

Genomic Selection in Sheep Breeding Programs

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ABSTRACT: Implementation of genomic selection in sheep breeding provides a number of challenges, compared to dairy cattle, because of the higher genetic diversity between and within sheep breeds, the cost of maintaining reference populations and the limited ability of individual breeders to invest in genotyping. Within this study, we compare theoretical and realized genomic prediction accuracies for traits in sheep and evaluate and describe implementation strategies for genetic selection programs. Based on modest genomic prediction accuracies and efficient genotyping strategies, it is feasible for well-designed breeding programs in sheep to apply genomic selection that are cost effective. A sustainable use of genomic selection in sheep requires cheap (i.e. low density) genotyping of large numbers of animals combined with imputation from high density information in select animals in order to provide predictability of breeding values that extend across the breed.

Keywords: Sheep breeding; Genomic selection

Introduction

Animal breeding research and development in the last decade has been dominated by the potential of genomic selection. Little more than a decade after the paper by Meuwissen et al. (2001) was published the technology of cheaply genotyping a large amount of DNA markers has been established. Dairy breeding programs were the first to adopt genomic selection, as it was easy to show benefits (Schaeffer, 2006). The main traits in the dairy breeding objective are sex limited and genomic selection allows accurate selection of young males, therefore making the expensive progeny testing schemes nearly obsolete. Moreover, dairy AI companies are relatively large and can easily afford genomic testing of bulls. Technically, it was also easy to achieve high genomic prediction accuracies, as there were thousands of progeny tested Holstein Friesian bulls available for inclusion in the reference population, all belonging to a population with a relatively small effective size.

In sheep, the situation is quite different. For a breeding technology such as genomic selection to establish successfully, a number of conditions need to be met. First, it has to be economically viable, i.e. the cost needs to be offset by sufficient benefits. These benefits are realized through a higher value of the annual genetic improvement, or, in some cases, a reduced cost by replacing another more expensive selection strategy. This economic potential de-

pends on the genetic variation in profit and how easy breeding objective traits can be measured and selected for. The second condition relates to the structure of the breeding industry. In sheep and also beef cattle, there are many independent operators, mostly with a small size business. This makes it difficult for individual breeders to invest much in genetic improvement, also because only a small proportion of the overall benefits of genetic improvement are returned to the breeder. Therefore, breeders tend to seek low cost approaches when it comes to genetic improvement. A third condition is the technical feasibility; how easy is it to realize the potential benefits and is genomic selection accuracy of sufficient precision feasible at a reasonable cost? The sheep situation is challenging as a large genetic diversity exists in sheep, both between and within breeds. As a consequence, a much larger number of animals is required for a reference population

The aim of this paper is to review the various aspects of implementing genomic selection in sheep breeding programs, including the potential to increase rates of genetic gain, the size and structure of reference populations that are needed, the costs and benefits for individual breeders that invest in genotyping and additional trait measurement. We will use examples from the work undertaken by the Australian Sheep CRC to illustrate various aspects of implementation, and we discuss the potential to improve the technology further. In a companion paper, Swan et al. (2014) discuss the inclusion of genomic information in the national genetic evaluation system for sheep. The paper focuses mainly on the breeding program aspects, and emphasizes the technical issues related to the genetic structure of the sheep populations, including a use of crossbreds, and how they impact on the design of reference populations. We predominantly focus on sheep that are improved for meat and/or wool objectives, and largely ignore dairy sheep.

Potential benefits of genomic selection of sheep

Traits with a moderate heritability that are easy to measure are relatively easy to improve. If traits can be measured cheaply, on both sexes and before time of first selection, the accuracy of estimating breeding value (EBV) at first age of selection can be high. In that case, genomic testing will have limited benefits as the increase in selection accuracy will only be small, and there is little opportunity to decrease generation interval. Table 1 compares the additional accuracy of estimated breeding value of 1 year old males as well as the additional gain in genetic improvement

when including a genomic test of the selection candidate. Selection was assumed optimized across age class; the extra rate of genetic gain is therefore not only a result of more selection accuracy, but also of a reduced generation interval, as more young animals are selected if their EBV accuracy increases. In the comparisons, the heritability (h^2) and trait measurability are varied and the reliability of genomic prediction was assumed equal to r^2 , implying that for all traits a similar number of animals were used for prediction. Table 1 also shows cases where selection is on a correlated trait, which is relevant for selection on traits related to carcass value. The benefit of GS is clearly highest for traits that are more difficult to measure and have low heritability. The maximum benefit is a doubling of genetic gain. The benefit is highest for traits that cannot be measured at all, unless such traits have very high correlations with measured traits

Potential benefit can be evaluated for a combination of traits, each with benefits varying according to conditions outlined in Table 1. We have compared the benefit for some common selection indexes used in Australia. For this we assumed genomic prediction reliabilities as currently achieved in Australia (Daetwyler et al., 2012; Moghaddar et al, 2014). These reliabilities are on average closer to about $\frac{1}{2}h^2$, and therefore smaller than the accuracies assumed in Table 1. The benefits were higher for indexes aimed at dual purpose wool and meat production (~15%) compared with those for meat indexes (~5%). The reason is that adult wool production and reproductive performance determine much of the profitability of dual purpose enterprises and these traits cannot be measured at an early age, whereas growth and (scanned) carcass traits can be measured before selection. However, when actual carcass and meat quality traits would be included in the breeding objective, benefits for meat sheep would be larger.

Table 1. Percent increase in selection accuracy and rate of genetic gain for single trait genomic selection¹ for various degrees of heritability² (h^2) and trait measurability.

Trait Measurability	$h^2 = 0.1 = r^2$		$h^2 = 0.3 = r^2$	
	Acc	Gain	Acc	Gain
< 1 year, both sexes	15	7	12	7
> 1 year, both sexes	68	19	59	37
>1 year, females only	119	27	112	52
on Corr. Trait, $r_g = 0.9$	-	-	20	26
on Corr. Trait, $r_g = 0.5$	-	-	76	86

¹Genomic selection reliability assumed equal to h^2 .

²Listed heritability values refer to trait under selection, i.e. to correlated trait if applicable

In summary, additional rates of gain in sheep as a result of applying genomic selection are currently between 5% and 15%. The additional gains could be increased if the genomic prediction accuracy increases, which can be achieved over time by using larger reference populations.

Predicting genomic selection accuracy

The accuracy of genomic breeding values (GBV) based on DNA marker genotypes can be predicted from theory (e.g. Daetwyler et al., 2008; Goddard, 2009; Goddard et al., 2011), assuming that prediction is based on a reference population of animals with phenotypes and genotypes for the same DNA markers, and these markers are linked to quantitative trait loci (QTL). The accuracy depends on i) the proportion of genetic variance at QTL captured by markers and ii) the accuracy of estimating marker effects. The proportion of genetic variance at QTL captured by markers (b) depends on LD between markers and QTL, which in turn depends on the number of markers (M) and the number of 'effective chromosome segments' (M_e); $b = M/(M_e + M)$. Goddard et al (2011) suggest to approximate $M_e = 2N_e Lk/\ln(2N_e)$ (- note that the original paper uses log, but this should be the natural log-), where N_e = effective population size; L = average chromosome length; k = number of chromosomes. The accuracy of estimating marker effects depends on the captured genetic variance as a proportion of the total variance ($b \cdot h^2$), the number of (unrelated) animals observed in the reference population (T), and the 'effective chromosome segments'. Fewer segments requires estimation of fewer effects, hence more accurate predictions of each segment. This accuracy is expressed as the variance of the estimated (random) marker effects (\hat{q}) as a proportion of the variation in true marker effects: $V(\hat{q})/V(q)$. This term is estimated as $\theta/(1+\theta)$, where $\theta = Th^2b/M_e$. Reliability of GBV is then $r^2 = b \cdot V(\hat{q})/V(q)$ and the accuracy is the square root of this value.

Effective population size. Critical parameters in these predictions are M_e and N_e . Both are not easy to estimate or approximate. M_e depends on the effective population size and the length of the genome. The effective population size can be approximated from population parameters, or estimated from genotypic data. However, it is not always easy to determine what exactly constitutes 'a population' in sheep. There are many breeds, there are composites, and there are sub-populations within breeds. For example, within the merino breed there are substantial differences between 'fine wool' and 'strong wool' types and these are subpopulations within a breed. Kijas et al. (2012) estimated effective size population size for various breeds, including merinos ($N_e = 853$) and Border Leicester ($N_e = 243$). Goddard et al. (2011) suggested also that the term M_e could be derived empirically, based on genotypic data. They suggested taking as a measure the variation in genomic relationship as deviation from the expected (pedigree) relationship. However, similar to studies estimating N_e , such an exercise will depend on the sampling of subjects across the various genetic structures within a population. Traditionally, sheep industry is characterized by many independent flocks, each being a relatively closed nucleus, especially in merino. Theoretical predictions are based on a homogeneous population ignoring any genetic structures or family relationships. In fact, these predictions for an animal that is a member of the same population, but not directly related by pedigree to animals measured in the reference

population. To some extent, the word ‘population’ could be replaced by breed, but strains within a breed are probably best considered as separate population. For example, (Daetwyler et al. 2012a) found that fine wool merinos can be predicted well from a group of other fine wool merinos, but this reference would not be informative about predicting a member of the strong wool strain. Hence, predictions of GBV accuracy are difficult since in practice it is hard to determine N_e and M_e . Comparing predicted and realized accuracies seems therefore important.

Design of reference populations

In traditional breeding programs, we can distinguish between breeding objective traits that are easy to improve and those that are hard to improve. The second group contains both easy to measure traits and hard to measure traits. Easy to measure traits could be still hard to improve, because measurement is sex limited or later in life such that selection accuracy of young breeding animals (esp. males) is limited. Improvement is possible but slow, as generation intervals will be longer. Example traits are milk production, reproduction and adult wool traits. If these traits are commonly recorded in breeding programs, genomic selection is easier to implement as there will be a lot of potential reference animals with phenotypic information available to use for genomic predictions. There is no need to design specific reference populations as previous cohorts of sires with estimated breeding values (EBV) could be genotyped to predict the GBV of a new cohort of young sires. Traits that are not commonly measured could also benefit from genomic selection, but they require the more expensive option of new reference populations to be created based on measurement of both phenotype and genotype.

The two main design questions about a reference population are i) how large should it be? and ii) which animals should be in it? The first question is most important as the size is directly affecting cost as well as the accuracy of genomic predictions, and therefore the benefit gained with genomic selection. The latter question refers to the genetic composition: which breeds, how many from each breed, which sires, how many progeny per sire, which dams? Current evidence is that genomic predictions in sheep do not extend across breeds (Daetwyler et al, 2012a). The implication is that separate reference populations are needed for each breed. Then, within breeds, it is important to know whether selection candidates should have relatives in the reference population in order to get an accurate GBV.

Clark et al. (2011) illustrated how accuracy is affected by relatedness. They predicted a test set of animals based on a reference population that was either highly or moderately related, or unrelated to the test set. The key results are presented in Table 2. For closely related animals, the accuracy of pedigree based Best Linear Unbiased Prediction (BLUP) was high and the accuracy of Genomic BLUP (GBLUP) was slightly higher. For moderately related animals, genomic prediction accuracy was lower, but pedigree based BLUP was much lower and even zero if only a one generation pedigree was used. For the ‘unrelat-

ed’ test set, pedigree based BLUP had virtually zero accuracy but GBLUP still gave a decent accuracy (0.34). They showed this accuracy to be similar to the theoretical GBV accuracy using Goddard (2009) and therefore considered these to be ‘baseline accuracies’, relevant for individuals that are not directly related to the reference, but are member of the same breed (or breeding population). The average GBV accuracy of selection candidates will be somewhat higher if they have direct relatives in the reference population. One could argue that prediction from relationships can also be based on pedigree and are therefore not a feature of genomic prediction. However, this distinction is irrelevant when predicting the merit of a selection candidate. The relevant question is how measuring and genotyping a certain group of animals will affect the accuracy of genomically enhanced EBVs (GEBVs) of a group of genotyped selection candidates, and how that compares with not genotyping them. A desirable feature of a very large reference population is that the GEBV accuracy is similar for all selection candidates and does not rely on the degree of relatedness. This is simply the result of larger reference populations producing more accurate GBVs, such that the difference in GEBV accuracy between related and unrelated animals will reduce.

Table 2. Comparison of prediction accuracy between groups differing in relatedness with the reference population for pedigree based BLUP prediction based on a shallow pedigree (BLUP-S), a deep pedigree (BLUP-D) and genomic relationship matrix (GBLUP)¹.

Method	Close	Distant	Unrelated
Relatedness with reference	0-0.25	0-0.125	0-0.05
Method	Accuracy		
BLUP-S	0.39	0	0
BLUP-D	0.42	0.21	0.04
GBLUP	0.57	0.41	0.34

¹ Results after Clark et al. (2011).

Animals to be tested in the reference populations should be selected from a diverse genetic background within the breed, but also from family lines that can be expected to contribute to the future gene pool in that breed. So there needs to be a balance between merit and diversity. A good strategy is to measure and genotype progeny from young sires of high genetic merit, yet that are relatively unrelated to each other. The number of progeny tested per sire should be small, because smaller progeny groups allow testing more sires which is desirable from a genetic diversity as well as an ‘industry engagement’ point of view. In specially designed reference populations, the number of collected phenotypes will be the limiting factor, and all recorded progeny should be genotyped. A strategy where only sires are genotyped requires a lot more recorded progeny. For example, for $N_e = 250$, $h^2=0.3$ and 2000 progeny measured and genotyped, the GBV accuracy is 0.27. The same accuracy would be achieved if 1300 sires were genotyped, each

with 10 progeny, where ‘heritability of progeny mean’ is equal to 0.45. Hence, genotyping just the sires is only a good strategy if phenotypic data is abundant, as fewer animals need to be genotyped to achieve the same accuracy, but a lot more recorded animals will be required.

The size of a reference population will determine the accuracy of GBV. Although it is hard to give exact numbers required to achieve certain accuracy, it is clear that many animals are needed. For traits that are measured already, the main investment will be in genotyping costs, and as indicated before, genotyping sires can be the most effective strategy. If phenotypes do not yet exist in abundance, e.g. for carcass or meat quality traits, then a much larger investment is required into both phenotyping and genotyping. Note that a reference population can be built over time. There is some evidence in real data that the accuracy of genomic predictions deteriorates if reference animals are more distantly removed from animals to predict (Wolc et al., 2011). Therefore, an Australian reference population was established with the aim to refresh it at least every two generations. Assuming a generation interval of 4 years, this translates roughly to adding about $N/8$ animals each year if a reference set of size N is required. The number added each year vary therefore from a few hundred to more than 1000 for the more diverse merino breed, with on average between 10 and 15 progeny tested per young sire. Those numbers are large for the smaller breeds, which will have difficulty to assemble enough young sires and only submit a small quantity of records to the database each year. As genomic prediction currently do not extent across breed, it is therefore difficult to predict genomic breeding values for the smaller breeds.

Empirical evidence of genomic prediction accuracy

Real data can be used to check whether the reliability of genomic selection can be accurately predicted using theory. Various Australian studies have reported on the genomic prediction accuracies achieved in real data (Daetwyler et al, 2010, Daetwyler et al, 2012b, Moghaddar et al, 2013). Accuracies generally varied from less than 0.2 to 0.5. As predicted by theory, genomic accuracies were generally higher for higher heritable traits, and there was some increase in accuracy when more animals were in the reference population. However, this increase was generally less than expected. Figure 1 shows that for many traits, a doubling of the reference set did not result in the accuracy increase as expected based on the theoretical prediction. Only some traits increased more than expected, but the method of comparison is sensitive to low initial accuracy and random error. Accuracies for prediction in the merino breed were generally higher than expected based on the large diversity in the breed. The evaluated accuracies were corrected for some of these effects as far as they could be determined from pedigree. However, it is likely that GBV predictions are affected by some remaining effects due to underlying genetic structures in the population. This would give a lift in accuracy of GBV, but a relatively smaller increase when more data is used to predict them. Furthermore, the theoretical predictions assume individuals in the

reference set to be unrelated to each other, whereas in reality they often have covariances due to relationships.

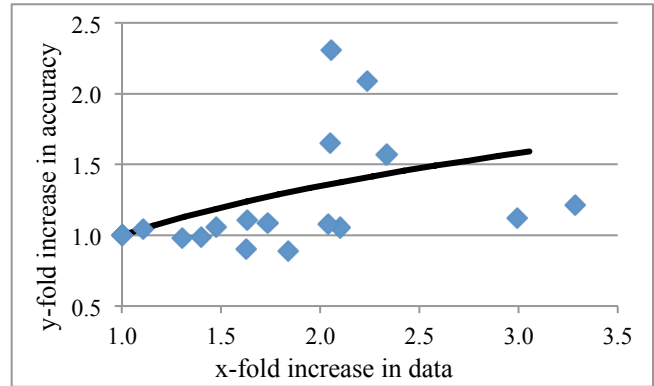


Figure 1. Realized increase in genomic prediction accuracy versus increase in reference population size. Each dot represents a specific trait change after adding more data, the line represent the expected rate of increase based on Goddard et al. (2011).

The reference population used for genomic prediction was multi-breed and consisted of many crossbreds. For the results presented in Figure 2, we only counted the number of breed specific haplotypes. The rationale is that haplotypes from one breed are not expected to contribute to genomic prediction of another breed, at least not with the 50k SNP chip that was used. Moghaddar et al (2013) found that accuracies were highest when the reference set had a maximum proportion of haplotypes from the breed to be predicted, and adding data from other breeds tended to decrease predicting accuracy. Hence, rather than predicting from a generic multi-breed reference set, it maybe be more appropriate to predict from a reference set that only contains haplotypes related to a specific breed .

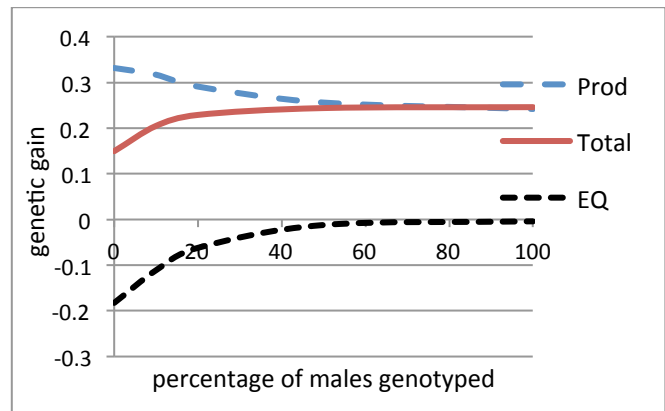


Figure 2. Response to selection for a production trait selected in stage 1 and an eating quality (EQ) trait, added as GBV after stage 1, as a function of the percentage of males genotyped, assuming an unfavorable genetic correlation of -0.5 between the traits, GBV accuracy is 0.3.

The accuracy of genomic prediction can be tested in a validation set (or test set) of animals whose GBV are predicted from marker genotypes only, and then compared

with a realized value. If the observed values are accurate EBV based on many progeny, then the correlation will approximate the accuracy of predicting breeding value. If the observed values are phenotypes, then the correlation needs to be adjusted for the correlation between phenotype and true breeding value (which is equal to h). One validation set can be used, for example when there is a distinct set of genotyped individuals with accurate EBVs. Otherwise, cross-validation can be used where the whole dataset is divided into n sub sets, and $n-1$ of these subsets are used as a reference set to predict the values in the n^{th} set, which is then test set. This process can be repeated n times, such that there are n independent samples of accuracy. The sampling of the sub sets in cross validation can be important. Since we want to validate genomic predictions across-family, the subsets should not be randomly sampled, but they should be sampled as whole families, such that a test set individual does not have direct relatives in the reference set. In general, in validation it is important that data used for the predictions does not contain observations that are also used in the validation (e.g. progeny of sires who's EBV is validated). To account for population heterogeneity, accuracies should be estimated as genetic correlations from a bivariate analysis with proper genetic models for both test set and validation sets.

Strategies for implementation

Implementing genomic selection in a sheep breeding program requires the existence of a reference population with animals having both genotypic and phenotypic data, and individual breeders willing to invest in genotyping selection candidates. Creating an initial reference population is a large investment that is unlikely going to be made by individuals, hence assistance from levy payers and government (research) grants is commonly required. In Australia a reference population could be based on two resource populations initiated by the Sheep Genomic Project (White et al, 2012) and the Australian Sheep CRC (van der Werf et al., 2010), giving more than 15,000 genotyped animals from various breeds, each with a large number of measured phenotypes.

To assist breeders in their decision to invest in genotyping their selection candidates, we modeled predicted benefits and balanced them against the associated cost of genotyping. In a number of individual case studies those models were discussed with breeders and findings were presented and discussed with a wider audience of progressive breeders with an interest in the technology. Predicted benefits were derived from realized GBV accuracies in the CRC research program (see previous section) and existing selection indexes. In general they depend on the variation in genetic merit for profit (as measured by the SD of the breeding objective) and the selection accuracy achieved with current (non-genomic) measurement strategies. An important factor is whether breeders are able to mate their stock within the first year (at 7 months of age) as genomic information is relatively more beneficial for GEBV accuracies of younger breeding animals.

For individual breeders, there are various ways to save on genotyping costs. Firstly, genotyping of females is less efficient due to the lower selection intensity in females. In a merino dual purpose index, genotyping only males gave 18% more response, while genotyping both males and females gives 22% additional response. Therefore, while genotyping costs are relatively expensive, it is not efficient to genotype females unless some are selected for intensive use via reproductive technologies (Granleese et al., 2014). Secondly, breeders can apply two-stage selection. Genotyping only about 20% of a young sire crop, would give more than 80% of the additional benefits of genomic selection when genotyping all males (Figure 2). If the information added by the GBV is small, then a even smaller proportion should be genotyped. However, with multi-trait breeding objectives there may be unfavorable correlations, in which case a larger proportion should be genotyped. Consider a hypothetical situation where the first stage selection is on a production trait that is negatively correlated (-0.5) to a meat eating quality (EQ) trait and the latter can be predicted only via a GBV. Results in Figure 2 show that the overall response is close to maximum with only 20% selected, but a larger proportion genotyped would allow more emphasis on the EQ trait, thereby avoiding the EQ trait to deteriorate. As also pointed out by Dekkers and van der Werf (2014), both overall response and individual trait responses should be considered as genomic selection tends to cause a shift in responses towards the hard to measure traits.

Evaluating cost and benefits for individual breeders can result in break-even figures for genotyping young males. Examples of such calculations were reported for beef cattle by van Eenennaam et al (2012), using cumulative discounted expressions of selected sires. A critical factor in a cost benefit analysis is the proportion of the benefits that can be recovered by the breeder, as this is typically very low in animal breeding. We found that under modest assumptions, the break-even price of genotyping did not exceed the actual cost if the breeder recovered only 5-20% of the extra benefit. Such results depend heavily on the efficiency of the operation, e.g. the proportion of young males sold. Horton et al (2014) used models of 2- and 3-tier breeding systems, and optimized net present value. They confirmed optimal proportion of males genotyped to be typically around 20%, and genotyping cost in the nucleus did not exceed 5% of the total additional benefits of genomic selection. Further work would need to show whether there is a place for genotyping females and individuals in lower tiers when genotype costs decrease, potentially leading to a higher degree of openness of the nucleus. Such scenarios are more likely to be implemented if genotype costs decrease over time. Future studies could also consider whether breeders should genotype (and phenotype) more animals in their nucleus flock to contribute to predicting accuracy of their selection candidates. Animals in a breeders' flock are genetically more related to the selection candidates and using Goddard et al (2011) we can predict for a larger and more distant reference population (e.g. $T = 4000$ and $N_e=500$) a similar prediction accuracy as with a smaller more related reference population (e.g. $T=1000$, $N_e = 75$).

Conclusion

This paper has focused predominantly on breeding programs for meat and wool sheep and dairy sheep have been largely ignored. Sheep breeding programs for wool and/or meat can benefit from genomic selection by increasing rates of genetic gain, with more emphasis on traits that are otherwise hard to improve. Because of the large genetic diversity within and between sheep breeds, a large number of animals are required for reference populations. Therefore, it would be particularly useful for sheep to have genetic markers that can predict genetic differences across breed. High density and sequence information might help to achieve this. On the other hand, for a sustainable introduction of genomic selection in sheep breeding, cheap genotyping tests are needed. This might be achieved by lower density marker panels that can be imputed to a higher density. More development is needed to fit these strategies together in a delivery system to sheep breeders. This scenario is only viable against a background of continuous trait recording and sophisticated genetic evaluation systems.

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