Title:
Use of commercial data in genetic evaluations

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Biographical sketch (please do not exceed 250 words):
I grew up in Walden, Colorado where I was actively involved in agriculture from a young age. My parents owned a small cow-calf operation which enabled me to raise my own animals through 4-H. After high school, I attended the University of Northern Colorado (UNC) where I received my bachelor’s degree in pure mathematics with an emphasis in statistics. I then attended the University of Nebraska-Lincoln (UNL) for a masters in statistics under the direction of Dr. Steve Kachman. Currently, I am pursuing a PhD in animal breeding and genetics at UNL under Dr. Matt Spangler. My research has revolved around genomic prediction in cattle. Previously, my research consisted of evaluating the accuracy of predicted molecular breeding values using different clustering methods and response variables. Currently, my research involves using simulation to explore the use of pooling genotypes and phenotypes in order to cost effectively use phenotypes from the commercial sectors of the cattle industry to enable more accurate genetic predictors within the seedstock herds. The concept of pooling involves collecting tissue samples from a group of animals and then combining the DNA of those animals to be genotyped as one. The hopes are to then be able to assign a fraction of the group to multiple ancestors, including sires and dams, and use the group’s average performance as a “phenotype” in genetic evaluations. The benefits of this research include the possibility of incorporating a vast amount of commercial level data into genetic evaluations.

Advisor Name:
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Advisor Approval:
I certify that I have read and had sufficient time to provide feedback on the attached literature review.

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Introduction

Genetic evaluations produce estimated progeny differences (EPD) for traits using data largely generated by the seedstock sector of the beef industry. Some of these traits target economically relevant traits (ERT). By definition, true ERT are measured within the commercial sectors. Thus, the EPD produced using seedstock data are either for “presumed” ERT or indicator traits. Millions of records that represent the true ERT are recorded within the commercial industry every year. However, these records rarely make it into genetic evaluations because relationships that tie the commercial animals to the seedstock selection candidates are missing. Relationships between these groups exist, but pedigree information is often missing or incomplete. All commercial animals with records could be genotyped in order to estimate relationships, but this would not be economical. Nonetheless, inclusion of commercial data has enormous potential to increase the response to selection for traits that are economically important to the beef industry including feedlot performance, reproductive longevity, disease resistance, and carcass merit. An optimal solution would be to collect the true ERT from commercial herds and estimate relationships between commercial animals and seedstock animals in an economical manner for use in genetic evaluations.

Review of Literature

Economically relevant traits

Economically relevant traits are traits that directly affect the profitability of a commercial system because they relate to either a cost or source of income (Golden et al., 2000). Examples of ERT include, but are not limited to, weight at time of sale (e.g. weaning weight direct, weaning weight maternal, carcass weight, salvage cow weight), calving ease, maintenance feed requirement, stayability, heifer pregnancy rate, tenderness, and days to finish (e.g. Golden et al., 2000). Enterprises may only identify a subset of these traits as ERT, which is specific to the production system. Take for example a producer who sells calves at weaning, and the price is determined by weight. An obvious ERT in this system would be weaning weight. However, if
another producer determines profit based on carcass weight, weaning weight is no longer an ERT, but could be indicative of carcass weight. Thus, not all traits that are recorded directly affect profitability, but are instead considered indicator traits of the ERT. These indicator traits are genetically correlated with the ERT. In the latter example, the ERT would be carcass weight whereas weaning weight would be considered an indicator trait.

Even though indicator traits do not directly affect the overall profitability of an enterprise, they are measured because the associated ERT are hard to measure or are expressed later in life. Furthermore, most data collection and selection decisions usually take place in the seedstock sector of the beef industry (Garrick, 2018). This has resulted in the collection of phenotypes that are convenient and easy to validate in resulting progeny (Garrick, 2018). Because true ERT are only expressed in commercial animals, the data collected from seedstock animals represent presumed ERT. Additionally, many ERT such as disease susceptibility and survival cannot be collected within seedstock herds, due to increased health conditions and more rapid replacements rates, or there is a genetic and environmental interaction between these traits within the commercial and seedstock herds.

When breeding objectives are defined and selection decisions are taken based on those objectives, only ERT should be included in the decision-making process. In fact, when ERT and indicator traits are used in combination to attain the same selection decision for one trait, the accuracy of that decision is decreased (Golden et al., 2009; Enns, 2013). Oftentimes, merit of an animal is not defined by just one trait, rather a combination of multiple traits. To combine multiple traits into one succinct value to inform the overall genetic merit of an animal, selection indices can be used in order to correctly weight the information (Hazel, 1943). When creating a selection index, typically two sets of traits are needed: objective traits – the ERT defined in the breeding objective, and selection criteria – the traits that are actually measured. Ideally, selection criteria would consist entirely of ERT. Sometimes these ERT are not measured or readily available, and so indicator traits are used as selection criteria (Ochsner et al., 2017).

Current genetic evaluations

By the year 2000, more than fifteen different EPD were produced within the national cattle evaluations. At that time, many of those EPD were for traits that addressed the same breeding goal, such as separate EPD for ultrasonically measured carcass traits and actual carcass
traits, but often could have led to selection decisions that were in contradiction of each other (Golden et al., 2009). Golden et al. (2000) realized the need to incorporate indicator traits into the analysis of EPD for ERT during genetic evaluations and that the EPD for indicator traits should not be published. This strategy would have eliminated the problem of which EPD to use for selection decisions. Unfortunately, today not all traits published are ERT (e.g. birth weight). Also, the number of published traits has increased, not decreased.

During the estimation of EPD, multivariate models are used to combine information from both the ERT and indicator traits. Because most phenotypes collected are from the seedstock industry, some indicator traits are more convenient, cheaper, or simply more practical to collect than the ERT. For example, ultrasound measurements from seedstock are collected more often than carcass data from progeny tests. The ultrasound measurements generally include intramuscular fat percentage, back fat thickness, and ribeye area which are indicator traits of carcass marbling, back fat, and ribeye area, respectively. The industry has taken a general consensus that ultrasound measurements of carcass traits are reliable indicators of the actual carcass data. Literature generally reports moderate to relatively high genetic correlations between the ultrasound and carcass traits (e.g. Moser et al., 1998; Reverter et al., 2000; Devitt and Wilton, 2001; Kemp et al., 2002). This literature justifies the use of ultrasound measurements in seedstock animals to inform selection criteria instead of collecting only actual carcass measurements from progeny test individuals, in which progeny tests are expensive and time consuming to develop. However, Reverter et al. (2000) cautions that genetic correlations are not always consistent across breeds or even between sexes within breeds. The genetic correlation between ultrasound and carcass rib fat thickness was estimated as 0.79, 0.99, 0.87, and 0.02 for Angus bulls, Angus heifers, Hereford bulls, and Hereford heifers (Reverter et al., 2000). Although generally high, genetic correlations between ultrasound and carcass data can range, thus varying in the validity as adequate indicators.

Additional indicator traits include scrotal circumference as an indicator for age at puberty of a sire’s daughter, which is an indicator trait for heifer pregnancy (Golden et al., 2009). Vargas et al. (1998) estimated the genetic correlations between scrotal circumference and age at puberty to be -0.31, which in this case is favorable; bulls with a larger scrotal circumference tend to have daughters that reach puberty earlier. However, Evans et al. (1999) and McAllister et al. (2011) both found the genetic correlation between scrotal circumference and heifer pregnancy to be near
zero. This suggests scrotal circumference is not a reliable indicator of the ERT heifer pregnancy. Therefore, heifer pregnancy phenotypes should be reported for genetic evaluations.

Many traits have a large economic impact within the cattle industry but do not have a breed-wide EPD associated with them. One of these traits is bovine respiratory disease (BRD), which has a large economic impact in the feedlot sector (Snowder et al., 2006). Griffin (1997) estimated BRD accounts for approximately 7% of the total production cost from weaning until the animal is received at the packer. When included in a terminal index, BRD morbidity had an economic value 10.65 times greater than days to finish (Buchanan et al., 2016). Hot carcass weight was the only other trait in the index to have a greater economic value than BRD morbidity; hot carcass weight was 11.47 times more important than days to finish (Buchanan et al., 2016). Other traits included in the index were yield grade, marbling, dry matter intake, and weaning weight. In regards to the lack of collection of disease susceptibility in seedstock or nucleus herds, this is especially true in the swine and poultry industries where nucleus herds are under strict bio-security measures (Ibañez-Escriche and Gonzalez-Recio, 2011). Although beef seedstock herds are not under such strict bio-security measures, true collection of disease phenotypes would mean introducing the pathogen of interest into seedstock herds, which is undesirable for breeding stock (Garrick, 2018).

Not only are many of the traits that represent the true economic drivers of cattle production such as animal health, feedlot performance, carcass merit, and female fertility not recorded within the seedstock herds, there can be a significant genotype by environmental interaction between the traits observed at the seedstock and commercial levels. Núñez-Dominguez et al. (1993) found the correlation of genetic expression between crossbred and purebred performance ($r_{PC}$) for growth traits averaged across progeny sired by three breeds of cattle (Angus, Hereford, and Polled Hereford) to be 0.93, 0.77, and 0.76 for weights at birth, 200 days, and 365 days, respectively. Newman et al. (2002) also found $r_{PC}$ less than 1 for post-weaning growth and carcass traits using progeny from five sire breeds (Angus, Hereford, Shorthorn, Belmont Red, and Santa Gertrudis) mated to Brahman dams. These deviations of $r_{PC}$ from 1 are likely to be caused by non-additive effects and genotype by environment interactions (Wei and van der Steen., 1991). Even though the difference between seedstock and commercial herds does not necessarily reduce to purebred and crossbred animals, it does begin to demonstrate the need for the utilization of commercial phenotypes within genetic evaluations.
Given the genetic correlations between indicator traits and the associated ERT are not one, data from the indicator traits do not explain all variation of the ERT. Thus, collection and utilization of ERT phenotypes in genetic evaluations would aid in faster genetic response. Millions of true ERT records (disease incidence, female fertility, growth traits, and carcass traits) are collected within the commercial sectors - cow/calf herds, feedlots, and packing plants - every year. However, most of this data does not make it into the genetic evaluations. This is simply because relationships are needed in order to connect information from family members’ performance. There are pedigree ties between seedstock and commercial individuals, but they are often not known for a variety of reasons. Sometimes pedigrees are not recorded, group mating leads to unknown parentage, or pedigree information does not follow the animals as they move along into different segments of the industry. Relationships could be estimated using genomics, but that would require every animal with a record to be genotyped. This is not an economical option, even as genotyping costs have decreased. Therefore, most of the phenotypes we are truly interested in are not included in the genetic evaluations.

Use of genomics in evaluations

Traditionally, relationships between individuals are quantified using pedigrees, which are then summarized by a numerator relationship matrix (A). These are the expected relationships between two individuals. For example, a parent and offspring are expected to share one-half of their genome while a grandparent-offspring relationship is expected to be one-quarter. This relationship matrix would then be used in BLUP evaluations, leading to estimates deemed as “traditional EPD”. Assume observations are modeled by $y = Xb + Zu + e$ where $y$ is a vector of observations, $b$ is a vector of fixed effects, $u$ is a vector of random genetic effects, $X$ and $Z$ are incidence matrices, and $e$ is a vector of random residuals. The solutions for the fixed and random effects can be obtained by solving

$$
\begin{bmatrix}
X'X & X'R_1Z \\
Z'R_1X & Z'R_1Z + G^{-1}
\end{bmatrix}
\begin{bmatrix}
b \\
u
\end{bmatrix}
= 
\begin{bmatrix}
X'Y \\
Z'R_1Y
\end{bmatrix}.
$$

It is also assumed that $V(u) = G = A\sigma^2_a$ and $V(e) = R = I\sigma^2_e$. Substituting in these variances and multiplying by $\sigma^2_a$ throughout leads to

$$
\begin{bmatrix}
X'X & X'Z \\
Z'X & Z'Z + \lambda A^{-1}
\end{bmatrix}
\begin{bmatrix}
b \\
u
\end{bmatrix}
= 
\begin{bmatrix}
X'y \\
Z'y
\end{bmatrix}.$$
where $\lambda$ is equal to $\frac{\sigma_e^2}{\sigma_g^2}$.

When pedigree relationships are unknown, or even when the pedigree relationships are known, genomic relationships can be estimated between genotyped individuals. The genomic relationships can be calculated as the covariance of the genetic effects of two individuals, where the genetic effects are measured as the genotypes of the individuals. The resulting genomic relationship matrix ($G$) can be easily substituted into BLUP evaluations, resulting in genomic best linear unbiased predictions (GBLUP) in which the random genetic effects are now genomic EBV (GEBV). With the inclusion of $G$ instead of $A$, $V(u) = G\sigma^2_g$, and $\lambda$ is equal to $\frac{\sigma_e^2}{\sigma_g^2}$. The assumptions of GBLUP are an infinitesimal model, meaning that there a very large number of loci each with small effects that influence a quantitative trait. It is known that realized relationships can deviate from the expected relationships due to Mendelian sampling. Because the $G$ matrix can partially account for Mendelian sampling and pedigrees are oftentimes missing or incorrect, genomic relationships provide more accurate estimates of relationship and thus increased accuracy of EBV (Hayes et al., 2009).

Previously, genotyped and non-genotyped animals were not included in the same prediction because methods did not exist to combine all the information into one relationship matrix for use in BLUP. Use of single-step GBLUP (ssGBLUP) combines phenotypic information as well as genotypic and pedigree-based relationships into one fluid step in order to estimate GEBV. During this process, the $A$ and $G$ matrices are combined in order to estimate the relationship matrix $H$ (Aguilar et al., 2010; Christensen and Lund, 2010). Just as before, the matrix $H$ can be easily substituted into the BLUP evaluations, and the random genetic effects are again GEBV. Single-step GBLUP would be an optimal approach to combine commercial phenotypes into the genetic evaluations if the commercial cattle either had a pedigree tying them to seedstock relatives or were genotyped. Given pedigree ties are often missing and genotyping all commercial animals is cost prohibitive, an extension of the previously described methods is needed to allow for the use of this wealth of commercial information in genetic evaluations.

*Pooling for GWAS*

Genome wide association studies (GWAS) are used in order to discover genetic variations that are associated with traits. These studies typically require a large number of
individuals to be genotyped, which can often be in the hundreds or thousands (Huang et al., 2010). Genotyping these large sample sizes can be one of the major limitations of this research even as the cost of genotyping has decreased over the years. However, pooling DNA for GWAS has been shown to reduce the cost associated with genotyping (Sham et al., 2002). This is done by selectively grouping animals based on a phenotype and then genotyping a combined pool of DNA (Darvasi and Soller, 1992).

Many studies have identified candidate quantitative trait loci through pooling DNA in humans and livestock alike. Huang et al. (2010) used pools of Holstein cattle that exhibited high and low blastocyst rate or fertilization rate. A total of 589 and 571 samples were available for fertilization and blastocyst rate, respectively. Two pools each of high and low rate were constructed for each phenotype, where pool sizes ranged in size from 42 to 49 animals. When testing the association between allelic frequencies and blastocyst rate or fertilization rate, 22 and 5 SNP were found significant, respectively. Results were validated with individual genotypes and found only six of the previously significant SNP were insignificant (P-value > 0.10). Importantly, the signs of the allelic effects were the same between the pooled and individual samples. Many other studies have also shown the use of pooled DNA for GWAS including low reproductive cattle with the presence of SNP mapped to the Y chromosome (McDaneld et al., 2012) and somatic cell score in Valdostana Red Pied cattle (Strillacci et al., 2014). These studies clearly demonstrate the power of pooled DNA testing and their ability to genotype a fraction of samples that would otherwise be needed for individual testing.

**Pooling for genetic prediction**

Pooled data for prediction has also been used in a variety of ways. Olson et al. (2006) investigated the use of pooled phenotypes and their effects on prediction accuracy using simulated data. Work such as this is practical when the phenotype of interest is inherently measured on a group or pen level or when group phenotypes are more cost effective than individual phenotypes. Several other studies have also investigated the use of pooled phenotypes for prediction in simulation and with real data sets. For example, Biscarini et al. (2008) used total body weight and total egg production in laying hens in cages of four, Biscarini et al. (2010) looked at total early egg production in laying hens in cages of four, Cooper et al. (2010) explored total pen intake with steers in pens of six to nine, and Su et al. (2018) used simulation with
varying group sizes from three to thirty. One of the major drawbacks of these studies was that all animals within the group or pen must be identified and connected to other animals with a pedigree. Additionally, results showed that pooled observations led to lower accuracies than when individual data was available and utilized (Biscarini et al., 2008; Cooper et al., 2010; Olson et al., 2006; Su et al., 2018). Nonetheless, pooled phenotypes could be effectively utilized in evaluations.

As seen previously, when pedigree information is not known, relationships can be derived through the use of genomics. Just as with GWAS, even as genotyping has become cheaper over the years, it still not economical to genotype every commercial animal we would like to include into the genetic evaluations. Recently, the innovative approach of using pooled phenotypic and genotypic data has been used for genetic prediction. Reverter et al. (2016) performed DNA testing on a group of animals based on results of a pregnancy test, and created a “hybrid” genomic relationship matrix (h-GRM) consisting of pooled and non-pooled animals. Genotypes of the pooled animals were given as the B-allele frequencies rather than traditional 0, 1, or 2 for AA, AB, or BB genotypes, respectively. It was concluded that the pooled genomic data can provide estimates of relationships with individual bulls currently in the herd or previously used, and the resulting h-GRM can be used to calculate GEBVs incorporating data from pooled, commercial level herds. Sheep were pooled based on dag scoreds and sex, and pooled DNA was used in order to estimate an h-GRM (Bell et al., 2017). Contributions of sires to each pool were estimated using simple linear regression and were shown to be equivalent to the GEBV that were estimated using GBLUP (Bell et al., 2017). Alexandre et al. (2019) simulated two traits and pooled animals based on trait one, trait two, a combination of both traits, or randomly and estimated the prediction accuracies of both traits. The highest prediction accuracy of a trait resulted from pooling based on the trait itself and lowest when the pools were constructed randomly.

A concern with pooled DNA is the addition of pool construction and genotyping errors. Kuehn et al. (2018) investigated the efficiency of estimated genomic relationship of pools to the animals contained in the pools and other potentially related individuals. It was found that the technical error, the error associated with genotyping the intensity of the fluorescent dye used to estimate the B-allele frequencies, provided a minimal contribution to the total pooled error. Additionally, it was suggested that large pools be utilized because they are less prone to pool
construction error – the planned representation of individual DNA to the pool. Thus, if large pools are used, minor errors in pooling allelic frequency can be assumed small. Kuehn et al. (2018) suggested pool sizes of at least 20. On the other hand, Alexandre et al. (2019) suggested pool sizes of 10 in order to retain prediction accuracy and save on the cost of genotyping.

**Conclusions and Implications to Genetic Improvement of Beef Cattle**

Traditionally, most phenotypes included in genetic evaluations have been collected within the seedstock sector of the industry. This strategy is not optimal because the traits collected are often indicator traits, not the traits that drive the profitability of the commercial industry. Even though statistical models can combine information from ERT and genetically correlated indicator traits, accuracy of the EPD would be higher if the ERT were directly measured. Given that it is less practical or less informative to measure some traits in seedstock, such as disease susceptibility, or there could be a considerable amount of genotype by environment interaction between seedstock commercial herds, it would be optimal to include the true ERT from the commercial herds. The needed phenotypes from the commercial sectors exist and are even collected, however this valuable information rarely enters genetic evaluations. This is because pedigree ties are lost as animals move through the industry. Genotyping could be used to resurrect the needed relationships, but this would require every animal that has a record to be genotyped. Economically, this does not make sense.

The use of pooling genotypes and phenotypes has the potential to reduce genotyping costs while simultaneously including thousands of records into genetic evaluations. Sires could then be evaluated for direct measurements of true ERT that are collected at the commercial level. This would aid in the evaluation of traits that are hard to collect or are not observed in seedstock herds. Therefore, there is potential for additional genetic response in the traits that drive the economics of the beef industry.

Research has been conducted within the realm of using pooled phenotypes for prediction. However, this research has required that pedigrees, even for the pooled individuals, be available. Other research has explored the use of pooled genotypes and phenotypes for prediction. These methods leave out other valuable information, the records and animals that are pedigreed but not genotyped. Pooled phenotypes and genotypes from commercial animals combined with current
single-step genomic prediction methodology may be a reasonable way to combine all available information with one evaluation in cost effective manner.
Literature Cited


