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# Genomic clustering helps to improve prediction in a multibreed population[1]

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**ABSTRACT:** Genomic prediction for crossbred beef cattle has shown limited results using low- to moderate-density SNP panels. The relationship between the training and validation populations, as well as the size of the reference population, affects the prediction accuracy for genomic selection. Rotational crossbreeding systems require the usage of crossbred animals as sires and dams of future generations, so crossbred animals require accurate evaluation. Here, a novel method for grouping of purebred and crossbred animals (based exclusively on genotypes) for genomic selection was investigated. Clustering of animals to investigate the genetic similarity among different groups was performed using several genomic relationship criteria between individuals. Hierarchical clusters based on average-link criteria (computed as the mean distance between elements of each subcluster) were formed. The accuracy of genomic prediction was assessed using 1,500 bulls genotyped for 54,609 markers. Estimated breeding values based on all available phenotypic records for birth weight, weaning gain, postweaning gain, and yearling gain were calculated using BLUP methodologies and deregressed to ensure unbiased comparisons could be made across populations. A 5-fold validation technique was used to calculate direct genomic values for all genotyped bulls; the addition of unrelated animals in the reference population was also investigated. We demonstrate a decrease in genomic selection accuracy after including animals from disconnected clusters. A method to improve genomic selection for crossbred and purebred animals by clustering animals based on their genotype is suggested. Unlike traditional approaches for genomic selection with a fixed reference population, genomic prediction using clusters (GPC) chooses the best reference population for better accuracy of genomic prediction of crossbred and purebred animals using clustering methods based on genotypes. An overall average gain in accuracy of 1.30% was noted over all scenarios across all traits investigated when the GPC approach was implemented. Further investigation is required to assess this difference in accuracy when a larger genotyped population is available, especially for the comparison of groups with higher genetic dissimilarity, such as those found in industry-wide across-breed genetic evaluations.

**Key words:** accuracy, beef cattle, genomic prediction, single nucleotide polymorphism



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## INTRODUCTION

Accuracy of genomic selection has been shown to be influenced by the number of animals in the genotyped reference population as well as the degree to which pairs of animals are related (Goddard, 2009). In beef cattle populations, when compared with dairy cattle, where genomic selection is highly accurate, there are fewer genotypes available and a lesser degree of linkage disequilibrium (**LD**) between markers. Crossbreeding is heavily adopted in the beef industry, leading to limitations regarding the degree of

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**Table 1.** Average breed composition as estimated by ancestral components in Admixture software (Alexander et al., 2009)

| | Breed[1] | | | | | | |
|---|---|---|---|---|---|---|---|
| Feature | BLK | RED | SIM | LIM | HER | CHA | OTH |
| Number of purebreds[2] | 160 | 23 | 191 | 60 | 23 | 107 | 4 |
| Average breed composition | 0.320 | 0.196 | 0.244 | 0.065 | 0.040 | 0.047 | 0.087 |

[1]Breeds were determined using pedigree information on available purebred animals. BLK = Black Angus; RED = Red Angus; SIM = Simmental; LIM = Limousin; HER = Hereford; CHA = Charolais; OTH = ancestry component not identified to contain any purebred animals.

[2]Purebreds were defined as having greater than 75% of ancestry component in Admixture.

relationship among animals. As many traits of economic impact are measured in crossbred populations, deriving accurate direct genomic values (DGV) for these animals has significant implications on many breeding schemes. It has been shown that one pure breed cannot be used as the sole reference population to estimate SNP effects in another breed (De Roos et al., 2008). It was shown, however, that when there is a component of a breed in a crossbred reference population, it can accurately estimate SNP effects for a purebred population that is one of the components of the crossbreeds (Hayes et al., 2009; Toosi et al., 2010). Expanding the reference population with animals of breeds that are not closely related to the validation population may lead to further inaccuracy in estimation of SNP effects. This study proposes a novel method for genomic prediction in a multibreed population, creating clusters of animals to be evaluated together (avoiding the incorporation of animals in the same evaluation if the relationship between them is small) while maintaining populations large enough to accurately estimate DGV. The accuracy of genomic prediction was evaluated by the correlation of DGV with 1) EBV obtained from BLUP methods and 2) deregressed EBV (**dEBV**). Results from the genomic prediction using clusters (**GPC**) application were compared against alternative scenarios that used a larger reference population augmented by the inclusion of animals from an unrelated cluster. This allowed the assessment of the effect on accuracy from GPC for a multibreed evaluation.

## MATERIALS AND METHODS

### *Data*

Genotypes were collected from routinely evaluated animals from the University of Guelph multibreed beef cattle population as well as a number of herds that are part of the Beef Improvement Opportunities (**BIO**; Guelph, Canada) data set evaluated in the last 6 yr in southern Ontario and composed of purebred and crossbred beef cattle. Numbers of purebred animals of each breed as well as the average breed composition of the crossbred animals (*n = 932) are presented in* Table 1: 51.6% Angus (Red and Black Angus), 24.4% Simmental, 6.5% Limousin, 4.7% Charolais, 4% Hereford, and other breeds composing the remaining 8.7%. All animals were genotyped using the Illumina Bovine SNP50_v1 Beadchip (51,620 markers) or the Illumina BovineSNP50 Genotyping BeadChip (54,609 markers; Illumina Inc., San Diego, CA). All the genotypes received from different locations were converted to a unique format that could be compared (AB format). The genotyping was accomplished on blood, tail hair, and semen samples. Genotypes of animals from the University of Guelph were also part of previous investigations, after approval from the University of Guelph Animal Care Committee based onthe recommendations outlined in the Canadian Council on Animal Care guidelines( Canadian Council on Animal Care, 2009).

Poor quality genotypes and individuals with potential genotyping errors were excluded from the analysis. The following quality control thresholds were applied on the data: SNP call rate < 0.95, minor allele frequency < 0.05, and sample call rate < 0.90. Forty-three thousand six hundred twenty-four autosomal markers remained for further DGV calculation after quality control.

Officially reported across-breed comparisons (**ABC; EBV/2**) for birth weight (**BiW**), weaning gain (**WG**), postweaning gain (**PWG**), and yearling gain (**YG**) were provided by BIO for all animals ($n$ = 1,500). The ABC, derived from multibreed beef cattle data and BLUP methods (Sullivan et al., 1999), were multiplied by 2 to create EBV to assess accuracy of genomic selection in a multibreed beef cattle population. Breed composition of the crossbred and purebred animals was calculated using Admixture software (Alexander et al., 2009) and was determined solely by marker investigation without adding pedigree information. Default parameters were used in Admixture, and the number of groups to sort animals was selected by using pedigree data, starting with a biologically relevant number of groups ($K$ = 6) and increasing that number until no purebred animals were found in the same grouping as a purebred animal from another breed. This gave a final $K$ value of 10 for admixture. Groups that were composed of the same breed of animals, along with the corresponding crossbred animals, were grouped together, leaving 7 groups, 1 for each breed and 1 group that contained no purebred animals (the number of groups

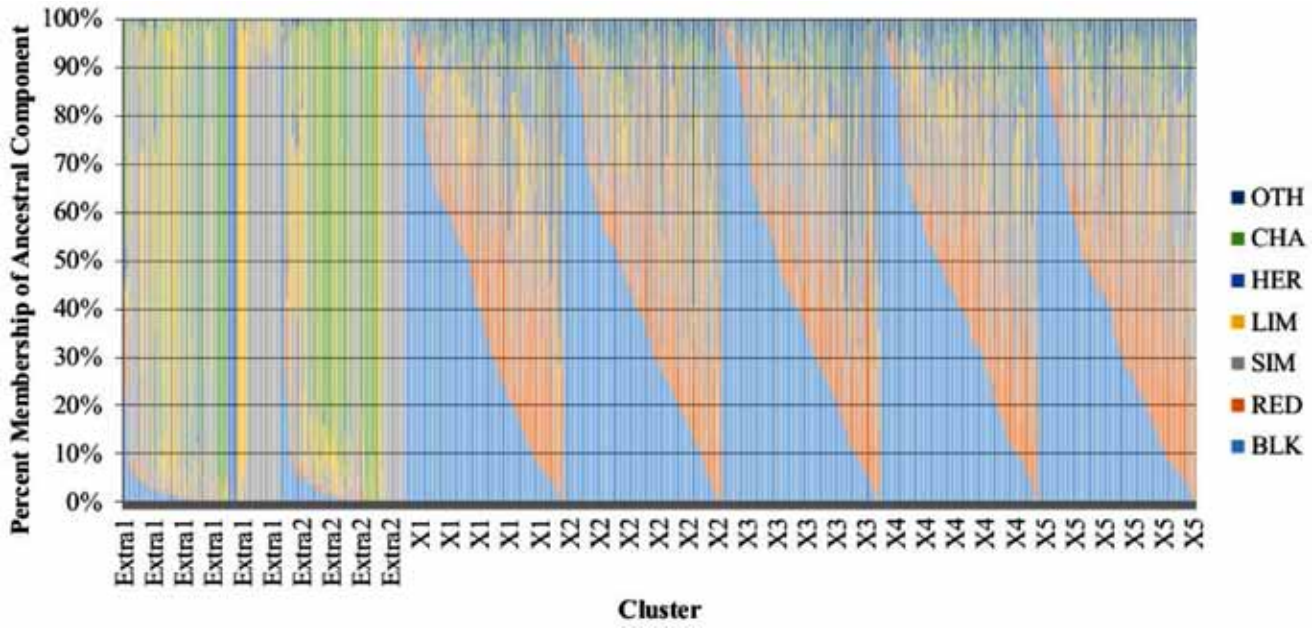


**Figure 1.** Per animal breed composition as estimated by ancestry components in Admixture software (Alexander et al., 2009). Breed definitions were determined using pedigree information on available purebred animals. CHA = Charolais; HER = Hereford; LIM = Limousin; SIM = Simmental; RED = Red Angus; BLK = Black Angus; OTH = ancestry component not identified to contain any purebred animals.

reported here is not related to the number of groups after applying clustering methods, which will be presented in the remaining part of this manuscript). Figure 1 shows breed composition for all animals based on estimated ancestry components taken from the breed composition (**Q**) matrix as calculated by Admixture (Alexander et al., 2009). In Fig. 2, we present a flow chart that illustrates the analyses performed in this study.

### *Clustering*

Animals were clustered together into distinct groups to evaluate the impact of different clustering methods on the accuracy of genomic predictions. This was in an effort to create groups of animals that were genetically similar so that SNP effects would be consistent within these clusters, even if they were not consistent across the entire group of genotyped animals. The clustering approach requires a distance (or similarity) matrix for grouping the animals according to their genetic proximity. This relationship matrix between all animals was measured using 3 different methods: 1) based on the genomic relationship matrix (**G**) implemented by VanRaden (2008); 2) computing a modified version of the Mendelian inconsistency (**MI**) distance (counting the number of opposing homozygotes; Howie et al., 2012), which is a part of the parentage discovery process implemented in the BIO genomics pipeline to identify beef cattle with sires previously not assigned properly in the pedigree; and 3) by the Euclidian genotype distance matrix (**EDM**) among all animals (Gianola and van Kaam, 2008).

Because the EDM and MI clustering methods showed a correlation with **G** close to 1, results in this investigation will be reported based solely on the **G** clustering strategy. Clusters were applied in this investigation using the average link hierarchical clustering method implemented in the "hclust" function of the R (V3.02, http://r-project.org) "stats" package, aimed at identifying relationships among animals based on genetic similarity. The heat map R function was also used to plot the cluster results obtained in this study. As individual animals need to be efficiently added into clusters for further evaluations, the average-link method was preferred in our investigation. In average-link clustering, the distance between one cluster and another one is considered to be equal to the average distance from any member of one cluster to any member of the other cluster. The adoption of this method to allocate new animals for the next run, without running a clustering procedure, may accelerate the genomic evaluation process as well as reduce the risk of introducing this new animal into an inappropriate cluster. A new individual could be inserted in the same cluster of a preexisting animal based exclusively on the higher genomic relationship similarity (a process that demands only the **G** construction).

As the cluster is generated only by the use of genotypes, and not by phenotypes, there is no inherent bias to the process of placing animals into clusters. To ensure accurate genomic prediction, if a cluster contained fewer animals than required a reference population for a specific trait evaluation, animals from this cluster were combined with the nearest cluster, once

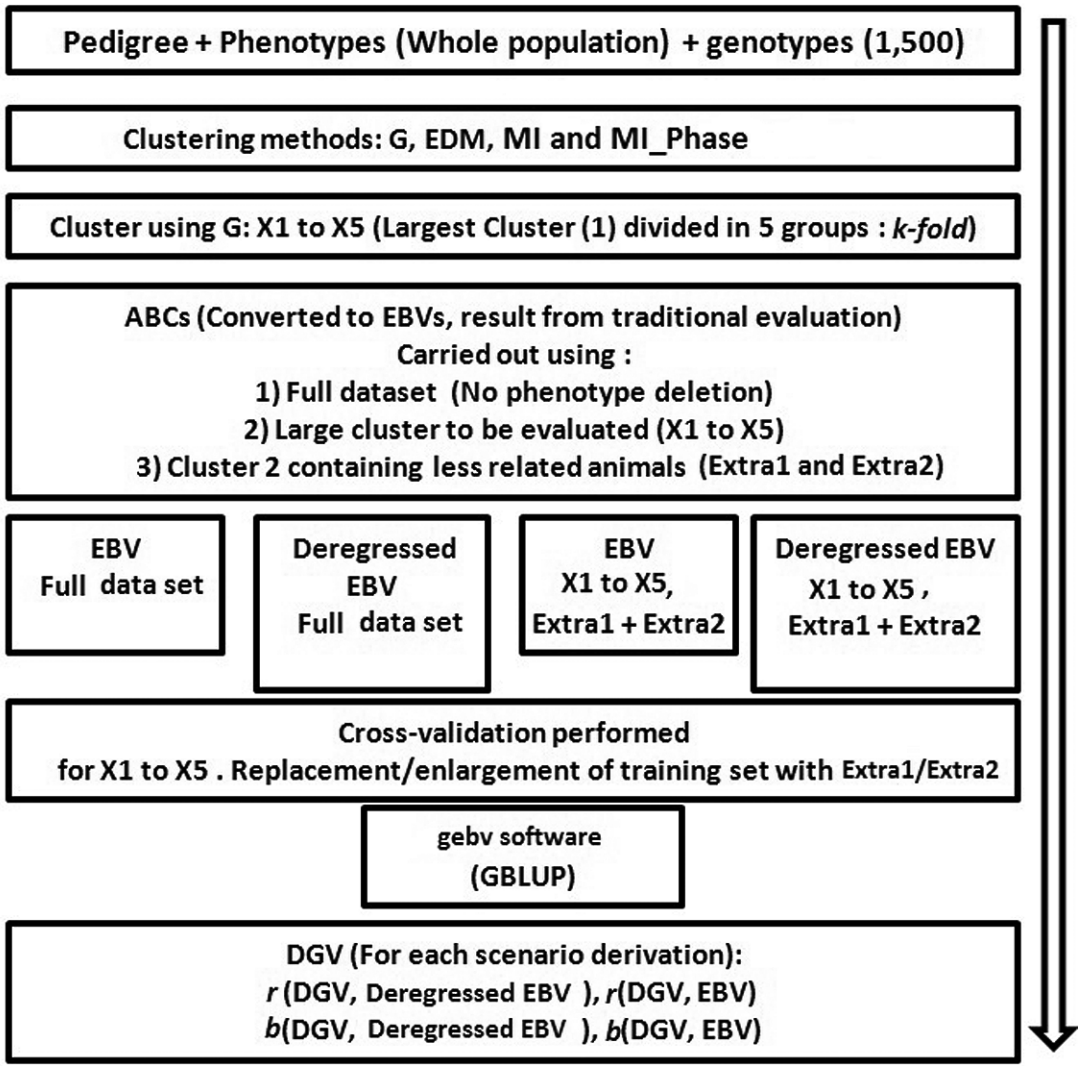


**Figure 2.** Overview of study design. A description of data flow and different scenarios tested using within cluster and outside of cluster genotypes as well as EBV and deregressed EBV to determine accuracy of genomic prediction using clusters. gebv software (Sargolzaei et al., 2009). G = the genomic relationship matrix; EDM = Euclidian genotype distance matrix; MI = Mendelian inconsistency; MI_Phased = a more complex version of the MI method; ABC = across-breed comparisons; GBLUP = genomic BLUP; DGV = direct genomic values group "Extra1" and "Extra2" are subsets of the cluster 2".

again based on the average of the dissimilarities between the points in that cluster with all other clusters.

A more complex version of the MI method (MI_Phase) was also explored. In this method, genotypes were first phased to separate heterozygotic loci into their parental haplotypes. These haplotypes were then used to calculate opposing homozygosity for each marker. Where there was a difference in the parental haplotypes of 2 individuals, the count increased. Based on the genotypes available in this study, large proportion of animals could not be accurately phased. As such, results from this method are not reported here, as fair comparisons with other clustering methodologies could not be made. In the future, this method could outperform the other 2, especially when applied for multibreed populations with strong pedigree information and larger genotyped populations and as phasing methodologies are improved.

Cluster results were then compared with breed compositions from Admixture to determine if crossbred animals were consistently clustered with other individuals with highly similar breed compositions.

### *Direct Genomic Value Estimation – Genomic BLUP*

Direct genomic values were estimated using genomic BLUP (VanRaden, 2008). The gebv software (Sargolzaei et al., 2009) was used to estimate DGV. Direct genomic values for each animal were calculated where the traditional pedigree based relationship matrix is replaced by **G** as calculated by

$$\mathbf{G} = \mathbf{XX'}/2\sum p_j(1 - p_j),$$

in which $p_j$ is the allele frequency of the jth SNP and **X** is an incidence matrix for SNP effects with elements

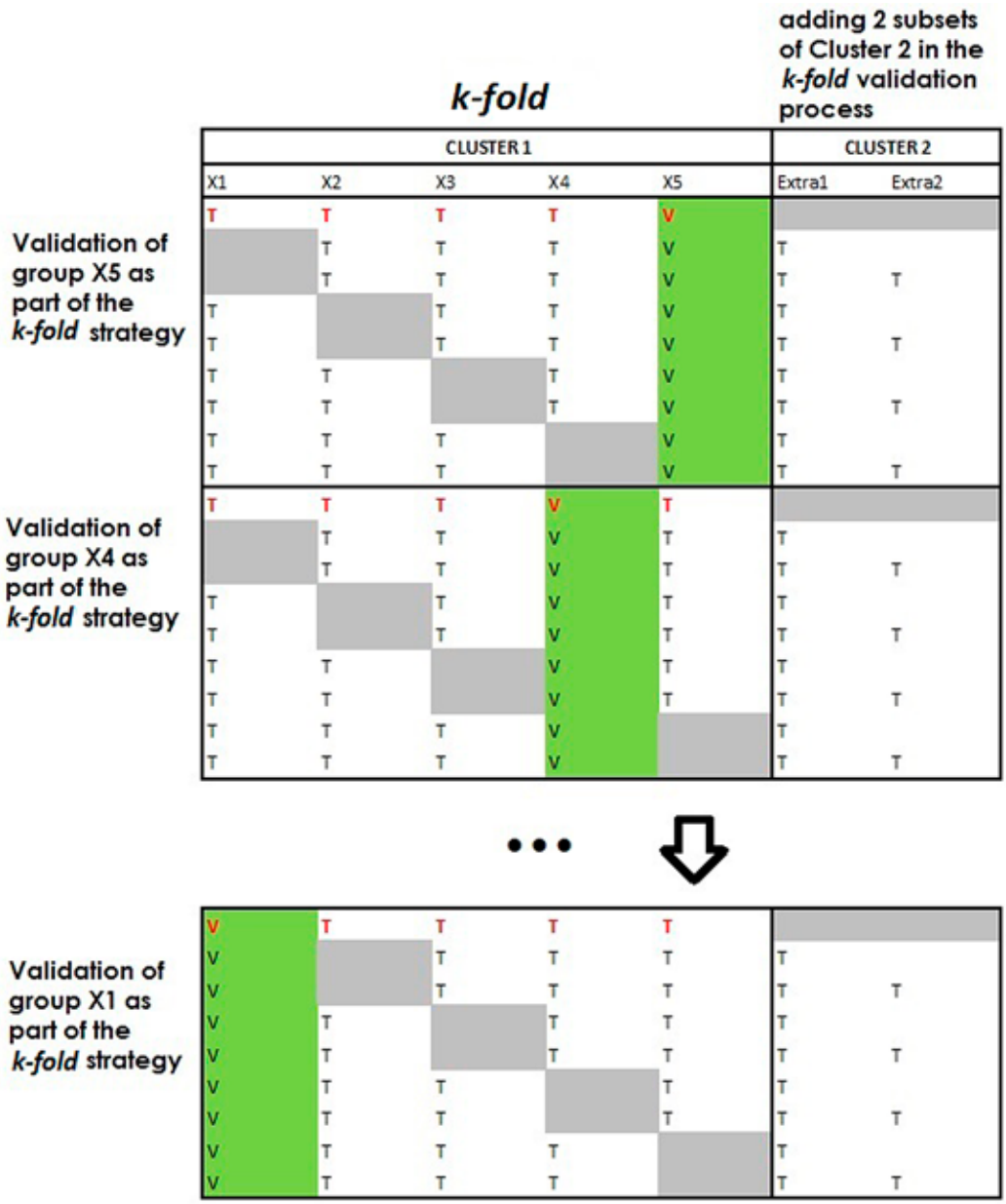


**Figure 3.** Overview of the validation process: The *k*-fold method is applied on 5 subsets (X1 to X5) of the largest cluster (1). Two groups from cluster 2 (Extra1 and Extra2) were added into the training population of cluster 1 (following the *k-f*old strategy) for validation of each of X1 to X5 subgroups to investigate the impact of genomic prediction accuracy after adding unrelated animals.

$X_{ij}$ equal to $0 - 2_{pj}$ (if homozygous 11), $1 - 2_{pj}$ (if heterozygous 12 or 21), or $2 - 2_{pj}$ (if homozygous 22) for a given animal i (VanRaden, 2008; VanRaden and Sullivan, 2010).

The DGV for each animal is then calculated as

$$DGV = \mathbf{G(G + R)}^{-1}(\mathbf{y} - \hat{\mu}),$$

in which **y** is a vector containing the EBV or a dEBV **(**VanRaden and Sullivan, 2010) to determine the impact of deregression in a population with low EBV reliability and **R** is a diagonal matrix with elements $\mathbf{R}_{ij}$ = (1/Rel) − 1, in which Rel is the reliability of dEBV.

Accuracy of DGV were then assessed by the correlations between the DGV and EBV (*r*(DGV, EBV)) and between the DGV and dEBV (*r*(DGV, dEBV)) in real data for each combination of scenarios as presented in Fig. 2.

### *Validation*

Two main clusters were defined based on the genomic similarity among individuals (based on **G**), where cluster 1 was the largest cluster (n_Cluster1 containing 1,065 animals and n_Cluster2 containing 435 animals). Individuals within each group shared a higher number of haplotypes compared with individuals placed in the other set. This investigation evaluated the impact on the


**Figure 4.** Genetic distances between individuals in the study population. Distances represented as cluster heat map calculated using the multidimensional scaling approach.

accuracy of genomic prediction for animals from cluster 1. Genomic predictions within cluster 1 were compared as well as by adding 2 less-related groups of animals (group "Extra1" and "Extra2," subsets of the cluster 2) into the training population exclusively composed of individuals from cluster 1. The *K*-fold validation process, as used by Saatchi et al. (2012), was applied in this study with some minor adjustments to evaluate the impact on accuracy of genomic predictions after including animals from cluster 2 (Fig. 3). In the *K*-fold method, the group of genotyped individuals (cluster 1) is divided into *K* (5) random subsets, wherein each set is used as the validation group, and is also used as the training population for each of the other ($K - 1$) groups. Each group is iteratively excluded from the estimation input EBV used to predict the marker effects, and, subsequently, DGV for the animals in that group are estimated from the remaining groups. Animals in the largest cluster (1), with EBV reliabilities greater than 0.5, were used and randomly sorted into 5 groups ("X1" to "X5") of equal size for the validation process above described. Each of these groups from cluster 1 included at least 200 animals. Subsets from cluster 2 (Extra1 and Extra2, containing 217 and 218 randomly selected animals, respectively) were added in the training set of cluster 1 to determine the effect of enlarging the reference population by inclusion of animals from the less-related clusters. This will determine which clusters should be excluded from genomic prediction based on distances between clusters.

After each group within the cluster was validated using the 4 other subclusters as training groups (as part of the *K*-fold validation process), a group of unrelated individuals (Extra1) was used to replace each of the other 4 subclusters (X1 to X4, if we consider the validation of X5) to validate each subpopulation. This can be seen in Fig. 3, where groups "X1" through "X5" are subsets of cluster 1. "Extra1" is the group that is added to the population to replace one of the other clusters for evaluation. This meant that 25% of the reference population was formed by animals outside of cluster for each scenario. An average of these 4 iterations was taken to determine the effect of using animals within a cluster

**Table 2.** Percentage of animals from each subpopulation of cluster 1 (X1–X5) with their own phenotype measured for birth weight (BiW), weaning gain (WG), postweaning gain (PWG), and yearling gain (YG) used for the EBV calculation before phenotype deletion (a deletion that occurs only as part of the cross-validation process)

| | Percent own record | | | |
|---|---|---|---|---|
| Subset | BiW | WG | PWG | YG |
| X1 | 99.06 | 97.17 | 29.72 | 61.79 |
| X2 | 98.11 | 94.81 | 16.98 | 56.60 |
| X3 | 98.58 | 92.92 | 23.11 | 57.08 |
| X4 | 95.75 | 91.51 | 19.34 | 47.64 |
| X5 | 98.58 | 96.23 | 19.34 | 58.49 |

vs. using less-related animals. Finally, another group of animals (Extra2) from the unrelated population cluster 2 was added to see the impact of having a larger population with weaker relationships to the validation population. This can again be seen in Fig. 3, as the additional animals added to the population are labeled as "Extra2." It is evident when looking at results from breed composition in Admixture that these animals are more distant from the main cluster and should not be included in the same population for genomic selection. Another set of analyses was performed, adding groups Extra1 and Extra2 into the reference population without replacement of individuals from subsets X1 to X5. Further demonstrating the relationship between animals, Fig. 4 shows a heat map plot to illustrate distances between each pairs of animals, calculated using a multidimensional scaling approach and hierarchical clustering techniques.

Scaling of genomic evaluation was checked by examining slopes of regression between DGV and either EBV or dEBV for animals in the testing set. This compares the scale of the DGV with that of the EBV or dEBV, where a number at or close to 1 indicates that they are on a similar scale and that there is no significant under- or overevaluation of genotyped animals relative to ungenotyped animals.

Traditional evaluations were also performed using the BLUP procedure to determine the accuracy of selection using no genomic information. These evaluations were performed not using clustering but using all available phenotyped animals, because in a population without genotypes, the clustering methods described here could not be used. In this case, **G** was replaced by the A matrix, and evaluations were performed using hundreds of thousands of animals with pedigree information, reflecting the true, most accurate traditional evaluations possible. Estimated breeding values were generated for each group by masking the phenotypes within a group and using all other available phenotypes to calculate an EBV. Table 2 shows the percentage of animals (before masking the phenotypes) in each subpopulation (X1 to X5) that had their own performance measured for each trait (BiW, WG, PWG, and YG) used during the EBV calculation as part of the BIO traditional genetic evaluation. Most individuals had their own records available for comparison for BiW and WG; however, for PWG and YG, a large proportion of the population did not have their own phenotypes, leading to a potential loss of accuracy in validation for these 2 traits.

Tables 3 and 4 display the average EBV and accuracies for BiW, WG, PWG, and YG for each subgroup of cluster 1 (X1 to X5) after deleting the phenotypes in each subgroup EBV calculation. Columns with headings ending with "-W" refer to the average EBV and accuracy within a subpopulation (validation population); columns with headings ending with "-R" refer to the EBV and accuracy for the 4 remaining subgroups averaged together (training population), where phenotypes were not deleted for the EBV calculation (e.g., for the group X1, "-W" columns represents the EBV and accuracies within a group and the "-R" columns report the same values for groups X2 to X5 averaged together). As presented in Table 4, averaged accuracies from the "-R" group, where the phenotype was not deleted, are much higher (16.87, 13.21, 12.08, and 13.00% for the traits BiW, WG, PWG, and YG, respectively) compared with the "-W" group. As the EBV accuracy depends on the amount of information, removing phenotypes returns a lower EBV accuracy.

## RESULTS AND DISCUSSION

### *Clustering Identifies Genotyping Errors*

There was one major cluster that contained only 1 animal using all 3 clustering methods (**G**, EDM, and MI). This animal was not found to be from a different breed origin than many of the other animals in the study population and was deleted from the analysis data set. This cluster could be explained by a genotyping error, an animal with very different lineage than the rest of the population regardless of breed composition, or the clustering algorithm being forced to create an unnatural number of clusters for the given data. This may provide a way to find outlier animals that will not be well predicted through genomic evaluation without having to have an accurate EBV to compare the DGV with. For young animals that may have genotyping errors, this will be valuable in excluding those animals from subsequent analysis and avoid decreasing the accuracy of genomic evaluation for all animals.

### *Genomic Prediction and Validation*

As shown in Fig. 2, validation was first performed on EBV that had not been deregressed. Accuracy was

**Table 3.** Average EBV values for birth weight (BiW), weaning gain (WG), postweaning gain (PWG), and yearling gain (YG) in each subpopulation of cluster 1 (X1–X5). Columns with headings ending in "-W" refer to the average EBV after deleting an individuals' own phenotype, and the group of column with headings ending in "-R" refer to the average EBV for the 4 remaining subgroups where the phenotypes were not deleted before the EBV calculation

| Subset | BiW-W | WG-W | PWG-W | YG-W | BiW-R | WG-R | PWG-R | YG-R |
|---|---|---|---|---|---|---|---|---|
| X1 | −7.12 | 79.36 | 80.1 | 158.7 | −6.24 | 76.92 | 74.58 | 155.3 |
| X2 | −5.14 | 80.58 | 72.14 | 139.86 | −4.58 | 79.14 | 72.24 | 152.6 |
| X3 | −5.32 | 80.2 | 73.12 | 158.78 | −5.6 | 79.14 | 72.84 | 158.1 |
| X4 | −5.74 | 76.2 | 74.56 | 150.98 | −5.84 | 79.56 | 75.38 | 154.5 |
| X5 | −5.98 | 79.14 | 76.08 | 154.24 | −5.84 | 78.52 | 74.02 | 152.74 |

**Table 4.** Average EBV accuracy of traditional evaluations for birth weight (BiW), weaning gain (WG), postweaning gain (PWG), and yearling gain (YG) in each subpopulation of cluster 1 (groups X1–X5). Columns with headings ending in "-W" refer to the average EBV accuracy after deleting an individuals' own phenotype, and the group of columns with headings ending in "-R" refer to the average EBV accuracy for the 4 remaining subgroups where the phenotypes were not deleted before the EBV calculation

| Subset | BiW-W | WG-W | PWG-W | YG-W | BiW-R | WG-R | PWG-R | YG-R |
|---|---|---|---|---|---|---|---|---|
| X1 | 58.22 | 54.69 | 52.69 | 53.01 | 74.15 | 66.94 | 62.14 | 64.78 |
| X2 | 57.34 | 53.82 | 49.76 | 52.07 | 74.85 | 67.65 | 63.00 | 65.56 |
| X3 | 57.66 | 54.13 | 50.53 | 52.59 | 74.94 | 67.84 | 62.98 | 65.64 |
| X4 | 57.44 | 53.92 | 50.01 | 51.84 | 74.48 | 67.33 | 63.08 | 65.43 |
| X5 | 57.46 | 54.03 | 50.20 | 52.21 | 74.05 | 66.89 | 62.37 | 65.31 |

calculated as the correlation of the across-breed EBV of each individual and the DGV estimated using the estimated marker effects from the training population for that iteration of the *k*-means clustering validation algorithm. A minimum EBV reliability threshold of 0.5 was set for all animals to be included in the validation steps to ensure that animals with very low accuracy EBV were not biasing the validation accuracy results. This, however, may not be a strict enough threshold, and EBV reliabilities should ideally be higher to validate the accuracy of genomic evaluations. However, in a beef cattle scenario where a reduced number of progeny is obtained per bull, this is not always possible (the males in this study were primarily yearling bulls, not proven sires). The average accuracy of across-breed EBV used for this study was 0.674 (average value for the 4 traits as presented in Table 4, in columns with headings ending with "-R"). Minimum thresholds were also set for animals from outside of the clusters, so all comparisons were consistent. As higher accuracy EBV are not available in this case, or in most scenarios using crossbred beef cattle, this is the best estimation of validation accuracy for this population. Table 5 displays the accuracy of genomic prediction for the cluster as an average of all subclusters. The regression coefficient (b) of genomic selection averaged across validation groups from k-fold validation is presented in Table 6. Also presented in Table 5 is the accuracy of prediction when a subcluster is replaced with animals from outside the cluster and when extra animals are added from outside the primary cluster. Table 7 shows scenarios similar to Table 5, except extra animals are added from the external cluster (Extra1 and Extra2) without replacing animals from the main cluster (Extra1). Scenarios presented in Table 7 that aimed to check reference set enlargement by adding unrelated animals without excluding 200 related animals as done by scenarios in Table 5.

In both Tables 5 and 7, a decrease in accuracy is observed in all scenarios including animals from cluster 2. As more animals from cluster 2 are introduced, prediction of marker effects for the validation population becomes less relevant. This implies that marker effects are not consistent across clusters. The primary cluster used for this analysis was mostly made up of crossbred animals as well as purebred Angus animals (Fig. 1). When some reference crossbred and purebred animals were replaced by purebred animals of the different breeds included in the Extra1 subset, a decrease in accuracy was seen. A loss in prediction accuracy when more animals are added from cluster 2 (Extra2) implies that having large populations for genomic selection is beneficial only if all animals in the training population are closely related to the validation population. It has been shown that across-breed genomic selection in purebred groups relies heavily on the degree of relationship between training and validation groups but can be effective if the relationships between the groups are high, as was shown in a population of purebred Angus and Charolais cattle (Chen et al., 2013). As we diverge from very similar animals, accuracies will significantly drop as marker effects become more reliant on animals from populations where there may be different QTL or, at the very least, different LD patterns between markers used and the underlying QTL. In theory, clustering creates populations more similar in genetic structure underlying phenotypic differences within populations than simply separating populations by breed composition. Table 7 (addition of animals from cluster 2 without the replacement of related animals [X1 to X5] from cluster 1 during the *k*-fold validation) showed accuracies slightly higher (less than 0.47% improvement across all scenarios) than the equivalent comparison presented in Table 5. Animals that were replaced according to the

**Table 5.** Accuracy (Pearson correlation) of genomic selection averaged across validation groups from *k*-means validation

| | Validation group (compared with dEBV[2]) | | | | | | Validation group (compared with EBV) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trait used in gebv[1] software | Within cluster 1 (*k*-fold)[3] | Replacing X1 to X5 with Extra1[4] | SE | Replacing X1 to X5 with Extra1 and adding Extra2[5] | SE | Traditional evaluation | Within cluster 1 (*k*-fold)[3] | Replacing X1 to X5 with Extra1[4] | SE | Replacing X1 to X5 with Extra1 and adding Extra2[5] | SE | Traditional evaluation |
| Birth weight EBV | | | | N/A[6] | | | 0.610 | 0.586 | 0.002 | 0.590 | 0.003 | 0.735 |
| Birth weight dEBV | 0.378 | 0.364 | 0.004 | 0.369 | 0.003 | 0.460 | 0.559 | 0.538 | 0.004 | 0.545 | 0.004 | N/A |
| Weaning gain EBV | | | | N/A | | | 0.522 | 0.495 | 0.003 | 0.501 | 0.002 | 0.688 |
| Weaning gain dEBV | 0.203 | 0.178 | 0.005 | 0.183 | 0.005 | 0.272 | 0.402 | 0.348 | 0.005 | 0.363 | 0.005 | N/A |
| Postweaning gain EBV | | | | N/A | | | 0.685 | 0.672 | 0.003 | 0.672 | 0.002 | 0.802 |
| Postweaning gain dEBV | 0.186 | 0.184 | 0.005 | 0.180 | 0.004 | 0.215 | 0.599 | 0.584 | 0.005 | 0.584 | 0.005 | N/A |
| Yearling gain EBV | | | | N/A | | | 0.650 | 0.638 | 0.002 | 0.640 | 0.002 | 0.768 |
| Yearling gain dEBV | 0.268 | 0.253 | 0.005 | 0.260 | 0.004 | 0.309 | 0.561 | 0.539 | 0.005 | 0.545 | 0.005 | N/A |

[1]Sargolzaei et al. (2009).

[2]dEBV = deregressed EBV.

[3]Validation using *k*-fold strategy: Each of the random subsets from cluster 1 (X1 to X5) were replaced by an equal sized group ($n = 212$) of animals from cluster 1(if validation was carried out for the subset X1, the remaining groups [X2 to X5] were used for replacement each time). Accuracy reported is an average of all *k* groups having had all other subsets replaced. Estimated breeding values calculated from across-breed comparisons or deregressed breeding values.

[4]Each of the random subsets (X1 to X5) were replaced by a group of animals of the same size (Extra1; $n = 217$) from the unrelated cluster 2.

[5]Each of the random subsets (X1 to X5) were replaced by a group of animals of the same size (Extra1; $n = 217$) from the unrelated cluster 2 and a second group was also included (Extra2) to enlarge the training set with unrelated animals.

[6]N/A = Not applicable.

strategy presented in Table 5 (around 200 individuals), kept in the reference population in Table 7 during the *k*-fold validation (X1 to X5), contributed toward this minimal accuracy improvement. However, even with the enlargement of the reference population, the accuracy remained lower compared with the within-cluster evaluation, confirming the negative impact of adding unrelated animals in the reference population.

Results from genomic predictions here are still inferior to traditional evaluations ("Traditional Evaluation" column in Table 5) without genomics for most traits. This, however, is not indicative that genomics will not work as well as or better than traditional EBV for these traits, especially as the training population of genotyped beef cattle with accurate phenotypes grows. Accuracies were conservatively calculated, with no correction for the accuracy of traditional EBV, dEBV, or DGV being compared. If a method to correct DGV accuracy was used, higher accuracies of genomic selection generally have been found (Saatchi et al., 2012). Also, as the population of genotyped animals in all breeds continues to grow, genomic selection will become more feasible for animals both within and outside of the largest clusters detected. Training population size has been consistently shown to be a strong indicator of genomic selection accuracy; however, for a crossbred population, using a sparse genotype panel, the importance of training population size becomes even more pertinent. Haplotypes between markers and potentially causative QTL may not be in the same phase across different breeds, as has been shown in dairy cattle (De Roos et al., 2008). A differing haplotype phase will lead to inaccuracy of estimating marker effects across a population, and if markers are associated with different variants on a QTL across animals in the training population, marker effects will generally regress toward 0 and the effects of certain QTL will be ignored. Although cross-validation is the best method to evaluate results in real data, the accuracy of input EBV being less than 1 can lead to incorrect conclusions about the validity of different methods. Accuracy of various methods is also highly dependent on population size, and the clusters built here vary in size, so the true cause of reduced accuracy is difficult to ascertain. Accuracy was also explored as the accuracy of the overall population; however, for some groups or individuals, the results may vary depending on breed composition and the potential effective population size of each breed.

Accuracies found in this study are similar to those found in both simulated and true populations of purebred beef cattle (Brito et al., 2011; Saatchi et al., 2012). This is very promising for genomics to allow crossbred cattle to be evaluated as accurately as purebreds and allow for more accurate selection when using crossbred animals as parents of future generations in composite breeding systems. When compared with other studies that have used crossbred animals as the training population, accuracies found here are similar or higher for traits of similar heritability, although population size and accuracy of trait measurement vary widely (Toosi et al., 2010; Mujibi et al., 2011). The heritability of traits

**Table 6.** Regression coefficient (*b*) of genomic selection averaged across validation groups from *k*-fold validation

| | Validation group (compared with dEBV[2]) | | | | | | Validation group (compared with EBV) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trait used in gebv[1] software | Within cluster 1 (*k*-fold)[3] | Replacing X1 to X5 with Extra1[4] | SE | Replacing X1 to X5 with Extra1 and adding Extra2[5] | SE | Traditional evaluation | Within cluster 1 (*k*-fold)[3] | Replacing X1 to X5 with Extra1[4] | SE | Replacing X1 to X5 with Extra1 and adding Extra2[5] | SE | Traditional evaluation |
| Birth weight EBV | | | | N/A[6] | | | 1.240 | 1.233 | 0.007 | 1.215 | 0.007 | 1.02 |
| Birth weight dEBV | 1.148 | 1.156 | 0.012 | 1.147 | 0.011 | 1.05 | 1.023 | 1.031 | 0.008 | 1.021 | 0.008 | N/A |
| Weaning gain EBV | | | | N/A | | | 1.321 | 1.400 | 0.007 | 1.367 | 0.007 | 0.93 |
| Weaning gain dEBV | 1.086 | 1.096 | 0.031 | 1.152 | 0.027 | 0.91 | 0.865 | 0.875 | 0.013 | 0.901 | 0.012 | N/A |
| Postweaning gain EBV | | | | N/A | | | 1.655 | 1.744 | 0.015 | 1.679 | 0.012 | 1.05 |
| Postweaning gain dEBV | 1.849 | 1.899 | 0.058 | 1.800 | 0.050 | 1.11 | 1.514 | 1.518 | 0.015 | 1.467 | 0.013 | N/A |
| Yearling gain EBV | | | | N/A | | | 1.518 | 1.662 | 0.014 | 1.599 | 0.009 | 1.02 |
| Yearling gain dEBV | 1.650 | 1.819 | 0.039 | 1.773 | 0.032 | 1.12 | 1.254 | 1.397 | 0.016 | 1.348 | 0.015 | N/A |

[1]Sargolzaei et al. (2009).

[2]dEBV = deregressed EBV.

[3]Validation using *k*-fold strategy: Each of the random subsets from cluster 1 (X1 to X5) were replaced by an equal sized group ($n = 212$) of animals from cluster 1(if validation was carried out for the subset X1, the remaining groups [X2 to X5] were used for replacement each time). Accuracy reported is an average of all *k* groups having had all other subsets replaced. Estimated breeding values calculated from across-breed comparisons or deregressed breeding values.

[4]Each of the random subsets (X1 to X5) were replaced by a group of animals of the same size (Extra1; $n = 217$) from the unrelated cluster 2.

[5]Each of the random subsets (X1 to X5) were replaced by a group of animals of the same size (Extra1; $n = 217$) from the unrelated cluster 2 and a second group was also included (Extra2) to enlarge the training set with unrelated animals.

[6]N/A = Not applicable.

used in this study as been found to range from 0.2 to 0.5 (Pravia et al., 2014). Accuracy varied with heritability, and, in general higher, heritability traits were more accurately evaluated. Weaning gain was poorly evaluated in this study, and this is likely due to both a low heritability as well as the low accuracy obtained from the traditional evaluation before the DGV estimation.

Table 5 shows the accuracy of DGV when using deregressed values as well as full EBV. Previous studies using deregressed values have shown low to moderate accuracies when using correlations with EBV or dEBV to measure accuracy (Weber et al., 2012; Neves et al., 2014). Deregression using low reliability EBV and parent average (**PA**) as an input can create difficulty due to potential overinflation of dEBV leading to an increase in variance in the genomic prediction model. For similar traits as used in this study, accuracies ranging between 0.18 and 0.28 were found; however, accuracies have been calculated variably across genomic selection studies (Neves et al., 2014). Accuracy values, when comparing with dEBV in this study, were worse than when using EBV, likely due to the increased variance of dEBV in comparison with EBV, leading to generally lower Pearson correlation values. Concordance with dEBV was similar to what previously has been seen using a similarly sized population and the 54,609 SNP panel (Weber et al., 2012) but slightly lower than when the high density SNP panel (777,967) SNP panel was used (Neves et al., 2014).

Slopes of regression between DGV and EBV or dEBV (Tables 6 and 8) were different from 1 for most traits, indicating that some scale issues exist for the genomic evaluations. This is consistent with the results found by other such studies in crossbred animals (Hanna et al., 2014; Hidalgo et al., 2015) as well as those in purebred beef populations (Neves et al., 2014). The observed difference in scale is likely, in part, due to the poor accuracy of EBV and dEBV that the DGV are being regressed on. The regression coefficient was similar in all scenarios, although it was found to be slightly closer to 1 in most cases when evaluated within a cluster. Direct genomic values were consistently scaled upward, with the lone exception being when dEBV were used to generate DGV and then compared with true EBV. In this scenario, a slight downward scaling was observed where DGV underestimated EBV values. This was, however, the lowest accuracy scenario when using EBV as the dependent variable in the regression. Genomic predictions are usually overestimated. The strong underestimation can be related to the limited amount of information used to calculate DGV or lack of an index to combine DGV with parent average. Further investigation on an appropriate index is required for multibreed genomic evaluations. The regression coefficient was generally lower when deregression was performed, showing that the parent averages being double counted through the individuals phenotypes caused an inflation of DGV to take place. This shows that although the dEBV led to lower accuracy of prediction, further comparisons of genotyped and ungenotyped animals is more realistic, and the loss in accuracy due to deregression may be indicative of the poor reliabilities of the crossbred ABC and

**Table 7.** Accuracy (Pearson correlation) of genomic selection averaged across validation groups from *k*-means validation when sets from the unrelated cluster (Extra2) were added in the validation process without replacing a set from the training population

| | Validation group (compared with dEBV[2]) | | | | | | Validation group (compared with EBV) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trait used in gebv[1] software | Within cluster 1 (*k*-fold)[3] | Adding Extra1 without replacing X1 to X5[4] (#) | SE (#) | Adding Extra1and Extra2 without replacing X1 to X5[5] (#) | SE (#) | Traditional evaluation | Within cluster 1 (*k*-fold)[3] | Adding Extra1 without replacing X1 to X5 (#) | SE (#) | Adding Extra1and Extra2 without replacing X1 to X5 (#) | SE (#) | Traditional evaluation |
| Birth weight EBV | | | N/A[6] | | | | 0.610 | 0.593 | 0.002 | 0.594 | 0.003 | 0.735 |
| Birth weight dEBV | 0.378 | 0.369 | 0.003 | 0.370 | 0.003 | 0.460 | 0.559 | 0.540 | 0.005 | 0.549 | 0.004 | N/A |
| Weaning gain EBV | | | N/A | | | | 0.522 | 0.499 | 0.003 | 0.512 | 0.004 | 0.688 |
| Weaning gain dEBV | 0.203 | 0.182 | 0.005 | 0.187 | 0.004 | 0.272 | 0.402 | 0.360 | 0.005 | 0.380 | 0.012 | N/A |
| Postweaning gain EBV | | | N/A | | | | 0.685 | 0.677 | 0.004 | 0.680 | 0.018 | 0.802 |
| Postweaning gain dEBV | 0.186 | 0.185 | 0.004 | 0.182 | 0.003 | 0.215 | 0.599 | 0.587 | 0.004 | 0.589 | 0.006 | N/A |
| Yearling gain EBV | | | N/A | | | | 0.650 | 0.642 | 0.003 | 0.643 | 0.002 | 0.768 |
| Yearling gain dEBV | 0.268 | 0.255 | 0.004 | 0.262 | 0.004 | 0.309 | 0.561 | 0.541 | 0.006 | 0.555 | 0.005 | N/A |

[1]Sargolzaei et al. (2009).

[2]dEBV = deregressed EBV.

[3]Validation using *k*-fold strategy: Each of the random subsets from cluster 1 (X1 to X5) were replaced by an equal sized group ($n = 212$) of animals from cluster 1(if validation was carried out for the subset X1, the remaining groups [X2 to X5] were used for replacement each time). Accuracy reported is an average of all *k* groups having had all other subsets replaced. Estimated breeding values calculated from across-breed comparisons or deregressed breeding values.

[4]A group of animals of the same size (Extra1; $n = 217$) from the unrelated cluster 2 was added in the reference set without replacing subsets from cluster 1 (X1 to X5).

[5]Two groups of animals (Extra1 and Extra2; each one with the same size, $n = 217$) from the unrelated cluster 2 were added to enlarge the reference set with unrelated animals without replacing subsets from cluster 1 (X1 to X5). Column headings ending with "(#)" must be compared with the corresponding columns from Table 5. The remaining columns from this table are identical to Table 5.

[6]N/A = Not applicable.

not indicative of a failure in the deregression procedure for these data. For PWG and YG, a greater variability in slope was seen, likely due to a much smaller proportion of animals having their own phenotype for evaluation, leading to a small scaling effect. Slopes of regression in Table 8 were slightly closer to 1 (0.02 as an average value across all scenarios) than those presented in Table 6.

The comparison of results from traditional evaluations was calculated as the regression between EBV (or dEBV) from the entire data set and the EBV calculated by removing phenotypes from the animals in a certain subcluster (X1 to X5) as part of the *k*-fold validation strategy. Higher accuracies of traditional evaluation suggest that genomic evaluation of crossbred animals, performed with a restricted reference population size, do not provide a significant increase in accuracy of evaluation, especially for PWG and YG, where a high occurrence of scale issues was seen in genomic evaluations. This should, however, be looked at critically, as the EBV used to compare accuracies between genomic and traditional methods were calculated using the same method as the dependent variable (full EBV) and inherently will be more accurate because of this. Further investigation repeating the same method in a population containing thousands of animals is warranted. One additional issue on multibreed studies using real data is the absence of equally distributed populations (same numbers of purebred animals from each breed or group as well as equal representation of crossbred animals with similar breed proportions) and the fact that each breed was originally generated under different selection intensity over the years. The best approach to verify the accuracy of genomic evaluation in a multibreed population is by simulation, at least until genomic selection has been implemented for several years and long-term genetic trends can be measured across a population. At this point, due to a smaller genotyped population and less LD than is seen in major dairy breeds or purebred beef breeds, implementation of genomic selection in crossbred beef animals remains ineffective.

Further analysis needs to be performed to determine the best way to evaluate individuals with a low relationship coefficient with the rest of the population. Even when 5 clusters were created, there were clusters of very few animals, and these individuals could not be evaluated within a cluster. It has been shown that these animals should not be included in analysis of animals that fit well into a large cluster. However, for evaluation of these animals themselves, a subsequent reclustering must take place to ensure a large-enough training population can be made to perform accurate DGV estimation. If a study is designed to target a specific group of animals, clustering methodologies that ensure a minimum population size can be used to build a cluster of animals around a

**Table 8.** Regression coefficient (*b*) of genomic selection averaged across validation groups from *k*-fold validation when sets from the unrelated cluster (Extra2) were added in the validation process without replacing a set from the training population

| | Validation group (compared with dEBV[2]) | | | | | | Validation group (compared with EBV) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trait used in gebv[1] software | Within cluster 1 (*k*-fold)[3] | Adding Extra1 without replacing X1 to X5[4] (#) | SE (#) | Adding Extra1 and Extra2 without replacing X1 to X5[5] (#) | SE (#) | Traditional evaluation | Within cluster 1 (*k*-fold)[3] | Adding Extra1 without replacing X1 to X5 (#) | SE (#) | Adding Extra1 and Extra2 without replacing X1 to X5 (#) | SE (#) | Traditional evaluation |
| Birth weight EBV | N/A[6] | | | | | | 1.240 | 1.320 | 0.008 | 1.178 | 0.009 | 1.02 |
| Birth weight dEBV | 1.148 | 1.150 | 0.009 | 1.141 | 0.010 | 1.05 | 1.023 | 1.016 | 0.006 | 1.001 | 0.007 | N/A |
| Weaning gain EBV | N/A | | | | | | 1.321 | 1.368 | 0.007 | 1.322 | 0.007 | 0.93 |
| Weaning gain dEBV | 1.086 | 1.092 | 0.027 | 1.113 | 0.020 | 0.91 | 0.865 | 0.921 | 0.009 | 0.927 | 0.011 | N/A |
| Postweaning gain EBV | N/A | | | | | | 1.655 | 1.711 | 0.012 | 1.733 | 0.011 | 1.05 |
| Postweaning gain dEBV | 1.849 | 1.881 | 0.045 | 1.749 | 0.059 | 1.11 | 1.514 | 1.489 | 0.011 | 1.421 | 0.014 | N/A |
| Yearling gain EBV | N/A | | | | | | 1.518 | 1.599 | 0.013 | 1.598 | 0.016 | 1.02 |
| Yearling gain dEBV | 1.650 | 1.820 | 0.036 | 1.690 | 0.016 | 1.12 | 1.254 | 1.303 | 0.012 | 1.309 | 0.015 | N/A |

[1]Sargolzaei et al. (2009).

[2]dEBV = deregressed EBV.

[3]Validation using *k*-fold strategy: each of the random subsets from cluster 1 (X1 to X5) were replaced by an equal sized group ($n = 212$) of animals from cluster 1(if validation was carried out for the subset X1, the remaining groups [X2 to X5] were used for replacement each time). Accuracy reported is an average of all *k* groups having had all other subsets replaced. Estimated breeding values calculated from across-breed comparisons or deregressed breeding values.

[4]A group of animals of the same size (Extra1; $n = 217$) from the unrelated cluster 2 was added in the reference set without replacing subsets from cluster 1 (X1 to X5).

[5]Two groups of animals (Extra1 and Extra2; each one with the same size, $n = 217$) from the unrelated cluster 2 were added to enlarge the reference set with unrelated animals without replacing subsets from cluster 1 (X1 to X5). Column headings ending with "(#)" must be compared with the corresponding columns from Table 6. The remaining columns from this table are identical to Table 6.

[6]N/A = Not applicable.

certain population. However, clustering in this way can lead to animals that are not strongly related being included in a population. Therefore, a balance is required between the number of animals to include in the reference population and the relationship of the selection candidates to the reference population. When implementing GPC in a commercial setting with a diverse set of breeds and populations being included, such as would be the case for a national commercial beef cattle evaluation in Canada, it is likely that some animals initially would be deemed unsuitable for prediction due to too few animals of sufficient relationship in the reference. Another challenge to overcome with GPC is that animals will be predicted from different reference populations and some effort will be needed to ensure animals can be compared across clusters in terms of their DGV, when possible. However, we feel these challenges can be overcome by adjustments on the genomic relationship matrix or by using methods that rely on the identification of haplotypes across different groups or clusters.

For genomic selection to be implemented in crossbred commercial beef cattle, a large reference population of animals with genotypes and phenotypes is required. Such resources are being developed, through recorded herds. The development of these resources could increase at an exponential rate with a step-change in genotyping technologies. Genotyping by sequencing, as one example, shows promise to provide high-throughput genotypes at lower cost (Clarke et al., 2014). In practice, genotyping by sequencing could offer medium-density genotyping along with parentage for the price point of parentage alone with current technologies. With costs of genotyping decreasing and accuracy of imputation methods increasing, building a reference population for crossbred genomic selection that will outperform traditional evaluation seems likely. Genomic prediction using clusters provides a means to build a better reference population in an efficient manner, for more accurate genomic selection with the type of crossbreed data that comes with a commercial beef cattle population, such as that seen in Canada.

This study provided an accurate strategy of grouping animals for subsequent multibreed genomic evaluation effectively incorporating crossbred animals. Grouping animals using a cluster strategy for genomic selection is more accurate and efficient than using all available animals. The population of 1,500 genotyped crossbred or multibreed beef cattle used in this study was not large enough to accurately implement genomic selection. There are large multibreed databases being developed that will enable genomic selection to be implemented in the future. The framework provided in this paper will allow for efficient use of genotypes for routine evaluation as more genotypes and phenotypes

become available. Further research is required to ensure these results are consistent across multiple traits that may have different genetic architectures, to determine the practical minimum size and degree of relationship within a cluster to ensure accurate genomic prediction for all individuals and to fine tune evaluations for animals that do not fit well into a cluster.

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