Genomic Selection in Dairy Cattle: The USDA Experience*

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Abstract

Genomic selection has revolutionized dairy cattle breeding. Since 2000, assays have been developed to genotype large numbers of single-nucleotide polymorphisms (SNPs) at relatively low cost. The first commercial SNP genotyping chip was released with a set of 54,001 SNPs in December 2007. Over 15,000 genotypes were used to determine which SNPs should be used in genomic evaluation of US dairy cattle. Official USDA genomic evaluations were first released in January 2009 for Holsteins and Jerseys, in August 2009 for Brown Swiss, in April 2013 for Ayrshires, and in April 2016 for Guernseys. Producers have accepted genomic evaluations as accurate indications of a bull's eventual daughter-based evaluation. The integration of DNA marker technology and genomics into the traditional evaluation system has doubled the rate of genetic progress for traits of economic importance, decreased generation interval, increased selection accuracy, reduced previous costs of progeny testing, and allowed identification of recessive lethals.

INTRODUCTION

Genomic selection in dairy cattle builds on a long history of data collection and evaluation methods suitable for reliably ranking selection candidates from very unbalanced field data. The use of artificial insemination (AI) and the possibility of diluting a single ejaculate to create many progeny resulted in a population structure with many very large half-sib families. Data collection is largely from monthly visits by a technician to collect milk weights, milk samples, and management information. This service is provided by farmer-owned cooperatives that are funded by the producers. Bulls are owned primarily by genetics companies, usually with international reach, that work with breeders and dairy farmers to obtain promising bull calves. Prior to genomics, bulls at approximately one year of age typically entered a progeny-test program as a method to determine their breeding value. Bulls were at least five years old when their semen could be marketed based on progeny-test results. The combination of massive historical phenotypic data, breeding organizations able to invest in technology, data processing and evaluation infrastructure, and a long generation interval made dairy cattle an ideal candidate for genomic selection.

HISTORY

For approximately 30 years, DNA markers have been used in many species for a broad spectrum of genetics research and diagnostic applications, such as parentage verification. Parentage verification began almost 50 years ago with the analysis of blood groups (1) but transitioned to genetic markers by the 1990s for dairy cattle (2). Linkage relationships between genetic markers and quantitative trait loci (QTL) provide genomic information that can be used with marker-assisted selection for traits of interest (3). Through the early and mid-2000s, such selection had only modest commercial success for livestock because of the cost of generating appropriate data sets as well as difficulties in the identification of major genes related to quantitative traits (4, 5). Traits of economic importance in dairy cattle usually are controlled by many genes with small effects (6). A large amount of data is needed to estimate those effects accurately, as well as dense markers to track the marker-QTL association across families.

In the mid- to late 2000s, assays were developed to genotype large numbers of single-nucleotide polymorphisms (SNPs) at relatively low cost. Although SNPs usually have only two alleles, the large number available across the entire genome allows tracking the inheritance of short chromosomal segments. Genome-wide selection had been proposed (7), but the resources needed to make the required DNA tools were not possible until the Bovine Genome Project was initiated in 2003 (8). To add to the SNPs identified from the Hereford genome-sequencing animal, low-depth sequencing from other breeds was used to generate information for SNP assay development. In 2005, ParAllele BioScience (now part of Affymetrix, Santa Clara, CA) released the MegAllele Genotyping Bovine 10,000-SNP Panel with 10,410 SNP markers (9). Despite immediate interest in using this assay as a platform for testing genomic selection in accessible commercial dairy populations, the SNP markers were not well distributed across the genome in relation to linkage disequilibrium, and the panel was not well suited for the purpose of genomic selection. The need for a better SNP assay based on an informative SNP marker within each block of linkage disequilibrium across the entire genome was recognized (10); approximately 250,000 well-distributed SNPs would be needed to capture all linkage-disequilibrium blocks for Holsteins (9).

In early 2006, the US Department of Agriculture's (USDA's) National Resource Initiative (now the Agriculture and Food Research Initiative, part of USDA's National Institute of Food and Agriculture) funded two projects at the Bovine Functional Genomics Laboratory (now part of the Animal Genomics and Improvement Laboratory, Beltsville, MD), part of USDA's

Agricultural Research Service. The first project was for the creation of the Bovine Gene Atlas, an expression compendium constructed from complementary-DNA tag sequences generated from a Solexa (now part of Illumina, San Diego, CA) sequencing platform to help annotate the bovine genome and find functional candidate genes near marker effect locations (11). The second project was for the development and testing of large-scale bovine SNP genotyping for use in genomic selection. Concurrently and in collaboration with USDA, similar projects were funded for developing SNP tools for research in beef cattle (University of Missouri, Columbia, MO) or for populations in Canada (University of Alberta, Edmonton, AB, Canada). Eventually the lead investigators from these four projects and scientists from USDA's US Meat Animal Research Center (Clay Center, NE), the National Association of Animal Breeders (Columbia, MO), and Illumina formed the iBMC Consortium to develop a bovine assay with nearly 60,000 well-distributed SNPs that could be used for testing genomic selection and genome-wide association studies in cattle (12).

Development of a new bovine SNP assay was expected to be a simple task because approximately 2.3 million SNPs had been deposited into the SNP database of the National Institutes of Health's National Center for Biotechnology Information from the bovine genome project (13). However, preliminary testing of those putative SNPs revealed a validation rate of approximately 40%; furthermore, in silico mapping of SNP frequency relative to chromosomal position revealed long genomic regions (>5 Mbp) that were devoid of SNPs because of homozygosity in the Hereford cow (L1 Dominette 01449) used initially to generate and assemble the *Bos taurus* genome sequence (14). A new strategy for rapidly generating SNP content was conceived that used Solexa short reads from reduced-representation libraries of animals from the genotyping populations. This strategy was the first demonstration of genotyping by sequencing using next-generation technology, because the sequencing depth allowed for validation of the SNP genotypes in the target population. During development of the first commercial bovine SNP assay by the iBMC Consortium, a spacing algorithm also was developed to allow selection of SNPs for assay design based on genome position and minor allele frequency by breed from the sequencing data (14). More than 58,000 SNPs were submitted for the design of Illumina's BovineSNP50 Genotyping BeadChip (15), and those included USDA parentage SNPs. The first genotypes prior to commercial release were analyzed in September 2007, and the commercial SNP manifest was determined by the iBMC Consortium using the HapMap DNA panel and the sequence discovery animals (14). In December 2007, the Illumina BovineSNP50 BeadChip was commercially released with a set of 54,001 SNPs.

In July 2010, Illumina released two new genotyping chips: the low-density Bovine3K chip with 2,900 SNPs (16) and the high-density BovineHD chip with 777,962 SNPs (17). The BovineLD chip with 6,909 SNPs was released by Illumina in 2011 and was a significant improvement over the Bovine3K chip because it used the same chemistry as the BovineSNP50 chip and had more SNPs. Because the BovineLD chip could be customized with additional SNPs, several proprietary chips [particularly from Zoetis (Kalamazoo, MI) and Neogen (Lansing, MI)] were based on it. As of April 2016, genotypes from 21 chip types were in the database maintained by the Council of Dairy Cattle Breeding (CDCB, Bowie, MD) for use in genomic evaluation of US dairy cattle.

Genotypes for more than 15,000 animals that had been processed by the iBMC Consortium in the fall of 2007 were used in initial research to determine which SNPs should be used in genomic evaluation of US dairy cattle. Some SNPs had a low call rate, poor calling properties, or a high correlation with other SNPs and were excluded (18). Genotypes also were checked for parent-progeny conflicts and other inconsistencies. By using simulation, genomic evaluation methods were developed (19) and then tested using the genotypes of more than 5,000 progeny-tested

Holstein bulls that had become available by December 2007. Phenotypic and genotypic data from a reference population were used to estimate the effects of the SNPs on performance. Reference animals have been genotyped and have traditional evaluations that do not include genomic information. Genomic evaluations for animals without traditional evaluations can be calculated by using the estimated SNP effects (19, 20). In April 2008, the first unofficial USDA evaluations based on SNP genotypes were released to the US dairy industry for approximately 730 Holsteins. Official USDA genomic evaluations were first released in January 2009 for Holsteins and Jerseys, in August 2009 for Brown Swiss, in April 2013 for Ayrshires, and in April 2016 for Guernseys. Because of financial support from the National Association of Animal Breeders for genotyping the majority of the progeny-tested bulls in the reference population, the AI organizations received the exclusive right to have males genomically evaluated until May 2013. Initial genotyping and processing of commercial samples were provided by GeneSeek (Lincoln, NE; now part of Neogen) and the Genetics & IVF Institute (Fairfax, VA), which were joined later by DNA LandMarks (Saint-Jean-sur-Richelieu, QC, Canada; defunct as of June 2015), Genetic Visions (Middleton, WI), and Zoetis Genetics (Kalamazoo, MI).

Many other countries now use genomic information in their genetic evaluation systems. New Zealand began use of the BovineSNP50 chip for its evaluations in 2008, and Australia's first official genomic evaluations were released in 2011 (21). Canada, which collaborated with USDA in developing genomic evaluations, released official genomic evaluations in 2009 (22). EuroGenomics was established in 2009 by five European breeder-owned companies (representing Belgium, Denmark, Finland, France, Germany, the Netherlands, and Sweden) to improve evaluation accuracy in each country by sharing genotypes for reference bulls (23). As part of that cooperative effort, a data-exchange system was developed for the BovineSNP50 BeadChip and a customized Netherlands chip (24). Beginning in March 2010, EuroGenomics began to extend its collaborative effort and now has a reference population of 33,000 bulls (**http://www.eurogenomics.com/about-eurogenomics.html**). Reference population numbers reported by countries that participated in Interbull (Uppsala, Sweden) genomic evaluations for protein yield (25) in April 2016 are shown in **Table 1.**

In March 2011, agreements between the Cooperative Dairy DNA Repository (CDDR, Beltsville, MD), the Associazione Nazionale Allevatori Frisona Italiana (Cremona, Italy), and DairyCo (now AHDB Dairy, Kenilworth, Warwickshire, UK) provided for the exchange of genotypes for Holstein bulls to increase the US, Italian, and UK reference populations. CDDR made a similar agreement with the Holstein Association of Switzerland (Posieux, Switzerland) and Swissherdbook Cooperative Zollikofen (Zollikofen, Switzerland) in September 2015. In April 2016, a one-time exchange of 3,000 Holstein bull genotypes was undertaken with the National Livestock Breeding Center (Nishigo-mura, Fukushima, Japan). An agreement between CDDR, the Canadian Dairy Network (Guelph, Ontario, Canada), the American Jersey Cattle Association (Reynoldsburg, OH), and VikingGenetics (Assentoft, Randers, Denmark) added over 1,000 bulls to the US Jersey reference population in December 2012. For Brown Swiss, an agreement between CDCB and Interbull provided over 5,000 bull genotypes in July 2014, primarily from Europe, through the Intergenomics program.

In March 2013, a cooperative agreement was signed between USDA and CDCB to transfer the service responsibilities of the genetic evaluation program to the dairy industry (26). The CDCB staff assumed the responsibility for receiving data, computing the evaluations, and checking and distributing the results. The research and development functions remained with USDA through the Animal Genomics and Improvement Laboratory (formerly the Animal Improvement Programs Laboratory, Beltsville, MD).

Table 1 Numbers of Holstein bulls in reference populations of countries that participated in Interbull genomic evaluations for protein yield in April 2016[a]

Country	Canada	Germany	Denmark–Finland–Sweden	France	Italy	Nether-lands	United Kingdom	Australia	Belgium	Spain	Poland
Canada	**29,101**										
Germany	1,970	**33,127**									
Denmark–Finland–Sweden	1,739	31,069	**31,747**								
France	2,010	27,947	27,587	**29,725**							
Italy	24,478	1,280	1,111	1,313	**24,805**						
Netherlands	2,074	28,823	28,353	25,251	1,353	**30,222**					
United Kingdom	25,919	1,779	1,578	1,803	24,263	1,868	**26,206**				
Australia	510	382	368	374	305	478	511	**3,369**			
Belgium	1,207	889	799	865	673	897	771	223	**2,493**		
Spain	1,694	30,318	30,116	27,636	1,130	27,836	1,522	357	804	**30,898**	
Poland	139	2,498	2,622	2,567	137	216	164	107	175	2,631	**2,748**

[a]Data reported by Interbull (25); reference population size in bold on diagonal, and bulls in common between reference populations below diagonal.

CURRENT US GENOMIC EVALUATION SYSTEM

Nomination

Since genomic evaluations became official in 2009, genotypes that are usable for genetic evaluations have been received for over 1 million animals (**Table 2**). The availability of lower-cost chips has made whole-herd genotyping common and has led to a preponderance of females among the genotyped animals (**Figure 1**). From May 2015 through April 2016, almost 359,000 low-density chip genotypes (319,918 Holstein and 38,883 Jersey) received by USDA were usable for the calculation of genetic evaluations; 91% of those genotypes were for females (27). With the popularity of genotyping chips, SNPs are gradually replacing microsatellites for parentage verification.

As of April 2016, eight AI organizations, four breed associations, three genotyping laboratories, and the National Association of Animal Breeders had met quality certification requirements and been designated by CDCB as nominators of animals to receive genomic evaluations (28). These nominators arrange for a DNA sample to be collected and sent to a genotyping laboratory (29). Many samples are bar-coded, which facilitates sample processing at the genotyping laboratory. The nominator is expected to enter information for each animal in a database maintained by CDCB before the DNA sample reaches the genotyping laboratory. The nomination is through either a web interface or pedigree records that contain sample identification. The breed associations use the pedigree record option for nearly all their nominations, as do the larger genotyping laboratories and several of the larger AI organizations. All nominators use a query for confirmation, updates, and problem resolution. The goal of the nomination process is to have pedigree information for an animal in the database before its genotype arrives and to assist in matching the identification associated with the genotype with the animal's information in the database.

Table 2 Genotype counts for April 2016 US genomic evaluations of dairy cattle[a]

Breed	Chip density of <40,000 markers				Chip density of ≥40,000 markers				Imputed		All genotypes
	Young		Old		Young		Old				
	Male	Female	Male	Female	Male	Female	Male	Female	Young	Old	
Ayrshire	155	2,540	22	91	709	1,139	740	60	14	22	5,492
Brown Swiss	1,573	2,265	29	1,525	7,830	186	6,389	196	221	117	20,331
Guernsey	4	1,338	0	191	115	22	451	340	0	12	2,473
Holstein	83,623	649,752	136	194,656	59,599	43,966	30,935	33,648	1,713	3,514	1,101,542
Jersey	9,889	69,077	37	46,688	4,839	913	4,770	1,946	53	304	138,516
All	95,244	724,972	224	243,151	73,092	46,226	43,285	36,190	2,001	3,969	1,268,354

[a]Genotype counts are grouped by density of genotyping chip, animal age, and animal sex. Counts for imputed genotypes also are shown and are grouped by animal age. Animal age was determined by lack (young) or presence (old) of phenotypic information (inclusion in the reference population). Data reported by the Council on Dairy Cattle Breeding (27).

Genotyping

The genotyping laboratories extract DNA from the sample. In 2015, DNA sources sent to the laboratories included tissue (64%), hair (31%), blood (2%), nasal swabs (<1%), and semen (<1%); 3% of DNA sources were unknown (G.R. Wiggans, unpublished observations). Amplification and fragmentation of the DNA, hybridization to a genotyping chip, labeling, and genotype detection take three days. Data generated from a laser reader are clustered to determine SNP genotypes (30). The SNP genotypes and corresponding identification information are transferred to CDCB.

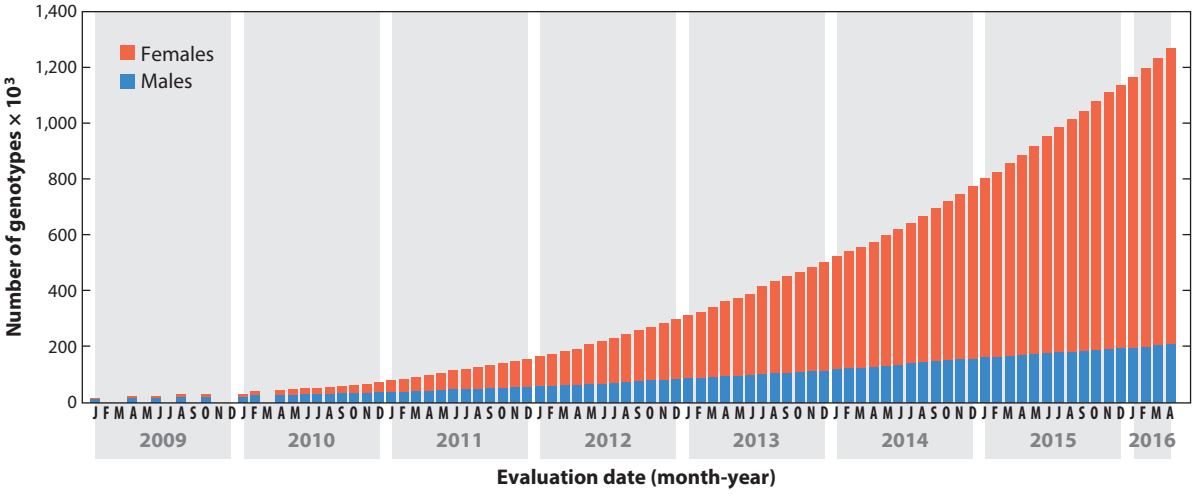

Figure 1

Number of genotyped animals included in US genomic evaluations for dairy cattle since January 2009. Official US genomic evaluations were first released to the dairy industry in January 2009 for Holsteins and Jerseys, in August 2009 for Brown Swiss, in April 2013 for Ayrshires, and in April 2016 for Guernseys. Data for figure generation were reported by the Council on Dairy Cattle Breeding (27). Months without data represent months in which official evaluations were not released.

Genotype Storage and Validation

The genotype database can store multiple genotypes for an animal (29). Chip identification and sample location on the chip are used to identify a sample uniquely. This method of identification was chosen because errors in sample collection and labeling as well as upgrading an animal's genotype from lower to higher density can lead to multiple genotypes for the same animal. Genotypes are checked on an animal basis for call rate and parent-progeny conflicts. Through comparison with all other animal genotypes, a conflict also is designated if a parent-progeny relationship is found that was not found in the pedigree. A report is returned to the genotyping laboratory for any SNP with a call rate of less than 90%, a departure from Hardy-Weinberg equilibrium (the difference between the number of observed and expected animals with heterozygous genotypes), or parent-progeny conflicts of more than 2%. Those checks are used to measure genotype quality, and the genotyping laboratories are requested to investigate any submission with more than 10 SNPs that do not meet one of the quality measures. Based on initial submission results, laboratories often are successful in reclustering problematic SNPs to reduce the number of SNP conflicts. As new chips are added and enough data have accumulated, SNPs are checked on a chip basis; SNPs from one chip may be excluded from use, whereas those from another may be used. The database allows for storage of genotypes from chips with differing numbers of SNPs; currently, 21 chips are supported. Although comparisons of SNP genotypes from different chips are supported, they are limited to SNPs in common.

Many conflicts related to animal identification can be resolved. If a genotype indicates that the sire listed in the pedigree is not correct, an alternative sire may be suggested. Identical genotypes for two animals often are the result of embryo splits or identical twins. Bulls have only one X chromosome; therefore, their genotypes for X-specific SNPs appear to be homozygous, a characteristic that can be used for sex validation. However, some cows inherit both of their X chromosomes from the same male ancestor and can appear to be male; their genotypes are accepted if a common male ancestor can be found. All genotyping chips except the BovineSNP50 include Y-specific SNPs, which are used in sex validation. Usability of genotypes is evaluated whenever the pedigree of a genotyped animal changes.

Genotypes are checked using breed-specific markers to verify that the reported breed matches the animal's actual breed as part of routine data edits. An animal's breed is validated using SNPs that are nearly monomorphic in one breed and have fewer than 30% of animals homozygous for that allele in another breed. A total of 723 SNPs have been selected for breed validation: 267 for Holsteins, 223 for Jerseys, 200 for Brown Swiss, 21 for Guernseys, and 12 for Ayrshires. The number of SNPs for which a genotype differs from the monomorphic genotype is counted separately for each breed. An animal is assumed to be a different breed or a crossbreed if the count for its specified breed is too high.

Genotype Preparation for Use in Genomic Evaluations

The SNP genotypes for each animal are extracted from the database. During extraction, multiple genotypes for an individual animal are merged; preference is given to the genotype with the most SNPs that are usable for genomic evaluation. Genotypes for identical twins and animals from split embryos are harmonized. Currently, 60,671 SNPs are used for US genomic evaluations (31), but no one genotyping chip includes all those SNPs. Because genomic evaluation requires a genotype for every SNP, imputation (32) is used to fill in any missing SNP genotypes for all chips. Imputation involves splitting a genotype into paternally and maternally contributed chromosomes (haplotypes). The inheritance of haplotypes is traced and used to fill in any missing SNPs. If a pedigree source is not available, the most common haplotype that does not conflict is used. The

findhap program (33) is used for imputation of genotypes included in US genomic evaluations. For dams without genotypes, genotypes are imputed if the number of genotyped progeny and mates is sufficient to reach a call rate of 90% on an allele basis; dams with imputed genotypes have been included in genomic evaluations since April 2010.

Estimation of Single-Nucleotide Polymorphism Effects

The effect of each SNP on a traditional evaluation is estimated for over 30 traits (**Table 3**). The traditional evaluations are deregressed to make the data more like individual records. Then the deregressed traditional evaluations are regressed on each of the SNP genotypes (19), where the genotypes are expressed as the count for one of the alleles (0, 1, or 2). The solution is the effect on each trait from replacing one allele in the SNP genotype with the other allele. In addition to individual SNP effects, a polygenic effect is estimated to capture genetic variation not accounted for by SNPs (19).

Most SNPs have small effects that are distributed evenly across all chromosomes but are not necessarily the same for all dairy cattle breeds. The largest effects for milk and fat were found on chromosome 14 for Holsteins and Jerseys (but not for Ayrshires and Brown Swiss); those effects were associated with the *DGAT1* (diacylglycerol O-acyltransferase 1) gene (34). An increased effect for protein was also found on chromosome 14 for Jerseys. Methods to visualize SNP effects have been developed (35), and Manhattan plots of the effects for all evaluated SNPs are available through CDCB for traits of economic importance depending on breed (36). **Figure 2** shows a Manhattan plot for SNP effects included in December 2015 US genomic evaluations for Holstein net merit, a genetic-economic selection index for lifetime profitability based on yield, conformation, health, and fertility traits (37, 38).

Calculation of Genomic Evaluations

An animal's genomic evaluation includes a genomic prediction (estimates of SNP and polygenic effects) as well as information from traditional evaluations that was not already included in the genomic information. To determine what traditional information was accounted for by genomics, a traditional evaluation is calculated only for the animals with genotypes (subset evaluation). The genomic prediction, traditional evaluation, and subset evaluation are combined through a selection index (20).

Measure of Evaluation Accuracy

Reliability is the accuracy measure for evaluations and shows how much information contributes to an evaluation. For genomic evaluations, reliability includes daughter equivalents from genomics, parent average, and other information from traditional evaluations not accounted for through genomics. The genomic contribution is approximated by a function of the weighted sum of the genomic relationships of the animal with the reference population; the weight is the reliability with the component for parent average removed (39). Because genomic relationships with reference animals and their evaluation reliability are the primary accuracy determinants, the genomic contribution is lower for less-related animals (e.g., those with foreign ancestors or subsets that contribute little to the current population).

To have SNP call rate affect reliability, reliabilities are converted to daughter equivalents and discounted if the call rate is low or if accuracy decreases because of imputation (29). The discounted daughter equivalents then are converted back to reliabilities. In May 2016, reliabilities for official

Table 3 Dairy cattle traits that are evaluated genomically in the United States by breed

Trait	Ayrshire	Brown Swiss	Guernsey	Holstein	Jersey
Milk (kg)	✓	✓	✓	✓	✓
Fat (kg)	✓	✓	✓	✓	✓
Protein (kg)	✓	✓	✓	✓	✓
Fat (%)	✓	✓	✓	✓	✓
Protein (%)	✓	✓	✓	✓	✓
Productive life (months)	✓	✓	✓	✓	✓
Somatic cell score	✓	✓	✓	✓	✓
Daughter pregnancy rate (%)	✓	✓	✓	✓	✓
Sire calving ease		✓		✓	
Daughter calving ease		✓		✓	
Sire stillbirth rate (%)				✓	
Daughter stillbirth rate (%)				✓	
Heifer conception rate (%)	✓	✓	✓	✓	✓
Cow conception rate (%)	✓	✓	✓	✓	✓
Final score	✓	✓	✓	✓	✓
Stature	✓	✓	✓	✓	✓
Strength	✓	✓	✓	✓	✓
Body depth				✓	
Dairy form	✓	✓	✓	✓	✓
Rump angle	✓	✓	✓	✓	✓
Rump width	✓	✓	✓	✓	✓
Rear legs (side view)	✓	✓	✓	✓	✓
Rear legs (rear view)		✓		✓	
Foot angle	✓	✓	✓	✓	✓
Feet and legs composite				✓	
Fore udder attachment	✓	✓	✓	✓	✓
Rear udder height	✓	✓	✓	✓	✓
Udder cleft	✓	✓	✓	✓	✓
Udder depth	✓	✓	✓	✓	✓
Front teat placement	✓	✓	✓	✓	✓
Rear teat placement				✓	
Teat length	✓	✓	✓	✓	✓

predicted transmitting abilities for milk yield based on all genotype densities ranged from 73% to 79% for 96% of young Holstein bulls (**Figure 3**).

The increase in evaluation reliability of Holsteins from including genomic information (**Table 4**) can be observed by comparing August 2011 traditional parent averages for young bulls without daughter information, their August 2011 genomic evaluations that include SNP and polygenic effects (estimated from the August 2011 reference population and traditional parent average), and their December 2014 daughter deviations deregressed from traditional evaluations. Mean reliability for August 2011 genomic evaluations of young Holstein bulls across all yield, health, and fertility traits was 68%, and reliability gains over parent average ranged from 8 (sire

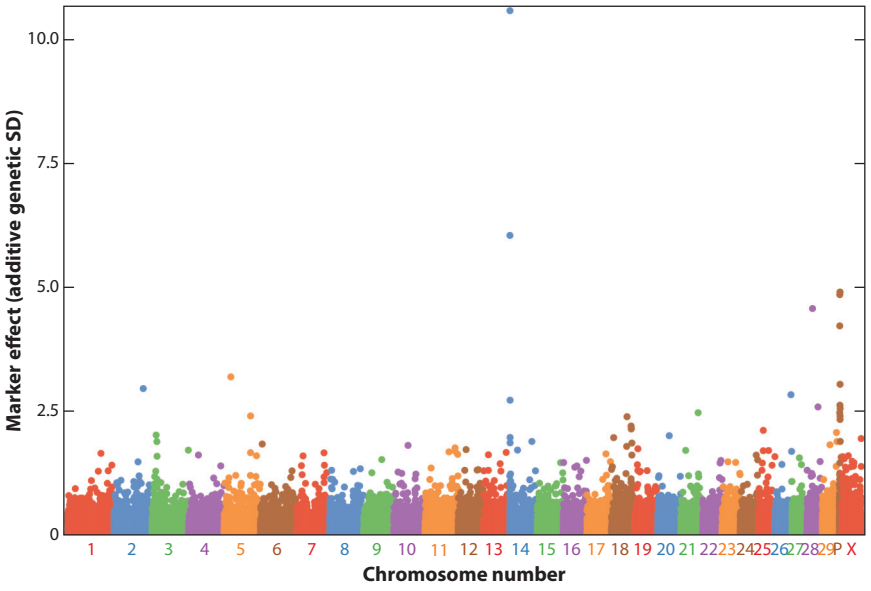

Figure 2

Manhattan plot of single-nucleotide polymorphism (SNP) effects included in December 2015 US genomic evaluations for Holstein net merit. Absolute values of effects for markers on the same chromosome are plotted in the same color; the pseudo-autosomal region of the X chromosome is designated as P. The distribution of SNP effects is useful for identifying which SNPs have a large effect on a trait. For example, a SNP on chromosome 14 is in close linkage with the *DGAT1* (diacylglycerol O-acyltransferase 1) gene in Holsteins and Jerseys. More details about such plots may be found in Cole & VanRaden (35).

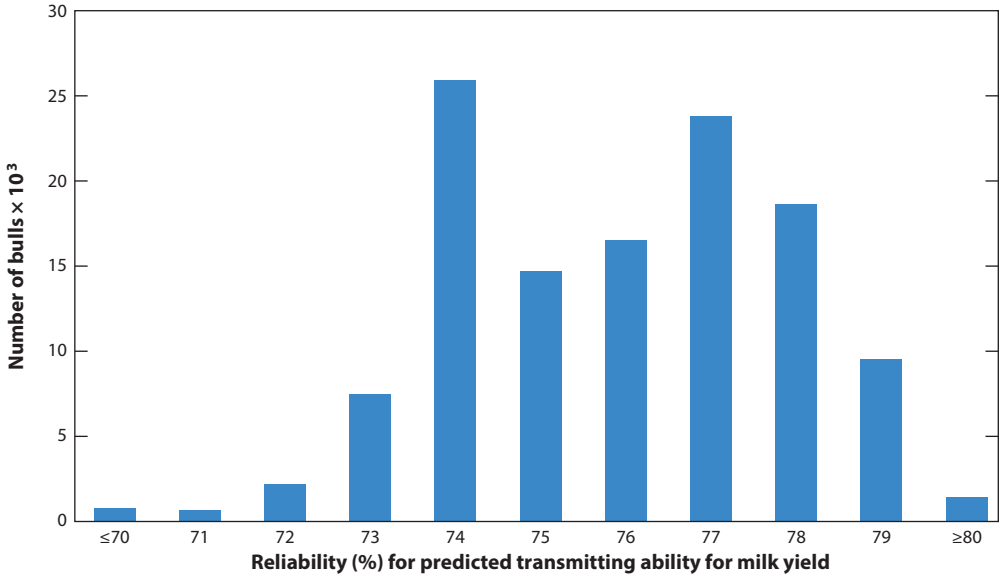

Figure 3

Reliabilities for predicted transmitting abilities for milk yield of young Holstein bulls. These bulls were born since June 2011 and had no traditional evaluation as of May 2016. Update of data in Wiggans et al. (29).

Table 4 Increases in reliability of US genetic evaluations of Holsteins from including genomic information[a]

Trait	August 2011 reliability (%)			Coefficient of determination (×100)		Regression coefficient	Bias[c]
	Parent average	Genomic evaluation	Gain[b]	Parent average	Genomic evaluation		
Milk (kg)	38.5	72.5	34.0	28.2	56.8	0.99	−73.1
Fat (kg)	38.5	72.2	33.8	23.8	52.4	0.87	−1.7
Protein (kg)	38.4	63.3	24.9	30.6	51.3	0.89	−1.6
Fat (%)	38.5	96.9	58.5	24.6	73.0	1.11	0.0
Protein (%)	38.4	87.4	49.0	29.8	71.6	0.95	0.0
Productive life (months)	32.7	66.5	33.8	27.4	47.3	1.19	−1.1
Somatic cell score	35.3	71.5	36.2	19.0	44.5	1.03	0.3
Daughter pregnancy rate (%)	32.7	57.9	25.2	17.4	30.2	1.32	0.1
Sire calving ease	25.4	49.7	24.4	15.8	31.9	0.79	0.0
Daughter calving ease	14.0	54.4	34.1	5.6	19.5	0.92	−1.8
Sire stillbirth rate (%)	24.6	30.7	7.8	12.9	18.0	0.71	−0.1
Daughter stillbirth rate (%)	29.5	75.5	57.0	8.1	24.4	1.09	0.0
Final score	36.9	62.1	25.2	17.7	35.1	0.80	−0.2
Stature	38.8	74.3	35.4	28.2	58.6	1.00	−0.3
Strength	38.0	72.2	34.2	18.9	44.4	0.98	−0.1
Body depth	38.2	73.7	35.5	21.6	48.3	0.96	−0.2
Dairy form	38.0	75.8	37.7	21.6	50.5	1.06	−0.3
Rump angle	38.4	75.1	36.7	17.0	47.8	1.04	0.0
Rump width	37.7	69.9	32.3	20.4	44.8	0.95	−0.2
Rear legs (side view)	37.9	61.9	24.0	21.5	38.5	0.98	−0.1
Rear legs (rear view)	36.7	60.9	24.2	6.6	20.7	0.87	−0.1
Foot angle	37.3	57.6	20.3	21.7	34.6	0.81	−0.1
Feet and legs composite	37.1	56.5	19.4	7.0	18.2	0.72	−0.2
Fore udder attachment	38.1	75.9	37.8	19.0	47.7	1.00	−0.3
Rear udder height	37.9	62.7	24.7	21.0	38.6	0.90	−0.1
Udder cleft	37.7	61.8	24.1	23.6	40.2	0.99	−0.2
Udder depth	38.6	84.1	45.5	13.3	50.7	1.08	−0.3
Front teat placement	38.2	72.6	34.5	15.1	41.6	1.03	−0.3
Rear teat placement	38.0	72.3	34.3	15.6	40.8	1.13	−0.3
Teat length	38.3	71.5	33.2	24.2	50.7	1.07	0.0

[a]Observed reliabilities in August 2011 for traditional parent averages and genomic evaluations of young bulls without daughter information, coefficients of determination between August 2011 evaluations and December 2014 daughter deviations deregressed from traditional evaluations, coefficients for regression of December 2014 daughter deviations on August 2011 genomic evaluations, and bias in genomic evaluations by trait. Genomic evaluations include single-nucleotide polymorphism and polygenic effects estimated from an August 2011 reference population (genotyped animals with traditional evaluations) and August 2011 traditional parent averages. Update of data in Wiggans et al. (29).

[b]Genomic reliability minus parent-average reliability.

[c]December 2014 daughter deviation minus August 2011 genomic evaluation.

stillbirth rate) to 59 (fat percentage) percentage units. A similar Holstein cutoff study conducted in September 2014 for heifer and cow conception rates (M.E. Tooker, unpublished data) reported reliability gains of 25 and 38 percentage points, respectively.

Coefficients of determination (**Table 4**) are a measure of the relationship between August 2011 evaluations and December 2014 deregressed daughter deviations. The coefficients of determination for Holsteins ranged from 6 (daughter calving ease) to 31 (protein yield) for parent average and from 18 (sire stillbirth rate) to 73 (fat percentage) for genomic evaluation. For both parent average and genomic evaluation, coefficients of determination were lower than respective reliabilities because reliability adjusts for differing amounts of information (error variance) and because selection had occurred in the genotyped population.

A regression coefficient close to one indicates that a one-unit difference in the genomic evaluation results in a one-unit change in the trait. Holstein coefficients for regression of December 2014 deregressed daughter deviations on August 2011 genomic evaluations (**Table 4**) ranged from 0.71 (feet and legs composite) to 1.32 (daughter pregnancy rate).

Bias in Holstein genomic evaluations was measured by subtracting August 2011 genomic evaluations from December 2014 deregressed daughter deviations (**Table 4**). A negative value indicates that the August 2011 genomic evaluation overestimated the December 2014 deregressed daughter deviation. Genomic evaluation underestimated later daughter deviation for only two traits (somatic cell score and daughter pregnancy rate). No bias was found for 6 of the 31 Holstein traits.

Distribution

Official genomic evaluations for US dairy cattle are calculated monthly. At each triannual release (April, August, and December) of official traditional evaluations, all genomic evaluations are released. Between those releases, genomic evaluations are not released for marketed bulls to prevent fluctuation between official evaluations. Genomic evaluations of foreign bulls are provided only to the nominator and only until 15 months of age unless an AI service fee has been received by CDCB.

In 2014, USDA developed preliminary genomic evaluations (40) to enable earlier culling decisions by producers and to smooth the workloads of genotyping laboratories. Those evaluations are calculated weekly, and only newly genotyped animals (or those with conflicts that were corrected) are processed using SNP effects from the previous official evaluation. CDCB sends the preliminary evaluations to nominators, dairy records processing centers, and breed associations so that they can be transferred to animal owners. Preliminary evaluations are labeled as unofficial and are not allowed to be used for marketing animals or germplasm.

EFFECT OF GENOMIC SELECTION ON THE DAIRY INDUSTRY

Genomic selection has profoundly affected genetic improvement of dairy cattle. Producers have accepted genomic evaluations as accurate indications of a bull's eventual daughter-based evaluation, and over half of matings are to young bulls with genomic evaluations. The AI organizations no longer rely on progeny-test herds to determine which bulls to market, and they purchase young bulls based on genomic evaluations. Both heifers and bulls are genotyped usually before they are one month old, and some embryos are genotyped before implantation. Herds that supply young bulls have had to specialize further to be competitive. With the nearly exclusive focus on high evaluations, embryo donors are highly selected, have genomic evaluations themselves, may have been purchased at high cost, and likely are virgin heifers. Genomic evaluations have reduced the concern about bias in the evaluations of top cows because the cow's own performance is not part of the genomic evaluation for a virgin heifer.

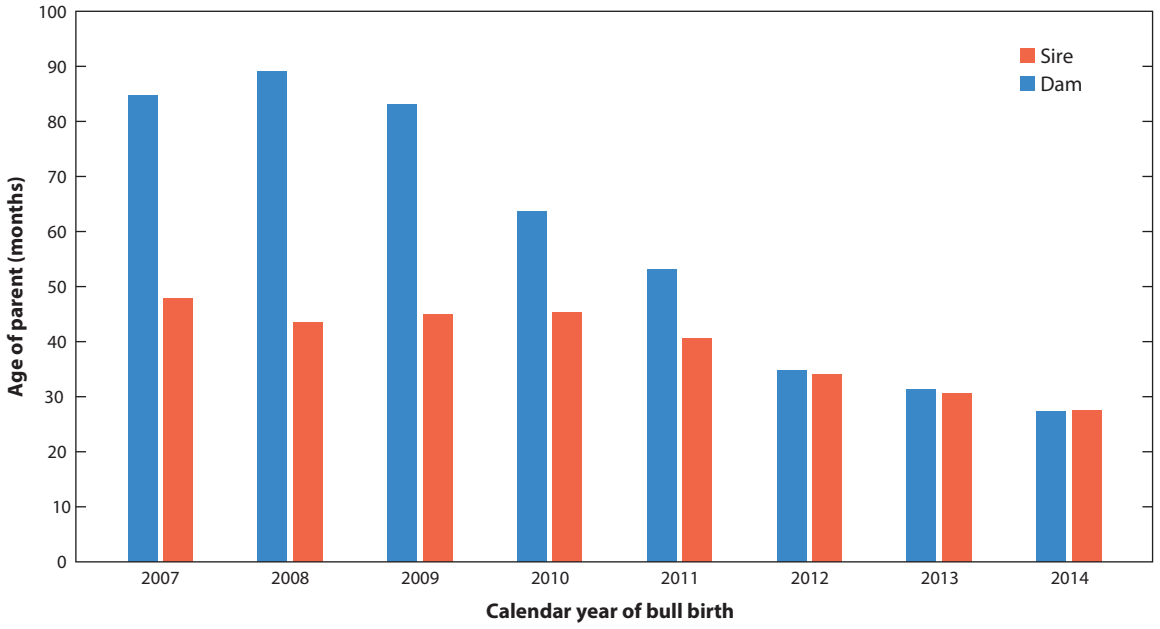

Figure 4

Ages of sires and dams of marketed Holstein bulls by bull birth year.

The age of parents of marketed bulls has steadily decreased since the start of genomic selection (**Figure 4**). The greatest decrease has been for bull sires because young bulls with genomic evaluations have replaced progeny-test bulls; all young bulls purchased by major AI organizations now are selected based on genomic evaluations. Similarly, virgin heifers are now the most common bull dams, and the ages of both sires and dams are near the biological minimum. These reductions in parent age for marketed bulls are the primary driver of the gain in the rate of genetic improvement because they have essentially halved the generation interval, thereby doubling the rate. The rate of improvement in average net merit has nearly doubled for Holstein bulls since the implementation of genomic evaluation in 2010 (**Figure 5**).

The benefit of genomics is greatest for traits with low heritability and ones that can be observed only late in life (such as longevity) because the increase in reliability provided by genomics is greatest for those traits (41). For cows, a genomic evaluation typically will have a higher reliability than would be achieved from their own records and has the advantage of being available shortly after birth. The industry requested weekly genomic evaluations because they are perceived as sufficiently accurate to select future replacements and allow culling of other females, thereby avoiding rearing costs.

Besides genetic evaluation, genomics can be used for pedigree discovery, determination of breed composition, mating programs, and tracking of inbreeding. If ancestors have been genotyped, pedigree information can be completed or corrected for many animals. In the United States, approximately 87% of bulls and 41% of cows had a probable maternal grandsire confirmed by genotypes submitted for genomic evaluation in 2014 (42, 43). Breed composition for crossbred animals can be estimated based on the breed-specific markers, and in 2016 USDA developed a breed base representation value to report the percentage of DNA contributed to an animal by each of the five breeds currently evaluated genomically (44). Controlling inbreeding is important

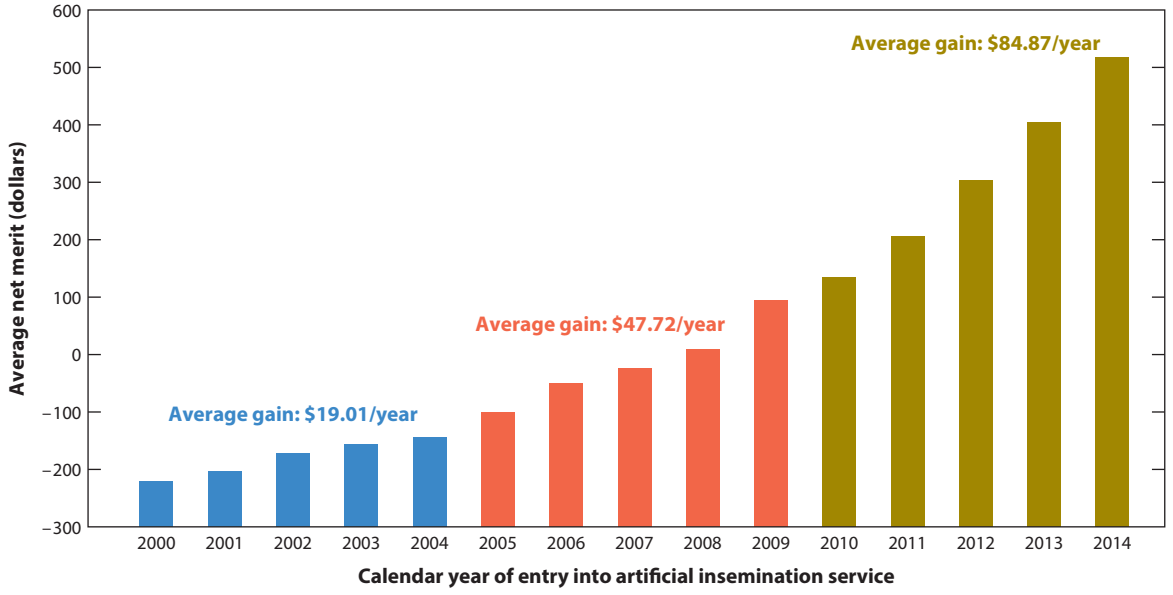

Figure 5

Net merit in April 2015 of marketed US Holstein bulls that entered artificial-insemination service in 2000 and later. Net merit is a genetic-economic index that was developed as a lifetime profit function that uses actual incomes and expenses for traits of economic importance (37). The economic values and traits included in the net merit index are updated as needed to reflect changes in the dairy industry, and the latest revisions were made in 2014 (38). The data for figure generation were provided by the Council on Dairy Cattle Breeding (**https://www.cdcb.us**).

because of its effects on production efficiency and fertility. Inbreeding for US Holstein cows born in 2015 is estimated to be 6.6% (45) (**Figure 6**). Genomic inbreeding is easy to estimate and can be used to control inbreeding in the next generation of animals by computing genomic relationships for potential mate pairs through mating programs (46).

Another benefit of genomics is the detection of carriers of undesirable recessive characteristics. A routine part of imputation is phasing the genotype into maternal and paternal haplotypes. If a particular haplotype is never found to be homozygous even though homozygotes are expected based on haplotype frequencies, that haplotype may be a recessive lethal (47). Where carrier sires are detected to have reduced fertility, a haplotype affecting fertility is declared (48). The imputation process is able to predict carrier status for other gene tests based on the tested population.

FUTURE OF GENOMIC SELECTION IN DAIRY CATTLE

The competition for position in the market based on animal rankings for genomic merit is fierce and includes genetics companies from around the globe. In North America, more than $14 million has been spent on genomic selection guided by SNP chips, and the pace of genotype testing is not diminishing. Even with all this investment and incredible gains in genetic improvement, the dairy industry is faced with several challenges that will require further adoption of new technologies to solve.

First, potential noise in the genomic evaluation system could be addressed by whole-herd parentage. Incorrect parentage can be as high as 20% in some herds. However, no economically feasible testing for parentage is available yet that is attractive to breed associations and producers alike.

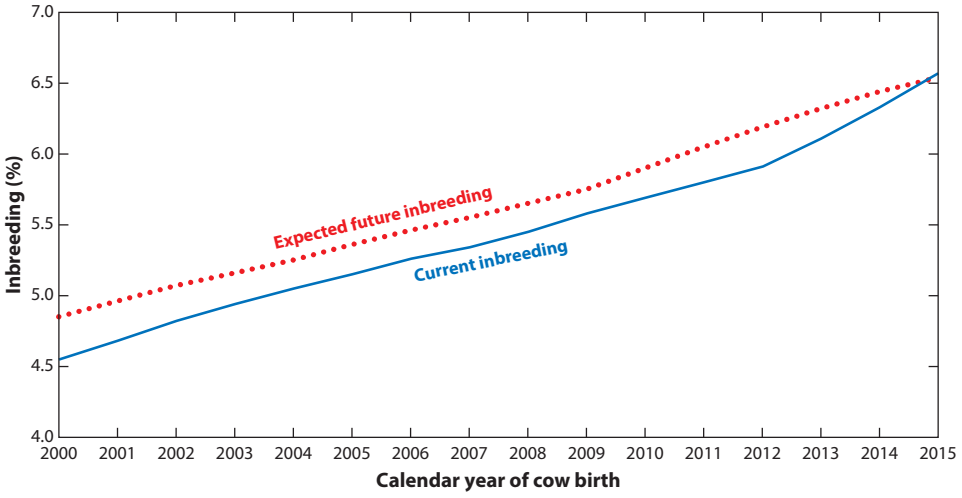

Figure 6

Inbreeding trends in April 2016 for US Holstein cows born since 2000. Current inbreeding reflects the accumulation of inbreeding from past selection; expected future inbreeding indicates the average inbreeding that would occur from random matings within breed. The data for figure generation can be found at **https://www.cdcb.us/eval/summary/inbrd.cfm**.

The current state of genomic prediction has also diminished the value of milk recording. If the dairy industry reduces recording of yield data, a long-term negative effect on the future accuracy of genomic selection is possible. In contrast, the amount of on-farm data collected for other functional traits is growing. However, those data are not always captured in a centralized database. Big-data organizational issues will continue to be challenging for the dairy industry, as well as reconciling the intellectual property assets associated with research discoveries from new phenotypic data and sharing of those data within the current genomic selection systems available to producers. For example, integrating genomic selection with new phenotypes like feed efficiency, nitrogen excretion, reproductive longevity and efficiency, immune response to bovine respiratory disease and bacterial infection of the mammary gland, and resistance to heat stress has potentially tremendous value to producers. Such traits provide options for better selection of animals that fit their production environment and are a means to increase efficiency and profit margins.

To address some of these issues, the investment in genomics has expanded beyond SNP chip tools and now includes funds for developing new diagnostics for phenotype and whole-genome sequencing. Whole-genome sequencing can lead to refinements in selection methods for mates and possibly allow genotyping by sequencing to replace linkage disequilibrium methods for genomic selection. Because genotyping by sequencing makes possible the coverage of large portions of the genome and varying genotype quality by individual, it may have some potential advantages for genomic selection in livestock. Accuracy of genomic evaluations could be improved by increasing the size of reference populations, and selection intensity could be increased by genotyping a larger number of selection candidates (49).

Before genotyping by sequencing becomes a reality, other less challenging methods from a big-data perspective are being attempted. More than $3 million has already been invested globally in whole-genome resequencing of the most influential bulls in the popular dairy breeds, with several potential outcomes. First, one hypothetical way to increase accuracy of genomic selection is to select animals based on the genotypes of their quantitative trait nucleotides. Sequence data

provide a means to investigate underlying mutations for quantitative trait nucleotides. Sequence data can also be used to improve imputation from low- or medium-density SNP chips to the high density of sequence-based genotypes prior to genomic evaluation. The impact of such new methods would be to reduce costs of genomically screening animals while increasing selection accuracy. Sequence data from influential bulls also is a resource for investigating gain- and loss-of-function polymorphisms.

One additional technology that has great potential for changing the direction and intensity of selection is the use of nucleases to edit the genome (50). Obvious candidates for application of this technology are editing elite genetics within the horned dairy breeds for polledness to address an animal welfare issue (51) and introducing natural adaptations to thermal stress discovered in Senepol cattle, a polled beef breed developed in the tropics (52). Polling dairy animals through precision crossbreeding or editing has already been demonstrated (53). Of course, this technology could also be used to fix additive traits such as milk production, which would greatly accelerate genetic progress by modifying multiple quantitative trait nucleotides in a single generation across multiple sire lines (54). The potential for nonmeiotic allele introgression or precision breeding to change methods of genomic selection and genetic improvement strategies employed by producers is tremendous. The actual commercial application of this technology could happen rapidly. However, it may be dependent on resolving inconsistencies between government regulatory policies on food additive and drug definitions and continuing consumer acceptance of food products that already are generally recognized as safe, which are alleles currently present in the genomes of food animals from natural selection or traditional livestock breeding.

CONCLUSION

The dairy industry continues to be the leader among food animal commodity groups in the successful adoption of advanced technologies. Dairy cattle breeding has been revolutionized by the use of genomic selection, and the rate of genetic progress has doubled through the increased accuracy of estimates of genetic merit for young animals. Genomic evaluations are based on genotypes that are checked extensively for quality, and they become more accurate as animals are added to the reference population. The latest integration of DNA marker technology and genomics into the traditional evaluation system has changed the industry considerably by decreasing generation interval, increasing selection accuracy, reducing previous costs of progeny testing, and identifying recessive lethals.

DISCLOSURE STATEMENT

Wiggans became a paid technical advisor for the Council on Dairy Cattle Breeding since his retirement in June 2016. The authors are not aware of any other affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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RELATED RESOURCES

Animal Genomics and Improvement Laboratory, Agricultural Research Service, US Department of Agriculture **https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-agricultural-research-center/agil/**

Bovine Gene Atlas (an extensive compendium of bovine transcript profiles) **http://bovineatlas.arl.arizona.edu/**

Bovine Genome Project, Baylor College of Medicine–Human Genome Sequencing Center **https://www.hgsc.bcm.edu/other-mammals/bovine-genome-project**

Council on Dairy Cattle Breeding (official source for U.S. genetic evaluations) **https://www.cdcb.us/**

Animal Improvement Program [USDA project ARS-8042–31000–101–00] **http://aipl.arsusda.gov/**

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