepsilon = 0.50$	$\varepsilon = 0.90$	$\varepsilon = 0.10$	$\varepsilon = 0.50$	$\varepsilon = 0.90$	$\varepsilon = 0.10$	$\varepsilon = 0.50$	$\varepsilon = 0.90$
Δ_G (genetic SD)	Selection round 3	0.97 (0.004)	0.97 (0.004)	0.96 (0.004)	0.96 (0.004)	0.96 (0.004)	0.95 (0.004)	0.93 (0.004)	0.92 (0.004)	0.92 (0.004)
	Selection round 10	3.44 (0.02)	3.48 (0.02)	3.58 (0.02)	3.42 (0.02)	3.45 (0.02)	3.56 (0.02)	3.31 (0.02)	3.32 (0.02)	3.31 (0.02)
RC_{HOM} (%)	Selection round 3	−0.04 (0.03)	−0.03 (0.03)	−0.03 (0.03)	−0.14 (0.03)	−0.14 (0.03)	−0.15 (0.03)	−0.15 (0.03)	−0.16 (0.03)	−0.14 (0.03)
	Selection round 10	−0.45 (0.05)	−0.56 (0.05)	−0.41 (0.05)	−0.73 (0.05)	−0.92 (0.05)	−0.78 (0.05)	−0.79 (0.05)	−0.91 (0.05)	−0.78 (0.05)
F_{ST}	Selection round 3	0.003 (3.50×10^{-5})	0.002 (3.50×10^{-5})	0.002 (3.50×10^{-5})	0.003 (3.50×10^{-5})	0.002 (3.50×10^{-5})	0.002 (3.50×10^{-5})	0.003 (3.50×10^{-5})	0.002 (3.50×10^{-5})	0.002 (3.50×10^{-5})
	Selection round 10	0.012 (1.79×10^{-4})	0.008 (1.79×10^{-4})	0.004 (1.79×10^{-4})	0.012 (1.79×10^{-4})	0.008 (1.79×10^{-4})	0.004 (1.79×10^{-4})	0.011 (1.79×10^{-4})	0.009 (1.79×10^{-4})	0.006 (1.79×10^{-4})
RC_{MAF} (%)	Selection round 3	0.16 (0.07)	0.12 (0.07)	0.03 (0.07)	0.37 (0.07)	0.35 (0.07)	0.26 (0.07)	0.40 (0.07)	0.39 (0.07)	0.29 (0.07)
	Selection round 10	2.26 (0.14)	2.03 (0.14)	1.10 (0.14)	2.81 (0.14)	2.76 (0.14)	1.88 (0.14)	2.87 (0.14)	2.85 (0.14)	2.14 (0.14)
RC_{MONO} (%)	Selection round 3	−6.54 (1.90)	−6.39 (1.90)	−9.35 (1.90)	−12.11 (1.90)	−13.18 (1.90)	−12.30 (1.90)	−14.81 (1.90)	−16.30 (1.90)	−16.41 (1.90)
	Selection round 10	−15.17 (2.82)	−13.88 (2.82)	−1.08 (2.82)	−27.55 (2.82)	−24.42 (2.82)	−7.62 (2.82)	−32.88 (2.82)	−31.04 (2.82)	−22.10 (2.82)

[1]Standard error is shown in parentheses.

[2]EBV = estimated breeding value strategy; PEN-EBV = penalized EBV strategy; GFI = genomic future inbreeding strategy.

[3]Δ_G = cumulative genetic gain; RC_{HOM} = relative change in genome homozygosity; F_{ST} = fixation index; RC_{MAF} = relative change in average minor allele frequency; RC_{MONO} = relative change in the average proportion of monomorphic markers.

Table 3. Least squares means for the interaction between germplasm exchange strategy and the size of exchange ($N_{Exchange}$) on measures of within-population genetic gain and homozygosity, and across-population genetic diversity at selection rounds 3 and 10[1,2]

		EBV		PEN-EBV		GFI	
Parameter[3]	Time point	$N_{Exchange} = 10$	$N_{Exchange} = 100$	$N_{Exchange} = 10$	$N_{Exchange} = 100$	$N_{Exchange} = 10$	$N_{Exchange} = 100$
Δ_G (genetic SD)	Selection round 3	0.97 (0.01)	1.17 (0.01)	0.95 (0.01)	1.13 (0.01)	0.92 (0.01)	0.99 (0.01)
	Selection round 10	3.45 (0.02)	3.82 (0.02)	3.41 (0.02)	3.77 (0.02)	3.30 (0.02)	3.34 (0.02)
RC_{HOM} (%)	Selection round 3	0.01 (0.03)	−0.08 (0.03)	−0.10 (0.03)	−0.43 (0.03)	−0.12 (0.03)	−0.69 (0.03)
	Selection round 10	−0.40 (0.07)	−0.69 (0.07)	−0.76 (0.07)	−1.07 (0.07)	−0.75 (0.07)	−1.64 (0.07)
F_{ST}	Selection round 3	0.002 (3.32×10^{-5})	0.002 (3.32×10^{-5})	0.002 (3.32×10^{-5})	0.002 (3.32×10^{-5})	0.002 (3.32×10^{-5})	0.002 (3.32×10^{-5})
	Selection round 10	0.009 (1.48×10^{-4})	0.005 (1.48×10^{-4})	0.008 (1.48×10^{-4})	0.005 (1.48×10^{-4})	0.009 (1.48×10^{-4})	0.005 (1.48×10^{-4})
RC_{MAF} (%)	Selection round 3	−0.005 (0.06)	0.09 (0.06)	0.23 (0.06)	0.78 (0.06)	0.25 (0.06)	1.29 (0.06)
	Selection round 10	1.68 (0.08)	1.85 (0.08)	2.37 (0.08)	2.58 (0.08)	2.43 (0.08)	3.89 (0.08)
RC_{MONO} (%)	Selection round 3	−7.37 (2.31)	−12.24 (2.31)	−14.85 (2.31)	−26.87 (2.31)	−16.81 (2.31)	−32.22 (2.31)
	Selection round 10	−14.93 (3.10)	−8.27 (3.10)	−26.06 (3.10)	−22.79 (3.10)	−33.84 (3.10)	−37.68 (3.10)

[1]Standard error is shown in parentheses.

[2]EBV = estimated breeding value strategy; PEN-EBV = penalized EBV strategy; GFI = genomic future inbreeding strategy.

[3]Δ_G = cumulative genetic gain; RC_{HOM} = relative change in genome homozygosity; F_{ST} = fixation index; RC_{MAF} = relative change in average minor allele frequency; RC_{MONO} = relative change in the average proportion of monomorphic markers.

stud level. This was done because AI companies currently control and manage a large portion of elite sire families, and improvements to the genetic diversity of animals at this level can trickle down into animals at other levels of the dairy sector.

Within each population, we opted for a breeding scheme design with moderate and very high selective pressure for selecting females and males, respectively. In addition, our design allowed for bulls and dams of high genetic merit to stay in the stud population for multiple selection rounds (overlapping generations). The moderate selective pressure on females and the use of overlapping generations were chosen to avoid premature exhaustion of genetic variation and to allow for substantial genetic progress while keeping trait genetic architectures simple (only additive variation). In reality, genetic variation is rarely fully exhausted, and genetic progress can be maintained by the continuous recruitment and transformation of nonadditive variation into additive variation (Dudley, 2007). The simulation of uniform family sizes instead of the more realistic nonuniform numbers of progenies per parent was chosen to keep the simulation simple and the interpretation of results straightforward. Instead, we opted to generate 5 offspring per mating, allowing for progeny from high-merit bulls and cows to be overrepresented in the selected population from the selection process.

To assess the effects of selection strategy, we simulated several options. We included realistic strategies, such as using EBV or EBV penalized for expected future inbreeding (PEN-EBV), as well as strategies representing the extremes of selection, such as the use of TBV or random selection. The PEN-EBV method was first proposed as a way to control for future inbreeding effects and to facilitate the identification of animals that would better serve to outcross. This method initially used relationship matrices built from pedigree information but has since been modified to use relationships built from genomic information (VanRaden and Smith, 1999; VanRaden et al., 2011). In our study, we used a genomic relationship matrix for the adjustment; however, genomic expected future inbreeding can also be obtained using runs of homozygosity relationships (Pryce et al., 2012). Pryce and colleagues (2012) found that the correlations between the off-diagonal elements of matrices built using pedigree and genomic information ranged from 0.67 to 0.87, depending on pedigree depth, and the correlations between the off-diagonal elements of matrices built using pedigree and genomic information were as high as 0.76. This same study found that a genomic relationship matrix built using a medium-density panel performed best to minimize progeny inbreeding (Pryce et al., 2012).

In terms of genetic progress, each selection strategy performed as expected, with selection using EBV or

PEN-EBV achieving approximately three-quarters of the genetic improvement achieved by direct selection on true genetic merit, which was in line with the level of accuracy chosen. Penalizing the estimated genetic merit resulted in about 0.15 genetic SD less genetic progress in the long term compared with no penalization (EBV strategy). The correlation between adjusted and nonadjusted breeding values has been previously found to be very high (VanRaden and Smith, 1999).

The greatest differences between the PEN-EBV and EBV selection strategies came when observing their influence on genomic homozygosity. After 10 selection rounds, the PEN-EBV strategy was the only strategy to consistently provide a decrease in the average homozygosity within each population.

We found that germplasm exchange that takes into account genetic merit (EBV and PEN-EBV exchange strategies) provided substantial benefits in short- and long-term genetic progress, compared with not performing exchanges. Other methods that try to balance genetic gain and reductions in the rate of inbreeding without the use of germplasm exchange can see some genetic progress affected due to the need to reduce selection intensities (Weigel and Lin, 2002). Germplasm exchange strategies that target genetic merit can bypass these limitations through the ability to cast a wider net in search of germplasm from males of high genetic merit.

We found that a higher correlation between traits and a more sizable exchange increased the level of long-term genetic gain achieved by exchanging animals using EBV and PEN-EBV, although only the size of germplasm exchange can be manipulated in real-world situations. In this study, we also assumed that males could be picked for exchange with the same amount of accuracy as the accuracy of within-population selection. In reality, the prediction accuracy of across-population breeding values could be lower; this is especially true when populations are related to a low degree and the genotyped reference population does not represent all populations and environments (van den Berg et al., 2019; Rezende et al., 2020). However, the advantage in short-term genetic progress seen when exchanging animals using the GFI or RAND strategies over no exchange highlights the usefulness of outcrossing as a general strategy to introduce genetic variability that can be exploited for selection purposes.

Germplasm exchange using the PEN-EBV or GFI strategies performed well for decreasing the gain in average population genomic homozygosity under the EBV selection strategy and increasing the reduction of this metric under the PEN-EBV selection strategy. However, although the overall homozygosity decreased across the 10 selection rounds under these 2 exchange strategies, we observed a decrease in the rate of homozygosity loss toward the latter generations in all populations. This result is indicative of increased homogeneity between populations and of lower benefits from germplasm exchange between genetically similar populations. Germplasm exchange using these strategies, particularly GFI, resulted in more across-population genetic diversity compared with other strategies. The magnitude of the benefits of germplasm exchange using these strategies will depend on the relationship between populations and the extent of germplasm exchange.

The 2 main factors that need to be considered for germplasm exchange between AI stud populations to be readily adopted are (1) the potential for larger benefits for genetic gain and genetic diversity and (2) assurance of equality in perceived benefits so that no one stud benefits more than the other. We believe the latter is the biggest hurdle for any simulated exchange strategies to see any real-world implementation. For this same reason, we decided to examine the interaction between germplasm exchange strategy and population. Population 1 enjoyed a greater benefit of germplasm exchange using the PEN-EBV strategy compared with other populations. However, this was likely due to the way the simulation was constructed (see "Traits" subsection in Materials and Methods), where the trait selected by population 1 had genetic correlations with the traits selected by populations 2 and 3 of equal magnitude and which were larger than the genetic correlation between the traits selected by populations 2 and 3. Germplasm exchange agreements with only 2 parties involved would not suffer from this perceived imbalance.

CONCLUSIONS

Our study found that selection on breeding values penalized for expected inbreeding can effectively maintain genetic progress while decreasing overall homozygosity. We confirmed the validity of germplasm exchange as a strategy to maintain long-term genetic gain and increase genetic diversity. We explored several germplasm exchange strategies and found that each can be beneficial depending on the industry's need. Germplasm exchange based on the genetic merit of males can accelerate genetic progress while preserving or enhancing genetic diversity. At the same time, exchange with the goal to minimize kinships can provide rapid improvement in most of the measured metrics of genetic diversity while also providing benefits to long-term genetic progress. Further research is needed to assess the overall benefits of such strategies for all stakeholders involved. Nonetheless, our study provides valuable findings for developing more sustainable breeding programs and highlights the ability to balance genetic progress with maintaining genetic diversity.

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Nonstandard abbreviations used: Δ_G = cumulative genetic progress; ε = correlation parameter; F_{ST} = fixation index; GFI = genomic future inbreeding value; MAF = minor allele frequency; PEN-EBV = penalized EBV; RAND = random selection; RC_{HOM} = relative change in average genomic homozygosity; RC_{MAF} = relative change in average MAF; RC_{MONO} = relative change in proportion of allele marker fixation; TBV = true breeding value; TBVa = TBV across population; TBVw = TBV within population; TGV = true genomic value.

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