Breeding Focus 2016 – Improving Welfare

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Preface

The inaugural 'Breeding Focus' workshop was held in 2014 to outline and discuss avenues for genetic improvement of resilience. The Breeding Focus workshop was developed to provide a forum for exchange between industry and research across livestock and aquaculture industries. The objective of Breeding Focus is to cross-foster ideas and to encourage discussion between representatives from different industries because the challenges faced by individual breeding organisations are similar across species. This book accompanies the Breeding Focus 2016 workshop. The topic of this workshop is 'Breeding Focus 2016 - Improving welfare'.

> *"Animal welfare means how an animal is coping with the conditions in which it lives. An animal is in a good state of welfare if (as indicated by scientific evidence) it is healthy, comfortable, well nourished, safe, able to express innate behaviour, and if it is not suffering from unpleasant states such as pain, fear, and distress. Good animal welfare requires disease prevention and veterinary treatment, appropriate shelter, management, nutrition, humane handling and humane slaughter/killing. Animal welfare refers to the state of the animal; the treatment that an animal receives is covered by other terms such as animal care, animal husbandry, and humane treatment."* (World Organisation for Animal Health 2008).

Animal breeding offers opportunities to improve the state of animals. Existing methodologies and technologies used in animal breeding can be used to improve welfare of animals on farm while maintaining productivity. Welfare and productivity are not necessarily in opposition because several welfare measures are genetically independent from productivity traits. Further, it is often economically beneficial to improve welfare traits. These aspects provide ample opportunities to improve both welfare and productivity through selective breeding.

The chapters of this book describe existing frameworks to define welfare of animals and outline examples of genetic improvement of welfare of farm animals. A reflection on ethical issues of animal breeding and welfare is presented and further avenues for genetic improvement of welfare are discussed.

We thank all authors for their contributions to this book and their presentations at the Breeding Focus 2016 workshop in Armidale. Each manuscript was subject to peer review by two referees. We thank all reviewers who generously gave their time to referee each book chapter. A special thank you goes to Kathy Dobos for looking after all details of organising this workshop and for her meticulous work on putting this book together.

Susanne Hermesch and Sonja Dominik

Armidale, September 2016.

Using genomic prediction for footrot resistance in sheep based on case-control industry data

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Abstract

Footrot is a highly contagious hoof disease of sheep and other ungulates that has substantial welfare and economic impacts. The extent to which animals are affected by footrot is heritable. However, there are some significant operational limitations to applying traditional pedigree-based selection methods for increasing resistance to footrot. The New Zealand Merino sheep industry have investigated genomic tools in order to use unpedigreed industry animals with footrot phenotypes to predict genomic breeding values. It is imperative to evaluate the accuracy of such genomic predictions. Using cross-validation techniques and a range of reference data sets, we demonstrated a wide range in the average accuracy of prediction for genomic breeding values (GBVs). These were highest with large reference data sets (which included contrasts within flock) and were reduced with lower reference data set size and when predictions were made for flocks outside the reference set. Further analyses will be performed when industry genotypic data are finalised, including validation for sires in ram breeding flocks. However, this preliminary study suggests that there will be some merit for genomic selection against footrot based on industry data.

Footrot

Footrot is a highly contagious and difficult to manage hoof disease of sheep and other ungulates that has substantial welfare and economic impacts. Footrot begins as an interdigital dermatitis, which is followed by formation of lesions on the interdigital wall of the hoof and subsequent separation of the hard horn from the foot, called under-running (Bennet and Hickford, 2010). Footrot can result in poor feed intake, losses in production, a reduction in wool strength and in the worst cases, death from a combination of starvation, thirst and other systemic bacterial infections that occur in sheep that spend prolonged periods recumbent (Stewart, 1989). The disease involves the interaction between gram-negative anaerobic bacteria: *Dichelobacter nodosus* which helps with the transmission of the disease from infected sheep to soil or environment to uninfected sheep; and *Fusobacterium necrophorum* that causes the inflammation of the hoof and lameness (Burke and Parker, 2006).

Footrot is one of the most costly diseases in sheep producing countries worldwide. This is due to both production losses and increased costs for preventive measures and the treatment of affected animals. Lane *et al*. (2015) estimated that footrot cost Australian producers $32M per year when virulent, or $12.1M when conditions were more benign, mostly due to production losses. Nieuwhof and Bishop (2005) calculated that a reduction in the incidence of footrot has a proportional effect on 42% of the costs associated with lost production and treatment of infected animals. Reducing the incidence of footrot in populations through genetic improvement is therefore a highly desirable option to improve welfare, and reduce production losses, prevention and treatment costs. Several studies have demonstrated that selection is feasible to prevent and reduce the incidence of footrot (Conington *et al*. 2008, Nieuwhof *et al*. 2008, Raadsma and Dhungvel 2013, Raadsma and Conington 2011, Raadsma *et al*. 1993, Raadsma *et al*. 1994, Skerman and Moorhouse 1987, Skerman *et al*.1988), but operational limitations must be considered.

Preliminary results

While it has been well established that genetic variation for footrot resistance is available for exploitation, industry-based breeding programs intended to reduce footrot genetically face several obstacles for the implementation of traditional genetic evaluation procedures, which require both pedigree and phenotype data. Firstly, stud (ram breeding) flocks wish to remain footrot free, particularly in countries like Australia or the UK where legislation restricts movements and sales of footrot affected animals. Therefore, footrot phenotypes are never realised in these flocks. Secondly, footrot challenges vary in field (industry) data, and differences in the observed incidence essentially depict variability in environmental factors and virulence, as well as genetics. Thirdly, footrot phenotypes need to be accurately scored on individual animals, distinct from other foot conditions, and with the knowledge of a common status (e.g. treated vs untreated animals). Finally, industry flocks are typically un-pedigreed, and therefore genetic connections between stud and industry flocks will generally be unknown. Since footrot phenotypes are relatively poorly recorded in stud flocks, and data should also represent the effects of multiple strains of footrot prevalent across a range of environments, using data from industry flocks has some merit.

In September 2010, the New Zealand Merino Company initiated a project aimed at developing a genomic breeding value for footrot, with the objective of targeting resistant animals for breeding to provide a permanent genetic solution for footrot. A range of data collection strategies have been employed. These include: 1) genotyping affected and unaffected animals in commercial industry flocks, and 2) more detailed scoring of phenotypes for footrot in central testing flocks. In this paper we investigate the accuracy of genomic predictions of footrot resistance from affected and unaffected animals in industry flocks, using cross validation techniques.

Overview of data

Data were provided by the New Zealand Merino Company, comprising information from 61 industry flocks, representing predominantly Merino sheep. The genomic data included 50,000 SNP marker genotypes for a total of 4,543 animals, reported with affected/unaffected phenotypes for footrot. However, some flocks did not have genotypes available for both affected and unaffected animals at the time of analyses, and are therefore uninformative. Additional genotypic data was obtained for stud rams within the NZ Merino industry, which were widely used and which should have some (unknown) genetic relationships with flock rams producing progeny in the industry flocks. Genotyping was not performed for the flock rams or industry ewes, which had no phenotypic data of their own.

Footrot phenotypes

Footrot phenotypes can be recorded using different scoring strategies:

- Categorical scores from 0 to 5 per hoof (Egerton and Roberts 1971), being 0 for not affected and ranging from 1 to 5 to represent different degrees of severity of footrot, from water maceration (1) to chronic footrot (5).
- Binary scores: 0 for unaffected (clean) and 1 for affected sheep.

The first scoring method is the most informative because phenotypes represent variability of severity between animals and hooves, assuming constant challenge, and alternative trait definitions can be defined for analyses (e.g. average score, highest score). In contrast, binary scoring does not discriminate amongst individuals for the severity of infection within affected sheep.

In all participating industry flocks, footrot phenotype was scored as a binary trait, based on the presence of at least one severely affected foot (i.e. score 4 or 5) to define an affected animal. All affected animals were subsequently genotyped. "Clean" animals initially selected for genotyping were reassessed at a later date, and only those that remained unaffected over an extended challenge period were genotyped. Therefore, approximately twice as many clean animals were identified for genotyping initially, to make allowance for clean animals which were reassessed as affected prior to genotyping. Consequently, the case control data represented a contrast between animals with either severe infection or sustained resistance, within mob. The sample of animals genotyped was also targeted to obtain approximately equal numbers of animals which were affected and unaffected, within each flock. The preliminary distribution of unaffected versus affected animals per flock is shown in Figure 1, which demonstrates that this target was difficult to achieve across all flocks. Due to the normal commercial practices of syndicate mating and unsupervised lambing (i.e. no mothering up), traditional pedigree was not available in these industry flocks. Therefore, sampling of animals to be genotype could not be done on the basis of known pedigree relationships. Genotyped industry rams had no footrot phenotypes, and were not direct sires of lambs scored in the data. Informative flocks generally represented a single breed, with one exception.

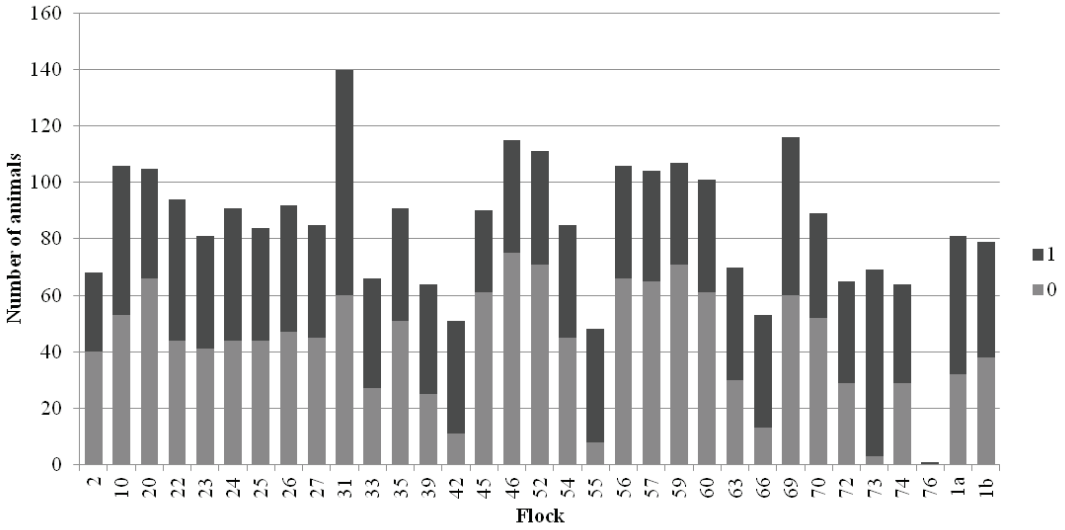

Figure 1. Number of animals with footrot phenotype 0 or 1 per flock

Genomic selection for binary traits

With the present availability of genomic data and the continuous improvement of the tools available for genomic analysis, investigation of hard to measure traits (e.g. footrot) has become possible through the analysis of data using genomic selection (Meuwissen *et al*., 2001). In principle genomic information can be used to predict continuous and categorical traits (Biscarini *et al*. 2014). Most of the literature available has focused on predicting continuous traits. However, there are few studies that focus on genomic predictions for categorical traits (Biscarini *et al*. 2014, González-Recio *et al*. 2008; Manor and Segal 2013, Ornella *et al*. 2014, Villanueva *et al*. 2011, Wang *et al*. 2013). So far the only genome wide association study to identify important molecular polymorphisms for footrot scores has been published by Mucha *et al*. (2015) for Texel sheep. Previous work on a specific genomic test developed in New Zealand for Merino and mid micron sheep breeds (Escayg *et al*. 1997, Hickford *et al*. 2004), based on the DQA2 gene marker in the MHC complex of genes, has been used to identify sires whose progeny will be more resistant to footrot in New Zealand Corriedale. However, the expected associations have subsequently not been observed with high enough accuracy to be useful in other breeds (Conington *et al*. 2008, Mark Ferguson, pers. comms, 2016), motivating further genomic work.

Genomic Breeding Values for Footrot (GBV)

Preliminary genomic breeding values (GBV) for footrot status were generated for all animals using the GBLUP method with the following linear model:

$$y = Xb + Zg + e_i$$

where **y** is the vector for binary footrot phenotypes, ***b*** included fixed effects of contemporary group defined as farm, year of birth and sex; ***g*** is the vector of additive genetic effects accounted for by all marker information with $\boldsymbol{g} \sim N(0, \boldsymbol{G}\sigma^2 g)$, ***X*** and ***Z*** are incidence matrices relating fixed and additive genetic effects to phenotypes. The genomic relationship matrix (**G**) was constructed according to VanRaden (2008). Preliminary examination of the **G** (not presented) confirmed that animals genotyped were generally only lowly related, both within and between flocks, and with the genotyped stud rams. This demonstrated that when the number of animals genotyped is relatively low (N<100) for case-control sampling, common family structures (parent-offspring, half- and full-sibs) may not be evident in genotyped animals from industry flocks.

Cross validation

Cross validation was subsequently performed to establish the accuracy with which different sets of reference data could be used to predict footrot outcomes in other (non-reference) flocks. As with traditional breeding values, one of the advantages of genomic selection is the prediction of genetic merit for unobserved events (e.g. genomic breeding values, Hayes *et al*. 2009a). However, it is important to evaluate the accuracy of such predictions - one method to do this is k-fold cross validation.

It has previously been demonstrated that the accuracy of genomic selection, defined as the correlation between true and predicted genetic breeding values, depends on the reference population size (number of records), effective population size, genetic relationship between reference and validation populations, marker density, amount of linkage disequilibrium between quantitative trait locus and markers, and the effective number of chromosome segments, along with the heritability of the trait (Daetwyler *et al*. 2010, Goddard and Hayes 2009, Hayes *et al*. 2009b, Luan *et al*. 2009, Meuwissen 2009, de Roos *et al*. 2009, Toosi *et al*. 2010, Zhong *et al*. 2009) and the method to estimate marker effects (Meuwissen *et al*. 2001). Since the genetic relationships between animals and flocks in these data appeared to be low based on genomic relationships, we investigated how the construction of the reference population would influence the accuracy of prediction.

Reference data sets

Four different scenarios for the reference data sets were investigated. First, half of the animals from the entire population (N~1800) were randomly selected as reference set to estimate the genomic breeding values (GBV) for the rest of the population representing the validation set. This procedure was performed ten times, sampling new reference sets at random each time, to obtain the average correlation between predicted GBV and corrected phenotypes.

The second scenario consisted of using information of all 32 effective Merino flocks (EMF, N=2771) to predict outcomes for the remaining 29 flocks, excluding each time in the reference set the flock being predicted, uninformative flocks and the flocks containing other breeds. An effective flock is defined as a flock in which both footrot phenotypes (affected or unaffected) were represented.

In the third scenario, only the 12 most informative Merino flocks (IMF, N=1166) were used to predict GBVs for the rest of the flocks. The most informative flocks were the subset of data with close to a 50:50 ratio of animals unaffected/affected and of reasonable size (at least 100 animals or more genotyped within flock).

Finally, information from each effective Merino flock was used individually to estimate the GBVs for animals in other flocks.

Prediction accuracy

Prediction accuracy was calculated as:

$$CV_{acc} = r(GBV, FR_{res})/h,$$

where FR_{res} corresponds to the footrot phenotype corrected for contemporary group using the complete data set and h is the square root of the heritability (Legarra *et al*. 2008). The heritability for footrot was assumed to be 0.30.

Evaluation of the predictive accuracy, estimated by comparing the GBVs with the true phenotypes corrected for contemporary group was investigated through cross validation. With random selection of approximately half the animals to include in the reference set, the prediction accuracy of GBV accuracies averaged across the 10 replicates was generally high (~0.56). However, when the reference data sets were restricted to EMF or IMF flock subsets, prediction accuracy varied from below 0 to 0.67 (Figures 2 & 3 pages 108 and 109), averaging 0.20 (EMF=0.23, IMF=0.18). A negative accuracy reflected a negative correlation between predicted GBVs and adjusted phenotypes. In flocks with low accuracy, the proportion of animals whose phenotypes (affected vs unaffected) did not reflect predicted GBVs (excluding their own data) generally increased proportional to the incidence (mismatches – Figures 2 & 3 pages 108 and 109). Using a single informative flock to predict the rest of the flocks, the prediction accuracy decreased to 0.06, on average, across flocks (results not shown). Low accuracy of prediction would be expected in this scenario.

These results illustrate the wide range in estimated accuracies for genomic prediction, depending on the industry reference data set used. Generally, reference animals present within the same flock maximised the accuracy of prediction for validation set animals. However, when predictions were made for flocks not included in the reference data, accuracy was increased using a larger reference set (eg EMF vs IMF). These results demonstrate that even without known pedigree structure and footrot data collected in an industry setting, GBVs had some predictive capacity. However, these estimates are affected by the magnitude of the assumed

heritability, which cannot be assessed from the data provided, and the case-control nature of animals sampled for genotyping. Therefore, further work is required to cross-validate GBVs derived from a case-control reference data set within other independent flocks where both genotypic and phenotypic data are available. This work will be performed when genotypic data in all industry flocks used in this study has been finalised.

Scoring to improve accuracy of genetic evaluation (genomic or otherwise)

Previous results have shown that there is loss of information when phenotypes are binary because the data reflects incidence but not severity, compared to other trait definitions which also accommodate differences in the severity of infection and the number of feet infected. Using a second data set from a central testing flock (pedigree known), it was demonstrated that using ordered scoring (0-5) and/or averaging scores across hooves increased estimates of heritability compared to estimates obtained from the binary (0/1) scores in these data. Similarly, a trait definition such as the highest score among hoofs is suboptimal in this respect because it represents one score on one hoof. Without standardised scoring across all industry data, difficulties during the data analysis (e.g. variance, scale, incidence issues) can be hard to overcome. Therefore, it is recommended that for future studies footrot scores should be recorded using an ordered 0 to 5 scale per hoof (Egerton and Roberts 1971), being 0 not affected and from 1 to 5 representing different degrees of severity of footrot.

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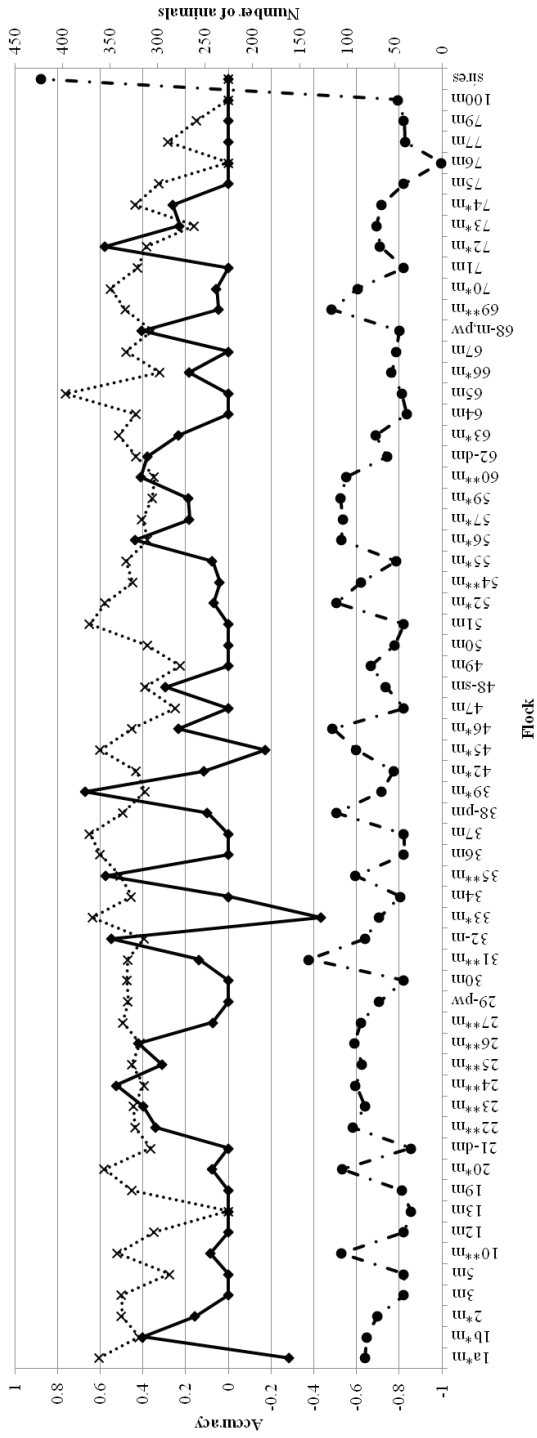

*Figure 2. Cross-validation accuracy per flock using as reference set for effective Merino flocks (*or **, EMF). Letters indicate breed of the animals in the flock: m: Merino, dm: Dohne, pw: Polwarth, pm: PollMerino, sm: Samm.*

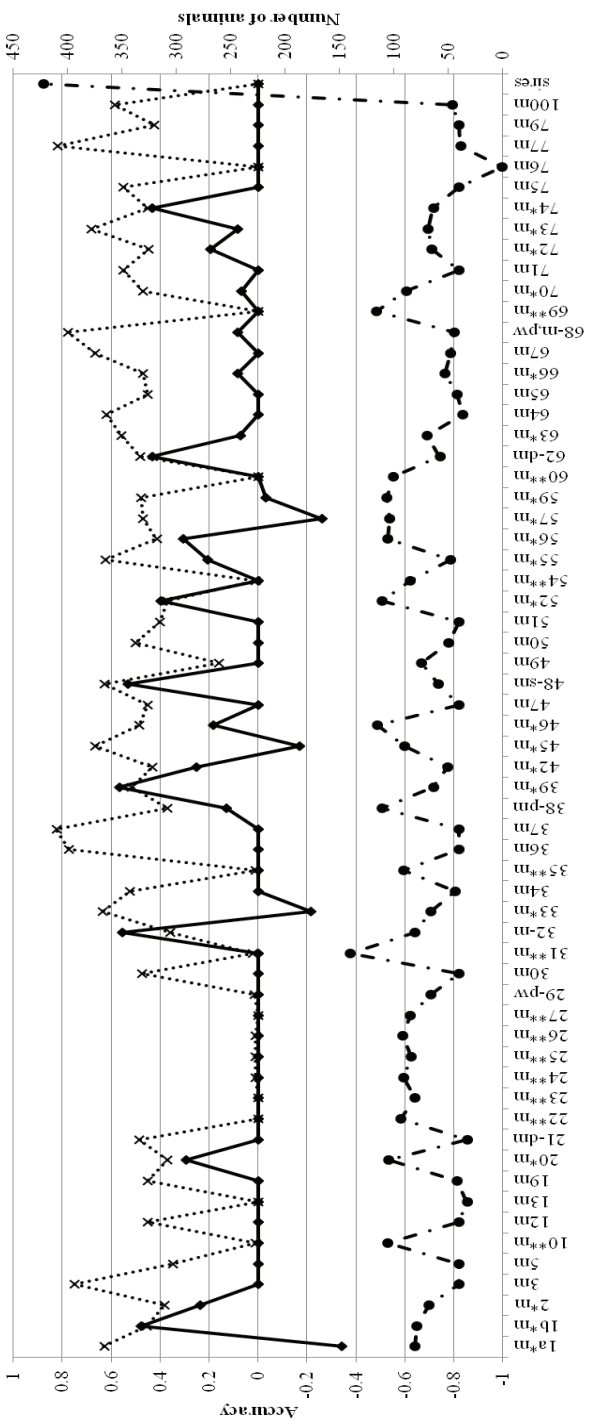

*Figure 3. Cross-validation accuracy per flock using as reference set for the combination of the most informative merino flocks (**. IMF). Letters indicate breed of the animals in the flock: m: Merino, dm: Dohne, pw: Polwarth, pm: PollMerino, sm: Samm.*

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