Applied Animal Genomics: Results from the Field

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Abstract

Genomic selection (GS) is the use of statistical methods to estimate the genetic merit of a genotyped animal based on prediction equations derived from large ancestral populations with both phenotypes and genotypes. It has revolutionized the dairy cattle breeding industry and has been implemented with varying degrees of success in other animal breeding programs, including swine, poultry, and beef cattle. The findings of empirical field studies applying GS to the breeding sectors of these main animal protein industries are reviewed. Several translational considerations must be addressed before implementing GS in genetic improvement programs. These include determining and obtaining economically relevant phenotypes and determining the optimal size of the training population, cost-effective genotyping strategies, the practicality of field implementation, and the relative costs versus the benefits of the realized rate of genetic gain. GS may additionally change the optimal breeding scheme design, and studies that address this consideration are also reviewed briefly.

INTRODUCTION

In 2001, Meuwissen et al. (1) published a seminal paper that envisioned a future in which a dense set of genetic markers spread evenly throughout the genome would be used to accurately predict the genetic merit of individuals. At the time it was published, the technology the authors anticipated, namely, genome-wide dense marker maps, did not exist, because no livestock genomes had yet been sequenced and the enabling technology of single-nucleotide polymorphism (SNP) chip genotyping platforms had not yet been developed. With remarkable foresight, this paper laid out an approach, subsequently termed genome-wide or genomic selection (GS), and the statistical methods that could be used to estimate the genetic merit of individuals based solely on a data set of phenotypes and genotypes derived from ancestral populations of the selection candidates. It also presented some of the statistical and operational problems that might be associated with use of this approach. Since that time, GS has revolutionized the dairy cattle breeding industry (2), and the technique has been implemented with varying degrees of success in breeding programs associated with other animal and plant industries.

Single-nucleotide polymorphism (SNP): a DNA sequence variation that occurs when an individual nucleotide is altered

Genomic selection (GS): the use of genetic markers spread throughout the genome to assist in predicting an individual's genetic merit

Estimated breeding value (EBV): within-breed evaluation of an animal's own genetic merit, equal to twice a predicted transmitting ability or an expected progeny difference

Effective population size: number of individuals in an ideal population with the same genetic drift and inbreeding rate as the population under consideration

Quantitative trait loci (QTL): genomic regions that influence quantitative, or complex, traits

Marker-assisted selection (MAS): a process that uses genetic markers to indirectly select for specific alleles

To understand how GS can accelerate the rate of genetic improvement, it is important to understand some of the basic principles of animal breeding. The purpose of selection programs is to accelerate the rate of genetic change or selection response per unit of time, ΔG, toward a given breeding objective. The classic equation for explaining ΔG, as described by Falconer (3), is

$$\Delta G = \frac{ir\sigma_A}{L},$$

where i is the selection intensity (the proportion of animals in a population that are selected to become parents of the next generation), r is the accuracy of selection [correlation between the estimated breeding value (EBV) and the true breeding value], σ_A is the additive-genetic standard deviation of the trait of interest (genetic variation in the population available for selection), and L is the generation interval (average age of parents when their offspring are born). Any technology that can act to increase accuracy, intensity, and/or genetic variation or decrease the generation interval has the potential to accelerate the rate of genetic gain. The reproductive rate of breeding animals and uncertainty about the true genetic merit of breeding animals make up the most important limiting factors in a breeding program. A range of approaches have been employed to modify the components of this equation in a breeding program, including performance recording of individuals and their offspring to increase the accuracy of selection; the use of assisted-reproductive technologies, such as artificial insemination (AI), to increase the selection intensity; crossbreeding and introgression to increase genetic variation in the population; and the use of gametes from prepubertal or embryonic animals to decrease the generation interval. Inbreeding decreases the effective population size, which can reduce the amount of genetic variation available for selection. In comparison with other factors in the equation, which can be modified quite extensively through the application of reproductive technologies, relatively little can be done to impact the amount of genetic variation within a breed.

Early attempts to increase the accuracy of selection using genetic markers employed blood groups to map quantitative trait loci (QTL) (4). Even in these relatively rudimentary studies, the authors reported "statistically significant associations between some blood genes and (milk) fat percentage" (4, p. 408). Since those early studies, many studies have attempted to find genetic markers, ranging from microsatellites to SNPs, associated with traits of economic importance (5). And whereas markers associated with simple qualitative or monogenic traits have been used to great effect to identify carriers of recessive alleles (6), traditional marker-assisted selection (MAS) approaches based on the identification of markers associated with QTL, using either linkage mapping or genome-wide association studies, have generally failed to significantly improve the

accuracy of breeding value estimates for quantitative or multigenic traits (5). This has been due in part to the overestimation of significant marker effects that occurs when many effects are tested for significance (7), as well as the fact that many small-effect QTL are missed entirely as a result of the use of stringent significance thresholds (8). Additionally, markers that were significantly associated with a trait in one population often were not confirmed or validated in an independent population (e.g., other breeds or families) owing to a high rate of false discovery and/or differences in the linkage disequilibrium (LD) between the marker and the QTL (9).

GS, however, uses high-density genotyping technologies to genotype individuals for many markers [for example, Illumina BovineSNP50 (10) comprises ~54,000 SNPs spanning the bovine genome], with the goal of identifying at least one marker associated with each QTL for a given trait. GS relies on a large number of individuals in a genotyped and phenotyped training population from which a genomic prediction equation is derived that can then be used to estimate the genomic estimated breeding value (GEBV), also known as the molecular breeding value (MBV) or the direct genomic value, of unphenotyped individuals from a selection candidate population based solely on their marker genotypes (**Figure 1**). In GS, the marker effect does not have to exceed a significance threshold to be included in the prediction equation; therefore, potentially all genetic variance associated with markers can be captured using GS. As with other forms of MAS, the additional genetic response relative to non-MAS is approximately proportional to the square root of the genetic variation explained by the markers or the prediction equation (8).

Several groups across the globe have implemented GS in livestock breeding programs (11). Although in simulated data Meuwissen et al. (1) found the accuracy of GEBV [i.e., the correlation (r) between the MBV and the true breeding value] to be 0.85, few empirical studies have achieved such high accuracies using real data; however, the definition of accuracy has varied among real and simulated data studies, making direct comparisons problematic (12). To implement GS, breeders must consider many translational questions, including the size of the training population, the number of markers to include in the genotyping platform, the statistical methodology and approach to incorporating the MBV into genetic merit estimates, the frequency of marker effect reestimation, and the economic break-even point of technology adoption. These translational questions vary by industry and are the subject of considerable research effort. Such deliberations are likely to become increasingly complex given recent progress in approaches to targeted gene editing (see sidebar, Precision Genetics). This review focuses on the findings of empirical field studies applying GS to breeding populations of the main livestock and poultry industries. GS may also change the optimal breeding scheme design, and studies that address this consideration are also reviewed in terms of the potential impact of GS on the breeding programs for various livestock industries.

Linkage disequilibrium (LD): the nonrandom association of alleles

Training population: a group of genotyped and phenotyped individuals used to estimate genomic estimated breeding value of unphenotyped individuals based on their genotype

Genomic estimated breeding value (GEBV): a predicted breeding value based on dense, genome-wide markers

STATISTICAL METHODOLOGY AND APPROACH TO INCORPORATING GENOMIC DATA INTO GENETIC MERIT ESTIMATES

The accuracies of MBV depend on the size of the training population, effective population size, genetic relationship between the target population and the training population, marker density, statistical method, heritability, and genetic architecture of the trait being predicted (13). To predict MBVs for animals that have genotypes but no phenotypes, the effect of the chromosome segments that carry the markers can be summed across the genome. When it comes to estimating the allelic effects of all of these markers in data sets of limited sizes, there are not enough degrees of freedom to fit all marker effects simultaneously using standard linear model procedures. A variety of statistical approaches have been proposed to overcome this large p, small n problem [i.e., estimating a large set of parameters (p) from a limited number of data points (n)] in the development of prediction

models for GS. These calculations all require some assumption to be made about the true distribution of the marker effects.

Best linear unbiased predictor (BLUP): a technique for estimating genetic merit by using pedigree information and estimating random effects

There is an evolving and rapidly expanding literature examining the statistical methods that are most appropriate for analyzing genomic data. Several approaches have been proposed for estimating marker or haplotype effects across chromosome segments for GS (14). The key difference between these approaches is the assumption they make about the distribution of SNP effects, which in turn reflects the distribution of QTL effects and the LD between SNPs and QTL. Mixed-linear-model approaches assume that the SNP effects are normally distributed, in which case the marker effects are best linear unbiased predictors (SNP-BLUPs) (1), which is equivalent to estimation of breeding values using BLUP, but with a genomic relationship matrix (G-BLUP) (13) rather than a pedigree-based relationship matrix. If the number of animals in the training population is fewer than the number of markers, the G-BLUP model is often preferred for computational reasons, as it results in fewer equations to solve than does the SNP-BLUP model (2). Bayesian regression models assume a nonlinear distribution of the SNP effects, including a *t*-distribution, which assumes many small effects but allows some SNPs to have a moderate to large effect (Bayes A) (1). Other approaches assume a mixture of distributions, with some fraction (π) of the markers having a zero effect and the remainder ($1 - \pi$) having a *t*-distribution [Bayes B (1); Bayes Cπ (15)]. One of the disadvantages of these approaches is the need to set or determine the proportion of markers that have no effect for each trait in a multiple-trait genetic evaluation. Gianola et al. (16) provide a more complete explanation of these methods and their relationship to quantitative genetic models.

PRECISION GENETICS

Traditional animal breeding programs have long selected for breeds specialized for their intended purpose, such as milk, meat, or egg production (152). Genomics has enabled the use of DNA markers and GS to accelerate genetic progress. However, to date breeders have worked with the genetic variation present in a given breed or breeds to direct genetic change. Introgression of a new trait from an outlying breed into a highly specialized breed is typically a time-consuming process requiring several backcross generations to eliminate linkage drag and restore production to pre-introgression levels. In highly specialized breeds, this limits the amount of foreign genetics that can be introduced into a breed or a closed breeding population.

New precision gene-editing techniques [e.g., zinc finger nucleases, meganucleases, transcription activator-like effector nucleases (TALENs), oligonucleotide-directed mutagenesis, and clustered regulatory interspaced short palindromic repeat (CRISPR)/Cas-based RNA-guided DNA endonucleases] offer an approach to enable introduction of desirable alleles into the elite germplasm of a given breed, without the need to bring along the unwanted genetic material that accompanies traditional backcrossing and introgression strategies. These techniques create double-stranded breaks at a specific location in the genome, and repair can be directed by a template carrying the desired allele. For more information on this approach to direct targeted homologous recombination, the reader is referred to Tan et al. (153).

As genomic discovery proceeds to identify the function of allelic polymorphisms, such targeted gene-editing strategies likely will be employed to selectively introduce beneficial alleles from one breed into the genome of elite seedstock of another breed. For examples, TALENs were used to introduce a bovine *POLLED* allele from a beef breed into fibroblasts derived from a horned dairy bull, and other performance-enhancing and disease-resistance alleles were introduced into pig, goat, and cattle fibroblasts (154). These allelic introgression approaches offer a powerful new approach to accelerate the genetic improvement of livestock in the future.

The incorporation of genomic data into genetic evaluations often involves a multistep procedure that requires (*a*) traditional evaluation with an animal model, (*b*) extraction of corrected phenotypes or pseudo-observations for animals with marker genotypes, and (*c*) estimation of marker effects (17), assuming some prior distribution of SNP effects. The genomic information is then combined with the traditional evaluation using a selection index (18). Single-step approaches, which incorporate all pedigree, genotype, and phenotype information available from both genotyped and ungenotyped animals in a training population, have been proposed as a more streamlined alternative (19, 20). These single-step G-BLUP approaches involve integrating the pedigree and genomic information into a single relationship matrix. Some of the advantages of this approach are that it uses pedigree and phenotypic information from ungenotyped animals in

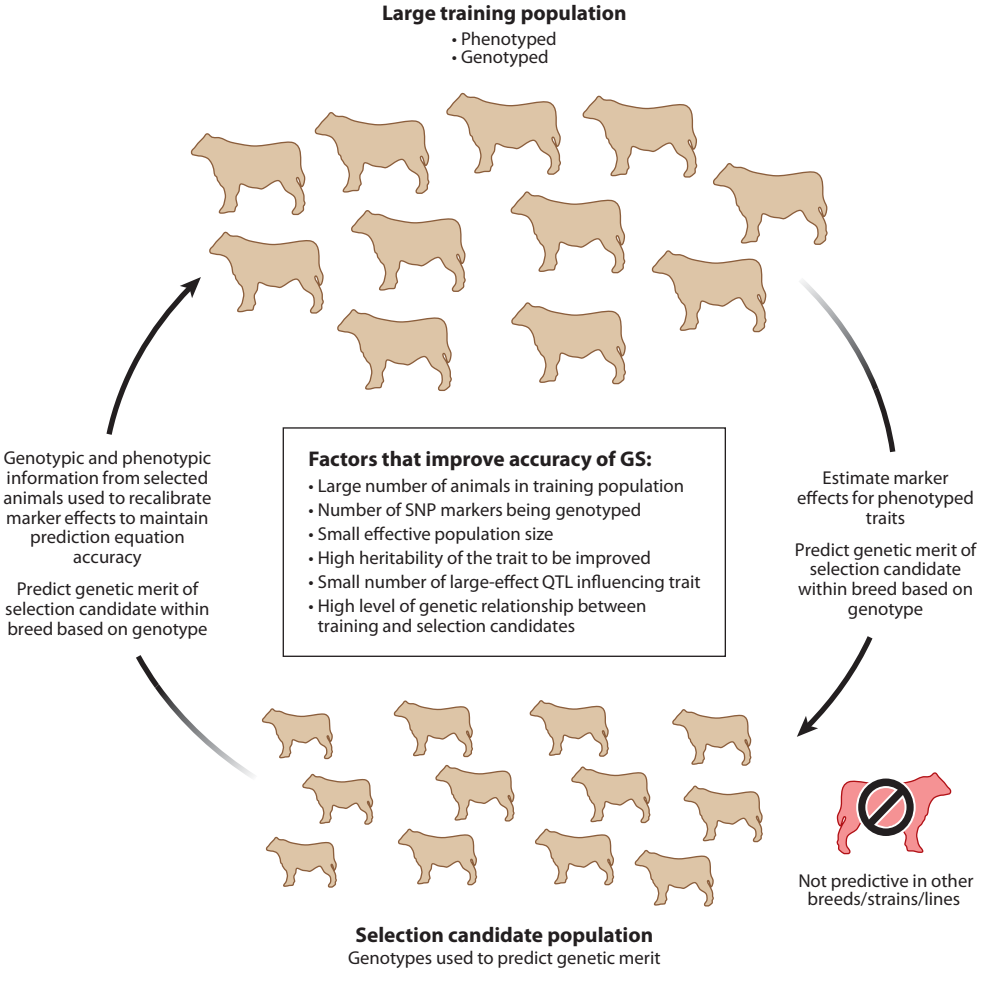


Figure 1

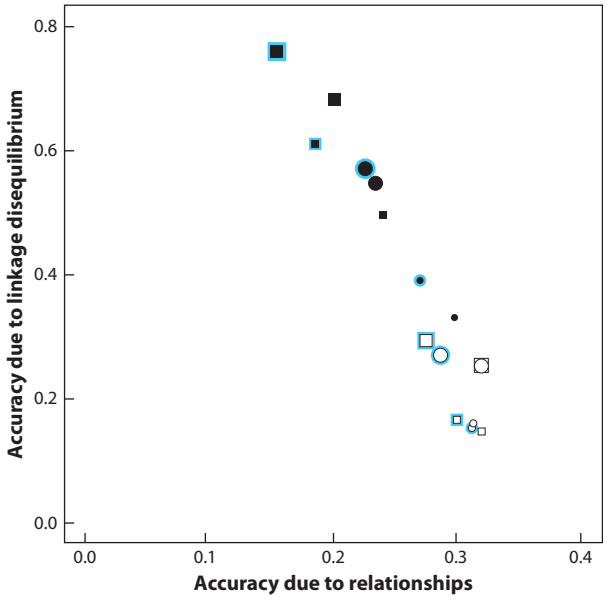
Overview of principles behind genomic selection (GS). GS relies on a large number of individuals in a genotyped and phenotyped training population from which to derive a genomic prediction equation. This equation can then be used to estimate the genomic breeding value, also known as the molecular breeding value, of unphenotyped individuals from a selection candidate population based solely on genotype. Abbreviations: QTL, quantitative trait loci; SNP, single-nucleotide polymorphism.

addition to that from genotyped animals and that it is well suited to multiple-trait analyses (21). A disadvantage is that it currently assumes a distribution of equal variance for each marker, which may not be true for traits with some large-effect loci, although for most traits this assumption yields accuracies that are similar to those obtained when a nonlinear distribution of SNP effects is assumed. However, these methods require careful scaling of the genomic relationship matrix to be consistent with the pedigree-based relationship matrix (19, 22). This single-step G-BLUP approach was found to be particularly powerful for low-heritability traits in a field broiler data set, in which it resulted in GS evaluations that were 50% more accurate than genetic evaluations based on phenotypes alone or genomic evaluations based solely on the smaller subset of animals in the training population that had both genotypes and phenotypes (23).

For traits that involve a limited number of large-effect QTL (e.g., coat color, milk fat, fatty acid composition of meat), methods that allow a fraction of the markers to have zero effect have typically resulted in more accurate predictions than have those that assume all SNPs have a non-zero effect (24). However, the differences detected between contrasting statistical models in real-world evaluations of GS accuracy typically have not been as large as those reported in simulation studies. It is unclear if this is because the genetic architecture of real traits is more infinitesimal than has been suggested by QTL-mapping studies or whether other characteristics of the data (number of markers, length of LD, relationships among animals) prohibited greater distinction between models (14). In field implementation, the G-BLUP approach is attractive because its implementation is fairly straightforward using existing genetic evaluation software. Statistical methods that allow for a large proportion of SNPs to have zero effect may become increasingly important when there are very large numbers of SNPs in the analyses (25), as might be expected from whole-genome sequencing (2).

Results from the application of GS in several livestock species have shown the superior accuracy of genetic predictions that include genomic data relative to traditional evaluations based on pedigree and phenotypes (18, 26–30). The accuracy of MBV is derived from two sources: The first source is markers that capture additive-genetic relationships but that are in linkage equilibrium with QTL (linkage), and the second is due to markers that are in LD with QTL (31, 32). The accuracy of GEBV is expected to be more persistent across generations than the accuracy of pedigree-based EBV because marker-based relationships resulting from LD are expected to erode more slowly than pedigree relationships (33), which are reduced by 50% at each meiosis in outbred populations (34). Linkage will also decay more rapidly with increasing genetic distance between the training and target populations than will LD relationships. To obtain accurate predictions on individuals that are unrelated with the training data, a large number of markers and training records are required to identify markers in LD with QTL (35). Jannink et al. (36) broke down the accuracy of GS into that contributed by LD and that resulting from linkage for varying training population sizes, marker numbers, and trait architectures. The proportion of GS accuracy attributable to LD increased as the marker density and training population size increased (**Figure 2**). Bayes B was more effective than SNP-BLUP at capturing LD between markers and QTL. Because these marker-QTL linkages are tight, recombination does not cause them to decay rapidly, and accuracies from Bayes B persisted longer than those from SNP-BLUP (36). Habier et al. (37) found that the accuracy of GEBV based on additive-genetic relationships declined with increasing training population size, depending on the extent of LD and the level of additive-genetic relationships, and they suggested that modeling polygenic effects using G-BLUP jointly with GEBVs using Bayesian methods may help to prevent that decline.

Without routine retraining, the accuracy of genomic prediction equations will decay over time (38), although this decay is slower if the accuracy is derived largely from markers that are in LD with QTL. Wolc et al. (34) recommended retraining every generation when GS is used in closed



QTN: quantitative trait nucleotide, a causative single-nucleotide polymorphism resulting in quantitative trait loci

Figure 2

Decomposition of genomic selection (GS) prediction accuracy using the method of Habier et al. (31). On a genome comprised of seven 1.5-M chromosomes, individuals were generated using a coalescent assuming an effective population size of 100. Round and square symbols, ridge regression and Bayes B, respectively. Symbols with and without blue outlines, 40 quantitative trait loci (QTL) and 200 QTL, respectively. Black and nonblack symbols, 4,000 and 400 markers, respectively. Small and large symbols, training population size of 400 and 2,000, respectively. Figure adapted with permission from Jannink et al. (36).

breeding populations. This may change in the future as sequencing costs decrease and whole-genome resequencing data become available on many influential founder animals (39). With whole-sequence data, the causative SNP resulting in the QTL (also known as QTN) will be among the millions of polymorphisms that are genotyped (40). As a result, the accuracy of MBV will not rely on markers in LD with QTN but rather will conceptually include the QTN themselves. Marker panels that include QTN were found to have improved predictive ability compared with those that excluded causative mutations (41). In a simulation study, whole-genome-sequence information was found to improve the accuracy of GS relative to the accuracies available with dense SNP chips, and perhaps as importantly, estimates of SNP effects made in one generation remained accurate ten generations later (42).

RESULTS FROM THE DAIRY INDUSTRY

Genetic change is best accomplished by selecting candidates based on an economic index ($Index) composed of genetic merit estimates for economically relevant traits weighted by marginal economic values. Indexes are derived from breeding objectives that take into account traits most closely associated with income and expenses. The dairy industry economic index, Net Merit ($NM), has changed over time (**Table 1**). The emphasis on yield traits has declined as fitness traits have been introduced. Also, as the emphasis on protein yield increased, milk volume became less important because of the high correlation between those two traits. In the 2010 $NM economic selection index, the trait milk yield has a zero weighting. Production traits currently represent 35% of the selection emphasis within $NM, with the remaining 65% being placed on functional traits (43).

Progeny testing: evaluation of offspring to determine an individual's breeding values

Feed efficiency: an animal's ability to convert feed intake (input) into body mass (output)

For more than half a century, progeny testing has been the foundation of genetic selection programs in dairy cattle (44). Several factors make progeny testing especially advantageous in dairy cattle, most notably widespread use of 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: roughly 90 kg of milk, 3 kg of fat, and 3 kg of protein per year over the past decade (**https://www.cdcb.us/eval/summary/trend.cfm**). 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 (45). 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 how efficiently an animal uses feed for milk production (feed efficiency).

Table 1 A history of the main changes in US Department of Agriculture (USDA) genetic-economic indexes for dairy cattle and the relative emphasis (%) on traits included in the indexes (http://aipl.arsusda.gov/reference/nmcalc.htm)

	USDA genetic-economic index (and year introduced)							
Traits included	Predicted difference $(1971)	Milk, fat, protein $(1976)	Cheese yield $(1984)	Net merit $(1994)	Net merit $(2000)	Net merit $(2003)	Net merit $(2006)	Net merit $(2010)
Milk	52	27	−2	6	5	0	0	0
Fat	48	46	45	25	21	22	23	19
Protein	—	27	53	43	36	33	23	16
Productive life	—	—	—	20	14	11	17	22
Somatic cell score	—	—	—	−6	−9	−9	−9	−10
Udder composite	—	—	—	—	7	7	6	7
Feet/legs composite	—	—	—	—	4	4	3	4
Body size composite	—	—	—	—	−4	−3	−4	−6
Daughter pregnancy rate	—	—	—	—	—	7	9	11
Service sire calving difficulty	—	—	—	—	—	−2	—	—
Daughter calving difficulty	—	—	—	—	—	−2	—	—
Calving ability (CA$)[a]	—	—	—	—	—	—	6	5

[a]**CA$**, an index that includes sire calving ease, daughter calving ease, sire stillbirth, and daughter stillbirth.

Dairy cattle improvement programs are also well suited for GS (1), because individual animals with high EBV have sufficient value to offset the costs of genotyping, and because large reference populations of bulls with highly accurate estimates of genetic merit exist for the purpose of estimating SNP effects with Bayesian regression models or for calculating genomic predicted transmitting abilities (GPTA)[1] with G-BLUP. As of November 2013, the US Department of Agriculture Agricultural Research Service Animal Improvement Programs Laboratory (Beltsville, MD) database contained the SNP genotypes of more than 522,800 dairy bulls, cows, heifers, and calves. These animals were genotyped with a variety of commercially available chips, including arrays with 3K, 6K, 9K, 50K, 80K, 648K, and 777K SNPs (**https://www.cdcb.us/Genotype/cur_freq.html**).

Genomic predicted transmitting ability (GPTA): a calculation of genetic merit based on genotypic, phenotypic, and pedigree information

Predicted transmitting ability (PTA): within-breed evaluation of an animal's parental genetic merit based on information on an individual and relatives

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 (46). Roughly 45,000 SNPs are used in routine genomic evaluations, and for animals that have been genotyped with low-density chips (e.g., 3K, 6K, or 9K), the remaining SNPs can be imputed with 90–99% accuracy based on the medium- and high-density genotypes of reference animals in the same breed (47, 48). In this manner, low-density genotyping of cows, heifers, and calves on commercial dairy farms is possible for less than $50 per animal, and after genotype imputation, their GPTA values are sufficiently accurate for selection and culling decisions (49, 50). For cows with phenotypes, as well as for cows and bulls whose offspring have phenotypes, the published GPTA values represent a combination of pedigree, phenotypic, and genomic information, whereas for young bulls and heifers without phenotypes, the published GPTA values reflect only pedigree and genomic information. In both cases, the GPTA values are published on the same genetic base, scale, and units of measurement as those for animals that have not been genotyped, with the only difference being higher accuracy for genotyped animals and a G indicator on their predicted transmitting ability (PTA) values and selection indices.

The increases in reliability (REL = squared accuracy) of PTA for young calves and heifers owing 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 (46). For protein yield, which has a heritability of approximately 30%, the amount of information provided by a young calf's pedigree is equivalent to having approximately 7 daughters with phenotype, whereas the amount of information provided by the calf's genotype is equivalent to approximately 34 additional daughters. In contrast, for daughter pregnancy rate, which has heritability of approximately 4%, the amount of information provided by the calf's genotype is equivalent to approximately 131 additional daughters.

Selection of dairy bulls has changed dramatically in the era of GS. North American dairy farmers currently have access to semen from hundreds of young genome-tested Holstein, Jersey, and Brown Swiss bulls without progeny of their own. In fact, the number of young AI bulls currently marketed based on GPTA values exceeds the number of progeny-tested bulls 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 approximately 30 months, as opposed to roughly 72 months when using traditional progeny-tested bulls.

[1]Genetic evaluations can be expressed as either a predicted transmitting ability (PTA), an expected progeny difference (EPD), or an estimated breeding value (EBV). All are measures of performance relative to a base population. PTA and EPD indicate the difference in performance that can be expected from an animal's offspring relative to the base; an EBV is the genetic merit of the animal itself relative to the base and, therefore, is equal to twice its PTA or EPD.

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 3 and 4** (51).

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 daughters, recording his daughter's phenotypes, and predicting his breeding value based on progeny information using pedigree-based BLUP. At this point, the bull can be identified as a sire of future AI bulls [the sires-to-sires (SS) selection pathway], and if his semen is used immediately to inseminate elite cows and heifers, his first sons will be born when he is approximately 63 months of age. In an aggressive breeding program based on GS, a young bull can be identified as a sire of future AI bulls as early as one or two months of age, and as soon as he reaches sexual maturity his semen can be used to inseminate elite cows and heifers (52). His first sons will be born when he is roughly 21 months of age, which means that we can achieve a threefold reduction in generation interval in the SS selection pathway. An obvious extension of this strategy is to also use GS to identify potential dams of future AI bulls, the dams-to-produce-sires (DS) selection pathway, at a young age and propagate them via embryo transfer or in vitro fertilization as yearling heifers, as opposed to waiting for them to complete one or more lactations. In this manner, the generation interval for the DS selection pathway can also be reduced, from approximately 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 only on pedigree and performance data, and this further accelerates the rate of genetic progress per year.

Historically, the weak link in dairy cattle improvement programs has been the dams-to-produce-daughters selection pathway, owing to poor accuracy and low selection intensity (53). The REL of traditional pedigree-based PTA values for cows on commercial farms has tended to be low, and high rates of culling owing 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 use 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 costs associated with rearing animals that are unlikely to perform at a profitable level once they reach lactating age. In herds that lack pedigree data, genomic testing of all heifer calves and culling of the poorest 10%, 20%, or

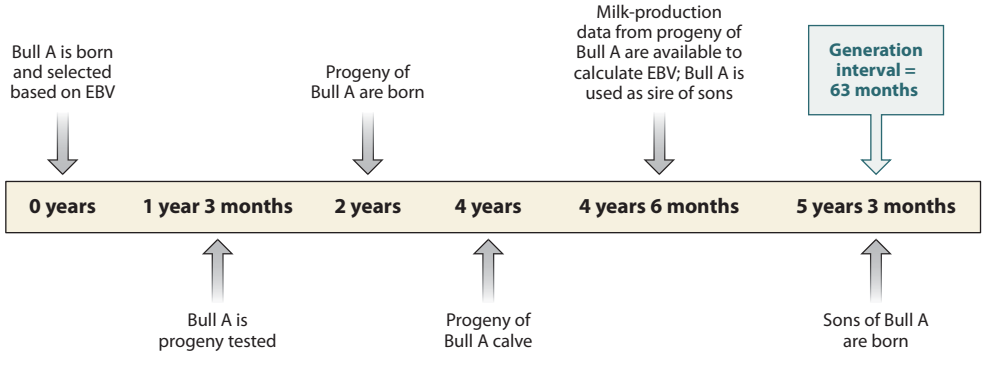


Figure 3

Timeline of a traditional artificial insemination breeding program based on progeny testing. Adapted from Schefers & Weigel (51). Abbreviation: EBV, estimated breeding value.

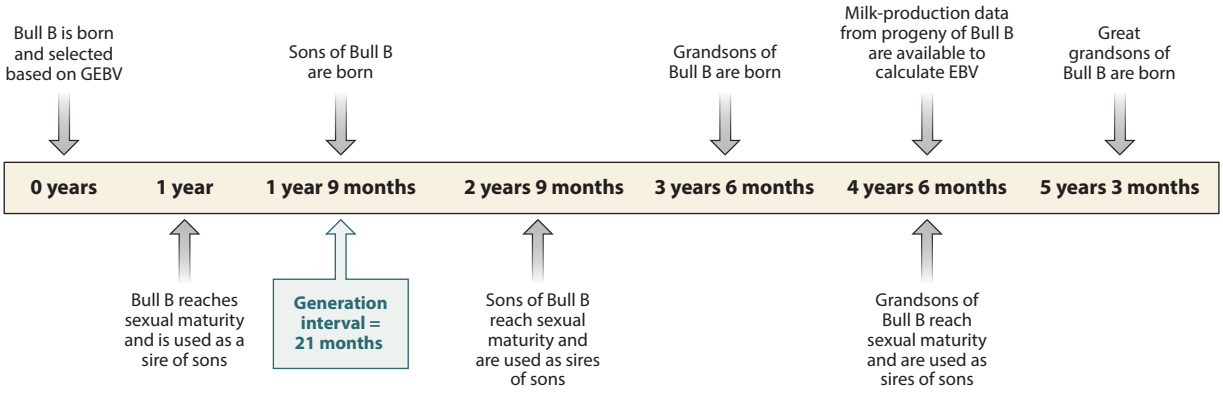


Figure 4

Timeline of an aggressive artificial insemination breeding program based on the use of genomic bulls as sires of sons. Adapted with permission from Schefers & Weigel (51). Abbreviations: EBV, estimated breeding value; GEBV, genomic estimated breeding value.

30% based on GPTA was found to be a cost-effective herd-improvement strategy. Similarly, in herds with known sire identification or complete pedigree information, genomic testing of the bottom 50% of heifer calves based on pedigree index and culling of the bottom 10%, 20%, or 30% based on GPTA were also found to be cost effective (54).

Inbreeding has long been a concern in dairy cattle breeding programs, and breeders try to achieve a balance between rapid genetic progress and maintenance of genetic diversity (55). GS 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 the use of AI and embryo transfer or in vitro fertilization technologies, respectively. However, an advantage of GS is that it facilitates within-family selection decisions among animals with identical pedigrees (26). For example, in a traditional pedigree-based selection program, an elite cow might produce three full-sibling sons by embryo transfer, and one of these sons may 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 embryo transfer, and the son with the 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 (56). Genomic data can provide more precise measures of inbreeding than can pedigree-based inbreeding coefficients (57), which reflect expected inbreeding, and genome-based mating programs can accommodate both additive and dominance effects (58). 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 use genome-based mate-selection programs that consider average heterozygosity, dominance effects, and lethal defects.

Although the primary objective of GS in dairy cattle is to increase the accuracy of GPTA for young selection candidates, related activities, such as fine-mapping of 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, a genome-wide association analysis identified numerous candidate genes and chromosomal regions affecting production, health, fertility, and conformation traits in Holstein cattle (59). Interestingly, several SNP haplotypes were identified that were

abundant in the heterozygous form and yet were never observed in homozygous form in Holstein, Jersey, and Brown Swiss cattle (60). Furthermore, sires that carried these haplotypes tended to exhibit reduced conception rates and increased stillbirth rates when mated to daughters of bulls that carried the same haplotypes. In one of these haplotypes, a nonsense mutation in the *CWC15* gene was identified that appears to be responsible for decreased fertility in Jersey cattle (61).

Heterosis: improved performance in hybrids as compared to purebreds

In summary, the impact of genomics on dairy cattle breeding programs has been enormous, and the pace of change has been breathtaking. Within two years of the commercial availability of the first BovineSNP50 chip (10), the vast majority of AI bulls and elite cows were genotyped, and routine selection decisions used GPTA rather than traditional pedigree-based PTA. 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 use 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 to generate extra females, cull inferior animals early, enhance genetic progress, and reduce feed costs. Lastly, GS will allow the improvement of traits such as feed efficiency and fatty acid composition of milk (62), 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.

RESULTS FROM THE SWINE INDUSTRY

The swine industry focuses on the cost-effective production of high-quality pork, thereby contributing to food security (63). The system for pork production can be separated into a reproduction phase, which consists of females (sows) that are bred to produce high-quality piglets, and a grow-finish phase, which raises these piglets for market. A growing proportion of the pork-production industry is controlled by a limited number of large companies that capitalize on vertical integration and contract production (64). **Figure 5** illustrates the typical breeding pyramid used for genetic improvement and production. Sows in the reproduction phase are typically crossbreds (F1s) to capitalize on heterosis for reproduction and maternal traits. Breeds or lines that produce the crossbred sows are selected for reproduction and maternal traits (fertility, litter size, litter weaning weight), along with growth rate and leanness (backfat) (65). To produce market piglets, sows are bred to a terminal sire line that is selected primarily for growth rate, leanness, reduced mortality, and meat quality, resulting in crossbred market pigs to further capitalize on heterosis for growth and fitness (65). The maternal and terminal breeds or lines that feed into the reproduction and grow-finish phases are increasingly controlled by private breeding companies, although the presence of individual breeders and cooperative breeding programs persists in some countries.

To implement genetic improvement in the pure lines that contribute to commercial production, companies maintain multiple nucleus populations with extensive phenotype recording, genetic evaluation, selection of parents, and rapid turnover of generations to maximize rates of genetic gain while limiting rates of inbreeding (65). Through these efforts, rapid rates of genetic gain can be achieved for traits such as growth rate and backfat. These gains are then disseminated to the

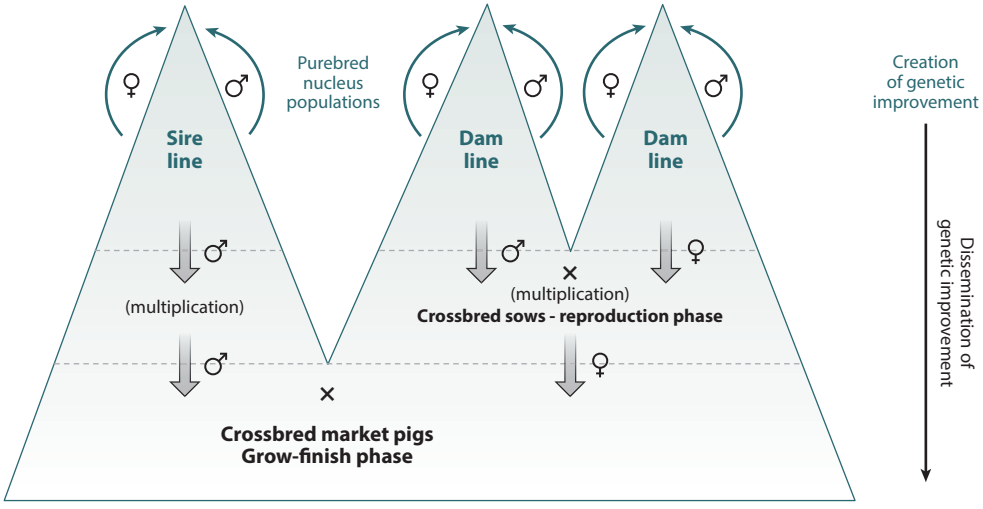


Figure 5

Pyramidal breeding program typical for genetic improvement programs in poultry and pigs. Data recording and selection take place within multiple pure breeds or lines at the top of the pyramid under strict biosecurity and superior management. Superior genetic material developed in the nucleus is passed on or disseminated to the commercial-production sector, often through a multiplier phase to increase the number of breeding parents, and crossed with improved stock derived from other purebred populations to capitalize on heterosis and breed.

reproduction and production phases of the commercial industry in the form of semen (AI), boars, or gilts (young females).

Although this system of genetic improvement has resulted in substantial rates of genetic improvement (66–68), several limitations exist: (*a*) Rates of genetic improvement are limited for female reproduction traits, such as litter size, because these traits have low heritability and are observed only on females and only after animals have obtained reproductive age. Thus, accuracies of selection for these traits are limited, in particular for males. (*b*) Most meat quality traits can be measured only on the carcass and, thus, require information to be collected on relatives of the selection candidates, resulting in limited accuracies of selection. (*c*) Nucleus herds are operated under tight biosecurity. Although necessary to ensure that disease-free breeding stock can be provided to customers, limiting data collection to the nucleus herd also limits the ability to select for disease resistance. In addition, performance data collected in the nucleus and on purebred animals may not correlate well with performance of their crossbred descendants in the field because of genotype-by-environment interactions (G × E) and/or genotype × genotype interactions (dominance, epistasis) (69, 70). Thus, the ability to obtain genetic improvement for traits that are relevant in the field through genetic selection based on data collected in the nucleus is limited. One strategy to overcome the latter is to select purebred animals in the nucleus based on the performance of their crossbred progeny or sibs in the field (71, 72). This has been implemented in some breeding programs but requires extensive logistics in the form of tracking pedigree in commercial farms and collecting phenotypes in the field (73).

Since the 1980s, the use of genetic markers has offered great promise to address the above limitations to genetic improvement in the pork industry. Commercial availability of the Halothane or stress gene (74) as a genetic test to select against the detrimental effects of this gene on meat quality represented one of the earliest success stories of the use of markers for genetic improvement in livestock. This was followed in the 1990s by the use of a limited number of proprietary genetic

markers developed using the candidate gene approach (75). Potential benefits of using markers in pig breeding were characterized by simulation studies (76) and shown to be cost effective (77, 78). Some sectors of the industry capitalized on these advances to some extent prior to the recent development of SNP panels (5). **Figure 6** illustrates the evolution of the development and use of markers by one of the leaders in the industry, Pig Improvement Company (PIC) (79–81). Following the initial wave of genetic markers using QTL mapping and candidate gene approaches in the first decade of this century, PIC employed several in-house, higher-density SNP panels (starting with 1,000 SNPs in 2002 and 7,000 SNPs in 2008). Large numbers of animals were genotyped, and GWAS was used to identify SNPs with effects on various traits, which were then incorporated in genetic evaluation (**Figure 6**) (82).

Pig Improvement Company (PIC): a business dedicated to producing improved breeding stock for the pork industry

Porcine reproductive and respiratory syndrome: a viral respiratory disease in pigs that can result in reduced farrowing rates and increased abortions or stillborn piglets

A real technology breakthrough came in 2009 with the release of the 60K SNP panel for pigs (83). Several simulation studies showed that the use of such a panel for GS could in principle overcome many of the limitations that were previously identified as being associated with traditional approaches for genetic improvement in terminal sire lines (84), in maternal lines (85), and for crossbred performance in the field (86, 87). It was clear from dairy cattle that, with a sufficiently large training data set, the use of a 60K SNP panel could result in sizeable increases in accuracy of EBV in pigs as well (88, 89). However, compared with dairy bulls, the value of a selection candidate in pigs is much lower in relation to the genotyping costs for GS to be implemented, and opportunities to reduce generation intervals are limited. Thus, initial strategies were to use the 60K panel to develop trait-line-specific low-density panels of up to 200 SNPs (90). For most traits, these have been replaced by the approach of using equally spaced, low-density SNP panels and imputation, as Habier et al. (91) proposed. This strategy has been implemented in PIC's routine genetic evaluation program using a low-density panel of approximately 450 SNPs (92). High-density SNP genotyping of all breeding males, low-density genotyping on dams and selection candidates, and sophisticated methods for imputation (93, 94) have resulted in imputation accuracies of up to 97% (95) at a dramatic reduction in genotyping costs. Single-step G-BLUP is being used to incorporate genomic information in routine genetic evaluations on a within-line basis, and strategies to select the optimal proportion and which animals to genotype (96) are being employed.

Although GS appears to be the method of choice for most traits of economic importance, it requires a continuous input of phenotypic data for retraining. Thus, investments in phenotypic data recording must be maintained, including recording of phenotypes in the field, although the need to track pedigrees through the system may be reduced (97). For some traits of economic importance (e.g., disease traits), routine extensive data recording in the field may not be possible. Thus, for such traits, there will be an ongoing need to develop small marker panels for genetic selection based on identified QTL or, ideally, the causative mutations. One example is the recent discovery of a genomic region on chromosome 4 that affects piglet response to infection with the porcine reproductive and respiratory syndrome virus (98), which is the most costly disease in pigs. The release of the swine genome sequence (99) will aid in such discoveries.

Implementing GS on a routine basis requires large investments in development of software, databases, tissue or DNA storage, and computing infrastructure. In addition, large training data sets with genotyped and phenotyped animals must be developed separately for each breed or line for which GS is implemented because training across breeds has not yet been shown to be effective. Because selection and breeding decisions are made on a continuous basis, streamlined logistics and pipelines for tissue and phenotype collection, DNA isolation, genotyping, genotype imputation, and genetic evaluation are needed. These investments and developments have been made in house by some of the larger breeding companies but may require sharing of resources to be effective for small- to medium-sized companies.

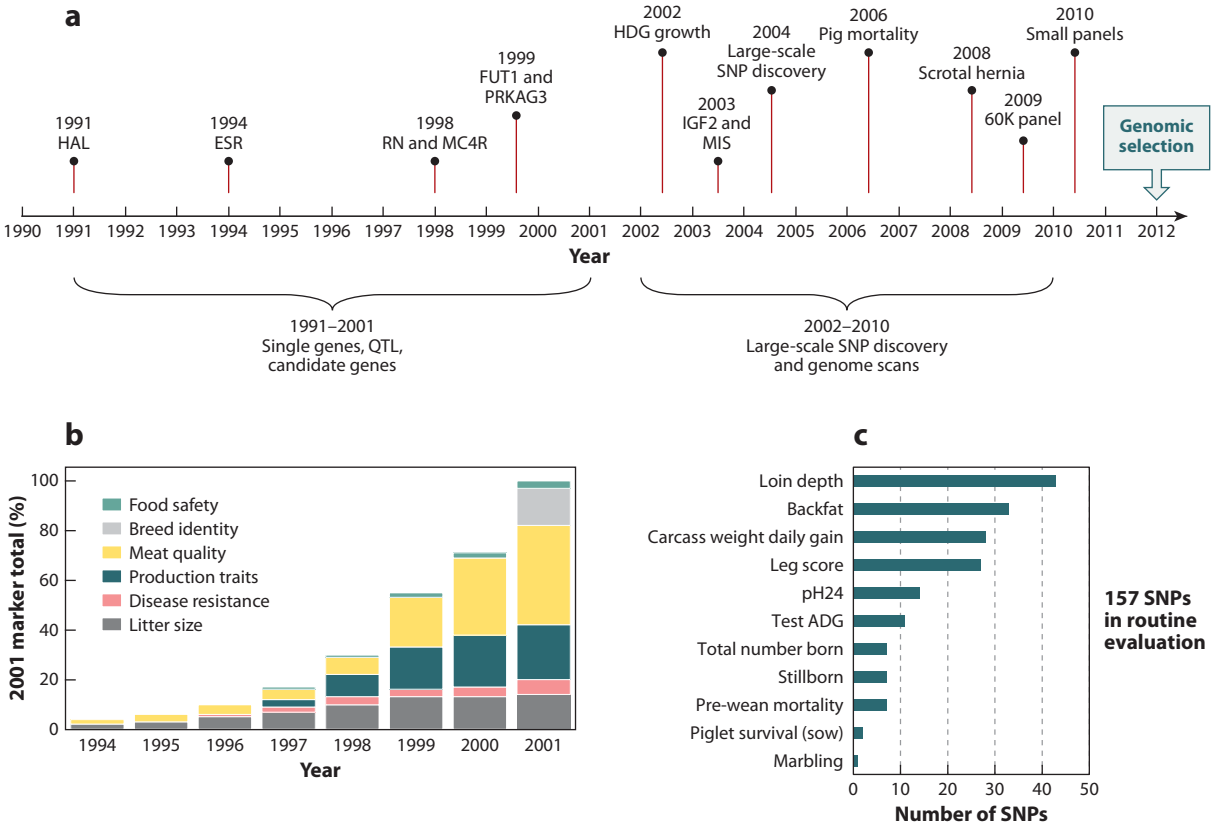


Figure 6

Timeline showing the historical use of DNA markers in swine genetic improvement (*a*), as well as the application of these markers to traits of interest in the breeding program (*b*,*c*), by one of the leaders in the industry, Pig Improvement Company. Abbreviations: ADG, average daily gain; QTL, quantitative trait loci; SNP, single-nucleotide polymorphism.

RESULTS FROM THE POULTRY INDUSTRY

Through egg and meat production, the poultry industry provides at least one-third of animal-derived food globally (100). Eggs and poultry meat accounted for 59 million and 90 million metric tons, respectively, of the worldwide food supply quantity in 2009 (101), nearly a fivefold increase over the past 50 years, and they will continue to be a vital source of protein as the world population continues to grow. Poultry meat is the main meat consumed in the United States (102), and it is projected to overtake pork as the most consumed meat worldwide in the next five to six years. Production on this scale is possible because of the highly specialized, mechanized, and commercialized structure of the modern poultry industry. Poultry production involves an often vertically integrated system of hatcheries, producers, and growers. Intense industry competition has resulted in a relatively small number of large international companies dominating the commercial breeding programs. Over 90% of global poultry breeding stock is managed by three companies selling to a worldwide market (103).

Derived from the red junglefowl (*Gallus gallus*) of Southeast Asia, domestic chickens were kept primarily for their eggs, and chicken meat was viewed largely as a by-product of egg production

until the late 1920s. Dual-purpose breeds paved the way for the transition to dedicated broiler chickens, and the genetic improvement of commercial stocks began in the 1940s. As demand for poultry products increased and technology and breeding practices evolved, strains of layers for high egg production and feed efficiency were created. In broilers, an emphasis on hybrid vigor resulted in systematic matings that involve crossing different breeds, strains, or inbred lines. In comparison with other livestock species, chickens can achieve a faster rate of genetic improvement owing to the combination of shorter generation intervals, large numbers of progeny, AI technology, and defined closed genetic populations. These factors allowed for the extremely successful application of genetics to poultry production traits. Havenstein et al. (104) compared the performance of contemporary 2001 broilers to a line that was randomly bred since 1957 (**Figure 7**). They estimated that at least 85% of this remarkable improvement in performance can be accounted for by genetic changes resulting from combined selection by poultry breeders for growth, body composition, feed efficiency, reproduction, health, and welfare.

This potential for improvement in performance has resulted in the application of intensive selection to both broilers and layers. The comparatively rapid reproduction rate means that a large number of generations have been exposed to intensive selection. Poultry breeding programs generally involve crosses between four breeds or lines: Grandparent or great-grandparent lines that have been phenotyped for critical production traits (G0 or G1) are crossed to produce parent lines (F1), which are crossed to produce chicks. Each bird can produce over 200 offspring at each generation (**Figure 8**). The specialized nature of these lines means that they are essentially closed breeding populations, with virtually no gene flow between commercial and noncommercial populations. Additional increases in productivity are achieved through the exploitation of heterosis.

Current breeding programs are improving the efficiency of meat production in the broiler industry by 2–3% per year. In the United States, growth rates and breast meat yields continue to improve by 0.74 days and 0.5% per year for a broiler grown to 2.27 kg, respectively, whereas the feed-conversion ratio (kg of feed required to obtain one kg of growth) is decreasing by 0.025 per year. At the same time, the livability (survival expectancy) of broilers is improving 0.22% per year, and condemnation rates have decreased 0.7% per year (100). This underscores the importance of combined selection for many traits, including robustness, specific and general disease resistance, and absence of metabolic defects in the breeding objectives. Egg layers have been selected for multiple traits, including egg number, egg size, egg quality, livability, persistency of production,

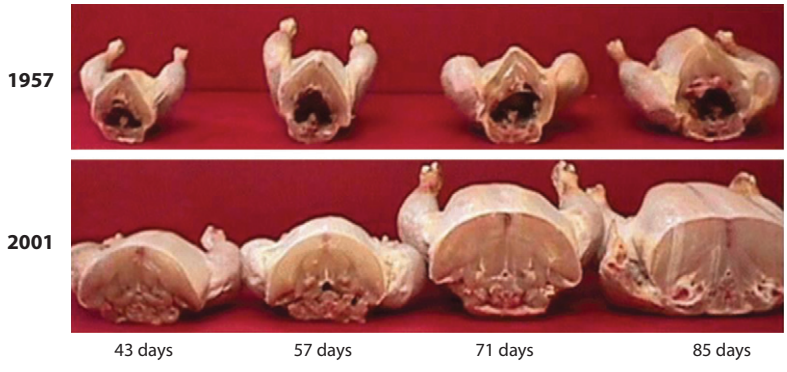


Figure 7

Contemporary comparison of 1957 control and 2001 selected broiler carcasses slaughtered at different ages. Photo by G.A. Havenstein (155).

feed efficiency, and mature body weight. Although some of these traits have negative correlations with each other, US industry estimates show that the egg number is improving by more than one egg per year per individual and the feed conversion ratio is improving by 0.01 per year. Additionally, livabilities to 60 and 80 weeks of age are improving by 0.12% and 0.18% per year, respectively (100). These data highlight the genetic progress that has been achieved by the poultry industry using traditional selection techniques.

The publication of the draft chicken genome sequence in 2004, and the release of the second assembly in 2006, shed light on the differences between chicken and mammalian genomes (105), allowed for the identification of ~3 million SNPs (106), and resulted in the subsequent development of 60K (107) and high-density 600K SNP genotyping arrays for the chicken (108). The availability of these genomic resources allows for greater accuracy and earlier determination of the genetic makeup, and selection, of candidate breeding animals (109). In poultry, GS may also be especially powerful when phenotypic selection is not possible, for example, for egg traits in males (110).

Currently, GS is being tested in commercial chickens, and breeding progress, especially in layers, is showing promise (111). Increases in accuracy were evaluated when selection for layers was carried out at a very early age, prior to phenotypes being available on selection candidates or their siblings, and at a later age. By including high-density (23.4K) SNP genotypes in genetic evaluations, accuracies of EBV were increased up to 200% for selection at an early age and by up to 88% for selection at a later age (109). Late-age selection represents a scenario where genomic information is used to increase accuracy of selection in existing layer breeding programs, particularly in the case of males, which in current breeding programs are primarily evaluated based on sib information. However, the structure of the chicken breeding industry and the need for effective training programs for the successful implementation of GS require retraining of the genomic

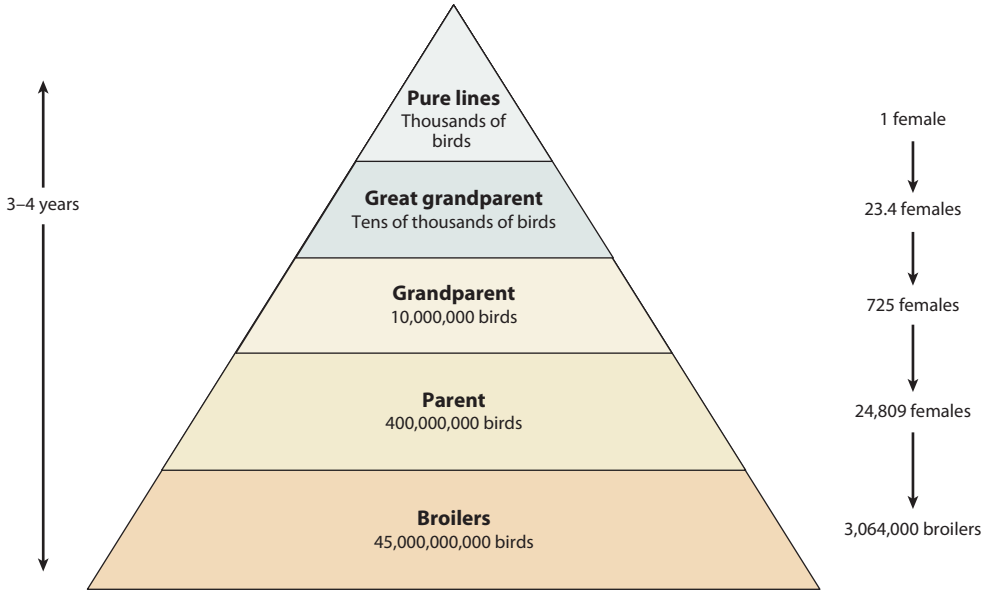


Figure 8

Broiler industry structure and global estimate of bird numbers (modified from Reference 100) alongside estimates of timeline and genetic expressions derived from a single pedigree female broiler chicken (Dr. Rachel Hawkin, Cobb-Vantress, personal communication).

predictions at regular intervals (38). This also allows for responses to new mutations or the possible fixation of major QTL alleles. A study of the accuracy of GEBVs using real data on egg production and quality traits in layer chickens showed that, when training was on data from generation 0, the accuracy in generation one was 0.43, but it dropped to 0.33 in generation two. In contrast, when data from generations zero and one were used for retraining, the accuracy in generation two increased to 0.49. The results of this study suggest that retraining should be done every generation for GS in closed populations (34).

Limitations of the application of GS technology in poultry breeding programs lie in the cost effectiveness of this approach, given the need to develop training populations and routine genotyping of the large numbers of selection candidates that are produced each generation. As commercial birds are typically hybrids from a four-way cross, the effort and expense of developing phenotyped training populations is quadrupled compared with those for dairy cattle. In addition, broiler lines have no association with layer lines, and even white and brown layer lines are genetically distinct. Therefore substantial investment will be required to develop line-specific training populations, in addition to the ongoing costs of genotyping each generation of selection candidates.

Traditional breeding programs have been successful in using pedigree and relatively inexpensive trait information, and the added cost of GS must be recovered through improved product performance. The additional cost of GS must eventually be paid for by customers purchasing the genetically improved birds. Until that time, the substantial investment in developing the training populations must be prefinanced by the breeding company until it can recoup the investment through the sale of more valuable products.

Although GS has the potential to be expensive, breeders have begun to implement various strategies to minimize the costs of genotyping and retraining. Higher accuracies can be obtained by combining data from populations with and without genomic data using single-step G-BLUP, and costs associated with large-scale genotyping can be reduced by imputing high-density genotypes from low- or reduced-density SNP chips (112). This method was demonstrated in a population of brown egg layers in which, after two generations of high-density genotyping of all parents, sires were high-density genotyped in generations three through five, and dams were either high- or reduced-density genotyped for one to two generations. As the number of reduced-density-genotyped dams increased, a steady decline of accuracy was observed, suggesting that high-density genotyping of dams may need to be selectively implemented to maintain accuracy comparable to that achieved by using high-density panels (113).

In another study that investigated the potential application of genotype imputation, a portion of birds from a commercial broiler line were genotyped on a low-density panel, and the rest were genotyped on a high-density panel. Missing genotypes were imputed for birds with reduced-density genotypes, and GEBVs were calculated. In comparison with EBVs from pedigree-only selection methods, the accuracy of GEBVs was 7–8% higher for one trait, body weight, and 4% higher for a second trait, hen house production (114). Additionally, a simulation study based on a real broiler pedigree of 13 generations compared the accuracy of GEBV based on high-density genotypes, GEBV based on equally spaced low-density genomic estimated breeding values, and traditional BLUP over four generations based on four different combinations of low- and high-density genotyping. The results showed that a combination of low- and high-density SNP panels could be employed to rationalize the cost of genotyping. Use of low-density panels resulted in 88.8% of the accuracy generated with a high-density panel at generation four (115).

Effective implementation of GS may require a complete redesign of breeding programs to optimize the selection intensity applied to young animals based on the improved accuracy enabled by genomic information. This was investigated on an experimental basis by splitting a commercial

brown layer line into two sublines (116). One subline was selected based on own record and pedigree information with a traditional one-year generation interval, whereas the other was selected based on genomic information with the generation interval reduced to six months. To reduce costs, the size of the GS subline was reduced by a factor of five, and cross-classified mating was introduced to compensate for the decrease in effective population size. Both sublines were selected based on an index combining 16 traits. Genomic BLUP and Bayes B methods were used to estimate GEBV. Selected parents from generations preceding the base population were genotyped with a 42K Illumina SNP chip to provide information about marker effects, as were all selection candidates. Retraining was performed in every round of selection. Inbreeding level was monitored, and matings of close relatives were avoided in both sublines. The accuracy of GEBVs was shown to be higher and more persistent than that of pedigree-based EBVs. The accuracy of predictions varied substantially between traits and generations. Genomic regions explaining the largest proportion of genetic variation were identified for all studied traits. By the end of the two-year experiment, the rate of genetic progress in the GS subline was superior for the majority of traits, although the GS subline was slightly more inbred than the pedigree-selected subline (116).

Breeding goals may also be refined with the advent of the genomics era. Currently, issues facing the poultry industry include control of infectious diseases, namely avian influenza, Marek's disease, *Salmonella,* and *Campylobacter* (117, 118). The application of genomics may be the best approach for selection of birds with improved disease resistance (119). The structure of the breeding industry and the three- to four-year timeline to product require breeders to think ahead in preparing for future opportunities and challenges, including consideration of public opinion regarding traits such as animal well-being and housing system desirability (110).

Other Avian Species

The rapidly decreasing costs associated with whole-genome sequencing and SNP identification and genotyping are also enabling the sequencing of other poultry species. In 2010, the turkey genome was completed, primarily by next-generation-sequencing methods, for one-fiftieth the cost of the chicken genome (111, 120). After chicken, turkey is the second most-consumed poultry meat worldwide (101). The availability of the turkey genome sequence allowed for the identification of 5.49 million SNPs. Analysis of these SNPs showed that all commercial lines have a common origin and that the turkey genome is much less diverse than the chicken genome. Additionally, the Beijing Genome Institute (BGI) has completed the duck genome sequence. Through the BGI's 1,000 Plant and Animal Reference Genomes Project, several other avian species are in the process of being sequenced or are on the list of species to be sequenced in the near future.

RESULTS FROM THE BEEF INDUSTRY

The US beef industry consists of many herds spread over a wide geographic location. It is composed of five main sectors: seedstock, commercial, feedlot, processor, and end-user (retail). There are several thousand seedstock breeders and over 750,000 commercial producers (**Figure 9**). The industry includes nearly 30 breeds, although at the seedstock level the top five breeds comprise nearly 80% of all registered animals. The main constraints to greater industry-wide genetic progress are the segmented nature of the beef industry and the large number of relatively small breeding operations. Increased rates of progress with the potential to have widespread impact on the commercial production sector are more likely if larger breeding operations develop in the

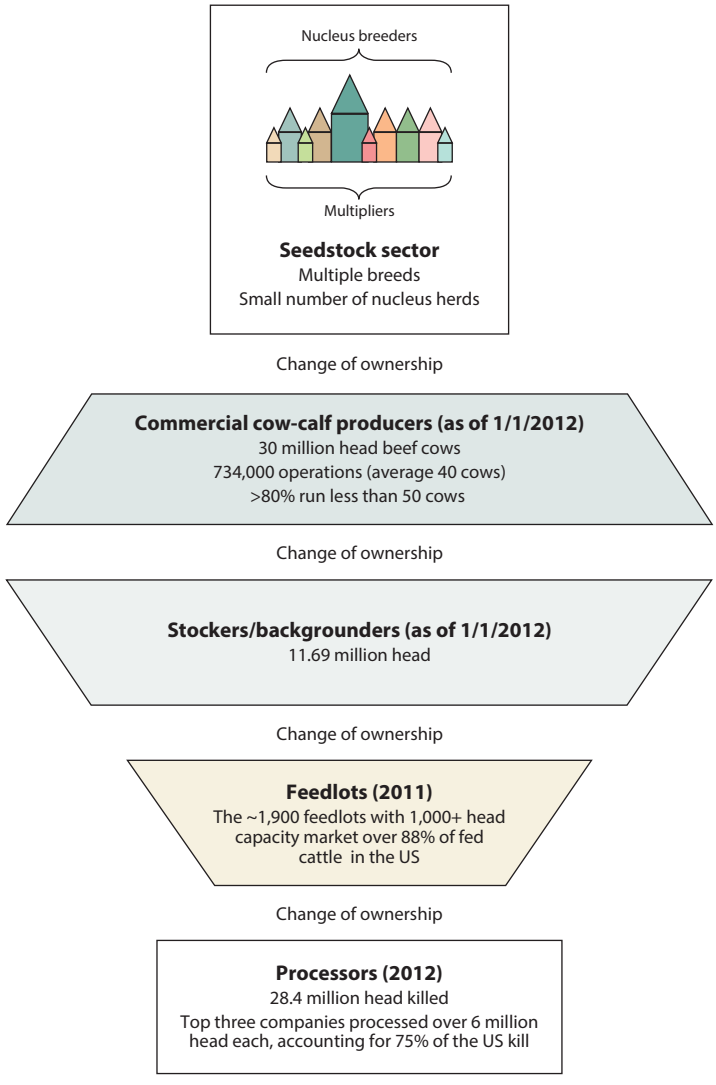


Figure 9

US beef industry structure. Numbers based on US Department of Agriculture National Agricultural Statistical Service.

future. Individual breeders are generally too small to have their own closed breeding program, and they regularly rely on the importation of genes into their herds. From a beef industry perspective, breeders who generate SS sires and DS dams are effectively the nucleus breeders. In the US Red Angus population, only 153 seedstock herds (3.6% of all herds in the pedigree) produced 50% of the SS animals (121). Typically, animals change ownership multiple times in the production chain, and phenotypic performance in downstream segments (e.g., feed efficiency in the feedlot, carcass quality, eating satisfaction) is rarely relayed back to the breeding sector. In contrast to more vertically integrated industries, this results in market failure because breeders are rarely rewarded

for developing breeding programs that maximize profit for the entire industry. Additionally, in the absence of phenotypes from the commercial, feedlot, processing, and retail sectors, it is difficult to make genetic improvement for traits that are measured in these sectors.

Expected progeny difference (EPD): within-breed evaluation of an animal's parental genetic merit based on information on an individual and relatives

There are no well-defined breeding goals for national beef cattle improvement in the United States. In contrast to other countries that have developed a total production $Index for whole-industry economic merit (122, 123), much of the US beef industry still largely relies on expected progeny difference (EPD) for individual traits rather than an economic index. This is in marked contrast to swine, poultry, sheep, and dairy cattle industries, for which such indexes are the fundamental driver of selection decisions (124). The focus of GS in the beef cattle industry has been to increase the accuracy of EPD on young animals or to provide new EPDs as selection criteria for economically relevant traits that were not formerly included in national beef cattle genetic evaluations (NCEs) (e.g., beef tenderness, feed efficiency).

The adoption of GS in the beef industry has been slow compared with that in the dairy cattle industry (39). There are many reasons for this disparity. First, there are many breeds with varying characteristics designed to fit the different environments associated with beef cattle production. Additionally, the beef industry does not use AI very heavily. As a result, fewer high-accuracy sires are available to provide a within-breed reference population. Additionally, there is no obvious beneficiary willing to pay for the development of phenotyped and genotyped training populations, such as the AI studs provided for the dairy industry, owing to the lesser use of AI in the beef industry. Consequently, the development of training populations in the beef cattle industry has been somewhat disjointed. Some companies, such as GeneSeek® (formerly Igenity®) and Zoetis (formally Pfizer Animal Genetics), saw this void as a business opportunity (28) and paid for the genotyping of semen collections from AI sires put together by individual researchers (125) or developed their own training populations. This involvement of commercial genomics companies introduced a proprietary component into the process of ranking animals based on genetic merit (28) and made it difficult to obtain validation data of the resulting genomic predictions (126). As of 2013, two ~$75 products are being offered for the genetic evaluation of Angus cattle, the GeneSeek® Genomic Profiler Bovine HD™ (GGP-HD) test (which replaced the 384 SNP Igenity Profile) (GeneSeek®, Lincoln, Nebraska) and a 50K SNP chip offered by Zoetis (Kalamazoo, Michigan). The companies report MBVs to the Angus Association, and the genomic data from these two companies are incorporated into the Angus Association's NCEs on a weekly basis for the traits listed in **Table 2**.

Table 2 reveals some translational considerations with regard to GS in beef cattle. The first is that the accuracy of 50K-trained predictions varies depending upon the training population. This can be seen when comparing the Zoetis 50K data between Australia and the United States and between 2012 and 2013. Predictions trained in the United States were not as accurate when applied to the same breed in another country. In 2013, the Zoetis 50K genomic prediction equations for US Angus were recalibrated on a larger and more current training data set, resulting in an increase in accuracy.

In contrast to the poultry, swine, and dairy industries, where reduced SNP panels have been employed to enable imputation to a higher-density SNP platform (127, 128), commercial reduced SNP panels in beef cattle have been developed based on associations of the selected SNP with a subset of traits. This approach was examined in dairy cattle, where a study compared subsets of SNPs selected from the 50K chip for strong associations with nine dairy traits (129). Very few SNPs were shared between the different dairy traits, and at least 1,000 of the highest-ranked SNPs were required to obtain accurate predictions for each trait. Similar results were reported for Angus cattle, where the predictive ability of a reduced-SNP panel for feed efficiency dropped markedly as the number of SNPs dropped below 600 (130). Given the quantitative nature of most traits, it

Table 2 Genetic correlation between molecular breeding value and phenotypic trait of interest in two genomics companies in 2012 US Angus (150), 2012 Australian Angus (132), and 2013 US Angus (156)

	2012 (United States)		Australia	2013 recalibration (United States)	
Trait	Igenity 384	Zoetis 50K	Zoetis 50K	Igenity 384	Zoetis 50K
Calving ease direct	.47	.33	.24	.34	.61
Birth weight	.57	.51	.40	.42	.64
Weaning weight	.45	.52	.37	.38	.54
Yearling weight	.34	.64	—	.34	.66
Dry matter intake (component of residual average daily gain)	.45	.65	—	.27	.59
Yearling height	.38	.63	—	.24	.70
Yearling scrotal	.35	.35	—	.23	.73
Docility	.47	.60	—	.18	.67
Milk	.24	.32	—	.21	.38
Mature weight	.53	.58	—	.39	.51
Carcass weight	.54	.48	.34	.27	.57
Carcass marbling	.65	.57	.36	.34	.63
Carcass rib	.58	.60	.25	.29	.63
Carcass fat	.50	.56	.47	.22	.53

is unlikely that SNPs included in panels of less than 500 are in LD with QTL. This suggests that the accuracies for multiple traits associated with reduced-SNP panels that are not used for imputation are derived primarily from familial linkage (i.e., tracing family relationships), meaning that in the absence of retraining, accuracy would be predicted to decay over time, as can be seen with the Igenity panel (**Table 2**).

For breeds other than Angus, individual breed associations have developed their own training populations. They have genotyped AI bulls and obtained 50K genotypes from the influential bulls that were genotyped at the US Meat Animal Research Center (US-MARC) in Clay Center, Nebraska, as part of the 2,000 Bull Project. This project involved 50K genotyping of 2,026 animals from the 16 most prominent breeds (Angus, Beefmaster, Brahman, Brangus, Braunvieh, Charolais, Chiangus, Gelbvieh, Hereford, Limousin, Maine-Anjou, Red Angus, Salers, Santa Gertrudis, Shorthorn, and Simmental) in the US beef industry. Breed associations, in collaboration with the National Beef Cattle Evaluation Consortium, used these data to develop within-breed genomic prediction equations. The advantage of this model is that the breed association has access to the genotypic information and can use this information in conjunction with new performance and pedigree information in the breed database to continuously retrain prediction equations. Publications documenting the accuracy of genomic predictions in field data are slowly becoming available for beef cattle. **Table 3** shows the most current results from US breed associations (29, 30, 131). These data provide a guide to the accuracy of these predictions but do not represent the true correlation between the MBV and the true BV, because of the heterogeneity of variance among the deregressed EPDs (28).

Table 3 Realized accuracies (correlation between deregressed breeding value and molecular breeding value) resulting from genomic selection prediction equations trained in US beef cattle breeds[a]

Trait	Red Angus (6,412)[b]	Angus (3,500)	Hereford (2,980)	Simmental (2,800)	Limousin (2,400)	Gelbvieh (1,181)
Birth weight	0.75	0.64	0.68	0.65	0.58	0.41
Wean weight	0.67	0.67	0.52	0.52	0.58	0.34
Yearling weight	0.69	0.75	0.60	0.45	0.76	—
Milk	0.51	0.51	0.37	0.34	0.46	0.34
Fat thickness	0.90	0.70	0.48	0.29	—	—
Rib eye area	0.75	0.75	0.49	0.59	0.63	0.48
Marbling	0.85	0.80	0.43	0.63	0.65	0.56
Calving ease direct	0.60	0.69	0.68	0.45	0.52	0.48
Calving ease (maternal)	0.32	0.73	0.51	0.32	0.51	—
Scrotal circumference	—	0.71	0.43	—	0.45	0.50

[a]Data taken from References 29, 30, 131; D. Garrick, unpublished data (personal communication).
[b]Numbers indicate training population. The Red Angus training data set includes some Black Angus cattle that have expected progeny difference in the Red Angus Association.

For breeders to make the best use of genomic data, they must be combined with traditional sources of information (i.e., phenotypes and pedigrees) in genetic evaluations. There is a need to optimize the most suitable method to include genomic information in NCE, considering the type of genomic data available, the existing structure of the genetic evaluation system, and the commercial computing capacity. In some countries, a centralized body is responsible for beef cattle genetic evaluations (132, 133). However, in the United States, breed associations are responsible for genetic evaluations. MBVs are being incorporated into NCE to provide genomic-enhanced EPDs (GE-EPDs) to industry in a variety of ways. Swan et al. (134) provide a review of the methods. As discussed previously, in the United States the American Angus Association has partnered with genomics companies who retain ownership of the genotype information and return MBVs to the breed association, whereupon they are incorporated into NCE as correlated traits in a multitrait BLUP evaluation (135). As the genetic correlation between the MBV and the trait of interest increases, so does the accuracy of the GE-EPD. Other groups compute EPDs and MBVs independently and include both pieces of information in a selection index whereby each trait is weighted proportionally to the respective amount of genetic variation (18, 26) [e.g., BREEDPLAN in Australia (132)].

Many commercial beef cattle producers are taking advantage of the benefits of heterosis and are engaging in systematic crossbreeding or buying crossbred or composite bulls. Harris et al. (136) showed that prediction equations developed in one breed did not perform well in another breed. This was thought to result from a breakdown in LD between informative markers and QTL in across-breed predictions (33, 137). As has been discussed previously, it has also been shown that some of the accuracy associated with GS is due to the relationships between individuals in the training population and those in the selection candidate population (138), and this familial linkage source of accuracy is not expected to be predictive across breeds. It was hoped that pooling training populations across breeds, or training in multibreed populations, might improve the accuracy of predictions (139).

To investigate this further, the accuracy of genomic predictions derived from two large training data sets from the US-MARC were evaluated across multiple breeds and in crossbred cattle. The first training data set was composed of data from the 2,000 Bull Project. Deregressed EPDs (139a) were used as phenotypes for training the prediction equations. The second set was composed of 50K genotypes and adjusted phenotypes from 3,358 crossbred animals derived from the US-MARC Germplasm Evaluation Project (GPE). Although more genotyped animals were included in the GPE training population, less phenotypic information was actually assessed, as deregressed EPD in the 2,000 Bull Project population included data from multiple progeny records. Moderate genetic correlations (0.23–0.42) were found between 2,000 Bull Project–trained genomic predictions for growth traits in multiple purebred beef breeds. Lower correlations (0.19–0.37) were found when using the GPE-derived genomic prediction equations (140, 141). It was envisioned that the increased marker density of the Illumina 777K SNP chip would help improve the accuracy of across-breed predictions (13, 33), although preliminary data in dairy cattle showed only a small improvement resulting from pooling Holstein and Jersey populations that had real or imputed 777K genotypes (25). This suggests that because there are differences in the LD between single markers and QTL across breeds, pooling of data might actually dilute associations of markers with phenotypes.

To date, there has been limited adoption of GS in the beef industry, as the value proposition associated with improving the accuracy of NCE EPDs on young beef sires destined for natural mating pastures, where they might sire 100 offspring (142), is considerably less than that associated with seedstock animals that are destined to have thousands or even millions of genetic descendants. Many of the traits that influence the profitability of beef production are not currently included in NCE. This includes traits that are expensive or difficult to measure (e.g., feed efficiency and fertility), occur late in life (e.g., stayability), or are experienced by a downstream segment of the cattle industry, such that the relevant phenotypes (e.g., disease susceptibility in the feedlot) are never relayed back to the breeder. No preexisting database of phenotypes for these traits is available from which to form a training population. Some countries are taking advantage of electronic animal identification to start to compile a database of phenotypes from the entire production chain (133). Several large, publicly funded efforts are also under way in several countries to obtain large phenotyped and genotyped training populations for hard-to-measure production traits, such as feed efficiency, fertility, and disease resistance.

Pooling data across countries represents an attractive approach to increase the size of the training population for expensive-to-measure traits (143). It has worked in the dairy industry [e.g., in the Brown Swiss breed (144)], although this assumes minimal genotype-by-environment interactions and markers in tight LD with QTL. If markers are tracking familial linkage, this approach will improve the accuracy of prediction equations only if the populations share a common genetic base. The development of phenotyped populations with the thousands or tens of thousands of individuals that will be needed to obtain accurate predictions (13, 145) for these hard-to-measure traits represents a significant hurdle to the implementation and adoption of GS for these economically relevant traits in the beef industry. Ironically, these are the very traits that are most likely to benefit from GS, as no selection criteria currently exist for them. In the future, other traits, such as methane emissions and adaptation to climate change, may also become relevant to beef cattle breeding objectives (39).

IMPACT OF INDUSTRY STRUCTURE ON ADOPTION OF GENETIC TECHNOLOGY

Breeding objectives and industry structures vary considerably among the different animal agriculture industries. Genetic improvements prior to GS have been most pronounced in those

Table 4 Main factors that accelerate and impede the adoption of genomic selection for the major animal protein industries

Industry	Field implementation	Main advantages	Main disadvantages	Traits with genomic selection potential
Dairy cattle	Full adoption	Ready-made, large training population Uniform breeding objective Artificial insemination (AI) companies willing to fund genotyping to save progeny testing costs Great opportunities to reduce generation intervals Predominately one or two breeds High value per individual animal High degree of vertical integration in breeding sector and via price signals Moderate acceptance of $Index High use of AI Clear way to decrease generation interval	Few (<10) genetic expressions per commercial female Difficult for AI companies to protect their genetics from competitors; therefore, difficult for companies to differentiate product and justify investments in developing new traits	Feed efficiency Disease resistance Longevity Fertility Methane emission Lameness Metabolic disorders Milk fatty acid composition
Swine	Implemented by some commercial breeding companies; under evaluation by others	Vertical integration Uniform breeding objective Tens of millions of genetic expressions per elite seedstock animal Large number of offspring per female High control of environment Small number of owners High acceptance of $Index and technology	Low value per animal Need to develop training populations for multiple breeds Little opportunity to decrease generation intervals; therefore, rate of genetic gain improvement owing to GS is due mainly to improved accuracy Need to devise selective genotyping and reduced SNP panel strategy to optimize the genotyping cost:benefit ratio of GS	Meat quality Reproductive performance Feed efficiency Commercial crossbred performance Disease resistance Animal welfare

(*Continued*)

Table 4 (*Continued*)

Industry	Field implementation	Main advantages	Main disadvantages	Traits with genomic selection potential
Broiler	Partially implemented by commercial breeding companies	Vertical integration Uniform breeding objective High degree of vertical integration in breeding sector and via price signals Moderate acceptance of $Index Opportunity to select purelines based on commercial crossbred performance Selection for egg production traits limited in males	Low value per animal Need to develop training populations for multiple lines owing to hybrid nature (i.e., four-way cross) of production animal	Disease resistance Pathogen shedding Feed efficiency Animal welfare Commercial crossbred performance
Layer				Egg production traits Feed efficiency Disease resistance Pathogen shedding Animal welfare Commercial crossbred performance
Beef cattle	Limited adoption	High relative value per individual animal Many economically important traits have no selection criteria, and GS offers an approach to tackle these traits	Multiple breeds and breed associations collecting data Limited use of AI Limited data recording on economically important traits Few offspring per commercial female Crossbreeding is important No vertical integration No uniform breeding objective Market failure, little incentive to include downstream sectors in breeding objectives Low acceptance of $Index Large number of ranches/decision makers raising animals in very diverse environments (G × E) Ownership changes often No obvious way for private genomics investment to be recouped given industry structure	Feed efficiency Disease resistance Fertility Stayability Adaptability Methane emission

industries that have a highly structured breeding sector (e.g., pig and poultry) and a well-defined, profit-maximizing breeding objective. These species have high reproductive rates per female (**Figure 6**), and this allows incremental improvements in efficiency to be multiplied across many animals, which directly improves profitability as well as the investment that can be made in improving the accuracy of genetic merit estimates. A small number of animal breeding companies control the genetics of these vertically integrated industries. Industries that have less vertical integration (e.g., beef) have a large number of independent seedstock breeders and have typically made less genetic progress. Because the relative economic value of traits differs among industry sectors (e.g., fertility is a key profit driver for the commercial sector but is not important to the processing sector), in the absence of vertical integration it is difficult to develop a single, industry-wide breeding objective that is economically rational for all sectors. This leads to an important concept in animal breeding: the role of the decision maker (146).

Based on reported and ongoing studies, GS clearly has the potential to accelerate genetic progress. Selection index methods have been developed to evaluate the impact of GS on response to selection (97). A stochastic simulation study of GS that halved the generation interval in layer chickens from one year to six months showed that, with breeding program redesign, it was possible to increase the response to selection while controlling rates of inbreeding and additionally raising and phenotyping a smaller number of elite stock (147). Even in industries with well-structured breeding programs, there will be a need to examine the most cost-effective ways to implement GS, which animals to genotype, and at what density (96), in both the training and target population.

Table 4 summarizes some of the main factors that accelerate and impede the adoption of GS in the major animal protein industries. One of the most important considerations in applying GS to industry will be the development of statistical tools and software that allow the integration of genomic information into existing breeding programs in real time (148). Another important consideration will be cost effectiveness in comparison to existing strategies. Investments in new technologies, including GS, must be considered from the perspective of predicted benefit. Relatively few studies have examined the economic aspects of GS (52, 54, 128, 142, 149–151).

Clearly, further work is needed to determine the most cost-effective approach to capitalize on the opportunity offered by GS. Advances in sequencing technologies and genotyping by sequencing likely will have a transformative effect on the price of genotyping. This will undoubtedly accelerate the uptake of this technology in the field and may well result in the redesign of breeding programs. Groups that can organize themselves to take advantage of the rapidly declining cost of genotyping and capture the cumulative supply-chain value derived from using genomic information for multiple purposes will be ideally positioned to more fully realize the nascent potential of genomic information.

SUMMARY POINTS

1. GS relies on the availability of a large population of phenotyped animals with high-density genotypes to estimate the marker effects for a given trait across the genome. This enables the development of genomic prediction equations that can be used to estimate the GEBV of unphenotyped individuals based solely on their genotype.
2. Several statistical approaches, including several BLUP and Bayesian regression-model variations, have been proposed to estimate marker effects for GS. They differ based on the assumptions they make about the distribution of SNP effects.
3. GS has been shown to improve the accuracy of traditional genetic evaluations based on pedigree and phenotypes alone in several livestock species.

4. In dairy cattle breeding programs, progeny testing has been replaced by genomic testing and progeny validation, resulting in rapid improvements across multiple traits.
5. Biological limitations, costs, and industry structure influence the rate of adoption of GS in different livestock industries. High-density SNP genotyping of breeding males and low-density SNP genotyping of dams are successfully being used to impute genotypes, making GS more cost effective for the swine and poultry industries.
6. Prediction equations trained in one line or breed have not been shown to be accurate when used to predict in another. Training populations of genotyped, phenotyped animals must therefore be developed separately for each breed or line in which GS will be implemented. In addition, retraining of genomic predictions must be performed at regular intervals.
7. The segmented nature of the beef industry, the lack of a well-defined breeding goal for beef cattle improvement, and the large number of breeds have resulted in limited adoption of GS as compared with other industries. Breed associations have started to implement GS for some traits, although there is a paucity of large training populations for many economically relevant traits.
8. GS has the potential to accelerate genetic progress. The development of statistical tools and software, and the cost effectiveness in comparison with existing strategies, will be important for the integration of genomic information into existing breeding programs.
9. In the future, precision gene-editing techniques may be combined with genomic knowledge and understanding to further accelerate the rate of genetic improvement through the introduction of targeted beneficial alleles into elite seedstock germplasm.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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