Using Genomics to Improve the Genetic Potential and Management of Your Herd

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Pedigree-Based Selection

For more than half a century, progeny testing has been the foundation of genetic selection programs in dairy cattle (Robertson and Rendel, 1950). Several factors make progeny testing especially advantageous in dairy cattle, most notably widespread use of artificial insemination (AI) with frozen semen and the fact that nearly all traits of economic importance, including milk production, milk composition, female fertility, length of productive life, calving ability, disease resistance, and physical conformation, are sex-limited and cannot be measured until females begin lactating. Progeny testing has led to rapid genetic gains in production traits; estimated breeding values (EBV) of North American Holsteins have increased by roughly 90 kg of milk, 3 kg of fat, and 3 kg of protein per year over the past decade. However, genetic progress is limited by long generation intervals of approximately 7.1 and 3.9 years, respectively, for sires and dams of AI bulls (Normal et al., 2001). Furthermore, progeny testing is not a cost-effective method for improving traits that are difficult or expensive to measure routinely on commercial dairy farms, such as feed efficiency.

Whole Genome Selection

Whole genome selection, more commonly known as genomic selection (Meuwissen et al., 2001), refers to the study of differences between individual animals in the bovine genome sequence (single nucleotide polymorphisms (SNPs)) that can be used to predict economically important traits, such as milk production, milk composition, health, fertility, or longevity. The genetic information for a given calf, heifer, cow, or bull is compared with that of a reference population of older animals of the same breed. This reference population is composed of animals with known phenotypes that have been genotyped previously, and their phenotypic and genomic information are stored in an extensive database at the USDA-ARS Animal Improvement Programs Laboratory (AIPL, Beltsville, MD). Dairy cattle are particularly well-suited for genomic selection, because individual animals with high EBV have sufficient value to offset the costs of genomic testing, and because large reference populations of bulls with high reliability (REL) predictions of genetic merit exist for the purpose of estimating SNP effects or calculating genomic predicted transmitting abilities (GPTA). More than 650,000 dairy bulls, cows, heifers, and calves have genomic data in the AIPL database, and genomic predictions are available for Holstein, Jersey, and Brown Swiss cattle. The current cost of genomic testing is roughly $45 per animal with a low-density (9K or 12K) chip, whereas the cost of medium-density (54K) or high-density (648K or 777K) genotyping is two- to five-fold greater.

In North America, as in most countries with well-developed genomic evaluation systems for dairy cattle, genotype information has been incorporated into genetic evaluation systems in a nearly seamless manner (Wiggans et al., 2011). Roughly 60,000 SNPs are used in routine genomic evaluations, and for animals that have been genotyped with low-density chips the remaining SNPs are imputed with 90 to 99% accuracy based on the medium- and high-density genotypes of reference animals of the same breed (Boichard et al., 2012; VanRaden et al., 2013). In this manner, inexpensive low-density genotyping of cows, heifers, and calves on commercial dairy farms is possible, and after genotype imputation their GPTA values are of sufficient accuracy for selection and culling decisions (Dassonneville et al., 2011; Weigel et al., 2010). For cows with phenotypes, as well as cows and bulls whose offspring have phenotypes, the published GPTA values represent a combination of pedigree, performance, and genomic information, whereas for young bulls and heifers without phenotypes the published GPTA values reflect pedigree and genomic information only. In both cases, the GPTA values are published with the same genetic base, scale, and units of measurement as for animals that have not been genotyped, with the only difference being higher REL for genotyped animals and a "G" indicator on their predicted transmitting ability (PTA) values and selection indices.

The increases in REL for young calves and heifers due to genomic testing are remarkable. In US Holsteins, the average gains in REL for production traits are 29, 31, and 23% for milk, fat, and protein, respectively, whereas gains for fitness traits are 22, 27, and 22% for daughter pregnancy rate, somatic cell score, and length of productive life, respectively. For protein yield, which has heritability of approximately 30%, the amount of information provided by a young calf's pedigree is equivalent to about 7 milk-recorded offspring, whereas the amount of information provided by the calf's genotype is equivalent to about 34 additional daughters. In contrast, for daughter pregnancy rate, which has heritability of about 4%, the amount of information provided by the calf's genotype is equivalent to about 131 additional daughters.

Genomic Selection of Males

Selection of dairy bulls has changed dramatically in the era of genomic selection. North American dairy farmers currently have access to semen from hundreds of young genome-tested Holstein, Jersey, and Brown Swiss bulls that have no progeny of their own. In fact, the number of young AI bulls currently being marketed based on GPTA values exceeds the number of progeny-tested bulls being marketed, and several large breeding companies now derive more than 50% of their sales from young genome-tested bulls. Farmers that use young genome-tested bulls to produce their replacement heifers can reduce the generation interval for the "sires to produce daughters" selection pathway to about 30 months, as opposed to roughly 72 months with traditional progeny tested bulls. Furthermore, these young genome-tested bulls are often used to produce the next generation of AI bulls, and the impact on generation interval is dramatic, as shown in Figures 1 and 2 from Schefers and Weigel (2012).

In a traditional breeding program based on progeny testing, approximately 54 months are required for rearing a bull, collecting and distributing his semen, rearing his offspring, recording his offspring's phenotypes, and predicting his breeding value using pedigree-based BLUP. At this point, the bull can be identified as a sire of future AI bulls, and if his semen is used immediately to inseminate elite cows and heifers his first sons will be born when he is about 63 months of age.

In an aggressive breeding program based on genomic selection, a young bull can be identified as a sire of future AI bulls as early as 1 or 2 months of age, and as soon as he reaches sexual maturity his semen can be used to inseminate elite cows and heifers (Schaeffer, 2006). His first sons will be born when he is roughly 21 months of age, which means that we can achieve a three-fold reduction in generation interval in the "sires to produce sons" selection pathway. An obvious extension of the aforementioned strategy is to use genomic selection to identify potential dams of future AI bulls at a young age and propagate them via embryo transfer (ET) or in vitro fertilization (IVF) as yearling heifers, as opposed to waiting for completion one or more lactation records. In this manner, the generation interval for the "dams to produce sons" selection pathway can also be reduced, from about 38 months to roughly 22 months. Furthermore, the GPTA values of elite cows and heifers based on genomic testing have much greater REL than their traditional PTA values based on pedigree and performance data only, and this further accelerates the rate of genetic progress per year.

Genomic Selection of Females

Historically, the weak link in dairy cattle improvement programs has been the "dams to produce daughters" selection pathway, due to poor accuracy and low selection intensity (Van Tassell and Van Vleck, 1991). The REL of traditional pedigree-based PTA values for cows on commercial farms has tended to be low, and high rates of culling due to illness, injury, or infertility have typically prevented the culling of genetically inferior replacement heifers. However, culling rates on modern, well-managed free-stall operations tend to be low, and widespread usage of gender-enhanced (sexed) semen has generated an excess of replacement heifers. For the first time in history, dairy producers have an opportunity to improve the genetic potential of their herds by culling inferior females at a young age and, more importantly, they can significantly reduce the feed costs associated with rearing animals that are unlikely to perform at a profitable level once they reach lactating age. Weigel et al. (2012) showed that, in herds that lack pedigree data, genomic testing all heifer calves and culling the poorest 10, 20, or 30% based on GPTA is a cost-effective herd improvement strategy. Similarly, in herds with known sire identification or complete pedigree information, genomic testing the bottom 50% of heifer calves based on pedigree index and culling the bottom 10, 20, or 30% based on GPTA is also a cost-effective herd improvement strategy.

In a recent study at the UW-Madison Integrated Dairy Facility (Arlington, Madison, and Marshfield, WI), the actual first-lactation performance of Holstein cows was evaluated relative to their genomic predictions derived from DNA testing prior to 12 months of age. Based on results of the genomic testing, heifers were divided into quartiles (Q1=high, Q2=high-medium, Q3=medium-low and Q4=low) of genomic potential for milk yield. Figure 3 shows a scatter plot of GPTA for milk production and average daily milk yield, where each shape represents a

different quartile. Animals with average GPTA milk and average daily milk yield are represented by the circle in the middle of the graph. As shown below, 83% of heifers in Q1 (highest GPTA milk) subsequently exceeded herd average for actual daily milk yield, as compared with 61% of heifers in Q2, 39% of heifers in Q3, and fewer than 17% of heifers in Q4. Furthermore, no heifers from Q4 ranked near the top for daily milk yield when they reached first lactation, and only one heifer from Q1 produced significantly less than herd average. As shown in Figure 4, average first lactation daily milk yield of heifers in Q1 exceeded that of heifers in Q2 and Q3 by approximately 10 pounds, and it exceeded that of heifers in Q4 by more than 15 pounds. Thus, it is clear that genomic testing of heifer calves at a young age can provide farmers with useful information for making selection and culling decisions, which can reduce feed costs.

Managing Inbreeding with Genomics

Inbreeding has long been a concern in dairy cattle breeding programs, and animal breeders try to achieve a balance between rapid genetic progress and maintenance of genetic diversity (Weigel, 2001). Genomic selection programs can provide greater selection response per year and, like traditional pedigree-based breeding programs, individual sires and cows can have a tremendous influence through AI and ET or IVF, respectively. However, an advantage of genomic selection is that it facilitates within-family selection decisions among animals with identical pedigrees (Hayes et al., 2009). For example, in a traditional pedigree-based selection program an elite cow might produce three full-sibling sons by ET, and one of these sons would be purchased by each of the major AI companies. In a modern genome-based selection program the cow would also produce three full-sibling sons by ET, and the son with highest GPTA would be purchased by the company that had the first-choice contract. The other two sons would be culled, and the other two AI companies would select first-choice bulls from other families, thereby enhancing the genetic diversity of the AI sire population. On the farm, dairy producers manage inbreeding and reduce the probability of inherited defects by using computerized mating programs (Weigel and Lin, 2000). Genomic data can provide more precise measures of inbreeding than pedigree-based inbreeding coefficients (Bjelland et al., 2013), which reflect expected inbreeding, and genome-based mating programs can accommodate both additive and dominance effects (Sun et al., 2013). Because virtually every AI sire in the major dairy breeds has been genotyped, dairy farmers who invest in genotyping their cows, heifers, and calves can readily utilize genome-based mate selection programs that consider average heterozygosity, dominance effects, and lethal defects.

Although the primary objective of genomic selection in dairy cattle is to increase the accuracy of estimated breeding values for young selection candidates, related activities such as fine-mapping of quantitative trait loci (QTL) and detection of inherited defects are greatly facilitated by the availability of hundreds of thousands of low-, medium-, and high-density SNP genotypes. For example, Cole et al. (2011) carried out a genome-wide association analysis that identified numerous candidate genes and chromosomal regions affecting production, health, fertility, and conformation traits in Holstein cattle. Interestingly, VanRaden et al. (2011) found that several SNP haplotypes were abundant in heterozygous form in Holstein, Jersey, and Brown Swiss cattle, but these haplotypes were never observed in homozygous form. Furthermore, sires that carried these haplotypes tended to exhibit reduced conception rate and increased stillbirth rate when mated to daughters of bulls that carried the same haplotypes. In one of these haplotypes,

Sonstegard et al. (2013) identified a nonsense mutation in the CWC15 gene that appears to be responsible for decreased fertility in Jersey cattle.

Conclusions

In summary, the impact of genomics on dairy cattle breeding programs has been enormous, and the pace of change has been breath-taking. Within two years of the commercial availability of the first 50K array, the vast majority of AI bulls and elite cows were genotyped, and routine selection decisions utilized GPTA values rather than traditional pedigree-based PTA values. Genomic data are used to select every young bull that enters an AI company, and the overwhelming majority of cows, heifers, calves, and embryos that are consigned to public auctions are marketed based on genomic information. Progeny testing, in which selection and marketing decisions must wait until daughters' phenotypes become available, has been replaced by genomic testing and progeny validation, in which selection and marketing decisions are made immediately and reviewed later, when the bull's sons and grandsons are being marketed. New inherited defects have been discovered, and the search for QTL with large effects on performance, health, and fertility is faster, more precise, and much more efficient. Programs for mate selection and avoidance of inbreeding are changing rapidly, and widespread usage of genomic mating programs is imminent. Because of the availability of inexpensive low-density SNP arrays and highly accurate imputation algorithms, many farmers are using genomic testing in conjunction with sexed semen and advances in cow comfort to generate extra females, cull inferior animals early, enhance genetic progress, and reduce feed costs. Lastly, genomic selection will allow the improvement of traits such as feed efficiency, which are too difficult and expensive to measure routinely on commercial farms but are feasible for measurement in smaller reference populations such as experimental herds.

Acknowledgments

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Figure 1. Timeline of a traditional AI breeding program based on progeny testing (from Schefers and Weigel, 2012).
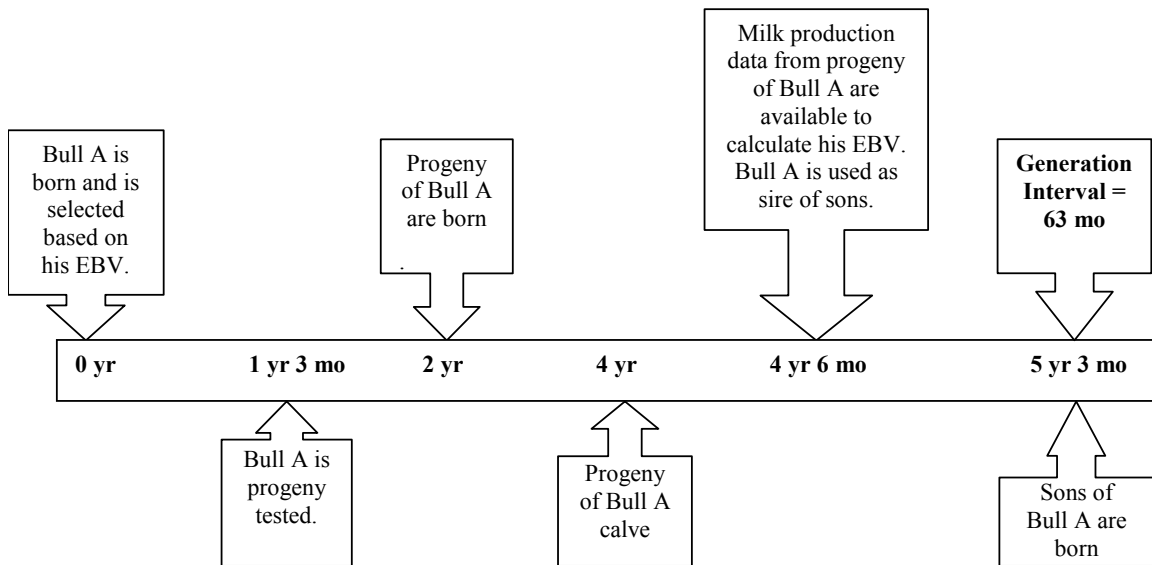

Figure 2. Timeline of an aggressive AI breeding program based on the use of genomic bulls as sires of sons (from Schefers and Weigel, 2012).
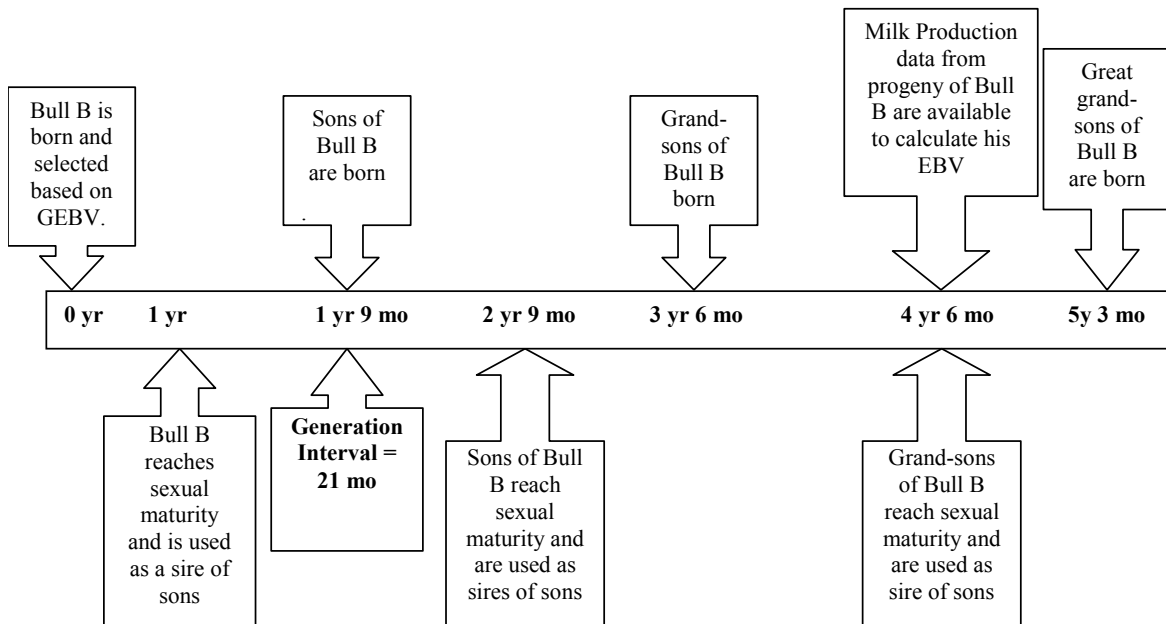
Figure 3. Comparison of GPTA for milk yield of 12-month old Holstein heifers in the UW-Madison herd with actual daily milk yield of the same animals during first lactation. The numbers shown on the graph reflect the percentage of animals in each GPTA quartile that exceeded herd average milk production during first lactation.
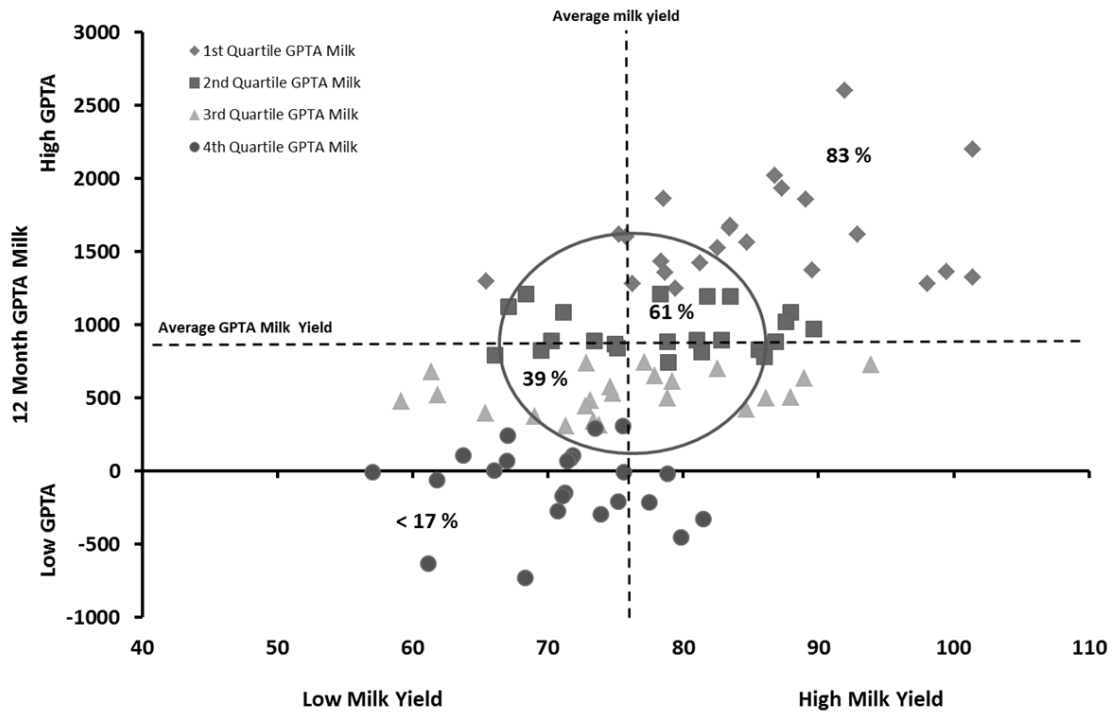

Figure 4. Average daily milk yield during first lactation, by quartile of GPTA for milk yield, for heifers that were genotyped prior to 12 months of age in the UW-Madison herd.

Figure 4. 1st Lactation Milk Yield vs. GPTA Milk Quartile.